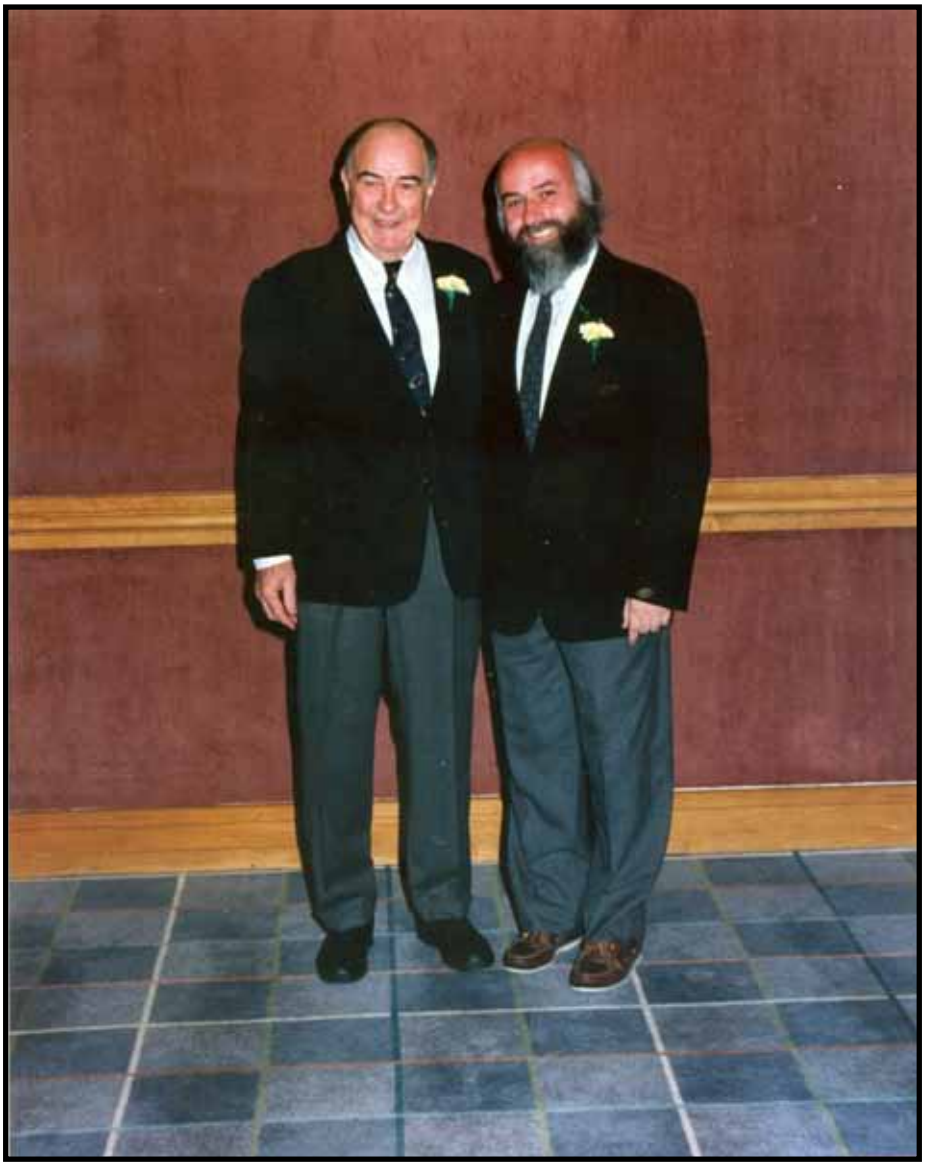
ICRO MAREMMANI

THE PRINCIPLES AND PRACTICE OF METHADONE TREATMENT



In memory of Vincent P. Dole,
friend and magister

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2 •

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Preface

Several articles in magazines and symposium speeches try to answer the question "What should the physician know?" I often feel doubts about what students should be expected to know to pass a general pharmacology examination. I usually tell students they should think of themselves as athletes, while their professor should be someone with such a deep knowledge of a discipline that he or she can communicate it spontaneously. General practitioners remain athletes, with their direct experience and constant updating enhancing their skills in the handling of complex clinical syndromes and their depth of knowledge in managing specific diseases and therapeutic approaches. This explains why I feel at a loss when they ask me what the basis of pharmacological and medical knowledge should be, or what it is essential to know about specific therapeutic issues. When speaking to audiences of general practitioners, I am usually requested - when it's a matter of explaining what disorder a drug should be used against, what the proofs and the terms of its effectiveness are, what its toxic effects are - to skip all the details and foregrounds about the pharmacological basis of how and why it works, because general practitioners are supposed not to bother much about such things. The adoption of an evidence-based substance vs. substance approach has shifted the focus of medical knowledge on to the statistical weight of clinical reports, whereas mere consistency with pathophysiological dynamics is not considered reliable as a predictor of effectiveness: in fact, clinical trials have often failed to confirm a hypothesis of effectiveness founded solely on pathophysiological speculations and open-label clinical reports. Nevertheless, the theoretical basis for the effectiveness of pharmacological treatment has not become irrelevant, and may provide warnings against risks that will not emerge from controlled clinical trials: that happened with -coxib drugs and cerivastatine, which were quickly withdrawn from the market due to surveillance warnings about toxicity - warnings which had been anticipated by preclinical pathophysiological investigations, but had not been expected on the basis of the results of later clinical trials. Often, it takes pathophysiology to inspire a clinical study, which then gives positive spin-off in return by providing evidence that deepens and enriches the level of knowledge about the biological basis of therapeutics. Medical discipline results from a continuous exchange between biological research and clinical practice through the channel of statistically weighted data.

Returning now to the question of "What should a physician know?", the answer should be translated into what each physician thinks he/she should know, into their curiosity and professional liveliness, into their need to deepen their knowledge. Both biologists and clinicians should avoid going into the fine detail of technical aspects of their practice, unless questioned about it by an audience. In any article, such details can be reported in a special section printed as a box kept separate from the main text, or else, in case of an oral presentation, the speaker may provide a reference list so that anyone can consult original data. Instead of boring an audience with superfluous notions; it is a speaker's interest and should be within his/her grasp to know many other things that will only emerge in the open discussion of scientific issues. Actually, "What should physicians know?" should be viewed as an open-ended issue.

This book is written by clinicians and appeals to clinicians. It features a great many pharmacological details about the pharmacological kinetics and dynamics of anticraving treatment. The clinical issues are discussed by psychiatrists with accuracy and by dedicating special attention to specific problems that emerge during the course of treatment, ranging between ordinary ones and quite unexpected ones. For each situation authors discuss the possible causes and review the different therapeutic strategies. The same issues seem to recur in different chapters, with special regard to anticraving treatment and different ways to reach the same solution from different viewpoints, while taking into account the variability of drug-related clinical situations and the need to use a variety of starting points.

For instance, treating a pregnant narcotic addict requires specific skills, while planning a treatment programme for jailed addicts calls for a specific knowledge of the prison environment and related legal issues. Nowadays, since addiction has become an endemic condition, it is expected to affect categories of individuals with higher exposure to risk factors, which probably include several psychopathological syndromes. As a result, it is crucial to anticipate possible dual diagnosis patterns, so as to be able to recognize them and handle such complex situations through specific treatment approaches.

Several chapters deal with psychosocial issues related to the world of addiction, with special reference to narcotics, both from a patient's and from the physician's point of view. This subject is faced without resorting to a meaningless even if politically correct approach. Drug addiction is presented as a psychiatric disorder and a curable condition: treatment can provide complete control of its symptoms by administering specific drugs in maintenance regimens of proved effectiveness. Other interventions may be useful, in some cases crucial, as in any other chronic disease, and comprise psychiatric and somatic treatments, individual counselling to help patients cope with the family and work environment. Authors specify the tasks of different staff members, whether medical or non-medical, who need to know how to deal with the patient, while avoiding uncertainty about professional roles and hierarchical relationships. The present manual looms as an easy-to-read volume, written by skilled professionals with technical competence and an aversion for dogmatism.

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Contents

INTRODUCTION

METHADONE TREATMENT

METHADONE TREATMENT IN SPECIAL POPULATIONS

1.1

Definitions

I. Maremmani

1. Habit

If a substance is used "habitually", that means it is consumed frequently, either continuously or intermittently. The habit of resorting to a substance depends on the subject's proneness to its use for a variety of reasons, the most frequent of which is self-stimulation and reward. Habitual use, or having the habit of using a substance, never looms as a disorder, although it may be of medical interest due to the substance's toxic effects. Although the habit of using a drug may be influenced by pharmacological means, an intervention of that kind would not have a medical meaning or goal [8, 9] .

2. Abuse

The term "abuse" indicates recurrent substance use despite known negative effects and consequences. In other words, a subject decides to engage in substance abuse beyond the threshold of unwanted consequences, but does so while experiencing a pleasurable or desirable state. Abuse may forerun addiction, but is not addiction itself; the relationship with the substance and the reward mechanism is still physiological, whereas the capacity to limit pleasure in order to avoid unwanted consequences is impaired. When control is lost over the capacity to interrupt a habit of consumption that no longer brings pleasure, independently of its increasingly negative consequences, we will use the term "addiction" [5].

3. Addiction

Addiction is a form of abuse characterized by the loss of control before substance use. For addicted subjects, the only chance of holding back from substance use is the absolute unavailability of the substance. In this case, the

subject abstains with varying degrees of discomfort. In any other case, the addicted subject will produce a stereotyped behaviour with a high level of impulsiveness, which increases when the subject's search for the substance is challenged by obstacles. In fact, the only obstacle which would extinguish the subject's desire to use the substance is its unavailability. Such uncontrolled appetition is called craving, and is the core symptom of addiction [1-4].

The concept of "control" usually refers to an incapacity to prevent negative consequences in social and productive terms. On medical grounds, control is maintained as long as subjects are rewarded by substance use and are capable of organizing their resources so as to keep themselves supplied with the substance, although negative social consequences may develop and involvement in substance use may leave no room for other life activities. The amount or frequency of substance consumption does not permit discrimination between a habit and a disease, nor do the toxic effects, the exclusiveness and intensity of engagement in substance use, or the level of social adjustment. The addicted subject loses the ability to handle his/her habit, and that is when the disease is born. A number of substance abusers apply for treatment when driven by legal issues, social impairment or lack of money, and succeed in stopping the habit when strongly challenged by its negative consequences. Others stop when the substance no longer gives them the desired effects, so that it is no longer worth the effort. Unlike simple abusers, addicted subjects may seek help even in the absence of psychosocial impairment or a history of adverse events. Heroin addicts, for example, can be classified in a variety of psychosocial categories, which comprise the 'stable' mode, that is, with no course towards social disruption, but with a stable, though not satisfactory, level of working activity and significant relationships. Besides this, the "two worlder" mode has been described; that term is used to evoke the condition of a subject who leads a normal life except for a recurrent involvement in clandestine, drug-related activities, crime included.

An individual who is thoroughly and exclusively dedicated to a substance which, in his intentions, will give him pleasure, without ever being able to attain this aim, and, despite the loss of general resources and a deterioration in the quality of life, is, by definition, addicted to that substance. A subject who complains about having no control over a habit (which implies a chronic discrepancy between the drive to use a substance and the intention to use it in a controlled way) is, by definition, addicted to that substance. However, even when a subject does not complain about an irreversible loss of control, a complaint about dissatisfaction or unhappiness from an expected source of pleasure, without a physiological evolution towards the extinction of appetitive behaviour, is enough to justify a diagnosis of addiction.

Addiction suits a variety of situations, some featuring a chemical substance as the object of craving, others featuring a situation or a gateway towards possible pleasure (such as pathological gambling).

4. Dependence vs. Addiction

Dependence is that pharmacological state in which someone is susceptible to emerging discomfort if deprived of a substance, but recovers a state of well-being when the same, or a cross-reactive, substance is reintroduced. Dependence may be spontaneous, or be the result of an acquired condition: insulin dependence is a spontaneous state in a diabetic person who has lost his/her endogenous resources. A diabetic will develop major metabolic disturbances as a result of insulin deficiency, but his/her metabolism will be restored by the provision of exogenous insulin supplies. Also, a person with a chronic self-immune disorder may be dependent on cortisonic drugs, which do not replace any lost function, but counteract a harmful pathophysiological process.

Secondary addictive features include a dependence on beta-blockers in a person with chronic high blood pressure, or the dependence on barbiturates of an epileptic. In this case, the abrupt interruption of exposure to the

substance will be followed by a rebound syndrome featuring symptoms opposite to those induced by the substance. Rebound symptoms are also the opposite of the symptoms that the substance is meant to counterbalance. The pharmacological basis for this phenomenon is known as tolerance, which consists in a progressive lowering of the sensitivity threshold in response to exposure to stable dosages. Tolerance is an elastic phenomenon; one result of this is that the interruption of exposure drives a tolerant subject into a sudden state of imbalance due to a relative deficiency of the substance; the outcome is that the system 'rebounds' by progressively lowering the sensitivity threshold until the original level is restored. Before the swing back is complete, the transient imbalance is expressed by rebound symptoms.

Rebound symptoms (commonly referred to as withdrawal symptoms) are usually transient. After withdrawal has stopped, the eventual state will depend on the reason why the substance was started. If there was a therapeutic reason, and the disease is a chronic one, the original disease symptoms will strike back. If the disease has been extinguished in the meantime, the subject will just be well. If the disease is a chronic-relapsing one, subjects may stay symptom-free for a period of variable length before they relapse.

For addicts who are receiving treatment, methadone dependence is a consequence of therapy. Its interruption means going back to the natural course of the addictive disease, which implies a perspective of relapse.

Addiction is a radically different condition. Addiction is a cerebral state consisting of a behavioural drive towards the consumption of an object, in response to a subjective feeling called craving, which is intense, self-synthonic and spontaneous; associated with an incapacity to control the urgency or exclusiveness of this drive through one's intentions.

Addiction may be compatible with a social life, intellectual and productive functioning, and an ability to keep the law, although it usually leads in the opposite direction. Anyway, it is, by definition, incompatible with a happy life and a satisfactory level of reward.

As noted above, on subjective grounds addiction is coupled with an intense feeling of desire, which cannot be handled (i.e., craving). In a condition of abstinence, craving will emerge sooner or later, regardless of withdrawal-related discomfort, and it will bring on relapsing behaviour. The old word for addiction was 'toxicomania', which was later replaced by the term 'drug-addiction' or 'drug-dependence'. The first word is more precise and less ambiguous, whereas drug-dependence should be avoided. In fact, 'toxicomania' suggested a 'toxic' effect coupled with an irresistible drive to use the substance, and recalled the concept of 'mania' as the psychopathological model able to describe the syndrome. Dependence on a toxic substance sounds meaningless: in a condition of dependence, that person is uncomfortable in the absence, not in the presence, of the substance. Even assuming that a toxic effect can be viewed as the price to be paid for gaining some kind of benefit from substance use, the cost/benefit ratio must be in favour of the benefit (as happens in the treatment of epilepsy, for example). The toxic aspect of dependence cannot be attributed to withdrawal, which does not develop if that person is constantly exposed to the substance, and it can be overcome by gradual tapering [6].

On the other hand, saying that someone is 'addicted to a toxic substance' provides a correct idea of the tragic tie between that person and the substance. Some addictive diseases also correspond to a state of dependence, but, if so, only for limited periods. Withdrawal is just incidental in an addictive syndrome, and does not add anything substantial in terms of diagnosis or prognosis, though it may change presentation symptoms. Stabilization dosages, too, are similar in non-tolerant subjects.

On clinical grounds, the course of addiction follows a divergent course from that taken by dependence:

a) the re-emergence of craving is not gradual; craving becomes intense even in the absence of tolerance;
b) when dependence on a narcotic sets in, it is complained about, since it makes substance use more awkward, and interferes with the original reasons for using narcot-

ics (those reasons were forms of reward);
c) during attempts to 'detoxify', the addicted person can buffer withdrawal symptoms by using a cross-reacting substance, or, possibly, by reacting in a 'cold turkey' way, that is, without getting any chemical help. Nevertheless, addicts continue to be incapable of preventing the development of relapses after detoxification.
d) In order to be able to handle withdrawal, the addict must achieve this without dealing with the substance, over which he has no control. That is why addicts can go through a 'cold turkey' experience, but are incapable of comfortably detoxifying by tapering narcotics.

5. Addictive ambivalence

In addicted persons, thoughts, affects and behaviours are all displayed ambivalently. This observable ambivalence mirrors a psychopathological one, which is itself an expression of a neurobiological 'conflict'.

Addicted patients, in fact, behave in a contradictory way: they apply for treatment with the aim of stopping their inclination to continue their substance use. Such behaviour corresponds to their intention, or 'will', as it is misleadingly called. A 'will' to stop addiction is usually claimed when help is being asked for, but the drive to reproduce addictive behaviours overpowers that 'will'. The diagnosis is "addiction" - a term that allows the identification of a category of 'difficult patients', who apply for a therapeutic intervention against a reckless behaviour that pulls in the opposite direction; these features provide the dynamics of what is called 'making allowance for disease'. To make the point more simply, addicted patients are unable to counteract the symptoms of their disease. Since addiction is centred upon craving, its course will drag the patient away from a therapeutic setting in imposing a self-perpetuating search for the substance.

Many develop an incorrect idea of addiction, mistaking it for a strong habit, and interpret a request for treatment as a tricky attempt to escape the consequences of one's illicit and disruptive behaviours. On clinical grounds, it is possible to discriminate between the hope of remission, which corresponds to intention and not to will, that is, an elaborate kind of thought inspired by personal experience, which can be translated into a series of graduated actions tending towards adherence to treatment, and is based on the activity of the cortical brain. Addictive behaviour, on the other hand, is produced by an instinctual drive which moves forward side by side with an affective state, remains self-syntonic and becomes more and more pertinent (an urgent priority). The instinct is directly reinforced by exposure to substances, and eventually becomes self-perpetuating by a long-lasting substance-produced imprinting. Because it is related to a subcortical brain activity, an instinctual drive takes the form of a rapid, one-step process.

Addictive behaviour is the result of a stronger, 'addictive' component, induced by substances and finding expression as an instinct, possibly reinforced by the substance itself, and a weaker, more rational component, which develops gradually, in accordance with the negative consequences of substance use.

The two dynamics, the addictive instinct and the anti-addictive intention, are challenged differently by the substance: in fact, the substance first has an impact on the instinctual component, and soon afterwards on the intention, through the main features of substance-related experiences. In fact, the honeymoon phase in which the person develops addiction always precedes the later stage in which an intention to quit will develop and overlap with the earlier intention. The same sequence is reproduced before and during relapses. Even if the intention to stay abstinent remains prominent after detoxification, a single episode of consumption is enough to trigger relapse; apparently sound intentions are quickly overwhelmed by quick instinctual dynamics that had apparently been extinguished [4]. It is a misconception to expect that continuous abstinence, possibly reinforced by environmental rewards, should restore an addict's capacity to

avoid substance use. Actually, as time passes, the intention to stay abstinent does not become sounder, but usually weakens and loses the urgency originally displayed at the time of detoxification treatment, when it was related to heavy global impairment. As conditions improve, time does not heal but brings on relapse. The addictive instinct, though without any reinforcement due to enduring abstinence, rapidly comes back to drive a person towards the substance against their own intentions.

In moving from relapse to relapse, a process of sensitivitization seems to take place: relapsing takes place more and more rapidly, and the period of latency between the first slip and full involvement in substance use becomes shorter. In the struggle between the intention to abstain and the drive to use, the odds are always loaded against the gambler, and the match lasts ever shorter times.

On psychopathological grounds, the ambivalence of addicts is founded on the core of addiction, that is the instinctual drive and its affective correlate (craving); these are self-syntonic. Some authors fail to recognize craving as self-syntonic and refer to it as compulsive (sometimes this term is used to indicate very intense craving with short-loop usage). The discrepancy between the intention to abstain and the drive to use may be mistaken for a compulsion, as long as the intention is mistaken for a drive.

The two components struggling in the addict's mind are not of the same kind, and do not come into opposition on the same level; the drive itself, in fact, is not ambivalent, and is clearly directed towards the substance. Craving, drive and behaviour are all clearly oriented towards the substance, which makes the whole complex a self-syntonic phenomenon. The intention pulling in the opposite direction cannot be referred to as self-dystonic (compulsive), since it acts on a different brain level, rational vs. instinctual. Resorting to the substance despite the intention to stop addiction is not a matter of compulsion; it is a conflict between a behaviour that is pursued and unwanted at the same time. The conflict takes place both during and after the behavioural output [5].

Ambivalence does characterize addiction at different degrees of severity. Higher severity corresponds to a greater discrepancy between intention and drive; the latter turns out to be even stronger. In a severely ill addict, with years of substance use and a history of repeated treatment failures, the intention to stop addiction may be sound and structured. However, the drive is always 'sounder' in the addict's brain. Therefore, since the drive is in the process of becoming more rapid, and can count on reinforcement, the intention to abstain is always weaker: in proportion, severely ill addicts become more willing to stop, but less capable of doing so.

A severely ill addict is usually pessimistic about acquiring the capability of stopping addiction, and staying detached from the substance. Because of this factor, along with greater psychosocial impairment and independent complications (e.g. infective diseases), the intention to abstain eventually weakens, so leaving further room for addiction. A hard-core addict will eventually think that the only realistic chance is to acquire partial control over substance use, which is the result of an addictive way of thinking and growing pessimism about a healing perspective.

Often, addicts need to be motivated, just because of such pessimism, while the addictive way of thinking is just a target of treatment. Motivation should not be mistaken for an element of treatment. No patient can be motivated so strongly as to make his/her intention prevail over the addictive drive. On the other hand, acting on motivation is a way of increasing the patient's trust and compliance with treatment, so restoring a healing perspective to their mind.

When addicted patients approach treatment settings, they are characterized by a spontaneous request for help, a different motivational status, and a constant ambivalence towards treatment adherence, which they may be aware of to a certain degree.

6. The insight of addicted persons

When patients ask for help, they are usually aware of the severity of their current condition, and realize that they have lost control over substance use. On the other hand, they have no real insight into the nature of the disease with respect to its chronicity, endogenous pathophysiology and irreversibility [7]. Addicts will think the problem is their recent past, instead of their future, and deny having any long-term problem with substance use control. In this way, addicts underrate or deny the risk of relapse, and aim to achieve a controlled use or a spontaneous abstinence, rather than a relapse-prevention treatment. As soon as they achieve a state of partial well-being, they will identify it with definitive healing. When relapses occur, they will think of each relapse as a separate episode, with its own precursors, reasons and treatment perspectives.

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1.2

Addiction Treatment: When will Medical Principles Matter ?

M. Pacini and I. Maremmani

The medical approach to human suffering consists in practical interventions which may vary in accordance with the types of symptom, but are rooted in a set of identifiable principles.

1) The principle of emergency overcome. Symptoms should be ranked according to their severity, and the severity of their expected consequences, so that those which can be identified as bearing the most dangerous consequences (e.g. death, organ failure or metabolic impairment) should be challenged as a priority. As far as addictions are concerned, patients may be intoxicated when asking for an intervention, be under the effect of multiple drugs, be traumatized, metabolically impaired, dehydrated or starving, or may display major psychiatric symptoms [1]. The emergency principle can be applied to whole population instead of single cases, especially during epidemics: when death rates are quite high and the chances of survival depend on the degree of severity, less severe cases may be treated as a priority, so as to stop them becoming more severe, on the assumption that interventions against severer cases would have little impact on the future situation. Obviously, in epidemics a population-based ratio may prevail on the individual-based ratio.

2) The principle of severity threshold. Under conditions that imply imminent risks, one main treatment objective should be to reduce the severity of symptoms. Interventions should at least aim to ensure a minimal level of functioning, so enhancing the probability that treatment can continue. The principle of severity threshold retains its validity regardless of how seriously the patient is impaired; in fact, those whose illnesses are most severe at the moment when they enter treatment are not necessarily those who are destined to have the worst or least satisfactory outcomes. On the other hand, it is true that severity is correlated with the risk of relapses [16].

3) **The principle of stabilization**. Once any treatment has proved to be effective in controlling the core symptoms of a disease, it should

be maintained and enhanced until a continuous, satisfactory balance is attained. Balance can be considered satisfactory when environmental factors have proved incapable of hindering the response to treatment or of jeopardizing the patient's well-being [8].

4) **The prognostic principle.** As long as we are able to anticipate the evolution of a situation on statistical grounds, the choice of one therapeutic regimen and its design through time represent the transition from the treatment of the acute phase of a disease and to its possible chronicity. Once acute symptoms have been buffered, most diseases need a maintenance regimen to keep the underlying processes under control. By definition, chronic disorders are, in fact, characterized by a spontaneous, autonomous self-perpetuating trend, which leads to persistence, recurrence and phases of rising severity. Despite this, patients with a chronic illness often put the blame on therapies, as if a given treatment were responsible for making that illness chronic. Given the illogical tendency to think that long-term regimens maintain proneness to relapses, rather than defending the results achieved so far against a spontaneously relapsing disposition, patients end up by feeling they will continue to be ill as long as they keep on attending treatments. It follows that the meaning of prognosis should be clarified from the start, so as to provide adequate linkage between the treatment premises (the nature of the disease), its course and the fact that the results that can be achieved will depend on the persistence of that treatment [9].

5) **Principle of improvement**. It is a common view, especially among social workers, that the golden therapeutic goal is to turn former addicts into ideal, highly productive, reliable citizens, who will act out a social and individual model that is completely opposed to their previous drug-related habits [2-4, 17].

All the findings that have won acceptance over the years, and the consensus of opinion surrounding any known disease, point in a different direction. The extent of achievable results is, firstly, limited by the severity of the disease, its chronicity, and the degree of damage already sustained. Medical treatment should always aim to achieve some improvement, and, if possible, to go on from there in the direction of eventual healing. A prognosis of healing is a statistical possibility, but it sets up a misleading perspective. Approaches that are founded on an effort towards healing as an immediate objective tend to be rather irrational, and to leave medical knowledge out of account. When medical treatments are, indeed, applied to achieve healing directly, they tend to lose their theoretical role, so that the supposed treatment ends up by leaving greater room for the disease to develop and become more severe. When healing is the question at issue, little effort is spent on improvement, balance or control, because these are all viewed as failures to achieve healing. From this perspective, successful treatment is no better than no treatment. By contrast, any period of clinical remission, no matter how brief, is highlighted as the proof that healing is possible, instead of being viewed as an interval that is only to be expected between relapses. In the end, individuals who have gone through healing-bound programmes are those most likely to fall into the categories labelled "dead, formerly healed", or those who became untreatable. Likewise, the time spent within such programmes will result in lower chances of achieving realistic goals, or of shrinking the therapeutic gap between targets and attainable levels of improvement [9]. From a physician's point of view, healing is a rare exception, just as the total impossibility of achieving any improvement is an exception, too. Medical treatment falls between these two extremes. In reality, neither the impossibility of healing nor the impossibility of achieving improvements should be considered defeats. The only true defeat comes from a failure to employ the therapeutic instruments that are available, through ignorance or through an irrational resistance to scientific principles, and from lack of determination in pursuing achievable results.

6) **Principle of specificity**. On technical grounds, one needs to know which programmes can be useful in achieving the goals

to be pursued. The successfulness of any treatment cannot be based on the soundness of the therapist's intentions, the strength of the patients' motivation or the alliance between patients and therapists. A disease is curable when there is at least one effective instrument to be resorted to, and its functioning can be handled scientifically in accordance with specific rules [5, 7, 9-11]. Considering all the principles of medical practice, effectiveness is the least understandable: the reasons for the success of some highly effective instruments remain unexplained. In other cases, the discovery of effective instruments was unexpected, while there are many examples of candidate instruments which turned out to possess little, if any, effectiveness.

In the light of the above principles, the treatment of narcotic addiction can be thought of as follows: addiction should be challenged as a highly curable disease, with no realistic perspective of healing in the short or medium term [10, 12-15]. The best approach consists in achieving a condition of therapeutic balance by an agonist maintenance regimen that aims to control and prevent relapsing behaviour [5, 10]. This approach should constitute the first-line intervention against narcotic addiction, in order to minimize the rate of patients who enter treatment under the burden of somatic or psychosocial concerns, and the average severity of developed impairment. Drug-free regimens that aim to achieve absolute healing should be regarded as anti-therapeutic, besides being ineffective. The sequence of treatment goals to be pursued comprises: survival, behavioural stabilization, medically-allowed rehabilitation. Eventually, after a long period of stability, medically supervised withdrawal is conceivable, though on a strict clinical basis and only if an extremely gradual schedule is adopted [6].

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1.3

Heroin Dependence

I. Maremmani and D. Popovic

Heroin Abuse is the failure to reduce or interrupt heroin/morphine intake administered daily for at least a month, with a consequent state of continued intoxication leading to overdose episodes that affect social or occupational activities. The term "Heroin Addiction" includes the conditions of tolerance and withdrawal. Tolerance is defined as the need for markedly higher amounts of the substance to achieve the same effect, or a decrease in the effects when constant amounts of substance are taken. Withdrawal is expressed through a characteristic withdrawal syndrome after the reduction or cessation of use. This definition has been transposed from the Diagnostic and Statistical Manual of Mental Disorders [1]. Both abuse and withdrawal may lead to a state of acute intoxication. The diagnostic attention given to withdrawal from opioids, however, is increasingly switching towards the concept of relapsing behaviour, which is a relapse into substance abuse after a more or less prolonged period of abstinence from the substance [18]. Based on the latest considerations on etiopathogenesis, clinical presentation, course, and therapeutic outcome, withdrawal while on opioids can be defined as a "chronic disease with a relapsing trend" in which, alongside opioid abuse and the state of addiction, an important role is played by the tendency to become chronic, as shown by the frequency of relapsing behaviour [19, 24].

1. Etiopathogenesis

Up till now no descriptive model of a phenomenon as complex as drug addiction has been sufficiently comprehensive and explanatory since, generally, each of them has been limited to the interpretation of some phases in the course of the disorder, instead of its complete evolution, and these models derive from a particular point of view [17]. Alongside partial models focusing on various social, environmental and cultural groups and subgroups, it has been decided to add a search for psycho-

pathological and psychodynamic factors as candidates for an interpretative hypothesis (Figure 1). Even though many studies have failed to reveal specific personality factors in drug addicts, there is an undeniable overlap between substance abuse disorders and psychiatric disorders, characterized by a variety of psychopathological and personality constellations. Impulsivity, inability to control anxiety, intolerance to frustration, dependent relations, egocentrism, are some of the characteristic, even if non-specific, personality aspects of drug addicts that show analogies with narcissistic personality disorder. The inability to confirm the existence of a 'specific personality' has led to an appraisal of drug addiction as a transnosographic disorder not associated with specific traits or a particular personality structure or mental disorder. From a psychoanalytical point of view, drug addicts present a regression to the oral phase of libidinal development, while external reality and instincts gradually lose their meaning. The 'need to take drugs' is correlated with relief from an unbearable psychological tension, since the drug addict, because of the extreme fragility of his/her defenses, cannot tolerate anxiety and depression. Thus the substance seems to function as a means of protection from narcissistic wounds resulting from the failure of an over-idealized Self. A consequence of the weakness of the Super-Ego is the ease with which the mental representation finds expression in unexpected and incomprehensible ways, through aggressive discharges, whether these are self-oriented, following a self-punishing, self-destructive path, or hetero-directed. In this sense, drug addicts' behaviour appears to be an attempt to adapt, by regulating and modulating emotional expressivity [17]. Some authors have suggested that drug addiction is closely related to manic-depressive psychosis: if, on one hand, the substance acts as a form of defense against depression, by making it possible both to obtain a state of 'artificial mania' and experience feelings of omnipotence, on the other hand, the withdrawal crisis is comparable to a depressive phase. Recent data highlight the existence of a high level of comorbidity of Substance Abuse Disorder and Bipolar Disorder in which the elevation phase, however, is primary and not due to substance-

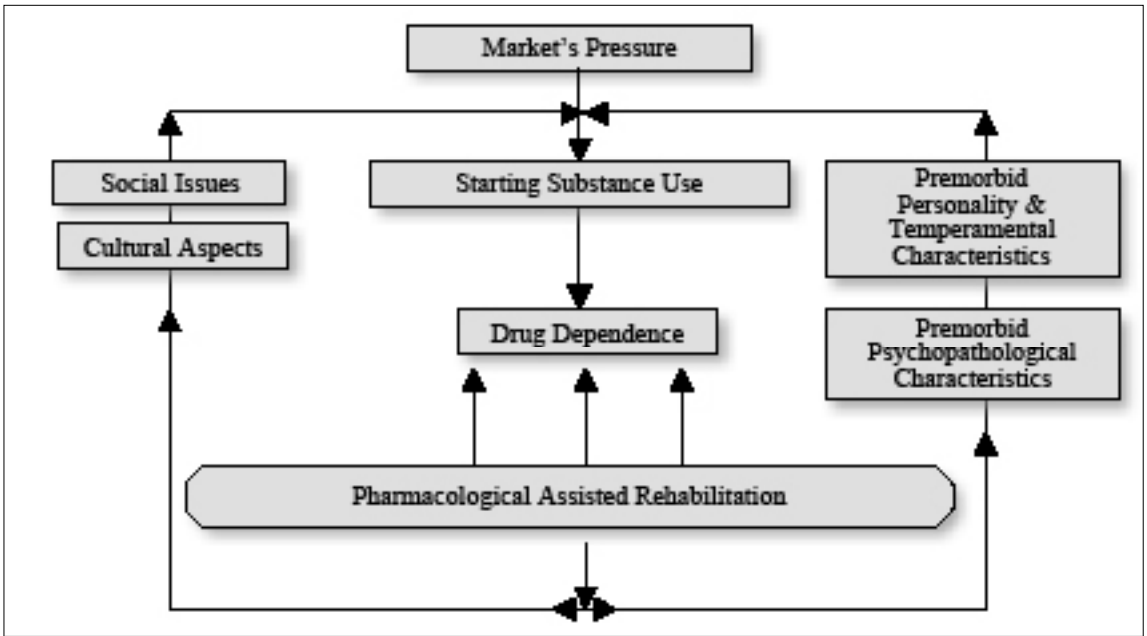

Figure 1. Etiopathogenesis of drug dependence

induced euphoria [20, 21]. In recent years there has been an epidemic diffusion of new abuse substances which, in terms of their modality of consumption and abuse-related behaviours, suggests that there is a new 'addict generation', with distinctive cultural, social and personality features. Rigid one-factor models have proposed a limited explanation of the phenomenon and of changes in addictive habits, but failed to consider the interactions between the individual, the environment and the substance. In order to achieve a better understanding of this reality, multifactorial models were adopted – models able to integrate the sociocultural situation, the pharmacological properties of the substance of abuse, personality traits and biological determinants. The individual was finally assessed, with reference not only to his/her psychopathological structure (mood disorders, anxiety disorders, psychotic episodes, personality disorders), including biological features, since there is evidence not only of a metabolic deficiency of the opioid endogenous system deriving from the prolonged use of opioids, but also to his/her genetic predisposition [12, 13, 32]. It is likely that the large-scale spread of the phenomenon of heroin abuse in Italy after the 70's is due to 'market' causes, in a process in which Italy was identified as an area of influence by drug dealers who were ready to recognize adolescents as 'possible consumers'. The 'consumer-competitive' mechanism typical of Western society, together with its 'adolescence crisis', link up with the pharmacological properties of substances of abuse; this linkage, in the case of prolonged use, was likely to culminate in addiction [9]. Whether substance-seeking is best viewed as a fashion within consumerism, or simply as a way of coping with emotional difficulties, or even as being a psychological expression of altered neurotransmitters, whenever the practice of drug abuse persists, factors such as tolerance, withdrawal and, at least partly, relapsing behaviour, are supported by neurobiological alterations to gratification brain circuits [4, 6-8, 36-40]. Following repeated opioid misuse, in fact, adaptation mechanisms develop through the opioid metabolism, based on a rise in the levels of enzymes (pharmacokinetic tolerance) and through a fall in the density of opioid membrane receptors, known as 'downregulation', a reduction in cellular response to the binding of the substance with the receptor, based on a lower availability of cAMP, inhibitory feedback on synthesis, and on endogenous opioid activity (pharmacodynamic tolerance). All this translates into a marked decrease in the effects of the substance with prolonged use of the same doses, and only a gradual increase in the quantity of substance taken will allow the desired effects to be achieved. Since the homeostasis of the organism can only be preserved in the presence of the substance, any abrupt interruption will lead to alterations that manifest clinically as stereotypical symptoms. The Locus Coeruleus [2, 3, 10, 14, 27-30, 34, 35] is a nucleus that plays a primary role in the psychopathological mechanisms of the Withdrawal Syndrome; its stimulation, in fact, leads to a series of symptoms that display many similarities with withdrawal behaviour. This nucleus contains more than 50% of brain catecholamine and is listed as responsible for phenomena such as anxiety and panic attacks. The Locus Coeruleus is innervated by fibres containing endogenous opioids with negative feedback action. The chronic administration of opioids produces a reduction in quantities of opioid receptors and a decrease in the release of Noradrenalin throughout the SNC resulting in an 'upregulation' of postsynaptic adrenergic receptors. The interruption of opioid intake removes the inhibitory action on LC neurons. Subsequently, the resumption of nuclear activities thus corresponds to a rise in noradrenergic effects due both to a sudden increase in Noradrenalin and to an increase in receptors. The term "secondary withdrawal syndrome" (otherwise known as "post-withdrawal" or "reflected" syndrome) stands for a series of physical, autonomic or psychic symptoms that may even appear a long time after the administration of opioids, unleashed by emotional evocation, mental images or the revival of situations and stimuli related to the drug addiction past [25, 26]. The Relapsing Behaviour may, in many cases, be the behavioural expression of a secondary withdrawal syndrome, and reveal a tendency

to relapse even in subjects who are highly motivated to implement withdrawal. Of course, other vulnerability factors such as interpersonal conflicts, frustrations, intolerable feelings of anger and anxiety, sadness and boredom can play an important role in determining a relapse. The neurotransmitter systems involved in opioid withdrawal are responsible for various functions, such as the regulation of pleasure/pain, storage and memory retention, attachment/avoidance conduct. At present, however, the complexity of the endogenous opioid system makes it difficult to determine the physiological behavioural effects typical of these substances, regardless of their involvement in the pathological behavioural aspects of opioid addiction.

2. Natural history of heroin addiction

Drug addict experience can be divided into three stages.

2.1 Encounter or "honeymoon" stage

In a normal, non-addicted person, the administration of opioids produces markedly positive feelings of well-being (Figure 2). The subject experiences an extreme sense of calm and relaxation, not without a certain amount of euphoria, even if this is quite different from the experience produced by the selective activation of the dopamine system, as occurs after the use of cocaine and amphetamine-like substances. Generally, substance administration is occasional and the subject expresses the conviction that he can voluntarily interrupt at any time. There is no outward sign of a genuine drug addiction behaviour; there is no tendency to increase the dose nor an irresistible desire to use it. There are no clear signs of a withdrawal syndrome. The situation is often underestimated both by the patient and the social environment, because neither is capable of recognizing the subtle signs of a dysphoria which becomes increasingly predominant.

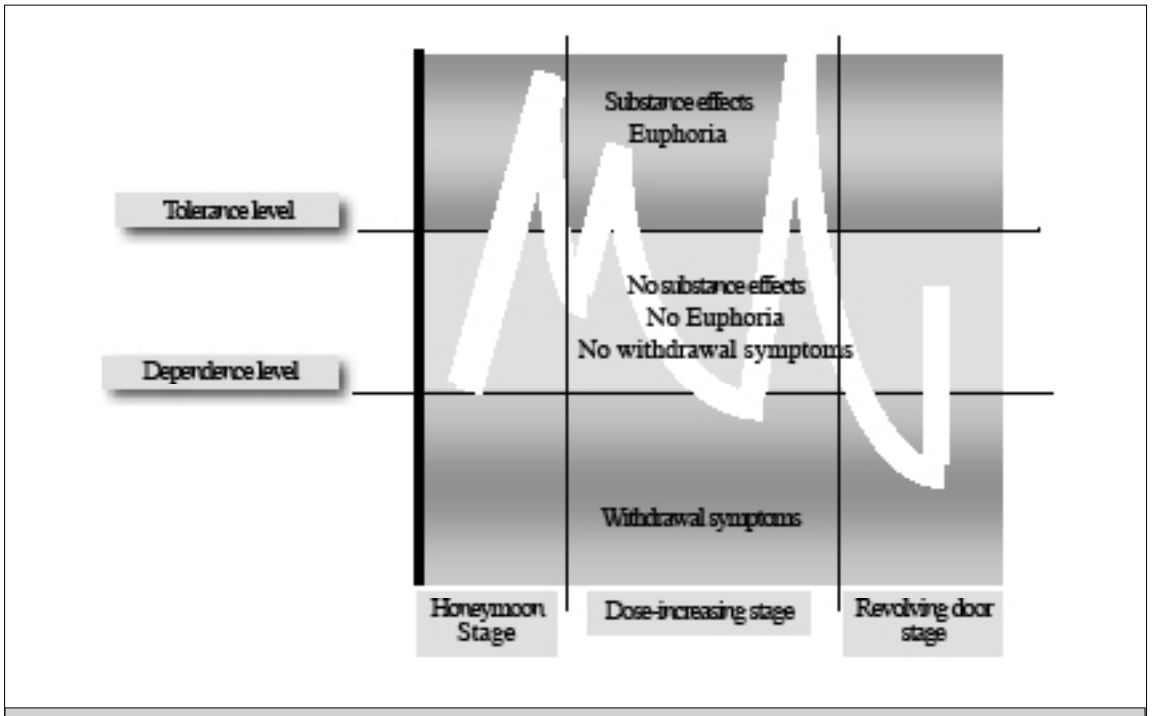

Figure 2. Natural history of drug addiction

2.2 *Intermediate or dose-increasing stage*

By maintaining a constant dose, euphoric effects tend to disappear gradually, while symptoms of opposite polarity appear, linked to a withdrawal syndrome that develops in parallel to the onset of tolerance. From being 'normal', the subject has gradually become addicted to a drug, and will have to increase the dose of the substance to allow the feeling of euphoria to be experienced once again. In any case, as a result of the same mechanism, the withdrawal symptomatology will become more severe. The need for the substance becomes increasingly more 'imperative' and, by continuing to abuse opioids, as well as intensifying the need to increase the dose, the subject will reach a point where the euphoric pole can no longer be reached and the patient will fluctuate between a greater and greater difficulty in maintaining normality and a progressively more severe psychophysical malaise due to the withdrawal syndrome. This is the condition of a decompensated drug addict. In more severe cases this condition evolves into a 'depravity' stage in which the subject is totally oriented, by any means, lawful or unlawful, moral or immoral, towards substance-seeking.

2.3. *Repeated detoxification or the "revolving door stage"*

After a more or less prolonged period of addiction, the impossibility of finding sufficient quantities of substance, or a self-awareness of his/her psycho-physical condition, spurs the heroin addict to make the earliest attempts to handle detoxification personally, and, later on, apply for help to social health services. At this point, the ordeal of relapsing behaviour begins. After a request for assistance that the subject conveys to others, and that is often sincerely motivated, 'after having reached the bottom', in most cases, the next development is the rigid positions taken by operators in the sector to 'quickly liberate' the person from the drug and set up psychological or social rehabilitation programmes (Psychotherapeutic or Community interventions). This often leads to a 'revolving door' situation, unfolding as a dramatic sequence of being treated, quitting the treatment, falling out, being arrested, being hospitalized, going back to treatment, and so on. This perpetuates the sensation of incurability in drug addicts and explains their mistaken belief that such situations are incurable in others. In this period, too, the risk of death from an 'overdose' is higher because, in a drug addict in detoxification, the gradual decline of tolerance to opioids appears alongside the onset of craving for the substance, which leads to the occasional use of heroin. The administration of a dose equal to the dose administered during the period of tolerance will, in these circumstances, cause an 'overdose' (Figure 3).

3. Typology of heroin addiction

The use of opioids interferes in various ways with the ability to reach a certain level of social adaptation [16]. The lowest level on this scale, corresponding to the maximum degree of maladjustment, is that of 'street addicts'. They often present the phenomenon of multiple substance abuse and an incessant demand for medical prescriptions, sometimes on the borders of legality, of any substance that can alleviate the malaise of going through a withdrawal crisis or that might ease the craving for heroin. Also, the percentage of criminal activity that aims to raise money for 'a daily dose' (or 'daily doses') is at its peak. The establishment of a therapeutic approach, which they reject, is extremely difficult, too. On the other hand, we can identify 'stable patients' or 'conformists' who lead an existence that is apparently acceptable to social conventions. They often manage to keep their job, which in some cases may be quite important, and do not present legal problems. They do not tend to group with other addicts. The 'destructive'or 'violent' addicts are immersed in their drug sub-culture and live in places and situations that are often at the limits of the law or may even be in open conflict with rules or conventions. They do not

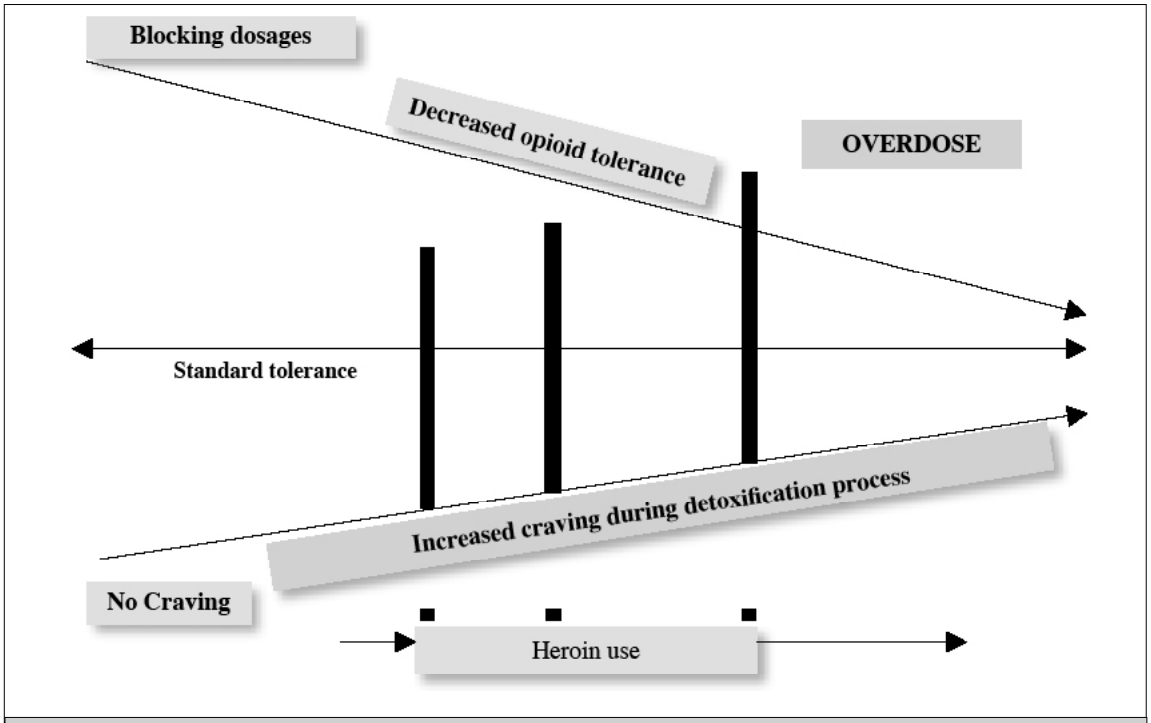

Figure 3. Overdose hypothesis

have an honest job and often engage in criminal activities in order to survive. They also present unmotivated episodes of aggression, which they decided on only to cause suffering to the victim. Those who 'live in two worlds' do not care about their criminal activities or living together with other addicts, but often have a regular job; these are the heroin addicts who are most socially dangerous, because of the serious problems they are likely to cause at work, both during acute intoxication and during a withdrawal syndrome. Finally, the 'loners' are not involved in the drug culture, do not have a stable job and in most cases live on State subsidies rather than on the proceeds of criminal activities. Very often they are carriers of serious psychopathological problems (Schizophrenia Simplex); this makes the concomitant drug addict behaviour very difficult to diagnose or treat properly.

From a clinical-nosographic point of view we can distinguish between 3 types of heroin addicts.

3.1 'Reactive' drug addicts

Often drug consumption is a response to social interaction and family issues. In this case, substance abuse can be called a normal adolescent crisis with concomitant specific personality traits and environmental difficulties without full-blown personality disorders. The lack of structured critical capacities impedes the rejection of a useless, harmful, but well-organized offer, such as that of heroin. Typically, heroin induces psychological barriers to its purchase, but there are moments in the life of a teenager in which he/she may can be caught off guard. These individuals' dominant clinical presentation is that appropriate to the 'honeymoon' stage, continuing over time, but continuous use can lead to an unfavourable evolution of the 'addiction'. Psychotherapeutic and educational assistance, associated when necessary with psychopharmacological therapy with opioid antagonists, is indicated for these subjects.

3.2 'Self-therapeutic' drug addicts

It is known that euphoric effect is not always sought after in a drug; initially, a subject often "actively seeks for a substance that will ease dysphoria and finds out that opioids are able to do this better than other drug categories". In other words, for some of those who approach drugs the concept of seeking for a drug functions as an unconscious attempt to provide self-therapy for previously existing psychopathological disorders that might benefit from that kind of drug. This concept was confirmed, even if in a partial and not univocal way, by the hypothesis of the role of endorphins in psychopathology. That role was tested by trying out different strategies; using opioid antagonists for the treatment of mental disorders; evaluating the results of the administration of endorphins; investigating baseline endorphin levels in psychiatric patients; stimulating the endogenous release through pain or stress induction or the application of electrodes in the brain. Even though the results of these studies have not yet permitted a clear vision of the problem, it is very likely that the self-administration of opioids, because of their antidepressant, anti-anxious and antipsychotic action, will take place in situations of psychopathological decompensation, in subjects affected by conditions of depression, psychosis, panic, social phobia and agoraphobia that often go unrecognized by family members and even by the physician. Only an early diagnosis and the prompt treatment of primary forms may be able to prevent the development of a form of metabolic withdrawal.

3.3 'Metabolic' drug addicts

Independently of the modality of the first encounter with heroin, after around two years of intermediate stage and especially during the 'revolving door' phase, a chronic form characterized by withdrawal syndrome, craving and relapsing behaviour develops. Treatment with long-term drug replacement therapy reinforced by psychological and social support in a perspective of late detoxification (Figure

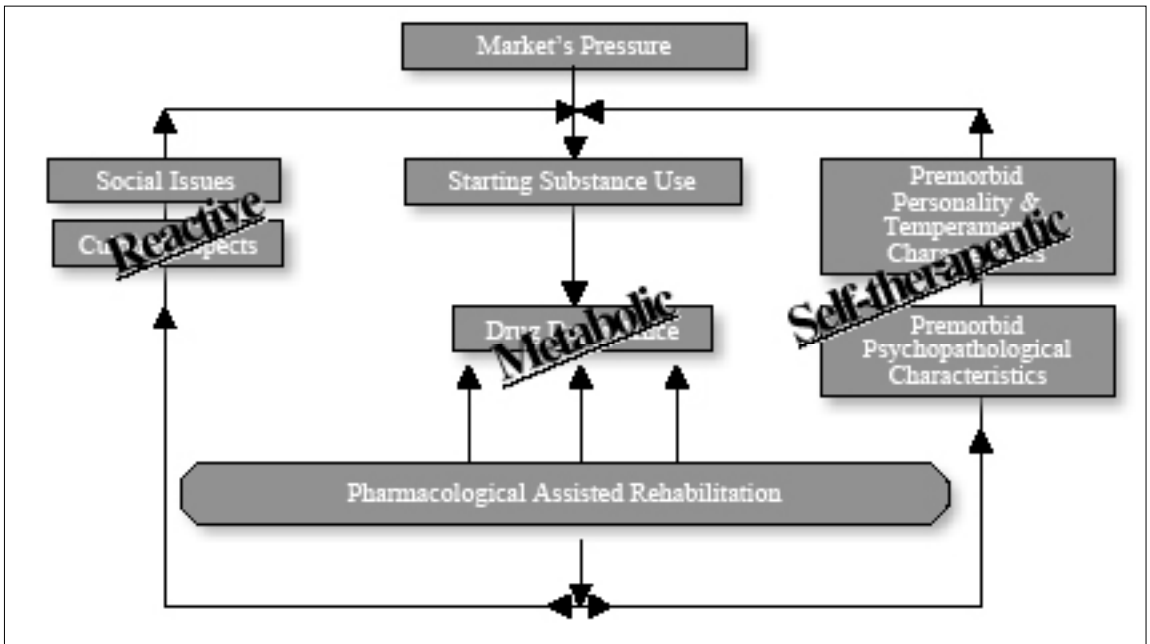

Figure 4. Typology of heroin addiction

4) is indicated for these subjects.

4. Clinical presentation

4.1 Intoxication

Heroin intoxication is not of strict medical relevance; only rarely do heroin addicts spontaneously seek a doctor's help. Somatic effects do not raise any particular concerns in the subject, even if they are often troublesome. These include insensitivity to pain stimuli, breathing difficulties, constipation, nausea and vomiting, miosis and orthostatic hypotension. From a psychological viewpoint, the subject appears to be euphoric, only rarely dysphoric, and generally seems to be calm, despite difficulties in paying attention and remembering ordinary items.

4.2 Overdose

An overdose event is hardly ever a serious, conscious suicide attempt. Very often it is due to lack of experience in a subject who is not yet tolerant to the drug and underestimates the amount of active product present in the 'dose'. Otherwise he might take the same amount of substance even after a short period of interruption of use of the drug. In this case tolerance, especially to the respiratory depressor effect, undergoes a rapid decline. Even subjects who underwent premature detoxification in Public Services may overdose for this reason. The subject might also mix heroin with other central nervous system depressants such as benzodiazepines and alcohol. Lastly, the quality of heroin can vary between different 'hits', but what counts is always the problem of tolerance. The impact of the substances used for cutting, contrary to common opinion, may cause other problems, but it is completely decoupled from overdose phenomena. The overdose syndrome is represented by the symptomatological triad: coma, miosis, respiratory depression, often with 2, sometimes as many as 3 or 4 events per minute. Hypotension, pulmonary edema, cyanotic skin and cold sweat are often present. Muscles appear to be hypotonic.

4.3 Tolerance and withdrawal syndrome

Tolerance develops to the analgesic, respiratory depressant and sedative effects, but not to miosis and constipation. The intensity of the withdrawal syndrome depends on the amount of substance that is taken and the speed of its elimination by the body. The syndrome is much more intense if it is precipitated by an antagonist such as naltrexone. In the case of methadone, the symptoms are analogous, but the onset of the syndrome is slower and less intense; on the other hand, the syndrome itself is much more prolonged, and may even continue for weeks. After 8 or 10 hours have elapsed, following the interruption of chronic heroin use, anxiety, yawning, sweating, tearing and compulsive searching for the substance appear. These symptoms become more and more severe, while insomnia, hot and cold flashes, together with fasciculation and muscle stiffness, abdominal cramps, mydriasis and tremors, appear too. After about 36 hours fatigue, severe nausea, vomiting and diarrhea appear, alongside increased blood pressure and body temperature, while the pulse shows hyperpnea. The symptomatic peak is reached after 48-72 hours, but the syndrome continues for 7-10 days. Sleep and mood disorders may linger for months.

4.4 Other opioid-induced disorders

For other disorders induced by opioid misuse, namely Intoxication Delirium, Psychotic Disorders, Mood Disorders, Sexual Disorders and Sleep Disorders, reference should be made to the clinical presentations of individual manifestations. These events can be observed both

in the State of Intoxication and during the Withdrawal Syndrome, and should be taken into consideration only if the severity of the symptoms exceeds the usual level of intoxication and/or withdrawal.

5. Diagnosis and prognosis

Currently a diagnosis of opioid withdrawal is adopted only if there is evidence of tolerance to the substance or withdrawal symptoms. However, many clinicians pay attention to a subject's behavioural history. There must be a period of pathological use of the substance, when it was impossible to interrupt, or periods when the state of intoxication persisted for most of the day. Overdose episodes, too, can act as strong indicators for the diagnosis. The disorder must last less than a month and there must be an impairment of social and occupational adaptation. To verify a state of withdrawal in the absence of symptoms of withdrawal, the use of the naloxone test has been widely proposed, but an accurate behavioural history, IV signs and, above all, a period of time spent in the 'revolving door' phase make recourse to this test unnecessary. Very often opioid addicts satisfy an additional DSM-IV Axis-I diagnosis for psychiatric disorders and/or an Axis-II diagnosis for personality disorders. Around 70% of heroin addicts present a multiple diagnosis [11, 22]. Despite the apparent inability to prevent relapsing behaviour in most heroin addicts, the widespread nature of the phenomenon and the high mortality involved, Opioid Dependence is a disorder that can be cured in a high percentage of addicts who survive the various stages of drug addiction. In particular, subjects who are not deeply involved in criminal behaviour can 'exit' through a process of maturation. Follow-up studies show that, among patients who entered any kind of treatment, 30% are no longer detectable 6 years later, while 5% are dead. Of the others, 5% are in prison; 23% regularly use opioids, 3% no longer use opioids, but have had relapses, and 12% are still being treated in a 'methadone clinic'; 8% no longer use opioids, but have switched to alcohol and other drugs, while 49% are not using any substance of abuse and are therefore considered clinically healed. Positive treatment outcome predictors include a good social and occupational adaptation prior to addiction, while a criminal past is a predictor of future maladjustment; psychiatric complications favour the worst prognosis [5, 15, 23, 31, 33].

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1.4

Heroin Dependence: Theory of Different Levels of Intervention

I. Maremmani

1. Background

Given the complex nature of heroin dependence there is no one method that is completely effective in the treatment of this pathology. Drug addiction varies in intensity and drug addicts are a heterogeneous group in terms of personal resources and coping ability.

The clinician's priority is to respond appropriately to each individual patient, by personalizing therapeutic planning (including different types of interventions) in an effort to improve the single drug addict's functioning. Treatment should be adaptable to the patient's changing needs thus providing long term continuity.

Presently, almost all researchers, in the field of drug addiction, are in agreement that the "retention rate" is a fundamental requisite for the successful outcome of any program [6]. This is obvious if one considers the official definition of drug addiction as a chronic and relapsing illness. Thus therapeutic planning must be adapted to the patient and not vice versa [21, 22].

If, as systematic observations reveal, many drug addicts may remain such for a long time, some for the rest of their lives, attempts to treat this vast group of subjects must not be abandoned. It would be sufficient to opt for long term treatment giving the drug addict the possibility to gradually recuperate bio-psycho-social functioning. This could be defined as clinical improvement even if "restitutio ad integrum" has not been achieved. It is the first goal of adequate pharmacotherapy and psychosocial treatment [17, 33].

Achieving this limited goal may be the best result possible for some, while for others it may open the door to being able to function well, long term in an opioid-free state. In both cases however, these subjects have a right to a normal life, to personal gratification, social respectability and physical and mental well-

being [9, 10, 19, 39].

The second step in therapeutic planning is monitoring patients during and after treatment in order to prevent and treat the inevitable relapses. Relapses are defined as "expected" in the therapeutic alliance. They should become predictable to both the clinician and the patient. Both must be ready to face the relapse with all available resources in order to maintain or exceed the prior level of functioning [24]. When a relapse occurs it should be seen as part of a normal process, not a failure, and the treatment plane should be altered in a way which is appropriate to restore the patients to the pre-relapse level of function. Withdrawal of agonist medication or discharge from treatment never accomplishes restabilization. These are destructive responses to substance abuse in a patient [7, 8].

It is important that the staff acquires a global view of the various types of treatment available. This view should include the probable outcome, length of time required, cost, indications and contraindications, as well as an understanding of when, for a particular patient crossover to another modality would lead to optimal therapeutic results [2-5, 13].

While comprehensive treatment programs attempt to deal with many of the problems associated with addiction, we feel that Therapeutic Community re-educational programs (TCp), when based on segregation and accusation, must not be utilized. Examples of this kind of treatment were common in Italy and in other European countries in the 70-80ies when stigma for heroin addicts was elevate and the treatment with opioid agonist was not accepted by politicians and strictly regulated [22]. Re-educational programs on which most of the Italian TCp are based are methods highly selective and beneficial to a very limited number of addicts, when pharmacological support is denied. In my personal experience, I could verify cognitive disorganization of patients who followed TCp tending to reinforce guilt and give the idea that drug addiction is an acquired vice caused by deviant behavior. In this way the patients found themselves defenseless and unprepared for relapses interpreting these to be an explicit sign of being irrecoverable. In these programs refusing the biological basis of addiction also family counseling is very harsh and often implies cutting ties with the patient who is described as "lacking in will and motivation". "Reaching the bottom", the most famous slogan of some Italian TC (CEIS group), for the heroin addict very often meant dying of overdose, or contracting AIDS or refusing all types of treatment [34].

Comprehensive treatments need a new philosophy of intervention. The staff must know the various levels of the treatment program and the policies inside these levels must not be contradictory.

2. Levels of intervention

Our theory of comprehensive treatment includes different levels of intervention which are:

Level 1: prevention. Level 2: harm reduction. Level 3: diagnosis and treatment of associated pathologies. Level 4: specific treatments. Level 5: rehabilitation and social integration. Level 6: prevention and treatment of relapses. These levels can be delivered individually or together in a coordinated manner, depending on the needs and willingness of the patient.

2.1 Level 1 (Prevention)

Currently an efficacious primary prevention model does not exist. Educational models based on particular cultural backgrounds are rarely acceptable to all.

Although drug dependence may have its roots in societal organization, or in consumerism, educational models alone are not effective preventive measures and may cause diametrically opposite results in social groups with different cultural backgrounds. Research has not discovered specific educational impairments nor temperamental types associated with drug addiction. A large number of subjects begin using drugs recreationally or to facilitate socialization without knowledge of the real risks

and consequences of drug abuse.

As a primary prevention model, we suggest a public health education program on the various psychoactive substances of abuse, effects, consequences of use and abuse, devoid of ideological and moralistic interpretations which often succeed in leaving a mythical and mysterious imagine which fascinates [36, 37].

If health education constitutes a valid primary prevention policy, secondary prevention (harm reduction, therapy, prevention and treatment of relapses) must not be overlooked.

Research indicates that the spread of heroin use correlates to precise market interests which are kept alive in certain well-defined conditions such as clandestineness which implies high cost, consumer-pusher phenomena and when effective therapy is lacking. Within this framework depenalizing drug use and treating drug addicts are essential cornerstones in the elimination of this problem [27].

2.2 *Level 2 (Harm Reduction)*

The aims of level 2 may be summarized as follows:

- reduce the social consequences related to addiction, such as: criminal activity, spread of AIDS, extinction of the consumer-pusher phenomena, elimination of the clandestine market with subsequent reduction of number of heroin users, and minor risks for the general population.
- protect heroin addicts from syringe related pathologies (HIV, hepatitis, vascular damage, endocarditis, overdose, withdrawal syndrome, etc.); this will prove advantageous for the patient and will reduce social costs.
- more accessible public health services for the heroin addict population [28-31]. Establishing the first contact between medical staff and addicts means (1) reaching a larger number of subjects; (2) offering accurate information regarding physical and mental well-being and therapeutic prospects [16].
- the possibility of an early diagnosis which is presently impossible since drug addicts live in clandestineness. The patient usually seeks help when the situation is no longer bearable and course progression is well advanced.

Proposable interventions at level 1 include:

- expansion of agonist opioid therapy programs such as methadone or other opioid therapies (LAAM, Buprenorphine). The Swiss experiments with heroin didn't support conclusive evidence [12]. They had not good control group and the heroin patients received much more psychosocial treatment than the methadone patients. Also, the heroin clinics were much more expensive to run than methadone programs and is unclear where heroin clinics fit into the overall framework of treatment programs .
- free distribution of disposable syringes
- instructions regarding self-administration of medications.
- information regarding first aid in case of overdose or withdrawal syndrome
- information regarding the risks and consequences of continued use of illicit drugs and modalities of treatment and rehabilitation.
- health education of HIV subjects

The operative phase of level 1 would be carried out by volunteers and specialized workers in "street units". Family physicians as well as ambulance paramedical personnel should also be involved. In this way a tight network of contacts between health services and drug addicts is assured and access to health services is facilitated.

The effectiveness of a pragmatic approach is widely demonstrated in the experience of countries such as England and Holland which have succeeded in limiting the spread of heroin addiction (e.g. in 1991 in the United Kingdom 8,000 heroin addicts were officially registered; there were no deaths due to overdose, the spread of AIDS was limited and restricted to subjects at risk, prevalently homosexuals. In Italy with its moralistic and repressive attitude, in the same period there were more than 320,000 heroin addicts, 1,200 deaths by overdose, widespread diffusion of HIV and 70% of

heroin addicts were seropositive).

The drawback of this first level is that it is not an actual treatment modality and therefore it cannot help patients recuperate bio-psycho-social functioning [16]. In order to achieve this goal we must pass to the next level of our program which includes services and more qualified personnel.

2.3 Level 3 (Diagnosis and treatment of associated pathologies).

At this level the specific treatment of drug addiction begins. The patient is examined by a medical specialist and other professional personnel in order to arrive at a diagnosis and establish a therapeutic plan appropriate for that subject. Scientific literature is in agreement in defining heroin addiction as an illness and experience shows that it is the patient's degree of impairment together with other factors that determine if a particular intervention is suitable or unsuitable at that time [32, 38]. The principal task of the specialized staff at this stage is to formulate a diagnosis. and identify potential resources (personal attributes, family members or social skills), that may help in rehabilitating the patient. This will be possible if interviewing techniques reactivate a two way communication in order to identify the needs of the patient and offer concrete proposals. Particular attention should be given to unsuccessful endeavors which are often indicative of errors in the interventions proposed or in monitoring of the patient.

This level requires more qualified personnel and specialized services. Specialized centers for the diagnosis and treatment of addiction are needed. These centers should be equipped to carry out research, collaborating with Ph. D. Research Programs in Drug Addiction, and educate and train specialized personnel.

Once a diagnosis has been made, the patient undergoes the appropriate therapeutic modality. The initial choices, however, should not be restrictive or rigid but rather open and interchangeable with other modalities. Only if the patient acquires and maintains a functional state will the staff be able to verify the choices made.

At the same time associated pathologies and psychiatric disorders are diagnosed and treated [1, 15, 20, 26, 35].

2.4. Level 4 (Specific treatments).

This level includes therapeutic and rehabilitate interventions after the patient has undergone clinical assessment. Generally patients may be divided into two groups:

- patients who do not require opioid agonists.
- patients who require opioid agonist long term therapy (Methadone/Buprenorphine Maintenance; LAAM Maintenance; Buprenorphine-Naloxone Maintenance).

2.4.1 Patients who do not require opioid agonists.

The patients included in the first group should satisfy the following requisites: they are subjects who meet DSM-IV or ICD-10 criteria for a substance use disorder; they have no psychiatric comorbidity [18]; low craving; good social adjustment; good family support with the possibility of a referring family member; these subjects are reliable and have good interpersonal relationships with staff [11, 14, 25].

It is important to underline that methods based on a "drug free state" are highly selective and applicable to a very small number of patients [23]; however some antisocial and very resistant addicts do very well in these programs and do not respond to anything else. It is understandable then, the caution needed before detoxifying patients, as well as, the need to control attentively behavior at risk and immediately admit the patient to an agonist treatment program if difficulties arise.

Methods for achieving a drug free state may be outlined as follows:

- Abstinence is controlled by psychotherapeutic support, with or without opioid antagonists.
- Self-help groups which encourage social

reintegration during treatment. Antagonists may also be used in this case.
- We suggest Therapeutic Community's (TC) with more flexibility and research to determine who fits best into the rigorous ones that currently dominate the scene. NIDA is supporting studies of more "flexible" TC's (those that use medications and treat dual diagnosis patients).

2.4.2 *Patients who require opioid agonist long term therapy.*

This group includes the large majority of drug addicts who seek help. They do not meet requisites for "drug free" programs which would be detrimental for these subjects.

The first task the staff must face is that of redefining the patient's expectations suggesting long term treatment which will probably be more successful and safer.

One should aim to set up services that are able to support and be integrated with a long term agonist therapy
- Basic counseling. Many patients on methadone or on other substitutive therapies who have obtained metabolic stabilization experience a return to normality; they become socially reintegreted especially if they have personal resources, help from family members (home, work, hobbies, etc). For these patients therapeutic success may be possible with specific information and treatment counseling.
- Treatment of psychiatric disorders with psychotherapy and/or pharmacotherapy along with drug counseling for patients with psychiatric disorders
- Self-help groups could provide solid support to those subjects who lack rehabilitative resources. In future we suggest that more attention be focused on these groups because they are at low cost, have been shown to be effective in other areas (alcohol, psychiatric pathologies, etc) and more subjects can be treated simultaneously.
- Residential communities. These communities would serve those subjects who need specialized social structures in addition to pharmacotherapy. They are drug addicts with serious psychiatric disorders as well as those addicts who find themselves jobless and homeless.
- In closing we would like to underline:
- The therapeutic communities would be linked to social agencies and other health services. They would no longer be reclusive structures and isolate the patient from his family and social ties. They must not create an artificial world in which recovery is obtained and quickly lost when the patient is released. Contrary to what happens in Italy, in the US, many TC's work very hard to integrate patients back into the real world prior to discharge. It is important to have a transition phase so as to help the patient overcome the problems associated with the artificial environment.
- The primacy of "drug free" programs should be abolished. Recovery cannot be associated with a "drug free" state. It should be related to the psychological and social functioning.

2.5. *Level 5 (Rehabilitation and social integration).*

This level foresees the complete rehabilitation of drug addicts independently of the kinds of treatment modalities in progress. The achievement of this goal varies (length of time and modality) according to the needs and the severity of illness of each individual. The interventions which allow the patient to achieve this status vary, for example: getting a job, reintegration into family life; methadone, LAAM, buprenorphine detoxification.

We would like to focus the need of those patients who cannot be deprived of agonist therapy due to biological determinants. A substantial part of the drug addict population who have good social and psychological adjustment require agonist therapy but not social support services. We consider these patients completely recuperated and feel that they are able to manage their pharmacotherapy i.e. as diabetics do.

For these subjects agonists availability should be convenient and interfere as little as possible with the patient's life, work and leisure time The patient could be entrusted with dosages that cover a longer period of time; family doctors would be able to prescribe methadone or other substitutive therapies. Any community health service could dispense of methadone or of other substitutive therapies under certification in order to facilitate the patient. On international level contacts could be established between the health services of different countries permitting the patient to travel freely. The organization of a heath service network would prove advantageous for the patient who need not travel great distances to reach specialized centers and at the same time these centers would not be overloaded with work-dispensing of methadone or of other substitutive therapies to patients who are rehabilitated, thus reducing social costs.

2.6. Level 6 (Prevention and treatment of relapses).

Given the definition of heroin dependence as a chronic and relapsing illness, it is logical to emphasize the role of prevention and therapy of relapses. This requires therapeutic modalities which help in conserving the skills and functioning level previously achieved by the patient. Thus patients would be rapidly readmitted to methadone or to other substitutive therapies (it is obligatory with recurrences) in order to prevent harm to the patient i.e. returning to street life. Treatment would be simplified in these programs as these patients have been rehabilitated in the past. In order to accelerate readmission to any health service the patient would be provided with documentation containing clinical chart data.

3. Conclusions

In conclusions, we have attempted to outline a rather complex strategy for the treatment of heroin addiction which we feel is scientific and pragmatic. Obstacles to the realization of this project are the political interference and cultural biases. What we can hope for is that educating the public will help correct the misconceptions that regard the problem of drug dependence.

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1.5

Scientifically Based Ethical Principles in Dealing with Heroin Addicts

M. Pacini and I. Maremmani

In a treatment setting for an addictive disorder, the relationship between physician and patient may be hindered by the nature of the disease itself. Insufficient knowledge of the dynamics of the disease may lead to interpreting some typical features or behaviours as an abnormal and unacceptable limitation on treatment feasibility [3]. In some ways, raising obstacles to certain kinds of interactions between the patient and treatment facilities may serve as a way of shifting patients towards a perspective of cure rather than a selfwise manipulation of resources. On the other hand, obstacles to treatment itself, especially if justified in terms of the presence of expected symptoms, simply mean treatment omission [5, 12]. Besides, patients often end up feeling guilty, or at least responsible, for the failure of a therapeutic attempt, no matter whether it is inappropriate or clumsy. As a rule, treatment programmes which require the patient's involvement in "stopping having the symptoms" have no effect other than discouraging the patient from making future attempts, while inculcating the idea of incurability.

1. Scientifically based ethical principles

The following ethical issues need to be accounted for when dealing with addicted patients.

1.1 Choice of treatment modality

In the patient's interest, it is up to the physician to make therapeutic choices. If the patient shows he or she is compliant with one treatment perspective, but not others, the decision to be made by the physician should not take the patient's preferences into account [9]. A doctor-patient relationship has a therapeutic basis, and it is bound to fail as long as it brings no therapeutic benefits. The first-line choice is the same for most patients, and corre-

sponds to an agonist maintenance programme [7]. Even if some patients, due to a lower degree of disease severity, may draw additional benefits from environmental interventions, or respond to antagonist maintenance, the choice of a broader-spectrum treatment modality will give them the advantage of a lower likelihood of relapse. The trend of matching less severely impaired patients with less effective treatment options has, over the years, made most such cases increase in severity due to treatment failure. In no case can the choice be restricted to "no treatment" or "waiting", in the hope that the patient will not relapse or will stop autonomously, after hitting the bottom. When choosing between therapeutic options, it should be remembered that effectiveness is not influenced by expectations of applicants or the intentions of promoters, but by scientifically documented properties [8]. So far, at least, any therapeutic programme which does not employ opiate-modulating drugs cannot be considered a reasonable option in the treatment of narcotic addiction.

1.2 Availability of treatment options

Since many treatment options exist, the actual availability of the most effective (agonist-based) programmes should be kept at the highest level; availability should be lower for less effective (antagonist-based) ones, and still lower for harm reduction. Harm reduction is characterized by a low threshold in terms of behavioural requirements, which means that almost anyone qualifies for admission to it, but high-threshold facilities should be those that are made most available, meaning that anyone may apply for them [6]. The Centre should keep high threshold treatment as the final goal, while continuing to run harm reduction programmes, in the attempt to make patients fit to be admitted to higher threshold programmes. Physicians should clearly reject any request that is not inspired by therapeutic purposes, or is inspired by unrealistic expectations about achievable results (e.g. results expected from detoxification, drug-free interventions and agonist-free interventions) [1]. The goal and the principles of any treatment must be clear from the beginning, whereas details and related explanations can be discussed later on. Whenever a centre can only provide applicants with one treatment option, agonist maintenance should be the choice, due to its broader spectrum. In this case, the threshold and waiting lists must be such as to allow patients to be followed up individually.

1.3 Therapeutic deal

While dealing with a disease which basically consists of the loss of behavioural control, it is paradoxical if behavioural control is made a requirement for staying within the programme. No physician should ever regard the persistence or recurrence of addictive symptoms as a valid reason for a patient to be terminated [11]. Patients applying for treatment are not in a position to make promises about how much they will "use", how strictly they will comply with the rules, or how sincere they will be in reporting their behaviours. All this may change in the case of stabilized patients, who have made room within their brain for self-aware choices, and can actually choose, day by day, whether to comply or not with the treatment regimen. It follows that the achievement or maintenance of abstinence as a requirement for beginning or continuing any treatment programme, respectively, are examples of inadmissible therapeutic deals. As long as addictive behaviours endure, therapies must be handled promptly and meaningfully with respect to the final goal. Only patients who refuse the physician's prescriptions, including attendance and sample delivery, can reasonably be terminated, or referred to a lower threshold programme. The patient is only responsible for compliance with treatment rules, not with substance use, and the physician is not there to prescribe a behaviour, but a therapeutic agent.

1.4 Negotiation

At first, allowing the patient to participate in therapeutic decisions may turn out to be helpful in establishing a good relationship [13]. Addicts usually try to manipulate the therapeutic setting, in a stereotyped way, and show apparent gratitude to those who allow them to do so. In reality, stabilized patients approve of physicians who refrain from involving them in therapeutic responsibilities, and are not influenced by their requests. A treatment which is founded, even if partially, on an addicted patient's decision, is bound to be a failure, and this can only be to the patient's detriment. Moreover, as long as patients directly interact with their symptoms, without the autonomous mediation of a sensible physician, they will stay convinced that a possible change in the course of addiction may depend on a variety of factors pertinent to the environmental sphere or to a paradoxical idea of motivation (the ability to resist one's drive towards the substance).

1.5 Refusal or interruption of treatment

Addicted patients are ambiguous by nature. However, the crucial factor which allows methadone treatment to be successful, is not of a motivational kind, but behavioural: the administration of certain doses for a certain time can make treatment effective, beyond the subject's intentions to stay off drugs. It is unethical to regard motivations, intentions or self-criticism as crucial for enrolment [13]. The presence of addictive symptoms, no matter how severe, is never a good reason to terminate a patient, unless they actually make it impossible for that patient to comply with the minimal rules of the programme. Minimal rules correspond to the features for effectiveness, that is, dosage and duration and registration of parameters. On the other hand, attendance of ancillary or higher threshold facilities cannot be considered as rules for any kind of patient in any kind of programme. In a way different from basic anticraving treatments, such facilities are optional and require the patient's active request to be regarded as viable. On clinical grounds, the stabilization obtained through anticraving treatment usually causes patients to become spontaneously willing to engage in higher threshold facilities for addiction, and capable of satisfying the corresponding requirements.

1.6 Change of treatment modality

The flow of patients' thoughts is spontaneously oriented towards cutting out medications, due to cultural bias. Sometimes, any such trend is favoured by suggesting or supporting the idea that a drug-free state is the gold standard, and indicative of therapeutic success. The result of following this line of reasoning is that potentially effective programmes may be prematurely aborted, so upsetting the therapeutic balance in favour of a fake perspective of healing. This revolving door mechanism is, sometimes, all that patients are offered at every stage of their addiction history, until death puts an end to it all. Lastly, it is risky and unjustified to shift to a newer treatment modality just for the novelty factor, once another modality has been tried and proved to be effective (e.g. abandoning methadone for buprenorphine, or an agonist for an antagonist) [2, 4, 10].

2. Conclusions

In conclusion, a physician who acts in accordance with intuition and common judgement, runs the risk of paving the road to hell with good intentions. The fact is that handling a request for treatment by a patient implies a fundamental question for any physician to ask themselves: "In what way and to what extent are my actions supposed to change the course of this disease?". The answer to this key question is often, to one's great surprise, far different from any common judgement.

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1.6

Pharmacology and Neurochemistry of Methadone

A. Vendramin and A. M. Sciacchitano

1. Introduction

Methadone is a synthetic opioid with distinctive pharmacokinetic and neurochemical properties which account for its being, to date, the most effective agent for the treatment of heroin addiction. Studies have proved that, for 50-80% of unselected addicts, methadone-based treatment programmes are crucial in improving general health conditions and social functioning, while increasing compliance rates with other non-pharmacological interventions [66]. In particular, methadone maintenance treatment, as long as it is delivered at adequate dosages, under medical supervision and on a regular basis, is effective in reducing and eventually extinguishing the craving for fast-acting opiates and the drug-seeking behaviours that are rooted in it [27, 87]. Moreover, the administration of methadone makes it possible to restore the balance between the functions that are typically impaired during phases of continued heroin use (e.g. the immune system, response to stress via the hypothalamic-pituitary-adrenal axis, and the hypothalamus-pituitary-genital one). On the other hand, it does not alter the level of pain sensitivity. More recently, methadone proved useful as one 'opioid rotation' solution for the management of severe pain, which is usually first treated by such opiates as morphine, codeine and buprenorphine [54, 93, 107].

2. Chemical profile

Methadone (Figure 1) was first synthesized in 1945 in the Hoechst Pharmaceutical Laboratories, in the context of a research project that aimed to find alternatives to morphine, with at least similar analgesic properties but fewer or milder side-effects. It is the first example of a phenylpropylamine derivative that is structurally dissimilar from morphine, but acquires a similar conformation in an aqueous solution. Such derivatives (methadone and l-

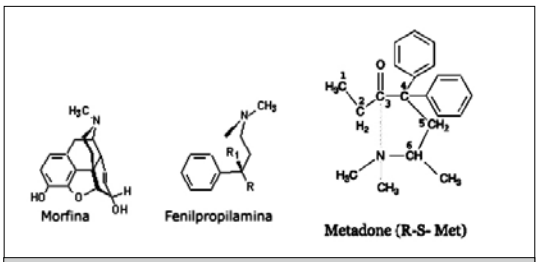

Figure 1. Neurochemistry of Methadone

α-acetylmethadol) are the results of the progressive simplification of original compounds such as epoxymorphinanes (nalorphine and nalbuphine), through morphinanes (levorphanol), benzomorphanes (pentazocine), phenylpiperidine (pethidine) and 4-anylpiperidine (fentanyl). A methadone molecule consists of two aromatic rings tied to a 4-C, the sequence proceeding to C5, C6 and eventually to one N basic unit. C3 is tied to an electron-attracting ketonic part. Since the C6 atom is asymmetric, methadone has two isomeric variants, which share the same structure, mirroring each other, but have a different spatial array, referred to as S and R. As to other analgesics, the two isomeric variants (or enantiomers) have certain specific biochemical properties. Methadone hydrochloride (6-dimetilamine-4, 4–dephenyl-etan-3-one hydrochloride or 4, 4-diphenyl-6-dimetilamine-3-eptanone) is a white, basic, crystalline substance (pKa= 9, 2), saturating water over 120 mg/ml, which may be made up of R-enantiomers (R-Met or l-Met), S-ones (S-Met or d-Met) or both in a racemic combination. Although most of the properties which make methadone useful in the treatment of heroin addiction and pain correspond to those of R-Met, methadone hydrochloride is usually employed as a 50% racemic mixture of the two enantiomers, in a variety of formulations that allow methadone to be administered in four different ways:

- 0.1, 0.2 or 0.5% syrup for oral administration;
- 5 or 10 mg tablets for oral administration;
- effervescent tablets containing 2,5, 5, 10 and 40 mg of the substance, for oral administration;
– 1 ml parenteral vials (10 mg/ml) .

For analgesic purposes, R-S Met is available in enteral and spray formulations [23, 24].

3. Pharmacokinetics of racemic methadone

3.1 Absorption

Methadone is well absorbed through any route of administration. After oral administration (as in the treatment of heroin addiction) the absorption of racemic methadone takes place quickly**,** and almost reaches completion (range 35-100%, average 80%) [33, 79]. The methadone absorption rate is influenced by the expression of intestinal P glycoprotein (P-gp), as for several other compounds (such as amytriptiline, digossine, diltiazem, domperidone, fentanyl, indinavir, loperamide, morphine, nelfinavir, ranitidine, verapamil). P-gp is involved in the phenomenon of multidrug resistance to chemotherapeutic agents; these are, in fact, pumped out from cells by P-gp membrane units [73]. The physiologic function of P-gp, which is expressed in several normal tissues, is that of preventing the absorption of toxic substances through internal and external surfac**es**, and favouring their elimination [5]. P-gp is a twofold structure weighing 170 KD, consisting of 1,280 aminoacids with 12 transmembrane traits and 2 ATP-binding extracellular domains [48]. The genetic source, known by the acronym MDR1, leads to different levels of P-gp expression, with a ten-time interindividual variability. The induction of P-gp is a plausible reason for the loss of responsiveness to morphine and to antiretroviral agents. In the case of methadone, the P-gp transfers it outside the intestinal epithelium, into the bowel cavity. As a result, when P-gp is expressed at a a high level, the administered drug is partly kept away from the blood stream [51, 70]. Moreover, this kind of action by P-gp across the blood-brain barrier is responsible for the passage of racemic methadone into the brain tissue, so affecting the binding rate of admin-

istered dosages and the incidence of therapeutic effects and side-effects [110]. The effects of orally administered racemic methadone are evident within 30′. At dosages between 3 and 100 mg/day, the enteric absorption rate is 92% [114]. The bioavailability of methadone is affected by the first-pass metabolism effect; it shows a lower rate with respect to other opiates (67-95%). The average time-to-peak is 2.5 hours for the syrup form [113] and 3 hours for the tablet form [82]. A single 100-120 mg oral racemic methadone dose causes a 0.5-0.9 mg/l plasma peak, and each 1 mg/kg oral dose increase corresponds to a plasma peak increase of 0.263 mg/l. Time-to-peak is 30′ in cases of intrathecal administration, 15-20′ for the epidural form and 12′ for the intranasal. When administered intramuscularly or subcutaneously, the same methadone dose is one and a half times more powerful and more rapid, but its effects persist for a shorter time. Methadone 50% lethal dose is 95 mg/Kg in oral form in rats, or 20 mg/Kg intravenously in mice.

3.2 *Distribution*

As with any other lipophilic substance, methadone has a high tissue distribution rate in man and in the other animal models that have been studied. In pregnant rat females, racemic methadone spreads to the brain (4.6), bowels (37.2), kidneys (27.6), liver (44.2), muscles (14.7) and lungs (156.3) – the respective distribution coefficients are reported here in brackets [43]. In other words, methadone spreads to blood and brain tissues only to a small extent, while reaching higher tissue concentrations in kidneys, spleen, liver and lungs. During pregnancy, it spreads through the placental barrier, so that its concentration in the amniotic liquid is similar to that in the maternal plasma. After single oral doses, its plasma kinetics can be described in terms of a two-phase open model. After absorption, about 98% of methadone passes from the central compartment (plasma) through to peripheral tissues (liver, spleen, kidneys, and lungs). On the other hand, in chronic administration regimens, a three-phase exponential model gives a better fit with actual observed kinetics. Anyway, as the concentration in tissues is higher than it is in plasma, the apparent distribution volume at the steady state (Vss) is greater that the actual normal volume (4.2-9.21/Kg in the treatment of heroin addiction and 1.71-5.341 in chronic pain treatment). About 2% of absorbed methadone remains in the plasma compartment: of this, 70-90% is bound to plasma proteins, while the remaining fraction is free, and it is this that is responsible for methadone's effects. In animal models, too, racemic methadone is bound to plasma proteins at similar rates [44, 47]. As it is weakly basic, methadone binds with a certain affinity to α_1-acid glycoprotein (AAG), which has a high affinity site for a variety of small basic molecules [94, 112]. AAG concentration varies in some physiologic and pathologic conditions which also affect the bound/free ratio of methadone. In fact, since AAG concentrations are higher under stressful conditions [84], the free fraction is lower in cancer patients and heroin addicts than in healthy volunteers [2, 16]. One further factor arises from the fact that methadone only binds to the ORM2A allelic variant of the AAG, not the ORMF one. Although methadone also binds to albumin to some extent, the variation of albumin levels has an almost negligible influence, if any, on the concentration of free methadone. In heroin addicts, sex and weight are responsible for 33% of the inter-individual variability of Vss: it is, in fact, higher in females, increases with weight and falls when the plasma concentration of AAG rises [96].

3.3 *Plasmatic kinetics*

Consistently with previously described mechanisms, the plasmatic clearance of racemic methadone after a single dose load takes the form of a biphasic curve: the first phase corresponds to distribution to the tissues followed by elimination through the kidneys ($t_{1/2}\alpha$ =14 hrs appr.), while the second phase corresponds to its more gradual elimination from tissues ($t_{1/2}\beta$ =54 hrs appr.). The overall result is that

the drug tends to accumulate within tissues in cases of repeated administration, until an equilibrium is reached that shows only minor fluctuations, mostly depending on whether administration takes place once a day or under a split dose regimen. Once a steady state has been reached (corresponding to four times the t ½ during which the drug has been administered at stable doses and time intervals) methadone's half-life is 28 hrs on average (varying between 4 and 91 hrs) [111]. On the other hand, in chronic regimens methadone has the property of inducing its own metabolism, so that the eventual half-life, after enzymatic induction has brought it to a stable level, may be rather shorter.

3.4 Metabolism

The bio-transformation of a drug plays an important role in its neutralization, by the synthesis of inactive metabolites. This process mostly takes place in the liver, following two main metabolic pathways. The first consists in the para-hydroxylation of the benzene ring, after which there is the reduction of the ketonic group, two methylations and conjugation with glucuronid acid. The second pathway combines N-demethylation with its cyclization to 2-ethyl.5-methyl-3,3,diphenylpyrrolidine and 2-ethyl-1,5-dimethyl-3,3diphenyilpyrrolidine (EDDP), which has a half-life ranging between 39.8 and 48 hrs [23].

These two metabolites are further transformed into a common hydroxypyrrolidinic product by aromatic hydroxylation. The second pathway combines N-demethylation with its cyclization to 2-ethyl.5-methyl-3,3,diphenylpyrrolidine and 2-ethyl-1,5-dimethyl-3,3diphenyilpyrrolidine (EDDP), which has a half-life ranging between 39.8 and 48 hrs [23]. These two metabolites are further transformed into a common hydroxypyrrolidinic product by aromatic hydroxylation. Methadone's metabolism is performed by the P450 cytochrome system (CYP450), mostly by the isoform 3A4, which is prominently expressed in the bowels and the liver [28, 29, 41]. In addition, isoforms 2D6 and 1A2 play a prominent role in the process [32] (Table 1).

Recently, on the basis of findings from in vitro studies, it was hypothesized that isoforms 2C9, 2C19 and, especially, 2B6 contribute to the metabolism of methadone [13, 33, 45, 70, 79, 109]. Isoform 2C19 seems to be involved to a higher degree during pregnancy, and to be responsible for the enhanced metabolic rate that appears during the second and third trimesters [80]. Differences in the expression of P450 isoforms are a primary factor affecting the inter-individual variability of methadone's metabolism. CYP450 can be induced, which means that the clearance of methadone by the cytochrome system is not easy to predict

Table 1. Metadone and P450 cytochrome

CYP3A4	Has a primary role in the R-S Met metabolism. Can be induced during the initial phase of MMT.
CYP2D6	Has a secondary role in the R-S Met metabolism and, in some cases can inhibit the enzyme.
CYP1A2 CYP2C9 CYP2C19	Are isoenzymes probably involved in the R-S-Met metabolism. Their role is still controversial.
CYP2B6	May play an important role in the R-S Met metabolism.
References: [13, 33, 45, 70, 79, 80, 109, 116]	
Leavitt, Addiction Treatment Forum (modified)	

on general grounds. In a steady-state condition, heroin addicts develop a metabolic rate that is three times what it was at the time of treatment initiation (first dose load)[96]. Since methadone can, over time, induce its own metabolism, long-term treatment may require dose increases in order to maintain the previously effective plasma level. The 3A4 induction apparently causes a 15% reduction in the average R-Met plasma level, although the level of 3A4 expression varies by as much as 11 or 30 times from one individual to another, in the bowels and the liver, respectively. The 2D6 isoform is expressed by 90-95% of Caucasian people. Those who lack this isoform (due to the absence of functional gene sequences) are referred to as low metabolizers, whereas those who have a normal activity (one or two copies of functioning genes) are labelled as extensive metabolizers. The characterization of the patient's metabolic status may be performed either with genetic or phenotypical methods. Among extensive metabolizer**s**, a subgroup of ultrarapid metabolizers, expressing three or more gene copies, can be identified by genetic probing: this subpopulation is 1.5% of the total population in Germany, 7% in Spain and 29% in Ethiopia. The same metabolic system is shared by a variety of compounds, and cannot be induced: some commonly used drugs, such as fluoxetine and paroxetine, can inhibit its activity. Methadone itself can cause 2D6 enzymatic inhibition to a certain extent [116]: extensive metabolizers who have added fluoxetine or paroxetine to an ongoing methadone regimen show an increase in R-Met (but not in S-Met) plasma levels with respect to the period before the introduction of the antidepressant [10, 30]. This finding suggests than 2D6 is somewhat stereo-selective for R-Met. In low metabolizers, amytriptiline, which is one 2D6 substrate, reduced methadone clearance, and methadone itself reduces that of desimipramine (another 2D6 substrate), probably through a competitive mechanism. CYP 1A2 is involved in the metabolism of several drugs, including clozapine and olanzapine. Its activity can easily be probed by caffeine administration, and is induced by tobacco smoking and inhibited by some drugs, the most common of which is fluvoxamine. The combination of fluvoxamine treatment with racemic methadone causes a major increase in both R-Met and S-Met plasma levels, so suggesting that CYP A12, unlike 2D6, is equally responsible for the metabolism of both enantiomers.

3.5 *Elimination*

Methadone hydrochloride is mainly eliminated through the kidneys. As much as 15-60% of a single dose is excreted in urine over the next /24 hours. On average, 20% of the administered dosage is excreted unchanged and 13% as EDDP. After repeated administration that kind of ratio is inverted [9]. Due to its lipophilic and basic properties, pH changes are crucial in determining the rate of methadone excretion: in fact, over a pH of 6, excretion through the kidneys falls to only 4% of the total. On the other hand, when pH is over 6, that rate may be as high as 30% [6, 55, 56]. In comparing situations in which pH values are equal, the interindividual variability in the clearance of methadone through the kidneys is reduced by 27% [96]. As for liver excretion, methadone can be classified as a drug with a low rate of hepatic clearance, around 3.1 ml/min/kg in heroin addicts or 1.5 ml/min/kg in chronic pain patients. Hepatic clearance also depends on the free rate of plasma methadone and on intrinsic hepatic clearance, which means the level of metabolic activity. As observed previously with reference to AAG levels, the rate of plasma protein binding also affects the value of hepatic clearance [2, 16]. Methadone is present in bile, too: as much as 20-40% of a single dose is excreted with feces, after its metabolization and glucuronidation. In some patients, methadone reaches higher concentrations in sweat than in urine. In cases of kidney failure, the interval between administrations should be adequately widened to allow for the degree of functional impairment. On the other hand, in stable hepatic disorders with different degrees of severity, cirrhosis included, dosage schedules may be maintained. Racemic methadone is also excreted through the breasts: almost 3%

of the daily dose administered to a mother is taken in by her newborn through her milk. In 6 cases out of 10 this quantity is not enough to prevent the onset of neonatal withdrawal. The data now available support the trend not to prohibit or avoid breast-feeding by racemic methadone-treated mothers.

4. Neurochemical properties

Like all other opioidergic drugs, methadone exerts its action by interacting with a system of three receptors, which, taken together, are referred to as "opioid receptors"; they are linked to G_0 or G_i proteins, and are normally stimulated by endogenous opioids. These opioid receptors are commonly indicated by the Greek letters μ, κ and δ or by the acronyms OP3 or MOR for μ, OP1 or DOR for δ and OP2 or KOR for κ [4]. Due to its negligible affinity for δ (IC_{50} nM 752 ± 686) and for κ (IC_{50} nM 1817 ± 573, in both cases in the bovine caudate nucleus) racemic methadone can be classified as a selective agonist of μ receptors (IC_{50} nM 5. 73 ± 1. 5 for μ_1 and 10. 0 ±3.1 for μ_2 in the bovine caudate nucleus) [68]. It was possible to map μ opioid receptors in thirteen brain areas of healthy individuals who had had a ^{8}F-Cyclofoxy probe administered to them, by using Positron Emission Tomography (PET) brain scan sequences. In a descending order of density values: thalamus, amygdala, caudate, insula, anterior cingulate and putamen, followed by medial frontal cortex, parietal cortex, cerebellum, lower temporal cortex, hippocampus, white substance and occipital cortex [59]. The human μ receptor unit is a surface protein of 67kDa consisting of a sequence of 372 aminoacids organized in seven hydrophobic transmembrane (TM) domains, with short extra- and intracellular loops. The N-terminal segment is extracellular, whereas the C-terminal segment is intracellular. Ligands interact with the extracellular portion of the receptor, and induce the activation of intracellular G proteins. The activation of G proteins causes neuronal inhibition by the reduction of adenyl-cyclase activity, the opening of a series of receptor-dependent K^+ channels and the blocking of voltage-dependent Ca^{2+} - channels. This cascade takes place around a relatively rigid self-regulating pathway involving the receptor-coupled protein-kinase units (GRK), by its recruitment, consequent receptorial phosphorylation and eventual interaction with β-arrestin. The μ receptor is the main feature responsible for several opioidergic effects, and its stimulation directly produces analgesia, respiratory depression, tolerance to narcotic effects and addiction. In MOR1 knockout mice (expressing no MOR), the lack of μ receptors renders these mice refractory to the main effects of morphine, both those with a therapeutic value and those that can be considered toxic: the same genetic product is thus responsible for an ensemble of effects. As expected, both analgesia and morphine toxicity persist in KOR1-knockout mice and DOR1-knockout ones [74]. Although only one gene encoding for the μ receptor has been cloned (located on chromosome 6 and comprising 4 exons and 3 introns), some variants were described, dependent on the use of selective ligands such as β-funaltrexamine (β-FNA), naloxonazone, naloxonazine and 3-methoxynaltrexone. β-FNA produces a dose-dependent stimulation of the receptor, and is used to recognize its presence and involvement in any supposed effect [3]. Unlike β-FNA, naloxazone and naloxonazine prevent some of the effects that are mediated by morphine, but not others, since they interact selectively with the μ_1 variant. Insensitivity to naloxonazine is responsible for respiratory depression and the inhibition of bowel motility, suggesting that possible μ_1-selective agonists may not share these two important collateral effects with morphine. The μ_1 subtype, which is exclusively supraspinal, is located in the periacqueductal grey substance, the medial hypothalamus and the great raphe nucleus. It mediates analgesia, psychomotor retardation and the increased secretion of prolactin. The μ_2 subtype has a similar distribution, but is found in the spinal cord, too. When coupled with μ_1 it mediates analgesia and is the one feature responsible for constipation, respiratory depression, and the improved muscular tone of the bladder and Oddi's

sphincter. Studies on the properties of morphine's metabolite, morphine-6-β-glucuronide (M6G), made things even more complex [86]: in fact, M6G binds to μ receptors selectively and with a high affinity. Its pharmacological profile is close to that of morphine and its analgesic effect is antagonized by naloxonazine. However, 3-methoxynaltrexone is effective against M6G-mediated analgesia at doses which are ineffective against morphine-mediated analgesia. On the other hand M6G also exerts analgesic effects in CXBK mice, which are refractory to morphine [18]. These data lead to the conclusion that another variant exists, apart from the already known μ_1 e μ_2; this third variant appears to mediate an analgesic effect through M6G or other 6-substituted analogues, such as heroin or 6-acetylmorphine [95]. One possible explanation **is** the existence of splicing variants from the same gene, exon 4 being replaced by other supplementary exons [85]. Also, two receptors may interact with each other and build a μ/μ or μ/δ complex, which could comprise various μ subtypes with partly dissimilar pharmacological properties. Studies have always indicated methadone's strong affinity for its receptor, but some differences have emerged. In Blake's study, based on the use of μ-transfected HEK 293 rat cells, methadone has a lower affinity than morphine (K_i 3, 51nM vs. 1, 41nM, respectively) [11]. On the other hand, in Raynor's study on COS-7 cells transfected with rat μ receptors, methadone has a higher affinity than morphine (K_i 0, 78nM vs. 14nM, respectively) [90]. In this latter study, methadone had a negligible (K_i ≥1000nM) affinity for δ and for κ receptors. The same authors showed that methadone and other opioid drugs have a higher affinity for human μ receptors in transfected COS-7 cells [91]. In conclusion, racemic methadone is a complete agonist of the μ receptor population, which swings between an available state and an inactive state. The affinity is higher for the active form than for the inactive. Methadone raises the absolute number of active (or activated) receptors (i.e. phosphorylated) and exerts maximal receptor-mediated effects, in a dose-dependent manner. Another distinctive feature of R-S-Met with respect to morphine is its non-competitive antagonism with respect to the NMDA receptor. The inhibition curve and its K_i for the displacement of its ligands are very similar to those of dextrometorphan, which is a typical NMDA antagonist. In particular, K_i of R-Met is μmol/L 3, 4 and that of S-Met is μmol/L 7, 4. NMDA antagonists are characterized by the property of preventing the onset of tolerance to morphine without interfering with its analgesic effects. The non-competitive antagonism exerted by R-S-Met should therefore favour the stability of its analgesic action in protracted treatment regimens, and would explain its negligible abuse potential, together with the absence of complete tolerance to some of its effects during long-term MMT at stable dosages [25]. Lastly, racemic methadone interferes with the reuptake of serotonin (5HT), and, to a lesser extent**,** with that of norepinephrine (NE) [20]. In rat cortical synaptosomes racemic methadone has a k_i of μM 0. 27 (±0. 038) against 5HT reuptake, which means a level close to that of desimipramine (μM 0, 43±0. 037) and minimal in comparison to fluoxetine's (μM 0. 049±0. 0046). This property is not maintained, however, after chronic exposure, at least in the rat model [46].

5. Specificity of the methadone μ–receptor interaction

5.1 Receptorial site binding

At oral dosages between 80-150 mg/day, as administered to tolerant individuals, racemic methadone does not saturate available receptors: in fact, the self-administration of heroin at doses higher than those usually employed can produce narcotic effects. Likewise, the administration of morphine, hydromorphone or fentanyl upon methadone for pain control is effective in counteracting break-through pain peaks. A study was conducted employing ^{18}F -Cyclofoxy in MMT patients taking dosages of 30-90 mg/day and plasma levels of 127-673 ng/ml (350 ng/ml on average):

a PET scan was performed 22 hrs after daily oral dose, and showed a 19-32% reduction in the expected binding rate in all the brain areas examined (thalamus, amygdala, caudate nucleus, anterior cingulate cortex, putamen) with respect to the brain of healthy controls [59]. In other words, approximately 24 hours after the previous administration, methadone has saturated 19-32% of μ receptors, including those which have been internalized. The rate of ^{18}F-Cyclofoxy binding reduction, though limited, is significantly related to plasma levels of racemic methadone. As a result, 60-80% of available μ receptors are free to interact with endogenous opioid peptides. Since opioid peptides are involved in the control of the immune and endocrine systems, with special regard to the hypothalamic-pituitary-adrenal axis, it can be hypothesized that the normalizing effect of MMT on these functions depends on the low occupancy of receptors at therapeutic dosages. In other words, methadone at dosages high enough to suppress the craving for heroin tends to have a rather conservative effect on the physiology of endogenous brain opioid systems.

5.2 Tolerance and endocytosis

Continued opioid use is characterized by the onset of pharmacodynamic tolerance, possibly combined with a pharmacokinetic component, at least for some compounds. Due to tolerance, when drugs are used continually, they lose their effect, so that higher dosages are needed to restore the desired effect. Tolerance also involves some therapeutic effects, such as analgesia, as typically happens in cases of pain treatment through the chronic administration of morphine [54]. Tolerance to morphine does not depend on increased biotransformation, but is typically pharmacodynamic. Cross-tolerance is one of the key phenomena on which the agonist treatment of heroin addiction is based. Fortunately, tolerance can be forestalled or can be made incomplete by the anticraving effect of opiate agonists. A variety of strategies can be resorted to in investigating the mechanism of tolerance and the distinctive features of each opiate agonist: on general grounds, it is agreed upon that tolerance is a result of a range of pharmacological and behavioural mechanisms, different circuits being involved, beyond the known roles of opioid receptors. On the other hand, it is likely that methadone tolerance is also due (quite probably, mainly due) to variations in the level of μ receptor expression [117]. The internalization of receptors was long considered to be the primary mechanism inducing change in the sensitivity of neurons to agonists. Research on populations of native neurons or transfected cell lines has shown that a cascade of events leads to the rapid desensitization and endocytosis of e μ receptors. The trimeric G protein, which comprises α, β and γ subunits, becomes detached from the receptors: while the α subunit inhibits adenyl-cyclase activity, the β/γ ensemble interacts with K^+ and Ca^{++} channels, and is linked to a GRK-specific kinase which phosporylates the μ receptor. The phosphorylated receptor interacts with a cytosol protein called β-arrestin, which becomes bound to it and prevents further interactions between the receptor and the G protein. The arrestin-receptor complex is internalized by a clatrine-mediated process of endocytosis, and is stored in the intracellular endosomal compartment. Afterwards, the receptor may be dephosphorylated by a phosphatase and be placed back within the cell membrane, which restores the neuron's sensitivity. Otherwise it may be catabolized in lysosomes without being dephosphorylated, which would correspond to a down-regulation of sensitivity. Opioids differ in their capacity to induce receptorial endocytosis, even if the pharmacological peculiarities that account for these differences are not clear. Etorphine, surfentanyl, methadone and DAMGO produce endocytosis to a greater extent than codeine, buprenorphine, heroin, morphine-6-glucuronide and, especially, morphine. DAMGO (Tyr-D-Ala-Gly-MePhe-Gly-ol-enkefaline) is similar to endogenous opioid peptides, and is referred to as a term of comparison with exogenous opioids. Some studies have referred to the capacity of opioid agonists to induce endocytosis as an inverse function of

the so-called RA/VE ratio, indicating the relationship between relative G protein-related activity and endocytosis. Morphine has a higher RA/VE, which means it produces a high level of G protein activation coupled with a low μ receptor endocytosis. By contrast, endorphins and opioids such as etorphine and methadone induce endocytosis to a greater extent with respect to their capacity to produce intracellular signal transmission (low RA/VE) [38]. More recently, it has been proved that the capacity of opioids to activate G-protein-dependent cascades, and thus to induce rapid desensitization, is a separate property with respect to their capacity to cause receptor internalization. Bearing in mind that DAMGO's properties in both cases are 1, the values for methadone and morphine are 0.98 and 0.59, and 0.58 and 0.07, respectively [14]. In other words, morphine's effectiveness in causing internalization (0.07) is far lower than DAMGO's (0.98) and methadone's (0.59), and does not reflect its capacity to activate G-proteins and promote desensitization (0.58). While it was previously believed that endocytosis is the reason for pharmacodynamic tolerance, lately evidence has been growing that internalization may play a role in counterbalancing the development of tolerance [38]. Moreover, morphine and heroin are not only capable of inducing tolerance, but are strongly addictive. Apart from this problem, methadone, which also produces endocytosis, does induce a lower degree of tolerance, and is effective in the treatment of heroin addiction. It has been hypothesized that those opioid agonists which induce a higher degree of tolerance do so because they endure longer in their interactions with the receptor: on this view, tolerance develops as a consequence of prolonged interaction with receptors, whereas endocytosis counterbalances this property by reducing the duration of ligand-receptor interaction, eventually limiting the degree of acquired tolerance. Chronic morphine treatment, both in cell lines and animal models, is associated with a compensatory up-regulation of cAMP synthesis, which may be one consequence of prolonged μ stimulation coupled with a low capacity of that ligand to induce endocytosis. On the other hand, the cAMP response to methadone exposure is significantly lower, which may reflect its greater capacity to induce endocytosis. The agonist-mediated activation of receptors, and then their desensitization and internalization, seem to constitute the three physiological phases of a functional dynamic cycle of normal opioid receptors. Tolerance to opioids may develop due to an abnormal activation profile, rather than to the down-regulation phenomenon alone. Abnormal activation would produce a response that differs from the normal functional recycling of receptors. In conclusion, methadone seems to resemble endogenous opioids in the profile that emerges from its receptor interactions; this may account for some of its therapeutic properties and its favourable long-term interactions with the opioid system.

6. Specificity of stereoselective enantiomers

Absorption and bioavailability are similar for R-Met and S-Met [67], although the former is twice as strongly lipophilic as the latter (57 of oil/water coefficient vs. 28). The difference in elimination half-life between the two enantiomers may depend on a different binding to plasmatic proteins (14% for R-Met vs. 20% for S-Met) [34]. Although that is not a large difference, it may be enough to account for the fact that R-Met's half-life is 38 hrs vs. 29 hrs. for S-Met. Average clearance of R-Met is 158 ml/min, while S-Met's is 129 ml/min. Apparent Distribution Volumes are quite variable, around 7 L/Kg for R-Met and 4 L/Kg for S. R-Met has a double affinity for the μ with respect to racemic methadone, similar to that of morphine. As for the μ_1 subtype, it is ten times higher for S-Met in bovine caudate that for R-Met (IC_{50} of nM 3, 01± 0, 18nM 26, 4 ± 3, 7) while values for μ_2 subtype are nM 6, 94± 1, 3 for R-Met and nM 87, 5± 9, 0 for S-Met [68]. Consistently with these premises, R-Met is 50 times more analgesic than S-Met [41]. R-Met prevents the onset of opiate withdrawal even at low dosages, while S-Met does so when administered at dosages of 650-1000

mg/day. S-Met has the distinctive property of its non-competitive antagonism to the NMDA receptor, which accounts for its capacity to antagonize NMDA-induced hyperalgesia and the development of morphine tolerance, after systemic or intrathecal administration. R-met is therefore able to replace the racemic form in the treatment of heroin addiction and pain, but the racemic formulation does show some advantages from a long-term perspective. S-Met alone, or when combined with morphine, may be effective against neuropathic hyperalgesia, or in increasing the analgesic effect in chronic morphine administration regimens [25]. As previously mentioned, racemic methadone inhibits the reuptake of serotonin (K_i of μmol/L 0, 014 for R-Met and μmol/L 0, 992 for S-Met) and norepinephrine (K_i of μmol/L 0, 702 and μmol/L 12, 7 respectively). In other words, it is 5 times more selective for serotonin than for norepinephrine, as R-Met has a greater affinity for both uptake systems [20]. S-Met is effective against coughing in the absence of any risk of producing respiratory depression. Several studies agree on the fact that methadone's effectiveness depends on the administration of certain dosages. The higher the dosage, the lower the risk of treatment dropout, so dosage adequacy is the main factor affecting the rate of therapeutic failure. Although 100 ng/ml was initially thought to be enough to ensure a good outcome, a stable response requires a level of 400 ng/ml. Recently, a correlation between R- and S-Met concentrations and treatment response has been defined: 250 ng/ml of R-Met are usually predictive of a response to treatment. Nevertheless, effective plasma concentrations of R- and S-Met, in cases where oral doses of racemic methadone are equal, and after accounting for body weight, vary widely between individuals –up to 16/17 times in the case of R-Met. In other words, oral dosages corresponding to effective plasma concentrations do vary widely, and may also depend on further variables, such as combined treatments that give rise to pharmacokinetic interactions. For some individuals 55 mg/day may produce effective plasma concentrations, whereas over 900 mg/day may be required in other subjects [31, 32].

7. Side effects

On the whole, MMT is well tolerated from a long-term perspective [83]. Possible side-effects which may develop and endure during opiate agonist treatment regimens depend on a variety of factors, including duration of treatment, dosage, the route of administration, age, concurrent organ impairment and combined treatments or psychoactive substance use. Transient adverse events such as rash or nettle rash may happen in cases of subcutaneous or intramuscular injection. Frequently reported effects include somnolence, hypotension, bradycardia, nausea, vomiting, swelling of hands or (more frequently) feet, disorders involving emetics, menstrual abnormalities, anorgasmia or delayed achievement of sexual orgasm, insomnia, constipation or excessive sweating. Since tolerance develops at variable terms for different symptoms, a low baseline tolerance is usually predictive of more severe side-effects in the early phases of treatment. It is very unlikely that side-effects will be so intense as to require treatment termination. They usually improve with dose adjustment or transition to an oral route of administration, although some cases may require symptomatic treatment. Sweating, constipation, sexual dysfunctions and sleep disorders tend to endure in the long term [62]: in patients taking dosages between 80 and 120 mg/day, sleep disorders, constipation and loss of libido are still present after three years in as many as 15-20% of cases, while excessive sweating persists as often as in one case out of two. Sedation is frequently reported in the early pha**ses** of treatment, after the first few days of steady administration. In these circumstances, sedation depends on the progressive increase of plasma concentration due to methadone's longer half-life, which corresponds to a rising narcotic effect in non-tolerant individuals. Temporary dose reduction or splitting the dose into two or three fractions during the day may be sufficient to counteract the sedating effect of peaking methadone. Once sedation has been extinguished, one may proceed with further dose increases as requested by treatment goals. In

other circumstances, sedation may be induced by a combination of alcohol with CNS depressants, bearing in mind that these depressants should not be co-prescribed to such patients anyway. As with other opiate agonists, another effect of methadone is that it reduces bowel secretion and motility, so causing constipation and/or awkward defecation due to the dehydration of feces. The development of tolerance to opioid-induced constipation is quite slow, so that constipation is usually a persistent side-effect. Diet supplements or changes, lubrication of bowels or pharmacological stimulation of motility may be beneficial. Nausea and vomiting, which are quite rare in untreated heroin addicts, depend on the stimulation of the Chemoreceptor Trigger Zone (CTZ) but also on the alteration of vestibular sensitivity, bearing in mind that the incidence of this disorder is greater in outpatients. In some cases, antiemetic drugs may be a rapid solution to acute symptoms. In elderly patients urinary retention may develop, due to the increased contraction of the inner urethral sphincter, so that untreated prostatic hypertrophy and urethral stenosis are not compatible with methadone treatment.Some patients experience weight gain, which is usually related to improved life quality but may also be a sign of increased alcohol consumption. Methadone is not toxic to the liver, and no abnormalities of liver function are expected during methadone maintenance, apart from those depending on concurrent liver disorders, which may worsen independently [64]. A history of acute hepatitis should be regarded as a reason for starting methadone treatment as a matter of urgency, since it usually indicates a higher risk of toxic effects caused by a lack of hygiene in injection practices. Methadone increases the liver synthesis of albumin, which is even greater in alcohol-using patients [60, 97]. Thyroxin and Thyroxin-binding-globulin levels are higher during MMT, but no reduction of free T4 was observed [62]. Possible higher values of total globulins or IgG and IgM may derive from pre-existing liver diseases. False positive results at tests for syphilis were observed [65] in over 30% of MMT patients, whereas absolute lymphocytosis can be found in 20%. However, MMT is not related to abnormalities in immune functioning [8, 21]. Methadone is responsible for some changes in endocrine functions: during the first three months of treatment a reduced response to metopirone due to the depletion of ACTH and cortisol can be observed [22, 61, 62, 65]. Abnormalities of this kind are fully reversible during treatment within four to five months after treatment initiation. As for sexual hormones, LH levels tend to fall, whereas FSH has no predictable variations. After one year of treatment, LH and FSH values are expected to fall to within normal ranges, while testosterone levels may continue at lower levels than normal. Delayed ejaculation, which is complained about by quite a few patients, may be handled by shifting the time of dose administration away from times of sexual intercourse, according to individual habits. Methadone causes an increase in prolactin levels during the first 2-8 hrs after administration. Differently from what can be observed with antipsychotics, a flattened circadian secretion rhythmhas been documented, which does not seem reversible while on treatment [65]. High prolactin levels may contribute to sexual dysfunctions, and also cause breast hypertrophy and galactorrhea. Bromocriptine may be useful in this case. No teratogenic effects have been attributed to methadone, nor have any been attributed to morphine or heroin to date [15]. Nevertheless, no appropriate studies on its possible mutagenic or teratogenic properties have been performed yet. Infants of mothers who use street heroin have a 50% likelihood of being born underweight. Low birth weight (below 2500 gr) and a shorter head circumference were reported in newborns from mothers under R-S methadone treatment. On the other hand, methadone treatment is related to a decreased incidence of spontaneous abortion, premature discharge or hyaline membrane disease. Despite a report that 33% of a group of newborns were born underweight, and that 60-70% showed signs of opiate withdrawal (neonatal withdrawal syndrome), no clear correlations with dosage and treatment status were defined [15]. Residual irritability, restlessness and episodes of desperate crying may recur, though to

a milder extent, throughout the first two or three months of life. Between 4 and 6 months of age those symptoms usually fade completely, and the rhythm of growth accelerates with respect to normality, so that by 12 months those newborns can be expected to be normal as to weight and height, that is, similar to infants of mothers without any history of addiction. Head circumference still remains around the 25th percentile at 6 months, and takes over 24 months to normalize. During the first two years, the course of mental and psychomotor development is normal, apart from a tendency not to express one's needs verbally **or** respond to verbal requests. The developmental outcome does not seem to relate to **the** duration of dosage of methadone treatment, or to neonatal withdrawal severity or APGAR score at 5' minutes after birth. Attention and language abnormalities fade by the time children start to go to school, since comparisons with control children show minimal differences. In general, children of addicted parents show rigid temperamental features, so that the initial features are more likely to persevere unchanged throughout the process of development. Some experience regular neurological and behavioural growth, and maintain the acquired stage of development later on, while others show early defects which are likely to persist throughout the process of growth. Those who have not shown neurological or behavioural abnormalities by 36 months of age are characterized by a higher cultural level of the mother and a stable family environment. On the whole, MMT should be considered the standard treatment for pregnant heroin addicts [80]. In treating pregnant heroin addicts, a couple of issues call for definitive clarification: neonatal withdrawal syndrome and methadone addiction. Neonatal withdrawal is elicited by the abrupt interruption of methadone supply to the fetus after the development of tolerance through regular exposure throughout pregnancy. Its distinctive features are its delayed onset and prolonged course. As for methadone addiction, authors agree that R-S methadone, when administered orally as in MMT for heroin addiction, has no addictive liability.

8. Potentially lethal adverse events

Acute methadone intoxication involves the automatic regulation of breathing, and is characterized by the triad: miosis, coma and respiratory depression.

Intoxication may happen accidentally, as when children ingest amounts of methadone left unlocked and within their reach. Otherwise, it may be due to a deliberate suicide attempt or an impulsive act of self-injury or suicidal behaviour by tolerant individuals. During the induction phase of MMT, patients run an overdosing risk which is 6 to 7 times that of untreated heroin addicts, and 42% of racemic methadone-related deaths take place in the first week of treatment [17, 118]. Lethal accidents often happen in the first three days [108]. That is why it is advisable not to administer more than 30 mg/day on the first few days, bearing in mind that the repeated administration of a stable dose will result in a progressive increase in peak levels for the first 4-5 days, that is, before the steady state is achieved. Urinalysis before admission by single-use sticks for morphinuria with a cutoff level of 2000 ng is advisable as a rule to check anamnestic data and identify low-tolerance individuals: in fact, some of those who have undergone self-handled detoxification may still have intense dysphoria, insomnia or diarrhea, despite the loss of tolerance, a factor that may itself lead to overmedication. Respiratory depression by methadone develops within 2-3 hours after intake, or within a few days after treatment initiation. In cases of intoxication, naloxone administration may quickly restore an adequate breathing function, and flumazenil may be useful, too. The patient must be hospitalized and closely monitored, repeating naloxone administration throughout the first 48 hours, in order to avoid re-intoxication after the fading of short-term antagonism from a single naloxone dose. Recently, authors have expressed concerns about the incidence of methadone-related ventricular arrhythmias [69, 115]. In January 2004 the Swiss Regulatory Agency indicated a risk of QT lengthening in patients receiving methadone for the treat-

Table 2. Substances which can produce opiate withdrawal when combined to methadone (modified from Leavitt, Addiction Treatment Forum)

Drug name	Notes/References
Buprenorphine, butorphanol, dezocine, nalbufine, pentazocine	Displace methadone from μ receptors [26, 57]).
Naltrexone, nalmefene, naloxone	Displace methadone from μ receptors [26, 57, 102].
Tramadol	Displace methadone from μ receptors [105].

Table 3. Substance which can interfere with methadone's metabolism and produce unpredictable effects when combined to it (modified from Leavitt, Addiction Treatment Forum)

Drug name	Notes/References
Alprazolam, alorazepate, estazolam, flurazepam, midazolam, triazolam	Potential interactions due to a common metabolic pathway through P450 [52]. May increase methadone's depressant effects on the CNS [102].
Cannabis	Presumable interaction due to a common CYP3A4metabolic pathway [52].
Didanosine	Reduces DDL concentration [89], not observed with gastro-resistant capsules [36, 42]
Dextrometophan	Methadone may increase its plasma concentration and effects [71].
Alpha-interferon + ribavirine	Adverse events may mimic opiate withdrawal, so that methadone dose increase may be decided on a wrong basis [99, 103].
Monoaminooxidase inhibitors	Potential adverse reactions reported [78].
Nifedipine	Methadone may increase nifedipine's concentration [71, 102].
Alfentanil, idrocodone, fentanil, meperidine, morphine, oxycodon, propoxyhen	Possible enhancing effects due to common metabolic pathways. Long half-life metabolites of meperidine and propoxyphen may reach toxic concentration [52].
Stavudine (d4T)	Methadone reduces d4T plasma level. d4T has no effect on methadone's plasma level [89].
Amitriptiline, desipramine, imipramine, nortriptiline	Association with methadone increases TCA toxicity [26, 88, 92]. TCA have a variable effect on methadone's plasma level [33, 79, 102].
Zidovudine (AZT)	Methadone increases AZT level by 40% ; adverse events of AZT are more likely [76].

Table 4. Substances which can decrease methadone's plasma level and/or diminish its effects (modified from Leavitt, Addiction Treatment Forum)

Drug name	Notes/References
Abacavir (ABC)	Methadone's level is decreased, and so is the peak of ABC [49].
Amprenavir	Induction of CYP3A4 may reduce methadone's plasma level [19, 33]. Amprenavir's level may also be reduced for the same reason [36]
Butabarbital, mefobarbital, phenobarbital, pentobarbital, secobarbital, others	Induce P450 [63]; Phenobarbital may cause a rapid decrease of methadone's concentration [49]. Usually methadone dose increase is required.
Carbamazepine	A strong induction of CYP3A4 may cause withdrawal . Valproate does not have a similar effect and may be a safe alternative [12, 98].
Cocaine	Increases methadone's dismission [79].
Desametasone	Induces CYP3A4 [33].
Efavirenz	Methadone withdrawal is common due to CYP3A4 induction. After three weeks of treatment with efavirenz, if methadone dose is not appropriately increased, the peak concentration of RS-Met is reduced by 48% [33, 75].
Ethanol in chronic exposure	Induces P450 [88].
Fusidic acid	Induces CYP3A4 [33, 106].
Heroin	Reduces the free fraction of methadone [79].
Lopinavir + ritonavir	Withdrawal may develop and dose increases be required. Ritonavir alone fails to cause a similar effect [19, 77].
Nelfinavir	Induces CYP3A4 and P-gp [33], but withdrawal is rare [77]. Nelfinavir's level too may be slightly decreased [19].
Nevirapine	Induction of CYP3A4, which may lead to withdrawal [33].
Fenitoina	Rapid reduction of methadone due to CYP3A4 induction [33, 63].
Rifampicine and rifampicine/isoniazid	Induce P450 and may cause severe withdrawal [33, 63]. Such effects are not produced by rifabutin [49, 71].
Spironolactone	Induces CYP3A4 [33].
St. John's wort (hypericum perforatum)	Induces CYP3A4; methadone's level is reduced by 47% [35, 100].
Tabacco (habitual smokiong)	Most reports indicate reduced methadone's effectiveness in habitual smokers [79, 104].
Urinary acidifiers (e.g. ascorbic acid)	The excretion of methadone through the kidney occurs more quickly at acid pH values [81, 102].

ment of addiction or pain. Between 1990 and 2003, out of a total of 272 methadone-related adverse event reports, physicians reported 42 cases of arrhythmia in 25 patients (20 males and 5 females, aged 40 on average) who had had a prescription of methadone for addiction treatment. Between April 2001 and August 2003 7 torsade de pointes and 14 QT prolongation cases were reported. Daily methadone dosages ranged between 40 and 1400 mg/day. In almost all these cases, known risk factors for arrhythmias were documented, such as a long QT, atrio-ventricular delay, bradycardia and electrolyte abnormalities. Several patients were HIV-positive or suffered from vital hepatitis. In some cases interaction with antidepressants, antimicrobial drugs or protease inhibitors was plausible. The OMS database includes 14 cases of torsade de pointes and 16 cases of QT lengthening, mostly reported in the USA. The Italian Ministry of Health recorded just one case of ventricular tachycardia in a male patient taking methadone as a supplementary medication. Patients taking racemic methadone who are also affected by cardiac diseases (such as cardiac failure, bradycardia, left ven-

Table 5. Substances which can increase methadone's plasma level or enhance its effects (modified from Leavitt, Addiction Treatment Forum)

Drug name	Notes/References
Cimetidine	Inhibits P450 [12, 102].
Ciprofloxacine	Inhibits CYP3A4 and CYP1A2 [33, 53]).
Delavirdine	Inhibits CYP3A4 [49].
Diazepam	unknown mechanism [33]. Sporadic reports [71].
Diidroergotamine	Inhibits CYP3A4 [106].
Disulfiram	Reported sedation after high disulfiram doses [12].
Ethanol in acute axposure	Competition for P450 [88].
Fluconazole	Inhibits CYP3A4 [33]; Increases methadone's plasma level [49]; Uncertain clinical relevance [71].
Grapefruit	Inhibits bowel CYP3A4 [51] and Pg-P [33]. This effect is not observed with other fruit's juices [58].
Ketoconazole	Inhibits CYP3A4 [33].
Eritromicine, claritromicine	Strongly inhibits CYP3A4. No cardiac or metabolic effects are reported for azitromicine [33].
Moclobemide	Inhibits CYP2D6 and CYP1A2 [33].
Herbal products such as :uncaria tomentosa, matricaria recutita, echinacea angustifolia, hydrastis canadensis, quercetina	Strongly inhibits CYP3A4, though no specific reports about methadone are available [100, 106].
Omeprazole	May obstacle methadone's absorption [102].
Fluoxetine, fluvoxamine, paroxetine, nefazodone, sertraline	Inhibits mainly CYP2D6 but also CYP3A4 and CYP1A2 [33, 71, 92].
Troleandomicine	Inhibits CYP3A4 [106].
Urine-alkalinizers (e.g. sodium bicarbonate)	Alkaline urine pH reduces the elimination of methadone through the kidneys [57, 102].
Verapamil	Inhibits CYP450 [71] Substance influencing cardiac conduction to a variable extent with potential arrhythmic properties in combination with methadone.

tricular hypertrophy, long QT syndrome) or electrolyte abnormalities (such as low magnesium, potassium, primary or secondary to diuretic treatment) should be cautiously evaluated through time. Likewise, factors which may cause a sudden increase in methadone concentrations in plasma should also be known and prevented. Lastly, chronic combined treatment with QT-prolonging drugs, such as class I and II antiarrhytmic drugs and antidepressants, should be assessed with great caution. One recent study by Maremmani et al. showed no correlation between methadone dosage and QT length in methadone-only treated addicts [72].

9. Pharmacological Interactions

Tables 2,3,4,5 report an updated list of known interactions with methadone.The progressive introduction of new active principles, together with the use of multiple drug treatment regimens, have raised the likelihood of significant interactions and complicated the parameters of clinical assessment and decision-making [1, 7, 50]. Up-to-date knowledge about the pharmacogenetics of drug treatment makes it easier to understand most of the pharmacokinetic and pharmacodynamic mechanisms involved in these interactions [37, 39, 40, 101]. Unfavourable and sometimes dangerous interactions may come from other drugs, over-the-counter products, legal and illegal recreational substances, or sometimes simply from certain types of food.

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1.7

Pharmacokinetics of Methadone

P.P. Pani

The efficacy of methadone in the treatment of opioid dependence can be ascribed to the ability that it, unlike heroin, has to maintain a stable concentration in blood and, therefore, in the action site located in the brain.

For any patient treated with methadone, it is possible to distinguish an antiwithdrawal dose – a dose large enough to avoid the onset of a withdrawal syndrome – and an anticraving dose – a dose that is able to reduce cravings for heroin and control the behaviour of subjects who might wish to search for it and use it.

The anticraving dose is usually higher than the antiwithdrawal dose. According to the literature on the subject there is a positive correlation between the dose of methadone taken and the outcome of treatment. By now there is a general consensus that, to be effective, the daily dose of methadone should range between 80 and 120 mg.

These general observations represent important points of reference for physicians working with heroin addiction. However, the existence of an important variability in the response to methadone in single subjects and between different subjects requires an evaluation of the various factors involved. The aim is to find the dose and the treatment regimen that will be most appropriate for each patient.

In this chapter we will take care of the determinants of variability in the response to methadone and of the interventions needed to handle it.

1. Methadone blood concentrations

When taken orally, methadone is absorbed slowly through the gastrointestinal tract. The maximum concentration is reached around the second to fourth hour after the ingestion, after which it falls gradually until the moment of the next ingestion (Figure 1).

If the daily dosage of methadone dosage is correlated with its concentration in blood, a graph of the type shown in figure 2 is ob-

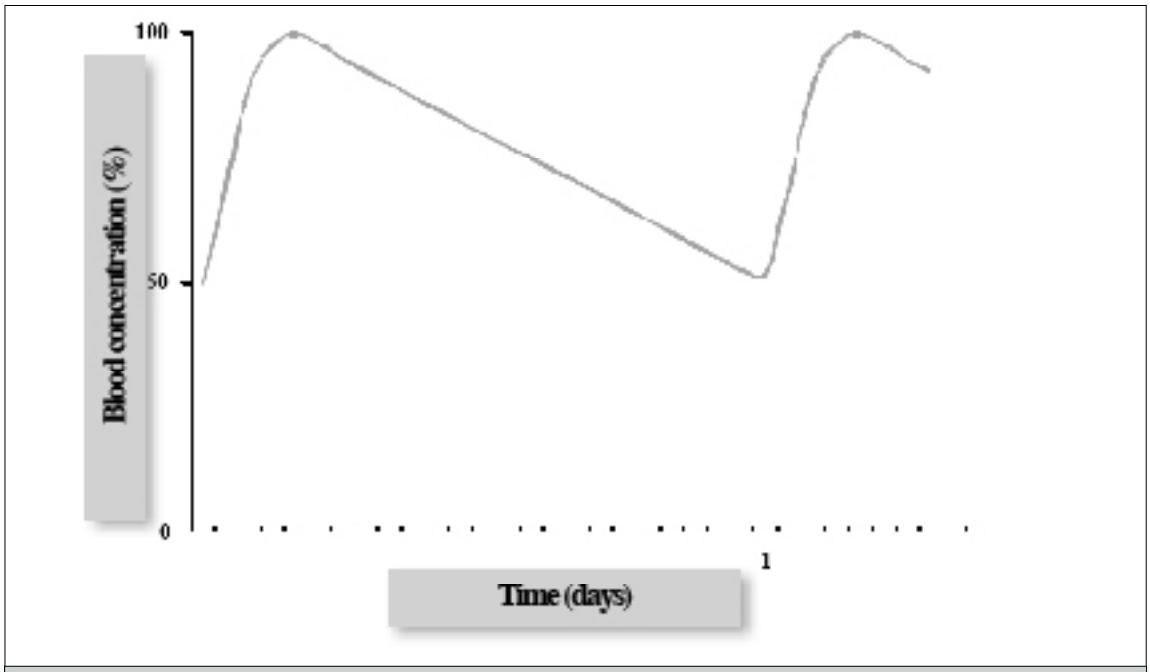

Fig. 1 Concentration of methadone in plasma: percentage variations over 24 hours

tained. This graph refers to 100 patients in methadone maintenance treatment, 24 hours after their previous dose. As can seen from the graph, the general rule according to which the higher the daily methadone dosage, the higher the concentrations in the blood will be is not necessarily respected. It can, in fact, be noted that there are patients who, even when they take methadone doses as high as 70–170 mg per day, have blood concentrations similar to those of patients whose doses are as low as 25 mg per day.

Blood concentrations of methadone are more reliable as an indicator of its concentration in the action sites than the dose taken. For this reason, methadone plasma concentrations measured after 24 hours have repeatedly been proposed as a parameter for the evaluation of the adequacy of treatment. At first it was thought that a methadone plasma concentration of 150 ng/ml would be required to provide sufficient protection against the use of heroin [1, 9]. Subsequently this value was modified: at present, a plasma concentration of between 150 and 600 ng/ml is considered necessary to gain control over craving [1, 6, 8]. Actually, important differences are found to persist in the way subjects respond to methadone, even when reference is made to methadone concentrations in plasma rather than methadone doses taken. Therefore, the therapeutic aims of terminating the use of heroin and ending craving can be achieved with plasma concentrations which differ in different subjects and differ too in a single subject under different conditions.

One aspect to be considered in evaluating the pharmacokinetic components of this variability it is the chirality of methadone. Methadone is usually produced and traded as a raceme divided fifty-fifty between its two isomers, R and S. Some of the features of the two enantiomers differ: these include half-life, receptor binding and opioid activity. For our practical purposes, we can assume that the R component is the active one. Methadone is mainly metabolized in the body by the enzymes of the P450 cytochrome system. The literature contains observations on the involvement of cytochromes CYP1A2, CYP2D6,

CYP3A4, CYP2C9 and CYP2C19, even though the contribution of each of these has not yet been clearly defined.

The existence of inter- and intra-individual variability in the enzymatic activity of these cytochromes on the two enantiomers is surely the foundation for the major variations found in the relative concentrations of S and R methadone in blood. In practice, while an individual taking his/her daily dose consumes 50% of R-methadone and 50% of S-methadone, the relative percentages of the two isomers in the blood show wide-ranging variations. The literature reports ratios between R and S methadone that vary as widely as 0.63-2.4 [7]. Since the R isomer of methadone is the active one, for practical purposes it would be better to measure the R isomer, rather than total methadone. Actually, patients treated with a given dose of methadone, present variability in plasma concentrations of up to 58 times, while dosing with R-methadone alone reduces variability to 41 times. Considering only patients who take no other medications, interindividual variability for the same dose of methadone ingested falls to 35 times for methadone as a whole and to 17 times for R-methadone [5]. One possible outcome, therefore, is that a subject may have a plasma concentration of methadone that is supposed to be appropriate, but actually consists predominantly of inactive S-methadone. Ideally, to have a more realistic picture of opioid activity at the receptor sites, the best parameter to refer to is the plasma R-methadone concentration.

With the aim of using methadone plasma concentration as a predictor of abstention from the use of opioids, the sensitivity and specificity of various different values of plasmatic concentration have been studied. When using the negativeness of the toxicological urinalyses for morphine over the previous two months as a parameter for abstention from the use of heroin, it has been observed, for example, that a level of 400 ng/ml whole methadone in plasma corresponds to a specificity of 81.1% and a sensitivity of 31.8%. This means that the probability of using heroin falls to 18.9% above 400 ng/ml, while the probability of ending the use of heroin is 68.2% at this concentration in plasma.

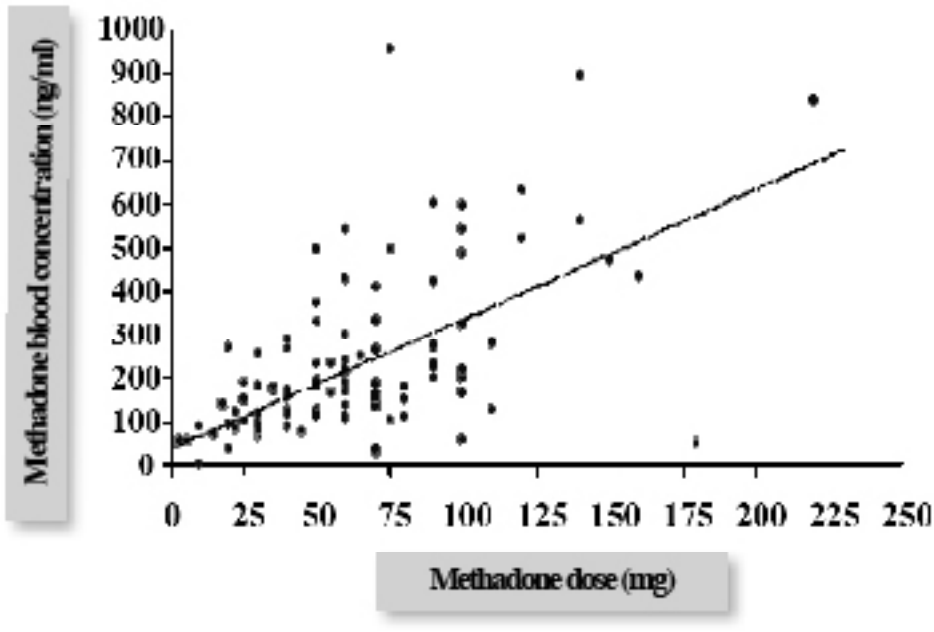

Fig. 2 Correlation between doses of methadone taken and concentrations in plasma 24 hours after administration in 100 subjects on methadone maintenance treatment

Moving now from the methadone raceme to R-methadone, it has been shown, by contrast, that a level of 250 ng/ml for plasma concentration corresponds to a specificity of 92.6% and a sensitivity of 24.7%. This means that the probability of using heroin falls to 7.4% when the R-methadone level exceeds 250 ng/ml, while the probability of ending the use of heroin is 75.3% for this plasma concentration [5].

2. Stability of concentrations in plasma

A pharmacokinetic characteristic common to substances of abuse is their short half-life. A sharp increase in concentrations in plasma and a short length of action characterize substances like heroin, cocaine and alcohol. The efficacy of methadone in controlling heroin addiction is based on the stability of its concentration in blood.

Actually this is a case of relative stability. As is shown in figure 1, methadone concentrations in plasma slowly fall from a maximum value recorded 2-4 hours after one intake, to a minimum immediately before the next. For long-term methadone administration, as in maintenance treatment, an average half-life of around 24 hours has been found. This means that at the end of the 24th hour after an ingestion, the concentration of methadone should have fallen to half its peak value.

It is only logical to wonder if, in the general run of treated subjects, the activity of organs and systems influenced by opioid action follows the oscillations of methadone in plasma. While the early studies on this matter do not show important modifications, subsequent observations carried out with objective instruments of measurement, reported important changes (in pupils diameter, skin conductance, and so on). More recently it has been clearly observed, when comparing subjects receiving methadone maintenance treatment for opioid dependence with healthy control subjects, that the former show major changes in parameters such as pupil size, pain sensitivity and respiratory frequency, with a fall occurring in concomitance with the peak for concentrations in plasma, and a rise in coincidence with the trough for concentrations in plasma [2]. Even the evaluation of important subjective parameters related to the psychic state showed significant differences when compared with healthy controls. In particular, mood tended to become depressed while moving away from the peak for concentrations in plasma, reaching its maximum deflection at the end of the 24th hour after the ingestion of methadone. It began to improve soon after the next ingestion of the medication, reaching a new maximum value that coincided with the new peak for concentrations in plasma [3].

These fluctuations in methadone levels in plasma can explain the presence of subjects who do not feel they are 'held' by the medication over the full cycle of 24 hours. These are the patients who show up early in the morning at methadone clinics, and complain about waking up too early, and about anxiety, restlessness, nausea, malaise which all disappear soon after methadone has been taken. It has been reported that a percentage of subjects as high as 34% do not feel they are being 'held' by methadone [4]. Actually, although a daily variation in the functioning of organs and systems influenced by opioid activity is a feature of the experience of most subjects, patients who do not feel they are being 'held' by methadone show variations that are significantly higher than in those who do feel that they are being 'held' by their medication [2, 3].

Even when there are alterations in the subjective state of patients in the 24-hour daily cycle, these do not actually show a close correlation with methadone concentrations in plasma. Instead, the ratio between peak and trough concentration seems to be the most important feature to be considered: the higher this ratio, the higher the probability is that the patient is suffering from a withdrawal symptomatology, even if a mild one, which appears daily when methadone in blood approaches the lower concentration. Dyer et al., in particular, have also pointed out that one critical aspect is the speed of falls in methadone concentrations in plasma. Even a small change in this value seems to be correlated with important modifications in the subjective status of the patient [3].

3. Methadone and mood

It is well known that the prevalence of mood disorders is higher in opioid addicts than in the general population. It is also known as it tends to decrease during methadone maintenance treatment [10, 11]. Opioid withdrawal syndrome includes symptoms like anxiety, restlessness, insomnia and depression, which are also part of mood disorders. From this perspective, the presence in subjects on methadone maintenance treatment of fluctuations in blood concentration of the medication sufficient to justify a withdrawal-like symptomatology should be considered also for their implications on affective pathology. In reality, it has been observed that in opioid addicts in methadone treatment there is an important and significantly alteration in psychological/psychiatric status with tension-anxiety, rage, confusion, depression, vigour, and that this symptomatology is subjected to daily fluctuations that coincide with those of methadone concentrations in plasma [3].

The already noted variability in the R and S enantiomer components in the methadone found in plasma certainly makes a contribution to mood alterations in patients on methadone maintenance treatment; in particular, a higher likelihood of withdrawal symptoms and alterations in mood tone has been observed in association with a relatively higher exposure to S rather than R methadone.

4. Determinants of variability

The determinants of this variability in the response to methadone can be subdivided into pharmacodynamic and pharmacokinetic ones. In reality, little is known still about the pharmacodynamic factors, while information on the pharmacokinetic ones is much more solid. The latter have been divided into genetic, physiological, pathological, and pharmacologic. Each of these factors can affect variations in response to treatment acting on many levels.

4.1 Genetic factors

Besides those involved in the response given within the central nervous system, genetic factors that directly alter the pharmacokinetics of methadone have to be considered, especially those that affect the activity of the microsomal systems in the liver that are dedicated to medication metabolisms.

The presence of a higher or lower level of activity of the CYPD2 cytocrome is, for example, responsible for a more rapid or a slower elimination of methadone, with a consequent shortening/lengthening of its half-life and a rise/fall in its levels in plasma.

4.2 Physiological states

Linkage between methadone and plasmatic proteins depends on the availability of the alfa 1 glycoprotein. In a condition of stress, the production of this glycoprotein rises, leading to a fall in the concentrations of unbound methadone – the active one.

Starvation or a diet rich in meat may lead to urine acidification. As methadone is weakly basic, acidification facilitates its urinary elimination with a consequent fall in its concentrations in plasma.

4.3 Pathological conditions

Pathological conditions may modify the kinetics of methadone in a direct way, as is the case with renal failure. The interference is usually indirect: one readily available example is the fall in the free fraction of methadone (consequent on any increase in the concentrations of alfa 1 glycoprotein) that is observed in neoplastic pathologies.

4.4 Pharmacologic interactions

Many drugs, depending on the various

steps of absorption, plasma protein binding, methabolism and excretion, may interfere with the concentrations of methadone in blood. In the last few years, interference at the level of the P450 microsomal system has been evaluated with special attention. This interference can translate into an induction of the methadone metabolism, with a consequent fall in its levels in plasma, or an inhibition of its metabolism, with a rise in methadone levels in plasma (refer to chapter ** for a description of single interferences).

5. Clinical approach

Physicians should be aware of the problem of variability in responses to methadone, and in the various factors involved. This will allow the right choices to be made in deciding on the most suitable actions – those that will allow anomalous situations to be corrected and guarantee the maximum degree of plasma stability to levels of methadone.

A patient who complains of not feeling "held" by the dose of methadone that has been prescribed deserves maximum attention; the same attention should be paid to a patient who continues to use heroin or other substances of abuse in spite of a dosage of methadone that is 'theoretically' adequate. In these cases it is fundamental to deepen the clinical investigation, by verifying, in particular, if the patient has any complaints about withdrawal symptoms and when they become manifest after methadone is taken. A crucial factor is that the clinical picture is often paucisymptomatic and characterized by subjective symptoms: insomnia, anxiety, restlessness and depression can be associated in various different ways and/or combined with craving, nausea and muscular pain. On rare occasions a patient does not refer his/her symptoms to a state of withdrawal, but to a physical or psychic state of discomfort. Investigations should explore the possibility of a rapid metabolization of methadone, interference deriving from a drug, an altered physiological state, or exposure to stress factors. One possibility to be considered and assessed in single cases, is that of controlling the interference (by suspending or replacing the drug) or modifying the dosage of methadone and/or the frequency of its administration. The dosage of methadone in blood may provide useful indications. The ideal should be that of being able to measure methadone plasma concentration at the end of 24 hours (if possible for R methadone), but also at the peak (at the end of the 4th hour).

Independently of the availability of methadone plasma concentrations, it should be borne in mind that the adequacy of a methadone dose is what will determine the endpoint of heroin use, the control of craving and the lack of side-effects. A careful evaluation of the state of the patient and his/her clinical evolution is needed to be able to maintain the dosage of methadone within the range of efficacy.

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1.8

Neuroendocrinologic Effects of Methadone Treatment

G. Gerra

The task of defining the neuroendocrinologic effects of methadone in humans can be recognized as extremely difficult and complicated, once it is considered that individuals who take methadone present prolonged exposure to heroin and other substances of abuse – substances that could themselves determine the biological alterations that have been detected.

Moreover, over the past few years a growing body of evidence derived from studies on biological psychiatry has revealed at-risk temperamental factors, personality disorders, and psychiatric disorders associated with drug addiction that may also prove to be linked with genetic and neuroendocrinologic alterations. In fact, neuroendocrinologic dysfunctions detected in subjects in methadone therapy might at least partly derive from previously consumed drugs and from biological correlates associated with personality traits; it follows that the data should be interpreted with great caution.

The main quality of methadone, as is widely recognized, is that of being a steady, slow-acting opiate agonist. In fact, its stimulation of mu opiate receptors, which is stable and long-lasting, is in sharp contrast with the continuous fluctuations of heroin kinetics; according to some authors, it is this stimulation that probably permits the normalization of all the dysfunctions caused by exposure to heroin [21]. In addition, it cannot be excluded that the stabilization of the stimulation of opiate receptors could account for the persistent modulation of the functions arising from the main neuro-hormonal axis [13].

1. Prolactin

The hypothesis that a chronic stimulation of the opiate receptors alters the functioning of the tubero-infundibular axis and the dopaminergic control of prolactin was first formulated a long time ago. Methadone produces an acute, major elevation of prolactin levels. This altera-

tion was not detected in subjects who were pre-treated with dopamine-agonists, suggesting that opiate-induced hyperprolactinemia is secondary to the lowering of dopaminergic tone [36]. The alteration of prolactin levels in patients in methadone therapy has been reported in various studies [4, 24, 39], with consequential impact on sexual functioning, fertility and menstrual irregularities. Previous studies have shown that vitamin B6 pyridoxine, a coenzyme implicated in dopamine synthesis, is able to reduce prolactin levels in methadone-treated subjects [39], once again indicating the probable role of dopamine in stimulating pituitary prolactin-secreting cells.

Higher levels of basal prolactin and an altered prolactin response to insulin hypoglycemia were detected in patients in methadone maintenance [41]. These findings point to a complex alteration of the control systems regulating hypothalamic-pituitary secretion, together with stress-response systems, which cannot be fully accounted for by the effects of methadone. Not surprisingly, the same authors have revealed a lower prolactin response in phobic patients, partly attributing the neuroendocrinologic alterations to the biological correlates of psychiatric comorbidity. When comparing subjects in methadone treatment with heroin addicts exposed to streetdrugs but not yet treated, hyperprolactinemia was only found in the latter, while the prolactin levels of methadone-treated patients showed no substantial alterations [27]. These findings, in contrast with previous data, suggest that heroin alters hypophysis secretion and that methadone promotes system adaptation, with the consequent normalization of prolactin, in accordance with other studies [30]. Likewise, elevated basal prolactin levels and a lack of response to TRH stimulation were observed in patients at the beginning of methadone treatment, with recent exposure to heroin and all the stressful conditions typical of non-treated addicts [33].

More recently, the dynorphine test was used to assess the functioning of the tubero infundibular dopaminergic system. In healthy subjects dynorphine increases prolactin levels [1]. In this study, carried out at Rockefeller University, no alterations of basal prolactin level were detected after the dynorphine test; despite this, a significant dysfunction of the prolactin response to the kappa agonist was recorded, although there was no way of concluding whether the dopaminergic alteration was secondary to methadone, to heroin exposure or to a psycho-biological condition primary to the addiction disorder. In a recent study, attention was once again directed to the possible relationship between methadone and alterations of the menstrual cycle, without definitively clarifying the mechanisms that would lead to the absence of the menstrual cycle [15].

2. Hypothalamus-Pituitary-Gonadal axis

Long-lasting concern over possible gonadic dysfunctions in patients in methadone maintenance has induced researchers to explore the impact of chronic opiate receptor stimulation on the hypothalamus-pituitary-gonadal (HPG) axis. In a study performed in 1981, a reduction of FSH levels was detected in patients in methadone therapy, while LH levels stayed in a normal range [24]. According to other authors, both LH and testosterone basal levels were reduced in subjects in methadone treatment [4]. A few years later, a study on 100 heroin addicts in methadone treatment produced evidence of a HPG axis dysfunction, with testosterone levels significantly below the norm [6].

Menstrual cycle dysfunctions in patients in methadone treatment have been signalled since 1968, with oligomenorrhoea and amenorrhoea [2]. These two disorders, however, present a notable individual variability and could be influenced by the continuation of heroin consumption during maintenance treatment. Studies on small samples of patients that had the aim of evaluating gonadotrophines and ovarian steroids over the menstrual cycle in methadone-treated subjects, yielded conflicting results; cycle interruption, with the absence of FSH and LH peaks and no evidence of any rise in progesterone in the luteal phase, was detected in some subjects, but not in others. There is still an ongoing debate over the

impact of methadone on the HPG axis and on the possible causes of oligo/amenorrhoea in drug addicts [31].

In a recent study, attention was once again focused on the possible correlation between methadone and alterations of the menstrual cycle, without achieving any definitive clarification of the underlying mechanisms [15].

In contrast with these findings, normal levels of FSH, LH and testosterone have been documented by some authors [27] in male heroin addicts in methadone maintenance therapy, associated with alterations of semen. Analogous alterations of the number and motility of spermazoids were detected in heroin addicts not in methadone treatment. In support of the hypothesis that methadone does not interfere with the integrity of the hypothalamus-pituitary-gonad axis, it was proposed that sexual dysfunctions in methadone maintenance patients may be due to coexisting psychiatric problems rather than being caused by methadone [34]: the demonstration of symptoms in the sexual sphere during the treatment of maintenance should stimulate the clinician to perform a careful diagnostic examination from a psychiatric point of view. Therefore, when phenomena emerge in the sexual sphere during maintenance treatment, it should prompt the clinician to proceed to a more in-depth psychiatric evaluation.

Contrasting data in favour of HPG axis dysfunctions being due to methadone treatment have been proposed as well. More recently, lower basal levels of testosterone, LH and FSH, together with a lower gonadotrophine response to the hypothalamic gonadotrophine-releasing hormone (GnRH), in association with a weak libido, impotence and gynectomasty in patients in methadone maintenance have been detected. A reduction of methadone dosage to 40 mg in these subjects determined the remission of hormonal alterations and a recovery in libido, suggesting a dose-dependent effect of methadone on testosterone and on the pituitary cell response to hypothalamic stimuli [30]. Likewise, even more recent data suggest significantly reduced testosterone levels in heroin addicts; these persisted after one year of methadone treatment, with possible implications for bone metabolism and degree of mineralization [40].

3. Hypothalamic-Pituitary-Adrenal axis

Hypothalamic-pituitary-adrenal (HPA) axis functioning may play a role in alterations induced by chronic exposure to opiates. These interferences may depend on the secretion of the hypothalamic corticotrophine-releasing factor (CRF) [25], as well as adrenocorticotrophic hormone (ACTH), a peptide synthesized from pro-opiomelanocortine, and therefore closely related to the endogenous opiate system [16].

While it has been hypothesized that heroin is able to modulate the secretion of ACTH and cortisole, as well as the HPA axis-mediated response to stress, no conclusive data are available on the role of methadone.

According to Kreek et al., methadone, considering its stabilizing properties, might promote regulation of the HPA axis, with normal levels of ACTH and cortisole, along with a well-preserved circadian rhythm of these hormones [23]. The same authors have verified a normal response to metopyrone, a medical substance that, through an 11-hydroxilasis blockade, and through the synthesis of cortisole, is, under normal conditions, able to induce an increase in the secretion of ACTH in patients compliant with a steady, stabilized methadone regimen [22]. The same authors have reported a normal response to metopyrone, a diagnostic drug that determines a rise in ACTH levels in normal subjects through the inhibition of 11-hydroxilasis and cortisole synthesis, in patients keeping to a stable methadone treatment regimen [22].

By contrast, according to other authors, the same test indicated a functional impairment of the HPA axis, indicative of a lack of inhibitory control of cortisole over ACTH [37]. Likewise, a certain level of cortisole suppression was detected in patients in methadone maintenance; this was associated with an exaggerated response to insulinic hypoglycemia when compared to healthy controls [41]. In this case,

there was no association between the excessive cortisole levels and the degree of depression, which means that the hypothesis that HPA hyper-reactivity may be related to psychiatric comorbidity must be discarded.

In disagreement with previous studies, which had reported a normalization of the HPA axis in methadone maintenance, the Rockfeller University group highlighted the presence of ACTH hyper-reactivity due to a lack of negative feedback from metopyrone, in patients with a problem of cocaine abuse during maintenance therapy [32]. It was therefore proposed that neuroendocrine alterations may be linked with personality traits rather than arising from exposure to heroin or methadone.

In accordance with previous observations, the same group reported an increase in plasma ACTH and cortisole levels after hCRF had been administered to patients in methadone maintenance, without being able to determine the underlying neurobiological mechanisms.

In various experimental protocols evaluating biological responses to stress, to aggressive behaviour and to negative emotions, abnormalities of the HPA axis were detected in drug-free heroin addicts [8, 12] and in subjects in methadone treatment [10]. An increase in cortisole and ACTH basal levels and an abnormal response to stress, already revealed in heroin addicts, independently of methadone treatment, was also detected in amphetamine-derivate misusers [10].

Likewise, an increased response of cortisole and MHPG to yohimbine, which increases noradrenergic activity, was detected in patients in methadone maintenance. These findings confirm the hypothesis that in heroin addicts alterations of neuroendocrinologic mechanisms persist during methadone treatment [35]. This kind of difficulty in stress response, viewed from a neurobiological standpoint, has been observed too in at-risk depressed adolescents and in various conditions of social maladjustment [9, 11, 28], and does not seem to be affected by long-term opiate treatment. It might represent one of the crucial dimensions in determining vulnerability to addictive disorders and an important risk factor for relapse, for patients already in treatment.

4. Endogenous opiate peptides

Initial reports, at the beginning of the 80s, suggested that chronic stimulation of opiate receptors may have an inhibitory effect on endogenous opiate peptide secretion. A direct and also an indirect reduction of beta-endorphins were detected by Gold in patients in methadone treatment [13, 14].

Later studies, however, found a substantial normalization of both plasmatic and liquoral beta-endorphin levels. On one hand, acute administration of opiates reduces beta-endorphin levels; on the other, the stabilization brought about by methadone readjusts the endogenous opiate syste, bringing a normalization of beta-endorphin values [18, 19].

The maintenance of normal-ranged liquoral levels of beta-endorphins in subjects in long-term methadone treatment confirms that the secretion of pro-opiomelanocortine remains intact in these patients [20]. The same Authors argue that the circadian rhythm of beta-endorphins and the response to metopyrone continue undisturbed in patients in methadone treatment [22, 23]. These findings conflict with hypotheses that claim there is an endogenous opiate system dysfunction as a result of exogenous opiate therapy.

5. Thyroid function

Methadone treatment does not seem to interfere with the hypothalamus-pituitary-thyroid axis; normal T3, T4 and TSH values, both basal and after TRH stimulation, have been detected in heroin addicts in methadone treatment [38]. A later study carried out on a larger sample of heroin addicts in methadone maintenance showed an increase in T3, T4 and tireoglobulin levels, but with normal levels of free fractions (free T3 and free T4) and TSH, in practice confirming the euthyroid state [5].

6. Glucose metabolism

Patients in methadone therapy display a delayed, attenuated insulin response to food ingestion, with resulting hyperglycemia [41]. It is not clear if this dysfunction is a result of an alteration of the enterohepatic axis, with possible opiate interference with pancreatic polypeptides [26], or else to a direct action on pancreatic delta cells [7].

Also insulin responses to both oral and intravenous glucose stimulation in heroin addicts, are similar to those detected in non-insulin dependent diabetes mellitus and are independent of methadone treatment [3]. In fact, heroin addicts with and without methadone therapy displayed the same dysfunctional responses, suggesting once again that the metabolic alterations that are detected are not due to methadone. Furthermore, after performing a glucose tolerance test on heroin addicts with and without methadone treatment, levels of glycosylated haemoglobin and serum fructosamine did not confirm the hypothesis of an altered glucose metabolism in heroin addicts [29].

7. Vasopressin

The possible interference of methadone on levels of vasopressin (antidiuretic hormone), as detected in animal models and hypothesized in humans, has not yet been confirmed by any noteworthy evidence. An inability to concentrate urine when dehydrated was detected in subjects in methadone treatment, but that could be due to opiate interference on the baroceptor system or to not-yet investigated electrolyte imbalances [41].

8. Catecholamines

Data indicative of a fall in peripheral norepinephrine levels in patients in methadone treatment, with a lowering of muscle sympathetic nerve activity [17], were not replicated in other experimental protocols, so that further investigation of these aspects is now needed.

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2.1

The History of Methadone Treatment

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1. On detoxification and anticraving therapies.

The use of opiate substances, either for medical or recreational purposes, dates back to ancient times [27]. The social alarm arising from reckless behaviours caused by craving for opiate drugs is far more recent. Although habitual opiate use could take place, as described in the biographies of famous historical characters, or even when documented anonymously among common people, the epidemic of opiate addiction quickly followed the commercial spread of morphine and related substances (in the late 1800s). In other words, the specific drug and the route of consumption were crucial factors in changing the role of opiates and making them harmful to society as a category [33]. Thus, the spread of morphine should be regarded as a milestone in the history of opiate use. Before morphine, opium use was disapproved by public opinion, because it marked a lifestyle based on a luxury, but was socially tolerated for two main reasons: its consumption was confined to opium rooms, with no dangerous impact on society, and opium-derived drugs themselves had irreplaceable medical properties. A radical change ensued; after morphine, the moral war against opium was refuelled by the epidemic of morphine addiction, which proved how opium-derived substances may have harmful consequences for individual health and social safety [1]: morphine addiction was the first case of mass addiction.

Drug sellers and smugglers were the first to understand the basic meaning of addictive behaviour, and the feasibility of inducing addiction through repeated exposure to certain substances: in fact, drug traders realized the economic potential of addictive drugs, and launched their product during low-cost trial periods, followed by a quick run-up in prices till they reached unbelievable heights; consumers were willing to pay those prices once addiction has hijacked their brain reward system [27].

On medical grounds, the reinforcing properties of older and newer opiates have been described, though it has never been clear where such properties may lead. For example, opiate use was tried as a way of helping to wean patients off alcohol, or off other opiates. Heroin, for instance, was effective in driving patients away from morphine, as long as patients showed they preferred heroin itself. In the medical instruction sheet for Bayer's heroin the reader is told that "morphine addicts treated by this drug quickly lose any craving for morphine". Apart from that specific attempt, which would turn out to be a failure due to the lack of knowledge about addiction biology, the idea of craving control by therapeutic drugs had already been conceived. Apart from medical objectives, Christian missionaries too showed interest in the opportunity to take advantage of heroin's reinforcing properties, and traded it to get people to join what was a new religion for them, and convince them to attend churches, in the hope that heroin would have an even stronger appeal than opium had done up till that point [8, 27]. Thus, they were just making a comparative experiment involving the conditioned behaviours of a human sample, using religious affiliation as an endpoint. Other fields of employment [8], such as the use of the same substance (morphine for morphine) at decreasing dosages for the treatment of withdrawal, failed to clarify the difference between detoxification and addiction control. Put simply, the fact that some dependent subjects found it impossible to carry out detoxification on their own by tapering dosages (when that could be done by opiate-free methods) suggested they had no control over the substance. Unfortunately, detoxification has remained the first and most commonly used, allegedly therapeutic approach to addictive diseases, despite predictably negative outcomes.

The first two attempts to administer anticraving treatment (heroin for morphine, cocaine for morphine) failed for two main reasons: on one hand, the putative therapeutic substance owed its effectiveness to a sharper reinforcing property, so that it only induced a harder form of addiction, though to itself instead of to the original substance.

In other words - in a way unlike modern anticraving treatments - those loomed as substitution treatments. Reinforcement was distinct from withdrawal control, as was made evident by the substitution of cocaine for morphine. Unfortunately, treated patients became addicted to the prescribed substance, or to both. The second reason for failure was that no longer-term intervention had been thought of: the interruption of the vicious circle between craving and tolerance was regarded as enough to break the cycle of relapsing behaviour. Nevertheless, it became clearer and clearer over the years that relapses are a core feature of addiction, so that no detachment from the substance can be stable or long-lasting unless the means by which detachment was achieved are retained.

In the USA, as early as 1914, the failure of therapeutic heroin led to the placing of a limit on the free employment of opiates for medical purposes, while physicians were allowed to prescribe morphine and heroin on a regular basis to morphine-dependent patients only. By using this strategy, opiate addicts were no longer socially disruptive, since they were hooked on a freely-delivered substance. On the other hand, they did not appear to proceed with any rehabilitation, and their quality of life stayed low. Moreover, something unexpected was taking place that would become increasingly evident in the course of time: prescribed opiates were diverted to non-addicted people, who bought them for recreational purposes. This meant that a legal channel had been set up for the general population to be exposed to addictive substances, outside medical settings. The fact that some doctors might decide to engage in drug trading with their patients was just a secondary consequence, not the actual cause of the phenomenon.

Eventually, regulations were imposed on the medical use of opiates (Conference on Opium, Geneva, 1924). Opiate use was permitted in either of the two following situations:

a) when withdrawal from morphine or heroin causes serious disorders, which cannot be treated effectively by resorting to other common medical techniques.

b) when patients are rendered capable of leading a normal or sufficiently balanced life after the administration of opiates at stable doses - usually low ones - , but fail to maintain their improvement in an opiate-free condition.

On that occasion the principle of maintenance as a strategy for long-term control of an addicted patient's behavioural balance and productive potential was formulated for the first time. However, the presciption of low dosages as standard practice can be seen a major limitation, now that the average level of effective dosages of opiate agonists can be reviewed with hindsight. Moreover, the benefit to the individual was described then in terms of productiveness and social harmlessness, while no definition of addiction as a source of individual discomfort was provided.

2. Methadone treatment

In the early 1960s addiction treatment reached a turning point: Dole and Nyswander pioneered clinical research on the properties of an opiate agonist, methadone, in subjects who were already undergoing treatment with morphine for opiate addiction [9-11, 15-18]. Up to then, substitution by morphine or heroin was the only therapeutic perspective, since detoxification was ineffective in ensuring the long-term prevention of relapse. The basic problem was that subjects on substitution treatment performed poorly on social grounds, even though their disruptive behaviors were extinguished. When switching from legal morphine to methadone, the first evident advantage was the chance to restore social and individual abilities to patients, as well as highlighting their quality of life. Positive results on small samples of hardcore patients became the basis for testing methadone treatment on larger samples, with results that brought further encouragement. In line with their original observations, Dole and Nyswander formulated a metabolic hypothesis for opiate addiction which moved sharply away from the concept of substitution treatment. The symptoms displayed by addicts (starting with craving) went into gradual remission when challenged with a re-balancing drug, such as methadone. The normalization by methadone of addictive behaviours happened at levels of stimulation which were far higher than those required to counteract withdrawal symptoms, and presumably targeted a kind of brain dysfunction that developed before tolerance, and persisted in detoxified subjects as a silent biological ground for relapse.

An increasing number of subjects were given methadone treatment in one of two different modalities: maintenance and short-term tapering. Short-term tapering turned out to be a failure, supporting the conclusion that no short-term methods exist that are able to give addicts long-term control over their symptoms. This statement has retained its validity up till now. On the other hand, maintenance produced stable results, in the medium and long terms. So-called detoxification procedures cannot be expected to provide a solution to addiction, whatever method is adopted. Retention rates and the latency of relapse after detoxification reach higher levels when the reversal of tolerance takes place more slowly, and when opiate agonists are employed. In other words, detoxification seems to work better as long as opiate agonists are being administered.

The spread of methadone maintenance programmes was also characterized by a discrepancy between scientific knowledge and clinical practice: in some cases professional staff were not given the requisite information about the pharmacology and behavioural properties of methadone; in other cases cultural bias acted as a brake on the correct application of acquired knowledge. The heterogeneity of results and outcome standards between programmes is mainly due to variations in the dosages employed, which may or may not be around the average effective dose value of 100 mg/day, and sometimes fail to reach the minimum average dosage (60 mg/day) [13, 14, 29].

In the USA detoxification - by whatever technique - is no longer featured among the possible approaches to the treatment of opiate addiction. Over the years, methadone maintenance has remained the gold standard of effec-

tiveness with respect to the other approaches that were scientifically evaluated (naltrexone, environmental isolation, slow or rapid detoxification, abstinence support, heroin maintenance, other psychopharmacotherapies). The stigma associated with methadone treatment continues to act as a major limitation on the correct handling of methadone programmes and the evaluation of their results. The main misunderstandings are those of viewing methadone as a legally delivered narcotic, perceiving methadone treatment as a way of replacing one narcotic by another, and interpreting therapeutic dependence as a synonym for legalized addiction.

These misconceptions are common even among physicians, and are the source of some unresolved "wars on words" in the field of addiction treatment [30].

Parallel to the progress made, from the earliest detoxification attempts to the spread of agonist maintenance, and from the concept of substitution to that of relapse prevention and behavioural normalization, scientific knowledge about the process of addiction has become deeper and sounder, too. A large body of research papers has provided information about average and minimum effective dosages, and an oral dose-response curve (Ball curve) [2-5]. A precise range of effective blood methadone levels [19-21] has been defined, corresponding to a wider range of oral dosages, all converging on the same circulating values through either a normal, a slower or a particularly active metabolism.

Most studies have been performed on sample populations of heroin addicts with a variety of somatic and mental problems, so that the effectiveness of methadone treatment on a range of comorbidity situations was demonstrated through real clinical case histories. Lastly, specific research explored the use of methadone during pregnancy, in subjects with hepatitis, hepatic and kidney failure, and liver transplantation [22-25], HIV infection [6, 7, 12, 26, 28, 32], and dual diagnosis [31].

The history of methadone treatment provides a curious example of how the same category of substances (opiates) can be the source of a disease but also its cure; and of how an agonist effect on receptors may, in some cases, correspond to the antagonism of a disease induced by other cross-reacting substances.

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2.2

Enrolment and Termination

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1. Admission

A diagnosis of opiate addiction is in itself a valid reason for allowing methadone treatment, as this is the gold standard for a relapse-prevention approach (see table 1) and the safest kind of intervention in any perspective [1, 2].

A methadone maintenance programme can be handled in such a way that it becomes effective against a wide range of addictive pictures, which may vary in the severity of addictive symptoms and the typology of associated illnesses.

Methadone maintenance treatment (MMT) leads to significant improvement that covers a range of different initial degrees of severity and a variety of situations: shorter or longer disease history, first episode or multiple relapses, high tolerance or no tolerance to narcotics, addicts only and mentally ill addicts. MMT is useful too in implementing 'harm reduction' strategies [12, 14, 16, 17].

Common addiction-related somatic concerns are compatible with methadone maintenance, and are expected to improve during the course of a successful programme. Pregnancy constitutes a priority for enrolment [4-6], along with HIV infection and liver diseases [7-9]. Adopting a logical, research-based line of inquiry, the effectiveness of methadone treatment was first assessed for hardcore addicts [3]; by now it can be acknowledged to be the gold standard for the average addict. It can, in fact, be considered the first-line option for any degree of disease severity. In other words, younger addicts at their first episode of disease, and/or with a short disease history (e.g. less than a year) should certainly be enrolled in a methadone maintenance programme. It is unjustified to think of methadone treatment as a 'heavy' or a 'chronic' form of treatment (as if an acute, disease-healing intervention were an available option, anyway).

It would therefore be a big mistake to regard methadone treatment as a last resort, an extrema ratio, for those who have nothing to

Table 1. Feasibility of methadone treatment
Enrolment criteria: First episode of narcotic addiction Mutiple-relapse narcotic addiction Narcotic addiction with additional somatic or psychiatric concerns Narcotic addiction during pregnancy
Programme termination: Refusal of the setting or the therapeutic instrument Self-interested handling of methadone Violent behaviour against staff, or against other patients 'Harm reduction'-like handling of treatment Persistent criticism about methodological aspects Refusal to undergo standardized clinical evaluations

lose. In reality, any patient who is diagnosed as a narcotic addict should be offered the most reliable and effective option, with the aim of stopping and reversing the addictive pathophysiology and gaining symptom control with a relapse-prevention guarantee in the long term. To date, such a guarantee for full-responders is inseparable from the maintenance of an agonist treatment regimen.

The Enrolment in a methadone maintenance treatment programme should follow three criteria:

a) **Rapidity.** Any request for treatment must be followed by enrolment, once a diagnosis of narcotic addiction has been formulated. Waiting lists should be viewed as no more than an exception that may occur in the case of unexpected epidemics. No patient should be admitted, who makes it clear that he/she is applying for something radically different from agonist maintenance, or would like a special, unorthodox schedule to be planned for him/her. Apart from that, possible incompatibilities between the attitude of a patient and the rules of the programme can best be evaluated during the course of treatment.

b) **Specificity.** Subjects who express a generic request for help without showing interest in the basic principles of agonist treatment (craving control, relapse prevention and rehabilitation), should be referred to a harm-reduction facility. In other cases, those applying for methadone treatment, should not be parked in harm-reduction-based waiting lists, but be admitted quickly. Waiting in harm-reduction contexts may negatively influence a patient's motivation to receive treatment, due to the underlying ambivalence of addictive states. Conversely, subjects who have only a poor motivation to receive treatment may be helped by correctly run harm-reduction interventions to become motivated to undergo structured treatment and become compliant with its basic rules.

c) **Case-planning.** The diagnosis should be as detailed as possible, in order to allow classification of the patient in terms of all the known predictors of effectiveness. For some categories of patients, expected stabilization dose values can be formulated, together with the probable chronology and latency of therapeutic goals. In addition, ancillary and complementary facilities can be planned in advance, so that they are automatically resorted to in specific phases of the programme.

2. Treatment termination

Methadone maintenance treatment requires patients to adhere to a few rules, which are intended to allow them to achieve satisfac-

tory results in fighting their disease.

The rules are not intrinsically therapeutic, but they do allow a drug to produce its therapeutic effects. Generally speaking, the patient must never be allowed to dictate or suggest any therapeutic measure, not just for technical reasons, as in any other therapeutic context, but because of the nature of addiction. Addicts, when left free to do so, are quite likely to steer a structured treatment towards a flexible and extemporary intervention, which is collateral to addiction and is not therapeutic at all. On this basis, the violation or rejection of any treatment rule is a good reason for treatment termination [10, 15]..

2.1. Rejection of the therapeutic instrument.

When applying for treatment, the patient must be informed that the programme is founded on the scientific use of methadone, with the aim of keeping addiction under control and maintaining remission in the long-term, that is, preventing its natural relapsing course. No patient should be allowed to insist on receiving facilities not included in the standard treatment package, or to adopt other treatment programmes at the same centre, for example naltrexone maintenance or buprenorphine, against the physician's judgment.

2.2 Frequency of attendance.

The frequency of supervised administration is decided with reference to treatment stage and patient symptom status.

The purpose of daily attendance is to ensure that the prescribed dose is administered to patients, considering that patients cannot be relied on to guarantee this themselves. Reducing the frequency of attendance should not be perceived as a way of verifying patients' reliability or giving them greater responsibilities. The advantage gained by the requirement of frequent attendance during the early phases of treatment is that it allows the degree of addiction severity to be assessed on the basis of the patient's reaction to treatment supervision.

Irregular attendance, skipping days of administration, and announcements of unavailability at the centre during the times when it is open to the public, are all behaviours indicating a greater degree of severity, and may prove to be incompatible with the continuation of treatment. If flexible attitudes are adopted in dealing with patients who show poor compliance with attendance rules, the results are:

a) delays in intervening to combat the causes of behavioural disorganization and poor compliance - delays that are usually correlated with the degree of addiction severity or with concurrent destabilizing conditions (such as polyabuse);
b) in the case of the average addict, a failure to ensure regular exposure to the therapeutic drug.

2.3. Dose and duration.

Patients should be given clear information about the difference between "having a personal opinion" about how treatment elements should be handled and "being able to make a free choice" about one's condition. As regards opinions, patients are allowed to hold any kind of opinion, because the question of what a patient may think about the effectiveness of treatment has no impact on its outcome. However, opinions tend to change in response to improvements in addictive symptoms; in most cases, these opinions turn out to be products of an addictive way of thinking. On the other hand, patients are never allowed to choose how they will be treated, which is one of the physician's prerogatives. Apart from the lack of specific skills, it is predictable that an addict would be likely to evaluate available therapeutic elements in terms of addictive symptoms, which means, in practice, in the direction of relapse rather than clinical remission.

On the other hand, addicts are welcome to report personal data on issues of tolerability and effectiveness. Nevertheless, many patients are unable to do more than complain about

dose and duration as if these were side-effects of treatment or unacceptable risk conditions; this should never be mistaken for a limitation on further methadone administration or a threshold of tolerability. Patients should be plainly told to stop criticizing treatment before its outcome can be witnessed and assessed in the light of a craving-free way of thinking. Patients who oppose increases in doses and long-term maintenance so as to render treatment unfeasible should be discharged and referred to harm-reduction facilities.

2.4 *Violent behaviour*

An outpatient setting is inappropriate for patients who give rise to concerns over aggressive behaviours, threats or damage [15]. In any case, physicians should be able to avoid eliciting aggressiveness from patients, since methadone treatment is highly effective in dealing with feelings of rage and hostility, and even with aggressive behaviours. As long as the patient allows the administration of methadone in a supervised manner, treatment should never be refused, especially to addicts who are undergoing withdrawal. Also, criticism deriving from symptomatic attitudes that emerge in behaviours, including ambivalence towards treatment, should not be challenged as disrespect, but handled with the aim of achieving stabilization. A judgmental approach should never be allowed to replace statements and prescriptions.

The aggressiveness of addicted patients can mostly be prevented or controlled by means of agonist treatment, and levels of aggressiveness show a tendency to fall while methadone doses are being increased. Symmetrically, anger, hostility and violence commonly characterize states of opioid impairment, when tolerance is not counterbalanced by enough endogenous or exogenous stimulation. Otherwise, a patient's degree of aggressiveness may be raised by concurrent stimulant, alcohol or benzodiazepine abuse, especially when levels of opioid stimulation fall below the patient's tolerance level [13].

Violent patients, who cannot be permitted to attend a normal outpatient facility, should be advised to undergo inpatient treatment, with the possibility of resorting to compulsory treatment if necessary. Past violent behaviours against staff do not count as a reason for excluding any patient from future treatment perspectives.

2.5 *Persistent heroin use, or relapse into heroin use*

Neither of these situations justifies treatment termination. If fact, they both impose the need for an adequate treatment regimen, either in terms of longer-term maintenance, or of higher-dose stabilization. It would be paradoxical, besides being unethical, to terminate patients when they begin to display typical addictive symptoms, no matter how severe. Such a course of action would mean considering core symptoms of a disease as exclusion criteria for treatment continuation. It is true that addictive symptoms are behavioural in nature, and can be expected to create interference with treatment procedures, but this just means that compliance with treatment rules should be regarded as a major therapeutic target, prior to the pursuit of stable remission. Most physicians tolerate ambivalence and opposition to treatment to a certain extent, but this means they will tend to marginalize more severely ill patients from treatment settings because most of them show low levels of spontaneous compliance. Forms of discrimination like these are not acceptable on ethical grounds, and are not compatible with the general philosophy of medicine. As for the question of latency of response to treatment, no time limitation exists after which a positive response is no longer achievable, even if it is true that most patients can be effectively stabilized within one year. It follows that patients who are still using heroin after a full year of treatment should be retained in treatment unless no rehabilitative result or symptom reduction has been achieved. In other words, a partial response is enough to justify treatment continuation. A strategy of

increasing doses to the highest documented value should be taken into consideration before labelling the patient as treatment-resistant or a non-responder [11].

Methadone maintenance treatment is the core of rehabilitation, and its standardized use paves the way to scientifically pursued rehabilitation, sometimes with no need for further psychosocial efforts. It is definitely absurd to ask patients to keep their symptoms under constant review as an important requirement for a good outcome, so sidelining pharmacological treatment as nothing more than useful support. In this sense, it would be paradoxical to terminate treatment for patients who are not abstinent, ascribing the unsatisfactory outcome to feeble will-power or inadequate self-control, instead of providing the patient with adequate methadone dosing.

Some patients resist treatment rules by threatening that they will 'get a fix' if they are not allowed to handle treatment themselves, so violating the standard rules. In other words, some patients pose the question of whether they will continue to attend the clinic in a self-interested way, as an alternative to dropping out, or as a way of avoiding discomfort and subsequent drug use despite ongoing treatment. This way of reasoning and of challenging members of staff is symptomatic of severe addiction, and should not be considered a negotiable request. It should sound absurd to physicians that patients threaten to engage in the same kind of behaviour they asked treatment for in the first place, as if were up to them to choose whether they should use narcotics on an environmental basis. Patients are not free to use drugs, and it makes no sense to allow them to do so as if it were a reaction to unjust rules and permissible as their free choice. Physicians should therefore never feel responsible for ongoing narcotic use by patients who fail to comply with treatment rules.

Moreover, negotiating with patients would create the impression that staff are responsible for the continuation of treatment, rather than the patient. On that basis, staff would end up pleasing the patient in order to achieve the objective of getting him/her to attend the clinic, even if only to follow some unstructured, ineffective treatment procedures.

Negotiation is not the right strategy for achieving compliance, and thereby stabilization. Non-compliant subjects should, rather, be referred to harm-reduction centres, while allowing no room for a negotiation of methadone maintenance treatment into a harm reduction hybrid with no prospect of stabilization.

2.6. Clinical and laboratory evaluations.

Patients who refuse to deliver samples for urinalyses or undergo clinical examination are usually driven to do so by the strength of their addictive symptoms. Any such failure to comply with the rules should be prevented by adequate dose-increasing schedules, and it might partly be overcome psychologically [15]; in this way the craving is likely to fade, so leaving room for collaboration. To this extent, a persistent refusal to be tested may be tolerated, as long as patients accept increases in their methadone dose or having any take-home privileges suspended. As a rule, when craving is kept under control, the patient will not refuse laboratory testing.

2.7. Data collection.

Patients must give their informed consent for data collection and storage, which is needed for the safe and effective handling of their condition. Patients who do not allow staff to gather and keep records of their personal data should be dismissed from the programme and referred to harm-reduction facilities.

Any decision to terminate the programme should be explained to the patient, in the hope that they will change their mind and ponder their refusal to comply, bearing in mind the possible benefits of treatment termination from a programme does not imply that it will be impossible to make further attempts.

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2.3

The Phases of Treatment

I. Maremmani and M. Pacini

A Methadone Maintenance treatment programme consists of four successive phases: induction, stabilization, maintenance, medication withdrawal.

1. Induction phase

As the starting phase of MMT, the induction phase has two main aims, which can be differentiated in chronological order:

a) to extinguish possible withdrawal symptoms at treatment entrance, by a dosage which depends on the current level of acquired tolerance to opiates. This aim is usually achieved in the first few days, sometimes in as little as 24 hours.

b) to increase the dosage up to a value which is beyond the reach of higher narcotic doses, and provide a narcotic blockade by the down-regulation of binding sites and massive competition with those still available.

This second objective can be achieved by increasing the starting dosage by a maximum rate of 25% every four days. Narcotic blockade starts at around 60 mg/day, even if this level is incomplete, because it can be overcome by higher narcotic (heroin) loads.

The starting dosage for withdrawal control usually falls inside a range of 20-60 mg/day, that is, below the threshold level for narcotic blockade. Some subjects, however, require higher dosages, of as much as 100 mg/day: despite this, induction should proceed to higher dosages for those subjects, too, since blockade should be based on the individual's recent tolerance to street narcotics, not to an average value. For heavy users, therefore, narcotic blockade must be able to guarantee full blockade against heavy loads of street narcotics. Heavy narcotic users do, in fact, resort to very high loads in order to keep feeling the 'rush', beyond the control of withdrawal, whereas an addict with low tolerance can obtain the same effects with lower narcotic loads. As a rule, therefore, the final level of tolerance to opiates as a result of induction will be higher than

whatever it was at treatment entrance.

Some safety rules should be borne in mind during the induction phase, as brilliantly pointed out by Payte [24].

Safety rules are important, since a majority of methadone-related deaths among people who are in treatment take place during the first ten days of methadone administration [2, 5, 29].

First of all, the patient's level of tolerance should be defined, and his/her daily condition monitored until blocking dosages have been reached without adverse events. It should be remembered that methadone blood levels and peaks rise steadily during the first few days, until a steady-state kinetic pattern has been established, even when the dosage is kept stable.

For non-tolerant subjects, the starting dosage is 10±5 mg, whereas for current users whose tolerance is unknown, one can start with 20±5 mg. If the patient's tolerance is known, starting dosages can be 20-40 mg; if withdrawal symptoms persist or worsen, these can be repeated at 2-hour intervals (when the level of methadone in the blood is peaking). The average anti-withdrawal dose is about 30 mg. However, if, on the first day, a dose is administered all at once, without being titrated on a clinical basis (withdrawal symptoms at 2-hour intervals), it may be effective on the first day, but may still lead to intoxication when repeated on the second or third day. The final methadone blood levels will rise steadily during the first few days, filling the gap between tolerance balance and lethal intoxication. As methadone is a slow, long-acting opiate, the development of intoxication is not immediate but gradual, and accumulation is expected before the steady state condition is reached. Also, signs of withdrawal are easier to recognize than signs of intoxication. Although coma is the eventual outcome of opiate intoxication, the pre-coma phase may be characterized by insomnia and psychomotor excitement, which may lead to it being mistaken for withdrawal, so prompting the administration of extra methadone.

Increasing the dose from the first day after withdrawal has been verified is, needless to say, extremely hazardous. If a patient reports feeling "completely well" throughout the first 24 hours, the dose probably exceeds his/her tolerance level. If the patient feels "wonderful", or even "better than ever before" after the first dose, intoxication may follow the administration of similar dosages on the following days. Euphoria following first-day methadone dosage should therefore be regarded as a warning for possible intoxication to come.

When patients are not tolerant (for example, in the case of patients discharged from prison, after detoxification and in a drug-free regimen) the induction schedule should be particularly cautious, with smaller increases at longer intervals (applying a minimum of five days). Safety rules for induction are summarized in table 1.

To exemplify, if a non-tolerant patient is given a dose of 30 mg on the first day, and the same dose is repeated on each of the next few days, the risk of methadone-related death by breath arrest will be at its highest on the 4th and 5th days (when methadone peaks before the onset of the steady state pattern). In other words, a single 30 mg dose is not by itself lethal to a non-tolerant subject, but the repeated administration of a non-lethal dose for four or five days may prove to be lethal [6].

Once a steady state has been established, increases in dosage are no longer hazardous, as long as the suggested increases specified above are respected.

Also, it is not advisable to administer the dose all at one time, on the grounds of the apparent severity of withdrawal: higher scores on withdrawal scales do not always correspond to higher levels of tolerance. Higher levels of withdrawal discomfort cannot be viewed as a good reason for challenging the patient with higher methadone dosages without titration (e.g. 60 mg as a single dose). Also, while titrating the anti-withdrawal dose, urinalyses can reveal the presence of any other substances (e.g. alcohol and benzodiazepines) which the patient could have become tolerant to, or which the patient could currently be intoxicated by.

The induction phase is immediately followed by the stabilization phase. A narcotic

Table 1. Methadone treatment. safe induction recommendations
Early Induction
Early dose adjustments to reach the "Therapeutic Window" as determined by established opioid tolerance
"The Comfort Zone". Increase dose daily until patients comfortable during methadone peak levels (3-8 hours after dose), then hold dose for 3-5 days to reach steady-state before further dose adjustments
Remember steady-state pharmacology
Effect of **a** dose IS NOT determined by clinical presentation at 24 hours
Initial doses WILL NOT "hold" for 24 hours
Effect of a given dose is based on status at 3-6 hrs. The patient doing well at 3-6 hours does not need a dose increase, even if showing signs/symptoms of withdrawal at 24 hours. If patient thinks an increase is needed, repeat dose from previous day and ask patient to return in 3-4 hours for further assessment
Any sign or symptom of over-medication during early induction requires a dose reduction
Beware the subtle signs/symptoms of overmedication: feeling good, extra energy, staying awake to work, etc
Patients may need more time not more medication
From Payte (2004): Heroin Addict Relat Clin Probl 6(1) pag. 37

addict induced by up to 80 mg/day of methadone usually still craves for narcotics. His/her craving may have become even worse than before, and be reported in a special way by the patient, who has become aware of having been led into a condition of reduced sensitivity to opiates. Addicts who were still feeling their rush, maybe at low dosages, may have found their craving exacerbated at blocking dosages, and may react by increasing their attempts to handle treatment themselves. The transition from a blocking to a stabilizing dosage should therefore be implemented as quickly as possible, in order to minimize dropout rates. Because of the nature of addiction, the patient will insist on dose reduction, in order to be able to feel the effects of narcotics without having to spend much. The physician must reject this reaction, which is an expression of craving, so as to achieve stabilization. Bearing this aim in mind, psychoeducational sessions may be a useful way of making the patient aware that the physician too is mindful of the presence of craving, the rising discomfort caused by the absence of narcotic euphoria, and the attempts being made to keep one's dosage limited or tapered back - and that opposition to demands for dose reduction is the exit route out of craving, although the patient may feel sceptical about it.

Therefore, the non-compliant behaviour of the addicted patient should not be disapproved of as a boycott on treatment, but be challenged as one target of the treatment itself.

2. Stabilization phase

Once blocking dosages have been reached, treatment proceeds with the aim of extinguishing addictive behaviours and avoiding relapses [23]. Stabilization is enough, despite the apparent short-term interruption of narcotic use, since core addictive symptoms are still present, and need to be counteracted by further therapeutic means [11]. In fact, an addict who is under narcotic blockade but is still craving for narcotics will not automatically work for rehabilitation, or stick to the aims of treatment,

but will tend to drop out or break treatment rules until stabilization has been achieved.

A minority of addicts become stabilized as soon as they take blocking dosages, even if these are below 60 mg/day, but as a rule one will have to increase the dosage after successful induction. As long as they receive anti-withdrawal dosages, patients mostly feel better and gradually lose their urgent motivation for treatment. When moving on to blocking dosages, many patients will start feeling like leaving the programme, since their craving will overwhelm their feeble motivation for treatment. This makes it imperative that clinicians should not overrate the strength of motivations to treatment as expressed during withdrawal and induction, or mistake them for an actual insight into the nature of the disease. When reaching the range of blocking dosage, the transition to anticraving dosages should be achieved as quickly as possible.

In the past, the only feasible way to stabilize a patient was to observe his/her behaviour day by day, and adjust treatment elements on a case by case basis. It was possible to deepen the knowledge about the issues of stabilization dosage and time required for stabilization. In the present situation, as soon as such items of knowledge have been acquired, they should be applied, in order to shorten the latency for stabilization and increase dosages automatically to certain thresholds, instead of proceeding step by step. In other words, for a number of different categories of subjects, stabilization can be planned as early as treatment entrance.

In the complex patterns of psychic impairment of addicted people, craving for narcotics is a constant, but it may not be the only destabilizing factor. Cravings for other substances and other mental disorders may play a significant role, too. Besides this, subjects with little or no residual craving for narcotics may still be in a mental condition which does not favour, or actually impedes, the treatment process. For instance, some psychiatric disorders may keep individuals completely unstable despite their continued abstinence from opiates determined by anticraving treatment. In some cases, significant psychiatric symptoms are evident from the beginning (e.g. psychomotor excitement, delusions or hallucinations). In other cases, psychiatric disorders will emerge later on, or will only become evident after the remission of acute intoxication. This often occurs with affective disorders, which may comprise persistent dysthymic states (termed 'long-term withdrawal') and which only improve after several months. Another case is that of intermittent, cyclic affective disorders which may become evident during apparently successful stabilization, and suddenly hamper the rehabilitation process. A manic phase of a bipolar disorder may develop after months of opiate abstinence and treatment compliance; to illustrate this, it may be pointed out that the consequences, behavioural disruption and lack of insight brought about by such phases are no less severe than those brought on by addiction [13, 14].

On practical grounds, polyabusers are likely to need higher stabilization dosages [15]. For cocaine abusers this may be due to the useful antagonist effect of methadone towards the behavioural toxicity of cocaine. Alcohol abusers, on the other hand, have a spontaneous tendency to stabilize at lower dosages, probably because of the synergy between alcohol and methadone in reducing craving for opiates. This synergy is only apparent, however, because it is not equivalent is terms of rehabilitative potential: alcohol abusers may stay in treatment and remain abstinent from opiates, but will probably fail to return to a normal level of functional efficiency, despite partial improvement. Moreover, ongoing alcohol use, even when not in an addictive mode, is a risk disposition for alcoholism. So too, cocaine users may find that the unpleasant effects of their addiction are masked by methadone, but the unfavourable effects of their cocaine-seeking behaviours, including the risk of developing a full-blown cocaine addiction, will not be extinguished [13].

Dual diagnosis subjects need higher stabilization dosages, and take longer to reach such dosages, beyond the time technically required to gradually increase doses [13]. Our impression is that the typical delayed recurrence of manic or mixed states in these patients does not allow their level of stability to be mea-

sured early in the course of stabilization. As a result, the dosage cannot be increased earlier, while dose adjustments can only be made after symptom-free observation intervals, unless contingency planning has been undertaken from the outset.

3. Maintenance phase

The MMT philosophy is centred on the goal of its maintenance phase, which is to preserve stabilization. The philosophy of maintenance comprises two principles, the first static and the second dynamic. The static principle is to continue using the combination of therapeutic elements which has led addictive symptoms to extinction, and has allowed the achievement of a satisfactory level of personal and social functioning. Rehabilitation is the dynamic aspect. The reconstruction of whatever has been obstructed, damaged, hampered or cancelled by addiction does take place on the foundations of ongoing treatment. Ongoing treatment is the only form of intervention able to ensure that the circuit between psychosocial functioning and addiction-related cerebral damage operates positively, by keeping the pathophysiology of the disease under control ("detached"), and avoiding symptoms that might emerge and interfere. As a result, the individual is free to decide and evolve. Rehabilitation, therefore, does not become a definitively acquired result or an achievement, but should be considered as a reversible result kept feasible by the maintenance of treatment, at least over the first few years. Rehabilitation does not correspond to a situation of positional equilibrium, but marks a balance between two active drives, one towards relapse (the underlying disease) and the other towards remission (ongoing treatment).

Even a short-term interruption of treatment is therefore bound to result in a reactivation of the circuit between psychosocial functioning and the altered brain, in a way that rehabilitation will be counteracted by whatever instructions are given by the addictive brain [26-28].

Maintenance corresponds to the concept of therapeutic dependence, to be interpreted in a positive way, as a therapeutic tutoring of cerebral functioning through which rehabilitation can proceed spontaneously [7, 8].

During the maintenance phase all facilities which favour, boost, or quicken rehabilitation are welcome. The same interventions which would be useless for street addicts, or for patients at an earlier stage in the course of treatment, become potentially useful once stabilization has been achieved. It should be borne in mind that rehabilitating a patient does not mean shifting the focus of treatment from pharmacological to psychosocial grounds; it just means a continuing concentration on what has been made possible by ongoing pharmacological treatment. In other words, the goal of rehabilitation has a wider scope than just symptom control and relapse prevention, but does not replace these. In a chronic disease, in fact, no discontinuation of treatment goals is possible: an integrated treatment programme will always, before and during rehabilitation, rely on a bio-pharmacological basis [10, 16]. Later psychosocial interventions on stabilized patients must be thought of as supplementary rather than complementary. Lastly, a number of addicts may be not in need of any rehabilitative effort from the outside, but be able to benefit enough from basic treatment to enter into a spontaneous process of self-directed rehabilitation.

3.1 Duration of treatment

Generally speaking, treatment can never be labelled as no longer necessary, because there is no available time limit at which the likelihood of spontaneous relapse falls to zero [3, 9, 25]. When evaluating whether treatment can be suspended, one should consider the following:

1) therapeutic dependence is by all means preferable to disease chronicity;
2) remission by treatment is far more likely than spontaneous remission (which is an exception);
3) for untreated subjects, premature death is the most likely way for addiction to come

to a spontaneous end.

Although there is no predefined term for treatment to stop, it can be said that a minority of treated subjects (5-20%) are found to be dependent on treatment after as long as 10 years of disease remission. The majority usually accomplish the phase of medication withdrawal within 10 years, running only a low risk of relapse.

Duration of treatment is crucial for success. The longer the treatment lasts, the farther the person proceeds in terms of rehabilitation. Even when no immediate relapse takes place, one disadvantage of premature treatment withdrawal is often what could be labelled as psychosocial 'freezing': the subject fails to make any further progress on psychosocial grounds; as a result, levels of perceived stress increase, and the subject is held back. Likewise, the quality of life is limited and nothing is more than satisfying.

Our advice is to avoid withdrawing subjects from treatment (or decreasing their dosages) in any of the following situations:

1) Addiction is in remission and the patient has started rehabilitating.
2) Addiction is in remission and rehabilitation has already been achieved to a certain extent, but new and stressful factors are emerging, even if these may be due to the enrichment of social life and an increase in productive potential. Subjects bearing the burden of acquired opioid damage may feel distressed by circumstances which stimulate normal subjects, such as new responsibilities at work or social challenges.
3) Addiction is in remission but narcotic-related stimuli are well represented in a patient's daily life environment.
4) Addiction is in remission, but the subject maintains a low productive potential, and complains about low energy and intolerance to stress (in this case, a dose increase or antidepressant treatment should be considered).
5) Addiction has been in remission for years; methadone maintenance only, in the absence of additional psychotropics, has been marked by the stable remission of severe psychiatric disorders along with addiction.

4. *Medication withdrawal*

See chapter about Medically-supervised withdrawal.

5. *Treatment control measures and treatment rules*

Frequency of attendance is usually correlated with the fulfilment of therapeutic goals [1, 18-21]. When patients are in a critical condition, they may need daily checking, and during the first few days of treatment the effects of medications should be checked frequently, if necessary more than once a day during the early stages of induction.

Later on, daily attendance may still be functional to treatment, since addicts tend to self-handle medications regardless of therapeutic goals. The main risk is not the diversion of methadone, but that the patient is not going to take the prescribed doses. Addiction, like the most other psychiatric disorders, but unlike other somatic illnesses, is characterized by no or little insight, so that the patient is incapable of behaving in a way that favours a good outcome. The truth is that addicted patients will welcome any anti-withdrawal treatment or short-term measure to improve their present discomfort, but will fail to adhere to any structured, long-term intervention, or will try to discontinue it as soon as they feel any improvement. On the whole, addicts assume treatment is useful for 1) buffering withdrawal; 2) restoring their sensitivity to opiates and eliminating physical dependence, so reducing the waste of money spent to feel euphoria from narcotics; 3) getting help when conditions are critical, such as moments when they have run out of money and can no longer rely on social support.

The frequency of attendance should therefore depend mainly on the severity of addic-

tive symptoms. In relation to the phases of treatment, frequency should be:

a) **daily.** This is typically required during induction. The involvement of significant ones in the administration of daily doses may allow patients to attend less frequently than daily, but not before blocking dosages have been achieved. Opening hours of treatment units should not be limited to 9 to 5, let alone limited to a few hours early in the morning, as often happens in some countries. Once blocking dosages have been reached, attendance should still be required daily in the following situations:
   1) The patient has a low level of compliance (skips days, insists on dose reduction, refuses to swallow the entire dose in front of the staff or throws up after leaving the room).
   2) The patient used to be stabilized, but has since relapsed.
   3) The patient is a polyabuser of synergic drugs or has current severe psychiatric symptoms that need daily checking.

b) **twice a week**. This may be a reasonable compromise to allow working activities and a productive life. Actually, any service will allow a take-home privilege from the start, at least for closing days (Sundays), so initial attendance is less than daily. Our view is therefore that there is no real need to pass from daily to weekly attendance through an intermediate twice-a-week phase.

c) **weekly.** Patients are given take-home doses for six days after taking their methadone dose in front of the staff on the day of delivery. This is only advisable when compliance has been satisfactory for some time and stabilization has been achieved. Administration of the entire methadone dose in front of the staff once a week is the simplest way of checking that patients are tolerant to that dose, which means they have been taking that amount during the past week. It should be noted that this kind of test is behavioural rather than pharmacological, since the patient is not required to continue waiting throughout the expected blood peak of methadone (which lasts 2-6 hrs): what clinicians need to verify is whether the patient refuses to take the prescribed dose, which would mean he/she has not been taking it (losing tolerance), and wants to avoid overdosing or having blood levels raised up to a blocking level on that day. Refusing to take the entire methadone dose in front of the staff should be viewed as a symptom of addiction.

Take-home may be suspended in the following cases:

a) The patient misses appointments for delivery, just skipping a couple of days or an entire week, which clearly means he/she is not taking as much methadone as prescribed.

b) The patient rejects prescriptions, insists on taking lower dosages and/or withdrawing the medication as soon as possible. Reducing dosages in take-home regimens is acceptable when patients have been stabilized for a long time, but never because the patient has requested it. Conversely, if a patient insists, at any stage, on reducing the dosage, that should be regarded as a risk disposition to relapse, and may even justify a decision to return to a supervised daily administration regimen.

c) The patient diverts take-home methadone, selling it or just giving it to friends. In such cases, it is preferable that the patient should not be challenged with legal issues. Physicians should remind patients that if any behaviour is legally censored, that goes against prescriptions to the patient: more specifically, the medical reason for suspending take-home is not because the methadone was sold, but because that stands as evidence that the patient had not been following prescriptions.

In conclusion, take-home may be suspended when patients behave in such a way that they can no longer be considered eligible for take-home (see chapter).

d) **less than weekly**. In this case, general practitioners can directly provide patients with monthly prescriptions, allowing patients to receive supplies of methadone from pharmacies. As for weekly take-home, patients need to have been stabilized for a long time. The patient should be requested to take methadone under the prescribing physician's supervision on the day of prescription delivery, in order to be able to check compliance through the behavioural testing of tolerance. Patients who no longer take methadone should be followed up regularly, in order to prevent them from relapsing after not being in touch for months, which increases the likelihood of a severe relapse. Moreover, the worsening of psychosocial adjustment could be monitored regularly, and agonist treatment restored if necessary, without leaving the patient with the exclusive responsibility for his/her problems, with only a poor prospect of rehabilitation.

6. Methadone maintenance in different settings

Stabilized patients can be followed up in a variety of settings: psychiatric in- and outpatient units [15], addiction treatment units, private practices, methadone clinics, residential centres [4], jail [12, 22], general practice [17].

Some settings are inappropriate for certain stages, before the achievement of stabilization, because some basic therapeutic elements may be unavailable. Generally speaking, the best solution for the treatment of addictive diseases is a dedicated clinic, employing a staff with skills in addiction medicine and psychiatry. The presence of physicians with other skills, such as infectivologists, allows patients the benefits of a better therapeutic setting, applying the principle of one doctor's shopping. Further staff specialized in steering the process of rehabilitation is advisable, though this may be helpful to stabilized patients only.

Patients with special health concerns may be referred to specialized centres for their individual needs.

What is really missing in the field of addiction treatment is the availability of facilities with first-aid units linked to residential centres, which would meet the needs of homeless addicts who cannot be stabilized effectively in the street.

In other circumstances, coercion may be needed to satisfy the patients' request for treatment, so that jail or psychiatric wards may be the only suitable settings. Patients may be admitted to compulsory treatment and discharged in a free environment after induction has been accomplished.

On the other hand, some settings have little impact on the therapeutic course: short-term hospitalization, for example, does not make it possible to reach a high level of tolerance, and does not increase the likelihood of retention in treatment. Waiting lists to enter residential centres, in the absence of methadone treatment, are equivalent to a temporary and unjustified lack of treatment. One may say that methadone treatment is not the rule within residential centres (so-called therapeutic communities), so patients will probably have to be weaned off methadone before admission or immediately after admission. The same happens in the case of jailing. A drug-free condition, and a consequent admission into a therapeutic community, often correspond to what families "fancy" and patients prefer, when they wish to lose their acquired tolerance to opiates or 'take a breather' on psychosocial grounds.

Requiring the withdrawal of treatment as a criterion for admission into a therapeutic community is in conflict with any claim to a therapeutic perspective for addiction.

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2.4

The Issue of Dosage

I. Maremmani and M. Pacini

The complex of addictive symptoms, comprising the affective, the cognitive and the behavioural, may be controlled by a range of different methadone dosages for different individuals, or for the same individuals at different times or stages of their addictive history [1].

A minority of subjects can be stabilized early on, with dosages below 60 mg/day, whereas a majority can be stabilized on a dosage ranging between 60 and 140 mg/day, depending on the severity of addictive symptoms at the time of treatment initiation [9].

Other subjects require higher dosages, in some cases of as much as 1200 mg/day [13, 18].

Lastly, some subjects require minimal dosages (e.g. 10 mg/day) to be maintained in the long-term. This is needed to allow them to stay functional and avoid relapses, even when no worsening of clinical conditions and no relapse took place during a gradual tapering from higher dosage levels [11, 12]. Better said, the variability of dosage should be referred to methadone blood levels, that is, the biologically active portion of administered dosages [5, 6]. Since methadone blood dosing is not performed as a routine (as it is in the case of lithium and some anticonvulsants), and can be replaced by 'on-the-spot' clinical evaluations, almost all available data are expressed in terms of oral dosage, leaving out methadone pharmacokinetics such as intestinal absorption and P450-related liver metabolism. Studies carried out to investigate the correlation between oral dosages and expected blood levels indicate that higher dosages depend on a condition of rapid liver metabolism: as a result, subjects needing two-to-ten times as much as the average oral dosage turn out to have the same expected blood levels as those requiring average-to-low oral dosages. Indirectly, in the absence of direct blood dosing, a condition of rapid metabolism can be inferred from the absence of expected metabolic interactions which would increase blood level, or lead to reports of symptoms indicative of emerging withdrawal before daily administra-

tions (e.g. insomnia, sweating, shivering, runny nose, and yawning early in the morning, in cases where administration is scheduled for the morning). The average effective methadone dosage, that is, the maintenance dosage, is around 100 mg/day (± 40 mg). The need to employ dosages over 140 mg/day is far more likely than a stable response with lower-than-60 mg/day dosages. On clinical grounds, the terms 'high' and 'low' dosages are meaningless unless in comparison with one another. The terms 'higher' and 'lower' may be used to indicate how a dosage value can be ranked in comparison with the effective average.

Beyond that, dosages can be classified as 'lower-than-adequate' or 'adequate', in terms of their impact on the course of the disease (non-stabilized or stabilized, respectively), at least up to the highest documented value of 1200 mg/die.

1. Anti-withdrawal dosage

The administration of dosages of up to 60 mg/day is usually successful in buffering, or preventing, symptoms of withdrawal, in case the level of tolerance to opiates can be roughly quantified. In (typical) circumstances, where an individual's present tolerance to opiates cannot be estimated, the initial dose should not exceed 20 mg. If withdrawal symptoms persist or worsen after two hours, the same dose can be administered a second time, and so on at two-hourly intervals until withdrawal symptoms start to become less severe. To facilitate such decisions, physiological parameters (consciousness and wakefulness, myosis and breath rate) should be recorded from the beginning and re-checked at expected peaking times after each single administration (these are given every two hours, approximately). It should be borne in mind that, when a dose is repeated by using more than just one dose on the same day, the final peak induced is higher than in the case of the earlier dose(s), due to a cumulative effect. No further dosage is required, and none should ever be administered, unless withdrawal symptoms persist or continue to worsen [21, 22]. Such an administration schedule is effective and has proved to be the safest in managing acute withdrawal within the first 24 hours. From the second day on, the cumulative dose applied on the first day can be safely administered every day in the morning.

In cases of ongoing or upcoming withdrawal from known dosages of methadone, a patient can receive his/her habitual dose, unless one or more days have passed. If one day has passed, one can administer half as much as the habitual dose, gradually raising the dose until the original value is reached within the next three days. If the subject has not been taking any opiate for two days, one third of the original methadone dosage is the advisable starting dose, followed by a gradual increase up to the original value within 5 days. If three or more days have passed since the last known administration, the safest option is to employ the acute withdrawal first-day schedule. If there has been recent exposure to various different opiates (e.g. if heroin is being used during methadone maintenance, or if methadone is being self-administered due to heroin unavailability) the safest rule is to assume that the individual is tolerant to the dose of the weakest opiate habitually administered (methadone, or heroin with respect to the previous examples) [21].

2. Induction dosage

The medically assisted raising of tolerance levels (induction) is the phase leading from a state of balanced somatic tolerance to opiates towards the extinction of relapsing behaviour. Induction may start right after the buffering of withdrawal, or directly in the initial phase of treatment, if no withdrawal is expected (i.e. with non-tolerant treatment-enterers).

Since peak blood levels of methadone tend to rise during the first few days, before tolerance has had time to develop, subsequent dose increases should not be made more often than weekly.

For as long as the first three days after

the resolution of withdrawal, it is advisable not to increase the dosage further. At a later stage, dose increases can be as high as 10 mg per week. Usually, patients who are tolerant to higher dosages can have their dose increased safely by higher amounts (20 mg per week). On the other hand, if patients are tolerant to lower dosages, especially in the presence of any factor acting in synergy with opiates (e.g. alcohol or benzodiazepines) rates of increase can be kept lower (5 mg per week). The crucial leading general concept is that the equivalent 'excess' corresponding to equal differences in oral dosages is inversely related to the level of baseline tolerance.

For subjects who are non-tolerant to opiates when starting treatment, the induction phase should proceed very cautiously, never exceeding the low threshold increase of 5 mg per week.

Induction should be interrupted when there are symptoms of opiate intoxication or adverse events related to methadone (e.g. itching, cholestasis) [22].

A patient entering the blocking range (usually above 60 mg/day) may report an undefined form of discomfort due to the interference with heroin's expected effects: a situation of this type does not justify any dose-reduction or limitation of scheduled dose-increases.

Needless to say, ongoing opiate use while on methadone treatment does not increase the risk of overdosing, since opiates are competitive at the same receptorial binding sites, and there cannot be any kind of additive effect between them. On the other hand, the risk of overdosing through the self-management of an abused opiate is curtailed both due to competition with methadone and to increased tolerance (cross-tolerance). Even when a subject self-administers higher drug dosages in order to overcome his/her acquired tolerance to methadone and feel the 'rush', the risk of overdosing is comparable to that of an opiate-naive individual who takes average street doses of the drug.

It is unsafe to administer methadone at increasing dosages together with other potentially synergic agents or metabolic competitors, because this will result in unpredictably higher methadone blood levels and a greater likelihood of methadone intoxication.

3. Stabilization dosage

When the patient has been kept abstinent from street opiate use for at least six months, and is free of major psychopathological symptoms, one can refer to the highest methadone dosage taken for at least two weeks in that period as the stabilization dosage, meaning that the patient is stably guaranteed against the risk of relapse by treatment at that dosage.

The time needed to reach the stabilization dosage varies; it is, predictably, longer for higher dosages. It should be noted that some patients, such as those with a dual diagnosis for DSM-IV TR axis I mood disorders, take a particularly long time. Moreover, some patients may need to have their dose adjusted on account of somatic or cerebral changes (e.g. increased body mass index, pregnancy, stressful life events, or, alternatively, because of quick progress in rehabilitation and a return to social life). The outcome is that a stabilization dosage can be interpreted as a stable target to be pursued through the use of a flexible dosage. In fact, the goal of maintenance (see next paragraph) is to preserve and restore stabilization, mainly by adjusting pharmacological treatment [21].

4. Maintenance dosage

The ultimate aim of maintenance mirrors one primary reason for treatment initiation, that is, individual and social adjustment. As a result, ongoing rehabilitation, even beyond the level recorded before the onset of the disease, does justify continuation of the maintenance phase. The loss of individual and social functioning during methadone treatment, even when this occurs in the absence of full-blown psychopathology or relapse, should be interpreted as signs of inadequate dosing, and lead to adaptation of the stabilization dosage [15].

5. Dosages in relation to phases and pharmacology

As a rule, the anti-withdrawal dosage is lower than the stabilization dosage, although the gap is extremely variable. The blockade of a street opiate's effects usually corresponds to a threshold of 60 mg/die of methadone, and becomes stronger at higher dosages [2-4]. Narcotic blockade is therefore likely to start taking effect at anti-withdrawal dosages, before a full anticraving (stabilization) dosage is reached. Independently of this, a small minority of narcotic addicts stop using street opiates in the absence of narcotic blockade (below 60 mg/day), which indicates that craving suppression can be achieved directly, without interfering with the effects of self-administered narcotics. In any case, the interference with narcotic effects achieved by a heightened tolerance (i.e. by induction on full agonists) is far more effective than that granted by antagonists. The induction of high levels of tolerance to opiates, in other words, is crucial for narcotic addiction treatment to be successful. For some addicts, who are tolerant to multiple synergic drugs (e.g. opiates and benzodiazepines), anti-withdrawal dosages tend to be quite higher, so that they may already be in the blocking range. In order to rule out any confusion arising from baseline withdrawal, subjects should first be 'detoxified' as a preliminary to induction into methadone by using slow dose-increasing schedules. In approaching the average patient, anti-withdrawal, blocking and stabilization dosages are best reached sequentially, through gradual dose increases.

6. Principles of good clinical practice

6.1. Categories of patients who normally require lower dosages:

a) patients with liver or kidney failure. It should be borne in mind that patients with chronic liver diseases are not expected to metabolize methadone to a lower extent than healthy subjects, so much so that subjects with chronic hepatitis C require higher methadone dosages due to an acceleration of the liver metabolism [20].
b) patients who also take drugs which raise expected methadone blood levels [10].
c) patients who request a reduction in their dose after years of successful maintenance, in the absence of any narcotic use, though minimal. Such patients may have their dose tapered to lower values and still maintain a satisfactory level of individual and social adjustment [17].

Patients who do not tolerate effective methadone dosages should be directed to buprenorphine maintenance. The combination of sub-effective methadone dosages with ancillary facilities, such as psychosocial treatment or psychotherapies, though potentially useful, is not the best choice, since the latter do have a significant impact on rehabilitation when core symptoms are under control due to pharmacological treatment [23].

The patient's request to keep dosages low despite the presence of addictive symptoms, or a past history of good response to lower dosages, is not a criterion for avoiding the employment of average effective dosages.

Pregnancy is by no means a good reason for using lower dosages; the induction of a pregnant narcotic addict into methadone should follow the general rules [7, 8].

6.2. Patients requiring higher dosages

As already mentioned, patients who consume high amounts of street opiates require higher withdrawal dosages, and, as a result, higher stabilization dosages. Moreover, some categories of patients are likely to require higher stabilization dosages regardless of baseline levels of withdrawal. Knowing the target dose in advance makes it possible to proceed by adopting a dose-increasing schedule without wasting time, so shortening the time needed to

achieve stabilization.

a) Patients with a dual diagnosis for mood disorders or psychotic disorders [14, 16, 19];
b) polyabusers;
c) patients treated with drugs which accelerate methadone's liver metabolism [10].

6.3. Dose increases

The following situations require increases in methadone dose:

a) patients who report gathering extra methadone on the black market. Increasing the patients' dosage, contrary to what one might think, leads to a fall in the demand for methadone outside therapeutic contexts. Moreover, an increase in methadone employed for therapeutic purposes will result in a reduction of illegal methadone employed for non-therapeutic practices. Methadone holds no spontaneous appeal to narcotic addicts, but it may be resorted to occasionally by them to buffer withdrawal, or to detoxify in order to be able to start again on cycles of euphorizing narcotic use. When self-administering methadone for non-therapeutic purposes, addicts typically use low dosages, falling in the 'anti-withdrawal range';
b) patients who still use heroin, although less often than before;
c) patients who report craving, or behave as their aim were to increase the likelihood of their being offered the drug, or be able to purchase it, even when no actual relapse has taken place yet;
d) patients who are being treated with a drug, or drugs, which accelerate the methadone metabolism;
e) pregnancy, beyond the sixth month.

6.4. Dose Reductions

The following situations may justify a reduction in methadone dose:

a) patients who start treatment with a drug that inhibits the methadone metabolism during the treatment period;
b) medically supervised withdrawal (see chapter).

On the basis of current trends, unjustified dose limitations or reductions can be said to be considerably more likely than unjustified dose increases. Moreover, the risk of unnecessary dose increases, unless too steep, are limited to a few side-effects, whereas the use of inadequate dosages or the premature reduction of dosage may favour a relapse, or hamper the process of rehabilitation.

The following cases of dose reduction or limitations can be considered as malpractice, since they loom as a self-justifying aim:

- reduction of the stabilization dosage before a two year maintenance period has elapsed;
- reduction of dosage in cases of persistent, though occasional, narcotic use;
- reduction of dosage to satisfy a patient's request;
- reduction of dosage before full rehabilitation is achieved;
- reduction of dosage in dual diagnosis patients stabilized by methadone monotherapy, with a history of refractoriness to standard psychiatric therapies or in the absence of other potentially effective psychotropics (it is worth noting that the subtraction of methadone treatment, with the aim of replacing methadone with another psychotropic on the grounds of narcotic addiction control, is never advisable).

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2.5

Long-Term Perspectives

E. Trogu and P. P. Pani

1. Premise

Once addiction sets in, even if a late spontaneous remission cannot be excluded, it is likely to last for several decades. A variety of factors are relevant to the initiation of opiate narcotic use. Once a person has experienced the effects of illegal narcotics, an evolution towards abuse is possible, and one probable outcome is addiction. Out of 10 individuals who try heroin, 3-5 become addicted at some stage. Once addiction has developed, periods of active use alternate with drug-free intervals which may continue for decades. Addictive symptoms are directly related to as many as 20-25% of the deaths of narcotic addicts.

Addiction is a chronic disease:

- It is characterized by a set of commonly shared signs and symptoms, regardless of race, personal details and socioeconomic variables.
- It has a relapsing course, which, in the absence of treatment, must be considered its standard prognosis.
- It implies a high level of subjective discomfort and an incapacity to behave in line with one's intentions, especially as far as pleasure, motivation and self-stimulation are concerned.
- It is characterized by an altered state of the brain's opiate metabolism, which tends to resist healing, even after a long period of stable abstinence from narcotics, as shown by Kreek and colleagues [17]. The main clinical element mirroring this kind of damage is craving, which is the pathological equivalent of desire.
- It 'runs in the family' in a way homologous to, or displaying indirect indicators shared by, various forms of abuse/addiction impulsiveness and affective instability.
- Standardized treatment can modify the natural course of the disease, regardless of other factors.
- Its distinctive clinical picture is 'craving', which is responsible for a high percent-

age of post-detoxification relapses.

Any rehabilitative effort, even if strong and long-lasting, will be ineffective, if applied alone, in preventing relapses. On the other hand, a correct pharmacological regimen, with craving as the clinical target, allows rehabilitation to proceed, at times spontaneously.

Long-term methadone treatment counteracts and curtails the abnormalities displayed by an addict's brain [15]. Moreover, methadone treatment normalizes the hormonal dysregulation accompanying narcotic addiction, for instance, the excessive cortisol release elicited by stressful events [17].

2. Duration as a predictor of outcome

Methadone maintenance treatment has no pre-defined duration. This perspective was presented as an original feature of effective methadone treatment in the very first studies by Dole and Nyswander [4, 5] in the 60's, but it continues to be controversial. The first long-term observations about methadone treatment were published by Gearing in 1974 [10], as an independent evaluation of Dole's treatment programmes at Manhattan General Hospital at the end of ten years. Results indicated a global positive impact as evaluated by such parameters as reduction of disruptive and criminal behaviour, increase in productivity, craving control and abstinence from narcotic use, as well as engagement in other treatment programmes designed to challenge further substance use disorders, mental illness, and somatic diseases. Evidence of this kind, followed by further confirmation, led to the spread of methadone maintenance treatment programmes.

Appel and colleagues [1] compared patients in treatment for over 10 years with others treated for less than five, on the basis of variables such as number of arrests, hospitalizations, resorting to first aid care, working status, and other substance use: patients treated over longer periods proved to do better, especially as regards number of arrests and working status. Kott [16] examined a population of patients whose length of time spent in treatment varied considerably (1-6 years) in a cohort perspective, showing improvement for all groups through time in terms of arrests, working status and social skills (including rises in personal income as witnessed by the ability to pay for treatment with one's own resources). The results recorded for 'office-based' treatment regimens showed similar results.

Ball and Ross [2] indicate duration as the most relevant factor in influencing outcome, together with dosage, level of staff competence, good staff-patient relationships, and allowing patients admission to take-home regimens.

3. Long term safety

Research and clinical studies suggest that, on medical grounds, MMT can be considered safe [3]. Kreek showed that methadone is free of toxic effects and its side-effects are acceptable in the long term (14 years or longer for adult patients and 5 years or longer for underage youngsters) [17].

Novick [28] confirmed a high safety level among patients treated for 11-18 years, and the absence of unexpected adverse events. Long-term treatment is neutral on the heart, lungs, live, kidneys, bone, blood, brain and other vital organs. Recent studies [1, 12, 16, 21, 31, 33] and the Cochrane review [8] agreed with previous evidence: as in Dole's early works [6, 7], recent studies [31] report the absence of treatment-related mortality in a group of 158 patients observed under treatment for over 15 years. The Consensus Conference of the National Institute on Health [25] concluded that the "safety and effectiveness of opiate agonist maintenance has been undoubtedly proved". As for cognitive functions, Wechsler rating scale scores indicated no impairment over a 10-year treatment period [11].

Before the spread of MMT, death rates in the USA ranged from 13 to 44/1000 inhab, 21/1000 on average. Interestingly, after MMT had spread, these rates fell to 13/1000 inhab on average. In Switzerland, the spread of MMT was followed by a sharp decline in the incidence of lethal overdoses [30]. The most

compelling evidence of the impact of MMT on survival rates emerges from the comparison between MM-treated subjects and other addicts: in studies dealing with this issue, the death rates of MM patients are less than one third of those among non-MM addicts [13, 25].

4. Maintenance dosage and the problem of premature withdrawal

Effective methadone dosage is reached during the stabilization/maintenance phase, on Payte's definition [29], and corresponds to the achievement of craving extinction, narcotic blockade, and abstinence from narcotics. Once stabilization has been achieved, ongoing methadone administration has the aim of maintaining the state of clinical remission. This form of stability is made possible by a stable binding balance with available opioid receptors, which allows methadone's activity on the opiate system to persist indefinitely, as long as the dose is held stable (over periods of up to 20 years, or even longer) [18]. Nevertheless, some patients may require dose adjustment as time passes. Remission should never be the only reason for a decision on dose reduction. In fact, this is one major concern about the long-term handling of methadone maintenance by physicians and its perception by the patient: the 'lower is better' approach stems from the conviction that maintenance is just a delay, though necessary, in achieving a drug-free state. If this way of thinking is adopted, the philosophy of methadone maintenance is completely lost, and the idea that treatment is 'the real enemy' grows in the patient's mind to the point where compliance is endangered. Other groundless notions support such a feeling, such as those of the supposedly lower toxicity associated with lower-dose maintenance, and the need to step closer to eventual medication withdrawal by staying low on one's dose. Some myths about methadone are widespread among street addicts and physicians, such as the idea that it is toxic to the bones, or that it is harder to do without than heroin itself.

Actually, one study [22] found that the higher the maintenance dose (80 mg in this case), the higher the probability that the patient will become drug-free. On the other hand, other studies reported the consequences of premature medication withdrawal: Ball and Ross [2] found a 82% relapse rate into intravenous narcotic use among detoxified subjects after 10 months, 50% of relapses taking place in the first three months. Older addicts may stay abstinent, but with a higher risk of switching to heavy alcohol use. Dole and Joseph [7] also reported the failure of detoxification to reduce relapse-related mortality.

Physicians should not suggest medication withdrawal or force the patient to undergo it. A major part of the global treatment effort should, in fact, be directed to getting the patient to stay in treatment comfortably for as long as necessary. A diagnosis of addiction is enough, even without considering the likelihood that the patient has suffered from multiple relapses or has already reached a revolving-door stage, to justify long-term treatment. The urgency of the need to become drug-free, mirrored by the quickness of detoxification procedures, stems directly from the idea that one can manage to 'quit addiction' by quitting treatment. A state of well-being is not predictive of stable abstinence when it is reached quickly (or abruptly, as in ultra-rapid detoxification); in other words, it does not correspond to a lower risk of relapse. Also, with regard to environmental factors, becoming drug-free in favourable environmental conditions - an event sometimes described by patients as 'turning over a new leaf' - does not correspond to any newborn balance. Long addiction histories clearly show how periodic abstinence and apparently spontaneous remission are the rule between relapses. A healthy lifestyle with habitual abstinence from the use of any substance, alcohol included [32], is a positive predictor on rehabilitative grounds, but is not reliable as a predictor of no further relapses. In conclusion, if detoxified or rehabilitated patients start complaining about re-emerging drug-related thoughts and cravings, or slips, they should be started on treatment again [20].

5. Cultural factors and their interaction with maintenance treatment

Methadone treatment is strongly stigmatized by public opinion. The main point at issue is that this treatment is often seen as ruling out any possibility of true healing by making the patient's condition chronic and merely replacing heroin with methadone, while adding a risk of worsening the original condition through the accumulation of chronic toxic effects.

According to McLellan [23, 24], scepticism of this kind originates from the groundless conviction that addiction is a transient disorder, rather than a chronic illness. On that view, the quality of a treatment can be judged by its power to extinguish the disorder in the short term, with the implication that no relapse can be expected unless it arises from a patient's wilful intention. Addiction is thought of in a different way from other chronic disorders, so that people often fail to understand that remission means symptom extinction and the normal functioning of the individual. Problems arise because the persistence of symptoms after treatment reduction or discontinuation is regarded primarily as a proof of the treatment's ineffectiveness in extinguishing the original disorder. The focus of judgement is not on what an addictive disease implies by definition - chronicity, and, along with that, proneness to relapse - but on treatment, with perspectives driven by an unrealistic expectation: that short-term healing is attainable. For any chronic disorder, the right premise to obtaining good results is a long-term maintenance of the therapeutic state, with no limits to duration and medication dosage. Methadone treatment corresponds to the general rule of maintenance treatment for chronic disorders: the expected results must be rooted in the effects of ongoing treatment - craving control, the prevention of continuous use and polyabuse, narcotic blockade, the normalization of functions while allowing ample scope for rehabilitation and psychosocial interventions, crime control and reduction of infective risk).

A drug-free and treatment-free condition coupled with a good prognosis (i.e. low risk of relapse) still remains an ideal condition: to date, however, there are no technical instruments available to make this possible for the vast majority of narcotic addicts [25]. On the other hand, we can provide those patients with a treatment regimen that can control their disease in the long-term, if necessary throughout their lives.

One day, it may be that methadone-maintained subjects who started treatment at a younger age, and at adequate dosages - subjects who are still in treatment years later - will have a realistic prospect of staying out of treatment with only a negligible risk of relapse.

Concerns about retaining patients in treatment prompt the need to minimize the drawbacks of methadone maintenance treatment. Patients may drop out because of heavy side-effects, or because the treatment is too expensive, or else interferes with normal daily life and working activity. It is true that methadone maintenance does not have a heavy impact in terms of side-effects, but, especially in the long term, the requirement of weekly attendance, let alone daily attendance, is an important drawback, and is perceived as creating a stigma, in the sense that it makes patients feel different from other categories of patients [25].

Different treatment settings have been experimented so far, such as office-based and primary care programmes, where opiate-addicted patients are managed like any other category of ill people. Taken together, those de-stigmatizing settings are referred to as 'medical maintenance'.

6. Medical maintenance

The expression 'Medical Maintenance' indicates a treatment stage at which rehabilitated addicts can be integrated into the normal health system. They no longer need to be treated in dedicated clinics, as in front-line maintenance programmes, but are referred to general practitioners or private physicians, as with any other category of patient [19]. Medical Maintenance allows continuing metha-

done maintenance in a way that is specifically suited to rehabilitated patients who work regularly, abstain from street drugs and have no relationships with other 'active' addicts [27]. Medical Maintenance offers a way of making long-term treatment as compatible as possible with a normal life, for patients who have been asymptomatic for years. Another factor to be consdered is that rehabilitated patients usually dislike attending clinics where they meet active addicts, whereas in these settings they are rewarded by an increasing level of autonomy and trust. Self-esteem is positively influenced when reasons for the imposition of cultural stigmas, such as treatment promiscuity or strict supervision in specialized clinics, are eliminated [27].

The first attempts date back to 1985, when Dole and Nyswander transferred 25 methadone-maintained patients to a general medical setting [27]. Patients had been selected by applying the following criteria: at least five years of standard treatment, regular and licit working activity for the last three years, no record of criminal activitiy; no alcohol or substance use; satisfactory compliance with treatment; affective stability; no relationships with active addicts (in order to avoid diversion).

Patients were evaluated monthly, had to deliver a urine sample and took their whole day's methadone dose under supervision, but received a take-home supply for the following 28 days. Medical concerns and other problems were discussed on the spot.

That original pilot programme was gradually expanded. A follow-up study on the first 40 patients reported a 94% retention rate and a low incidence of substance use [26, 27]. About 6% of patients were sent back to standard methadone maintenance due to loss of some inclusion criteria, such as abstinence from substances (cocaine, 12%, was the most frequent). Some 5% were withdrawn from methadone. The perception of the regime by patients was sharply positive, both in terms of effectiveness and setting [27].

Schwartz [33] performed a 12-year follow-up evaluation on 12 patients treated in a GP setting and reported a 28% dropout rate. As few as 0.5% of urinalyses turned positive for some substance of abuse, while no cases of methadone overdose or diversion were documented. Participants reported significant improvements in their quality of life.

Salsitz [31] examined 158 patients followed up for 15 years by Medical Maintenance and found an 83.5% compliance rate, retained patients reporting fewer obstacles in improving their working and private life. As many as 8% became drug free after 17.7 years on average. Death rate was 13%, with no cases due to methadone-related causes, while nicotine smoking was indirectly responsible for 40% of deaths. The most frequent cause of treatment failure was crack/cocaine use.

Fiellin [9] compared a standard methadone treatment setting to a primary care access setting in a controlled, single-blind randomized manner. Patients were less stable on average, because they had been abstinent for at least one year (instead of three). Patients were evaluated over a six-month period, with weekly access. Whenever appropriate, patients were granted ancillary facilities. The only difference between groups concerned the patients' satisfaction with treatment, a higher number of primary care probands rating it as excellent. Physicians were highly satisfied with their work with these patients. Episodic substance use was frequent in the whole sample (52% slipped at least once on some illicit drug), and 20% were clinically unstable. Authors conclude that primary care can be equivalent in terms of effectiveness, and superior on rehabilitative grounds, but only a subgroup of patients are suitable for such a regimen.

The 'shared care' model [34] consists of a group of specialized physicians and dedicated social workers collaborating with a network of GPs. Brooner performed a multicentric randomized trial [14] which proved that Medical Maintenance can be successful when run within a standard medical setting. Authors also point out that the intensity of care should be based on clinically assessed needs, in accordance with a 'stepped care' model: patients are given additional care when necessary, but step back to the standard level of care when their need disappears.

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2.6

Medically Supervised Withdrawal from Methadone

I. Maremmani and M. Pacini

The progressive tapering of methadone to reach a level of tolerance may be prescribed for various different reasons and be performed in a range of settings. On medical grounds, methadone tapering should only be started when some rationale is in place with regard to the treatment of opiate addiction. Conversely, tapering should not be tried when it is expected to heighten the risk of relapse, or worsen the expected outcome of concurrent medical or psychosocial problems. Also, dose reduction should never be thought of as a 'step forward' towards an ideal drug-free condition; any such view would make treatment seem an unjustified prolongation of higher dose maintenance.

Any schedule of methadone tapering should be referred to as 'medically supervised withdrawal' or 'medically supervised subtraction' of therapeutic methadone, instead of the unjustified and misleading expression 'detoxification'.

The medically supervised withdrawal of methadone (MSW) may be the end phase of a methadone maintenance treatment programme. Withdrawal from methadone may be accomplished through a variable degree of tapering and by using various different time terms.

When tapering is quite slow, no withdrawal-related discomfort is reported. When, on the other hand, tapering starts after a maintenance phase with no recent dose reduction, discomfort of varying degrees may develop, depending on how steep the tapering is. MSW is conceptually different from any dose reduction requested or performed by the patient, against or without medical advice. In either of these two cases, the dose may be reduced, but selfwise dose reductions should never be rated in the same way as a medical prescription, since their meaning usually carries an opposite implication (craving-related), or leads to an opposite result (a worse outcome).

MSW can be proposed when patients are stabilized at a 50 mg/day dosage or less. MSW should not be initiated for patients stabilized at blocking dosages: those patients may become suitable for MSW after a long period of

stabilization at lower dosages, but should not pass from a condition of remission at blocking dosages to a high-risk condition like that corresponding to possible sensitivity to opiates (no narcotic blockade). As a rule, the risk of relapse should never increase sharply, as it does when the reduction of anticraving coverage is coupled with the loss of narcotic blockade, which may turn a slip into a full and fast relapse due to reinforcement.

An acceptable degree of tapering is by 5-10 mg steps down to 20 mg/day, as intervals of this kind leave time for possible withdrawal discomfort to be extinguished before taking further steps [8, 9] (Figure 1). An acceptable time interval between reduction steps is 15 days. Below 20 mg/day, tapering may proceed by taking 5 mg steps.

During tapering, the relative weight of dose gaps should be taken into account, rather than absolute dose values. In fact, considering equal dose gaps between different tapering steps, withdrawal discomfort varies according to the corresponding level of up-regulation of the neuronal opiate metabolism. As a rule, stepping down from higher dosages is more comfortable than applying reductions from lower dosages (with reference to a full blockade threshold). The last 60 mg are the most awkward to taper, unless the tapering schedule is stretched out so as to last longer, proceeding by taking shorter steps. Patients who report no discomfort when quickly tapering from higher dosages should therefore be warned that this has no prognostic meaning, and is due to a non-linear dose-effect relationship between dose reduction and withdrawal. In some centres, the tapering schedule used is 1 mg/day, which is meant to minimize withdrawal-related anxiety and objective symptoms. In reality, this procedure is not reasonable, since it does not account for the pharmacological profile of methadone, which implies late-onset withdrawal, so that the effects of successive 1 mg/day dose reductions accumulate after the first week, when 'unexpected' discomfort starts to rise. Usually, patients undergoing a tapering schedule like this ask their physician to keep

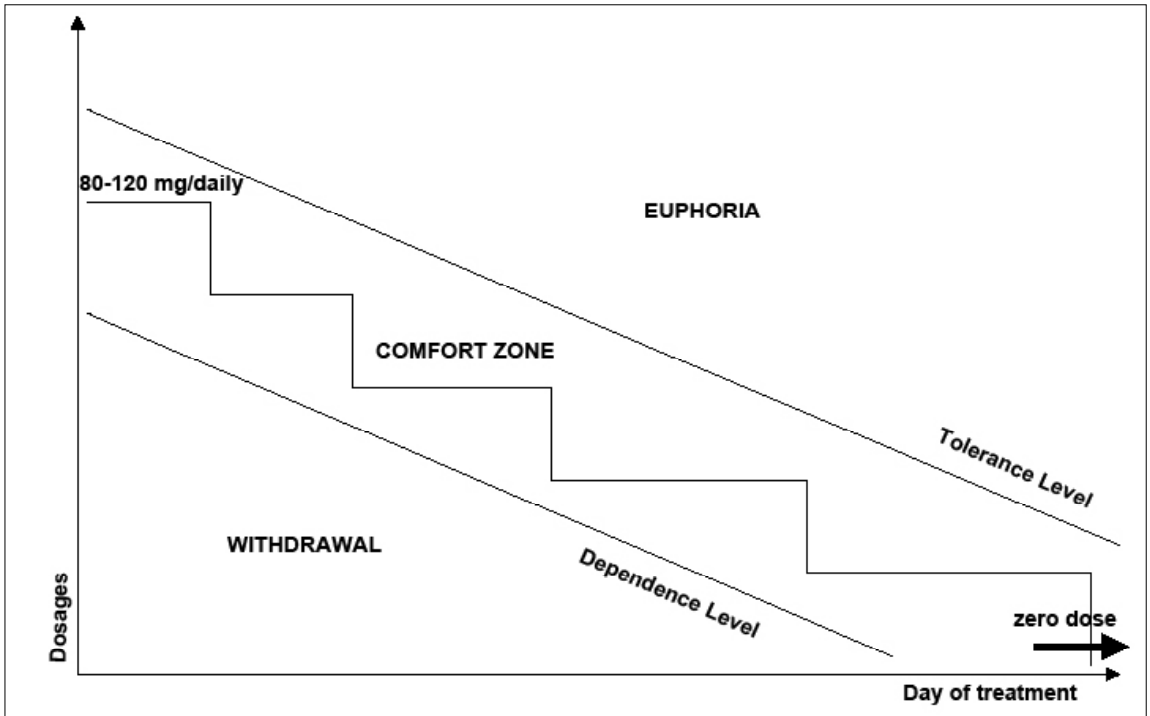

Figure 1: Methodology of Methadone Maintenance: Reduction of Medication after Maintenance

their dose stable for some time before reducing again, or return to an intermediate value.

A reduction based on 5-10 mg step reductions makes it possible to challenge the patient's opiate system by applying a significant stress, and verifying the clinical significance of the corresponding reaction. If any discomfort is experienced, MSW should be discontinued and the previous dose should be restored. Clinical worsening is a good reason for stepping back and restoring the latest known stabilization dosage.

The patient's will, or his/her urgency, should never be considered a clinical reason for applying MSW [1, 2]. If the patient has reduced methadone in a self-wise manner, the physician should not resort to MSW as a resource for proceeding with methadone tapering in a supervised way, since any such decision would lack a rationale. Likewise, in the case of a self-managed dose reduction, treatment should not continue at the dose decided by the patient; the original stabilization dosage should be restored. As already stated above, it is counter-therapeutic to regard self-wise handling of methadone as an acceptable behaviour by proceeding in the same direction or not stepping back and returning to the latest prescribed dosage.

MSW is suitable when patients are in at least one of the following categories:

- a minimum of two years of maintenance, with a minimum of one year of stable abstinence from narcotics;
- no substance use during narcotic abstinence, with special regard to alcohol, benzodiazepines or sedatives;
- global rehabilitation, with a sharp change in the patient's lifestyle.

MSW carries a certain degree of risk when it is undergone before the rehabilitation process is complete, with major psychosocial problems still present [4].

MSW must be performed without resorting to anti-withdrawal drugs, including benzodiazepines [6]. Urinalyses should be performed weekly during MSW, together with alcohol-related tests. The need to buffer clinically significant discomfort is a reason for discontinuing MSW and restoring the previous stabilization dosage. Likewise, MSW is absolutely unreasonable for patients testing positive for substances or alcohol, or if there is any clinical evidence of relapse or of a switch to another class of drugs [5, 7]. It should be remembered that alcohol and benzodiazepine abuse is made more likely by inadequate methadone coverage [3], and that a high proportion of benzodiazepine abuse in narcotic addicts is induced by medical prescriptions.

Using benzodiazepines to accomplish MSW more comfortably is, firstly, a conceptual mistake, since MSW becomes an objective rather than a clinically funded procedure. Secondly, the adoption of MSW would result in the subtraction of a relapse-preventing treatment regimen coupled with the induction of another addictive syndrome (benzodiazepine or alcohol-related) with poorer treatment outcomes [7].

Actually, MSW should not be thought of as complete when methadone dose is zero: a follow-up is needed to discharge the patient from the programme, and this must include urinalyses and clinical evaluation. Any degree of worsening of the patient's condition, on any grounds, may be a reason for restarting methadone induction, up to the latest stabilization dosage [4].

When MSW is justified in terms of the past therapeutic course and the patient's current clinical condition (i.e. prognostic judgment) no additional means are needed for it to be accomplished. Similarly, the need for rapidity or ultra-rapidity in performing MSW is limited to conditions in which patients are forced to live in geographical areas where methadone treatment is unavailable, or in situations where it is not even feasible (e.g. under war conditions).

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2.7

Relapse Prevention and Handling

I. Maremmani and M. Pacini

1. Supervised abstinence in a treatment-free regimen

In the absence of ongoing effective treatment, a diagnosis of heroin addiction carries a lifetime risk of relapse. To date, no evidence has been put forward to attest to a way of predicting future relapses or discriminating between low- and high-risk forms of the disorder. The only useful features are the following clinical ones: severity of the disease before the onset of treatment; the time spent under treatment in a condition of symptom remission; the results that have been obtained in response to the ongoing treatment regimen, including the course of psychosocial rehabilitation. The course of rehabilitation to be prescribed after the withdrawal of treatment must be taken into account, too [1-3, 5-7].

Patients and significant ones should be clearly informed about the risk of relapse as something linked to the lifetime persistence of a metabolic abnormality of the opiate system, corresponding to a diagnosis of opiate addiction. Patients may still have a low risk perception, a factor which in itself favours new episodes of narcotic use: unlike what happened at the beginning of the disease process, single episodes are enough to trigger immediate, full involvement in addictive narcotic use, instead of a gradual intensification of narcotic use over a period of several months. The outcome is that periods of latency between single use episodes and addictive use become shorter and shorter through relapses, indicating an increased sensitivity to narcotic reinforcement which does not tend to dwindle over time.

As a result, abstinence in a treatment-free regimen needs supervision, which is required to check whether rehabilitation is proceeding despite treatment withdrawal and to evaluate the advisability of restoring some treatment regimen in order to prevent relapse.

Some patients may be in need of maintenance treatment, as when it is implemented for psychotropic purposes, beyond any risk of relapse. Opiate agonists may be useful as

alternative therapies for the control of pathological anxiety, affective imbalance and painful syndromes, and may prove to be a unique resource for subjects with a history of narcotic exposure, who tend to be resistant to standard psychotropic medications.

Some patients with a dual diagnosis may stay symptom-free under a methadone-only maintenance regimen, which is a reason for thinking of longer-term maintenance as a solution to other psychotropic treatment regimens of undefined effectiveness and tolerability [10]. It follows that, in those dual diagnosis patients, agonist treatment should be considered as a means of relapse prevention with regard to the ensemble of neurobiological vulnerabilities.

On clinical grounds, the risk of relapse into addictive narcotic use should be considered as significant in the following situations:

- the subject has gone back to his/her original environment after a period, no matter how long, of residence within a protected environment; or is going through stressful events or routines (even if with positive results, subjective satisfaction and increased productivity) which are harder to cope with than during treatment;
- rehabilitation is incomplete, despite the availability of resources in the environment;
- single use episodes, even when there is no short-term relapse into addictive narcotic use;
- the patient has a dual diagnosis showing improvement on psychiatric grounds under a methadone-only regimen, but has recently worsened, even if there are no signs yet of addictive behaviour;
- the subject is convinced he/she has a second chance of becoming a controlled narcotic user.

When these are the circumstances, it is advisable to restore the previous treatment regimen.

2. Handling relapse

Engaging again in narcotic use despite an intention to stay abstinent sums up the clinical and prognostic meaning of addiction as a disease. Relapsing behaviour is the core feature of addictive diseases, and, when never witnessed directly at an earlier stage, it brings confirmation of a diagnostic hypothesis of drug addiction [8, 9].

When approaching a relapsing patient who is already under treatment for addiction, disappointment, concern and surprise are unacceptable reactions from any staff member. Relapse is fully consistent with the reason why the patient was considered to be in need of treatment in the first place, and testifies to the inadequacy of the ongoing treatment regimen, so indicating the need for treatment implementation or dose adjustment.

On clinical grounds, one can distinguish between two kinds of relapse: minor relapses ('slips'), consisting of single use episodes with a self-limiting course (without any resumption of continuous use); and major relapses, which correspond to renewed use, showing similar patterns and involving similar amounts as before treatment. Slips must be accounted for as potential major relapses which have been shielded by ongoing treatment, and would have turned into true relapses in the absence of treatment. Major relapses indicate the inadequacy of treatment, and they may simply depend on dosage. It is important to question the patient about the effects of self-administered narcotics during relapses: if the patient resorts to narcotics, it means no actual narcotic blockade is in place, or that it is not yet complete. However, dose-adjustment is usually required to challenge major relapses and lead them to extinction.

On the whole, relapses of either rank should be handled as follows:

a) increasing the dosage in order to pursue a state of narcotic blockade, and a stronger anticraving effect;
b) regular urinalyses;
c) supervised dose-administration at regular intervals in order to ascertain the level

of tolerance. If necessary, take-home can be suspended.

Sadly, the most common reason for relapse under treatment is premature dose reduction or treatment withdrawal. It is important to bear in mind that relapses following dose reduction must not be ascribed to acute withdrawal symptoms: addicted patients are capable of handling withdrawal symptoms by asking for dose adjustment or a slower tapering schedule. On the other hand, when a relapse is spontaneous, re-emerging addictive symptoms render patients incapable of asking for help, and lead them to narcotic use. Thereby, relapsing should not be interpreted as a reasonable reaction to withdrawal. Addicts who experience methadone withdrawal tend to handle it by resorting to non-opiate drugs, rather than stepping back on their methadone tapering. Narcotic use by former heroin addicts must always be rated as a sign of addiction.

Hence, physicians should not retry tapering or medication withdrawal after an initial attempt has been followed by relapse. The rapidity of tapering just does not matter.

Patients who express urgency about accomplishing the withdrawal of treatment despite their relapsing behaviour should be informed of the clinical meaning of their present condition. Physicians should never evaluate a patient's claimed good intentions to abstain as the predictor of a positive outcome.

Later relapses have the same meaning with respect to previous dose reductions of medication withdrawal.

The patient's reaction to relapse carries an important meaning. As a rule, patients will tend to report slips, and minimize or deny relapses. Also, they will tend to be concerned about a single slip and be unreasonably optimistic about a relapse, in an attempt to convince others that relapsing is due to special circumstances and does not need dose-adjustment. Alternatively, patients may suggest that treatment be withdrawn or tapered, since it has proved to be ineffective in controlling craving. Attitudes like these simply correspond to how addicted patients are likely to react with respect to treatment in general, and are attributable to the intrinsic ambivalence of addiction [4].

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2.8

Adverse Events During Methadone Treatment

I. Maremmani, A.G.I. Maremmani and M. Pacini

1. Global toxicity

Methadone maintenance treatment is a safe therapeutic regimen [45, 48, 50, 52, 57, 78]: being in treatment, even for as long as 18 years, has never been related to a greater risk of organ failure, structural or functional damage. Higher dosages (over 100 mg/day) are no more toxic than lower ones [80]. The fact that methadone has such a low level of toxicity is surely a great stroke of good luck for a treatment which is meant to last a long time and go through a long maintenance phase. Methadone continues to be the most effective and widely used option for narcotic addiction treatment; stated in the simplest terms, it can be agreed that "the main and most relevant impact of methadone maintenance treatment upon the health status of addicted patients is the transition from impairment to well-being [77]".

Many believe that methadone-treated subjects should be viewed as if lobotomized, or as if they behaved like a brain-dead zombie. There is no scientific evidence to support such attitudes; methadone-treated subjects, unlike narcotic-users, cannot be distinguished from normal subjects. Possible differences depend on past narcotic use history, not on ongoing treatment. Psychomotor functioning and readiness show no significant differences with respect to normal subjects [32]. Methadone-maintained subjects, as long as they are not abusing any other psychotropics, can be considered fit to drive [2 , 17 , 36 , 58 , 82 , 86]

2. Side-effects

Some methadone-related side-effects fade during a course of treatment, once the induction phase has been completed, while the patient is developing tolerance to the stabilization dosage. Later dose increases may be followed by similar effects due to acquired tolerance being overcome, although this is less probable, since the actual impact of dose increases is

lower when starting from a higher tolerance level. In other words, an increase of 20 mg over a tolerance level corresponding to 60 mg/day will have a greater impact than a similar 20 mg increase from a 140 mg/day tolerance level.

Somnolence, concentration impairment, poor short-term memory, nausea, dizziness, swelling due to water retention simultaneously with reduced urine volume, hypotension or bradicardia are all possible abnormalities that tend to re-adjust as a course of treatment goes forward. The pain threshold, which usually rises initially during induction, also tends to return to the level it had before treatment, or with treatment at lower dosages [39 , 40, 48].

Other expected side-effects, such as excessive sweating, constipation, irregular menstrual patterns, sexual dysfunctions, increased appetite and weight gain, do improve as a rule, although more slowly, and sometimes persist in the long-term at stable dosages. Excessive sweating is reported by as many as 50% of methadone-maintained patients: it corresponds to normotonic sweating, without abnormalities of serum electrolyte levels [1]. Dosage reduction is one simple way of reversing excessive sweating. Also, a multiple case-report article suggests the effectiveness of biperidene, an anticholinergic drug, to counteract methadone-induced sweating [6].

Constipation affects about one third of methadone-maintained patients [49 , 61], depending on reduced bowel motility. Diet supplements (fibres) or variations (food with high amounts of unabsorbed remnants which increase bowel motility and/or the water content of feces), oil to soften fecal clots, laxative agents with a variety of action mechanisms can be tried. Severe constipation justifies limitations on the containment of dosage. Methylnaltrexone, a peripheric opioid-antagonist, may be used to counteract opiate agonism on the bowels without antagonizing methadone's action on the central nervous system [4, 30, 38, 56, 74, 81].

Reduced sexual drive is rather common [61]; it is one major factor influencing compliance with the maintenance regimen and the use of functional antagonists such as cocaine [11 , 12, 29, 35 , 85 , 89]. Bromocryptine has proved to be useful in treating sexual dysfunctions during methadone maintenance, probably due to its pro-dopaminergic action, which counterbalances methadone-induced hyperprolactinemia [83]. However, reduced free testosterone may be the reason for sexual impairment, regardless of prolactin levels. Other dopaminergic drugs or sildenafil-like drugs may be effective resources, too. (Deglon, personal communication).

Some patients report insomnia during treatment. First, intoxication (stimulants) or withdrawal (benzodiazepines, alcohol) must be ruled out. Apart from that, one cause may be a fast methadone metabolism, so that the nighttime fall in methadone blood levels is greater than expected, even when no full-blown withdrawal develops: in that case, split-dosing may be a solution. Sleep-inducing drugs may be used, preferably excluding fast-acting benzodiazepines, and resorting to anti-histaminic agents, or antidepressants with sedative properties (trimipramine, mirtazapine). Neuroleptic drugs may be a good choice for psychotic or excited patients, but they do tend to have a negative impact on mood [65].

Weight gain is variable and is unrelated to dosage. Food restriction and/or physical activity are, presumably, just as effective. Weight gain is quite likely during the induction phase, and is partly due to the swelling caused by water retention. Slow-acting diuretics may be a temporary solution.

3. Intolerance to methadone

As with any other therapeutic drug, idiosyncratic intolerance to methadone is a possible outcome. Some individuals may turn out to be intolerant regardless of dosage, that is, at starting doses in the earliest phase of treatment. Intolerance may comprise dysphoria, bowel subocclusion or occlusion due to the suppression of bowel motility, pancreatic injury due to the spasm of end-coledochus and subsequent elevated biliar duct pressure, severe impairment of sexual functioning or a neuroleptic-like state of sedation and the slow-

ing of cognitive and motor functions.

General 'discomfort' while the dose is being increased usually indicates the addicted brain's reaction to the establishment of an opioid blockade, and must be challenged by planning a schedule of dose increases to achieve a satisfactory anti-craving effect.

Addicted patients may also amplify the psychological discomfort caused by side-effects and a slight neuroleptic-like effect during the induction phase, which may be no more than a way of inducing case managers to step back from a dose-increasing schedule or persuading them to allow patients to decide how much methadone should be administered to them.

Patients should be reassured about the biphasic effects of methadone on mood and cognitive functioning, with an early phase characterized by a neuroleptic-like effect of variable weight (conversely, some patients may experience an analeptic effect), followed by a later phase with a neutral or favourable effect on vigilance, memory and psychomotor functioning.

4. Methadone overdose

The risk of methadone overdosing must be rated with reference to the current level of a patient's tolerance to opiates. Patients with an unknown – presumably low or zero – tolerance must use caution in starting methadone treatment. Subjects who have discontinued methadone a short time before must be restarted on methadone very gradually, possibly as naive patients if more than two days have passed (see the chapter on phases of treatment and induction). A patient's sensitivity to opiates may be enhanced by drugs which decrease the metabolism of methadone by the liver or compete for the same metabolic pathways, or by synergic compounds such as alcohol and benzodiazepines. Dose increases in polyabusers of gaba-ergic drugs and alcohol must be introduced very cautiously and under strict supervision, preferably in an in-patient setting. Apart from cases comprising urgent medical needs, methadone should be started alone, without any association with other potentially interacting drugs, while the patient's tolerance is being heightened to allow narcotic blockade to be achieved. Methadone itself has a favourable impact on a variety of psychiatric symptoms, so that additional psychotropic treatment can be safely postponed.

As the patient's tolerance increases, the decrease in numbers of available receptor sites causes a fall in the risk of overdose [37]. The concurrent consumption of heroin during methadone treatment does not carry with it a heightened risk of opiate overdosing; conversely, it is safer than heroin consumption alone at equal doses, because of the competitive effect of methadone and a higher level of cross-tolerance to opiates.

Methadone intoxication is characterized by the slow onset of the general symptoms of opiate intoxication, with dizziness, somnolence and sleep, possibly followed by coma, accompanied by miosis and respiratory depression, in some cases leading to respiratory failure, which may be the cause of death. Unlike heroin overdose, methadone overdose is a late-onset phenomenon, so a few hours are available in which a lethal evolution can be avoided. Asymptomatic patients must, in any case, be kept under observation for several hours.

When intoxication symptoms are displayed, the following measures must be adopted:

- in the case of respiratory depression, cardiopulmonary support;
- intravenous administration of a rapid-onset opioid antagonist (naloxone) in cases of respiratory depression or coma [84], at single charge doses of 0.4-2 mg, to be repeated at 3-5' intervals, and to be continued intravenously by infusion for up to 24 hours, due to methadone's longer half-life. If naloxone is discontinued too early, re-overdosing is expected due to the persistence of methadone in the body fluids that 'lie behind' naloxone's antagonism, which fades rapidly. Flumazenil may be administered to treat possible polyintoxication by benzodiazepines, which is frequently involved in methadone-related deaths and opiate overdoses in general.

In fact, morphine overdoses in the presence of benzodiazepines develop at lower morphine blood levels, indicating a synergic action between the two classes of compound [3 , 10 , 33 , 34 , 53 , 54 , 55].

In subjects who are not tolerant to opiates and take much higher doses accidentally, naloxone may be started in correspondence with methadone's expected peak blood level (2-6 hrs) while naltrexone may be administered immediately, orally or by intramuscular injection. This procedure allows the patient both acute and long-lasting protection, by naloxone and naltrexone, respectively [5]. The quantity of naloxone needed to reverse the overdose symptoms makes it possible to estimate the excess of opiate over the patient's tolerance level (i.e. in the case of non-tolerant patients, the entire methadone amount). On that basis the physician can decide how much long-acting antagonist to use to prevent re-overdosing in the next 24-36 hrs.

Patients who throw up within one hour after taking methadone orally are at lower risk, and do not need preventive treatment. Naloxone should be administered in cases of worsening symptoms of intoxication. Also, patients who report having taken less than 1 mg/kg methadone, without any consumption of benzodiazepines and/or alcohol, can be managed in the same way. Observation should, however, continue for 8 hours, and parameters of opiate intoxication must be registered at regular intervals.

5. Methadone and liver function

Methadone is not toxic to the liver, either acutely or in the long term. It can be safely used, with appropriate dose adjustments, in patients with severe liver impairment and liver failure, unless hepatic functions are worsening [47 , 51 , 78]. HCV-positive patients require higher dosages in cases with active hepatitis, due to an increased metabolic elimination of methadone by the cytochromal system [71].

Liver transplantation can be performed safely in patients maintained on methadone [16]. In a 1999 study, 185 case files of methadone-maintained transplanted patients were reviewed: their life expectancy was similar to other categories of transplanted patients [42 , 60]. The relapse rate after transplantation was 12%, which is, in any case, lower than that among transplanted abusers who were not on methadone treatment [16].

6. Cardiac safety during methadone maintenance

Major concerns about the cardiac safety of opiate agonists have already resulted in the withdrawal of LAAM [27, 28], due to a supposedly considerable risk of fatal arrhythmias. Following a few case-reports and a small size sample study conducted on methadone-treated subjects who had experienced critical arrhythmic episodes, similar concerns have been extended to methadone [44, 46].

Methadone administration causes the QTc interval to increase in length as a trend, by an estimated 8% in a sample of 132 treatment starters. The effect is reported as dose-dependent up to 150 mg/die, at least in healthy probands. The length of QTc in methadone-maintained heroin addicts, at effective and stable dose levels, tends to be higher than expected as for the general population. On the other hand, the evidence does not show QTc reaching its highest value at the methadone peak time in treatment-starting subjects. Actually, the relationships between QTc length and administered dosage have been determined both in asymptomatic treated addicts [66] and for a small group of treated subjects undergoing arrhythmic crises [44, 46], but were not found in the group of 83 heroin addicts followed by Maremmani and colleagues on a methadone-only maintenance schedule, at variable dosages averaging about 90 mg/day[64]. Moreover, other authors, who had initally reported that the length of QTc length is dose-dependent, eventually rectified that by stating that the weight of the methadone administered is just a partial consideration, even if a specific correlation is left standing [44, 46],

Within a dosage range that is representative of treatment samples, methadone has been proved to induce ECG abnormalities leading to no arrhythmic accidents. Cases reported in studying methadone-related arrhythmias are characterized by far higher dosages. In particular, subjects receiving prescribed methadone for chronic pain control are those who take the highest daily dosages [31, 44, 46]. In the field of opiate addiction treatment, higher methadone dosages are often needed in response to an accelerated methadone metabolism, and correspond to normal methadone serum levels, as was demonstrated for HCV-positive subjects and primarily fast-metabolizers [70]. On the other hand, daily oral dosages of over 200 mg, which had been raised to that level to meet the need to buffer re-emerging chronic pain, could actually correspond to methadone serum levels that are higher than usual. In fact, the methadone serum values reported by Krantz and colleagues were higher than average, in a sample half of whose participants were patients with chronic, painful syndromes [44, 46].

Needless to say, no single case-report is able to provide conclusive data because the isolated figures involved cannot, by themselves, possess statistical significance. Moreover, in one case there was earlier evidence of a normal QTc, at the same dose level; this patient had taken cocaine shortly before the onset of the cardiac arrhythmia (arrest), while in treatment with fluoxetine, olanzapine and trazodone [14]. In another case [73], data concerning ongoing therapies are missing, and methadone consumption had taken place independently of any prescription. Of the three cases described by Walker and colleagues [90], one also displayed hypokaliemia, another had a history of atrial tachi-arrhythmia, and all three were taking other agents, too. The HIV-positive patients studied by Gil et al. [31] were at risk of QTc lengthening precisely because of their viral disease [43], apart from displaying further risk features favouring QTc lengthening (electrolyte balance disturbances, abnormalities of cardiac motility, ongoing pharmacotherapies). Nor does Krantz and colleagues' 17-subject study authorize the view that there is any causal link with the investigated feature, methadone, because of the impossibility of ruling out other known risk factors for the same kind of arrhythmias. These latter authors themselves point out that the methadone dose only carries a 25% weight in determining the QTc length as measured during index arrhythmias, though its role is statistically significant: in other words, it appears to be a co-factor rather than the cause. The mean age of the sample subjects was 49 years, which is quite a high figure if compared to the average age of addicts, a consideration which applies to Walker's three cases, too. Differences that depend on age may also mirror a difference in the reasons that determine methadone prescription, especially pain control instead of opiate addiction.

Taking a comprehensive view, it can be stated that the prevalence of QTc values above the risk threshold (> 500 msec) is lower among treated heroin addicts [64, 66], while arrhythmia is exceptional (no cases reported).

On speculative grounds, some authors support the idea of a correlation between methadone and arrhythmic accidents by observing that rhythm parameters (rate and QTc length) change in response to methadone dose reduction or withdrawal: patients admitted for cardiac arrest or potentially lethal arrhythmia show a higher heart rate and a shorter QTc after their methadone is partly or totally withdrawn. First, specific anti-arrhythmic therapy had been started. However, the withdrawal of an agent from tolerant individuals, which tends to modify cardiac rhythm when administered, can reasonably be expected to be followed by modifications of the same parameters in the opposite direction, so displaying a 'rebound' swing. A single fact of that kind cannot constitute a strict proof of any causal link between methadone and the scope or degree of baseline rhythm features. Similarly, a patient who presents for a hyperglycemic crisis and is treated over a long period by cortisone maintenance, would display lower blood sugar values during cortisone tapering, without that constituting a clear proof of a causal role for cortisone in the current hyperglycemic episode.

Patients suitable for methadone treatment should undergo a cardiologic assessment in-

cluding a basal ECG, in order to ascertain possible risk conditions, such as a congenitally longer QTc or an intoxication-related longer QTc, before any methadone is administered, or at least before the methadone dose is raised above the individually acquired tolerance level. Medical assessment should also include electrolyte dosage, so that possible disturbances can be counteracted. As far as polyabuse is concerned, anticraving therapies may be the way to achieve satisfactory results, in cases where any are attainable. Enduring cocaine or stimulant use is an independent risk condition, to be treated as a separate problem. No combination is advisable, apart from critical need responses, between methadone and other psychotropics, before methadone dosages has been raised to average effective dosages. Above such values, a further increase in methadone dosages without resorting to a combination regimen may actually offer a safer solution. Adequate dosing is important in reducing cardiac risk: it should be borne in mind that electrocardiographic abnormalities are even more common among treated subjects with uncovered cravings than among untreated street addicts [59].

6. Stigma, prejudice and misconceptions

Cultural factors play an important role in conditioning the course of heroin addiction and effective treatment [7, 8 , 9 , 72 , 75]. Ignorance, prejudice and misconceptions, together with dogmatic thought, have always limited the spread and application of scientific principles to the treatment of addictive disorders by agonist drugs [87].

Evidence about narcotic addiction can be summarized as follows:

Narcotic addiction is a severe chronic disorder, whose development depends on a variety of factors; despite this, it has the feature of being self-maintaining, independently of any single factor.

The exposure to some opiate drugs produces persistent damage to the brain opioidergic pathways [88]. The conditioned reactions of an apparently normal brain persist for years in a narcotic-free condition. Detoxification is followed by a relapse after an interval of variable length. A drug-free condition following detoxification is equivalent to waiting for a relapse without any preventive resource. Rehabilitation after detoxification is possible, but is likely to be interrupted by relapses.

Methadone treatment is best for the vast majority of narcotic addicts, in terms of narcotic use reduction/extinction and rehabilitation. Despite that, principles of successful methadone treatment are seldom applied [18-20, 21, 22, 23, 24-26, 79]. The corpus of research on methadone treatment comprises thousands of papers, which makes it one of the most studied drugs in the history of medicine [15, 62].

Nevertheless, prejudice is common among politicians, the general population, street-addicts, patients and even physicians and staff members.

One major misconception is that of ascribing chronicity to therapy rather than to the disease itself: one result is that methadone treatment is seen as the source of chronicity.

An unsustainable way of interpreting the concept of 'dependence' is another important point to discuss. It is often said that it is unethical to maintain a state of dependence by replacing one narcotic with another. By playing with words, the difference between a state of dependence brought about by a therapeutic drug and an addictive involvement in the use of a toxic substance is totally lost. Many people depend on therapeutic drugs for a variety of reasons, which means they can be symptom-free as long as they are taking a drug at stable doses in a maintenance regimen: chronic psychotics taking neuroleptics, bipolar subjects taking antimanic drugs, transplant-receivers taking immunodepressant agents, sufferers from heart diseases taking antiarrhythmics or anti-coagulants or vasoactive drugs, diabetics taking insulin or oral antidiabetic drugs. In all these cases relapse (not to mention the worsening of symptoms) can be expected after drug discontinuation; a rebound is possible, too. On official diagnostic grounds, methadone dependence cannot be classified as addiction, either: DSM-IV TR defines addiction as characterized

by :

- the reckless use of a substance despite individual suffering or damage comprising at least three of the following within a 12-month period:
- acquired tolerance, defined as the need to increase dosages in order to reproduce a pleasurable effect, together with a fall in sensitivity to the substance after regular use. Methadone treatment does not correspond to any such condition. Being stabilized means being able to stably obtain a therapeutic effect without the need to keep on increasing dosage.
- withdrawal, which is defined as the emergence of specific symptoms when exposure to the substance is abruptly discontinued, and the renewal of exposure in order to prevent or buffer withdrawal symptoms. Methadone treatment implies withdrawal in cases of abrupt discontinuation, but two points should be made: first, somatic dependence is crucial to increasing compliance with treatment, since it makes the premature discontinuation of treatment quite awkward. Second, in cases of treatment discontinuation, most addicts resort to street narcotics and do not 'relapse' into methadone use, but reapply for treatment as fast-narcotic relapsers.
- the substance is administered at higher dosages and for longer periods than those expected by patients. On the other hand, addicts tend to limit their methadone use in terms of dose and duration.
- a persistent intention to control the drive to use the substance, with recurrent failures to do so. Conversely, addicts dislike, and have no interest in, methadone: even when in possession of sufficient supplies, there is not one who fails to discontinue and abstain from it, despite withdrawal symptoms.
- plenty of time is spent supplying oneself with the substance, taking it and wearing off intoxication. Apart from the problem of having to spend time in reaching treatment centres, methadone-treated addicts do not experience any narcotic intoxication during the maintenance phase.
- involvement in substance use is a cause of social, work and leisure-time impairment. Methadone treatment is effective just because it promotes the opposite process, leading from impairment to rehabilitation.
- subjects endure in substance use though they are aware of being damaged and impaired by the substance. Actually, addicts continue to think methadone is harmful, despite the evidence of positive effects on their behaviours, because of cultural prejudice.

Some think of methadone as a pleasurable drug, that is, a legal narcotic. The truth is that methadone does not induce any heroin-like 'high' and cannot replace a heroin-induced high: addicts who take blocking dosages before stabilization is reached experience discomfort as a rule and would rather reduce their methadone dose so to be able to sense heroin. Methadone has no analgesic effects, either, in tolerant individuals. Obviously, methadone's action over the individual's tolerance level can produce favourable effects, but no trend towards methadone 'addiction' has been reported, and even illegal methadone use among heroin addicts does not usually correspond to abuse. Narcotic addicts resort to the lowest effective dosages; they do so in order to buffer withdrawal-related discomfort, and only when other street-drugs (narcotics but also non-narcotic agents such as benzodiazepines or alcohol) are unavailable. In narcotic-tolerant individuals, methadone has a normalizing effect when compensating for the individual's acquired level of tolerance [76].

The mass administration of methadone to treatment-seeking addicts is sometimes described as 'honey attracting flies', as if treatment with methadone actually meant that patients receiving it lose an opportunity to enter therapeutic communities or undergo detoxification, or are held back from such options by methadone treatment. The fact is that methadone-treated subjects are more likely to attend other facilities (medical, psychosocial, psychological), and are more likely to rehabilitate [13, 41]. Methadone treatment, far from implying

an exclusion from other routes to healing, is the key to taking advantage of all other therapeutic factors.

It must be added that the concept of healing needs to be reformulated. Improvement, ideally to a complete extent, rather than 'healing or nothing', has to become the realistic target. Therefore, once 'complete healing' is acknowledged to be an ideal condition, clinical remission should be considered the first step in that direction. A partial response, even though it does not permit a state of actual remission, should be regarded as a preliminary step towards remission, not as a failure. As far as treatment duration is concerned, clinical remission with evidence of long-term dependence on the maintenance of the treatment regimen, even if at minimal doses, is extremely close to 'complete healing', and should not be viewed as being in any sense a failure to heal.

It should be recognized that apparently 'healed' subjects quite often switch to other drugs, or fail to rehabilitate, even when there are adequate resources and opportunities. This condition usually corresponds to the 'hypophoric syndrome', a persistent impairment of the opioid metabolism capable of impeding rehabilitation when that metabolism faces a challenge from rising levels of environmental stress. Addicts who are discharged in a drug-free condition from jails or therapeutic communities usually subsist in a hypophoric state, eventually relapsing, or switching to another addictive syndrome. In line with the dopaminergic theory, which points to the mesolimbic dopaminergic pathway as the crossroads for any addictive substance, hypophoric addicts can be considered as cases of 'apparent healing' who retain their core dysfunction; sooner or later this determines a relapse or it continues to hold individuals back from rehabilitation [63 , 67, 68 , 69].

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2.9

Clinical Meaning of Urinalyses

I. Maremmani, F. Lamanna, B. Capovani and M. Pacini

Drug-screening plays a major role in the pursuit of rehabilitation within an integrated programme. Urinalyses provide important information about the course of treatment. The information that is acquired must be interpreted in relation to patients' behaviours and their psychosocial performance [2, 3].

1. The clinical use of urinalyses as a "behavioural challenge"

Urinalyses are complementary to clinical judgement in ascertaining a patient's current condition and is crucial in making therapeutic decisions. Basically, urinalyses give direct information about the use of a variety of substances, and make it possible to check whether methadone is present. No precise information can, however, be gathered about the amount consumed or the level of tolerance to methadone. Even so, important information can be acquired when performing urinalyses with regard to the patient's behaviour and underlying addictive symptoms. When patients refuse to deliver samples, or miss an appointment for delivery, the reason presumably has to do with core addictive symptoms, so a failure to deliver can be interpreted as a positive result for narcotic use.

Likewise, if patients refuse to collect their urine sample in the way requested by staff (so as to guarantee the reliability of results), addiction is the presumable cause, and the results can be assumed to be positive.

It may be of interest to ask the patient about results before the sample has been collected. Patients who claim negative results despite knowing they will turn out to be positive are still overwhelmed by addictive symptoms, and follow an addictive cognitive and behavioural style. This style includes the attitude that anything can be tried to convince others that nothing is going on: denying substance use may lead physicians not to collect the sample; it is possible, too, that positive results will be not be considered to be reliable if patients insist

on claiming the opposite. A counter-addictive style would be that of declaring substance use in order to have treatment enhanced or, if necessary, one's dosage increased, which is just what addicted patients tend to avoid.

In conclusion, urinalyses provide information about substance use and methadone consumption, whereas a patient's behaviour in the context of urinalyses is a source of important clinical information about the state of his/her addictive symptoms.

2. Collection of samples and ensuring the reliability of results

Biological (urine) samples should be collected on a regular basis, although it is better to ask patients to deliver samples at random rather than on predetermined days, so as to reduce the likelihood of cheating, which becomes more difficult and is, usually, awkward when it is tried 'on the spot'. A random pattern of sample collection also discourages sporadic substance use, as long as it happens in a non-addictive mode. A reasonable compromise between the automatic nature of regularly scheduled urinalyses and the usefulness of random collection is to perform urinalyses on a clinical basis, that is, when the patient's behaviour and clinical conditions indicate possible substance use.

If patients refuse to deliver samples or are caught cheating during sample collection, there is no need for actual urinalyses results, because a positive result can be recorded in any case (at least for the substance to which the patient is addicted).

The need for detailed and reliable urinalyses also varies according to the treatment stage: during earlier phases, for example, the evidence related to the patient's behaviour may be enough to justify therapeutic decisions, whereas reliable results are needed at a stage when symptoms have been absent for years. In fact, urinalyses become more useful when the patient has been abstinent recently, and a single episode of use does not automatically correspond to the re-emergence of severe addictive symptoms or to a fall in the level of psychosocial adjustment.

Some suggestions can be reported to minimize false negatives for morphine metabolites. First, the sample should also be tested for other possible therapeutic substances the patient is known to have taken (e.g. methadone, antiepileptic drugs, lithium, tryciclic antidepressants, phenothiazines).

The urine that is collected should be enough for two different analyses, one testing for substances and the other for general chemical and physical features, in order to make sure that the sample consists of normal urine; the patient may deliver altered urines (by dilution, for example), or a similar liquid (tea, for example). The collecting staff should check that the sample is warm (collected on the spot). Urine samples become opalescent and irregularly dense within 48 hours, which does not undermine the qualitative reliability of substance-screening tests. Otherwise, patients can be left alone in a closed room to collect the sample, if they are warned that they will be video-recorded and requested to perform the sample collection in such a way as to be clearly visible to the camera. In our view, it is better to control patients in that way, rather than supervising the delivery of samples and collecting them directly. In fact, direct control may leave no room for cheating, while the same patients may cheat if left on their own to collect the sample; the outcome is that indirect control measures allow more information to be collected about the patient's clinical condition.

According to Mark Parrino, president of AATOD, the best way to minimize cheating is to exclude the possibility that patients feel that the results of urinalyses will be the basis of any punishment against them.

As for positive results, the only clinical exception is speedball injecting; in this case the patient will test positive for both cocaine and morphine metabolites, without displaying any signs of relapse into the use of narcotics or a craving for them. In these circumstances, narcotics may be not craved for, but they are coupled with stimulants to amplify the euphorizing effect and neutralize symptoms of intoxication by a counterpolar action.

3. Therapeutic implications

The aim of urinalysis is to provide an objective check on a patient's condition in relation to their substance use behaviour. However, a clinical interpretation of behaviours is far more useful in gaining an understanding of how things are evolving during the course of treatment. Also, the clinical meaning of urinalyses needs to be interpreted in relation to the stage of treatment: the persistent positivity of urinalyses during the first weeks is normal, whereas an early negativization of urinalyses does not exclude the likelihood of relapse, and does not ensure that a given dosage will be adequate in the medium term.

Persistently negative urinalyses give a reason for not decreasing the dosage. Dwindling positive results, in the best cases tending towards zero, along with constant psychosocial improvement, define a condition of stabilization.

When dosages are reduced, the frequency of urinalyses should be increased, since the risk of relapse is supposed to increase.

Positive results after a period of negativity of any length is a reason for increasing the dosage. In no case should the use of any substance, especially narcotics, demonstrated by urinalysis, be followed by compulsory discharge from treatment or dose reduction [1, 2].

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2.10

The Take-Home as a Clinical Tool

P.P. Pani and I. Maremmani

The effectiveness of methadone maintenance treatment is based on its capacity to keep craving and addictive behaviour under control; as a consequence, drug-related concerns (crime, psychological and health issues) become less pressing and psychosocial parameters show gradual improvement [4-7].

Nevertheless, the quality of results does not depend only on the direct impact of the pharmacological regimen on core addictive symptoms. The first factor for any treatment to be effective is that a patient agrees to follow it and finds it compatible with a normal life. It is crucial, in other words, that an effective regimen should be made sufficiently liveable for patients to follow it in the long term.

The patient's compliance with treatment is influenced by a variety of factors, partly related to the drug (appeal, side-effects), and partly to the limitations and requirements of the programme (frequency of administration, frequency of control evaluations), and also by the way in which treatment is delivered (distance from treatment centres, availability of ancillary facilities, and cultural attitudes towards addiction and treatment) [12, 18, 20, 23].

A large body of research provides information about the appeal of methadone and its side-effects, showing that addicts are more likely to be willing to enter methadone programmes than other treatment options, such as therapy with naltrexone [2, 11].

As regards the issue of methadone's non-therapeutic use, it must be understood that a long-term treatment regimen cannot be conceived to continue on a daily administration basis. Treatment must proceed in parallel with the process of rehabilitation, without ever coming to constitute an obstacle. When patients start their programme, they attend the centre daily for supervised administration, but this level of control may be excessive for stabilized patients, who have a real need to attend less frequently in order to be able to work and lead a normal life. A lot of patients complain about the fact that ongoing treatment interferes to an increasing extent with the task of handling their job and life opportunities, side

by side with the general improvement in their state of health and the remission of addictive symptoms. It should also be remembered that, apart from work, leisure time and pleasurable activities there are other important elements in the process of rehabilitation and social adjustment. For some patients, bad health may be a valid reason for asking to attend the centre less frequently. One reasonable solution is to allow reliable patients (those with stably negative urinalyses and signs of progressive social readjustment) to self-administer the drug at home. On the other hand, take-home programmes may become a source of illegal street methadone. On scientific grounds, the option of take-home has been indicated as effective in increasing enrolment rates and the level of compliance with other treatment rules. More recently, it has been shown that programmes allowing take-home for eligible patients have higher retention rates [1, 15-17].

1. Guidelines for take-home

The original 'methadone clinic' programme was based on the daily supervised administration of the drug, which was the only reliable way to reach anti-craving dosages and maintain a state of narcotic blockade. Delivering methadone to drug-using addicts is likely to result in a diversion of amounts of methadone to the black market, where it is sold or traded for other substances. Apart from any legal concerns, from a physician's point of view any case of diversion basically means that the patient will be deprived of the programme's therapeutic potential, since the drug will not be taken in the prescribed amounts and symptoms will not be controlled. Moreover, the self-determined use of methadone keeps addicts away from structured treatment, since it has no impact of core addictive symptoms: street methadone is mostly resorted to as way of buffering withdrawal, at low dosages and occasionally when heroin is not available at all. Also, unsupervised methadone may be managed in order to reverse acquired tolerance to opiates, either heroin or methadone itself. The availability of illegal methadone may therefore be in direct contrast with the purposes of methadone maintenance programmes.

On the whole, stabilized patients should generally be allowed take-home privileges, in accordance with the priority of favouring the process of rehabilitation, but this option should be limited to reliable patients. Reliability should be based on a state of clinical remission of core addictive symptoms, rather than any judgement on the patient's personality or criminal history. As a result, when rehabilitation has been made viable by the ongoing anti-craving treatment, patients are empowered to arrange their lives according to social, family and work requirements.

Significant ones or external staff may be involved in the supervision of methadone administration, in order to allow take-home and be a source of reliable information about the patient's compliance and his/her adequate level of tolerance to opiates.

Take-home may sometimes be justified by the need to keep the patient away from a street environment close to the centre location, as long as some reliable significant one can supervise methadone administration in place of the staff. In urban areas with addiction treatment units practising harm reduction together with methadone programmes, younger addicts with short addictive histories may, for example, be allowed take-home in order to avoid daily attendance of a high-risk environment.

Take-home amounts vary from single daily to weekly supplies. Clinical and toxicological evaluations must be maintained and not be allowed to dwindle once take-home has been allowed in order to prevent diversion. On days when patients take delivery of their take-home supplies, they must take their daily dosage in front of the staff, in order to be considered reliable.

2. Effectiveness of take-home programmes

The earliest data about take-home methadone became available in the '70s, with the

aim of investigating the factors which influence compliance. Stitzer and coll. showed that allowing take-home renders patients compliant with the delivery of addictive counselling, as long as take-home is selectively allowed to those attending counselling sessions, by applying a mechanism of positive reinforcement. Giving patients a privilege like that of take-home dosages also proved effective in enhancing abstinence rates from a variety of substances (opiates, cocaine, benzodiazepines, cannabis) and increasing the likelihood of retention in treatment [3, 9, 13, 14, 21, 24, 25]. It should, however, be noted that only patients who have already decreased their opiate use to a certain extent are positively influenced by admission to take-home regimens, whereas other patients are not expected to benefit from the same privilege, and are at risk of becoming involved in diversion.

Michael Kidorf showed that take-home is linked with a higher proneness of patients to attend psychoeducational interventions that aim to consolidate and enhance the motivation to undergo treatment itself. This strategy may turn out to have a major impact on patients with addictive psychological and psychiatric problems, and polyabusers (cocaine, benzodiazepines) [10].

Research data from studies carried out in the 90s confirmed that take-home programmes are characterized by higher retention rates (19); vice versa, revoking the privilege of take-home without any clinical basis can have a major influence on the likelihood of dropout and relapse into substance use [17].

A later, end-stage extension of take-home programmes is what is called 'medical maintenance', where patients take delivery of monthly methadone supplies from their general practitioner, or a dedicated physician. As long as this option is restricted to patients who have been stabilized for years, studies show encouraging results in terms of relapse prevention, feasibility and safety [22].

Diversion from take-home programmes may be a source of street methadone availability: cases of overdose of untreated addicts who bought it or were supplied with it illegally have been reported [8, 26].

3. Conclusions

Among psychotropics employed in long-term treatment regimens, methadone is certainly an exception: other psychiatric patients are not requested to attend any treatment centre systematically, let alone daily during the first few years. For psychiatric patients, such a request would be considered as a way to make treatment incompatible with the patient's productive, social duties and private life. For instance, were bipolar patients asked to attend the clinic daily to receive lithium under the staff's supervision, they would hardly comply with such a rule.

Therefore, on one hand it may happen that addicted patients give up job and life opportunities in order to maintain their treatment status and avoid relapse. Hence, both patients under treatment and people who witness their condition from the outside may come to think that a narcotic-free life is not any better than before, even if it is longer and healthier. On the other hand, the nature of addiction is such as to make it necessary that treatment is strictly supervised at least until stabilization has been achieved. Unsupervised addicts, to a greater extent than other psychiatric patients, tend to be a rule unto themselves and instinctively reject any rule that may be experienced as a limitation on their access to narcotics, and continue to reason around the priority of controlled drug use for months while on treatment. Take-home without selection would probably result in low retention rates, since some addicts would prove to be incapable of respecting the few rules for the maintenance of a take-home privilege. Obviously, 'wild' take-home coupled with no control over patients' tolerance to opiates would decrease the likelihood of stabilization for enrolled patients, decrease the probability of future enrolment for street patients supplied with illegal methadone outside therapeutic rules, and increase the risk of breaking the rules. One major reason which justifies the prejudice against methadone treatment in the general population and among addicts themselves is the identification of methadone treatment and its results with whatever

derives from its improper and unsupervised use.

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2.11

Resistance to Treatment

I. Maremmani and M. Pacini

Based on the explanations given in the previous chapters about the theoretical and practical aspects of methadone maintenance, the definition formulated for therapeutic resistance should account for the failure of all viable and potentially effective therapeutic attempts made on behalf of a patient. Most of the addicts who were once labelled 'hard-core', as long as pre-methadone therapeutic standards were applied, would nowadays fit the stereotype of the potential methadone-responder. Relapsing behaviour after the reversal of tolerance (so-called 'detoxification'), the dependence of good outcomes on ongoing agonist treatment, the need for a long-term stable-dose regimen (maintenance), and the need for higher methadone dosages (over 100 mg/day) have become expected features for the vast majority of addicts [5]. None of what has just been said above should ever be taken to refer to an exceptional severity of addiction, nor should recidivism be considered a sign of greater severity.

Some patients, however, simply fail to benefit from available treatments, or only show partial improvement, without ever acquiring spontaneous control over narcotic use or stable abstinence. This may be due to clinical, toxicological and psychosocial features which have a negative impact on retention in a methadone programme. Moreover, polyabuse often hampers the achievement of satisfactory social adjustment, despite stable abstinence from narcotics. Lastly, some subjects may fail to reach satisfactory outcomes because of an intrinsic severity of the metabolic impairment underlying their addictive symptoms, despite the use of highest dose methadone for several months in a maintenance regimen [1-4, 6, 7, 10-12].

The issue of resistance is of major interest, though it looms as a problem of smaller proportions than it had not long ago, since agonist drugs are now available and standard treatment rules have been established. Resistance may be classified, in a chronological order that takes account of the phases of methadone treatment, as a) 'absolute' resistance; b) early attrition; c) dropping-out; d) relative resistance.

From a different viewpoint, it can be classified in pathophysiological terms as: a) addictive; b) polyaddictive; c) dual diagnosis-related.

Absolute resistance means never being able to enter any specific treatment programme, even when all types of programme were available and enrolments were correctly managed. Early attrition indicates the situation of patients who leave treatment during the induction phase, that is, before reaching a blocking dosage. Dropping out refers to a failure to remain in treatment as long as would have been required to reach stabilization. Relative resistance indicates a situation in which patients stay in treatment without achieving a satisfactory response in terms of rehabilitation, due to persistent drug use or polyabuse (table 1).

Some addicts, during some periods of their addictive histories, reject any hypothesis of long-term structured treatment; or, even if when they do apply for treatment, claim to be able to decide for themselves what is best for them, and refuse to submit to treatment rules.

With such premises in place, patients of this kind cannot follow any potentially effective treatment programme, and so remain un-

Table 1. Clinical phenomenology of "apparent" resistance and its meaning

Clinical Pictures	Meaning
Relapse after detoxification	Malpractice: detoxification is non a specific intervention
Relapse after more than one attempt of detoxification	Malpractice: persistent therapeutical omission
Narcotic use in the absence of withdrawal symptoms	Diagnosis of addiction
Narcotic use upon blocking dosages	Diagnosis of addiction Possible fast metabolism if narcotics are still fully sensed
Narcotic use at higher doses in order to overcome blockade	Diagnosis of addiction
Relapse after a long abstinence period	Diagnosis of addiction
Relapse after discharge from a MM lasting about one year	Diagnosis of addiction
Relapse after dose reduction	Diagnosis of addiction
Refusal to reduce the stabilisation dosage	Good insight
Relapse after discharge from a Therapeutic Community	Diagnosis of addiction Malpractice: residential treatment in non specific unless anticraving treatment has been performed in the protected environment
Relapse after a long period of pharmacologic stabilisation	Diagnosis of addiction
Relapse when psychosocial condtion are favourable	Diagnosis of addiction
Claiming to be able to handle narcotic use in favourable conditions	Diagnosis of addiction (no insight as a rule)
Disapproving of the increasing dose procedure	Diagnosis of addiction (no insight as a rule). Possible cultural conditioning
Poly-intoxication	Diagnosis of poly-abuse/addiction. Dosages may be inadequate (undermedication)

able to receive protection from the chronic, relapsing course of their disease. In other words, these patients show that they are completely resistant to treatment (absolute resistance) as long as their therapeutic career fails to proceed beyond enrolment.

Far more commonly, addicts may apply for treatment, only to leave earlier than planned, during the induction or stabilization phase. This tendency dwindles through time, so that dropping out is less likely among those who have stayed in treatment at least to up to a certain point in time. Dropping out is exceptional for patients who have been in treatment for years, and, as a rule, is caused by the loss of stabilization and the re-emergence of addictive symptoms. Dropping out always comes 'earlier' than stabilization, but we use the term 'early dropout' to indicate dropout cases that occur 'very early', during the induction phase. Early dropout is liable to occur in any programme, even if that programme is highly effective and employs adequate dosages with those who have stayed in treatment long enough to be stabilized. On the other hand, 'late' cases of dropout depend on the adequacy of treatment standards and the quality of patient-staff relationships, and may vary over a wide range.

When using average effective (around 100 mg/day) or higher dosage, and adjusting dosages on a clinical basis, it is possible to maximize retention rates among populations of subjects who have survived a 2-3 month period of early attrition. Conversely, the correct management of cases by pharmacological means is not enough to avoid some patients dropping out within the first 2-3 months. Therefore, a correctly planned methadone programme is still not viable for some patients, and does not ensure major improvement in insight and compliance in the short-term. Reasons for cases of 'early dropout' apparently belong to different spheres: practical difficulties in attending, daily survival, psychiatric impairment, behavioural instability and disruptiveness (such as that displayed by polyabusers). It should be noted that patients usually find a way to attend, despite unfavourable conditions and the presence of psychiatric symptoms. Our impression is that the most commonly featured reasons for 'early dropout' are no more than an expression of addictive symptoms, in other words, are an aspect of an uncontrolled drive to stay 'somewhere else' rather than in treatment, based on a twisted but automatic interpretation of 'being in treatment' as 'losing one's freedom to find and sense narcotics'.

Most patients fall into the categories described above. On the other hand, a minority can correctly be classified as 'relatively resistant'. To qualify as a condition divergent from 'absolute resistance', 'relative resistance' has to be understood as resistance despite ongoing adequate treatment and satisfactory adherence to treatment rules. Relatively resistant patients may continue to be prone to: a) relapse into use, though less frequently than before, and with a self-limiting pattern; b) regular use, at lower levels but without ever reaching abstinence; c) regular use at levels no lower than before, with a little improvement due to the prevention of withdrawal and the curtailment of criminal acts. Obviously, this kind of resistance can be distinguished from latency of response after several months of adequate treatment.

As for other diseases, partial response (points a) and b) of the previous paragraph) is not a good reason for discharging patients from treatment, which would mean restoring a higher grade of disease severity. In addition, a late-onset response should not be excluded in any case. To date, no standard index or retrospective evaluation can be resorted to in an attempt to label patients as 'resistant' to methadone treatment for life. Nor should patients be shifted to treatment options which are generally less effective and only suitable for low-severity addicts.

1. Addictive resistance

Addictive resistance is always a feature, just like any other core symptom of addiction, since it expresses the way an average addict interacts with the therapeutic system (table 2). Addicts are specifically resistant to effective treatments (long-term, structured) and handle

Table 1. Clinical phenomenology of resistance and its meaning

Clinical Pictures	Meaning
Not accepting treatment	No insight. Absolute Resistance.
Not admitting to have a disorder	No insight. Absolute Resistance.
Poor compliance to the program rules	Severely ill (likely to drop-out).
Discotinuing treatment without consulting the staff	Severely ill (likely to drop-out).
Trying to dictate therapeutic rules or decisions	No insight. Absolute Resistance.
Violence against the staff or other patients,	Severely ill. Absolute Resistance.
Dual Diagnosis with no compliance to treatment	No insight. Absolute Resistance
Being late and missing appointments	Severely ill (likely to drop out).
Satisfactory compliance, but ongoing narcotic use to a variable extent	Relative Resistance.

the elements of treatment, when allowed to do so in a self-wise way, in order to be 'free to find and sense narcotics'. For addicts who have short addictive histories and low levels of use, this attitude may be due to naivety and shared cultural misbeliefs about the nature of addiction. Conversely, in most cases resistance acts as an equivalent of ambivalence towards the use of narcotics: on one hand, the request to have the craving for narcotics suppressed due to the impossibility of dealing with it; on the other hand, the subtle thought of being able to reach some reasonable level of control and so becoming able to use narcotics in a more comfortable way. The expectation that treatment may be a short-term resource capable of favouring the onset of controlled narcotic use does not vanish, but often consolidates in a paradoxical way, after years of relapses.

Addicts are therefore likely to appear to collaborate with physicians, while aiming to exploit the therapeutic setting to regain control over the use of narcotics. When treatment happens to interfere directly with that use (as in a narcotic blockade), the patient will try to oppose the treatment rules and his/her ambivalence will become evident in terms of behaviour patterns.

Some addicts soon become incapable of complying with treatment rules. Usually, that happens with addicts enrolled in a condition of acute psychiatric impairment or polyintoxication, or as detainees: their apparent compliance turns out to be transient and related to a particular condition (e.g. imprisonment). Others may be interested in starting some treatment, with no precise intention about stable adherence. Others again may drop out after being abstinent for a short time and then claiming to have 'turned over a new leaf" with no risk-perception of possible relapse. The impact of treatment on a patient's insight is not itself favourable: in fact, when subjects enter treatment, they usually think they can no longer cope with narcotic use and are dependent on environmental resources (an external locus of control). Soon after withdrawal has been resolved, they will change their attitude to an 'internal locus of control' position, judging they can stay off drugs as a result of their own will-power. Thus the 'locus of control' fluctuates between two mistaken views, in a way dependent on mood states and the level of opioid activity, and it never corresponds to any deeper insight.

Addictive resistance can be overcome by repeating therapeutic attempts, implementing pharmacological treatment together with psychoeducation, or resorting to practical limitations on freedom (e.g. imprisonment) as a way

of replacing spontaneous compliance. In these circumstances, physicians should not negotiate with the patient about treatment rules, which would mean following his/her tendency to steer treatment towards substance use.

A patient who is currently resistant to treatment may be capable of attending a harm-reduction setting. If we consider different kinds of resistance in a hierarchical order, overcoming absolute resistance will come first, followed by overcoming relative resistance. In this way, patients who are absolutely resistant may be approached by harm reduction, in the hope that they will become more compliant while still relatively resistant. Patients can move up from the lower level of a non-specific treatment to more and more structured forms of treatment, until they show resistance to a higher level, but – a crucial factor for such dynamics – the selection must be made from a top-down basis. In other words, patients can be referred to harm reduction only after they have shown their resistance to agonist treatment.

Otherwise, if all patients are directed to harm reduction first, and agonist treatment is left as a side-issue to be proposed later, resistance to treatment will be reinforced as a result. Harm-reduction, which is a non-specific treatment, is the least selective (and is therefore suitable for anyone), but needs to be applied at a higher level of selection (only to those who are resistant to everything else).

A multi-level architecture for the organization of addiction treatment should account for resistance as being due to the dynamics of addiction itself, so that the prevailing strategy should consist in overcoming it, rather than adapting to it.

2. 'Dual diagnosis-related' resistance

Aggressive and dysphoric subjects are unlikely to be eligible for a structured methadone programme. Despite this, sub-effective methadone dosages may allow a reduction in aggressiveness and dysphoria and ensure a higher level of compliance.

Dual diagnosis should not be regarded as a known reason for resistance. Nevertheless, Axis I mood disorders, for example, are often a reason for early dropout. Interference of this kind is mostly due to states of mania or hypomania, in which subjects display superficial behaviour and have unreasonable expectations about their ability to control narcotic use. States of mood elation may actually be a reason for sustained abstinence after the interruption of treatment. Also, the quick withdrawal of methadone may result in phases of mood excitement, giving a short-lived impression of satisfactory craving control [9]. Since a manic phase is unstable by definition, any such balance cannot last long [8].

Depressive phases carry a lower risk of relapse, and often raise a need for assistance, which results in apparent compliance with rules and stable adherence.

Table 1 and 2 display the clinical types of resistance and pseudo-resistance, with corresponding explanations.

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3.1

Clinical Foundation for the Use of Methadone in Patients with Infectious Diseases

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The immune system is an organization of cells and molecules with specialized roles in providing defence against infection. There are two fundamentally different types of response against infections. However many times an infectious agent is encountered, innate or natural responses occur to the same degree, whereas acquired or adaptive responses improve on repeated exposure to a given infection. Methadone is a widely used synthetic 3,3-diphenylpropylamine opioid which acts primarily at the opioid receptor. Its most common use is in therapy for opioid dependence, but it is also being increasingly used in the management of chronic pain. Besides their therapeutic efficacy, opioids can produce several well-known adverse events, and, as has recently been recognized, can interfere with the immune response. Morphine may decrease the effectiveness of several functions of both natural and adaptive immunity, while significantly reducing cellular immunity, too. The first demonstration that the activation of opioid receptors within the Central nervous System (CNS) was capable of modulating peripheral immune parameters was presented many years ago following the in vivo administration of morphine in rats. Since then, a great deal of effort has gone into determining not only which immune parameters are modulated by the CNS, but also the specific action sites that mediate these responses, and how central opioid regulation influences the immune response.

1. Methadone and immune function

It is well known that opioids, especially heroin and morphine, suppress the immune system and lower resistance to various infections [83]. Human and animal studies have, in fact, shown that both innate and acquired immunity are significantly affected by these drugs [70, 91]. The acute and the chronic administration of opioids both induce inhibitory effects on humoral and cellular immune responses, including antibody production, natural killer

(NK)-lymphocyte activity, cytochine expression and phagocytic activity. The possible mechanism(s) of morphine-mediated immunosuppression may reside in the drug's ability to regulate the immune system either directly, by activating mu opioid receptors located on immune cells, or through an indirect central pathway, by activating mu opioid receptors in the CNS [69]. Receptors for opioids are expressed on the cell surface of mature lymphocytes, and are involved in mediating autocrine or paracrine types of response [13, 35, 53, 58]. Since the biochemical and hormonal perturbation that takes place during opioid withdrawal or intoxication has been implicated in opioid-induced immunosuppression [61, 62], it is possible that improvements in immune responses could partly depend on the constant activation of μ Opioid Receptors (MOR) that is present with methadone in contrast to heroin-injecting subjects. Consistently with this hypothesis, it was shown in a monkey model of AIDS that the administration of morphine according to an experimental design that prevented intoxication or withdrawal conditions, did not exert any negative impact on immune responses and HIV disease progression. These authors also reported that a structured discontinuation of opiate administration precipitated immune alteration [14], indicating that the tonic activation of the opioid receptors on the lymphocyte cell surface did not produce any immunosuppressive effect [80, 81]. In agreement with these data is the observation that short-acting opioid drugs such as morphine and heroin produce severe changes in the immune system [55], while long-acting opioid drugs such as methadone are able to progressively restore immune function and cytochine concentrations [46]. The significant decrease in NK cell activity observed after the administration of morphine directly into the rat right lateral ventricle was blocked by the central administration of the opioid antagonist, naltrexone, suggesting that the opioid agonist suppressed the NK cell function primarily through opioid receptors located in the CNS [26]. In addition, the suppression of mitogen-induced whole blood lymphocyte proliferation in rats was demonstrated in the presence of morphine, but not of its analogue, N-methyl-morphine, which cannot readily cross the blood-brain barrier [26]. Another mechanism that underlies the opioid-mediated modulation of the immune system is the ability of these compounds to influence immunocompetent cell production, as shown by the dose-dependent reduction in the numbers of T- and B-lymphocytes, NKs and monocytes/macrophages observed in the presence of morphine [72]. Opioids may also influence the immune function through activation of the descending pathways of the hypothalamus-pituitary-axis (HPA) and the sympathetic nervous system [83]. Activation of the HPA axis elicits the production of immunosuppressive glucocorticoids in the periphery, while activation of the sympathetic nervous system induces the release of epinephrine, nor-epinephrine and dopamine from adrenal medulla as well as from sympathetic nerve terminals innervating primary and secondary lymphoid organs [7, 16]. Both nor-epinephrine and glucocorticoids modulate the immune functions negatively by their action on leukocytes. In particular, the glucocorticoids play an important role in decreasing and regulating cellular immune responses [5]. Studies have shown that morphine treatments suppress immune parameters in mice through the HPA axis [60]. The ability of a centrally administered acute dose of morphine to inhibit either lymphocyte proliferation or NK cell activity appears to be primarily mediated by the sympathetic nervous system, whereas a more prolonged exposure to opioids alters the immune system predominantly by activating the HPA axis. In this respect it is interesting to note that long-lasting treatment with methadone can normalize the HPA axis – the axis that is altered in heroin abusers – as demonstrated in various clinical studies [21]. The normalization of HPA after prolonged treatment with methadone could play an additional role in restoring the altered immune function observed in heroin abusers. A receptor-mediated increase in the production of the transforming growth factor, an immunosuppressive cytokine, is another possible indirect mechanism which may account for the ability of opiates to suppress immunity [11].

A variety of changes induced by chronic ex-

posure to opioids have also been observed in the human immune system, by means of studies carried out in heroin addicts and in heroin withdrawal subjects. Govitrapong and colleagues documented a decrease in the immune system functions of both heroin addicts and subjects undergoing a short period of heroin withdrawal (between 15 to 21 days and 6 to 24 months). On the other hand, longer withdrawal periods, lasting over two years, were associated with a gradual return of some immunological parameters, such as the CD4/CD8 ratio and the absolute number of NK cell count, to normal levels [22]. From a pathophysiological viewpoint, the ability of heroin to induce immunosuppression may have some bearing on the higher rates of infectious diseases that are observed in heroin addicts, although the high percentage of infections among injecting drug users is probably related to drug injection procedures and life-style practices [18, 82]. In this connection, one interesting issue is how long-acting opioids are able to restore the immune system. In fact, both preclinical and clinical studies appear to indicate that not all opioid receptor agonists share the same immunosuppressive properties [70]. The hypothesis that significant abnormalities of cellular immunity in heroin abusers can be normalized by using long-term methadone treatment was formulated many years ago, in a pivotal paper that analyzed the T cell genetic damage induced by various opioids [40]. Follow-up studies evaluated several immune parameters, such as NK activity, T lymphocyte subset numbers and function and phagocytic physiology, in methadone-maintained patients in comparison with heroin abusers [52]. More recently, further studies attempted to find out whether the improvements observed in immune responses in the course of methadone treatment were due to the drug profile or to the lifestyle changes that take place in maintenance treatment [1]. Accordingly, a randomized clinical trial recently reported that methadone was able to activate the immune systems that had formerly been inhibited by heroin in addicted patients [47].

The most surprising result was that cytochine levels in subjects on methadone treatment were higher than those observed in healthy volunteers. This may suggest that methadone, unlike heroin, has a stimulatory effect due to the immunologic hyperactivation of an immune system that was formerly inhibited by heroin. Recently, our group has investigated the immune system function in former heroin addicts who have been in maintenance therapy with methadone for at least six months, comparing them with untreated heroin addicts who are still injecting heroin, and with healthy controls [71]. The proliferation rate of peripheral blood monocytes induced by phytohemoaglutinin in untreated heroin addicts was significantly lower than that observed in methadone-treated patients. Further, alterations of the Th1/Th2 balance and reduced levels of IL-4, TNF-, interferon were reported in untreated heroin addicts, with respect to methadone-treated patients.

Because of the AIDS epidemic, interest in investigations on how drugs of abuse, especially opiates, affect the immune system has greatly increased. Clinical studies that aim to evaluate the immune function of HIV+ subjects have shown that MMTs prevent the progression of HIV, which, however, does take place in those who continue to use substances of abuse such as heroin, cocaine and morphine [67, 77]; in fact, the relative risk ratio (RR) of developing AIDS is higher in HIV+ drug users who do not take methadone (RR of 1.78) than in patients in treatment with methadone. Remission from drug use is in itself a protective condition, even in the absence of pharmacological treatment (in this case RR is 0.66, much lower than that of active drug users) [87], but still greater protection is provided by MMT (RR 0.44).

Against the background of these epidemiological data, which are enough by themselves to justify the elective indication of MMTPs for HIV-positive drug users, in this kind of population some issues are left open in connection with certain alterations in lymphocyte functions during MMTPs. MMTPs make it possible to improve some immune system functions, but a number of dysregulations that are hard to interpret are observed in the immune parameters of these patients. In particular, the lymphocyte subsets CD2, CD3, CD4, CD8 and NK cells are better represented in patients

during MMTP than in heroin addicts who are still injecting heroin [52]; furthermore, during MMT there is an increase in lymphocyte subpopulations – in particular, of CD4 CD26, CD2, CD26 and CD8 – which are also functionally hypoactive [28]. These abnormalities of the immune system are most likely a result of acquired immunopathy due to chronic liver disease or to other infectious diseases that occur in this population [29] and, as such, have a tendency to decrease with the time spent in treatment [30].

The immune abnormalities which may be present in HIV+ subjects during their MMTP are probably associated with HIV infection itself, rather than with an immunosuppressive/immunodysregulatory effect of the drug. However, some aspects related to the management of therapy in patients moving towards AIDS as well as to humoral anti-methadone immunity (88% of HIV+ patients in MMTP have antimethadone antibodies [19, 20]), are points of interest that should be investigated further. In the current state of knowledge we can say that MMTP is able to improve the immune system functions in heroin-addicted patients who are not users of other substances and are not affected by other causes of immunodeficiency, such as HIV infection. Therefore any alteration in the immune system observed in this kind of patient during an MMTP deserves further clinical investigation [31, 50, 54].

2. Methadone maintenance and HCV infection

Hepatitis C virus infection (HCV) is a clinical disease often (64-88%) associated with heroin addiction [12, 24, 54, 59]. The chronic character of hepatitis C and its evolution towards hepatic insufficiency causes 9% of all deaths associated with methadone maintenance treatment (MMT) [2]. The increased infectiveness of the virus and the existence of modes of transmission that cannot be neutralized by the clinical control of drug addiction most probably underlie the increased infectiousness of HCV, compared to other infectious diseases related to addiction, such as HBV and HIV [6]. The major risk factors that are the basis of infectiousness in patients in MMT are the frequent inadequacy of methadone doses, resulting in the continuation of the use of heroin, and the intravenous use of cocaine. Retrospective studies have pointed out that seropositivity for HCV is associated with elements of the clinical picture that reflect both the duration and the severity of addiction [24]. In fact, in many heroin addicts, especially those who experience intravenous addiction, there is the copresence of one or more viral infections, such as HCV and HBV [24]. This finding in particular suggests that during the active phase of the disease, sources of infection associated with drug abuse practices are the main channels of infection for different pathogens. In HCV infection, cellular and humoral immunological mechanisms participate in viral clearance in the liver, peripheral blood and lymphatic organs. However, the role played by the immune system in the progression of chronic hepatitis in not completely clear and the mechanisms responsible for the persistence or viral clearance are still largely unknown. The activation of T cell responses is considered one crucial mechanism in the antiviral immune response against viruses [9, 15]. It is generally accepted that opioids may facilitate the outbreak of infections through marked immunomodulating effects on the immune response against a virus. Conversely, opioids seem to exert a biphasic action on cytokine production, as this action is mediated by endogenous opioids. In any case, opioid receptor overexpression or deficiency would predispose aberrant defensive mechanisms [57, 68]. Interferon in combination with ribavirine is currently the most effective therapy for patients with HCV infection, and the positive effects of this combination therapy may not be directly antiviral but mainly immunomodulatory [9, 15]. In this connection it is important to note that opioids are able to interact with the immune system, and different types of opioid receptors have been detected on various cell types, including blood mononuclear elements which differentiate as macrophages in tissue. In fact, suppressed NK activity was demonstrated in

heroin and in polydrug abusers and NK antibody dependent cell-mediated cytoxicity (ADCC) was present in injecting drug users. Conversely, some experimental data have shown that the opioid effects on the immune system are not necessarily deleterious; in fact, the endogenous opioid metenkephalin was seen to determine immunostimulatory activity on T cells. These different effects (inhibitory or stimulatory) of opioids on immune system functions could be explained by the method or duration of chronic drug use [56, 88]. However, it has been observed that the immune functions that become normalized in drug abusers on long-term methadone maintenance as a result of methadone's long-lasting action comprise the normalization of the HPA axis, the consequent persistence of the drug level, and the greater endurance of receptor stimulation [32, 45, 71]. Heroin addicts presented significantly low levels of NK cell activity, whereas patients treated with methadone over a long period, from 5 to 8 years, showed a progressive and constant normalization of NK cell activity. Likewise, data presented in the literature suggest that IL-2 and TNF-alpha production is a predictive index of a good response to IFN-alpha treatment in patients affected by a chronic hepatitis C virus, even in non-drug users. The plasma levels of TNF-alpha, IL-2 and IFN-gamma in patients affected by chronic active virus C hepatitis rose significantly in patients during methadone treatment [48]. Because of their poor compliance, drug users with HCV are usually treated for only a few months after the end of methadone therapy. Nevertheless, specific IFN therapy may be recommended in drug addicts during methadone treatment, since this period is immunologically favourable for antiviral treatment.

2.1 Methadone maintenance for HCV-positive patients

Chronic Hepatitis C, in its natural history, alternates between periods of persistence of the virus without clinical evidence of hepatic suffering, and periods of increased infectiveness, with or without the presence of specific or non-specific symptoms. In any case, the presence of severe chronic hepatopathy is not a clinical counterindication for beginning and/or continuing a pharmacological treatment with methadone [51]. The belief that people suffering from hepatitis C are intolerant to methadone and/or are more sensitive to unspecified hepatotoxic effects of methadone itself, is unmotivated. In any case, pharmacological treatment with methadone has a positive impact on the liver function of patients with HCV-related liver disease; in fact, plasma transaminase levels are higher in non-treatment than in cases of methadone treatment [39]. The lowering of plasma transaminases is probably related to the clinical remission of drug behaviours, and any direct hepatotoxic damage from a drug (as in the case of naltrexone) appears to be clinically less significant for the liver as compared with a clinical addiction not treated pharmacologically. Furthermore, long-acting opioids seem to improve the outcome of the viral infection, as suggested by the ability of methadone to significantly reduce the relapse rate of patients undergoing interferon and ribavirine treatment [48]. With hepatopathic patients, the choice of using a daily dosage of methadone below the levels recommended in the international literature has a clinical rationale only when there is a rapid progression of liver disease towards a form of cirrhosis. This clinical attitude has a pharmacological rationale, considering that in such situations, the sudden reduction of liver function resulting in a reduction of the hepatic absorption of methadone, will gradually develop tolerance to the amount given, with a subsequent increase in plasma concentration, when the quantities being administered remain constant. Normally, in a patient who has cirrhosis ab initio, the best recommendation is to use appropriately reduced posology and patterns of introduction [49, 51], whereas in patients undergoing active hepatitis, an increase in daily dosage may be required, since the activation of C infection can actually lead to an increase in the enzymatic activities that are responsible for the hepatic metabolism of methadone [42]. After all, the inclusion of

HCV+ subjects in methadone maintenance programmes appears to be a priority, not only for the remission of the underlying disease but especially since the progression rate of hepatitis C is lower in these treatment conditions. The clinical measures to be taken in managing drug addicts suffering from HCV, should include: (1) the enrolment of the patient in an MMT as quickly as possible; (2) the initiation of a parallel treatment to reduce the possible consumption of alcohol and cocaine; (3) verification of the presence of antibodies to HAV and HBV and possibly an immunoprophylaxis treatment through vaccination; (3) an assessment of the desirability/feasibility of starting a specific antiviral therapy for HCV [85].

2.2 Antiviral therapy in MMT patients

The treatment of HCV infection with interferon and ribavirin proved feasible in patients who had good compliance with methadone treatment, regardless of the presence of a dual diagnosis (62% of the sample) or the continued use of alcohol (21%) and drugs (31%) during the antiviral therapy itself [79]. The data reported in the literature indicate the presence of a satisfactory and stable clinical response to the antiviral therapy among heroin addicts in MMT – a response which is quite similar to that observed in non-addicted patients treated for HCV infection (40%) [79]. In a population of non-selected patients, a number of factors such as older age, prevalence of significant psychiatric disorders, a more advanced hepatopathic stage and the use of opioid drugs have a negative impact on the response to antiviral therapy (29%) [12, 79]. In the selection of patients to be directed to an antiviral treatment, it should be borne in mind that a priority should be given to those for whom methadone therapy is not only able to determine the remission of drug addiction, but also control over the use of other drugs, so avoiding any indication of suitability for the treatment of patients with a low probability of clinical response to antiviral treatment. From this perspective, pharmacological treatment with methadone offers the most effective therapeutic strategy for drug-addicted patients to get anti-HCV treatment. The incidence of mood disorders, states of anxiety and depressive symptoms in patients secondary to treatment with interferon and ribavirine in patients in MMT is similar to that seen in non-addicted patients, but the severity of the sequence of symptoms is less marked in patients treated with methadone [73]. In order to reduce the side-effects of antiviral treatments on mood, the following are effective: a) an increase in the daily dosage of methadone during antiviral treatments; b) the preventive use of antidepressant drugs (SSRIs). In patients in MMT, cases of drop-out from antiviral treatments are not correlated with therapeutic status nor with the presence of mood disturbances, depression in particular.

3. Methadone maintenance and HIV infection

3.1 Methadone and prevention of seroconversion

The enrolment of heroin patients in MMT programmes is a particularly effective measure for the prevention of HIV virus transmission [4, 17, 84]. Indeed, several retrospective epidemiological studies have provided evidence that in a population of people addicted to heroin, those who had been enrolled in MMT before 1981 showed a lower incidence of death caused by AIDS than those who received pharmacological treatment after 1981 [75]. During the period corresponding to the epidemic diffusion of HIV infection, the terminal phase of the viral infection was the most important cause of death among those treated with MMT, in spite of the decline in the importance of other causes of death related to drug addiction [2]. In this sense, MMT seems to have played a protective role, especially in patients who were enrolled before the epidemic diffusion of HIV and who presented a condition of serum negativity to the HIV virus. Those pa-

tients have consequently maintained a negative serological status as a result of their pharmacological treatment in the years when the HIV epidemic was spreading. The hypothesis of protective action from MMT is strengthened by the observation that some patients who had been enrolled in MMT before 1981 and left the treatment for 1 year during the period when the epidemic was active, after which they re-enrolled in MMT, died of AIDS [75]. In order to reduce the spread of HIV among addicted people, optimization of the strategy should aim to achieve early enrolment in the treatment, so reducing their exposure time to risks of infection. Once enrolled in an MMT treatment, the protective role of these agents tends to persist in proportion to the rate at which good therapeutic results, especially withdrawal from the endovenous use of drugs of abuse, are achieved. Indeed, when starting MMTs, HIV-negative subjects maintain serum negativity both in the short [27], medium [92], and the long term, providing that the treatment is carried out uninterruptedly [50]. As already stated, continuity in treatment is the main feature on which the protective role towards serum conversion for HIV is based: subjects suspending the treatment tend to show a higher degree of serum conversion [3, 10, 90] with respect to those who remain for longer periods in pharmacological treatment. This effect is already clear-cut as little as 18 months after the interruption of methadone treatment, (3.5% vs 22% of serum conversions for HIV among subjects treated with respect to those who have interrupted the treatment) [43]: any relapse in the use of abuse substances is thus readily followed by the reappearance of the use behaviours that facilitate the spread of the HIV virus. However, one noteworthy underlying factor is that, even in MMT-treated subjects, rates of serum conversion are not completely suppressed [44, 76]: indeed, an epidemiological investigation carried out in the United States showed a serum conversion rate of 1.3% even among patients who were treated for at least one year during the epidemic diffusion of HIV infection between 1985 and 1990. In this connection, it can be presumed that some of these subjects have relapsed into using drugs of abuse at the end of their pharmacological treatment, with the consequent adoption of risk behaviours for the transmission of infectious diseases related to dependence. From a clinical viewpoint, the real evaluation of MMT efficacy in preventing HIV from spreading among people addicted to heroin is correlated with the efficacy of this treatment in controlling possible relapses into any recourse to drugs of abuse. Short-lasting pharmacological treatments or those carried out with inadequate and/or sub-therapeutic dosages fail to provide satisfactory protection from the risks of contracting the infection. Lack of protection may become evident both during the treatment, in the case of subtherapeutic dosages, and after the end of the treatment, in the case of unduly short-lasting programmes – those carried out below the "security limits" [34]. Furthermore, the use of subtherapeutic treatments, based on dosages that are ineffective in reducing heroin craving, must itself be considered a negative feature that weakens retention in treatment [25, 74] and predisposes the subject to a relapses into heroin use. Reduction of the risks of infection in subjects addicted to heroin with unsafe behaviours is extremely important, especially for the kind of population being considered, since the subjects who are a target for the infection also represent the 'reservoir' of the infection itself. Consequently, in this population the probability of transmission of the disease is quick to show the typical features of an epidemic diffusion. In this regard, a study carried out in Vienna has shown that all the subjects entering an MMTP from the second half of the 1980s onwards displayed a progressive increase in the rate of positivity to the infection (from 8.5 to 29.7%); this increase abated in conjunction with the growing use in the district of Vienna of methadone treatment, which led to a reduction, even if modest, of the rates of infection (from 29.7% to 26.9%) [36]. This reduction does not seem to be exclusively due to fall in the availability of subjects who might have been infected, since one distinctive feature of the addicted population is the high turnover of subjects. This observation is confirmed by a comparative analysis carried out in several European countries, which reported that the high

percentage of intravenous drug users (IDU) treated with MMT is inversely proportional to the prevalence of HIV infection. In addition, countries with a low prevalence of HIV infection are characterized by a rise in the number of cases between 1987 and 1992. During that time lag period, the European countries which had both a low prevalence and a low incidence of the infection were further distinguished from the other European countries by having a much higher percentage of drug addicts enrolled in MMTs [63-65, 86, 92].

3.2 Behavioural targets in methadone maintenance

The appearance of a full response to methadone therapy, as a consequence of withdrawal from taking drugs of abuse, induces a reduction in risky behaviours [75, 90]. However, a beneficial effect on the risk of contracting infectious diseases related to dependence can also be recognized in heroin addicts who respond, even if partially, to treatments. Even if these individuals do not stop taking heroin during MMTP treatment, it is well documented that in these cases patients who are still heroin-addicted at least reduce syringe interchange significantly [78, 89]; from a behavioural viewpoint this is interpretable as an increase in attention towards their own safety (the tendency "to borrow a syringe" is, indeed, weaker than the tendency "to loan a syringe") [78]. It is also evident that a reduction in the frequency of taking drugs of abuse is paralleled by a reduced tendency to interchange syringes [8]. This last phenomenon can be partly related to a higher tendency to take drugs occasionally and on their own, with a less recurrent use of drugs taken together with those who are defined as "needle mates" [23, 33, 90]. However, some data in the literature suggest that even when greater attention is given to rules on hygiene, such as the washing of used syringes, this may not be accompanied by behavioural changes in the habit of interchanging syringes [3]. A limitation of sexual promiscuity is another important issue to be considered in preventing the spread of HIV infection. MMT subjects reported having had fewer partners in the period preceding the interview [23, 37, 38, 86, 90], even if, from this standpoint, there are conflicting data in the literature [3, 33, 78]. Furthermore, the number of partners in the year preceding the interview proved to be inversely proportional to MMTP duration [38], confirming the importance of treatment retention as a stabilizing factor. Viewed as an isolated factor, retention in treatment seems to be directly proportional to the daily dosage of methadone. The sexual activity of subjects undergoing treatment persists as a result of the search for personal satisfaction, while prostitution tends to become less common. Although there is no general consensus on the possibly higher attention displayed by MMTP patients to condom use [23, 37, 41, 86], the concept of sexuality for these patients is mostly oriented towards the search for personal satisfaction, with the consequent exhaustion of a series of phenomena which favour promiscuity, such as prostitution [86]. An indirect, but significant, demonstration of the usefulness of methadone treatment as a tool for the prevention of the spread of HIV infection is the fall observed in serum conversion between sexual partners in MMTP patients [76]. A possible explanation for the discrepancies in the data on risky sexual practices is based on the presence, among MMTP patients, of subgroups of patients with unsafe behaviours, which are not directly related to the use of heroin, but to the use of other drugs of abuse, such as cocaine and/or patients with mental diseases unrelated to dependence [10]. There is, however, a common consensus on the evidence that MMTP treatments are effective in reducing the risks of HIV infection risk that derive from risky behaviours [65].

3.3 Methadone and the reduction of infection risk in low threshold programmes

Harm Reduction (HR) traditionally sets a premium on handling the contingencies of a specific case or of an illness by adopting measures that aim to prevent and/or reduce risks

deriving from drugs of abuse, rather than planning a specific therapeutic programme that aims for a clinical resolution of the illness itself. By contrast, when the path chosen is that of a specific intervention on drug dependence, the dominant idea is that the use of sub-therapeutic dosages of methadone or of non-continuous cycles of methadone therapy are useless, since these interventions will not lead to recovery from the illness. One outcome of this dichotomy has been that the tool 'methadone' has been segregated exclusively for use in specific, structured programmes. Furthermore, "HR" programmes are prevalently based on non-pharmacological interventions, such as the distribution of condoms, contingent support, or, when intervention is pharmacological, it is exclusively carried out with symptomatic drugs. In our opinion the true intrinsic difference in HR does not depend on the means to be used, but on the need to use both pharmacological and non-pharmacological approaches, in relation to the therapeutic needs of a target patient who displays poor compliance and/or is characterized by having to face degrading psychosocial conditions. In any case, HR programmes should refrain from excluding a pharmacological tool such as methadone. Indeed, even in subtherapeutic dosages, besides its contingent usefulness in combating the anti-withdrawal syndrome, pharmacological treatment with methadone could be particularly useful in reducing some risky behaviours that may lead to a rise in the transmission of infections. In general, infections transmitted in this way are a consequence both of a partial effect on craving, and of a 'cooling' effect on peaks of psychopathological distress, which are often associated with impulsive behaviours that themselves lead to leading to risky behaviours. In most cases such behaviours are not under the patient's control and therefore place him/her in a condition of higher vulnerability to the transmission of infectious diseases related to dependence. In addition, any reduction in the need to consume drugs of abuse, as well as in ideation in their favour, allows the 'on the road' drug abuser not only to participate more advantageously and directly in informative campaigns, but also to take in what can be learned on these occasions. The utility of prevention campaigns, which is already evident in the absence of pharmacological adjuvants [6], might therefore be enhanced, even in the absence of any drastic reduction in the chronic use of drugs of abuse. When the impact of MMTP is reduced, that is undoubtedly linked to a significant increase in the risks and the damage associated with drug dependence [23, 66].

4. Conclusions

Although many advances have been made in understanding the effects of opioid drugs on immune response, the real clinical relevance of these effects has only emerged recently. It has been definitively shown that not all opioid drugs share the same immune profile. Chronic morphine administration in animals and long-term heroin in humans have consistently been associated with immunosuppression and a higher rate of infection. Conversely, it has now become clear from human and animal studies that methadone is not only devoid of any intrinsic immunosuppressive effect but that it is able to progressively restore immune system functions. This effect may partly depend on the ability of methadone to restore the HPA axis function, which is altered in heroin-dependent patients, or by the long-lasting activation of opioid receptors both in the central nervous system and on immune competent cells. The immunorestoring properties of methadone are key factors in the treatment of concurrent infections, such as HCV, which are frequently associated with heroin addiction. In fact, evaluation prior to, during and after methadone treatment has revealed that heroin addicts with HCV can be successfully treated with pegylated interferons and ribavirine, suggesting that therapy should be initiated during the MMT to achieve a more sustained response. Indeed, it is evident that the objective of achieving adequate control of addiction and of concomitant infectious diseases by choosing either immunosuppressive drugs or drugs characterized by immunoneutral or immunos-

timulating effects could become an important focus of attention in the future in opioid therapy. It must be added that further clinical studies are needed to gain a better understanding of the impact of chronic opioid treatment on the immune system.

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3.2

Clinical Foundation for the Use of Methadone in Dual Diagnosis Patients

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1. 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.

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.

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.

2. Treatment of personality disorder during methadone maintenance

Treece and Nicholson verified that some personality features (according DSM manual [1]) 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 [170].

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 [170].

Our group verified that methadone dosages depend on the grade of psychopathology and aggressiveness at treatment entrance [113]. 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.

3. Treatment of mood disorders during methadone maintenance

3.1 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, impair-

ment 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 [117]. 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 [115, 116, 118, 129]. 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%) [34]. 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.

3.2 *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 [79, 82, 181]. 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 [62, 150].

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 [5, 9, 12, 163]. 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 [97].

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) [165].

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 [165].

3.2.1 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 [162] was documented. Amitryptiline partly controls withdrawal symptoms in abstaining volunteers [162]. 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 [183]. 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 [82]. 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 [39]. The natural course of depressive symptoms after methadone initiation is marked by a gradual decrease in severity that continues through the first eight months [42, 142, 158, 166, 176]. 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 [42, 142, 158, 166, 176]. Caution is also needed in the light of several cases of tricyclic abuse that have been documented in the literature [30, 164]. 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 (Serotonergic System 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) [71]. Sertraline increases methadone blood levels during the first two weeks of administration [124]. 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 [17, 38].

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.

3.2.2 *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 [99]. 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 [124]. 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 [32, 52, 128].

Lithium-methadone interaction have been suggested on an experimental basis, but has not yet been clinically confirmed [73, 74]. Fenythoin, carbamazepine and phenobarbital strongly decrease the bioavailability of methadone, so causing opiate withdrawal [124]. Valproic acid and the latest anticonvulsants do not seem to have this effect.

3.2.3 *Opioidergic agents*

3.2.3.1 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) [6, 83]. 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 [54]. 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 [113]. In a two-year follow-up, methadone maintenance seemed successful in achieving major mood stabilization in bipolar I patients [98]. Though contrasting data do exist [43, 134], 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 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" [44].

Table 1 shows pharmacological interactions and dosages in heroin addicts with mood disorder psychiatric comorbidity as recorded in the experience of the PISA-SIA Group.

3.2.3.2 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 [173]. It has been

Table 1. Pharmacological interactions and dosages in methadone maintained heroin addicts with mood disorder psychiatric comorbidity according to the experience of PISA-SIA Group

	Dosages (mg/daily)		
	Min	Mean	Max
Bipolar patients			
Methadone, stabilization dosage	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
Unipolar depressive or dystymic patients			
Methadone, stabilization dosage	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

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 [103]. 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 [122]. 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 [107]. 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 [100, 114].

3.3 Recommendations

Table 2 shows the PISA-SIA (Study and Intervention on Addictions) Group recommendations for patients with mood disorders.

Table 2. Treating mood disorders in heroin addicts. PISA-SIA (Study and Intervention on Addictions) Group recommandations

A.	Remember that antidepressant pharmacotherapy alone does not extinguish addictive behavior in heroin addicts
B.	Apply antidepressant properties of long acting opiates
C.	Use over-standard doses of methadone (over 120 mg/day)
D.	Remember that antidepressant medications (especially SSRIs) increase methadone blood levels
a.	Use SSRIs in methadone rapid metabolizer patients
b.	Use caution during MM induction phase
c.	Do not use SSRIs during the 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 IMAOs 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
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 behavior in heroin addicts
L.	Use caution with carbamazepine. Increase methadone dosage if carbamazepine is necessary
M.	Prefer valproic acide
N.	Use litium in compliant cocaine abuser heroin addicts

4. Treatment of anxiety disorders during methadone maintenance

Most addicted patients display symptoms of anxiety at some time during their addictive history [35-37, 64, 72, 86, 89, 92]. 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.

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.

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 [80], if heroin itself produces few strong sensations, or else to make a subject feel "high" [182, 183]. 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 [157]. 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 [24, 80, 82, 91, 147, 162, 182, 183]. 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 [24, 70, 164] According to the Treatment Outcome Prospective Study, between 5% and 16% of methadone-maintained subjects have been using benzodiazepines weekly or less often [75]. 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) [67]. 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 [178]. Benzodiazepine-abusing methadone patients may display oversleeping, ataxia, speech difficulties, and even anger attacks [80]. 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 [110].

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 (Table 3) indicate that the

Table 3. Pharmacological interactions and dosages in methadone maintained heroin addicts with anxiety comorbidity according to the experience of PISA-SIA Group

	Dosages (mg/daily)		
	Min	Mean	Max
Panic disorder patients			
Methadone, stabilization dosage	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 dosage	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

average methadone dosage needed to stabilize heroin addicts with a dual diagnosis of 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). Consistently with such observations, naltrexone has been shown to elicit anxiety in non-addicted, as well as addicted patients [103].

The anxiety disorders of heroin addicts can also be treated successfully with antidepressant drugs and buspirone [51]. 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.

5. Treatment of psychotic disorders during methadone maintenance

Previous suggestions [16] 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 [84, 132]. 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 [141], which ranged between 11% and 19% in different surveys [29, 53]. Moreover, the major studies [11, 126, 140, 160] 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 [127]. 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 [11, 148].

Some authors [148, 160] 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.

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 [15, 31, 58, 66, 68, 161, 167]. 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.

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 [135, 145, 146].

5.1 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 [19, 22, 41, 159, 184, 185]. 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 [119, 120]. Psychotic who are also abusers show a less favourable response to TAs, presumably due to the propsychotic 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 [19, 159]. 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 [121]. 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 [4, 23, 94].

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 [120]. 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 [48, 49].

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 [77, 96]. 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 unfavourably 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) [90]. Risperidone, which has the highest specificity for D4 receptors, has not yet been evaluated on this issue.

5.2 *Methadone and antipsychotics*

The concurrent use of antipsychotics in methadone-maintained psychotics can be considered acceptable and helpful [28, 81]. When combined with methadone, low dosages of TAs such as chlorpromazine, flufenazine and haloperidol are needed in controlling psychotic symptoms [162]. 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 4 shows the methadone and antipsychotic dosages needed for psychotic heroin addicts. Clinicians should be particularly careful during the 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

Table 4. Pharmacological interactions and dosages in methadone maintained heroin addicts with psychosis and violent behaviours according to the experience of PISA-SIA Group

	Dosages (mg/daily)		
	Min	Mean	Max
Methadone, stabilization dosage	30	140	290
Typical antypsychotics (Haloperidol equivalent)§	3	7	9
Clozapine	100	150	300
Olanzapine	10	10	20
Risperidone§	2	4	6
Quetiapine	25	50	100
Valproic acide	80	100	110

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

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.

5.3 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 [21, 90]. 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 [21].

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 [131].

5.4 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, 3]. 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.

5.5 Recommendations

Table 5 shows the PISA-SIA (Study and Intervention on Addictions) Group recommendations for patients with psychotic disorders

Table 5. 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.

6. Treatment of violence during methadone maintenance

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 [57, 65, 154-156, 175].

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:

the *nucleus proprius* of the terminal stria and the *nucleus accumbens*, as modulators of defence [7, 59, 60, 63, 125, 138, 153].

the periacqueductal grey substance, which produces/enhances defence [10, 152, 151].

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 [18, 45, 76, 136, 137, 139, 168, 179].

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 [154].

6.1 Opiates as anti-aggressive 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 methadone 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 suppose that 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 [104]. 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 [108, 112]. 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 [98].

Further information about the relationship between opiates and aggression comes from our clinical observations on agonist- or antagonist-maintained populations [106]. 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 [102]. Within the same study, a case was reported of a bulimic patient who developed panic attacks in the early phase of treatment with naltrexone [103]. 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 [114].

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 [177]. In fact, the administration of opioid-antagonists to autistics was not followed, as in drug addicts, by any withdrawal symptoms [85, 130]. 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-medication, rather than to seek euphoria. According to Khantzian [77], 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 [27, 172], 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 [77].

7. Treatment of alcoholism during methadone maintenance

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 [133]. Patients who continue to drink, despite severe or advanced somatic consequences, display a peculiar form of depression [133]. Alcoholism stems from depressive states, which are mostly of minor severity and a disguised kind [174]. 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 [88].

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 [20]. DSM also 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 [5, 8, 13, 14, 25, 33, 61, 69, 87, 123, 144, 149]. 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 [25]. 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 [143]. 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 [5, 61]. 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 [5, 61, 180]. 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 [5]. 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 [143].

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 methadone 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 [109, 110].

7.1 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 [40, 140]. 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 [55]. Since both addictions need to be treated at the same time, disulfiram was tried first on methadone-maintained patients, but, though the complete safety of the combination was ascertained [26, 93, 169], its efficacy is still controversial, as disulfiram is mostly equivalent to placebo [93]. 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 [93]. 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 6 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

Table 6. Pharmacological interactions and dosages in methadone maintained alcoholics heroin addicts according to the experience of PISA-SIA Group

	Dosages (mg/daily)		
	Min	Mean	Max
Methadone, stabilization dosage	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

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 [97]. 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

7.2 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 [46, 47, 78, 95, 171]. 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 [50, 56, 101, 111]. 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 [105].

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 poly-abuser 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.

8. 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 [108]. 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.

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

Table 7 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 1). 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 8). 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.

Table 7. First day, weekly first month dosages in double diagnosed heroin addicts according to the PISA-SIA group experience

Methadone dosage	Uncomplicated heroin addicts	Double 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

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 administered,

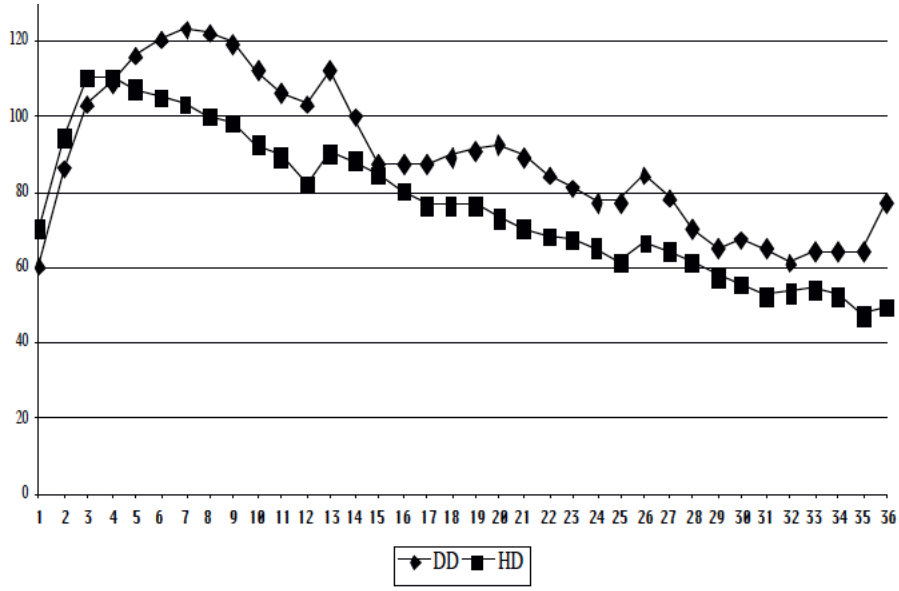

Figure 1. 36-month dosages in dually diagnosed patients in the experience of the PISA-SIA Group

Table 8. 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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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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3.3

Clinical Foundation for the Use of Methadone in Polyabuse Patients

I. Maremmani, F. Lamanna and M. Pacini

1. Handling alcohol abuse during methadone maintenance

The available data are in agreement that it is quite common for addicts entering a Methadone Maintenance Treatment Programmes (MMTP) to have a history of alcohol abuse; the impact of MMTPs on pre-existing alcohol abuse turns out to vary widely, whereas the results of MMT in cases of heroin use show close similarities [13, 16, 17, 20, 21, 27, 29, 56, 58, 61, 64, 65]. Moreover, the possible increase in alcohol consumption during MMTP develops alongside dwindling heroin use, which suggests a negative correlation between the two, at least in programmes in which dosages are kept low [1, 26].

Alcohol use shows as increasing trend among self-detoxifying and detoxified heroin addicts who undergo naltrexone treatment, suggesting that alcohol serves as a means of compensation for the unavailability of heroin [38, 51, 52]

Whatever craving may emerge, as long as detoxification is proceeding and as long as abstinence continues, addicts may succeed in providing clean urinalyses by switching to cross-acting substances. Whatever the therapeutic setting may be, in the addict's natural environment alcohol consumption may compensate for the lack of heroin availability (due to poverty, somatic impairment, temporary lack of supplies), the outcome being that this becomes a common means of self-managing opiate craving [50].

For heroin addicts, who have strong motivations to "turn over a new leaf", whatever proves to be useful in staying detached from heroin may be resorted to on a regular basis. In the case of other addictive substances, such as alcohol or cocaine, an apparent state of remission actually arises from a switch between forms of addiction. An iatrogenic way of favouring a course towards involvement with alcohol as a surrogate, would consist in skipping or interrupting effective treatment for heroin addiction. The premature removal of

agonist drugs, the easy availability of naltrexone programmes as the most suitable solution for addicts whose condition is mild, medically supervised detoxification programmes, and drug-free regimens are all examples of interventions which directly favour, or refrain from impeding, a switch away from the evolution of heroin addiction towards alcoholism. Conversely, when alcohol-abusing addicts are prompted to try methadone treatment, that may manage to preclude their consumption of alcohol in the short-term, so indicating how quickly and directly opioid agonism is able to act on alcohol craving in this population [10]. Rates of alcohol and heroin use are expected to change in a reciprocal way, according to Anglin's compensatory model [1].

As the results for heroin use were similar, higher methadone dosages were related to lower rates of alcohol and benzodiazepine use [39, 46, 47]. In our personal experience, we ascertained the relationship between methadone dosage and depressant abuse in one single subject over time: an increase in methadone dosage was quickly followed by a significant decrease in alcohol and benzodiazepine use, whereas stable-dose subjects went on abusing depressants at the same rate [39, 46]. When programmes are restricted to low dosages, they are likely to be spoiled by a high incidence of alcohol abuse – a situation that reflects the incomplete control these addicts have over cravings, masked by the coupling of methadone and alcohol. As a result, it may even seem that methadone treatment, when no other feature is specified, somehow favours the development of alcohol abuse [2].

When subjects are abusing cocaine, methadone dosage is significantly higher (130 vs. 65 mg/day, on average, $F\ 2.89$, $p = 0.04$). By contrast, when alcohol use is present in combination with cocaine, no difference is recorded, which may indicate that alcohol has an opiate-boosting function, automatically limiting the need for methadone coverage [46]. Other authors report that, contrary to their expectations, methadone dosages were higher in non-alcohol-abusing heroin addicts [53].

Specific treatments for alcoholism are compatible with methadone maintenance, with the obvious exception of naltrexone treatment. Disfulfiram can be combined with it [37]. Disfulfiram should not be introduced into a protected environment, leaving the results to be tested after discharge, since such a procedure would make the staff and the patient blind to the patients' current craving and the consequent risk of severe intoxication. Disulfiram treatment is not recommended in patients who are susceptible to binge-drinking episodes. Disulfiram should never be self-administered by the patient: one ingenious solution is that of making acceptance of disulfiram administration by the staff a condition for being given daily methadone. In this way dependence on methadone can be used to induce another therapeutic behaviour from the patient [36]. GHB can be used in combination with methadone (table 1). A partial reduction in craving by GHB may also make combined disulfiram treatment possible, until binge-drinking has been extinguished.

In our personal experience Clonazepam may be useful in treating alcohol abuse associated with benzodiazepine abuse. High doses of clonazepam reduce the risk of lethal intoxication by an alcohol-benzodiazepine combination. It is preferable to arrange for a high dose clonazepam induction during a brief hospitalization until doses around 8-10 mg are reached.

2. Benzodiazepine (BDZ) abuse during methadone maintenance

Benzodiazepines are widely and repeatedly prescribed to large populations of patients, with a trend towards unrecompensed long-term prescription, beyond actual effectiveness, which fades as tolerance develops. In this way, high numbers of psychiatric patients, usually suffering from mood or anxiety disorders, become dependent on low-to-moderate doses of benzodiazepines, and fail to break away from them, due to untreated underlying anxiety and dysphoric symptoms which worsen sharply when an attempt is made to taper. Actual benzodiazepine abuse is less common,

Table 1. Pharmacological interactions and dosages in methadone maintained alcoholics heroin addicts according to the experience of PISA-SIA Group

	Dosages (mg/daily)		
	Min	Mean	Max
Methadone, stabilization dosage	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

meaning by that term 'ongoing use despite recurrent intoxication symptoms' [8]. Abuse is sometimes a consequence of prolonged, unsupervised benzodiazepine prescriptions for an anxiolytic purpose, and is sometimes related to recreational use, together with other drugs [57]. Benzodiazepine abusers are highly concentrated (80%) among current polyabusers [49]. A lifetime comorbidity for any other drug abuse reaches 100%.

Typically, benzodiazepine abuse is combined with opiate or analgesic abuse (features found in 77% of all current benzodiazepine polyabuse pictures and in 67% of cases of lifetime polyabuse) [8, 28]. Alcohol abuse seems to have an inverse relationship, at least as a current combination, with BDZ abuse: even so, most current BDZ abusers do have a history of alcohol abuse. Thirteen % of BDZ abusers combine BDZ with cocaine, whereas lifetime comorbidity is less common. Seventeen % abuse two other kinds of drugs, together with BDZ. BDZ use brings with it poorer social adjustment and higher infective hazards [5, 6, 12].

Heroin addicts abuse BDZs for two main reasons. On one hand, they may be resorted to as anti-withdrawal medications. On the other, they may even be tried to boost the effect of opiates, and prolong their effect, as soon as it starts to fade. Some methadone-maintained subjects use BDZs habitually too, though rates vary widely (5-45%) [7, 18, 25, 31, 62, 70]. In this situation, the combination of therapeutic opiates with BDZs may induce a rapid though transient boosting effect which produces an opiate-related 'high'. In accordance with what may be expected from BDZ kinetics, the stable, non-euphorizing effect of a slow-acting opiate is converted into a fast-acting opiate rush. In a laboratory setting, diazepam pre-treatment reduced amounts of methadone that were self-administered by a sample of methadone-maintained heroin addicts [63]: the more diazepam is pre-administered, the lower the amounts of methadone that are self-administered afterwards. No change in expected diazepam or methadone blood levels was reported, so that the behavioural interaction is thought to take place at a dynamic level [55].

On this basis, the hypothesis that has been tested is that BDZ abuse is related to low-dose methadone treatment, below the threshold of average effectiveness (100 mg/day). In fact, the craving for both alcohol and BDZ was inversely related to methadone dose [39, 47]. When higher methadone dosages are employed (over 100 mg/day), BDZ abusers tend to stop polyabusing [6].

BDZs are characterized by a range of abuse potentials. Among street addicts, flunitrazepam and diazepam are far more common than oxazepam, [28]. In fact, flunitrazepam (4 mg) is euphorizing to methadone-maintained subjects [14]**.** On therapeutic grounds, we can state that methadone treatment at over 100 mg/day is effective in reducing alcohol and BDZ polyabuse, along with that of toxic opiates. Lower dosages may produce the extinction of toxic opiate use but leave room for BDZ and/or alcohol use to be initiated or to persist as a result of residual craving.

BDZ abuse that persists during a higher-dose methadone maintenance programme can be challenged effectively by clonazepam treatment [6, 69]. Induction into clonazepam should be performed cautiously. The principle is the same as that used with methadone treatment – the aim should be that of reaching a condition of BDZ-blockade by clonazepam tolerance (over the 6 mg threshold) and reducing levels of craving by residual agonist activity. Also, BDZ-blockade by clonazepam is a protective measure against episodes of fast-acting BDZ abuse.

3. Handling alcohol and BDZ polyabuse during methadone maintenance

Physician**s** may have to challenge different patterns of BDZ polyabuse:

1. patients maintained on ineffective dosages with morphine-positive urinalyses, who also use BDZ and/or alcohol
2. patients who have negative urinalyses for morphine but use BDZ and/or alcohol
3. patients who have negative urinalyses but have dual addiction to BDZ and/or alcohol

In patients with positive urinalyses, the methadone dosage must be increased to the effective anticraving dosage. Induction should be performed rather gradually, considering possible interactions with alcohol and BDZ. Hospitalization may be required. Once urinalyses have turned negative, the use of BDZ and alcohol should be given a second look.

BDZ and alcohol may persist even when urinalyses are stably negative for morphine. Methadone dose increase is recommended, until a blocking value is reached, in order to minimize the boosting effects of alcohol and BDZ on methadone. Lethal interactions are also reduced in patients with high levels of opiate tolerance.

It should be noted that patients who use BDZ and alcohol may tend to oppose dose increases, claiming that their abstinence from heroin at lower dosages is a valid reason for not increasing them further. Such stabilization cannot be considered secure, since control over craving has been partly achieved by having replaced heroin with BDZ and alcohol. The patient should be made aware that dose adjustment is required in order to make rehabilitation follow abstinence from opiates, which cannot be expected to happen if the use of BDZ and alcohol is allowed to develop or persist. Moreover, when the use of alcohol and/or BDZ does persist during treatment, even though they are not addictive at the beginning, this habit may evolve into actual dual addiction later on.

When clear signs of independent craving for alcohol or BDZ are recognized, specific interventions should be adopted.

The omission of correct dose adjustment in cases of BDZ or alcohol use is the basis of actual iatrogenic polyabuse. On one hand, no prevention or counteraction against polyabuse is being implemented. On the other, the combination of low-methadone dosages with the continuing consumption of BDZ and alcohol may directly favour the onset of habitual use in order to boost the effects of methadone itself.

Needless to say, the use of BDZ to favour detachment from methadone means placing patients in a situation where they are at risk of developing a liking for BDZ, especially when fast-acting BDZs are resorted to. Discharging patients after detoxification with prescriptions of BDZ but with no specific term must be viewed as both anti-therapeutic and pathogenic.

4. Handling cocaine abuse during methadone maintenance

Concurrent substance abuse during Methadone Treatment is a common problem which holds down retention rates and interferes with the achievement of satisfactory clinical outcomes both in terms of relapsing behaviour and as regards general health status and social adjustment [3, 9, 22, 23, 30, 33, 40, 48, 59]. As to cocaine, the prevalence of its use among patients in methadone treatment in the USA

increased by three times in the 1980s, with respect to previous estimates [11, 32, 48], so that cocaine has become the most frequently abused substance in that context. The prevalence of cocaine use in untreated opioid-dependent subjects ranges from 30% to 80%, and this phenomenon is still present in patients after a long period under methadone therapy, although treatment initiation produces a non-specific trend against any form of polyabuse, cocaine included [35]. In the 90's, it was proposed that cocaine abuse during methadone treatment might result from an inadequate methadone dose [19, 24, 66, 67]: the theory was that patients initiate or increasingly resort to cocaine and other non-opiate substances in order to achieve a change in their mood or function that is no longer accessible through opiate use, because of the blockade effect or the heightened tolerance.

While this theory has not yet been thoroughly comprehensively checked out, data showed that, when heroin abuse continues in methadone treatment patients, cocaine use may be associated with it, over a wider range of methadone doses [15, 41, 54].

Conversely, the counterbalancing effect of a tonic opiate may render individuals more tolerant to cocaine loads. Maremmani and colleagues [46] showed that cocaine abusers required higher methadone dosages to achieve and maintain psychopathological stabilization, while cocaine abuse was not extinguished. When alcohol was co-abused, methadone dosage was not dissimilar from controls. On the other hand, when heroin was combined with cocaine before treatment, levels of psychopathology, as evaluated by the examiner, were higher, although individuals tended to rate themselves as feeling "better" than heroin-only abusers [4].

On pathogenetic grounds, there is a large body of works that have suggested that a pre-existent psychiatric disorder or even a personality disorder could influence the addiction process and could determine different patterns of drug abuse [34, 42-44, 60, 68, 71]. The association between cocaine polyabuse in heroin addicts and a bipolar disorder has been reported recently [45].

Generally speaking, no standard treatment for cocaine addiction has been developed, whereas a variety of interventions have been shown to be useful in reducing otherwise unspecified cocaine (ab)use.

The administration of higher methadone dosages does neutralize the psychopathological effects of cocaine, but, just by doing so, one could delay the emergence of cocaine-intoxication symptoms, allowing patients to claim they are still quite balanced. On the other hand, psychopathological stabilization corresponds to greater retention in treatment. On these grounds, it is not clear whether to let cocaine abuse come to a psychopathological breaking point earlier, without increasing methadone dosages, in order to justify earlier intervention, though with some risk of dropout; or to buffer its psychopathological symptoms by increasing methadone dosages, with some risk of delaying actual intervention and favouring the transition from cocaine use to addiction.

Patients who use cocaine should not be allowed to take delivery of high amounts of take-away methadone, which may be traded for cocaine. If that happened, control over heroin addiction would be lost, too.

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3.4

Clinical Foundation for the Use of Methadone During Pregnancy and Breast-feeding

L. Finnegan, M. Pacini and I. Maremmani

1. Methodological and conceptual issues

In some cases, treatment of pregnant addicted women is flawed by major omissions and misconceptions. For example, methadone treatment is often regarded as substitution, pointing at its withdrawal-preventing usefulness, which has little to do with its actual employment in an anti-craving and behaviour-modifying view. The main goal of treating women with methadone should be that of minimizing illicit opiate use throughout pregnancy, and to permit them to normalize their health and psychosocial issues. Effective dosages are associated with better outcome. Opiate abusing pregnant women, who are currently receiving methadone treatment, should have their dose increased to control craving. The use of ineffective dosages will produce an incomplete opiate blockade and can be harmful to the pregnancy, causing an unstable intrauterine environment and potentially foetal withdrawal. Apart from a minority of addicted patients who are able to stop using heroin at low doses, the majority receiving less than 80 mg/day will continue abusing practices combining substances in a struggle against the blockade. In such settings, these low dose treated patients may have a worse outcome than untreated addicts. Since most authors agree on the global benefit of effective methadone doses on the course of pregnancy in opiate-addicted mothers, when evaluating treatment effectiveness, in addition to receiving adequate doses, they should be provided with comprehensive services within structured programs especially designed to meet their needs.

2. Premises

Heroin addiction during pregnancy is associated with increased rates of perinatal morbidity, including spontaneous abortion, premature delivery, meconium stained liquor, neonatal infection and withdrawal syndromes

varying according to which substance has been abused [18, 53]. Recurrent exposure to fast-acting, short-lasting opiates produces a condition of continuous swinging from states of opiate intoxication and withdrawal due to a heightened tolerance level to their narcotic action. Fluctuations of opioid concentrations result in an irregular blood supply to the utero-placental unit and the foetus suffers from recurrent hypoxia. Such a mechanism is responsible for delayed foetal development, foetal death and morbidity [18]. Providing opiates equivalent in potency, but characterized by long-lasting, slow-acting kinetics and administered in a maintenance schedule, will normalize opioid metabolism of tolerant individuals and prevent foetal damage.

As for addiction-related issues, a series of additive behaviours may imperil pregnancy: lack of use of sterile equipment, sexual promiscuity, the involvement in violent acts, decreased hygiene, environmental influences, poverty, and refusal to comply with the health supporting guidelines of treatment facilities. The main goal of effective addiction treatment is that of leading addictive behaviour to extinction and normalizing opioid metabolism. Beyond tolerance/withdrawal related issues, the clinical correlates of opioid metabolism are of a behavioural nature, so that increasing dosages of therapeutic opiates can override the compulsion to seek illicit opiates.

Some opiates, such as methadone, display pharmacological characteristics which allow a health-promoting interaction with the brain due to the possibility of behavioural control and long-term damage reversal, at least in less severe cases. Methadone maintenance has been the standard treatment, and the only treatment approved for pregnant heroin addicts [12, 34]. As for non-pregnant addicted individuals, adequate methadone dosing is crucial to enhance compliance to treatment guidelines and achieve health objectives [13]. Even at no blocking dosages, pregnant heroin addicts' behaviour is modified enough to allow attendance at healthcare facilities and to obtain abstinence from cocaine by voucher incentives [19, 32-34, 67]. Methadone treatment may render women capable of attending services without any short-term or monetary advantage [67]. Given the combined benefit for both the mother and the foetus, and the potential double damage caused by treatment omission or delay, pregnant addicts, who apply for treatment, should be given priority for enrollment in methadone maintenance programs.

3. Teratogenicity and pregnancy abnormalities.

No congenital abnormalities have been related to methadone. The widespread exposure of opioid abusing mothers to methadone in therapeutic settings provides an opportunity to normalize the pregnancy and prevent untoward damage to the foetus. When evaluations of drug-induced abnormalities are performed on neonates of women undergoing treatment, the role of poly-drug abuse and alcohol abuse should be considered [1]. Methadone exposed newborns have been reported to have higher birth weights and less morbidity than heroin exposed babies. A trend towards increased birth weight has been reported by Hagopian et al., 1996 [24]. No delivery abnormalities have been noted in women who have followed successful methadone maintenance during their pregnancy.

4. Methadone management during pregnancy.

Methadone metabolism in pregnancy is different than that of the non-pregnant patient and is influenced by the increased body fluid of pregnant women, especially during the 3rd trimester [68]. Methadone elimination is more rapid in pregnant women, so that the half-life is significantly shorter and methadone absorption may be also reduced [13, 30]. In blood sampled from the same subjects, peak methadone levels after equal oral dose loads are lower in the pre- than in the post-partum phase [43]. When withdrawal symptoms are monitored in a population of heroin abusing pregnant wom-

en entering methadone treatment at variable stages of their pregnancy, symptomatic women display methadone serum levels below the 0.211 mg/l [27], while administered dosages are similar. [Also a discrepancy seems to occur between higher methadone dosages and foetal serum levels of the drug: this latter tend to be similar regardless of increases of oral maternal dosages [14]. It should be remembered that different oral dosages may actually correspond to similar blood levels: therefore, such discrepancy may have no actual implication as long as the administration of methadone to pregnant women is rather based on clinical needs than on a scale of absolute oral dosage value [15]. As a consequence, some pregnant heroin addicts are provided ineffective medication due to unjustified cautions by the clinician [20].

5. Neonatal abstinence syndrome in methadone-exposed newborns.

Since opiates traverse the placental barrier and foetal tissues become tolerant to their presence, the sudden deprivation of an opioid source at delivery may result in a withdrawal state, called the neonatal abstinence syndrome (NAS). More than one substance may be involved, and one should be aware of the possibility of a combined tolerance to opiates and gabaergic neurodepressants (benzodiazepines). NAS occurrence is variable and is generally seen in 60 to 90% of exposed neonates [6, 16, 26, 54, 59].

NAS intensity is widely variable. Onset of abstinence seems to depend on the interaction between the newborn's slow metabolism and the agents' own slow dissociation from binding sites. Long acting morphine substitution is not preferable to methadone in preventing the occurrence or severity of neonatal withdrawal [21]. When buprenorphine was evaluated, withdrawal was rated as milder and hospitalization time was consistently shorter [56].

Symptoms generally occur within 72 hours. The course of withdrawal traverses a period of a week to several weeks with a gradual decrease in intensity within an undulating pattern. During this period the infant can gradually be stabilized [70]. Duration of hospitalization is generally longer for methadone than for heroin withdrawal. Polydrug abuse further contributes to the duration of withdrawal symptoms (Johnson et al., 2003). When morphine is used (as a tincture of opioid solution), lower dosages administered more frequently are associated with fewer days of hospitalization in comparison with higher dosages at longer dosing intervals [31]. An earlier (within the first three weeks), transient hyperphagic picture has been described which does not correspond to an increase in weight and appears to be unrelated to other withdrawal symptoms and maternal methadone dosage [49].

The relationship between NAS and maternal methadone dosage is controversial. Some authors have found no association with dose [4, 5, 24, 35, 37, 38, 42, 46, 51, 58, 64, 69], while other authors ascertained a dose-dependent relationship with regard to incidence and severity of abstinence in their samples [14, 26, 41, 47, 48, 50, 52, 53, 62, 63, 66]. Some of the studies evaluating this relationship used very low doses, far below average effective dosages. Such a methodological choice is likely to correspond to patients being treated at ineffective dosages and not representing the level of health and behavioural stability achievable by methadone maintenance. Anti-withdrawal and partially blocking dosages, such as those between 20 and 60 mg, do not suppress craving and favour the combination with other opiate-boosting or replacing drugs, such as benzodiazepines, leading to the misinterpretation of clinical findings. Patients, for whom a 20-30 mg dose is enough are likely to be low-severity individuals and will not abuse opiates during pregnancy; on the other hand, average-to-high-severity patients not provided with effective doses will continue abusing drugs when provided a 40-60 mg dose. In some studies, [10, 50], NAS severity is predicted by benzodiazepine and cocaine abuse, respectively, while no other opiate-related predictive factors are identified. The possibility of a combined withdrawal, (opiate and alcohol-benzodiazepines) may also be considered] [57].

Therefore, NAS will tend to be more severe for higher dose patients, whose dosage is still not enough. However, no difference is reported by Berghella and colleagues, who studied NAS in infants exposed to less than 80 mg/day to those exposed to more than 80 mg/day [3]. Sinha et al [63] report NAS being more often in need of morphine treatment in women taking higher methadone doses, but methadone-only exposed children are at lower risk of NAS than heroin-exposed ones. Overall, most results indicate NAS is less frequent in infants of methadone treated mothers than heroin using peers. Although there is a risk of NAS in methadone exposed infants, the syndrome is treatable and not lethal if it is assessed and managed appropriately. The NAS is overshadowed by the acquired gain in pregnancy and delivery outcomes and the mother and child's health status as well as many psychosocial aspects that can be ameliorated [29].

Many clinicians still practice medically supervised withdrawal from opioids during pregnancy [45]. Along the stated reasons for withdrawing pregnant women is to prevent NAS, prejudice or lack of knowledge about addiction and its clinical features [55]. Medical withdrawal is not indicated during pregnancy except in a few instances where logistics hamper the delivery of methadone maintenance.

Some clinicians have tried a fast detoxification procedure with the claimed aim of NAS prevention. A twelve-day schedule of methadone withdrawal shortly before birth resulted in 29% of relapses just after the schedule completion, and a global short-term abstinence rate of 59%, while 15% of newborns required treatment for a clinically relevant NAS [11].

Safe management of pregnant opioid addicted women should start by methadone maintenance at effective dosages. NAS resulting from methadone exposure should be evaluated by clinical surveillance and treatment when needed with an opiate at tapering doses [60]. Moreover, the administration of higher methadone dosages should never be offset by the priority to avoid neonatal withdrawal since NAS is manageable through adequate care and treatment, whereas damage resulting from untreated addictive behaviours can be permanent.

Opiate withdrawal can be effectively treated by following a tapering schedule [2, 56]. Shorter dosing intervals of opiate-containing solutions have been found to reduce the duration of withdrawal [9], Morphine solution is preferred for the treatment of NAS.

Breast feeding of mothers on methadone may be helpful in flattening the withdrawal slope to a drug-free state [21, 28, 44]. Breastfeeding alone is not likely to provide the infant with enough methadone supply, and is not always viable due to concomitant conditions, such as HIV infection. Barbiturate treatment may be indicated in addition to morphine when benzodiazepine withdrawal coexists.

6. Neonatal thrombocytosis

Increased platelet count and aggregating function have been reported in newborns of methadone treated mothers [6-8, 25], with an estimated prevalence of 3,65% [22]. A similar finding has been described in the offspring of opiate-tolerant female mice [7]. Platelet overcrowding may occur regardless of which opiate has been administered, that is both for heroin addicted mothers and opiate treated subjects. Its timing seems to follow that of neonatal opiate withdrawal, with a delayed onset one week after discharge and a protracted course lasting several weeks [22]. The causes and mechanisms of such a phenomenon have not been reported, however, the parallel evolution concomitant with the abstinence syndrome suggests it may be reversed by cross-tolerant opiate drug treatment.

7. Strabismus.

Surveillance for the development of strabismus is needed in children of opiate-dependent mothers. Available data do not indicate any correlation with either methadone dosage or altered opiate tolerance (NAS-related fea-

tures) [23].

8. Methadone for pain in pregnant women

Chronic pain control may benefit from increased long-acting opiate coverage without employing further analgesic agents. Breakthrough pain control needs fast-acting agents. Morphine is suitable to relieve acute pain in methadone maintained patients with its dosage to be established on a subjective basis. As a rule, methadone tapering during pregnancy is not recommended. Pain can be one possible consequence of lowered opiate coverage. Other combinations with non opiate analgesics may be considered [61].

Women receiving methadone for pain control during pregnancy deliver earlier, differently from methadone maintained pregnant heroin addicts [23]. Methadone for pain is administered for shorter periods and generally at lower doses than that used for the addicted individual. NAS has been observed in 11% of the neonates. Wholly, neonatal outcomes of methadone treated pregnant women differ along the reason for methadone administration (pain vs. addiction).

9. Early child development

Developmental delays have been reported in methadone-exposed babies [55, 72]. Growth is slower during the first trimester, but no difference in achieved dimensions is noted at six months: a compensatory acceleration of growth takes place farther from discharge. Head circumference is normal within one year of age [40] while no cognitive delay is documented during infancy [36, 39, 40, 65]. However, when methadone is provided to pregnant women at effective dosages within structured programs, newborns tend to weigh more and have a larger head circumference; the latter in proportion with the average dose administered during the third trimester [24]. Examining the possible factors which may contribute to developmental abnormalities in a group of children of addicted mothers treated with methadone, no relationship was documented with opiate-related characteristics, such as methadone dose and duration of exposure to methadone [17].

10. Breast-feeding

Breast-feeding is possible for methadone maintained women. The milk contains approximately 2% of daily dose and concentration [71]. Values range from 0,05 to 0,57 mg/ml for dosages varying from 10 to 80 mg/day [71]. Daily methadone exposure is approximately 0,02-0,09 mg/die, far below the theoretical lethal dose in non tolerant babies. On the other hand, such a dose is not enough to prevent NAS in opiate-tolerant newborns. However, methadone maintained mothers who breast-feed their babies should not stop abruptly if dosages are average-to-high [48]. A study linking prenatal methadone exposure to delayed development examined a group of women treated with an average dose around 40 mg, which does not shield against poly-drug abuse and addictive behaviours [70].

11.Psychological aspects

'Pregnancy', as a life event, is often experienced by patients, or suggested from others, as somehow psychologically linked with the natural history of addiction. Redemption themes should never be supported or induced, and pregnancy should never be considered as a healing opportunity through a withdrawal from therapy. In fact, expectations and motivational drives have nothing to share with the destiny of a metabolic disease. On the contrary, patients will have to be provided with adequate information on treatment opportunities and feasibility in order to complete pregnancy in the best way. A good counselor could motivate, through the experience of treatment

during pregnancy, a stronger relationship with the therapeutic program. In this case, pregnancy can really become a motivation to treatment and can be so turned into an "opportunity of treatment".

12. Parental role

Heroin dependence can compromise one's capacity to provide parental functions. The loss of maternal priorities in a heroin addicted woman with children allows us to understand its severity as a disease and its power to deviate behavior from instinctive and fixed patterns, such as that of maternal attachment to her infant. Feelings and emotions linked with the contact with and the responsibility for their children are often present in heroin addicted women. The incoherence between the importance that mothers claim to attribute to their children and their behavior, which is contrary to the maintenance of a parental role, is therefore an evident sign of addiction. Motherhood can represent in a women who is a drug abuser but not drug addicted, an opportunity to stop her abuse, however, this is not the case in the presence of drug addiction. The awareness of their one parental responsibility and the presence of maternal feelings can cause in drug addicted mothers demoralization, guilt and feelings of inadequacy and suicidal thoughts. Maternal psychotoxic effects of abused substances expose children to the risk of a chronic lack of emotional interaction, neglect and abuse and experiences of violence in their environments. Drug addicted women are conscious of what could improve their parental function (i.e. a behavioral control recovery), but are not able to plan a coherent, adequate line of conduct. Drug addicted women, as with most drug addicted individuals whose addiction is not very severe, aim to recover control of the substance of abuse, in order to continue its use freely, and resort to a treatment able to solve the critical situation of the moment. Questions such as home care or resorting to a family collaboration are considered secondary with respect to the solution of those linked with substance use. An anti-addiction therapy has to restore the mother so that she can maintain a parental role. Parental dysfunction is an expression of the disease of addiction and so its recovery has to pass necessarily through the treatment of the addictive disorder. As for every category of drug addicted individual, a therapeutic approach must have the aim of allowing patients to recover through a continuum between intention, planning and behavioral drives.

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3.5

Clinical Foundation for the Use of Methadone in Jail

I. Maremmani, M. Lovrecic and M. Pacini

1. The rationale of methadone treatment: as outside, so inside penitentiaries

To date, agonist maintenance has proved to be the most effective means of intervention on the core of opiate addiction. Although other treatment typologies can play worthwhile roles within a programme, they still loom as side approaches. In correctly structured programmes of intervention, they either stem from the pharmacological core of agonist maintenance; or, more exactly, function as pathways to bring specific agonist interventions within reach. The key issue of agonist treatment is the prevention of relapse and recidivism, to be attained by suppressing craving for heroin. Agonist treatment has got further beneficial characteristics: first, doses can be administered that will prevent heroin from being sensed, even if patients continue to inject heroin in the early phase of treatment (known as 'opioid blockade'). Eventually, in terms of therapeutic relevance, though firstly in chronological order, agonists provide prompt buffering against upcoming withdrawal.

Agonist management that aims to restore the pre-intoxication tolerance threshold can be ruled out as an effective therapy for heroin addiction. Moreover, although somatic balance is restored, psychic toxicity and tolerance to craving for heroin are anything but under control. At present, the latter situations are what most jailed heroin addicts live in, while there is no procedure available for reaching out to them through specific agonist (methadone or buprenorphine) programmes. Differences in the therapeutic destiny of prisoners do not mirror any actual difference on pathological grounds, as the illness is the same for jailed as for free heroin addicts, and for the same heroin addicts before, during and after imprisonment.

Those who oppose to this view can argue that anticraving therapies are pointless inside prison walls, because no control over the drive towards heroin or blockade of narcotic effects is needed, considering that street drugs are not available. Leaving aside the long-standing is-

sue of drug availability in jail, we prefer to focus on this question from a medical viewpoint. Agonist maintenance chiefly aims to prevent a spontaneously relapsing course. At the same time, it should bear in mind exactly which cerebral functions have suffered damage from chronic heroin exposure. Otherwise, it cannot provide any heroin-like subjective effect, as the misleading term "substitution therapy" suggests.

Transforming time spent in jail into therapeutic time offers advantages that do not stand or fall on the basis of whether addicts use drugs or not while imprisoned. As long as the ultimate criterion for assessing treatment effectiveness is the individual's adjustment in a free setting, a therapeutic regime with a standard dose and scheduling features will work in such as way as to increase the likelihood that prisoners will stay in touch with a therapeutic setting after their release. Even if it is not completely effective, this solution at least allows patients some protection against drug-related accidents. Supporters of pharmacological intervention [50] and supporters of community-based programmes [9,18] have both assessed the feasibility and usefulness of standard addiction treatment inside prisons, on the assumption that differences in treatment approach did not cancel the shared aim of preventing recidivism. The true promise of agonist therapies for addicted detainees is that of building up a subject's social reliability on scientific bases, while they are kept under control in a correctional institution. Otherwise, at present, released detainees usually reacquire their social freedom together with a certainty of relapse. Besides this, as long as pharmacological shielding is maintained, the individual's freedom continue to be linked with a guarantee of social harmlessness [38].

2. Towards a prison-based treatment for addiction

The 1950 OMS definition of addiction as a disease helped to ratify the changed scientific awareness of the role of psychopathology in the dynamics of drug-related phenomena. In line with the new view, imprisonment was no longer regarded as a means of intervening specifically against addictions; alternative measures were needed to allow detainees to benefit from free therapeutic settings. The law indicated drug addicts as a category that merited a therapeutic rather than a correctional solution, through what was called "therapeutic parole": even if the prison system in itself plays no therapeutic role, it may mark a crucial stage in the history of addiction. In fact, not every case is suitable for therapeutic parole. However, the health of addicts who cannot be selected as parolees can be preserved in other ways. On one hand, the law states the need to develop therapeutic programmes while time is being served, and on the other the need for continuity between therapeutic options inside and outside prison. Generalizing, minor offenders, who make up the commonest criminal typology among drug addicts, are best handled as mentally ill people, so therapeutic needs must prevail over the need for imprisonment. Whatever their crime, addicts who are unfit for therapeutic parole, show that addiction should continue to be recognized as a medical issue, that calls for specific intervention. It has been recommended that medical facilities for drug addicts should not differ from those offered to their free peers. Moreover, treatment should not be discontinued when passing from freedom to detention or the reverse. Correctional institutions should then be cooperating with the health system for free citizens. Lastly, detained drug addicts should be approached as subjects who come from the community and are, hopefully, destined to rejoin it (Oldenburg Conference on "Jail and Drug Addiction", March 12-14, 1999). A prison, just like a therapeutic community, can become a useful setting for starting subjects on treatments, the aim being to guarantee their social role in view of their future return to freedom. The control exercised by police within prison walls may help to promote the feasibility of treatments, by overcoming the lack of compliance that would cause treatment failure in a free setting. In other words, individuals who would be untreatable because of lack of compliance

or would never request any treatment as long as they were ill but free, may welcome the opportunity to receive treatment as long as they are deprived of freedom.

In recent times, changes have been made to the prison system in an attempt to organize a special setting for the handling of addicted inmates. There is, however, a risk that these innovations will develop without specific instruments for curing drug addiction, simply providing environmental, recreational and rehabilitative options which may be out target.

In our opinion an effort should be made to focus on the possibility of exploiting some of the features of prison life, which are needed anyway to ensure security, to enhance the impact and feasibility of therapeutic measures that specifically target drug addiction. When the law leaves no alternative but detention, this may create an opportunity to administer treatment [38] , and we could then start talking about "prison-based treatment initiation".

2. Effects of agonist treatment on addiction-related crime and handling of addicted detainees

2.1 Specific treatment for addiction and the prevention of criminal recidivism

Agonist-maintained heroin addicts have a 5% likelihood of being imprisoned at some point during a 7 year follow-up period [35] or 2% at the end of 12 years 46. To be under methadone maintenance implies a low risk of imprisonment both with respect to untreated peers [12, 20, 23, 25, 30-32, 34, 37, 40, 44, 52], and compared with the same subjects when they were not being treated [3, 13, 15, 39]. When treatment is discontinued, its protective value is lost as soon as addictive behaviour re-emerges — a moment that does not necessarily occur during withdrawal and that often follows an early period of abstinence. In fact, it is over the medium to long term that craving and addictive drives re-emerge, pushing the affected individual into a spiral of relapse which can now be expected to spin faster than in the past. In Italy it has been reported that 75% of imprisoned addicts had stopped their treatment over 60 days before being arrested, while only 3% were imprisoned in the short-term after treatment discontinuation [6]. It can be said that in Italy the spread and continuance of methadone maintenance was related to changes in addiction-related crime between '86 and '95, due to changes in the numbers of imprisoned subjects who were attending a methadone maintenance programme. The number of imprisoned addicts rose from 6,000 in 1986 to 13,000 at the end of 1995. On the other hand, the number of methadone-maintained subjects among the population of jailed addicts followed a different course: an initial increase was documented in the late eighties, while methadone treatment was spreading nationwide; this was followed by a steep fall in the early nineties, when the percentage dwindled from 33% to 3% [4] (See table 1 for details). In France, where agonist treatment started spreading in the nineties, the percentage of agonist-treated subjects among jailed addicts gradually fell. Experts at the French Ministry of Health have tried to explain this phenomenon as a preventive effect of the ongoing treatment, which tended to hold addicts back from imprisonment as the outcome of criminal involvement [21, 49].

Over 40% of all heroin addicts who had drug-related legal problems were imprisoned at some stages over a 20-year follow-up period [16].

The criminal career of heroin addicts who enter maintenance treatments shows a strong tendency improvement in terms of frequency of reimprisonment [3, 15, 35], number of detention periods and total time served while attending the programme [20]. Patients who agree to take 60 mg/day (the standard threshold for opioid blockade) are less likely to be sent back to prison than those who refuse to take blockade dosages [2, 48].

Conversely, unspecific treatments fail to affect the natural course of addiction and the addiction-related crime of former detainees [40].

Table 1. Incarcerated methadone-treated addicts in Italy

Survey term	Incarcerated addicts	Methadone-treated addicts	
		N	%
1996-12-21	6.102	252	4.13
1987-12-31	5.221	1.742	33.37
1988-12-31	7.500	750	10.00
1989-06-15	8.790	1.916	21.80
1990-12-31	7.299	184	2.52
1991-06-30	9.623	273	2.84
1991-12-31	11.540	378	3.28
1992-06-30	13.970	237	1.70
1995-12-31	13.448	391	2.90

2.2 The advantages of methadone maintenance for the prison environment

In Canada a heroin-addicted detainee made the first move by bringing the Kent prison system to court on a charge of therapeutic omission, because he had been denied the right to initiate a methadone maintenance programme while in jail [33]. In the Republic of Ireland it was the penitentiary police who proposed the extension of methadone maintenance inside prisons [24].

These two events should not surprise us if we consider the fact that detainees and prison guards are those closest to what happens inside penitentiaries: between 1989 and 1995 no drug-related deaths were recorded for methadone maintenance addicts: those dying from drug use were not receiving agonist treatment [14].

2.3 Dysphoria, aggressiveness and self-injuring behaviour

Aggressiveness in heroin addicts has more than one meaning. In most heavy heroin users it is closely related to the severity of addiction, and the intensity of craving. A minority of heroin addicts, who stand out as particularly violent, are characterized by extremely severe withdrawal symptoms, together with a harm-avoidant personality trait, which may be the behavioural expression of a biological predisposition to suffer great damage from chronic heroin exposure. In fact, sensitivity to heroin's behavioural toxicity (dysphoria and aggressiveness) and a disposition to develop addiction (with a quick transition from experimental to regular use) are interrelated, which suggests that aggressiveness and addiction-proneness share the same underlying biological structure. In the stereotypical heron addict, craving justifies symptoms of aggressiveness, and thereby mirrors the severity of addiction. In prisons, violent behaviour, suicidal and self-injuring acts are highly represented among the psychopathological events of heroin addicts. However, suicide and self-injuring behaviours are not most likely during withdrawal [19]. It must be born in mind that the risks increase in the medium term, so that it is malpractice to discontinue agonist treatment by tapering steeply, even if it is apparently safe to do so in the short term. The consequences of an opioidergic malfunctioning become evident over time, so that recently detoxified, un-medicated addicts may quite suddenly begin to behave aggressively. Patients benefit most from ago-

nist treatment, even when dosages are inadequate. Even so, higher agonist dosages are required when aggressiveness is high at treatment entrance. From another standpoint, ongoing naltrexone treatment brings with it a higher risk of aggressive and suicidal behaviours than methadone treatment does, as shown by comparing groups of patients who did not differ in aggressiveness or suicidal risk at treatment entrance. The need to act vigorously and immediately against aggressiveness, while concomitantly reducing craving and addictive behaviours was the objective that the prison officers had in mind in proposing the extension of methadone treatment inside prisons [24].

2.4 Unsafe practices

Before talking about possible pharmacological issues, it can reasonably be assumed that internal security measures against the spread of drugs are at least partly effective against drug-related events in prisons. On the other hand, given the promiscuity of the prison environment, and the grouping together of individuals riding the same craving *wavelength*, drug-related happenings tend to be uncontrollable, though infrequent [8, 21, 27, 42]. Moreover, drug-related risks inside prison are heightened by what is, on average, the greater severity of addiction of those who end up in jail — individuals who often display poor impulse control or antisocial personality disorders. Methadone maintenance favours an opposite trend for drug-related behaviours: treated individuals, unlike their untreated peers, show greater even while continuing to inject, and win a better level of impulse control. Conversely, when craving-related urges coupled with low substance availability are concomitant with a lack of therapeutic coverage, the risk to health rises steeply. By contrast, even when drug-using continues in jail, and returns to pre-incarceration levels soon after discharge, unhealthy habits (such as needle exchange and unsafe sex) remain uncommon amongst methadone-maintained heroin addicts [8, 51]. In a German survey, the risk for HIV seroconversion turned out to be negligible for methadone-maintained detainees, in sharp contrast with a 5.9/100 year/person rate for the whole prison sample, and 8.9/100 year/person among methadone-free heroin addicts [45].

It is logical to conclude that a specific therapy — one that aims to prevent relapse by craving suppression — should be regarded as first choice for detained, as well as free, heroin addicts. The data even allow us to state that addicted detainees are a category of choice for methadone maintenance, because of its striking efficacy on severe and high-risk addictive subpopulations.

In some cases addiction-targeting treatments are not feasible, due to medical incompatibility or absolute opposition by the patient, even when the consequence may be a longer prison term. In these cases, the controlled administration of heroin is justified on a scientific basis, as long as heroin-taking detainees are isolated from other prisoners with a heroin problem [32].

The provision of clean injecting equipment does not encourage substance use, while it is effective in reducing infective accidents (such as seroconversion and needle-exchange) [32].

Specific agonist-based intervention is, therefore, compatible with harm reduction in the same context. In fact, harm reduction does not hamper the spread of effective treatment; on the contrary, it helps to reduce the harm deriving from residual drug-taking activities that are not covered by the agonist treatment itself.

On the whole, substance use inside prisons can be countered in two separate directions: police controls limit the spread of drugs and, therefore, the incidence of drug-using. Specific interventions, on the other hand, should boost the effectiveness of police control by acting from inside the subject, and from within the addict population (by reducing demand). In this context, agonist treatment helps to prevent leaks within the control system from causing further damage beyond the mere use of drugs. Similarly, in a free setting, agonist treatment is

the simplest and cheapest way of curbing all drug-related phenomena.

3. The role of detention in the natural course of addiction and its therapeutic destiny.

3.1 A medical or an environmental problem?

Imprisonment necessarily impedes ongoing substance use. Nevertheless, abstinence, whether self-determined or forced, does not cause craving to dwindle, especially in the case of opiate addiction. This explains why there is a demand for narcotics from inside prisons, and why there is a need to counteract the spreading of narcotics inside prisons by police measures. The latter are undoubtedly effective in limiting drug using among detainees, but they do not hit the core of addiction. The main drive to substance use is not rooted in the prison environment: in other words, it is not a habit born inside the prison community, but the outcome of the grouping together of independently ill individuals who became addicted while free. Two intervention strategies should be distinguished: an aspecific one, aiming at the limitation of drug use behind bars (*supply reduction*), which is the task of the police system; and a second, more specific one, rooted in medical experience, which aims to reduce the appeal of drugs inside prisons (*demand reduction*) [47]. Similarly, the issue of substance use initiation within jail is linked with drug availability inside, but also with the demand for drugs by addicted habitual users. In fact, when no treatment coverage is provided, untreated heroin addicts may initiate their jail mates into the use of heroin. A prison setting may be useful in improving the prisoners's quality of life, but the control of addiction as a medical problem can only be achieved by a specific, individual-targeting intervention, which may also prove to be beneficial to the whole prison community.

Depending on whether treatment or absence of treatment is chosen, a prison setting may heighten or help to solve drug-related issues, both for the individual and the community [50].

3.2 Rationale of agonist maintenance in prison

A prison setting does not curtail the effectiveness of methadone maintenance on narcotic-seeking drives [11]. It follows that methadone treatment must be as readily available in jail as it is to free addicts [5]. Several programmes for narcotic addiction, though potentially useful for those who stay in treatment, were not complied with from the beginning by the standard heroin addicts [42, 43]. By contrast, a clinical trial run by the MTC project team where detainees were started on LAAM three months before scheduled discharge, 92% proved to be compliant in the induction phase [22]. A methadone maintenance programme bridging the transition from a prison environment to a free life outside, despite a noteworthy dropout rate after discharge (40%), makes it possible to set up a therapeutic relationship, which is likely to be renewed, at least on a yearly basis, even when patients have no real wish to comply with a structured programme [26]. The coercion implied by a prison-based programme is, in any case, useful in increasing retention rates, without hindering the effectiveness of a later free setting equivalent. It must be pointed out that any treatment effectiveness depends on the type of chemicals used: methadone itself may possess low effectiveness when administered without specific rules or objectives, merely to buffer drug-related discomfort. Predictably, the great majority of subjects will discontinue treatment after discharge, if not earlier during the induction phase, so missing the chance to bridge the transition from in-jail therapeutic initiation to outer stabilization. Even so, as many as 60% of patients who had gone through the induction phase by discharge time went on to attend a maintenance programme lasting over the next 6 months, and a further 30% did so for a shorter

period, at least saving themselves from relapse overdose events, which often occur among discharged agonist-free individuals. Addicted detainees should be empowered to attend the ongoing programme at the time of discharge, so as to accomplish the current phase (whether induction or stabilization), and, before that, they should be given the opportunity to start a structured programme while detained. The KEEP programme has been set up to implement this philosophy, so becoming the first experimental methadone maintenance programme for NYC Rykers' Island's detained addicts. One early, major result is that of upgrading detention time as an opportunity to get detainees started on addiction-specific programmes. As many as 85% of untreated detainees is under treatment at discharge and they are referred to the local treatment facility [48]. On medical grounds, a prison-based methadone maintenance programme is conceived to achieve two major aims: on one hand, as with all categories of addicts, the prevention of recidivism and relapse; on the other, the improvement of patients' quality of life during detention. Further, a methadone maintenance programme's objectives may be distinguished according to scheduled detention time, and therapeutic status at the time of imprisonment. Already stabilized patients, whatever their discharge schedule, should be kept on maintenance. Patients incarcerated while in the induction phase must reach a blocking dosage. Stabilization is achievable as an objective even in a prison environment; despite this, the return to freedom presents a new challenge for stabilization to continue. Methadone dose increase and other forms of therapeutic intervention may be required when freedom returns. In other cases, the loss of freedom may have been a major stress factor for stabilized individuals, so justifying dose increases or supplementary interventions in a prison setting. On the whole, dose increases are often necessary and feasible after release, while dose reductions or medically supervised withdrawal are to be avoided. In fact, patients should be returned to their original environment with an individual guarantee of future stability (i.e. dosage not lower than the previous stabilization value) or at least a standard guarantee (average stabilization dosages). In any case, an average dosage provides protection against narcotic overdoses after discharge. Dose reduction and medically supervised withdrawal carried out in prison leave discharged patients at high risk of behavioural instability and overdose events. It follows that these two procedures must be classified as malpractice. Even worse is the practice of tapering methadone and administering benzodiazepines as a means of buffering withdrawal; not only are patients deprived of their specific therapeutic coverage, but depressant polyabuse is favoured [29].

Some categories of patients should be referred to a methadone maintenance programme as a priority, regardless of treatment setting (whether free or prison-based): this is true of all addicts for whom enduring involvement with heroin may worsen or complicate concurrent somatic, psychic or psychosocial problems.

Methadone-maintained addicts are more likely to enrol in anti-tubercular programmes, and to accomplish the therapeutic schedule of chemotherapy [28].

Detained addicts who have undergone specific treatment in prison are less likely to have been sent back to prison or to have relapsed into substance use six months after release [36]. The best protected subjects are those who are still in treatment long after discharge, while treatment that is started in prison only to be discontinued soon after discharge is not effective as a means of long-term relapse prevention [17].

The option of having detention terms shortened as long as one agrees to attend a therapeutic programme might become a trend with a scientific basis. A spontaneous request for treatment is not predictive of better retention rates, but it is true that subjects who apply for treatment spontaneously have lower re-incarceration rates, while treatment discontinuation due to lack of compliance is as likely as for their coerced peers. As a result, treatment as an alternative to prison may prove effective in improving subjects' compliance and retention rates [1, 10]. Given that the effectiveness of treatment is not linked with treatment options,

which depends on a free choice, the motivation to enter treatment should not be considered crucial to a positive outcome. In any case, an application for treatment is at least partly the result of do-or-die psychosocial forks, such as being sent away from home, breaking up with one's partner, being parted from one's children, or losing one's job or income.

Some of the advantages of methadone treatment are indirect. For instance, it not only reduces the risk of seroconversion among seronegative addicts, but also among the seronegative non-addicted partners of seropositive addicts. Similarly, the achievement of behavioural control in subjects who entered prisons as heroin addicts makes it less likely that they will initiate non-abusing cell mates; this is far from being a secondary issue. In fact, as many as 3-26% of detained addicts reported trying heroin for the first time during a previous period of detention. Globally speaking, 0.4-21% of addicted heroin injectors started using heroin in jail.

3.3 Safe discharge

Discharge-related overdoses are far more likely soon after discharge (during the first two weeks) than later on [41]. This means that these events are not the result of a true relapse into regular heroin use, but are due to a sudden increase in craving, without any anticraving lock, hitting individuals when they are not tolerant. For some substances, such as cocaine, a substance-free period may be useful in reducing craving. Conversely, heroin-free time spent without any anticraving treatment is expected to result in a relapse. The discharge of non-tolerant individuals, kept drug-free in prison after detoxification and not given any agonist treatment, is hazardous. Paradoxically, the risks would be lower for subjects who had been using heroin throughout their detention. In no case should medical intervention raise risks higher than those made inevitable by the underlying disease.

A maintenance programme continuing at the time of discharge is best in terms of safety; this is true even if some addicts discontinue when they return to freedom. Protection against overdosing is equally effective during imprisonment, as it is afterwards, as long as treatment proceeds [22]. Discharged addicts should be tolerant to 60 mg/day at least. In no case should naltrexone administration be initiated, shortly before or shortly after discharge, because this constitutes a risk condition for relapse, and reliable relapse protection can only be provided by agonist treatment. Similarly, it would be reckless and pointless to start naltrexone medication in prison, as it is suitable in only a few cases, and needs to be evaluated when heroin is available (outside the jail).

3.4 Naltrexone

Alternative measures are feasible as long as subjects are compliant with treatment rules. When compliance is lost, so is the guarantee that the measures adopted will build up and maintain the subject's social function, or make treated patients suitable for attempts of rehabilitation.

The fork leading to social readjustment or to self-perpetuating dysfunction is closely related to the state of addictive dysfunction as measurable by core addictive symptoms. Undoubtedly, chronic or repeated acute intoxication openly hinders social adjustment, but its disruptive weight is hierarchically inferior to the addict's cognitive, affective and behavioural malfunctioning, all of which bias any future project for the addict to attempt, by shifting any effort towards the substance side. In fact, abstinence from drug-taking does not itself lead to the extinction of the addictive disease. On the other hand, anticraving interventions gradually bring abstinence into being in a spontaneous way, though substance use may be persisted during the early period of treatment. Despite all the knowledge acquired so far, agonist treatment is often regarded as a sort of substitution for heroin, and the substitution of heroin-derived opioid damage provided by therapeutic opiates is mistaken for a legal means for continuing an involvement

with narcotics. In reality, some opiates can be used for therapeutical purposes just because, for them, no positive reinforcement follows exposure, so that they do not share any of the rewarding subjective effects experienced with street opiates. In fact, one component of the rationale for their use is that their non-reinforcing property leads to an anticraving effect on subjects who have become hooked on abusable street opiates.

On the other hand, opiate antagonists are suitable for, and accepted by, mildly ill heroin addicts only, for whom social respectability or general health counts for more than the strong pleasure provided by the substance. Their awareness that they would no longer sense heroin because of an opioid blockade is enough to make them refrain from using it, despite their craving. In behavioural terms, we can say these addicts are less than severely ill, as witnessed by their willingness to adopt a treatment strategy which does not itself control craving, while it sharply limits rewards. In subjects who comply with naltrexone maintenance, and agree to undergo urinalyses, treatment has proved effective and safe. Retention in successful treatment has allowed naltrexone-maintained detainees to benefit from alternative measures [4]. Heroin-addicted parolees who spontaneously attend a naltrexone maintenance programme, are more likely to stay off heroin and less likely to be re-incarcerated within their first six months on parole [7]. These results are similar to those achieved with free heroin addicts, but they only fit a small minority of heroin addicts, who suffer from a mild form of the disease, and keep to a maintenance regimen, which is something sharply different from taking naltrexone shortly after a detoxification procedure.

A patient's determination to take naltrexone in the short term does not ensure a positive outcome. Generally speaking, there is no safe conduct in having addicted detainees discharged while on naltrexone; craving may emerge violently when the substance is available again after a period of isolation, and this heightens the risk of overdose. By the scheduled term for discharge, a therapy should have been started that is capable of making addicts tolerant to opioids and calming their craving at once. This objective is achievable by induction on methadone, with a dose of at least 60 mg/day.

4. Conclusions

Addiction itself is likely to cause legal problems and confrontations with authorities. Each legal incident may represent an additional problem, or, conversely, an opportunity to start a therapeutic programme, hopefully a specific one. Whatever the approach adopted, we aim to rehabilitate our patients and allow them to get back to their natural environment, bearing in mind that the best therapeutic choice in any setting, prison included, is that which has proved most effective in a natural setting. Agonist maintenance is currently the option which gives the best guarantees in terms of rehabilitation, relapse prevention and social adjustment goals.

Whether in public health or prison settings, addicts are sometimes given free access to off-target facilities, which do not even aim to achieve relapse prevention, but only to allow a drug-free condition, with no further guarantee that abstinence will be maintained.

The extension of methadone maintenance inside prisons, in the form of a multiple phase programme, is meant to be a specific therapeutic intervention for addicted detainees [5]. It does, in fact, offer the best way of controlling the core features of craving and relapse proneness regardless of environmental and setting differences. It is crucial to the aim of integrating the prison system in the web of addiction treatment services, as heroin addicts are naturally prone to go through incarceration experiences.

If we succeed in converting detention time into therapeutic time, detention may actually become meaningful for criminal heroin addicts.

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Appendix 1. Guidelines for imprisoned methadone-treated addicts by addiction phase at incarceration

Addiction phase	*Advisable conduct*	*Rationale*	*Malpractice*	*Side measures*
Maintenance phase	Confirm maintenance	Maintenance of results	Dose reduction	Psychotherapy, counselling
Agonist therapy, induction phase	Complete induction and transition to maintenance at standard effective dosages (80-120 mg/die)	Pursuit of stabilization	Tapering	Psychoeducation
Agonist therapy, tapering	Taper on according to schedule	Programme accomplishment	Quicker tapering	Counselling
Agonist therapy, to be stabilized	Clinical monitoring to achieve stabilization dosages	Pursuit of stabilization	Tapering	Counselling, Psychoeducation
Active user, under withdrawal	Start or adjust agonist treatment	Treatment initiation	No intervention, other psychotropics, detoxification	Counselling
Drug-free, naive addict	Start most suitable treatment (agonist maintenance as standard)	Get the opportunity to have addiction treated	No intervention	Psychoeducation, counselling
Drug-free, previously treated relapsed addict	Start agonist maintenance programme	Treat relapsing course	Detoxification	Psychoeducation, counselling
Drug-free, previously treated, abstinent addict	Monitoring	Prevent relapses in a low-risk condition	Regard as non-addict	Psychoeducation
Drug-free, alcohol/BDZ abusing heroin-free addict	Start agonist maintenance with agonist plus clonazepam	Prevent relapse or depressant-addiction due to undermedication	Detoxification only	Psychoeducation
Drug-free, cocaine abusing, no major heroin involvement at present	Start maintenance programme, reevaluate cocaine use	Prevent and treat abuse due to undermedication or indirect relapse into heroin	No intervention	Psychoeducation
To be detained for days	No change in ongoing regimen	Not enough time to operate	Dose reduction	

Appendix 1. Guidelines for imprisoned methadone-treated addicts by addiction phase at incarceration				
Addiction phase	*Advisable conduct*	*Rationale*	*Malpractice*	*Side measures*
To be detained for weeks	Accomplish the ongoing phase and proceed to the next	Confirm ongoing programme	Dose reduction or detoxification	
To be detained for months	Achieve stabilization and proceed to maintenance	Confirm ongoing programme, in view of parole	Dose reduction and detoxification	Psychoeducation. Brief psyshcotherapy
To be detained for years	Achieve stabilization and proceed to maintenance	Confirm ongoing programme, in view of term-reduction	Dose reduction and detoxification	Psychotherapy Psychoeducation
Scheduled discharged	Have the detainee induced on blocking dosages (higher than 60 mg/day) by the time of discharge		Dose reduction, detoxification or naltrexone	Pro-treatment and overdose-preventive Psychoeducation
Non-scheduled discharge	No change		Naltrexone	Overdose-preventive psychoeducation
Addicted detainees with children	Agonist Maintenance	Positive weighting of child custody-related issues		Psychoeducation Counselling
Aggressive addict	Agonist Maintenance	Anti-aggressive effect of agonists	Antagonists. Chronic Bdz administration	Valproic acid clonazepam, gabapentin
Paranoid addict	Agonist Maintenance	Anti-dysphoric properties of agonists	Antagonists	High-potency neuroleptics
Anaffective Addict	Antagonists	Anti-catatonic properties of antagonists		Low-potency neuroleptics (chlorpromazine-like) or atypical antipsychotics

Appendix 1. Guidelines for imprisoned methadone-treated addicts by addiction phase at incarceration

Addiction phase	*Advisable conduct*	*Rationale*	*Malpractice*	*Side measures*
Non-compliant addict	Propose therapeutic parole	Effectiveness of agonist regardless of spontaneous request for treatment	Let the patient choose	Psychoeducation
Suicidal addict	Agonist Maintenance	Antidysphoric and antiaggressive effects of opioids	Antagonists, Chronic Bdz administration neuroleptic drugs	Antidepressants and/or mood stabilizers
Somatically impaired addict	Maintenance programme	Anti e.v. injection effects of opioid		

3.6

Clinical Foundation for the Use of Methadone in Therapeutic Communities

M. Pacini, G. Giuntoli and I. Maremmani

1. Premise: addiction as a social disease

Addiction is born as a disease of the individual. As with any individual condition, whether physiological or pathological, the environment is affected as a result of the hijacking action of the disorder upon the individual's behaviours and attitudes.

Personal and family resources, affective bonds and social skills are gradually exploited by addictive drives and become ways to obtain supplies of the substance. Eventually, addicts will tend to handle their skills and points of strength primarily from a substance-related perspective, and will set aside original purposes and dynamics. When substance supplies are enough, or faster channels are accessible, addicts leave their social life and productive commitments behind them, and any request coming from the environment becomes a source of stress and conflict. Both for the addicted person and their significant ones, engagement with the substance stands as the main reason for that attitude of conflict. Problems between the addicted person and the environment worsen as the core addictive symptoms worsen, and may also fluctuate in response to the person's current socio-economic status. Comparing equal levels of craving, poorer addicts will enter into conflict with society and engage in criminal activities earlier than their richer peers. Over time, however, the disorganizing influence of craving is bound to exert an equalizing effect on rich and poor addicts, driving both categories towards the same kinds of sociopathic behaviours.

All in all, even if drug addiction can be described in terms of a disease with social symptoms, it basically remains a disorder of an individual's brain, upon which community- or individually-oriented feedbacks lose their power to exercise any positive influence. On the other hand, society can play a crucial role in favouring, and acting as a guide to, treatment-seeking addicts. Far from stating that social factors may be curative of the disease itself, what can be said is that potentially

effective therapeutic instruments, and channels leading to treatment options, are always in society's hands. From the moment a drug addict asks for generic help, society's answer can make a difference, as long as it is based on scientific evidence and provides strong support on cultural and interpersonal grounds (laying the foundations for the 'therapeutic alliance'). For any treatment-seeking addict, the first answer to society should be the chance to enroll in an agonist maintenance programme. For patients who are absolutely resolute in resisting such a setting, harm reduction may be a temporary solution, mainly because of the hope that resistance to actual treatment may be overcome as time passes. Therefore, any low-threshold intervention should include dynamics which tend to promote the patient's transition to a higher threshold programme, in order to provide him/her with a higher grade of achievable results.

'Community' or 'residential' programmes, usually referred to as 'therapeutic communities', need to be reclassified as psychosocial interventions, in order to clarify their ancillary and complementary role to a disease (i.e. as providers of brain-centred intervention).

From this standpoint, some residential programmes are unacceptable on medical grounds, while others can be included in integrated treatment programmes for categories of subjects displaying basic critical features (e.g. the homeless, the mentally ill). In other words, a residential setting may represent the missing link between the disease and treatment for those who also need social support outside their own setting and massive rehabilitative resources. A residential setting may also be a chance for the very severely ill to start treatment and build up some motivation to continue along that path, as long as it detaches the patient from anti-therapeutic environmental factors (such as street life, family conflicts, poverty or geographic isolation).

2. No-Methadone Residential treatment: A rehabilitative paradox

So far, methadone has been available within therapeutic communities in order to accomplish detoxification procedures, as a preliminary to initiation of the actual 'therapeutic' programme. This practice can be defined as a rehabilitative paradox. By limiting access to psychosocial treatment to methadone-free patients, the rehabilitative potential of patients is sharply reduced, so paving the way to the failure of rehabilitation as a whole, no matter if early results are encouraging, since no protection against predictable relapse is allowed for. Methadone-treated addicts are more likely to be willing to engage in psychosocial rehabilitation, which actually means a better treatment outcome.

Especially if addiction treatment is conceived, as it was originally, as rehabilitation of the individual's free will and social functions, methadone itself may be enough for patients to achieve that objective, without any additional psychosocial interventions. Beyond that, methadone has proved that it can function as a gateway for addicts to proceed along rehabilitative programmes: in its presence, the programme continues to be accessible, whereas, without it, rehabilitation becomes awkward or is reversed by re-emerging addictive symptoms. Authors already talk about "pharmacologically assisted rehabilitation" [4, 6, 9, 10], but it would be even more correct to resort to the expressions "pharmacological access to rehabilitation" or "pharmacological enabling of psychosocial treatment". De Leon and colleagues state that residential treatment may be useful in [1] providing relief from a state of drug-abuse and [2] allowing the implementation of a productive and socially constructive lifestyle, "*for those who follow a methadone maintenance program*". The same authors indicate the effectiveness of methadone maintenance integrated with community treatment ("TC methods"), which is compared with methadone treatment alone [2].

Otherwise, treatment modality 1 or 2 alone can be expected to have an impact on addiction that will vary according to baseline disease severity. Mildly ill individuals, with no dual diagnosis, may show initial improvement by either treatment modality, and are regarded as those who display the most satisfactory outcome.

The issue of an intention-to-treat perspective, that is, what retention rate can be expected with a subject whose illness is of average severity when these modalities are applied, is often neglected.

Moreover, when improvement is achieved without the employment of pharmacological means, these results are regarded as "more promising", in line with a cultural bias. Anyway, severely ill addicts, some of them possibly with a dual diagnosis, may be retained in therapeutic communities, but their outcome tends to worsen over time, contrary to expectations. This course it just the opposite of what happens to methadone-maintained subjects, whose outcome tends to improve over time [8].

3. Therapeutic Communities as a chance for treatment

In general, addiction treatment should always be available within any residential setting claiming to be "therapeutic". Furthermore, therapeutic communities may offer a bridge towards treatment to particular categories of patients, by prompting them with basic psychosocial interventions (e.g. homing) right from the beginning. The benefit for patients is the focus of this integrated approach: resources are organized in a hierarchical order such that the first one to become available is that which enables the patient to benefit from the next one, too. The provision of psychosocial facilities to addicts with overwhelming cravings but no protection against relapse would leave a gap between therapeutic premises and rehabilitative goals.

Therapeutic communities should provide addicts with a safe and protected environment, human support and isolation from stressful social challenges, in order to favour the onset of methadone treatment.

Otherwise, the only function of some therapeutic communities is to provide protected environments where addicts just search for temporary relief and a break, in order to prepare for a new wave of substance use, this time, at least in their minds, under better control. In such a setting, preliminary detoxification is no more than a gateway procedure to a relapse-prone condition, and is literally 'craved for' by addicts, since it enables them to reverse tolerance and intoxication, and start back on substance use at a lower initial expense. Nor is a therapeutic community able to achieve any therapeutic impact other than through interventions that remain external to a core condition, such as detoxification in response to addiction.

When combining psychosocial interventions with detoxification, the higher rate of detoxification achieved is the only result [1], while there is no impact in terms of relapse prevention.

Thus, the detoxification of addicts with the help of psychosocial intervention is a choice that is not only without any relapse-preventing value, but actually favours the relapsing course of addiction, as long as it goes along with the patients' addictive way of thinking.

The fact the addicts require some protected environment to undergo successful withdrawal from therapeutic opiates (methadone, buprenorphine) is likely to reflect average-to-high levels of craving. In a study on 215 methadone-maintained patients showing no satisfactory response, only 44% managed to go through with withdrawal from methadone, even though they were in a protected environment; in addition, as many as 21% applied for methadone treatment again after reaching a methadone-free condition, and some dropout from treatment took place soon afterwards. A second look at these data indicates that some patients simply feel pushed towards relapse, others end up achieving "no result" and go back to their original treatment, and some others become less likely to stay in treatment after going through this unproductive detoxification cycle [5, 7]. Certainly, dose-adjustment and retention support would be more reasonable objectives of integrated psychosocial interventions than the withdrawal of medication can ever be.

A variety of artificial environments may set up a possible venue for treatment: therapeutic programmes may take place in jail, residential

settings, specialized inpatient clinics or hospital wards.

Each environment matches the specific needs of some categories of addicted persons, so enhancing their motivation, minimizing attrition and favouring longer-term compliance.

A unique treatment network should take on the task of directing different categories of patients to specific treatment programmes, targeting the shared core symptoms of their disorder, which is the common formal basis of their condition.

4. A classification of therapeutic communities for drug addicts with respect to therapeutic instruments

4.1 Therapeutic communities.

Any community offers a specific treatment facility for drug addiction; an obvious instance is agonist maintenance for opiate addiction. All phases of treatment should be viable in the residential setting (induction, stabilization, maintenance). The only treatment phase which should, preferably, be performed outside is that of medication withdrawal. Besides treatment, various psychosocial interventions may be provided in order to improve productive and social skills [3].

4.2 Non-therapeutic Communities.

Any community which offers some basic facilities (e.g. a home, food, hygienic surveillance, general health care, human support) but fails to provide specific treatments for addiction, inevitably fails to offer protection against withdrawal. Communities which provide psychopharmacological treatment to opiate addicts as a compromise between pharmacological treatment and a methadone-free condition are a recent example of a community that is non-therapeutic. The only advantage of non-therapeutic communities is that they may delay complications and lethal events, without having any fundamental impact on the likelihood of relapse. At most, non-therapeutic communities can be viewed as harm reduction, as long as no cultural bias against specific treatment is inculcated in the patient's minds. Nevertheless, possible harm reduction is usually counterbalanced by unrealistic expectations and the support given to blindness over the dangers of relapse; these factors hamper the self-help potential of relapsing patients and their significant ones' reactions on such occasions.

4.3 Anti-therapeutic communities.

Some residential centres have explicit criteria which sound like a paradox not only with respect to addiction treatment, but even to harm reduction. Those centres actually admit low-craving individuals, who have reached a drug-free state spontaneously, and have accomplished rapid detoxification procedures while queuing up to be admitted, and showing respect for community rules. In other words, severely ill addicts are excluded from treatment by the same criteria which should function as therapeutic. The adoption of evaluation systems which only measure improvement in retained individuals, or do so at predetermined observation terms, are just a way of avoiding an intention-to-treat perspective. One could say that anti-therapeutic communities work best for substance abusers who are not addicted. In fact, it is not uncommon for diagnosis to be based exclusively on the generic reason of a request for admission based on 'problematic drug use' rather than on a diagnosis that differentiates between use, abuse and addiction. Addicts going through anti-therapeutic communities run the risk of relapsing into more hazardous conditions, dying before admission or after discharge. Some prisons, considering the trend towards withdrawing medication before scheduled discharge and the subsequent trend towards lethal overdosing after discharge, are one example of what an anti-

Table 1. Differential Characteristics between Therapeutic Communities

	Therapeutic Community	Non-therapeutic Community	Anti-therapeutic Community
Use of methadone during the programme	Available	Available	Unavailable
Opportunity to start methadone treatment inside the community	Yes	No	No
Use heroin at entry into community	No reason for refusal	No reason for refusal	Reason for refusal
Use of medications to detoxify patients inside the community	Available	Available	Unavailable
Use of methadone to detoxify patients inside the community	Available	Available	Unavailable
Opportunity to continue methadone maintenance	Yes	Yes	No
Dosage of methadone at programme termination	Generally not modified	Slow reduction	No
Overdose prevention at programme termination	Methadone blocking dosages	None: naltrexone	None
Control over alcohol and CNS depressants	Yes	Yes	No
Enrolment of families, mothers with children, pregnant women	Yes	Yes	No
Enrolment of methadone-maintained pregnant women	Yes	Yes	No
Concomitant use of other substances of abuse	No reason for refusal	No reason for refusal	Reason for refusal
Aims of the treatment	Treatment of the illness	Mortality reduction, harm reduction	To cure patients
Outcome evaluation	Follow-up	Follow-up	Programme termination
Philosophy	Evidence-based medicine	Harm Reduction	Not medically oriented, drug-free

therapeutic setting means.

Differential features of these three types of therapeutic communities are reported in table 1.

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3.7

Clinical Foundation for the Use of Methadone in General Practitioner's Office. Italy as Case Study

A. Michelazzi, F. Vecchiet and I. Maremmani

1. Introduction

Prescribing methadone as a replacement treatment became possible for the general practitioner (GP) in Italy after a national referendum in 1993 which modified the existing legislation on drug use – law No. 309 – by allowing GPs to make use of a therapeutic tool, methadone, which had previously been prohibited to them. In Trieste and other Italian cities, such as Cagliari and Arezzo, some pioneering experiments took place in this field during that period, and made a new treatment option available to heroin addicts [4, 8, 9]. It should be stressed from the outset that this therapeutic approach sees methadone as an effective tool for treating heroin addiction, and considers heroin addiction to be a chronic relapsing illness, which, as such, can be treated pharmacologically using the instruments made available by accredited scientific research.

The question of the medical and psychosocial complexity of heroin addiction is clearly fundamental here, and must be adequately addressed, without ever overestimating that complexity to the point of demanding a level of specialized knowledge beyond what is required in providing a satisfactory response to the needs of the patient/addict. Opiate addiction affects individuals from all socio-economic backgrounds, and may be further complicated by the co-presence of other addictions such as polydrug dependence, as well as various kinds of primary or secondary psychiatric disorders.

Having said this, it is undeniable that offering inadequate care to the patient or excessively penalizing him/her, makes it more likely that a 'simple' heroin addiction will become polydrug abuse or a psychiatric disorder caused by the additional stress placed on the patient's original condition. Hence the importance of making sure this does not occur through preventive measures of a pre-primary, primary or secondary nature. The safety and

effectiveness of replacement treatment at the maintenance doses that are used to detoxify opiate addicts, and/or taper where possible, are now widely accepted by the international scientific community [2, 3]. The general practitioner is a professional who, after appropriate training, is able to intervene rapidly, but also in a context that is unique for its therapeutic potential [1, 5-7, 10-12].

In the next section, alongside an account of how the treatment protocol developed, we shall describe in greater detail the advantages of this model of care, which can be summarized briefly as follows:

1) The 'large containers' for drug addicts are gradually emptied;
2) A doctor-patient relationship develops which shows certain similarities to the kind of relationship that develops in situations involving other chronic relapsing illnesses;
3) A new level is established that functions as an interface with other levels of care, so as to optimize responses.

2. The impetus for change

The institutional arrangements for treating addiction were laid down in what became known as the Jervolino-Vassalli Law of 1990, which decreed that the Central Drug Treatment Services (CDTSs) would be the only places where the addict could receive replacement medication. The only replacement drug allowed at that time was methadone, and the dosages and methods of administration varied – as they still do – from one treatment centre to another. The result was, and still is in many cases, that a large number of patients were herded together into a few institutional 'containers' where the service available to them often becomes more like a disservice, for the following reasons:

1) keeping a large number of addicts in the same place encourages an exchange of abnormal 'identities';
2) the CDTSs themselves can end up becoming a place for illegal drug dealing;
3) the concentration of a large number of addicts in one place can lead to bad feelings and protests from local residents;
4) there are often too few staff members employed in the CDTS for them to be able to cope properly with the demand;
5) the criteria for recruiting, monitoring and managing the treatments are often excessively standardized and regimented, with rules that make it difficult for patients to become re-integrated in the social framework (rigid time schedules for methadone administration, difficulty of obtaining take-home doses, suspension of treatment after following repeated relapses).

The disservice that follows often leads addicts to accentuate certain aspects of a personality already ravaged by drug dependence or the mental illness that is complicating diagnosis, while staff members end up playing a role uncomfortably similar to that of a public warden co-responsible for coping with a form of deviance not manageable within the 'classic' institutional circuits – psychiatric services, prisons, and drug rehabilitation communities. The network of institutions becomes a trap, and the patient all too often falls victim to it.

Their recognition of the severity, in medical terms, of the biological trauma inflicted as a result of repeated self-administration of a toxic substance, causing neurochemical changes in the brain and eventually a neuro-psycho-endocrinal disorder – opiate dependence – led a number of general practitioners in Italy to take advantage of the legislative modifications to the existing Law on Narcotics – the Jervolino-Vassalli Law (no. 309) – introduced by the national referendum of 1993. These doctors began to treat patients suffering from heroin addiction pharmacologically, using methadone as their replacement medication. This is a method of treatment which relies on a tool endorsed by the international scientific community to treat an illness caused by the action of a substance which has damaged the brain – damage which may prove to be irreversible – and brought about related psycho-physical alterations. These are the alterations which are characteristic of the set of symptoms that

are peculiar to opiate addiction. Of course, as a form of medical treatment it had to have its own set of criteria and take on a form compatible with the institution that was already operative at the local level, the Central Drug Addiction Service.

3. The general practitioner and treatment in the doctor's surgery

Opiate dependence is considered by the general practitioner to be a chronic relapsing illness, a chronic illness which, just like any other, can be treated but not necessarily cured. Like any relapsing chronic illness, there can, of course, be relapses, and there may be inadequate patient compliance with treatment; it may present complications of a psycho-social nature requiring an approach that is integrated with other health services (such as the Drug Addiction Service, the psychiatric services, and social workers). It can be complicated by other illnesses which either need preventive treatment or call for a prompt response from a multispecialist perspective (e.g. that might involve liver disorders or infectious diseases). For optimum treatment, it is an illness which entails the close monitoring of certain biological parameters.

As we noted above, in Trieste, immediately after the 1993 Referendum, a few doctors, including the authors of this chapter, began to prescribe methadone to heroin addicts, and set up an Association of General Practitioners for a Local Response to Drug Addictions (the Italian acronym was COMBATT), which soon became part of the Italian Association for Drug Addictions (SITD), an association which offered scientific advice and support, and helped to make the practice of prescribing methadone more widespread in Italy.

The main questions that arose were the following:

3.1 How is the methadone prescribed?

In Trieste, we chose to adopt the method of prescribing referred to in Article 43 of Law 309 (CTU 309/90), which does not entail keeping a register of supplies or a safe in which to store the drug. The reason for this decision was to avoid keeping methadone in doctors' surgeries, which could have made it a target for burglaries. The patient collects the drug from the pharmacist with a prescription made out in the special prescriptions book for narcotics, and then comes to the doctor's surgery to drink the dose under GP supervision, as often as is deemed necessary, depending on the patient's reliability and the level of stabilization reached in the treatment. Prescriptions cannot be made for more than eight days' supply; in any case, the patient has to drink the dose in front of the doctor at least once or twice a week to allow assessment of tolerance levels. Actually the law has changed, infact there is a modification of CTU 309/90 which requires a therapeutic plan which must be done inside a pubblic service. This should assure a better collaboration between general practictioner and public service.

3.2 How are the urine tests organized?

The frequency with which patients' urine is tested is determined by the patient's degree of reliability and the level of stabilization reached in the treatment. The urine samples must be produced in such a way as to allow staff to be sure of the identity of the individual who produces them. The patient can go to the Central Drug Addiction Service, to a local health clinic where GPs are on duty (see next paragraph), or to the surgery of his/her own doctor, who will make sure that the sample is delivered to the laboratory. Some private laboratories offer this service, too. Actually we are reorganizing the presence inside the local primary health care clinics functionally to the new law.

3.3 Which patients can be entrusted to the care of a GP, and how many?

Initially, drug addicts came to be entrusted to the care of GPs almost by chance, as patients happened to hear about the new opportunity of being able to obtain methadone from GPs, the only limit being the small number of GPs in Trieste willing to carry out the treatment, and the condition that the patient was not allowed to receive other treatments (from the Drug Addiction Services or another GP) at the same time. Thanks to an increasingly effective level of communication with the Central Drug Addiction Service, and the experience gradually gained by GPs, it became possible to establish some basic guidelines in deciding whether a patient could be taken into a GP's care:

a) A maximum of 5 patients per doctor's surgery.
b) Only patients with proven reliability in terms of certain parameters (family more present than not, employment, no criminal charges pending, no serious mental illness, no polydrug abuse). These are the same parameters as those set out in the Italian Ministry of Health guidelines (Circular No. 20, Gazzetta Ufficiale, September 1994).
c) A consensus of opinion with the Drug Addiction Service as well as with the patient, about the treatment protocol: dosage, type of treatment, method of consignment, type of psychotherapeutic and social support, method of biological monitoring, and so on.

This collaborative approach led to our signing a Common Protocol with the Department of Addictions, which made it possible to provide financial incentives for GPs who were willing to treat patients with opiate addiction in their own surgeries.

3.4. How reliable is the patient/addict? What are the contro-indications to caring for them in the setting of a GP's surgery? What are the prejudices surrounding this idea?

Undoubtedly, it was, and still is, received opinion that the patient/addict is unreliable, and by nature inclined to take personal advantage of every situation he/she may come across. What the patient wants is a substance that will make him/her feel well, and not ill, without worrying whether this feeling of being well or ill coincides with what we mean by a healthy state or a sick one. It is also received opinion that these patients are capable of aggressive behaviour if their requirements are not met, and of illegal actions whenever they get the chance.

Our daily experience in our surgeries has led us to conclude, however, that as long as the number of patients on methadone in each surgery is kept small, it is possible to build a relationship based on trust, obviously as long as the patient's needs' are taken into account without preconceived ideas about the use of the replacement medication. By 'preconceived ideas' we mean the types of opinion that often make health professionals insist on tapering methadone doses when the conditions are, or insist on low doses of methadone when these are clearly not effective, or again, insist on the supervised administration of the drug when the patient has a job and his/her working hours make it impossible to come to the doctor's surgery every day. This does not mean that the patient can have as much methadone as he/she 'wants' or can be allowed to do what he/she 'wants'. It means applying the codes of good practice which have emerged from successful procedures that have been applied within the scientific community, while respecting the needs and rights that are respected as a matter of course when patients have other disorders. Once the patient is being treated properly, many of the possible reasons he/she might have for behaving aggressively or engaging in illegal activity disappear, and he/she becomes a patient like all the others, with an increasing awareness of a patient's rights.

Clearly, there exists a sub-population of drug addicts with severe psychiatric disorders, or with histories of polydrug dependence which cannot easily be treated in a GP's surgery, and this is one of the reasons why a

multi-specialist approach is so important, allowing collaboration with those departments that are able to give a more targeted response whenever this is necessary. With this in mind, in Trieste we decided to set up an intermediate treatment level in the local primary health care clinics.

4. General practitioners and daily practice in local primary health care clinics

This chapter concern the situation before 2006. As already said, actually, the practice inside the local primary health care clinics is a work in progress

In 1993, as we mentioned above, there was a fundamental change in the approach to the treatment of heroin addiction. At first, this new approach to treatment – caring for heroin addicts as patients in GPs' surgeries – seemed to be the solution to the problem, but, with the passing of time, new and seemingly insurmountable obstacles emerged to the idea of basing a treatment programme for heroin addicts solely on care in a surgery setting.

One of the obstacles GPs had to face – and it was all too frequent – was responding to pressing demands from their most difficult patients for help with problems unrelated to the replacement drug regimen, such as issues related to psychiatric and psychological topics, and a need for counselling and advice over family matters, unemployment, and housing.

Perhaps thanks to these more demanding patients, it was decided to try to deal with some of these problems by setting up a surgery at the district level, as a kind of 'intermediate' structure situated between the surgery of a GP as an individualized care setting appropriate to 'stabilized' patients, and the Central Drug Addiction Service, which was able to rely on the expertise of specialists, and to dedicate special attention to the most problematic patients. Once a suitable place had been found (a surgery located in one of the district health clinics) and staff had been recruited (GPs and nurses), we started to use methadone treatment with the heroin addicts who were suitable for this kind of treatment – fairly well-balanced subjects with the occasional relapse into heroin use, but with the backing of a reasonably good social and welfare network.

The setting we chose to offer treatment in was that of a 'normal' surgery in a district health facility. The city of Trieste is divided into four health districts, each with its own health clinic. We insist on the importance of the idea of normality, because we believe drug addicts are normal patients who happen to need long-term treatment, just because they are suffering from a chronic illness. Patients of every kind can be found in a district surgery waiting-room, and so far there have been no unpleasant incidents, so the clinic's daily routine has never been disrupted.

The surgery for drug addictions is open for one hour a day from Mondays to Fridays, with take-away doses given to patients for weekends or longer periods around public holidays. Whenever possible, we prefer to give weekend doses of methadone to a family member (whether a parent or grandparent, a husband or wife) because, by doing so, a further opportunity is opened up for the patient's resocialization. The opening time for surgery tends to be from 12.30 to 13.30, to help patients who work, although a fixed time is obviously a limit in itself for people with a job. The fact that a different doctor is on duty each day, and each of the doctors involved covers only one hour a week, means that the nurse, who is present every working day, is absolutely vital for the continuity of care, as he/she is able to keep doctors informed about any problems that arise with their patients on days when no doctors were present (each doctor has a maximum of four patients in care). At this district surgery level, the Common Protocol drafted together with the Central Drug Addiction Service involves very close collaboration in deciding treatment regimens. As soon as the district level treatment programme was set up, however, a number of problems arose.

For GPs:

1) An ever-increasing number of drug users asked to be taken on by a GP for methadone maintenance and medical care.

2) After an initial phase in which a large number of GPs joined the treatment programme (about fifty, which was a fifth of all the GPs practising in Trieste), the number levelled off, making it impossible to take on any more patients.
3) We had thought that, after an initial treatment phase of being stabilized in the district surgery, the drug user would then be able to go back to the surgery of his/her GP, who would then continue to care for a patient who by then was already stabilized by applying an effective treatment regimen.
4) The role of the health district would therefore be to attract the drug users who were reluctant to talk about their problem with their GP, since the district obviously provides a more anonymous setting both compared to the surgery of a GP, where the patient and his/her family may be known, and to the Central Drug Addiction Service, which, even if it is a specialized service, may make the drug user feel marginalized.

For the Central Drug Addiction Service:

The high number of drug users coming to take their methadone every day in the Service's two structures (one situated in the grounds of the old psychiatric hospital, the other in a condominium on the outskirts of town) caused two different kinds of problem:

a. the gradual depersonalization of the doctor-patient relationship: the addict became a number, or a dose by which he/she was identified;
b. the increasing exasperation of local residents with the uncivilized behaviour of patients in the street outside the condominium, with brawling and drunkenness causing disturbances.

By opening the district level surgeries, it was hoped that the Central Drug Addiction Service would be relieved of a lot of its work, so allowing it to improve its collaboration with GPs, and provide specialist support and backup with respect to the various forms of rehabilitation necessary. These include psychosocial services, offering help in resocializing the drug user as regards family and personal relationships, and rehabilitation in terms of education and training, which are useful for reintegration into the workplace.

The opening in the winter of 1997-1998 of four district surgeries for methadone maintenance did indeed solve the Central Addiction Service's problem with the antisocial behaviour of its drug users; it also marked the beginning of a long series of discussions between GPs and the staff from the Central Service as the best place for organizing supervision of the state of abstinence from illegal opioids on the part of our patients.

As laid out in the legal regulations (which, incidentally, require the individual's identity to be determined without specifying how this should be done), the Central Service expected strict monitoring of the urine tests, with samples produced under supervision.

By violating the trust which should exist between health professional and patient, this inflexible interpretation of the rules on toxicological testing led the patient to seek various ways of faking the urine sample, thereby spoiling a relationship which had often been difficult to establish, and turning the urine test into a police-like inspection, with prompt punishment at the first sign of a positive result for the presence of heroin. The punishment took the form of prescribing rapidly tapering doses of methadone until toxicological tests for opioids became negative again, and the temporary impossibility of resuming replacement treatment. In practice, what happened was the opposite of what is supposed to happen in cases of relapse into substance abuse.

Instead of pondering over a relapse and, if possible, finding its cause, perhaps with the help of improved psychological support, the drug user is left alone in the worst state of interior conflict, exposing him more than ever to the risks connected with heroin use (buying methadone on the 'grey' market, if not actually giving up everything, and going back to drug abuse).

In our opinion, the experience gained in the district surgeries has given us an excellent opportunity to provide the best possible care for our addicted patients, not just from the medical point of view, but above all as regards the

patient's family and social situation, and employment status. With the addition of this new intermediate level, there are now three health structures providing care for this kind of patient:

1) The Central Addiction Service;
2) The district surgery;
3) The GP's surgery.

The path that a drug user might follow (though not necessarily in this same order) begins with the Central Addiction Service, whose staff members know the patient personally, are familiar with the individual's specific problems and set up the treatment plan (not limited merely to prescribing methadone). He/she then moves on to the district surgery structure, where, as we have said, a fairly well stabilized patient can get away from the large numbers of users who congregate at the Central Service; the final step is the GP's surgery, where this kind of patient is taken on just like any other patient who has a chronic illness, and is cared for with prevention measures, treatment, periodic check-ups and everything else that can help him/her to keep well.

After five years' experience with district surgeries, it is now time to draw some conclusions. If drug addiction is an illness, and we think it is, it must be treated as such. As with any illness, there is a professional, the doctor, who has a job to do: this job consists of knowing all about that illness and finding out about the best ways to treat it (we cannot talk about curing it, since we are well aware that we are dealing with a chronic illness which is subject to relapses). So it is unclear why this opportunity should be given to someone with heart disease, in the knowledge that we can improve his quality of life without having to reproach him for eating too much or threatening not to prescribe any more drugs the first time he dares to smoke a cigarette (that is, if we have succeeded in persuading him to give up smoking, and, anyway, how can we check whether he starts again?). Then there is a patient who has to be made aware of his condition. When we have become convinced of these starting points, then we have set up a doctor-patient relationship that can be built on and reinforced. The trust we place in our drug-dependent patient takes it for granted that he/she should tell us everything that has to do with a possible relapse of his/her illness, ranging from a wish to take the illegal drug again to the explanation, if there is one, of why he/she actually did use it again. The trust our drug-dependent patient has in us is that we will always use the best treatment available in our therapeutic model, without making moral judgements about past behaviour in deciding whether to begin treatment or continue it.

Is this model of care applicable at the District surgery level?

It might be pointed out that many of the functions currently performed by the district surgery could be carried out in the GP's surgery, if a more 'constructive' relationship could be established with the specialists of the Central Service.

At present, the aim of the District surgeries should be to facilitate this relationship and provide training opportunities for the GPs who are interested in treating drug users, while simultaneously promoting access to the District Surgery for patients from the Central Service who, once stabilized, can be discharged into primary care and be looked after by their own GP. These aims are difficult to attain, however.

One possible solution might be to formalize the GPs' surgery-based treatment of addicts, by including it in the General Practitioner's Contract. In this way, the function of the District Surgery would be transformed; indeed, it would no longer need to exist, since opiate addiction would be considered simply as an illness, even if with its own specific characteristics, to be treated with adequate support provided by specialist services.

5. Relations with the central drug addiction services

In Trieste, the Central Drug Addiction Service was willing right from the outset to work together with new institutional agents, namely those GPs who had started treating heroin addicts with methadone in their surgeries. In fact,

a dedicated team was soon in place within the Department for Addictions, with the specific task of collaborating with GPs. Then working groups were set up (consisting of GPs and DAS staff) in which treatment protocols were designed both for the general practice setting and district health clinics.

The Central Service also offered to play the role of 'institutional representative' within our Local Health Agency, so as to deal with the various problems as they arose, such as getting approval for the Agency Proposal on financial incentives for GPs working in the District surgeries, mediating at the regional level to get methadone defined as a Class A drug (so making it free of charge on prescription) and, lastly, putting forward for approval by the National Drug Fund a project involving GPs' surgery-based activity with drug users.

At the moment, this kind of collaborative relationship still exists, with the various institutions having different roles and responsibilities in a shared care approach arrangement which seems to work.

The financial incentive is now an official voice of the GP's pay packet, specific for opiate addiction care.

Obviously, the Central Service is able to provide a variety of institutional responses depending on the patient's needs, from prevention and low-level intervention, to rehabilitation, support for incarcerated drug users, social assistance (protected jobs, income support, and so on), and also organizing stays in residential therapeutic communities.

General practitioners are able to provide a satisfactory, innovative response to patients without a lot of complications; with appropriate backup from specialist services, they are also able to care for more complex cases. In district surgeries, for example, it is easier to manage a more complex case through a collective approach. Figure 1 and Table 1 show the roles and functions of the various agents who contribute to the institutional network in Trieste.

6. Conclusions

The decision by primary care physicians in Trieste to treat patients who are heroin-dependent in a general practice setting has undoubtedly been fruitful, both from the point of view of the enhanced autonomy and 'freedom' of patients, and of the specialist institutions, who have seen their caseload diminish considerably and have made valuable new allies in their struggle to deal with opiate dependence and so save lives.

In Trieste, it has been proved that this approach is feasible, valid, and cost-effective. Obviously, the forms that this kind of care may take can vary, depending on where it is being implemented. In any case, primary health care providers in Europe, Australia and North America are being utilized successfully as methadone prescribers, while, in some countries, buprenorphine has come to be preferred because of its greater ease of use.

The crucial step forward is to recognize the fact that most heroin addicts have a chronic illness, and overcome the prejudices that may derive from a limited acquaintance with the problem, prejudices that lead to attitudes of blame and social exclusion towards addicts, whether young or old, based on value judgements of a moral nature which have nothing to do with sound medical practice.

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4.1

Psychoeducation and Counseling for Methadone-Treated Patients

I. Maremmani, G. Giuntoli and M. Pacini

The term 'psychoeducation' refers to a form of communication that acknowledges a patient's role in understanding the nature and coping with the dynamics of his/her disease. The basis of this exchange is the patient's trust in the physician's skill, which is the general basis of any patient-physician relationship in a treatment-request setting. The purpose of psychoeducation is to get the patient to stick to treatment rules, while avoiding or actually countering the power of misleading convictions and drives.

Psychoeducation may be applied to many situations characterized by psychic disorders, and is useful when the request for treatment is not expected to be consistent with the patient's insight, so that poor compliance and ambivalent behaviour can, as a rule, be expected soon after treatment initiation, whether stably or in a fluctuating manner. No psychoeducation is feasible when no insight at all is present, nor can any be recuperated by means of treatment. That is the situation in delusional disorders and psychotic states in general.

Psychoeducation can be implemented during any phase of treatment and at any stage of the disease, except for emergency conditions.

Although we have defined psychoeducation as a form of acknowledgement, it is not to be understood as an oral, interactive version of an informative brochure about drug-related pathology. Rather, it is a strategy of interaction which aims to guide a patient's way of thinking away from a relapse-favouring setting to a treatment-compliance context. Its true result is not a series of elements of knowledge about addiction, but a psychological exit route from the conditioning effect of addiction on a patient's cognitive orientation. Obviously, psychoeducation is unable to produce any substantial improvement in the absence of effective treatment, so that it should not be confused with some sort of abstinence-oriented psychotherapy or the encouragement of abstinence on rational grounds [3].

Addicts are usually experts on the risks and effects of substances of abuse, and they are often able to focus on the core dynam-

ics of their addictive disease when reporting their problem spontaneously (the instinctual drive to repeat a certain behaviour, the self-perpetuating course of craving, the repercussions on their life and goals, and the parasitic action upon the general level of pleasures and drives). On the other hand, addicts cannot prevent their relapsing behaviour, because that is the main result of the strong instinctual drive towards substance use. It follows that the cognitive setting of a typical addict will be that of 'defending' his/her freedom to use drugs, although they have just agreed on the fact they are slaves to their addiction. A typical addict will automatically reset in order to favour ongoing use, rather than treatment maintenance according to standard rules, which are perceived as a form of control. In other words, they can be expected to react as if they were avoiding becoming enslaved to treatment, and were struggling to get back to free substance use again.

The automatic drive towards substance use does induce a cognitive style, which can be the sole and crucial obstacle to allowing effective treatment to continue long enough to produce results. Besides, baseless opinions about addiction are widely rooted in the cultural mainstream, so that addicts are led to think that their ideas are obvious, reasonable and scientifically founded.

Cultural prejudice is particularly harmful because it runs parallel to the patient's spontaneous ambivalence and disturbed insight. Psychiatric patients, in fact, are victims of cultural prejudice to a greater extent than other categories of patients, who have enough psychic

balance to overcome it and defend themselves against their disease by complying with treatments.

Treatment-seeking patients are usually led by current critical conditions (general impairment, withdrawal), but have partial insight; in other words, they are aware that craving is the main reason for relapse. On the other hand, they have no disease awareness, which means they deny any chronic risk of relapse or lack of control: relapse and control are seen as dependent on their current involvement in drug use (in quantitative terms), so that spontaneous abstinence is mistaken for remission, and subsequent relapse is seen as a distinct episode in their addictive history. Moreover, it is just when patients achieve relief from acute discomfort that their insight takes a step back, in the sense that they will probably claim they are able to handle their cravings and substance use. Nor will they accept any relapse-prevention perspective, as they will be blind to the concept of addiction as a chronic relapsing disorder. Psychoeducation is a technique that aims to promote a different view of the problem and a higher level of insight.

Patients are quite likely to report unfounded and misleading convictions about their therapeutic needs and the characteristics of therapeutic techniques [1, 2, 4]. This is the typical situation that can be approached by psychoeducation, as long as the acute phases have been treated. No judgmental attitude is allowed, since this kind of intervention is based on a therapeutic alliance, and when patients perceive some moral orientation in the physician's attitude, their trust is hampered, and hostility is favoured.

A second important basis of knowledge in delivering psychoeducation is the question of addictive ambivalence. Patients are torn apart by two conflicting drives, a hypertrophic one towards substance use, and a weaker one towards treatment compliance. Patients often ask for some sort of permission or approval by the doctor when making their decisions about treatment, although it may be clear that they are doing the opposite of what has been prescribed. This kind of attitude should not be read as distrust or hostility, but simply as the combination of the two unequal drives. Physicians should count on their professional role to prevent the patient from feeling approval of their anti-therapeutic decisions and opinions. The negotiation of treatment and dropping out should not be a reason for heated confrontation with the patient: conversely, physicians should coolly maintain their therapeutic standpoint and reject any compromise between correct treatment and addictive ambivalence [5, 6].

Psychoeducation is usually awkward at the beginning, because of the patient's resistance, but it is an effective means for making the

Table 1. Treatment specificity

Disease-favouring thought	Treatment-favouring feedback
I must get off drugs: the solution is to stop and stay clean. This time I must find the way to do the trick. I have tried so many times already – this time I mustn't fail!	Stopping may be more or less awkward, but it only produces an interval between relapses, since that is the nature of the disease.
I should move to another town, abroad maybe, change the whole environment. I will not be able to stop as long as I stay here.	As long as one craves for the substance, the environment can only make just a temporary difference.
I must join some therapeutic community	Staying in a community is more of a challenge than entering it. On the other hand, isolation gives no guarantee of relapse prevention once back in the outside world, no matter how long one has been inside.
I should get back to the old times, using it only over the week-ends; that works as long as I don't go too far and put a limit on it.	Getting back to pleasant and controlled use is just what addiction makes impossible, once it has developed.
This time I may try using it from time to time as the solution, I just have to be careful not to start using it regularly…	Starting with lower doses, or less frequently, is just a prelude to dose increases and regular use, which will actually happen more quickly than expected. Maintenance of control is just impossible once someone has become addicted.
I want no substance at all in my body; therapies are all the same; I do not want to get hooked on medical drugs!	Medical drugs and drugs of abuse are radically different, so that their being chemical in nature is not the key issue.
I must work it out by myself.	Addiction will not allow you to. It is not reasonable to condemn oneself to certain failure when treatment can make improvement possible. Ill people are not required to prove anything; so it is pointless for a patient to struggle in complete isolation.
Maybe hitting the bottom is what I need to get the motivation to stop.	'Hitting the bottom' may actually mean dying or losing any chance to move up again. When the disease becomes more severe, it allows no higher insight or capacity to reverse its course; in fact, the real situation is usually the opposite, but combined with a higher chance of a tragic end.
There is no chance that a medicine will change my mind!	Certain behaviours can be controlled through pharmacological treatment.
I am really motivated to stop using it. Medical treatment is not necessary if you really try hard enough…	Motivations have nothing to do with one's capacity. Addiction does not allow people to go ahead with their projects for staying clean.

doctor's leading role sounder. If the 'human touch' can be crucial in persuading the patient to decide to ask for treatment after the resolution of acute symptoms, cognitive conditioning by psychoeducation is crucial to getting them channelled towards effective treatment, in their own interest [1]. If these premises are fulfilled, the therapeutic response is bound to convince patients that they have been well advised. Psychoeducation may not be successful at the first

Table 2 . The concept of loss of control and the irreversible nature of relapsing behaviour in addictive diseases

Disease-favouring thought	Treatment-favouring feedback
As long as I take methadone I am addicted.	Addiction may be impossible to heal, but methadone treatment can keep it under control and allow you to lead a normal life.
I cannot continue treatment my whole life long!	We do not actually know whether life-long treatment is needed for every patient. In any case, treatment is the only reasonable way of improving the chances of healing.
If I start taking methadone, I will become a chronic addict.	Addiction is itself a life-long problem. Methadone allows it to be kept under control, throughout one's life if necessary.
It is pointless to take methadone, If I want to use heroin, I can do it all the same.	Methadone treatment can influence one's will and put a stop to craving.
When you are really motivated, you don't need any methadone.	Addicts want to quit by definition, and the reason why the want to is that they cannot do it in an automatic way, because of addiction.
I once stopped using drugs for long, and I needed no methadone at the time !	Addicts usually stop from time to time. Methadone treatment aims to prevent relapses, rather than allowing drug use to be interrupted.
I am not an addict, I have been clean for many days.	Addiction means being incapable of carrying out an intention to stay clean. Stopping is easier than it seems, whereas avoiding relapses is impossible.
I managed to stop, so I cannot be considered an addict.	To regain self-control while on treatment is the prime goal of treatment, and success depends on that.
Do you think I am not using heroin just because I am taking methadone?	Methadone treatment is the only factor that differentiates between being with or without stable control (even if abstention is not complete); all the rest follows, and derives from the acquired freedom to choose.
What if I stop taking methadone? I would be sick !	Tolerance to methadone and susceptibility to withdrawal is a feature of treatment and not of addiction.
Once you start taking methadone, it becomes impossible to stop.	Getting off methadone is common among addicts, who hate going through methadone withdrawal because it takes longer. The reason is that methadone is not craved for. The urgency to get off methadone is usually a symptom of disease severity.
I don't want to depend on methadone for the whole of my life !	The alternative is to depend on the disease.
It has been a long time since I started taking methadone, so now there is no way I could have a relapse …hasn't the time come for me to get off treatment ?	Treatment duration is a key factor to reducing the likelihood of relapse after treatment termination. A good response to treatment is not predictive of successful abstinence after treatment termination.
If I stop using heroin and start taking methadone, that's just another drug problem !	Craving is a characteristic of heroin, and not of methadone. The chronic use of methadone does not induce any methadone addiction, while it allows the remission of heroin addiction.

There must be a way to get rid of addiction without any maintenance treatment !	To date, no such method has been discovered.
My intention is to taper gradually and eventually get off methadone.	Gradual tapering makes no difference, the result of treatment termination is a higher likelihood of relapse.
Methadone helped me, but I managed to quit because I decided to do so.	The only known factor allowing disease control is methadone treatment. One's own resources can develop in the room left free by craving.

attempt. However, when dropouts come back to ask for treatment, they have implicitly accepted the doctor's role, as long as they had perceived it as sound and specific in the past. Patients may adhere to treatment on the basis of their healthy mental functions, while their unhealthy functions will be restored later by ongoing treatment. Treatment negotiation, as well as a patient-specific approach from the very beginning of treatment, will lead ambivalent patients to ineffective treatment attempts, far from any actual healing perspective.

The issues of psychoeducation correspond to what the doctor knows about the biology of the disease. A golden formal rule is that of adapting the patient's resources to the rules of effective treatment, rather than adapting the latter to the patients' requests or behavioural

Table 3. Mechanism of treatment functioning and the course of response

Disease-favouring thought	Treatment-favouring feedback
I do like the effect of drugs, so I will never be able to stop.	Pleasure is obviously the key to substance use, but treatment does not deal with the pleasure that derives from using substances, and is not hampered by itspositive relationship with the effects of the substance.
I have had a relapse because the environment is hostile towards me.	Addicts relate to certain environments because of their addiction; addiction pollutes social relationships in a predictable way. The environment is not the key at all.
The reason why I started was... The reason why I got hooked on it was…	'Reasons' do not apply to addiction, which is a self-perpetuating phenomenon. Reasons may come into play before addiction develops, but afterwards they don't influence its course, positively or negatively.
The problem is with my mind	This kind of problem is centred on the head – in concrete terms, the brain – and that is where therapy counts.
The real problem is that I can't always find as much of the drug as I need; even when I succeed, it takes me a huge effort to get hold of it.	Effort is a consequence of addiction. If any balance were possible, the effort would be far less.
It is my choice to stop or continue…	A choice implies the capability not to perform a behaviour, which excluded in cases of addiction.

inclinations. The patients should develop the idea that the doctor has some specific, sound and independent know-how about treatment. Patients should give up the idea that their opinions are as important as the doctor's, in a peer-to-peer exchange of views. Later on, patients feel relieved when they can count on a physician who will not be influenced by their own inappropriate suggestions or anti-therapeutic insistence. Arguments may be common in the early phases, but when patients choose to comply with treatment, this transition marks a radical reversal of their cognitive setting.

The doctor should reject any view according to which 'believing' in some treatment will make it effective, which mirrors the patient's misconception that control over addiction is made possible by one's own will. Patients usually think of standard treatment as consisting of foolish and superficial ways of approaching their problem, and will claim that their viewpoint on the disease is the best, because they are the ones who are addicted.

With respect to counselling, psychoeducation can be seen as a theoretical model targeting the cognitive distortions of addiction, which can also be addressed directly through counselling sessions. Moreover, psychoeducation may be used as the formal basis of counselling [3]. The sites that spread correct knowledge about addiction treatment techniques can be viewed as a virtual means of psychoeducation (Addiction Treatment Forum or National Alliance of Methadone Advocates, for instance).

The following issues may be discussed in psychoeducational terms: a) what is treatment specificity (table 1); b) the concept of loss of control and the irreversible nature of relapsing behaviour in addictive diseases (table 2); c) mechanisms of treatment functioning and the course of therapeutic response (table 3). Misconceptions are listed in the left-hand column, whereas the psychoeducational feedback to be given to the patient appears in the right-hand column.

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4.2

Motivational Interventions for Methadone-Treated Patients

A. Kantchelov

1. Introduction

Since the late 1980s the development of Motivational Interviewing and its adaptations has been acknowledged as the most important recent advance in the field of addiction treatment. Effective strategies, brief interventions and structured approaches have been developed to enhance client motivation, while clinicians' interest in motivational interventions has substantially increased. Surprisingly, it seems that theseinterventions have still not been given an adequate role in MMT programmes.

This paper aims to provide the best practical guidelines to methadone maintenance programme managers, programme planners, counsellors and clinical staff, to make them aware of the power of motivational enhancement strategies, to provide them with a taste for, and understanding of. the spirit of the motivational style of interacting with clients, and to enrich their clinical view with a highly effective method for helping clients to achieve behavioural change. It presents an outline of the theoretical background, outcome research, rationale for use and state-of-the-art practical methods for implementing motivational interventions that can be integrated into the MMTP context and daily work.

This paper is closely based on a thorough view of the research literature and on well-grounded empirical findings; it is organized within the Transtheoretical Model, which offers an integrative framework for conceptualizing and implementing behaviour change among people who have a problem of substance abuse.

It presents a motivational communication style for working with clients, based on the most advanced technologies, which have been developed in the field of psychosocial addiction treatment and the enhancement of motivation and behaviour changes, and it is specifically designed to match the clinical needs

of an MMTP.

There are many ways in which motivational concepts, principles and interventions can be applied in an MMT setting. The main aspects and practical implications of the motivational approach in an MMT are discussed with emphasis on style, spirit, strategies and ways of incorporating it into MMTP clinical work and into the treatment model. The principles, strategies, methods and interventions described here are explicitly intended to help clinicians facilitate change in MMT clients. They can be used as a stand-alone treatment, can be integrated with a broad range of other treatments and strategies, and can also be used to prepare a motivational foundation for other therapeutic approaches within MMT.

2. The role of counselling and psychosocial services in MMT

A number of studies have stressed that although methadone maintenance treatment has powerful effects in terms of stabilizing clients, keeping them in treatment and making them available for psychosocial interventions, a purely pharmacological approach will not be sufficient for most patients, and better outcomes are associated with higher levels of psychosocial treatments [4].

The best treatment retention percentages and the best outcomes, evaluated in terms of improved social functioning, were seen in the initial methadone clinical trials [7] in programmes characterized by the careful screening of clients, adequate dosing policies and extensive adjunctive services. The extent to which counselling is an important part of MMT was also addressed by Ball and Ross [1] in their correlational study. They noted that both staff and patients viewed counselling as the most important component of the rehabilitative aspect of methadone treatment. Their results strongly suggest that MMTPs which delivered more counselling tended to have better outcomes. The highly positive effect of psychosocial services was clearly confirmed by McLellan et al. [13].These authors concluded that methadone alone may only be effective for a minority of patients, and argued that the addition of counselling, and of medical and psychosocial services brought dramatic improvements over the effect of methadone alone.

3. Theoretical framework: the transtheorethical model

In recent times, the treatment of addictions has been dominated by the so-called Transtheoretical Model (TTM), proposed by Prochaska and DiClemente [20, 21, 22, 23] and revised by Prochaska et al. [24, 25] and DiClemente and Prochaska [6]. The model is 'transtheoretical' in that it is not based on any school of therapy, but offers an integrative framework for understanding and intervening with human intentional behaviour change and practical guidelines, irrespective of the therapist's favoured approach. The model proposes three organizing constructs: the stages, the processes and the levels of change.

3.1 The stages of change

The stages represent the dynamic and motivational aspects of the process of change over time. Five sequential stages have been identified; people pass through each of these in the course of changing a problem. These stages seem to apply equally well to self-change and to therapy-assisted change. In or out of therapy, people seem to pass through similar stages and employ similar processes of change:

1. **Precontemplation:** During this stage, individuals are unaware of the nature and extent of a problem needing to be changed, or are unwilling to change problematic behaviour.
2. **Contemplation:** In this stage people are aware that a problem exists and have got to the point of seriously thinking about overcoming it, but have not yet made a commitment to take action.
3. **Preparation:** This stage constitutes a reso-

lution of the decision-making task; in this stage, individuals intend to take action, and there is a commitment to a plan for change to be implemented in the near future.

4. **Action:** This is the stage when the plan for change is implemented, active coping is initiated, and the actual change in behaviour occurs. This is when individuals modify their behaviour, experiences and/or environment so as to overcome their problems.
5. **Maintenance**: In this stage, already achieved behaviour change is sustained, and people work to integrate it into their lifestyle, to stabilize behaviour, to prevent any relapse and consolidate the gains attained during the action stage.

Once change has become completely integrated into his/her lifestyle, an individual can exit from or terminate this process of change. It is normal to go through this whole process several times before a stable form of change is achieved. Relapse is viewed not necessarily as a failure, but as a normal, predictable part of the process, and as a stage of growth with its own opportunities. Working with patients during the period when a relapse is likely is essential to ensure continued change [8].

3.2 *The processes of change*

The processes have been derived from many diverse theories of behaviour change and are at the heart of the Transtheoretical Model. Ten processes have been reliably identified: raising of consciousness, self-re-evaluation, environmental re-evaluation, dramatic relief, social liberation, self-liberation, counterconditioning, stimulus control, reinforcement management and helping relationships.

The processes are intended to clarify the type of activity that is initiated or experienced by individuals in modifying their behaviour. According to the model, particular processes employed at particular stages are responsible for movement through the stages of change [6]. Generally speaking, cognitive strategies should be more appropriate to clients in the early stages of change, and behavioural strategies should be more appropriate at the action stage of change [2].

3.3 *The levels of change*

Individuals have multiple problems that interact with the process of changing any single addictive behaviour. The concept of levels of change incorporates the realization that individuals are at different stages of change with respect to different problem areas, and that addictive behaviour always occurs within various interrelated levels of human functioning. These levels are organized hierarchically as follows: symptom/situational, maladaptive cognitions, current interpersonal conflicts, family/system problems, intrapersonal conflicts.

The Transtheoretical Model provides a foundation for the development of practical strategies and interventions in countering addictive behaviours.

3.4 *The concept of motivation*

Motivation plays an important role in people's decisions to change their behaviour and substance use. It has been defined as "the probability that a person will enter into, continue, and adhere to a specific change strategy" [5]. A key dimension of motivation is adherence to or compliance with a change programme, so motivation may be thought of as the probability of a certain behaviour.

Miller and Rollnick [17] suggest that motivation should not be thought of as a personality problem, or as a trait that a person carries through the counsellor's doorway. Rather, motivation is a person's present state or stage of readiness for change, which may fluctuate from one time or situation to another. Most importantly, a person's motivation can be influenced by attuned clinical interventions and is

affected by how he or she is treated by clinical staff. Thus, increasing motivation becomes an inherent and central part of the professional's task. It is the counsellor's responsibility to motivate — to increase the likelihood that the client will follow a recommended course of action directed towards change.

There is no doubt that for patients in MMT the intake of an adequate dose of methadone is of dominant importance, but it is also clear that the success of methadone programmes is closely related to strictly following a therapeutic regimen and programme rules, while applying a range of psychosocial interventions. The participation of patients in these activities is based on their level of motivation to do so [28].

3.5 Stage-specific interventions

What motivates people to engage in treatment, progress in therapy and continue to progress after therapy is receiving interventions and treatments that match their current stage of change. Motivational interventions are a powerful tool in assisting clients to move through the stages of change. They are invaluable and most appropriate for the early stages of precontemplation, contemplation and preparation, and again in the relapse stage. Individuals in the action and maintenance stages may need skills, training in addition to motivational strategies (Table 1).

* **Precontemplation stage — building readiness:** A person in the precontemplation stage needs information and feedback to raise his/her awareness of the problem and of opportunities for change. The major strategy here is to raise doubts in clients about the harmlessness of their substance use patterns, and increase the clients' perceptions of risks and problems with their current behaviour.
* **Contemplation stage — increasing commitment:** The key here is to help the contemplator think through the risks of the problem behaviour and the potential benefits of change, and to instil hope that change is possible.
* **Preparation stage — getting started:** The main task here is to help the client develop plan for change that is acceptable, accessible, appropriate and effective, and determine the best course of action to take in seeking change.
* **Action stage — reaching change:** The goal here is to help the client implement the action plan by achieving change.
* **Maintenance stage — stabilizing change:** Helping the client maintain the achieved change, integrate it into his/her lifestyle, prevent relapse and keep the client in treatment are the main goals for the therapist at this stage.
* **Relapse — stop and start again**: The counsellor's tasks here are to help the person avoid discouragement and demoralization, reframe the relapse crisis and help him/her see the crisis as an opportunity to learn rather than a failure, and to initiate another change attempt to change by renewing the processes of contemplation, preparation, action and maintenance.

3.6 Assessment of stage status

Several different methods of measuring a client's stage of change are now avialble. Of these, the most commonly reported in the current literature are the Staging Algorithm [24] and the University of Rhode Island Change Assessment (URICA) Scale [12, 11], along with the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) [16] and the Readiness to Change Questionnaire [27]. Given that the client's readiness for change tends to fluctuate, the therapist's judgment of the client's current stage of change based on material presented during the counselling session is of indispensable value.

4. The Method

The motivational approach begins with the

Table 1: Appropriate Motivational Strategies for Each Stage of Change

Client's Stage of Change	Appropriate Motivational Strategies for the Clinician
Precontemplation The client is not yet considering change or is unwilling or unable to change.	Establish rapport, ask permission, and build trust. Raise doubts or concerns in the client about substance-using patterns by Exploring the meaning of events that brought the client to treatment or the results of previous treatments Eliciting the client's perceptions of the problem Offering factual information about the risks of substance use Providing personalized feedback about assessment findings Exploring the pros and cons of substance use Helping a significant other intervene Examining discrepancies between the client's and others' perceptions of the problem behaviour Express concern and keep the door open.
Contemplation The client acknowledges concerns and is considering the possibility of change but is ambivalent and uncertain.	Normalize ambivalence. Help the client "tip the decisional balance scales" toward change by Eliciting and weighing pros and cons of substance use and change Changing extrinsic to intrinsic motivation Examining the client's personal values in relation to change Emphasizing the client's free choice, responsibility, and self-efficacy for change Elicit self-motivational statements of intent and commitment from the client. Elicit ideas regarding the client's perceived self-efficacy and expectations regarding treatment. Summarize self-motivational statements.
Preparation The client is committed to and planning to make a change in the near future but is still considering what to do.	Clarify the client's own goals and strategies for change. Offer a menu of options for change or treatment. With permission, offer expertise and advice. Negotiate a change--or treatment--plan and behaviour contract. Consider and lower barriers to change. Help the client enlist social support. Explore treatment expectancies and the client's role. Elicit from the client what has worked in the past either for him or others whom he knows. Assist the client to negotiate finances, child care, work, transportation, or other potential barriers. Have the client publicly announce plans to change.

Table 1: Appropriate Motivational Strategies for Each Stage of Change

Client's Stage of Change	Appropriate Motivational Strategies for the Clinician
Action The client is actively taking steps to change but has not yet reached a stable state.	Engage the client in treatment and reinforce the importance of remaining in recovery. Support a realistic view of change through small steps. Acknowledge difficulties for the client in early stages of change. Help the client identify high-risk situations through a functional analysis and develop appropriate coping strategies to overcome these. Assist the client in finding new reinforcers of positive change. Help the client assess whether she has strong family and social support.
Maintenance The client has achieved initial goals such as abstinence and is now working to maintain gains.	Help the client identify and sample drug-free sources of pleasure (i.e., new reinforcers). Support lifestyle changes. Affirm the client's resolve and self-efficacy. Help the client practice and use new coping strategies to avoid a return to use. Maintain supportive contact (e.g., explain to the client that you are available to talk between sessions). Develop a "fire escape" plan if the client resumes substance use. Review long-term goals with the client.
Recurrence The client has experienced a recurrence of symptoms and must now cope with consequences and decide what to do next.	Help the client reenter the change cycle and commend any willingness to reconsider positive change. Explore the meaning and reality of the recurrence as a learning opportunity. Assist the client in finding alternative coping strategies. Maintain supportive contact.

assumption that the responsibility and capacity for change lies with the client. The style and strategies of the interventions are based on the use of empathy and warmth, not authority or power, and developing non-judgmental and collaborative therapeutic interactions. Increasing client motivation is seen as a central part of the clinician's task. The counsellor works to elicit the client's own concerns. When the client (rather than the counsellor) formulates the reasons for change, the client's internal motivation is harnessed, and he/she is more ready for change. Most of the work to be done involves exploring a client's ambivalence about change, matching interventions to the client's current stage and level of readiness for change, and employing motivational strategies to mobilize the client's own resources in achieving change.

4.1 Motivational interventions

A motivational intervention can be defined as any clinical strategy or method designed to enhance client motivation for change. Motivational interventions can involve a variety of approaches, ranging from brief interventions, client assessment and feedback, counselling, single or multiple sessions, to formal structured therapy, which may be thought of as ele-

ments of a continuum of care. The focus here is on interventions designed to enhance intrinsic motivation and readiness for change.

4.1.1. The FRAMES approach

Miller and Sanchez [15] analyzed the content of brief motivational strategies and described six counselling elements that appeared to be the commonly used 'active ingredients' in effective brief interventions. These are summarized in the acronym "FRAMES":

* Feedback regarding personal risk or impairment is given to the individual following an assessment of substance abuse patterns and associated problems.
* Responsibility for change is attributed squarely and explicitly to the individual.
* Advice about changing (reducing or stopping) substance use is clearly given to the client by the clinician in a non-judgmental manner.
* Menu of self-directed change options and treatment alternatives is offered to the client.
* Empathetic counselling, showing warmth, respect, and understanding, is emphasized. Empathy entails reflective listening.
* Self-efficacy or optimistic empowerment is engendered in the person to encourage them to change.

4.2 Structured motivational intervention models

4.2.1 Motivational interviewing

Motivational Interviewing (MI) is an approach designed to help clients reach a decision and build commitment to change. It is a client-centred, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence [18].

The spirit and style of MI are central to the approach. The counselling style is a quiet and eliciting one. The therapeutic relationship is more like a partnership or companionship rather than a division of roles between expert and recipient. In MI the counsellor does not assume an authoritarian role, and avoids teaching and telling clients how to change or what they should do; rather, he/she works actively towards building a commitment to change. Responsibility for change is left to the client. It is the client's task, not the counsellor's, to articulate and resolve his/her ambivalence. The counsellor seeks to create a positive atmosphere that is conducive to change and is directed to helping the client examine and resolve ambivalence.

Readiness for change, as well as resistance and denial, are not viewed as a trait in the client, but as a fluctuating product of the interpersonal interaction between client and therapist, and feedback regarding therapist consulting behaviour. The overall goal is to increase the client's intrinsic motivation, so that change arises from within, rather than being imposed from without. When this approach is enacted properly, it is the client who presents and voices the arguments for change, rather than the therapist. The appearance of a motivational interviewing session is quite client-centred, yet the counsellor maintains a strong sense of focus, purpose and direction, along with clear strategies and skills for pursuing that purpose, and actively chooses the right moment to intervene in particular ways at crucial moments [17].

There are five broad clinical principles in MI that give the context regarding the'why' of practice. These are: express empathy, develop discrepancy, avoid argumentation, roll with resistance, support self-efficacy. They underlie the specific practical strategies ('how-to' elements): ask open-ended questions, listen reflectively, affirm, summarize, and elicit self-motivational statements (Change Talk) (Table 2). A fundamental goal in MI is to have clients present and voice arguments for change. One major task of a counsellor is that of leading the therapeutic process in a way that facilitates clients to express self-motivational statements. Hearing oneself state the reasons for change is a powerful way of increasing personal motivation.

MI incorporates two major phases of the

Table 2. Sample Questions to Evoke Self-Motivational Statements
Problem Recognition What things make you think that this is a problem? What difficulties have you had in relation to your drug use? In what ways do you think you or other people have been harmed by your drinking? In what ways has this been a problem for you? How has your use of tranquillizers stopped you from doing what you want to do?
Concern What is there about your drinking that you or other people might see as reasons for concern? What worries you about your drug use? What can you imagine happening to you? How much does this concern you? In what ways does this concern you? What do you think will happen if you don't make a change?
Intention to Change The fact that you're here indicates that at least part of you thinks it's time to do something. What are the reasons you see for making a change? What makes you think that you may need to make a change? If you were 100 percent successful and things worked out exactly as you would like, what would be different? What things make you think that you should keep on drinking the way you have been? And what about the other side? What makes you think it's time for a change? I can see that you're feeling stuck at the moment. What's going to have to change?
Optimism What makes you think that if you decide to make a change, you could do it? What encourages you that you can change if you want to? What do you think would work for you, if you needed to change?

therapeutic process, building motivation for change and strengthening commitment to change.

4.2.2 Brief motivational interventions

The research literature shows brief adaptations of motivational interviewing (AMI) effective for a variety of problems, common in MMTP, which are not affected by methadone alone (like problem behaviour, problem drinking and non-opiate substance abuse). Also, brief AMIs have turned out to be as effective as much longer treatments.

In their review on the effectiveness of AMIs Burke, Arkowitz and Dunn [3] drew the following conclusions: AMIs are more effective than no treatment and are as effective as credible alternative treatments; AMIs are effective both as stand-alone treatments and as preludes to other treatments; outcomes of AMIs are not only statistically significant, but also clinically significant; most of the studies deal with alcohol-related problems and addictions, and most of them are quite strong in external validity (i.e. results can be generalized to other settings, problems and populations); brief AMIs perform as well as long AMIs and as more extensive alternative treatments.

4.2.3 Motivational enhancement therapy (MET)

MET is a brief adaptation of MI that incorporates a 'check-up' form of assessment feedback. It is a systematic intervention approach designed to produce rapid, internally motivated change through mobilizing the client's own change resources. The integrated MET approach was delineated in a detailed therapist manual for work with problem drinkers [19], developed for Project MATCH, and was later adapted for clinical work with drug abus-

ers by W.R. Miller [14].

In MET, treatment is preceded by a battery of assessment instruments. The initial two sessions provide the client with objective feedback regarding his drug use and related problems and focus on building motivation and strengthening commitment for change. The subsequent sessions serve as periodic reinforcement and check-ups of progress towards change and make specific use of the follow-through strategies - reviewing process, renewing motivation, redoing commitment.

MET consists of four to twelve sessions to be completed within a period of three months.

Project MATCH [26], the largest psychotherapy outcome study conducted to date, found that 4 sessions of Motivational Enhancement Therapy proved to be as effective as two longer treatments (12 sessions of cognitive-behaviour therapy, and 12 sessions of AA-based treatment) in the case of problem drinkers.

4.2.4 *The structured stepped model for motivational interventions in MMT*

Examining the work carried out by clinical staff in MMTPs, Ball and Ross [1] concluded that most of it can be more properly described as casework, rather than counselling, which deals with day-to-day issues, mostly of a practical nature. How these interactions are conducted, and particularly the attitude of staff members, is probably the next most important determinant of treatment effectiveness after an adequate dose of methadone [10].

Based on these findings, a structured set of motivational interventions was developed as a stepped model, specifically tailored for dealing with everyday contacts with clients, routine problems, tough and conflicting situations, and difficult clients in methadone maintenance programmes [9]. It creates the programme's spirit and therapeutic context, which turn every contact with clients into part of the overall flow of interventions, which aim to achieve better psychosocial adjustment and positive behaviour change.

The Model is designed as a stepped scheme, with 5 levels of stepped interventions:

The first, most brief and most simple intervention is the Simple Reflection, performed by the nurse at methadone delivery. It is very brief and may take the form of an open-ended question, to be followed by a simple reflection, an amplified reflection, or a double-sided reflection, and concluding with a brief reframing or summary.

The 2nd level intervention is the Brief Motivational Intervention, delivered for 3-5 minutes by the case-manager; it is based on the FRAMES strategies. These two interventions are routinely practised in everyday contacts with clients and form the dominating style of staff communication with clients.

The 3rd level is the Brief Motivational Session, which is highly structured, and delivered by the case-manager in Motivational Interviewing style for 10-20 minutes.

The 4th level intervention is the Full Motivational Session; this takes 30-60 minutes and is delivered by a counsellor who is qualified and experienced in motivational interventions. It implies the principles and strategies of Motivational Interviewing, and has a strong focus on a particular problem or problem behaviour.

The last, 5th level, is the Motivational Encounter with the Team. It is applied with the most difficult clients — those that break programme rules in a harsh way, that are aggressive and impulsive, and capable of creating serious problems — the people that are most difficult to deal with. This encounter is structured in a non-judgmental, supportive, caring and empathetic way, and is concise, focused and directive.

The main principles of implementing the model imply routine implementation of less intensive interventions, while the more difficult clients and the more complex problems are assigned to more experienced counsellors, who are responsible for structuring more intensive and specific interventions. Interventions are matched up with specific problems, situations and the individual characteristics of clients.

4.2.5 *Group work models*

Many motivational activities and strategies

can take place in increasing the effectiveness of group work. In recent years there has been a raising interest in developing structured motivational approaches for group work based on the Transtheoretical Model and on Motivational Interviewing principles (see the Resource List). It should be borne in mind that conducting motivational interviewing-based therapy in a group setting is considerably more complicated than individual treatment, and requires a high level of training and counselling skills.

5. Addressing specific problems in MMTP

Incorporating motivational interventions and approaches into MMTP services may greatly enhance the likelihood of client change, treatment effectiveness and the overall quality of services. Some of the ways in which motivational interventions can be used involve addressing specific problems and treatment issues; they can be applied as a means for: rapid engagement to facilitate treatment referral and treatment entry, an empowering brief consultation for clients already placed on waiting lists, a preparation for treatment to increase engagement, retention, participation and compliance, overcoming client defensiveness and resistance, working with difficult and coerced clients, dealing with conflicting situations in a positive way, providing an introductory motivational boost for the inclusion of other therapeutic components, or else a prelude to further treatments, stand-alone interventions or a counselling style to be used throughout the course of treatment.

Research testifies to these effects: clients who receive MI at the beginning of treatment are likely to stay in treatment longer, work harder, adhere more closely to treatment recommendations, and experience substantially better treatment outcomes than those who received the same treatment programme without MI. Additional MI was found to facilitate treatments as different as cognitive-behavioural skill training, twelve-step and disease model counselling, and methadone maintenance [18].

5.1 Engagement and retention in treatment

Motivational interventions can be a useful adjunct to increasing client engagement, retention and participation in treatment. A single session (or a couple of sessions) of motivational interviewing added to the routine protocol at the beginning of treatment, prior to entering treatment, or as part of the assessment or treatment entry procedure, may result in better forms of involvement in later treatment, better retention and more favourable outcomes.

5.2 Compliance and non-compliance

Here non-compliance is viewed as a largely motivational issue, and is discussed from the perspective of the Stages of Change Model. Client non-compliance may arise when the client is in the precontemplation or contemplation stage, and is not yet ready for action-oriented interventions, but may feel prematurely pushed to action. Such clients need specific interventions to resolve their ambivalence and enter the stages of preparation and action.

Another possibility is that the non-compliant behaviour arises as a result of underlying client resistance due to an inappropriate interaction with a counsellor, with staff or a prescribing physician. This is where the MI strategies for rolling with resistance should be applied.

5.3 Difficult clients, coerced clients, and conflicting situations

The motivational approach provides alternative ways for dealing with problem situations and clients in a positive way by implementing interventions that are directive, yet non-judgmental, empathetic and caring, while

providing a basis for reframing the conflict into an opportunity for positive behavioural change, and for communicating with clients through therapeutic negotiation, instead of confrontation and conflict.

Difficult and coerced clients are at least as amenable to a motivational counselling style as any others. Research now demonstrates that positive treatment outcomes are associated with a high level of empathy in clinicians, as reflected in their warm, supportive listening. If clients receive interventions appropriate to their motivational stage, they may become invested in the treatment process and benefit from oportunities for positive change.

5.4 Use of motivational interventions in comprehensive MMT programs

Motivational interventions can be effectively integrated into more comprehensive treatment plans for clients in MMTPs. These approaches can be particularly useful in MMT when they are used to address specific client target behaviours, problems and issues in the treatment process that may be difficult to change by standard action-oriented approaches. Motivational interventions can be used with clients before, during and after substance abuse treatment.

The most obvious integration is to offer a motivational intervention as a first consultation and prelude to other services. Another option for integration is to use motivational interventions as a counselling and communication style that can be used in parallel with other methods throughout treatment. A third possibility is to keep motivational interventions in the background, to be returned to when motivational issues emerge in the further course of treatment.

These three applications can be integrated into a comprehensive intervention method, where the first session is strictly motivational interviewing, eliciting and listening to the person's concerns and reasons for change. Feedback of assessment results in an MI style begins in the second session, followed by a thorough functional analysis of substance use in the person's life. All this is then drawn together in a treatment plan, drawing on a menu of CBT skill-training modules to address specific goals for change. These modules are then delivered within an MI style, and the counsellor can fall back on MI whenever particular motivational issues or obstacles arise. Personal choice and autonomy are emphasized throughout treatment [18].

5.5 Use of motivational interventions in low-threshold MMT programmes

Motivational interventions can be particularly useful in treatment programmes with limited staff, resources, time, numbers of adjunctive services and treatment components, numbers of individual sessions and consultations per client, and particularly in cases where only one intervention can be offered. Brief motivational interventions may be applied in dealing with specific problems in helping to maintain a user-friendly atmosphere and good client-staff relations and communication.

6. Training issues

Although brief interventions can be administered by a wide range of professionals, practicing therapy requires training in specific therapeutic modalities. Therapists should be sufficiently well-trained in the motivational approach and should not rely solely on reading texts to learn this approach. This chapter is not designed to teach clinical skills. To train clinical personnel, there is a need for specialized training courses. These are provided by qualified trainers from the Motivational Interviewing Network of Trainers. A key to acquiring the necessary skills for MI is practice with feedback and under supervision.

7. Conclusion

Implementing a motivational approach in MMT acts as a powerful resource in positively influencing in a positive way the dominant programme atmosphere, staff-client interactions, quality of services and programme functioning as a whole. There are various ways in which motivational interventions can be successfully applied in MMT. The evidence to date is very encouraging in suggesting that even brief interventions can enhance client motivation and trigger significant improvement and change. The use of these promising methods in the future will depend on the creativity of clinicians and researchers in adopting, adapting and evaluating motivational interventions to make them more widely and effectively implemented in MMT clinical practice for the good of our clients.

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RESOURCE LIST

The following texts are highly recommended as key resources for detailed information on theory and practice of motivational interventions:

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- WWW.MOTIVATIONALINTERVIEW.ORG
- STAGES OF CHANGE READINESS AND TREATMENT EAGERNESS SCALE (SOCRATES)
  This instrument is in the public domain and may be obtained by contacting its author:
  William R. Miller, Ph.D.
  Director Center on Alcoholism, Substance Abuse, and Addictions 2350 Alamo SE University of New Mexico Albuquerque, NM 87106 Phone: (505) 768-0100 Fax: (505) 768-0113, E-mail: wrmiller@unm.edu
- UNIVERSITY OF RHODE ISLAND CHANGE ASSESSMENT SCALE (URICA)
  This instrument is in the public domain and may be obtained by contacting its author:
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4.3

Psychotherapy for Patients in Methadone Treatment

E. Bignamini and S. Zazza

1. The management of Methadone treatment

Patients in therapy with methadone obviously do not originate from a homogeneous series of clinical situations. Morever, treatment with methadone assumes particular characteristics, revealing the therapeutic route within the entire care system (not in the medico-pharmacological system alone), and in the specific physician-patient-drug interaction.

In clinical practice, therefore, there are patients who take high and constant doses of a drug while showing satisfactory results and a good level of compliance with prescriptions, patients trapped in a pattern of increases in dosage, or in a series of repeated, inconclusive attempts to scale down, "phobics" who never accept adequate doses of the drug, and "anxious" patients who, at the end of their scaling down, cannot let go of the last few milligrams.

From these few examples it will be clear that the management of methadone treatment requires the doctor to have a good range of relational and psychopathological competences and be attentive in assessing the non-pharmacological factors involved that are viewed as "confusing" in scientific research on the efficacy of a drug (and which researchers attempt to eliminate through suitable methodologies, such as double-blind, randomized and controlled studies), factors that have proved to be precious, powerful tools in implementing the action of the drug as part of an integrated strategy.

Successful pharmacological treatment necessarily implies an effective but also partly instinctive and intuitive management of the relationship with the patient through which the authority of the doctor, the patient's faith in improvement together with the motivation to achieve it, adequate expectations of the value of the drug, confidence in the service being provided and reassurance of anxieties, can all be transmitted.

Apart from the basic relational aspects

guaranteed by the professional qualifications of the doctor, specific psychotherapeutic intervention may be necessary. Drug addiction is a "pathological condition correlated with an alteration of the system of gratification and with a coercion of the modality and the ways in which the subject achieves pleasure, characterized by cravings and by a relationship with the object (substance, situation or behaviour) distinguished by reiteration and marked difficulty in giving it up" [4, 5]. This conceptualization stresses all the biological, psychological and behavioural aspects that sustain the pathology in question in an inseparable way. The "pleasure disorder", as drug addiction may be defined, is the result of an imbalance which involves, and is determined by, all the dimensions of the individual. One therefore faces specific psychopathological aspects which should be treated on the psychotherapeutic plane in order to achieve a positive overall result from the treatment.

In addition to what has already been said, psychotherapeutic intervention may be necessary for other psychopathological disorders which often accompany and are tangled up with drug addiction, and which are currently conceptualized as "double disorders" or "double diagnoses".

2. Specific treatment nuclei in the psychotherapy of drug addiction

Independently of the aetiology (which is much discussed: it can now be recognized that a multiplicity of the factors involved – genetic, environmental, pharmacological, psychological and cultural, are modulated differently in each subject, so determining the pathology) and of the socio-economic-cultural conditions, the drug-addicted subject, once the condition of drug addiction has been ascertained, finds himself facing several psychopathological problems typical of his condition.

The encounter with the substance leads to a radical transformation: the subject's experience changes him deeply, as it affects the deepest biological and psychological dimensions. This change becomes the subject's key experience and is unforgettable; all other experiences will be compared with it and, without an adequate personal response, those other experiences will remain secondary to it. What else could provide similar gratification, pleasure, or oblivion? And why should the patient give it up? The prize is so great that obtaining it is worth more than his own life. Even when everything seems ruined by drugs, the habit is so deeply rooted that it cannot be exchanged with anything else. Morever, the life-style imposed on the drug addict is very stressful and exciting, and its attraction is a worthwhile compensation for impending depression, which will make the addict adopt maniacal defence mechanisms.

It is not possible to go any further into the psychopathological aspects in this paper. I need only say that, even if in different forms and dimensions, drug addicts share the following features:

a) *Greed*: a voracious oral drive to get "everything immediately", and a maniacal triumph in the destruction of every obstacle (a mechanism that can be made to work in the care programme – which should itself be fast and painless).
b) *Compulsion:* the onset of desire, sly and tumultuous; this puts every other object out of focus, changes the value of things and one's way of thinking, and is followed by the motor release of acting out the addictive event, and then by the down phase, so determining a traumatic, destabilizing emotive and cognitive discontinuity.
c) *Mourning for the lost object:* the drug-object leaves a deep emptiness which is difficult to fill up with other less totalizing and gratifying objects. The patient experiences existential disorientation in which the prevalent feeling is nostalgia for what has been left behind and cannot be substituted. Furthermore, as the mourning is metaphorical and depends on a choice made by the subject, a choice which can never be reversed, the thoughts and mood of the patient swing between a desire to give in and a desire to abstain.
d) *Regrets for the fusional-heroic dimension:* the

high emotional level connected with the life-style of the drug addict sustains great, heroic experiences (even if these may be tragic) which offer a sense of gratifying, though illusory, fullness. The involvement of the profound, archaic structures connected with pleasure strengthens the sensation of living a totalizing experience which will alter the boundaries and forms of external objects and of the components of the self, so offering an exalting perception of fusion. Giving up drugs does not cancel the memory of the experience which, in time, undergoes a transformation that removes the negative aspects (which motivate change) and retains the positive ones (which increase the risk of relapses). Life without drugs often offers dull, grey and depressing panoramas that comprise no trace of greatness; the process of adaptation to a "normal" life does not proceed spontaneously or coherently.

These features, which become fixed in a pattern constituting the specificity of the drug addiction experience, require psychotherapeutic treatment whose objective is the resetting of the strategies of gratification and of one's plans for life. These general concepts are applied through specific techniques in different psychotherapeutic schools and are often carried out in a variety of distinctive organizational care settings.

3. Psychotherapeutic methodologies

3.1. Psychodynamically oriented therapy

According to psychodynamic theory, addiction is the result of a failure to succeed in dealing with ambiguous and/or anguish-generating deeds.

There is the attempt to solve and subdue an inner conflict between clashing requests deriving from different needs, or to replenish the shortfall in psychic structures that have been missing or inadequate.

The subject may think: "By taking action, I will obtain a chemical substance 'outside me' that will magically solve my problems". That is a misleading approach; the trouble brought by addiction is bound to deep emotional needs that have not been worked out at the level of the Ego, or to a situation of evolutional impairment that stops the individual feeling whole or self-confident.

The addicted character then transforms the process of elaboration into an "immediate gratification" relational model, involving an acting-out — the well-known "everything now" greedy attitude.

In a regular structure, a dynamic balance between three registers develops the individual personality:

- Intellectual register (thought)
- Somatic register (body)
- Behavioural register (action)

In an addicted structure, the behavioural scheme is bound to prevail. A recollection, or the meaning of an experience, means getting through an event, which must be re-represented verbally through language.

The recollection process can take place if the newborn's "empty mouth" is filled by the words of the person who enacts the mother function, by words spoken to the newborn and over the newborn, and by thinking about him as a complete being. As a result, emptiness, instead of being frightening, is a way of opening oneself to others through the mediation of language.

This does not occur with addicted individuals, who convert the process into an act of taking in. (That act involves the utilization of an external object that is able to magically heal an emptiness that can never be accepted, because it is primarily experienced as a source of anguish and persecution).

Olivenstein [18], in discussing addicted individuals, depicts a "broken mirror evolution stage".

This evolution stage occurs between the newborn's 6^{th} and 18^{th} months, at the time when a newborn should structure a different Ego detached from the mother's Ego: in pathological individuals, their relationship with the mother is the obstacle in attempting

this evolution stage; the mother experiences the newborn as her vanished desire and not in itself. ("We find ourselves looking at a mirror carrying a fragmented image that is capable of bringing the baby to a later stage, where there is a unifying identity between the mother and its own Self").

In talking about the narcissistic personality organization of his subjects, Green [13] identifies a "dead mother affliction". In this affliction, the mother is physically near, but gives her son an objectively devitalized relationship, within which the son's real needs are not perceived or satisfied.

The result is a double impact on the to-be-addicted baby's psychic development:

"Unconscious identification with the dead mother": between mother and son an inverse relationship is structured, with the assisted becoming the assistant. It is now the baby who feeds the dead mother in an exclusive, totalitarian relationship.

"The collapse of making sense": the baby hasn't got the skills needed to make sense of the accidents that happen to him, so that his experience loses its meaning.

Physical and psychical experience is absent, and so is the opportunity to be sustained; the body is unable to experience the agreeable integration dimension essential to an adequate narcissistic development [20]. "A well-structured narcissistic process lies in the maintenance of the unity and solidity of the Ego, which continues to stand whole and solid at every moment of life, without being corrupted or lacerated by a variety of psychophysical adjustments to the external world and to the internal world of emotions and drives").

According to authors whose work is based on psychoanalysis, heroin addiction is the symptom of a breakdown located in the "oral phase" of the evolutionary path. This phase accounts for the whole range of psychopathologies comprising the key elements of orality, separation and the differentiation between Self and non-Self.

The peculiarity of this psychotherapy technique is its transference and counter-transference analysis. The object of that transference and counter-transference analysis is the patient-therapist relationship, inclusive of: "all the phenomena establishing the patient-psychoanalyst relationship"[15]. Transference and counter-transference have to be conceived as interactive concepts, so allowing "transference" to be defined as everything contributed by the patient to the therapeutic relationship at the present moment or as a habit belonging to their past relationship, and "counter-transference" as the therapist's emotional reaction towards a given patient in their specific relationship. In the opinion of some authors, the patients that should react best to this kind of therapy are those with a strong motivation, possessing reflective and introspective skills, which drug addiction has mainly developed through intrapsychic conflict (e.g. Cancrini [6, 7]: "reactive drug addiction"); according to other authors, the therapy is functional for motivated patients who are affected by drug addiction and a strong psychopathology, but not by antisocial personality distress.

3.2. Systemic relationship psychotherapy

According to this therapy, drug addiction is a symptom of major distress in the patient's parental relationship system, and a failure in the management of distance in important relationships, whose opposites are union and identification.

The family, as a unit made up of different but related individual parts, is described as a "system".

Relationship-forming family members identify, from different points of view, what happens in the system to develop a circuit of mutual influences.

The family system accomplishes two main functions. The first is *stability*; in time it allows the subjects to recognize that specific group of people as "his family" (family identity). The second is *flexibility*; it allows the family to recollect and reorganize in an unending process of adjustment of the distances within emotional links when critical events or potential causes of unsteadiness occur.

Cirillo and co-workers [8] suggest an aetio-

pathogenetic, trigenerational model for heroin addiction. They have collected the emotional history of three family generations (the third is the one that includes the addicted child), which is useful in understanding the process that brought about the current pathogenic structure.

The observed generations are connected by a shared factor: some of the parents had, on their own account, been "needy" sons or daughters in some respects, without receiving recognition or understanding of that "neediness".

Generation by generation, this condition of deprivation is passed on; three main parent-child relational exchange forms have been located within this model:

a) *Mimic caring:* Whoever takes care of the baby proposes a form of nursing founded on a non-real emotional baby's needs, so that the relational exchange become illusory. (It is as if the carer were to say, "I am taking care of you to satisfy my parental needs, as I myself am an unfulfilled child".)
b) *Advantageous caring aimed against the spouse:* A mother or father, more likely the mother, is over-committed to the child; this over-commitment is turned to advantage in stepping up the war against the other parent. (This intense but false relationship leaves the child confused and unable to discover the trick.)
c) *Dumping:* According to these parents, their children seem not to exist; they justify dumping them as an objective necessity, but the problem is that there is no evidence that the parents have any plan for the family. In this kind of psychotherapy, the most commonly used techniques are those of prescription and restructuring.

The prescription, which is given to the family by the therapist, may vary in its contents, covering the structural rules within the family, its specific communication patterns and/or the symptoms themselves. Prescriptions are used to strengthen the evolving process between therapeutic meetings or to reveal within the family the difficulty of enacting the prescriptions.

The restructuring makes it possible to bring new sense and value to the verbal realities expressed during the therapy. In this way, therapist and patient are able to build up a new reality: "Restructuring is a therapeutic technique bringing into play the concept that all the rules, all the secondary realities, are minor and life is what it is said to be" [22].

The patients that should react best to this treatment are those that have a primary network of helpers willing to cooperate; their symptoms should be recollected and maintained by a dysfunctional relational process. (E.g. – Cancrini (1984): Addiction associated with personality disorders and neurotic addiction) [6, 7].

3.3. Cognitive-behavioural psychotherapy

These psychotherapeutic models offer no aetiological definition of addiction and the borders between the different approaches are usually blurred, so fusing the models into an integrated whole called cognitive-behavioural.

The aim of the behavioural model is to teach the patient self-control by applying techniques able to modify his mistaken behaviour.

Throughout an analysis of inputs, the therapist drives non-adaptive reactions on the behavioural level by exactly defining the kind of problem to be solved.

Among currently practised techniques, we should recall systematic withdrawal and operational conditioning.

The purpose of systematic withdrawal is to teach patients how to transform an unacceptable behavioural reaction into an adaptive one by acknowledging a hierarchy of stimuli which have prompted a mistaken reaction up till the present.

Patients are increasingly provided with hierarchies, in accordance with the increasing difficulty of facing a stimulus.

The structure of operational conditioning is based on the assumption that a subject's reactive answer will be repeated if it is followed by a "pleasant" (as defined by the subject) conse-

quence (positive reinforcement) but will not be repeated if it is followed by an "unpleasant" one (negative reinforcement).

When a therapist applies this model, he or she will study and analyse the behaviours to be retained and learned, and those that are to be discouraged.

The purpose of the cognitive model is to explain the process that causes the patient's return to an addicted state and the continued use of toxic substances, so as to teach the patient some cognitive analytic skills and emotional control pertinent to the use of substances.

Cognitive therapy evaluates the automatic thoughts, the convictions, and the "make-believe" that set up interference between an event and its emotional and behavioural consequences.

The modification of deeply held beliefs leads to a change in convictions and, therefore, in automatic thoughts, so generating a transformation in behaviour and emotion. This therapeutic model considers psychological problems to be the result of how individuals consider themselves, the world and the future.

There are probably some mistaken adaptive beliefs or cognitive distortions capable of generating psychological problems if they are used as primary mental organization schemes to evaluate and elaborate externals inputs.

Three areas are considered to generate changes in drug addiction:

a) Beliefs about the use of drugs and addiction-induced behaviours (the aim being abstention from the use of drugs);
b) Thoughts on life, the self and the future (the aim being growing confidence in one's self and in others);
c) The learning of social skills, self-evaluation and techniques for self-help (the aim being growing levels of self-esteem and gratification).

Marlatt and Gordon's cognitive models of substance abuse consider a circularly linked, seven-step process, with the last step linked to the first by a feedback method, while a "relapse" may occur at any moment in the process [16].

According to this model the most useful techniques are questionnaires or "self-evaluating" schemes, together with a diary consisting of daily entries written by patients to express their thoughts and emotions.

Before being admitted to this therapy, patients are asked to comply with the therapist's requests (this includes homework) and to accept the status of the therapist as the one in charge of what is to be done [10].

3.4. Group psychotherapy

The group treatment of addicted patients has developed both from clinical-psychoanalytic theory and cognitive-behavioural theory.

The psycho-educational group, as the setting for cognitive-behavioural group therapy, has the aim of developing an awareness about the practical, medical and psychological consequences of drug addiction through discussions, the provision of informative materials and teaching sessions. This kind of group is often used as a starting step in a therapeutic programme.

The monosymptomatic group of analytic therapy [9], a kind of group psychoanalytic therapy, has the goal of transforming the Self by allowing psychic structure maturation, adequate communicational and social abilities (pointing to socially oriented interpersonal aspects linked with drug addiction) and an integration of the mind-body relationship. These goals comprise the healing of symptoms and the restoration of psychic functionality.

The recollecting function group, RFG [24], is a short group experience for those shown to be suffering from a fragile Self by a psychostructural analysis diagnosis. The RFG goal is to strengthen the primary psychic functions –– recognizing your own Self and taking care of it. The heroin-addicted patient has a fragile Self that is insufficiently structured to mediate between instinctual needs and external reality. Group treatment permits a lowering of the stressful tension that may occur in an individual patient-therapist relationship that is invasive for the addicted patient: the group of equals makes acceptable and feasible a prox-

imity, while the equals are perceived as less exciting objects with a lower transference possibility.

4. Psychotherapy in public services

"Men live upon statements whose authenticity is related to the trust they give to the statements themselves" [2].

The psychotherapeutic treatment models discussed above have a specific setting, which should be functional to the work of "relational organization" to be carried out within the therapist-patient relationship.

The setting is the device that regulates the frequency of meetings, their mode (face to face, with or without a desk, a bed, an armchair or unidirectional mirror), duration of meetings, payment, and so on.

When an individual approaches a psychotherapist, he accepts the setting the therapist suggests; this setting then becomes the backdrop to the therapeutic process.

"When we translate setting as aspect or situation, we do not have to think about the situation seen by an observer, indeed we have to think to the situation produced by the act of observing itself involving a border, a limit. The setting is the establishment of requirements to observe and to study [3].

Organizing a setting in space and time is itself a therapeutic action; the creation of limits brings with it a therapeutic function of direction and control that is capable of structuring mental assets.

Whoever works in a public facility faces a more complex task related to the setting concept, so it may be helpful to consider the different acting levels playing a role when a patient arrives at a facility centre against drug addiction.

The bio-psycho-social characteristics of drug addiction call for a service able to provide integrated treatments, whether clinical or psycho-social-educational. Patients applying for help to a service attached to a National Health System clash with a group of professionals possessing a variety of different skills; when they ask them for help, they apply relational models and methods they are accustomed to and know well.

Public health services become an institutional environment for developing the help relationship, the Third, and structuring a triangular patient-operator-service relationship, within which each participant brings his or her own different culture, in terms of values and images.

These three hubs constitute a mutually interactive, triangular relationship; an analysis of what happens within it needs a self-reflective capability [1]. Every professional should use self-reflection about what happens in the relationship, real or imaginary, with the patient, but the institutional working group should itself have a self-reflective capability, which should be stimulated through the organization the group has given itself.

The form taken by the organization conveys and transmits the values embodied in the treatment typology offered to those requesting help [17].

Some addiction pathology service operators should have a specific psychotherapeutic training, to be able to evaluate this complex correlation of variables and levels in meeting patients, so benefiting the whole work group.

This professional training strengthens the context for the therapeutic act itself within a clinical planning system. The therapeutic act acquires a different significance, but it also allows an easier pathway for "what is happening" interpretative hypotheses, so giving sense to what seemed without sense at first glance.

According to addicted patients, pharmacological methadone therapy acquires the value of a "transactional object" in a doctor-patient relationship, so driving the acted-out communicative levels and also the representations given to the Self and to the Other in that specific relationship.

From this viewpoint, medicine is an object viewed "in transit" from doctor to patient, and is recognized by both as being a real "third" endowed with symbolic value.

Both actors in a doctor-patient relationship can use medicine to re-balance emotional distances, and re-define power positions, as

an offensive or a seductive instrument, or to implement a triangulation between operators capable of distinguishing "good" from "bad" operators.

The helper and the individual asking for help share the idea of a relationship they think they should have in their respective role-moments.

Parsons [19] presents the ill individual's requests within a patient-therapist relationship as:

- A lowering of everyday social, work, and family role responsibilities;
- The idea of healing as not being the outcome of a deliberate act;
- A wish for improvement from the current state of illness;
- A clear request for help or collaboration from the health system.

On the other hand, a drug-addicted patient who asks for help in an imperative mode ("everything now"), focusing all his needs on his physical condition as an evident and clear expression of suffering, undermines Parson's system of expectations.

With this kind of request as starting-point, it becomes essential for the health organization to decide on a therapeutic way of acting right from the patient's earliest contact with the health service.

If the physical problem was, for example, considered a minor one, in a theoretical dimension, a pharmacological therapy of regular dosage substitution would be considered "no good", and any patient unable to accept treatments other than clinical ones would be considered as "lost". Or if the health care institution was socially concerned and it considered collaboration as its standpoint, any addicted patient would be considered "hard" and "manipulative".

If a health organization was structured on a pedagogical command philosophy, the healing and treatment of patients would be based on a double and/or contradictory communicative system, resembling the "double bond" mirror messages between parents and addicted child.

The idea of taking action in an organized way, comprising plans for structures and procedures based on clinical and therapeutic knowledge at every step in treatment, opens up the opportunity of thinking of the therapeutic process as a co-construction between the health service and the patient.

This way of imagining the therapeutic process links, and defines as co-dependent, thought and action, organization and clinic; to reinforce the process by subsequent steps is the right way to approach patients.

A public service for drug addicts offering a "step by step" integrated multimode treatment should divide those steps into:

Therapeutic contract:

a) Definitions of timing and goals;

b) Verification of a patient's achieved goals.

Every step should be considered as an opening to further steps or on its own. Step-specific actions generate two-way information and knowledge both for patient and operator: the horizontal way refers to the growing relationship in a specific space and time (here and now) and the vertical way refers to a hypothesis on projects and future procedures (there and then).

Request for help in healing step: the patient is unwell and confused; he needs to be listened to. This is the first contact step. The service should be organized so as to be adequately restraining but reassuring, and it should be able to direct the request for help from the outset.

This step's main objective is to make a patient able to be aware that he is being listened to. It should be possible to give information on the functions of the service and the requests the patient will be subjected to.

At the end of this step the patient is allowed to choose whether he would like to start diagnostic treatment by signing a therapeutic contract agreement.

Diagnostic treatment step: the service has a commitment with the patient to produce a diagnosis able to help define the best treatment, and address individual problems. Every time a patient's requests or problematic aspects –– physical, social and emotional — emerge, the Service must respond with suitable treatments. The objective is not to "solve" problems, but to bring awareness, by means of treatment action, about the kind of relationship the patient

can build with the service, and about what he is asking for and what he is willing to do and to act on.

Targeted treatment step: this puts forward a therapeutic project based on the appropriate problem discussed with the patient in the previous step. Patients can access this step if a suitable problem has been identified. If a psychotherapist is required, the proposed setting could vary.

It is possible to reach agreement with a patient on a contract involving supportive psychotherapy, over a definite time-span, focused on limiting symptomatic behaviour, or a change-focused psychotherapy, or both at later or at different times.

The Guidelines to the psychotherapy of drug addiction [14] point to three steps in treating drug addiction:

a) Sobriety attainment step
b) To evaluate the degrees and consequences of using substances
c) To adopt methods for detoxification and abstinence
d) To adopt methods to safeguard abstinence as a precondition for psychotherapy
e) To diagnose and treat every associated psychiatric disorder
f) To involve each patient's family
g) Early restoring step (6-24 month abstinence)
h) Goal: abstinence
i) Supportive and directive psychotherapy
j) To act against addiction as a disease
k) Re-orienting of defences
l) To use psychodynamic techniques to strengthen the "12 step" principles
m) Advanced restoring step (1-5 years of abstinence)
n) Goal: awareness and psychological change
o) Traditional re-constructive psychotherapy
p) Consolidation of a patient's identity, with a continued focus on the centrality of the substance problem
q) Exploration of defences and deeper themes
r) Recollection of cognitive-behavioural controls

5. Psychotherapy and methadone treatment: possible integration

Psychotherapy and pharmacotherapy alone are not able to provide a cure for the majority of drug addicts. There are, however, still many theoretical and operative difficulties impeding the achievement of truly integrated therapies.

From the psychological standpoint, there are still many doubts about the possibility of carrying out psychotherapy with a patient being treated with methadone. It is true that resistance towards psychopharmacological drugs by psychotherapists has been reduced, but methadone is still considered to be a special case, and is liable to be considered a condition of exclusion from psychotherapy. The objections that are still made regard the capacity of the drug to modify the defences of the ego, along with the quantity of psychic energy available, to alter the expression of the personality by influencing the emotional and cognitive aspects of the patient, and to strengthen the subject's dependence and passivity. The patient in therapy with methadone is considered unstable, still sensitive to cravings for drugs and thus exposed to the possibility of altering his psychic state, by taking, if not heroin, cocaine or benzodiazepines, or drinking alcohol. When such patients are accepted into psychotherapeutic treatment (in groups, during intensive treatment), special attention is paid to the best way of managing patients who go to sittings under the effect of substances.

From the pharmacological viewpoint, a reductive attitude often prevails. There is a tendency to correct undesired behaviour in a "technical" way, negating the further (often vital) significance of the symptoms and, following the cult of the omnipotent drug, reintroducing the risk of biochemical moralism ("if the patient took the therapy correctly, everything would be resolved"), as if the problem were that of correcting imbalances between neuromediators, rather than that of managing a subject a vitally important issue when facing a poor level of compliance in the patient.

On the other hand, psychotherapeutic interventions are not applicable to patients who

are strongly destabilized and transformed by substances, just as pharmacological therapy constitutes a base on which other therapeutic and rehabilitative tools should intervene in order to complete care. The psychotherapist, together with the pharmacologist, should ask himself how much of the suffering expressed by the patient is tolerable, and whether it can be worked on to favour any opportunity to integrate psychic needs and aggressive components more effectively, or how far a drug can function as a sedative and an external integrator which momentarily reinforces weakened psychic functions that are probably incapable of sustaining an evolutive process. Conversely, from a psychic point of view, suffering may strengthen regressive phenomena which are then translated into resistance to treatment and into crystallization.

The question of integrated therapies is still open today. There are many problems in this area: indications about the different psychotherapeutic techniques; a typology of subjects and integrated diagnosis; different "weightings" of the two therapeutic components; what is sometimes a separation between the management of pharmacological and psychological therapies and, overall, a theory of the psyche able to keep mind and brain together. Prospects of progress in this field come from a methodology which is becoming more widely used, originating from American universities, of constituting interdisciplinary work groups, where different researchers are committed to the same problem, independently of the discipline to which they belong.

6. The efficacy of psychotherapy

Psychology has to defend itself from the aggression of mere techniques and from empirical evidence which has increasingly come to question its effectiveness.

It is not feasible to examine such a complicated theme in this context; the key points in this discussion have been recalled and summarized in a masterly way by Gabbard [12].

- The first area of research regards the interconnections between mind and brain: data are being collected through the techniques of neuro-imaging on the capacity of psychotherapy to modify brain activity. This strengthens the hope that intensive psychotherapy may have a significant impact on biological, as well as psychological vulnerability to psychic disorders [11].
- Other data testify to the advantages of psychotherapy in the treatment of patients with severe disorders. The association of psychotherapy with programmes of partial hospitalization seems to reduce the risk of suicide, self-offending acts, the need for later hospitalization and the incidence of depression and anxiety.
- Furthermore, some studies seem to demonstrate that patients treated with intensive psychotherapy continue to improve after treatment [21], and that the improvement acquired with psychotherapy associated with methadone treatment persists over a longer period than that obtained with the methadone-counselling association [23]. The methodology used in studies is changing; it now takes into consideration not only patients selected in academic contexts, but those in natural settings, complicated and unselected patients, so reflecting the "real world" to a greater extent.
- The other sector of evaluation has to do with the cost-benefit relationship: interesting data are being collected on the capacity of psychotherapy to reduce the cost of managing seriously ill patients, above all those with personality disorders (reducing hospitalization, the intensive use of health and emergency structures, and the frequency of suicide attempts and self-offence).
- Lastly, the psychotherapeutic formation of the doctor allows a better management of the relationship with the patient, which, as a result, seems to bring about greater patient compliance with pharmacological treatment.

In reality, it also seems that psychotherapy is preparing itself to respond adequately to the

requests of current culture, committing itself to serious research which removes it from the esoteric dimension, in order to evaluate what may be useful to introduce into daily clinical practice and the universe of real patients.

So far, the psychotherapeutic approaches which seem to satisfy the need to check up on the results obtained have mostly been those of the behavioural type, focused on changes in features directly observable even outside the psychotherapeutic setting and on the achievement of results expected from the context (family, society) in which the patient is inserted. Nevertheless, as regards the radical changes induced by the drug addiction of the subject and described previously, an approach capable of making him work out deep aspects of his psychic functioning seems fundamental, above all if one reflects on the direct linkage that the pathology of pleasure has with the fundamental existential dissatisfactions of the human being.

7. Conclusions

Drug addiction is a pathology which involves and modifies the functioning of the connections between the biological and the psychological, forcing us to face the unity and the complexity of the human being. The distinction between psychotherapeutic and pharmacological interventions highlights the need for scientists to simplify reality in order to manage it, rather than being a real distinction between different existential dimensions.

The clinical dimension, which should take account of the ideographic dimensions and which aims to treat the person cannot function effectively if it does not reconstitute the psychobiological unity of the subject.

Paradoxically, more effective pharmacological therapies highlight the need for their integration with a correct psychological approach, so as to implement all the transformational and evolutionary potentials of the treatment as a whole.

A more precise focusing upon the psychopathological aspects activated by drug addiction may allow a better evaluation of the efficacy of the psychotherapeutic approach, even beyond the exclusive evaluation of behavioural changes.

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5.1

Methadone and Treatment Quality. The EFQM Excellence Model

A. Flego

1. Introduction

In the technologically advanced world, providers of products and services have been dealing with the problem of quality, of how to assess its level, and of how to improve it continuously and systematically for many years. Therefore, this aspect cannot be eluded when scientifically planning and practically organizing a methadone treatment program.

The treatment with methadone, although it is safe and relatively easier than others, is still at the centre, at least in Italy, of a great controversy. This is mainly due to the fact that the controversy lies in the basic reasons of the treatment with methadone rather than in the effectiveness of this treatment.

For this reason, in a quality manual, this second aspect cannot be analysed without fully understanding the first.

2. Quality in the treatment of the addictions: search for a method.

What do we mean when we speak about 'quality'? The word suggests the concept of 'doing something better' or more precisely 'at the best'. It also suggests the concept of 'doing something better than before' or 'better than other people'.

There is a term more and more used that calls to mind this concept. It is the word 'benchmarking'. The word means to evaluate by comparison with a point of reference. Thus, we can compare different things to know which is the best or which performs better, but we can also see which is the lowest point – and this is very important when we speak about quality - under which a product or service is of unacceptable quality.

To decide whether the quality of a product or a service is acceptable or not means to 'plunge', as Cicourel says [1], in the 'study of the obvious'. It means to analyse what is taken

for granted in the common sense, 'the whys' of an action. This concept calls to mind that of 'rationale' in pharmacology, which does not only mean how to prescribe a drug but also why the drug is prescribed and why with such modalities.

A product or a service is of good quality if it corresponds to the purposes for which it has been realized and if it meets the user's requirements.

Nowadays, a car going at a maximum speed of 30 km/h and consuming 1 litre/km would be considered of unacceptable quality. One of the reasons is that it would not meet the driver's expectations with regard to medium speed and fuel costs. Moreover, it could not compete in a market where competition is based on different cost-performance ratios. However, the most important reason is that our daily living has elected as common 'value' – and has founded an epistemology on it – the choice of going at a speed between 100 and 130 km/h consuming 8 to 12 l/km. Finally, this habit is possible because the roads and highways can support such performances (although car accidents occur) and because a road code exists that regulates the matter and possible controversies. The benchmarking for the production of cars is based on these parameters and not on other ones. However, this epistemology – attribution of meanings – with regard to cars did not exist or was different in other times and nowadays it is different in other places.

Similarly, when considering illicit drug addiction, it is not possible to speak about quality without analysing the 'obvious' of the purposes of drug addiction treatments, that is, before founding a common epistemology. And in Italy, there is an epistemology chaos with regard to drug addiction.

For example, a treatment for heroin addicts that does not use methadone or uses it only at low doses and for short periods is still considered of good quality. The objection that this does not correspond to any scientific-based evidence does not weaken this position, because it relies on an epistemology other than that commonly defined as 'scientific'. Not only this epistemology is allowed but it is also part of the common feeling of the society and is sustained by the media.

For this reason, in our work, as well as in a quality manual, it is necessary to explicit some unbreakable assumptions on which to found a method to interpret events and interventions that can support quality assessment.

The assumptions are as follows:

1. Illicit drug addiction is a chronic and recurring disease, as pointed out by Mannaioni [2].
2. It produces physical and psychological suffering, in addition to social suffering, and part of it has a strictly biologic pathogenesis.
3. As in other medical fields, this suffering has to be treated on the basis of scientific evidence.

Thus, the scientific method becomes the model for clinical practice, as well as for benchmarking, which means that the conceptual model of choice is evidence-based medicine (EBM).

2.1. Continuous quality improvement (CQI).

The first operative concept regarding the quality assessment of a product was the 'quality control' concept. Initially, a product was checked at the end of the productive cycle and the defective items were eliminated before putting them into the market. Obviously, their costs were charged on the good items. However, this first attempt to evaluate quality was ineffective and expensive in the results and was soon replaced by a more rational action aiming at checking the 'process'. In this case, the causes of the defects were analysed and the intervention was on them in order to reduce or eliminate the defects. Thus, it was possible to save money and to sell at more competitive prices. This intervention mainly improved the use of the resources, thus reducing the number of reject items.

Soon it was clear that this process was neither punctual nor linear but circular, as shown in the following diagram (figure 1).

This model is based on the concepts by Deming [3] that define the cycle "plan-do-

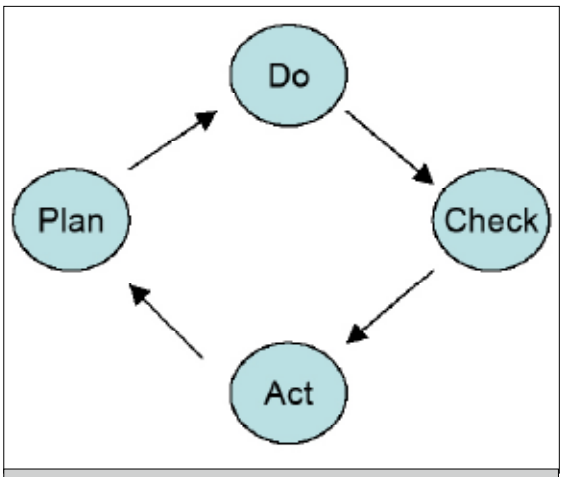

Figure 1. Circular process of CQI

check-act" (plan the actions, implement the actions, assess the effects, correct the actions) as a continuous cycle that constitutes the process of "Continuous Quality Improvement" (CQI). This model can be successfully adopted also in the sector of services production, including health care services. CQI has progressively replaced the previous, and perhaps more known, expression of "Quality Assurance", which was introduced in Italy by Perraro and Gardini [4] many years ago under the denomination of "VRQ – Verifica e Revisione della Qualità", in Italian language .

An important contribution to the theory of quality in health care services was made by Avedis Donabedian [5]. He defined the four basic dimensions on which quality analysis was to be performed: input (human, instrumental and financial resources), process (modalities to produce services), output (provided services) and outcome (results of services in terms of health improvement of the end users - individuals or, as in the case of prevention, population).

Because of their different nature, these four dimensions need different approaches during assessment and different means to assess them. However, a process of continuous quality improvement implies a continuous intervention on and monitoring of all the four dimensions because each can influence the final result or invalidate the improvement brought by the others.

The fourth dimension (outcome) deserves a particular attention because it implies the translation or not of efficient performances into efficacious interventions. The efficacy of an intervention is also guaranteed by factors external to the organization and related to environmental and social conditions on which health care workers cannot always act. From the methodological point of view, the assessment of outcome implies research models, such as Randomized Clinical Trials (RCT), which are not always feasible in normal health care organizations.

Therefore, while all health care organizations should implement a CQI process that takes into consideration the dimensions of input, process and output, the assessment of outcome is reserved only to some of them. However, all of the organizations can refer to the literature, in particular to that conducted according to Evidence-Based Medicine (EBM), of which the Cochrane Centres are an example in Italy.

A further development called "Total Quality", introduced by Deming and by Japanese researchers, has paid attention to the human factor as the main productive factor. The fundamental principle of this approach is that the best quality (or excellence) is achieved when all people participating in the production process are involved and motivated to pursue it. Thus, excellence is achieved when every employee of an organization does his/her work in a creative manner. This concept, as well as that of CQI, has merged into the more recent European Foundation for Quality Management (EFQM) model 1.

2.2. *The EFQM excellence model.*

The EFQM model represents a novelty in the panorama of approaches to quality. The novelty is not only temporal, the model is a recent one, but also of content because it introduces new concepts compared to the previous models. This innovative model perhaps can

be better implemented in the sector of health care and social security than more traditional models.

At present, it has been adopted by some important European businesses such as British Telecom, Volkswagen, Rank Xerox and Philips, and by some Dutch health care organizations, among which the Jellinek Zentrum (Amsterdam) for pathological addiction.

Some years ago, the European Commission started a research project called "ExPeRT Project" [6] to make a critical review of the most used models to guarantee quality in health care organizations in Western Europe.

From the study, it emerged that four models were widely used in Europe:

1. ISO approach
2. Accreditation of health care services
3. Peer Review
4. EFQM

The ISO model defines the characteristics or standards to which an organization and its functional procedures should conform to be considered of 'good quality'. Such standards represent a sort of norms, which sometimes are very detailed and mandatory. Based on these norms, a number of certification agencies will be able to grant a certification of quality.

Similarly, in the Accreditation model, a public actor (or a private one acting on behalf of the Government) assesses and checks the features and functioning of an organization. Then it issues an Authorization to Operate followed by and Accreditation, to be verified at fixed deadlines, that recognizes the organization and allows it to obtain public or insurance funding. This is the case of the American Joint Commission for Accreditation of Health-Care Organizations (JCAHO) which, on behalf of the Federal Government, recognizes hospitals and other health care organizations.

Peer Review means that an organization is assessed by experts from another organization who have the same professional competences and experience in the specific field. This model is more dynamic, more concerned with 'professional competence', and it is lesser bound to specifications or regulations.

The EFQM model has a more 'general' approach in that it deals with all the aspects of an organization, even those not usually standardizable. Moreover, it emphasizes 'quality management' at all levels as an integral and necessary part of the overall organization management. Finally, it favors the processes of 'organizational development' and CQI.

The EFQM Excellence Model is a model for quality management that has been formulated by the European Foundation for Quality Management and was revised in 1999 in Geneva.

EFQM is a non-profit, membership-based organization created in 1988 by the presidents of 14 leading European businesses such Bosch, BT, Bull, Ciba-Geigy, Dassault, Electrolux, Fiat, KLM, Nestlé, Olivetti, Philips, Renault, Sulzer, Volkswagen, with the support of the European Commission. By January 2000, it included 800 members from most European countries [38 countries) and most sectors of activity, including public administrations and health care organizations.

EFQM helps European businesses to improve their products and to provide better services by means of efficacious and state-of-the-art management techniques.

From the very beginning, the 'vision' of EFQM was to contribute to the creation of strong European organizations that applied the principles of Total Quality Management in their economical activities and in their relationships with the employees, stakeholders, customers, and communities in which they operated.

The mission of EFQM is:

1. To stimulate and help European organizations to participate in improvement actions aiming at excellence in terms of clients and employees' satisfaction, impact on society and economical results;
2. To provide support to the managers of European organizations to accelerate the process that sees total quality as a determinant factor to reach a global competitive advantage.

The introduction of Total Quality Management programs can result in important benefits for the organizations, such as growing efficiency, reduced costs, and greater satisfaction, which means better economic results.

The EFQM model is based on the concepts by Deming with regard to the continuous quality improvement through the cycle "plan-do-check-act", which constitutes the process of continuous quality improvement. As for the description of the organization, the EFQM model is similar to the model of Donabedian, which distinguishes structure, process, and outcome.

The EFQM Excellence Model was introduced in 1992 as a reference model to award the European Quality Award. It is the most used model in Europe to evaluate organizations. While the Quality Awards are limited to few users, the real measure of the efficacy of the EFQM model is its wide use as a management system and the associated growth of managerial capacities in organizational self-assessment.

Independently of the sector, dimensions, and structure or maturity, to be successful an organization has to define an appropriate management system. The EFQM model is a good tool to do this because it allows an organization to evaluate at what point it is in its way to excellence, it helps to understand the causes of failure, and it stimulates adequate solutions.

The innovations of this model are many compared to the previous models. Some of them are of particular interest for the health care and drug addiction therapy in Italy.

First, the EFQM model is European, which is not only a geographical connotation. One of the aim of EFQM is "to stimulate European organizations to achieve global competitive advantage, aiming at the satisfaction of the clients and employees, and at a positive impact on the society".

Secondly, the EFQM model is not 'normative'. The attention is not focused on conformity to specifications that are continually redefined. In fact, this model recognizes that there are many efficacious approaches and it fixes only few Fundamental Concepts, which can be implemented in different manners.

Moreover, EFQM updates the model taking into consideration the outcome of 'good practices' assessed in thousands of European and non European organizations. By this way, the model remains dynamic and reflects the present trend in management. The last revision was initiated in January 2003.

The approach with which an organization pursues and achieves its goals may vary and the assessment of the procedures and approaches is not based on conformity to standards but on the efficacy in achieving the results.

In fact, the EFQM model recognizes that there are many approaches to achieve sustainable excellence. Within these non prescriptive approaches, there are some Fundamental Concepts. They are non exhaustive and can be changed or integrated based on the improvements of the organizations that have reached excellence. At present, the fundamental concepts are:

1. Results orientation. Excellence is achieving results that delight all the organization's stakeholders (consigners, suppliers, employees, and final customers).
2. Customer focus. Excellence is creating sustainable customer value.
3. Leadership and Constancy of Purpose. Excellence is visionary and inspirational leadership, associated with constancy of purpose.
4. Management by processes and facts. Excellence is managing the organization through a set of interdependent and interrelated systems, processes and actions.
5. People development and involvement. Excellence is maximizing the contributions of employees through their development and involvement.
6. Continuous learning, innovation and improvement. Excellence is challenging the status quo and effecting changes by using learning to create innovation and improvement opportunities.
7. Partnership development. Excellence is developing and maintaining value-added partnership.
8. Corporate social responsibility. Excellence is exceeding the minimum acceptable level of functioning of the organizations and striving to understand and respond to the stakeholders' expectations.

Thirdly, the model has fully adopted the principles of Total Quality, i.e. it tends to em-

phasize the quality of people rather than procedures. If the goal of every single person of the organization is to provide a product or service of quality and if everyone can develop his/her creativity in pursuing quality, this will become a necessary value.

The EFQM excellence model is based on nine Criteria. Five of these - leadership, personnel management, policy and strategy of the organization, partnership and processes – are Enablers, and they enable an organization to implement its 'mission' and pursue its objectives. The other four criteria – customer results, people results, society results, key performance results – are Results, and they are the real object of quality assessment. The Result criteria cover what an organization has achieved. Results criteria are caused by Enablers and feedback from the Results help to improve the Enablers criteria.

The model, which recognizes different approaches to achieve sustainable excellence in all aspects of services, is based on the following assumption:

"Excellent results with respect to Performance, Customers, People and Society are achieved through Leadership which leads Policy and Strategy, that is delivered through People, Partnership, Resources and Processes".

The diagram of the EFQM model is as follows: (Figure 2)

The arrows indicate the dynamic nature of the model. They show how Innovation and Learning support the improvement of Enablers, which in turn improve Results.

The nine boxes represent the Criteria with which to assess the progression toward excellence. For each of the nine criteria, a definition explains what it means to achieve a high level in that Criterion.

Among Enablers Criteria, Processes and Leadership are considered the most important; among Result Criteria, Customer Results and Key Performance Results are the leading.

Each of these criteria can be investigated taking into account the 32 sub-criteria, 24 for the Enablers and 8 for the Results. These sub-criteria are used as areas of 'assessment', which are tools to assess, through clear and comprehensible examples, the 'status' of an organization.

Unlike others models, the EFQM model is not based on a definition of quality. In contrast, it considers quality management as an integral part of the management function, as well as of the professional functions present in an organization.

However, the real novelty of the EFQM model is that it allows and legitimate self-assessment, whereas one of the principles of the previous models was external assessment (certificate of conformity by external agencies in

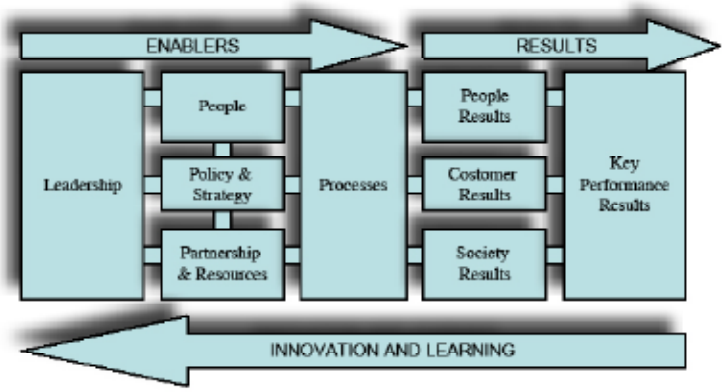

Figure 2. Diagram of the EFQM

the ISO model, review by public organizations in Accreditation, review by external professionals in Peer Review).

Self-assessment can be applied to small and big organizations, in the public and private sectors. An increasing number of organizations is using data from self-assessment in the planning of their activities and use the EFQM model to review them.

The EFQM model can also be used as a diagnostic tool to assess the present 'status' of an organization. By this process, an organization is able to better balance its priorities, allocate its resources and define a realistic activity plan. In doing this, the process of self assessment is important. EFQM gives the following definition:

"Self-assessment is a comprehensive, systematic and regular review of an organizations' activities and results referenced against the EFQM Excellence Model. This process allows the organization to discern clearly its strengths and areas in which improvement can be made. Through this process of evaluation, an organization improves the balance of its priorities, the allocation of its resources and produces a realistic plan of its activities".

It is clear that this model which allows self-assessment of all nine dimensions (Criteria) and throughout all the organization at almost no cost is preferable to external assessment, when the results are the same. Moreover, with an internal review there are fewer controversies between professional workers and management.

2.3. *Implementation of the EFQM model at Jellinek Zentrum - Amsterdam.*

The Jellinek Zentrum - Amsterdam is an organization with 500 health care workers that cure and care for 5,000 patients with addiction problems, distributed in 24 different programs of medical, psychosocial and rehabilitative treatment. The quality model adopted by this centre is based on the EFQM model and its results have been recently published [7-9].

The most interesting characteristic of the Dutch variant of the EFQM model is that five different phases of organizational development have been defined: Product Orientation, Process Orientation, System Orientation, Chain Orientation, and Total Quality.

Product Orientation is when the attention of the organization is on providing correct performances. For example, to define what is a good medical and toxicological assessment and a good pharmacological protocol.

However, the most important processes are Process Orientation, System Orientation, Chain Orientation, and Total Quality, which could be defined as 'meta-processes' because they integrate the interventions of different knowledges and disciplines.

At one meta-level, the management (e.g. the director of an Addiction Department) can maximize the probability that the services provided are correct without caring for them personally if the people are in the right place and if there are rules of collaboration and responsibility that are scientifically validated and accepted. The actors of these performances will guarantee the quality, especially if they are gratified with what they do. This is an example of process-oriented organization.

Considering the next meta-level, the organization can focus on the interactions between different areas of activity. In other words, it can study how different segments of intervention, which follow different logics and scientific knowledges, can integrate to meet the user's needs. Addiction departments offer a good example of system-oriented management in that different professionals interact, each with his/her own competence, to develop a multidisciplinary therapeutic and rehabilitative program. A system-oriented organization tries to govern these complex interactions on the basis of the context in which it works and monitors their effects on the end user.

In a chain-oriented organization, the attention of the management is on the problem of "therapy and assistance continuity". In other words, the attention is on the chain or sequence of events, some of them within the organization, which can produce a good therapeutic result if governed or can introduce bias and distortions if not. Some examples? The family

doctor who prescribes buprenorphine while methadone is administered; the therapeutic community that accept addicts without agreeing a therapeutic program with Addiction Facilities; a hospitalization which has failed because it was decided by the family without an agreement between health care workers of Addiction Facility and the hospital; a sudden release from prison without a program.

Because it implies non-hierarchical – i.e. partnership - relations, the chain-oriented management has to use new tools, ranging from external credibility for its workers to budget management in a therapeutic sense, for example negotiating funding to the communities in exchange of quality assessment of the services provided, formulation and assessment of operative protocols which, to function, have to consider the convergence of motivations and interests among all the organizations involved. In some ways, this action is diplomatic and can be synthesized as follows "to make a constant effort to orient all resources towards the health of the end user".

The last process is Total Quality. Every worker can work well if he/she is in the condition to do it. Many of these conditions do not depend on external factors or on top management. There are some organizational conditions that depend directly on the operative management.

The motivation of the workers distribute in a Gaussian curve; this means that, considering the good and the very good workers, there are high probabilities to comprise more than 80% of workers from the start. Moreover, it is known that money does not motivate people, and this applies also to people working in Addiction Departments.

They are much more motivated when they feel their work as "their own". Leadership also consists in having a direct or indirect relationship with all workers. In this relationship some messages should be clear: what is expected from the worker and why (i.e., the benefits for the end user), which are the margins of autonomy and creativity of each person (each person must benefit of such margins and they must be proportional to what he/she can give), and finally to whom, when and how to refer in order to work better and to present his/her own results (maybe also to obtain a reward).

The Jellinek Zentrum has been subjected to various assessments based on the EFQM model and different changes has been introduced in its organization in these years.

3. Methadone and quality

Until now I briefly exposed a new interesting quality assurance model. But how can it be applied to Methadone Maintenance Therapy Programs (MMTP)?

First, the planning of a treatment with methadone too can be divided in different components: mission, vision, enablers criteria, result criteria and self-assessment. All these components are essential but should be analysed and defined separately. In fact, every process to improve quality implies a clarification of its components, a sort of 'declaration' of how they should be, followed by a circular evaluation of how they are in reality in order to introduce changes leading to excellence.

3.1. The "mission" and "vision" of a methadone treatment program.

Because of the existence of more than one epistemological model on methadone treatment and of the confusion between them, as previously mentioned, is necessary to make a choice. Thus, starting from the three assumptions of the second paragraph, which are arbitrary for some people but which we consider fundamental to implement a scientifically evidence-based MMTP, it is possible to formulate a precise definition of the 'mission' of MMTP:

1. To reduce and eliminate heroin use, minimizing the risks of relapse and promoting such a state for a long period (months or years).
2. To stabilize as far as possible the psychic state of the patients without severe psychic diseases, eliminating craving and

preventing hypophoria.
3. To promote and favour, eventually in association with other therapeutic interventions, a change in the life of drug addicts, sometimes resulting in a long drug-free condition.

Such a general "mission" can be personalized according to the physical conditions, the whole diagnostic picture and the response to treatment of the patients. In fact, not all patients can achieve the above-mentioned goals to the level, but methadone should not be used systematically to pursue goals other than those, or else the intervention will be inefficacious and non scientific.

The "vision" of MMTP is a component that deals with the context in which one acts. In other words it forecasts the scenarios within which the treatment interacts and studies the impact of treatment on the health of the patient, in order to maximize it.

To define the "vision" adequately it is necessary to ask oneself some questions. These can be summarized as follows:

1. Questions concerning the epidemiology of the phenomenon investigated. For example, which is the prevalence of heroin addiction among our patients? Which is the rate of psychiatric comorbidity? Which is the rate of patients with complex organic disease?
2. Questions concerning the attitude of the health care workers. For example, which is the degree of acceptance of MMTP epistemology? How much are the health care workers convinced of its efficacy? Which interactions exist between operators with different professionalities with regard to methadone treatment?
3. Questions concerning the opinion of the society on methadone treatment, especially of the community in which one works. A greater social acceptance favors the treatment, also because it has a positive influence on the users and their families. If there is a scarce acceptance, some informative-formative interventions should be planned that modify the culture in a more favourable sense.

The great difficulties encountered by addiction treatment services to properly administer methadone in a hostile environment demonstrate how an intervention, although conducted following the state of the art, can have a greater or a minor impact on the target population according to the context. Moreover, hostile environmental conditions may lead to an inappropriate use of the drug. In Italy, for example, methadone have been used inappropriately for many years on the basis of ideological motivations.

It follows that the "mission" is associated with scientific knowledges that are recognized and codified in the literature, whereas the "vision" is associated with the context in which one acts. Thus, the "vision" is the interface between acquired scientific evidence and its transferability to a real context. It consists in an analysis of the situation and actions aiming at improving the feasibility of the mission in accordance with the above-mentioned circular process.

Some years ago, the Strategic Plan 2000-2005 of NIDA, the federal organization in USA dealing with drug addiction, started Clinical Trial Network aiming at increasing the use of scientific knowledge in the clinical practice by services for drug addiction. This because the transferring of acquired knowledge into clinical practice was contradictory and poor. Probably, this also occurs in Italy, although the issue has not been raised yet.

This can be due to an inadequate definition of the "mission", but also to a "vision" which is insufficient to efficaciously transform knowledge into adequate services.

As previously mentioned, methadone has proven inefficacious in contexts where people think that a heroin addict should not be treated with drugs and think that methadone is not therapeutic. Thus, a different epistemology of the context makes scientific evidence less efficacious in the practice.

From this, it is clear that the definition of "mission" is essential to plan an efficacious MMTP, and that the attention to "vision" and to the actions necessary to modify the resistance of the context is a necessary complement.

3.2. Enablers criteria

As previously mentioned, the Enablers Criteria of the EFQM model are Leadership, People, Policy and Strategy, Partnership, and Processes. What do they mean with respect to MMTP? Here are some examples.

1. The Leadership defines the "mission" and "vision" for all health care workers (see previous section). Moreover, it supports the principle that "there is always something which can be improved" in MMTP by introducing a periodic process of comparison and evaluation. It also makes sure that clear and univocal messages are received by the user as to the finalities and modalities of the service. Finally, the leadership identifies and promotes the changes that may be necessary while continuing pursuing the finalities described in the "mission".
2. People are crucial in the management of MMTP. Because the MMTP is a very wearing out component of our work, the staff must be in a sufficient number. Considering that a good service has to administer methadone every day, including Sundays and holidays, the minimum number of health care workers should be of one doctor and two nurses. The presence of other professionals is recommended. However, this is not always possible because the resources are few, but a good program for quality improvement should consider that the lower is the number of workers, the greater is the risk of workers' "burn-out". The problem is not only ethical (people working in unacceptable conditions) but also arithmetical. Fewer workers means an increasing "burn-out", which results in greater turn-over, which results in difficulty in finding new workers, which finally results in even fewer workers. A sufficient number of workers for the administration of methadone prevents this vicious circle and at the end it is a good investment. Moreover, the workers administering methadone should have access to accurate clinical and organizational protocols and should be trained to manage aggressiveness, violence and incongruous behaviours. These aspects are often left to the common sense and to the sensibility and abilities of the health care workers. A good quality manual for addiction services should contain protocols or procedures for these situations too.
3. Policies and strategies are the modalities with which the "mission" is oriented to the interests of the stakeholders. There are two types of stakeholders: the users and the consigners. In methadone treatment, the main interest of the users is to take the maximum advantage in terms of health, in the present and future time. Thus, the effect of methadone on users should be monitored at short, medium and long term in order to select those clinical and organizational behaviours that better pursue the goals of the "mission". The consigner is in this case the public administration because methadone is also used for the public health. Thus, strategies will be defined in order to reduce social problems (petty crime, hanging about the out-patient room) but also to reduce the spreading of transmissible diseases.
   Policies and strategies should be explained to the health care workers through a "key processes scheme". In this way, those processes that are determinant for the success or the failure of a strategy are emphasized. For example, the management of the external space of the out-patient room (when the resources exist) can influence the correct use of methadone and in the outcome of the therapy. The modalities to implement such a strategy should be made clear through a scheme of behaviour or protocol to be used by the health care workers.
4. External partnership and internal resources should be planned and managed. In the case of methadone treatment, possible partnerships are those with voluntary workers, and private or voluntary groups . These relationships should be codified in the framework of the so-called Enlarged Department. Such partnerships

can strengthen the efficacy of MMTP, especially in the rehabilitative sector. Another strategic partnership is with the police. The management of an out-patient room for MMTP implies security risks for the workers and the public order. For a correct collaboration with police, the privacy of the patients should be respected and the patients should be warned that no disturbances to the services are allowed, to defend both the workers and the rights of those users who behave adequately. This should be defined and advertised within the out-patient room activities. With regard to the internal resources, there is the problem of the continuous re-definition of the adequacy of the rooms and the furniture of the out-patient room, which must follow health care norms for security. A periodic review of these specifications by the health care workers should be a component of a good quality plan.

5. The processes are the heart of the added value of the service. The clinic of MMTP, according to the criteria of evidence-based medicine, is probably the most important process to manage systematically. The supply and custody of methadone and the thematic of giving the methadone to take home, the so called "entrusting", are other important processes to codify, to manage daily, and to review systematically. 'Entrusting' (how much methadone can be taken away, for how many days, and according to what criteria) risks to be the weak point of every service delivering MMTP. In relation to this matter, the differences between health care professionals should be minimized through a process of consensus conference, so as to offer to the other workers, starting from the nurses, and to the users themselves, a point of reference which is certain and rigorous. "Entrusting" practice can also lead to aggressive behaviour. In these cases, a change in the rules and behaviour should be planned and implemented in a progressive manner, informing the workers and the police, if necessary. The communications regarding the adopted procedures should be clear for the users.

So far, much has been said about quality, but anything is fixed and immutable. Indeed, in the search for quality- especially total quality – all the interested parts are involved in a continuous re-definition and elucidation of the above-mentioned contents.

3.3. Result criteria

A good elaboration and definition of the Enablers Criteria allows a correct planning of the Result Criteria: customer results, people results, society results and key performance results.

The continuous monitoring of the results is the most important aspect of the EFQM model. For all result criteria, two features are monitored: performance and subjective perception.

In the case of customers, the measurement of performance can be conducted through the identification of a set of clinical indicators which should continually monitored, such as the negativity rate of urine analysis, the degree of reliability of the patient (in this regard, the judgment should not be only a subjective one of the worker but objective and shared criteria should be defined), and the rate of "retaining in treatment".

In the case of people, each worker should be given precise objectives and the achievement of these is assessed according to the policy of the organization. However, the assessment is efficacious if two indications are respected: 1) it should be clear what is expected from the worker; 2) the evaluation modality should not be inquisitional or inspectorial, but colloquial and aiming at finding actions to improve performance.

In the case of society, the social perception of the activity of the service should be monitored. Sometimes, the society only sees the negative aspects of drug addiction (the presence of drug addicts in the streets near the out-patient service is often the object of animated discussions in population's meetings). In some way, this is physiological in that the existence

itself of drug addicts is not appreciated. However, this aspect should not hide other aspects such as improvements or worsening of the disturbance caused by drug addicts, which can be associated with precise and identifiable causes. In the case of worsening, corrective actions can be identified to be effected inside and outside the health care structures.

Finally, to monitor key performances, these should be first identified. In a service providing MMTP, key performances are few. For example, the identification of indicators for each of the three processes identified in the previous section: evidence-based medicine of methadone, supply and custody of methadone and the thematic of 'entrusting' with associated list of reliability criteria and flow-chart of assignment to the different phases and modality of treatment.

The dimension of subjective perception is more complex to monitor. However, it allows the identification of tools that can be adequate to: 1) give voice and visibility to the perception that users have of the given service; 2) give voice and visibility to the perception of the workers; and 3) monitor social perception.

Because the EFQM model is not prescriptive, the ways to implement these actions are various. Each person should identify the problems considered so far and should find solutions adapt for his/her context, placing them at others' disposal in a forum on quality.

In the EFQM model, each criteria is associated with sub-criteria. These consist of questions that must be considered. Finally, for each sub-criterion, there are guidance points. They are neither mandatory nor exhaustive, but they exemplify the meaning of the sub-criterion. The guidance points can be found in the publication of the EFQM Excellence Model. The Jellinek Zentrum has elaborated a specific Excellence Model, unfortunately not translated from the Dutch, which can be adopted for programs for addiction treatment, among which MMTP.

3.4. Self-assessment

As previously said, the EFQM model, unlike others, is not based on a definition of quality; thus, it does not assess the conformity to precise norms, but it assess the efficacy in the achievement of the goals. Moreover, unlike other models, it makes use of a process of self-assessment of the organization. Self-assessment is carried out on all nine dimensions – or criteria - through a tool called RADAR (acronym for Results – results with respect to the mission -, Approach – approach to the problems -, Deploy – use of resources -, Assess – assessment of the effects of the action -, Review – periodic review).

The RADAR system is the heart of the EFQM model. The above-mentioned elements represent five moments of a process of self-assessment that is built according to the following logic:

1. To determine the Results to be achieved as part of a process of definition of its policies and strategies. These results include organization performance, from the financial and operative point of view, and the perception of it that the stakeholders have.
2. To plan and develop an integrated set of Approaches to highlight the results.
3. To make these approaches explicit and available (Deploy) in a systematic way to guarantee their implementation in the organization.
4. To Review the approaches used through analysis and monitoring of the results achieved and through activities of continuous learning. Based on this, identify the necessary improvements and decide their priorities, planning and introduction.

When the model is used within an organization, the elements of Approach, Deployment, Assessment and Review have to be used for all Enablers sub-criteria, and those of Result for all Result sub-criteria.

The RADAR is used as follows:

Results

This aspect is concerned with the results achieved by an organization. In an excellent

organization, the results show a positive trend and a good performance, the goals are appropriate and in line with or superior to what is necessary, the performance can be compared with that of others and depends on a good approach to the problems.

Approach

This aspect is concerned with the plans of an organizations and the reasons for them. In an excellent organization, the approach has a clear rationale and well defined and developed processes, it focuses on the necessity of the stakeholders, it is consistent with the policies and strategies, and it is appropriately connected with the other approaches used.

Deployment

This is concerned with how much an organization is able to make the approaches visible to and usable by the workers. In a good organization, the approaches are used in a systematic way and in areas which are strategic for the organization.

Assessment & Review

These aspects are concerned with what an organization assesses and reviews both in the approaches and in the deployment. In an excellent organization, the approaches and their deployment are periodically reviewed, actions are activated based on the review results, and these are used to identify possible changes, to establish their priority and to plan their introduction.

Self-assessment of an organization can also be carried out through a tool called "Pathfinder Card", which helps identify the opportunities of improvement and plan the action of improvement. There is no score but a list of questions which can be answered in a short time. The logic is the same as that of RADAR, but it is simpler and less rigid. One or more Criteria, or any sub-criteria associated with them, and the corresponding questions of the card are selected. The questions are not mandatory prescriptions, but an occasion to reflect on each of the examined aspects: they provide indications on the critical aspects of the organization and on the possible actions of improvement.

Self-assessment of MMTP can be performed following the above-mentioned model, using the set of indicators described in the previous section. However, the model has to be adapted for drug addiction and obviously this can be done only by professionals working in that field. So far, the Jellinek Zentrum is the only organization that has developed a model specifically for addictions, which unfortunately is not yet available. In the future, the directions to follow are two: 1) to adopt the Dutch model; and/or 2) to elaborate an original model based on the specific context.

4. Quality in clinical practice: excellence

The EFQM model, and in some way also the other models, tends to trigger a virtuous circle in which every detail is considered. Excellence means to have achieved, by continuous adjustments following periodical assessments, 'the best possible' or 'sustainable quality'.

However, the change from a situation in which quality is not considered (or of precontemplation as Prohaska [10] would say) to one strongly quality-oriented is only the start. All organizations tend to entropy and all open systems (an organization is an open system) has to continuously work on homeostasis to maintain their identity in the interchange with the environment. Thus, Excellence also means 1) to maintain and progressively improve the level of all the dimensions and 2) to continuously change to adapt to new realities and new scientific evidence.

4.1. Quality of the pharmacological and non-pharmacological aspects and their integration.

The use of methadone in the treatment of drug addicts has been considered for a long time, in Italy as well as abroad [11-13], a 'minor evil' in which methadone was justified if the dose was increased and/or if it was associated with consultations, more or less psychotherapeutic, and social or rehabilitative activities, thus stimulating instrumental or 'liturgical'

attitudes [14]. That is, attitudes in which the patient was forced to accept things that he/she did not consider necessary in order to obtain methadone from the health care worker.

If methadone has to be used, this should be done in the best way possible. This means that, for the therapeutic teams of addiction departments, the drug should be "at the centre of the therapeutic program". This means that the drug, as main intervention, has to be measured in the clinical practice also in the absence of other interventions.

This point, which may seem obvious to some people, is still a cause of controversy which risks to feed an old problem. How can a tool that is not trusted by the therapeutic team be used at the best? [15;16]

In fact, as proven by the literature, a well managed MMTP may by itself eliminate the use of other opiates and modify the life style and quality of life of many heroin addicts. Evidence also exists [17] that interventions of psychosocial support have a good cost-benefit ratio if they are of modest entity, such as generic counselling. More intensive interventions are more expensive than useful where the diagnosis is of drug addiction not complicated by comorbidity, psychosocial situations particularly compromised, or severe polyaddiction.

Some patients present heroin addiction associated with one or more of the above-mentioned conditions. They are the so called "non responders", for whom MMTP does not produce the expected results [18-20].

Most of quality clinical practice is concerned with these patients, who represent a minority of the users but who have complex and severe clinical pictures.

An important quality goal in MMTP programs should be the identification of the problems of these patients and the development of tools to improve the services provided. For example, there are cases in which the dose of methadone has to be increased for pharmacological or clinical reasons, such as in the case of contemporary administration of nevirapina [21] in patients with AIDS-related pathology, or in the case of severe psychiatric comorbidity [22]. In other cases, complementary treatments such as counselling, psychotherapy, and social or rehabilitative interventions are necessary to cope with specific problems of the patient and to improve the prognosis and the outcome of MMTP [23-26].

Finally, there are situations in which the improvement of the rate of 'responders' is associated with organizational or communication factors. The cultural reference system – that is the epistemology with respect to methadone treatment – is important not only for the workers but also for the patients and their environment. The influence of the peers, also with respect to the credibility of the service, can be important to improve or not the outcome of MMTP.

Similarly, to give a picture of definite and reassuring rules to the patients with greater motivation or to strongly prevent patients from breaking a positive environment with a critic or instrumental attitude may increase the rate of the "responders".

The problem of the "non responders" should be dealt with according to an algorithm that can be formulated as follows:

1. To identify pharmacological causes (inadequate dosage, necessity of greater doses for particular problems) and corrective actions.
2. To identify organizational causes (relationship and communication with the patient) and introduce corrective actions.
3. To identify particular problems of the patient, such as comorbidity (organic or psychiatric), stress or situations of social discomfort, or presence of polyaddiction and activate other medical, social, and psychiatric interventions (intensive if necessary).

If none of the above-mentioned problems exists or if corrective actions has been successfully activated, the remaining cases of "non responders" represent , maybe, the not eliminable part of the phenomenon. However, at the end of the circular process of quality improvement, their number could be much more lower than the initial one.

The diachronic study of "non responders" in a service providing MMTP can offer an important representation of the characteristics of the customers and of the functionality of the

service, and represents a crucial element for benchmarking.

5. Conclusions: state of the art and open issues

The search for quality is a never-ending, dynamic process, and excellence itself is not definitive. As it has been demonstrated, it is a circular process that has to progressively improve the performances but also to defend itself from the natural entropy of not-managed situations (it has to continually introduce "negative entropy"). Finally, this process has to continually take into consideration innovations and new knowledges or 'scientific evidences'.

In my opinion, the EFQM model is more functional than others to the activities of addiction services, in particular those providing MMTP. In fact, these activities are at high rate of methodological uncertainty (the human factor is always dominant with respect to specifications and procedures) and require creativity and team spirit.

Moreover, this model shows the directions to follow and the goals to achieve, while allowing great freedom in the choice of the modalities to act. It is evident that an organization has to harmonize individual initiative in a common project. Therefore, there will not be individual paths to quality but paths of an organization, and the benchmarking will be based on the results achieved rather than on procedures adopted.

In our case, the "state of the art" identifies the organizational and operative modalities that achieve the higher rate of responders to MMTP and /or greatly reduce the rate of non responders among the more problematic patients [27-40].

Obviously, it is not a static and universal definition, but it is subject to continuous evolution. It is the result of the comparison of "the state of the art" of several organizations that measure themselves in a continuous action of benchmarking and choose as point of reference scientific literature. It is, as stated by the EFQM model of excellence, a definition of "good practices" continually proposed to other people working in the same field.

In this continuous search for quality, many issues remain open. In particular, three problems greatly influence the daily work of addiction services.

The first problem is the little flexibility of methadone, which continues to be the drug of choice, but which requires a daily administration, with the consequent organizational problems. With regard to this, it should be pointed out that the real or presumed superiority of LAAM has not been tested in Italy [41]. If LAAM is effective even in a small number of patients in MMTP, the fact that it has not yet been introduced means an increase of costs, in human, organizational and financial terms.

The second problem is the need for research, innovation and experimentation in the management of non responders, the number of whom has to be progressively reduced.

The third problem is the problem of 'entrusting' methadone. The degree of reliability of the patients should be better defined and better procedures, flow charts and protocols should be planned to decide how much methadone can be taken away, with what modalities and to whom.

In fact, from the therapeutic point of view, it is disadvantageous not to give a patient the possibility to responsibly manage its therapy. However, it is equally detrimental to trust a patient who is not able to responsibly manage his own therapy.

In the prayer of the anonymous alcoholics, they ask the 'superior being' for help to face what they can face, to accept what they are not able to face and to distinguish between the two situations. We, therapists of drug addiction, need help in this "understanding" and "distinguishing" action. And our superior being can be represented in part by a good model of continuous search for quality, scientifically based and shared among the professionals.

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Index

L

M

N

O

P

Q

R

S

T

U

V

W

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