Heroin Addiction and Related Clinical Problems

the official journal of

European Opiate Addiction Treatment Association
EUROPADEuropean Opiate Addiction Treatment Association

EUROPAD, formerly EUMA, was founded in Geneva (Switzerland) on September 26, 1994. It shall remain independent of political parties and of any government.

The vision

EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The Association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide.

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Methadone Treatment in Italy in the Third Millennium: Continuing Fear of Treatment

Icro Maremmani

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In Italy, in the third millennium, longstanding mistakes, together with newly emerging, mistaken attitudes, continue to block the objective of making clinical practice adhere to scientific standards, thus preventing healthcare standards from reaching higher levels of quality. Moreover, the authorities seem to be blind to the correspondence between the scientific adequacy of interventions and the consequent degree of control over addiction-related phenomena, such as drug-related crime, the spreading of infectious diseases, jail overcrowding and the social costs of crime repression and rehabilitation.

The prevalent attitude towards drug addiction, supported by unfounded psychological and psychiatric interpretations, is that addiction is a flexible state attributable to the lack of some balancing function, vaguely related to affective soundness and mood reactivity. Most people still take the view that addicts cannot help using drugs because of their need to avoid withdrawal, rather than the other way round [6], and that detoxification is therefore the best kind of intervention that medicine can offer to drug addicts. Relapsing into drug use is not interpreted as a core symptom of addiction, but as a feature of an addictive personality, which can, in any case, be handled by environmental and educational guidance. Each relapse is attributed to contextual factors, and mood swings in affective balance, instead of being read as episodes in a single disease, separated by clinically silent intervals [7]. Wherever there is the capability of interrupting the drug-using habit for some time, that is mistaken for remission, even if the data show that transient abstinence is the general rule in the history of addiction [16].

Most textbooks that deal with addictive diseases still discriminate – moving clumsily on conceptual grounds – between physical and psychical dependence – between physical and psychical dependence, viewing cocaine addiction as ‘atypical’ with respect to the model developed for narcotics, on the grounds that it is characterized by a prominent psychical dependence, while failing to recognize the primary psychopathological nature of craving and relapsing behaviour. Those authors totally omit any mention of the existence of an anticraving approach to drug addiction, and talk of therapeutic opiate agonists as a substitution treatment to be resorted to as a safer form of replacement during a detoxification phase which, they recommend, should last the shortest time possible. These viewpoints are easy to argue against [11]. It can hardly be denied that addiction belongs to the category of substance use disorders, but what is missing is the concept of addictive diseases as induced by chronic exposure to reinforcing stimulation, regardless of subjective effects, through a direct dependence on sub-cortical neurochemical pathways [14, 15].

The spontaneous chronicity of addiction is denied,
leaving no margin of doubt, together with the essential nature of craving as an overactive impulse towards reinforcing stimuli. Chronicity, as also automatic relapsing, are thought of as signs of greater severity, or toxicophilia, and automatically coupled with a negative prognostic perspective. For such addicts, standard maintenance programmes are admitted, though they are presented as harm reduction, and applied in a way that includes the malpractice of ineffective dosing and premature withdrawal of medications.

In Italy, throughout the eighties, the assumed gold standard was to expect and stick to unrealistic outcomes, such as a spontaneous remission due to a variety of unpredictable factors, which were vaguely located in the educational or psychosocial sphere. In that period, no differentiation was made between criminal users, socially impaired subjects and addicts; this lack of clarity has made it far more difficult to interpret outcomes in terms of empirical interventions. Later on, the level of scientific adequacy of treatments improved randomly, the general trend still mirroring the faulty conviction that addiction is sometimes a metabolic disorder, and that, in a metabolic stage, the right approach was to aim for harm reduction. By adopting that mistaken perspective, methadone maintenance was relocated within the cauldron of harm reduction: this shift made it possible to retrospectively justify therapeutic malpractice and the chronic use of ineffective dosages by claiming that methadone treatment is unable to provide any satisfactory outcome for the average drug addict.

Of all therapeutic programmes for drug addiction, methadone accounted for 45-50% in the 1997-2005 period; only 24-31% of all patients on methadone were receiving longer term treatment (> 6 months). In the 2000-2005 period, a trend gradually developed in favour of longer-term methadone administration (> 6 months), but one third of methadone programmes were still planned as short or medium-term [13].

In 2000, over 80% of Italian addicts were still being treated at an average dose below the 60 mg/day threshold of effectiveness: that figure was not attributable to the short term of observation, but tended to stay that low after months of treatment, regardless of clinical response [20].

In a study comparing the features of treatment-seeking addicts in my specialized university treatment unit, I noted that recent admissions corresponded to patients starting treatment at a younger age, but with a longer history of treatment failures. Surprisingly, methadone maintenance at effective dosages had not been tried in most cases before our evaluation [17]. In other words, despite a trend towards early intervention on substance abusers, no trend has developed towards the enrolment of patients into methadone maintenance treatment programmes as early as possible, using standard blocking dosages. Analysing the clinical and therapeutic history of enrolled patients, only a small minority could actually be labelled as “treatment resistant”, and rates of response to standard treatment have not changed through the years: against our own expectations, there was no trend for severe addicts to concentrate on second-level programmes, which means that the long-term revolving door stage of the average addict corresponds to a milder biological stage of their disease. A positive aspect can be recognized in the evidence that treatment starts earlier; a negative aspect surely consists in the omission of effective treatments for subjects who would be “full responders”, because they are affected by a milder form of the disease.

A structured survey about opinions on drug addiction and related issues showed that the level of knowledge has stayed low throughout the 1995-2005 decade, both among patients and the general population [19]. Regardless of the therapeutic setting, patients tend to share with healthy people the misconceptions that addiction is a multi-factorial condition with side medical symptoms deriving from intoxication and withdrawal, that it can heal in a favourable environment due to one’s strength of will, and that residential treatment is the key intervention in achieving long-term stability. Detoxification interventions have never been limited to functioning as the induction phase of antagonist programmes, for selected patients, and are still performed as standalone therapies, possibly returning the addict to his/her original environment with an increased risk of overdosing due to the loss of tolerance [9, 18, 21].

Almost any critical life event (imprisonment, pregnancy, hospitalization) is handled as an opportunity to achieve and maintain spontaneous abstinence, or taper medications, instead of becoming an opportunity to initiate or stabilize treatment. People seem to be in search of increasingly rapid methods for tolerance reversal, which are promoted as ‘detoxification’.

The impact of the newer resource against heroin addiction, buprenorphine, adds another point of view in clarifying the therapeutic trends in Italian public services. In the 2001-2005 period, buprenorphine treatment did spread all over Italy: nevertheless, its use has often been that of providing a smoother form of detoxification (58.4% in 2001, 36% in 2005), whereas buprenorphine maintenance (> 6 months) was the treatment adopted in 41.6% of these cases in 2001, a figure that rose to 63.9 in 2005. Surprisingly, in 2005 the rates of buprenorphine treatments with respect to all treatment programmes had jumped from 3.8% in 2001 to 15.3%, but in some regions values had risen above 25% [13]. Actually, it is likely that a subpopulation of addicts was shifted onto buprenorphine programmes although stabilization on methadone had already been achieved, the aim being to favour tapering and the withdrawal of any opiate treatment more comfortably than is thought to be possible with methadone.

In a 1997 study [9] conducted to ascertain the causes
of heroin overdosing, authors found that just one subject out of four was tolerant to opiates at times of acute intoxication, whereas 65.5% were not tolerant due to the detoxification they had undergone; 7.3% were receiving lower methadone doses (below 40 mg/die) than before because they were no longer in prison or protected environments. Although methadone maintenance at doses higher than 40 mg/die would seem to be protective (no case recorded), recent dropping out of methadone maintenance was the least likely status of overdosing addicts, followed by recent abandonment of naltrexone maintenance (1.8%). In other words, the vast majority of overdosing addicts, instead of being just chronically intoxicated, had been driven to a condition of enhanced risk due to an increased craving/tolerance ratio.

Another surprising corpus of data about overdoses, in Italy, reveals that the mean age of those who are overdosing has increased through the years 1996-2005, from 30-31 to 34-35 years old [13]. As a trend, it is not new, younger addicts who run the risk of overdosing before entering treatments, but those who started their first treatment programmes years before, which can only mean that the standard handling of drug addicts in the therapeutic web offers poor protection against overdosing. The likelihood of overdose just seems to be postponed to an older age bracket, suggesting that treatment programmes only provide transient protection against the consequences of addictive drug use.

On the whole, knowledge that methadone maintenance provides protection against overdoses [1-4, 12, 22], and other causes of addiction-related death seems to be ignored on grounds of clinical practice, although studies of this type have been performed on the Italian population [5, 10].

The evolution of knowledge in the field of therapy and the neurosciences has not been translated into the empowerment of interventions, in terms of outcome and the correction of chronicity. Psychiatry’s newborn interest in addictive diseases has been polluted by the confusion between drug use and addiction dynamics, the latter being implicitly regarded as a phenomenon secondary to more ‘classical’ psychiatric disorders. Attempts to challenge addiction by antidepressant treatment have resulted in the demonstration of the short-term effectiveness of almost any medication, but with two major limitations: the meaningless of short-term changes in a chronic relapsing disorder, and the employment of generic psychopathological endpoints, which simply confirm that some drugs are toxic, and that medically assisted detoxification provides patients with transient alleviation of their discomfort.

A further problem is that psychologists tend to elude the grounds of scientific measurement and found their practice on suggestions from case reports. Actually, the feasibility of psychotherapeutic approaches for drug addicts derives from the capability to interpret individual cases consistently with pertinent theoretical models. Against those who could object that no standardized treatment can be thought of in this way, and that interventions cannot even be planned, those practitioners are able to answer by referring to the concept of treatment tailored to the individual. Most psychologists and community operators are highly critical of any concept of treatment standardization that relies on shared, measurable core symptoms of addiction: to them, standard dosing, duration and remission are unwelcome as the basis for individual tailoring to psychosocial and psychological needs, but are treated as the neglect of differences between individuals. Dividing addicts into categories in order to identify programmes that are modelled on the needs of subgroups is seen as caging people into dead-end situations by applying artificial labels. Paradoxically, they argue that environmental and personal differences are a reason for not working on addiction-related similarities between affected individuals. Those who oppose statistically founded treatment still wave the flag that “Each case is a case unto itself”, so showing their failure to understand that tailoring has to come second to stabilization in a hierarchical order.

Their viewpoint is that the more a drug ties the patient to a longer-term regimen, the less it can be considered to favour progress towards remission: pharmacological dependence is read by them as a feature that is shared between addiction and therapy, and thus counterproductive to any perspective of healing. The underlying opinion is that dependence on a therapy is not therapeutic, but generates chronicity: on the contrary, a crucial basis of the effectiveness of agonist maintenance is the establishment and maintenance of a state of tolerance, at an even higher level than that induced by chronic exposure to heroin. As a result, physical dependence on the therapeutic drug is not a limitation in an agonist treatment programme, but a key for it to be fully effective: the treatment of addiction through to remission requires the patient to undergo a period at a heightened level of dependence, because only this ensures an opiate blockade and higher rates of retention in treatment, while partly overcoming the problems of lower or transient compliance [8].

Previously, the stigma against methadone patients seemed to be closely related to an extended prohibition, which was blind to the differences between illegal substances and therapeutic medications, and fond of a self-administered, drug-free solution. However, it has become clear that many of those who defended medications, did so by applying a kind of reverse prohibition, arising from the thought that substances, whether legal or illegal, can become additive due to their special status. On such a view, controlled heroin administration is preferable to methadone maintenance, and no actual difference is recognized between therapeutic opiates and toxic ones. The common ground of these two equally misleading conceptions, is the denial that addiction is a brain disease. In both conceptions, addiction is just a problematic form of drug use, and nothing more: in the
former it depends on individual deficiencies, in the latter on environmental factors. Moreover, addiction is supposed to stay flexible and reversible, so that the changes in the factors that influence the way people resort to drugs are thought to be crucial in turning addiction back into controlled drug use, or in turning it into lighter drug use. Resorting to maintenance treatments is regarded as a renounce to healing.

Evidence that healing without medical treatment is quite improbable will not change the views of those for whom the way in which healing should be is more important than the real likelihood of healing. One emblematic statement is that of an Italian therapeutic community director, who said that “some actually stop” after community treatment. As long as public opinion prefers a few isolated healings to a multitude of stabilized patients, recovery from this disease may just come about by chance, in cases of non-treatment. Scientific knowledge will continue to have little impact, as long as cases of successful treatment are read as failures by the dominant culture in Italy.

Unfortunately, it may be that this is not an exclusively Italian problem.

References


**Conflict of Interest**

No conflict of interest to report.

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Pharmacology and Neurochemistry of Methadone

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Summary

Contrary to what might be thought initially, the pharmacology of methadone is only partly known, and current research continues to investigate into its distinctive aspects. Clinical evidence provides key guidance to pharmacological research on the opiate system; on the other hand, evolving expectations from therapeutic drugs or putative agents for addiction treatment provide a key incentive to the broadening of pharmacological knowledge. Apart from the classic description of receptorial opioid agonism, narcotic blockade and tolerance/withdrawal dynamics, some crucial issues need to be clarified in a comprehensive way. For instance, studies have proved the importance of metabolic polymorphism in treatment planning and offered interpretations of apparent resistance to normal dosages, so authorizing the employment of high dosages on a sound pharmacological basis. Also, dosages should not be regarded as stable through time, especially in the first few months, and clinicians may schedule dose variations that take into account such expected variations while pursuing stabilization. Methadone’s action profile in the central nervous system is not exclusively based on opioid receptors, and a thorough knowledge of its ‘collateral’ effects may explain its beneficial action against specific psychopathological abnormalities. The role of the inactive enantiomer in the context of racemous methadone’s tolerability and action profile has also been outlined. Lastly, some of the therapeutic effects of methadone endure without being neutralized by the emergence of tolerance; one of these is its crucial anticraving property. In order to clarify this issue, the mechanisms of cell membrane endocytosis and signal transduction have been illustrated and compared between different opiates.

Key Words: Methadone; Pharmacology; Neurochemistry; Pharmacokinetics; Neurochemical properties; Receptor interactions; Side effects

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-α-acetylmethadol) are the results of the progressive simplification of original compounds such as epoxymorphanes (nalorphine and nalbuphine), through morphinanpes (levorphanol), benzomorphanes (pentazocine), phenylpiperidine (pethidine) and 4-allylpiperidine (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-dephényletan-3-one hydrochloride or 4, 4-diphenyl-6-dimetilamine-3-epitanone) 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 amitriptyline, digoxine, diltiazem, domperidone, fentanyl, indinavir, loperamide, morphine, nefinavir, 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 surfaces, 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 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 administered 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 (4.2-9.2 l/Kg in the treatment of heroin addiction and 1.71-5.34 l in chronic pain treatment). About 2% of absorbed methadone remains in the plasma compartment.

Moreover, 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 \( \alpha_1 \)-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 \((t_{1/2}\alpha = 14 \text{ hrs appr.})\), while the second phase corresponds to its more gradual elimination from tissues \((t_{1/2}\beta = 54 \text{ hrs appr.})\). 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 \( t \frac{1}{2} \) 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 glucuronoid acid. The second pathway combines N-demethylation with its cyclization to 2-ethyl,5-methyl-3,3-diphenylypyrrolidine and 2-ethyl,5-dimethyl-3,3diphenylypyrrolidine (EDDP), which has a half-life ranging between 39.8 and 48 hrs [23].

These two metabolites are further transformed into a common hydroxypropyrolidinic product by aromatic hydroxylation. The second pathway combines N-demethylation with its cyclization to 2-ethyl,5-methyl-3,3diphenylypyrrolidine and 2-ethyl,1,5-dimethyl-3,3diphenylypyrrolidine (EDDP), which has a half-life ranging between 39.8 and 48 hrs [23]. These two metabolites are further transformed into a common hydroxypropyrolidinic 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 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 isozyme is expressed by 90-95% of Caucasian people. Those who lack this isozyme (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 metabolizers, 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: 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 that 2D6 is somewhat stereo-selective for R-Met. In low metabolizers, amitriptyline, 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 G0 or G1 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\textsubscript{50} 752 ± 686 nM) and for κ (IC\textsubscript{50} 1817 ± 573 nM), in both cases in the bovine caudate nucleus) racemic methadone can be classified as a selective agonist of µ receptors (IC\textsubscript{50} nM 5.73 ± 1.5 for µ\textsubscript{μ} and 10.0 ± 3.1 for µ\textsubscript{δ} 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 \textsuperscript{18}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 amino acids 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 adenylyl-cyclase activity, the opening of a series of receptor-dependent K\textsuperscript{+} channels and the blocking of voltage-dependent Ca\textsuperscript{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), naloxonazine, naloxonazone 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, naloxonazine and naloxonazone prevent some of the effects that are mediated by morphine, but not others, since they interact selectively with the µ\textsubscript{μ} variant. Insensitivity to naloxonazine is responsible for respiratory depression and the inhibition of bowel motility, suggesting that possible µ\textsubscript{μ}-selective agonists may not share these two important collateral effects with morphine. The µ\textsubscript{μ} subtype, which is exclusively supraspinal, is located in the periaqueductal grey substance, the medial hypothalamus and the great raphe nucleus. It mediates analgesia, psychomotor retardation and the increased secretion of prolactin. The µ\textsubscript{δ} subtype has a similar distribution, but is found in the spinal cord, too. When coupled with µ\textsubscript{μ} 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 CXBR mice, which are refractory to morphine [18]. These data lead to the conclusion that another variant exists, apart from the already known µ\textsubscript{μ} e µ\textsubscript{δ}: 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\textsubscript{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\textsubscript{i} 0, 78nM vs. 14nM, respectively) [90]. In this latter study, methadone had a negligible (K\textsubscript{i} 2±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\textsubscript{i} for the displacement of its ligands are very similar to those of dextromethorphan, which is a typical NMDA antagonist. In particular, K\textsubscript{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 favor 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, of µM 0.27 (±0.038) against 5HT reuptake, which means a level close to that of desmipramine (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 adminis-
tered 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 breakthrough pain peaks. A study was conducted employing 18F-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 18F-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 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 consid-

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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 μ1 subtype, it is ten times higher for S-Met in bovine caudate that for R-Met (IC50 of nM 3, 01± 0, 18nM 26, 4 ± 3, 7) while values for μ2 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 (Kion of μmol/L 0, 014 for R-Met and μmol/L 0, 992 for S-Met) and norepinephrine (Kion 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 phases 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-globulins 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 metopiron 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 rhythm has 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

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

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Notes/References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine, butorphanol, dezocine, nalbuphine, pentazocine</td>
<td>Displace methadone from μ receptors [26, 57]).</td>
</tr>
<tr>
<td>Naltrexone, nalmefene, naloxone</td>
<td>Displace methadone from μ receptors [26, 57, 102].</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Displaces methadone from μ receptors [105].</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Notes/References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam, alorazepate, estazolam, flurazepam, midazolam, triazolam</td>
<td>Potential interactions due to a common metabolic pathway through P450 [52]. May increase methadone’s depressant effects on the CNS [102].</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Presumable interaction due to a common CYP3A4 metabolic pathway [52].</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Reduces DDL concentration [89], not observed with gastro-resistant capsules [36, 42].</td>
</tr>
<tr>
<td>Dextrometophan</td>
<td>Methadone may increase its plasma concentration and effects [71].</td>
</tr>
<tr>
<td>Alpha-interferon + ribavirine</td>
<td>Adverse events may mimic opiate withdrawal, so that methadone dose increase may be decided on a wrong basis [99, 103].</td>
</tr>
<tr>
<td>Monoaminooxidase inhibitors</td>
<td>Potential adverse reactions reported [78].</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Methadone may increase nifedipine’s concentration [71, 102].</td>
</tr>
<tr>
<td>Alfentanil, idrocodone, fentanyl, meperidine, morphine, oxycodon, propoxyphen</td>
<td>Possible enhancing effects due to common metabolic pathways. Long half-life metabolites of meperidine and propoxyphen may reach toxic concentration [52].</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Methadone reduces d4T plasma level. d4T has no effect on methadone’s plasma level [89].</td>
</tr>
<tr>
<td>Amitriptiline, desipramine, imipramine, nortriptiline</td>
<td>Association with methadone increases TCA toxicity [26, 88, 92]. TCA have a variable effect on methadone’s plasma level [33, 79, 102].</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>Methadone increases AZT level by 40% ; adverse events of AZT are more likely [76].</td>
</tr>
</tbody>
</table>
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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 persist 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

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Notes/References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>Levels of methadone fall, as does the peak value of ABC [49].</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>The induction of CYP3A4 may reduce methadone’s plasma level [19, 33]. The level of Amprenavir may be reduced too, for the same reason [36].</td>
</tr>
<tr>
<td>Butobarbital, mefobarbital, phenobarbital, pentobarbital, secobarbital, others</td>
<td>All of these induce P450 [63]; phenobarbital may cause a rapid decrease in concentrations of methadone [49]. An increase in methadone dose is usually required.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>A strong induction of CYP3A4 may cause withdrawal. Valproate does not have this effect and may be a safe alternative [12, 98].</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Increases the elimination of methadone [79].</td>
</tr>
<tr>
<td>Desametason</td>
<td>Induces CYP3A4 [33].</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>The induction of CYP3A4 often results in abstinence from methadone. After three weeks of treatment with efavirenz, if the dosage is not raised appropriately, the peak concentration of R-S-Met fall by as much as 48% [33, 75].</td>
</tr>
<tr>
<td>Ethanol in chronic exposure</td>
<td>Induces P450 [88].</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Induces CYP3A4 [33, 106].</td>
</tr>
<tr>
<td>Heroin</td>
<td>Reduces the free fraction of methadone [79].</td>
</tr>
<tr>
<td>Lopinavir + ritonavir</td>
<td>Withdrawal may develop and dose increases be required. Ritonavir alone fails to cause any such effect [19, 77].</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Induces CYP3A4 and P-gp [33], but withdrawal is rare [77]. The level of nelfinavir too may be slightly decreased [19].</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Its induction of CYP3A4 may may lead to withdrawal [33].</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Rapid reduction of methadone due to CYP3A4 induction [33, 63].</td>
</tr>
<tr>
<td>Rifampicline and rifampicline/isoniazid</td>
<td>These induce P450 and may cause severe withdrawal [33, 63]. Rifabutin doesnot produce these effects [49, 71].</td>
</tr>
<tr>
<td>Spiironolactone</td>
<td>Induces CYP3A4 [33].</td>
</tr>
<tr>
<td>St. John’s Wort (hypericum perforatum)</td>
<td>Induces CYP3A4; the level of methadone is reduced by 47% [35, 100].</td>
</tr>
<tr>
<td>Tabacco (habitual smoking)</td>
<td>Most reports indicate a reduction in the effectiveness of methadone in habitual smokers [79, 104].</td>
</tr>
<tr>
<td>Urinary acidifiers (e.g. ascorbic acid)</td>
<td>The excretion of methadone through the kidney occurs more quickly at acid pH values [81, 102].</td>
</tr>
</tbody>
</table>
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

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

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Department of Psychiatry-Addictology in Paul-Guiraud Hospital, Villejuif, France

Summary

Nowadays, cannabis is the most widely used illegal drug in France. Epidemiological studies have shown that in schizophrenic patients the risk of developing cannabis dependence is six times what it is in the general population. However, debates on the real chronology of the appearance of psychiatric disorders and addictive cannabis behaviour are ongoing. The aim of this article is to try to find out how best to interpret the association of cannabis and premonitory symptoms through a review of the literature. Some recent longitudinal studies suggest a potential role for pre-existing troubles, taking the view that cannabis would only aggravate them and turn them into schizophrenic symptoms. By contrast, other studies propose a causal linkage as well as a dose-effect relationship between cannabis consumption and the appearance of schizophrenia. Conclusion: The methodology of these studies limits the possibility of a reverse causality. In addition, it must be noted that some research teams excluded from their cohort subjects who presented psychiatric disorders at entrance. Cannabis appears to be a risk factor for psychotic disorders, because it interacts with a pre-existing vulnerability. Neuroimagery research will make it possible to clarify the common cerebral mechanisms of cannabis and schizophrenia.

Key Words: Schizophrenia, premonitory symptoms, cannabis, vulnerability

Nowadays, cannabis is the most widely used illegal drug in France. Over the last decade, the number of consumers has continued to increase. The study carried out by Bersani et al. [4] revealed that in schizophrenic patients the frequency of cannabis consumption is 4.6 times the figure for the general population. 15 to 40% of schizophrenic patients have experienced at least once in their life an episode of cannabis dependence or abuse according to CIM-10 criteria.

Epidemiological studies show that cannabis abuse prevalence is markedly higher in psychotic persons than in those who are free of symptoms of that type [5], and that in schizophrenic patients the risk of developing cannabis dependence is six times what it is in the general population [10].

The high frequency of this comorbidity brings us back to multiple etiopathogenic hypotheses connected with the sequence of this association: we need to inquire: ‘Is cannabis a cause or a consequence of a psychotic disorder?’.

It is difficult to distinguish the outset of a schizophrenic disorder in the early stages of a cannabis-related intoxication, all the more so since these diseases tend to develop insidiously. Schizophrenic disorders are frequently preceded by unspecific premonitory symptoms such as withdrawal from society, loss of interest in usual activities, temper, body neglect or peculiarities in behaviour that may, by themselves, tend to encourage cannabis consumption. The chronology of the disorders does not seem to be clearly defined: It seems that cannabis abuse often comes prior to the psychiatric disorder, but that its onset comes after the premonitory symptoms in as many as two-thirds of these cases [6, 12].

Diachronic evolution of these disorders: Some patients who present signs of ‘vulnerability’ (‘non-pathological’ characteristics) will reveal premonitory symptoms that precede the transition phase to the first psychotic episode (profile a). None of these transitions is ineluctable. In particular, most of the ‘vulnerable’ subjects will never evolve into a pathological state. Likewise, some subjects
who show premonitory signs will never evolve into a constituted psychotic state (profile b). Consequently, it is preferable to use the notion of a mental state with a higher risk of psychotic transition than that conveyed by the term ‘premonitory symptoms’ (figure 1).

The 2003 Consensus conference on early schizophrenia notably recommended “rapidly making a diagnosis so as to promote the rapid setting up of a treatment, guaranteeing a better prognosis”. According to our review of the literature, some studies have taken these premonitory

Figure 1. The most frequent time sequence (from M-O Krebs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Age/Gender</th>
<th>Follow up</th>
<th>Evaluation of the psychiatric becoming</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fergusson et al. (2005)</td>
<td>1055</td>
<td>18, 21,25 Male and female</td>
<td>25 years</td>
<td>Prospective study</td>
<td>Early and repeated Cannabis use; as well as premonitory symptoms increase the development of psychiatric symptoms.</td>
</tr>
<tr>
<td>Henquet et al. (2005)</td>
<td>2437</td>
<td>14 et 24 years Male and female</td>
<td>4 years</td>
<td>Prospective study</td>
<td>The existence of premonitory symptoms and teenage consumption increase the risk of contracting a psychosis.</td>
</tr>
<tr>
<td>Degenhardt et al. (2003)</td>
<td>Patients born between 1940 and 1979</td>
<td>15 et 60 years Male and female</td>
<td>30 years</td>
<td>Pooling the analysis of 8 cohorts</td>
<td>Cannabis precipitates the appearance of premonitory symptoms and aggravates the prognosis of vulnerable patients. No causal relation.</td>
</tr>
<tr>
<td>Verdoux et al. (1996)</td>
<td>79 Students</td>
<td>?</td>
<td>?</td>
<td>Questionnaires</td>
<td>Cannabis precipitates or emphasizes psychotic experiences in vulnerable patients.</td>
</tr>
</tbody>
</table>
symptoms into account and drawn a conclusion as to whether or not they have any influence on the consumption of cannabis (Table 1).

Debates on the real chronology of the appearance of psychiatric disorders and behaviour showing cannabis addiction are still ongoing; to date, the time sequence cannot be precisely determined. Moreover, contradictory data have emerged, depending on the studies and their methods of investigation [3].

The interpretation to be given to the association between cannabis and premonitory symptoms appears to be a very difficult question; the aim of this article is to find out if subjects with psychiatric disorders use THC (tetrahydrocannabinol) as an automedication, which might convert the premonitory symptoms into psychosis or if, conversely, the use of THC is a risk factor in developing a psychosis.

Retrospective studies showed that THC consumption precedes the beginning of psychotic disorders [8]. Nonetheless, the limit is that the retrospective dating of premorbid disorders is often a very complicated matter [1, 12, 13].

1. Cannabis induces psychotic disorders

The cohort studies (Table 2) drew the conclusion that there is a causal relationship between THC consumption and psychosis development, as well as a dose-effect relationship. The cohort led by Van Os in 2002 [11] found the same results: There is a causal relationship that is independent of the premorbid disorders; evaluated by the diagnostic interview at entrance, and during the follow-up. Its principal limit was the low number of entrances and the short length of the follow up.

The Arsenault cohort [2] turned out to show similar outcomes. Teenage cannabis consumers (15-18 years old) had more psychotic symptoms in adulthood than non-consumers. The main strength of this study is that it took into account the existence of morbid disorders at the age of 11 and concluded that adulthood psychosis was closely related to cannabis consumption, but was independent of pre-existing premonitory symptoms. Its limit was the lack of memorization (retrospective evaluation through auto-questionnaires).
2. Premorbid disorders induce and precede cannabis consumption

A prospective study carried out by Miller et al. in 2001 on a population of ‘high risk’ selected patients pointed out that there is a positive temporal relationship between THC consumption and the existence of psychotic disorders. They showed that, in subjects presenting early forms of schizophrenia, toxic consumption was twice what it was in the control population. Cannabis appears to be temporally linked to psychotic disorders.

Longitudinal studies (Table 1) highlighted the fact that the existence of premorbid disorders is a risk factor in increased cannabis consumption, which might make the premonitory symptoms evolve into schizophrenic psychosis.

Fergusson (New Zealander cohort) [7] showed that prolonged and premature cannabis use contributes to the development of psychoses, particularly when premonitory symptoms pre-exist. In 18-year-old cannabis using patients, the relative risk was assessed as being 3.7 times what it is in non-consumers. That same risk ratio falls to 2.3 for 21-year old patients.

Henquet [9] came to the same conclusions when leading a prospective study on 2,437 patients followed up over a period of 4 years: Precocious cannabis consumption and the presence of premorbid disorders precipitate the schizophrenia symptoms in patients with premonitory symptoms.

A 2003 Australian analysis pooled the results of eight cohorts [5] selected from a population of male and female patients aged between 15 and 60; the follow-up lasted as long as 40 years. The authors concluded that cannabis turns the psychotic symptoms into schizophrenia and have proposed a time sequence in which the consumption of cannabis comes after premonitory symptoms and before schizophrenia.

2.3 for 21-year old patients.

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3. Concluding remarks

Cannabis appears to be a risk factor for psychotic disorders, as it interacts with a pre-existing vulnerability.

Considering this undeniable link, regardless of its actual direction, the screening of the teenager population turns out to be essential and to be of major interest, when it comes to public health and prevention.

High performance prospective studies based on an effective methodology, taking into account staggering factors, environment and family history need to be carried out. We will definitely find far more new information when neuroimagination makes it possible to clarify the common cerebral mechanisms of cannabis and schizophrenia, especially those involving the endocannabinoid system.

References

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present review.
Alcoholics With a History of Heroin Consumption: Clinical Features and Chronology of Substance Abuse

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Summary

In our clinical experience, when alcohol is used as a surrogate for heroin, social adjustment improves, although the metabolic destiny does not change, and the medical outcome is worsened to some extent by alcoholism itself. Alcohol abusers with a history of heroin use engage in alcohol use in a more intensive way. Alcohol consumption is higher right from the start, and reaches higher maximum levels, whereas heroin use dwindles, in some cases to extinction. The results of our studies support the hypothesis that alcohol replaces opiate craving in former heroin consumers who break away from heroin, and often become alcohol abusers or at least increase their use of alcohol.

Key Words: Heroin Addiction; Alcoholism

1. Not only one kind of alcoholic

Studies on the psychopathology of alcoholic patients began in 1940 (3); the early studies aimed to identify homogeneous groups, if any, sharing psychopathological and behavioural features (e.g. 4; 2; 5).

The search for subgroups of alcoholics was not only focused on the identification of groups of patients who were homogeneous in their psychopathology: many studies have attempted to consider other variables along with psychopathological profiles, so targeting what Babor et al. (1) defined as “multidimensional alcoholism”. This kind of research aimed to evaluate whether alcoholics can be considered a heterogeneous group not only because of their psychopathological traits, but also on the basis of family, behavioural and other psychosocial variables and by exploring the possibility of splitting series of alcoholics into clusters sharing similar characteristics.

In Babor’s (1) research a Cluster Analysis was performed by taking into account personality, sociodemographic, and epidemiological variables. Groups were characterized as follows:

Type A: later onset, fewer childhood risk factors, less severe dependence, fewer alcohol-related physical and social consequences, less treatment for alcohol-related problems, fewer psychopathological dysfunctions, and less distress in the areas of work and family.

Type B: more risk factors linked to the family environment, earlier onset, higher severity of dependence, polydrug abuse, more chronic treatment histories, more severe psychopathological dysfunctions, more stressful life events.

More recently, the idea that alcoholics may be split into different clusters has received additional support from biochemical research: many trials have failed to validate the pharmacological treatment of alcoholism provided for a cluster of alcoholics selected only on the basis of their alcohol dependence. It has, for example, been argued that there may be different subgroups of alcoholics who demonstrate different sensibilities in their response to pharmacological treatments, as shown by the outcomes of treatments for alcoholics based on naltrexone (NTX), a drug that blocks opioid receptors.

Moreover our group has identified, in a series of patients attending the alcohol unit of La Sapienza University of Rome, a number of homogeneous subgroups selected according to the criteria made available by the literature (6).

As shown above, especially in a type B according to Babor’s classification, polydrug abuse proves to be
common, and in the present paper we report the preliminary data given by a study that has focused on the relationship between alcohol and heroin abuse/addiction in our patients.

2. Alcoholics with a history of heroin consumption in our clinical experience

We reviewed 507 consecutive records of subjects who had been referred for the treatment of problematic alcohol use at the outpatient treatment centre for alcohol-related pathologies, in “La Sapienza” University, Rome, during the 2004-2007 period. Subjects systematically underwent psychiatric evaluation employing DSM-IV TR criteria for alcohol-abuse and dependence, in a condition of current sobriety and in the absence of withdrawal symptoms.

A history of heroin use (HU) was found in 80 subjects (15.8%). Heroin use status and history were examined in greater detail: 65 former regular heroin consumers had been heroin-free for at least the previous two years, while 14 had been using heroin infrequently (up to once a month). Regular heroin use had started at 21.47±7.8 years old on average, and had lasted for 9.69±5.8 years. Patients with a history of heroin use (HU) were slightly younger (41.51±7.2 vs. 44.65±10.9; p = .002), and more likely to be currently unemployed (37.5% vs. 20.1%; p = .001). Age of first alcohol consumption and age when regular drinking began were similar, but both initial and maximum peak consumption levels were higher (11.44±9.4 vs. 8.82±7.6; p = 0.035 and 25.62±11.6 vs. 21.65±12.2; p = 0.016, respectively). Dual diagnosis rates were similar between groups. Global social functioning was slightly lower among HU (60.00±11.9 vs. 64.38±9.9; p = 0.013).

In a chronological order, regular heroin use followed the first episode of alcohol consumption after an average interval of 7 years (t = 4.595, df 46, p < .001), but was contemporary with the onset of regular alcohol use (t = .953, df 46, p = .346). The extinction of heroin use came far later (8 years on average) than the onset of regular alcohol use (t = 3.873, df 25 p = .001). Although the first contact with alcohol always preceded the first contact with heroin, two sequences of lifetime polyabuse were possible: 31 subjects (38.3%) became alcohol abusers first, and subsequently heroin abusers; 49 (61.7%) started abusing alcohol during or after their heroin abuse period. A difference could be found between subgroups in terms of age of first contact with alcohol: the age at which former heroin abusers had started abusing alcohol (27.31±7.3) was greater than that of former alcohol abusers (23.92±9.6; p = .001) and of those who were alcohol abusers only (16.94±2.3, p = .008).

Our data support the idea that a history of exposure to opiates and subsequent opiate use disorder is a frequent background in subjects who apply for alcohol abuse treatment; moreover, a history of opiate use is related to higher levels of initial and peak alcohol consumption. They are also younger and more of them are unemployed: taken together, these characteristics form a profile that corresponds exactly to that of type B alcoholics in Babor’s classification.

In reviewing lifetime chronologies of substance abuse, a predictable shift from regular opiate abuse to regular and heavy alcohol abuse is supported by the data. Alcohol consumption does, in fact, turn out to be higher from the beginning: it reaches higher maximum levels while heroin use dwindles, in some cases to extinction. Thus it is quite likely that alcohol can function as a replacement for opiate craving in former heroin consumers who have broken away from heroin, in some cases becoming alcohol abusers and in others increasing their alcohol use habits.

References


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Contributors

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Conflict of Interest

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Opioid Dependence and Quality of Life: Changes in the Heroin Epidemic

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In the drug abuse arena, Health Related Quality of Life (HRQL) can play a helpful role in (a) assessing the impact of drug use on a subject’s quality of life; (b) comparing the degree of impairment in relation to the general population or to other chronic conditions; (c) evaluating changes after treatment is provided and (d) comparing subgroups of drug users. In fact, HRQL has been used, among other variables, to assess treatment outcomes. As HRQL comprises subjects’ perceptions of their health, it offers another way of assessing health status.

In Barcelona, estimates of how the incidence and prevalence of heroin use evolved, based on data collected from heroin users who initiated their first treatment for heroin dependence between 1991 and 2003 [5], show that heroin use started in the early seventies without becoming a conspicuous problem until the early eighties. As in the rest of Spain, it was a very important public health issue by the end of the eighties, and this continued into the early nineties, when its prevalence reached its highest point, decreasing afterwards, though its incidence had begun to fall much earlier.

Since the early nineties, in Barcelona, we have measured the HRQL of heroin users in several different studies. In most of them we used the Nottingham Health Profile (NHP), a generic instrument, mainly to evaluate changes related to methadone maintenance treatment (MMT) [2-4, 6]; but also another generic instrument, the SF-12 [1].

Our first study, which began in 1992, analysed 135 subjects: 69% were males, with a mean age of 29.6 years and an average of 10.2 years since first heroin use; 90% were injectors and 65% were HIV+. The mean value for the global NHP score was 56; this improved to 26 after 12 months in MMT. The corresponding value for the general population was 16 [6].

In a second study, beginning in 1996, to evaluate different intensities in MMT support, 586 patients starting their first MMT were studied: 78% were males, with a mean age of 31 years (SD 6.7) and an average of 10 years since first drug use (SD 5.7); 58% were current injectors and 25% were HIV+. Mean global NHP score was 41 at entry to treatment; this improved to 17 after 12 months in MMT [3, 4].

Another study, which began in 2000, was designed to study psychiatric comorbidity in patients entering MMT, while assessing its impact on HRQL. The instrument used on that occasion was the SF-12, which has two component summary scores, one physical, the other mental. 189 subjects were recruited in 3 drug treatment centres in Barcelona: 77% were male, had a mean age of 33.8 (SD 7.5) years and an average of 11 years since their first heroin use; 70.4% had injected in the past, 51.4% were current injectors, and 24.3% were HIV+. Mean physical (44.1) and mental (36.9) component scores showed impairment by comparison with standardized values for the general population (50), but no differences were observed in terms of comorbidity [1].

Further results on the HRQL of Barcelona heroin users came from a wider study that assessed multiple issues in young heroin users (18 to 30 years old) recruited outside treatment centres in three Spanish cities (Barcelona, Madrid and Seville). The Barcelona subgroup included 364 subjects: 69% were men, with a mean age of 24.9 years and an average of 7.3 years since first heroin use; 75.8% were current injectors and 17% were HIV+. Their mean global NHP score was 32.8.

Taking all these results together allows us to evaluate the evolution of heroin users’ health impairment at different stages of the heroin epidemic, its improvement during methadone treatment and its relationship to values for the general population. The changes observed need to be analysed, taking into account variables that...
evolved during the epidemic and that are included in HRQL, such as the proportion of intravenous drug users, proportion of subjects with positive serology to HCV, and polydrug use.

References


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TO THE EDITOR: Opioid dependence remains a serious global problem. Compared with the general population, opioid-dependent individuals run a much higher risk of death, infectious diseases, and psychosocial problems. The successful treatment of opioid addiction with methadone, a full agonist at the mu-opioid receptor, or buprenorphine, a partial agonist at that receptor, depends on the use of doses high enough to block the effects of other mu-opioid agonists, such as heroin. Long-term results from studies on major outcomes have shown that maintenance therapy with methadone- or buprenorphine-based regimens limits opioid use and the damage associated with it. For methadone-treated patients, age, non-white race, earlier age of addiction onset, cocaine use, and involvement in illegal activities, have been linked to a negative or less satisfactory outcome [1, 3]. Also, the presence and severity of psychiatric comorbidity is a possible reason for treatment failure or limited improvement [4, 8, 10-13, 15]. In assessing treatment methodologies, methadone dosage, skipping doses (negative predictor) and the availability of take-home medication (positive predictor) have been identified [1]. In a previous study we demonstrated that the presence of dual diagnoses, when these are defined as psychiatric comorbidity preceding the onset of regular heroin use, is the best predictor of relapse-free survival in treatments in which the average observation period lasted as long as six years, regardless of other sociodemographic and clinical features. This finding is limited to patients who stay in treatment for at least one year [5].

Regarding buprenorphine, the length of continuous opioid use and the age at onset of opioid use, were recently found to negatively predict outcome [14]. In addition, a higher level of psychopathological symptoms, and a lower level of psychosocial functioning predict a negative outcome [9]. Buprenorphine seems to be more effective in opioid-dependent patients affected by depression, probably due to its kappa opioid-receptor antagonist action, and its capacity to counteract dysphoria, negativism and anxiety [2].

Currently, comparative studies are rare. The study of Marsch et al., [7] is probably the first to demonstrate that predictors of treatment success appear to be largely similar in LAAM, buprenorphine, and methadone treatment for opioid dependence.

We can generalize by stating that it is very difficult, with heroin addicts, to find single factors that strongly favour the selection of one medication over others.

In a recent study [6] we investigated the effects of methadone treatment and buprenorphine treatment on retention in treatment, urine drug testing results, psychiatric status, social adjustment, and quality of life among patients involved in long-term treatment with the medications mentioned above. Two hundred and thirteen patients (106 on buprenorphine treatment and 107 on methadone treatment) were enrolled in this open study at the 3rd month of their treatment and followed up until the 12th month; those who left the programme before the end of the 3rd month of their treatment were excluded from the study sample. The results of this study...
show statistically significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for both medications, suggesting the long-term efficacy both of methadone and of buprenorphine treatment on symptoms of opioid addiction and quality of life. For information about the evaluation at the beginning of the treatment, the third month evaluation and the twelve month follow-up, please refer to our previously published paper [6].

In this letter we report the results of a new analysis carried out on data used for this study, which aimed to ascertain which patient or treatment-related features, assessed in a standardized way at the treatment entry, do have an influence on retention in treatment.

Firstly patients were clustered in various subgroups on the basis of socio-demographic and clinical variables, and then retention in treatment was compared (survival analysis and Leu-Desu statistics), according to clustered subgroups, between patients treated with buprenorphine or methadone. For the purpose of this analysis, the term “completed observations” refers to patients who left the treatment after relapsing into addictive behaviour, while “censored observations” refers to patients who are still in treatment “as a stabilized patient” at the end-point or who leave treatment for reasons unrelated to the treatment itself (e.g. patients moving to other towns or who undergo periods of imprisonment for past criminal activities), or patients successfully detoxified after a maintenance period. In our high-threshold facility we consider patients to be “stabilized” when, after a safe induction into treatment, they increase their doses until the point is reached where there is no more than one urine drug screen which is positive for illicit opiates, cocaine or benzodiazepines, in the previous sixty-day period.

Statistical analyses were carried out using the SPSS package. Since this is an exploratory study, statistical tests were considered significant at the p < 0.05 level. No differences between patients treated with buprenorphine or methadone were found according to gender (males/females), age (< 25 yr old/> 25 yr old), civil status (never married/married), education (> 8 yr/< 8 yr), work (white collar/blue collar/unemployed), welfare benefits (presence/absence), income (lower/adequate), living (alone/with family).

No differences were observed between heroin addicts treated with buprenorphine or methadone when considering patients with minor/no problems and patients with major problems in the following areas of social adjustment: work, family, sexual activity, socialization-leisure time and legal problems. Similarly no differences were found between the two groups when considering patients with or without concomitant use of alcohol, CNS-depressants, CNS-stimulants, hallucinogens, cannabinoids, or polyabuse.

Lastly, no differences were observed between patients treated with buprenorphine or methadone according to the following drug addiction history variables: somatic concerns (presence/absence), mental status (symptomatic/asymptomatic), frequency of heroin consumption (less often than daily/at least once a day), addictive mode (stable/unstable), heroin use (continuous/periodic abstinence), clinical stage (early stage/late stage), presence of stressors before heroin use (presence/absence), first treatment (yes/no), heroin use (earlier/later), age of onset (earlier/later), long treatment latency (>3 yrs/<3 yrs). “Stable” (kind of lifestyle while using heroin) signifies that the patient maintains productivity and that he/she is not engaged in street crime despite major individual and relational impairment. The “late stage” is generally called the “revolving door” phase, a term applied to patients who undergo a series of relapses and repeatedly fail to maintain abstinence.

The only feature that seems to influence the outcome of our patients seems to be dual diagnosis. Considering patients with this feature, 76.74% of 22 who were treated with buprenorphine and 83.67% of 27 who were treated with methadone were ‘censored’ at the end of the observational period (Leu-Desu statistics 1.00 p=0.31). On the other hand, 90.91% out of 84 patients without dual diagnosis who were treated with buprenorphine and 66.67% out of 80 patients who were treated with methadone were ‘censored’ at the end of the observational period (Leu-Desu statistics 4.59 p=0.03). Patients with dual diagnosis survived in treatment regardless of the treatment used. A significantly higher percentage of patients without dual diagnosis survived in treatment, after one year, when treated with buprenorphine.

Although caution should be adopted in discussing results from an open, non-randomized study, these results seem to confirm how hard it is to find predictive factors capable of providing strong guidance in the selection of buprenorphine or methadone in heroin addicts. In any case, it should be borne in mind that, while the presence of dual diagnosis does not seem to influence survival in patients treated with methadone or buprenorphine, the absence of dual diagnosis does seem to predict a more favorable outcome for patients treated with buprenorphine.

References


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Echoing the Patient’s Lack of Insight: A Role We Must Avoid Playing

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TO THE EDITOR: Spoken introduction opening Eminem’s Relapse album (2009), partly dealing with a “drug problem” with benzodiazepines.

[Dr. West:] Morning, Marshall.
[Eminem:] Morning, doc.
[Dr. West:] So we’re discharging you today, how are you feeling?
[Eminem:] Anxious.
[Dr. West:] Anxiety?
[Eminem:] Well, anxious to get home, anxious to get back into the world, Nervous.
[Dr. West:] Nervous? C’mon, Marshall, you’re a big boy now. Sounding like a bit of a baby, you can do this. You found a sponsor yet?
[Eminem:] Um, not yet. but I mean, but when I get back...
[Dr. West:] Well, if you find one, you find one. If you don’t, you don’t.
[Eminem:] Well, yeah, I mean I godda start going to meetings first and... Wait, what?
[Dr. West:] Well, you don’t absolutely have to go to meetings and it’s not like a requirement that they fit into your schedule we know you’re a busy person.
[Eminem:] But I thought sobriety was the most important thing?
[Dr. West:] So what else are you thinking?
[Eminem:] Um, well, I know I godda start practising the steps, and I mean learning them, and start being able to apply them.
[Dr. West:] Steps?
[Eminem:] Yeah, steps.

[Dr. West:] There’s a lot of them, aren’t there?
[Eminem:] Well, twelve.
[Dr. West:(with a spooky voice)] Christ, I don’t even know them all.
[Eminem:] Really?
[Dr. West:] Anything else?
[Eminem:] Um, well, I mean the only other question I have was like, what do I do if I find myself in a situation where maybe somebody is drinking around me or something like that and I get tempted to?
[Dr. West:] Take a drink.
[Eminem:] What?
[Dr. West:] Take a drink and y’know, take the edge off.
[Eminem:] Take the edge off? Man, if I ever take a drink I already know what that’s gonna lead me to.
[Dr. West:] What, you mean these? *shakes pills*
[Eminem:] Man, what the fuck?!
[Dr. West:(with a spooky voice)] Marshsall, what’s the matter, darling? Having some doubts already? Marshall, you can’t leave me, you’ll never leave me, Marshall. We’ll always be together, Marshall. Marshall?... Marshall?!
[Eminem:] Fuck you Man, No, no, no, NO!

Eminem speaks as any sensible patient would. Dr. West’s superficial and irresponsible attitude is a paradox: the doctor seems to be reasoning as a patient with no insight would, and eventually changes his voice into that of some kind of ‘demon’ embodying relapse which is
found that their behavior was controlled by treatment of addiction. To their own great surprise, many patients
took the opportunity to rehabilitate in a way that included a reversal of their attitude towards abstinence, and gave them the oppor-
tunity to engage in relapse. In some cases, such
as those involving narcotics, relapsing after detoxification bears a higher risk of death and a lower likelihood of finding obstacles to substance use, since the healed body, brain included, and the restored social surface will only go to increase the impact of the subsequent relapse. In fact, as long as general impairment is functional to treatment-seeking, even in the absence of any insight, detoxification may make patients slippery in their rejection of structured treatment and relapse prevention, due to the illusion that addiction can be cured through the improvement of collateral damage, such as tolerance. Doctors should take sides with patients – a response that should not be mistaken for taking sides with the illness. Since addiction splits the patient’s viewpoint in two, with a discrepancy between intention and will, no therapeutic alliance can be founded upon the patient’s free will. In my experience, a good number of patients feel extremely grateful to doctors who refrained from encouraging any attitude towards abstinence, and gave them the opportunity to rehabilitate in a way that included a reversal of their personal views and opinions about the dynamics of addiction. To their own great surprise, many patients found that their behavior was controlled by treatment they adhered to against their own beliefs, and managed to stay off drugs without developing a drug-free attitude as a basis for abstinence. Eminem’s Dr. West is what our patients usually perceive in forming an idea of the doctors they get in touch with, that is, a meaningless figure who actually ends up by overlapping with the natural course of the disease by helping them to be ready to relapse, just as they would if they were on their own, by approving of their good intentions, again, just as they would if they were on their own or, even, by giving them good instructions which quickly fade away as soon as they are discharged back on the street and craving is automatically reborn. Actually, physicians and all staff members should support addiction disease treatment rather than abstinence. Otherwise, we are all condemned to play the pathetic and ridiculous roles of our patients’ alter egos, by illuding them as they would like to illude themselves, that the achievement of sobriety is the first step towards successful relapse prevention.

The literature had dealt with the issue of abstinence support and motivation. However, when such concepts are applied within real settings, they are often misunderstood. Abstinence support should, rather, be focused on addiction-related anhedonia, which endures even in the absence of craving, as a sign of the twisting of pleasure-seeking pathways by a hypertrophic substance-oriented memory. Otherwise, most abstinence supporters just end up ‘sponsoring’ a drug-free lifestyle, as if the attitude towards drugs in general was the source of all evil. Also, the risk of relapse tends to be handled as some sort of pitfall in the patient’s skills of self-reliance: relapsing is regarded as a stage in an evolving relapse-proneness, which is thought to play the crucial role. In this view, addiction is born from a controllable part of the person’s brain, only to become uncontrollable later, once one has “taken the edge off”. In other words, the patient’s skills in coping are mistaken for actual self-reliance against the dynamics of addiction, while intoxication proneness, rather than primary relapse-proneness, comes to be seen as the real enemy. When motivational treatment is applied, in several cases it is not the stage of development of the patient’s motivation to undergo treatment which is evaluated and guided, but the patients’ motivation to abstain. Techniques which grant the patient a better degree of control against relapse should never include sobriety or self-reliance as a requirement, since addiction, by definition, robs people of their self-reliance.

In conclusion, we should avoid playing Dr. West’s role, directed to echoing the patient’s misleading ideas, which are functional to believing that some control is possible, by lying to oneself about the idea that this can come through sobriety. Any Dr. West who suggests to the patient that they are the key characters in their healing process will just build an alibi for them to sponsor their relapse. The only sponsored mental skill will be a persistently low level of insight.
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Following the Role of the Funding Source text, authors are required to declare their individual contribution to the manuscript under a subheading Contributors.

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