

Clinical foundations for the use of methadone. Italian Consensus Panel on Methadone Treatment

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Methadone maintenance is intended to be part of a long-term therapeutic plan of variable length, which allows opioid-dependent persons to lead a normal and productive life. Methadone is a synthetic opioid with peculiar kinetics, which accounts for its merits as a means of therapeutic intervention on opiate addiction. After oral administration, it is wholly absorbed through the enteric (intestinal) wall, and is not subject to a first pass metabolism in the liver; as a result, it can be up to 98% bioavailable. The peak level in the plasma is reached as late as 2-4 hours after intake - that is, quite slowly. Its subjective effect is perceived as a feeling of well-being beginning 20-30 minutes after administration and lasting for as much as eight hours. The intensity of the perceived effects depends on the subject's baseline condition: if opiate withdrawal has begun by the time of administration, the subjective effect will be described as intense relief; otherwise, in a condition of chronic administration, the effects may only be perceived by subjects who are explicitly asked to check for their onset. After the first administration, methadone's plasma half-life is biphasic, showing a quite rapid early phase (lasting about 14 hrs.) during which methadone spreads into the body tissues, followed by a second, prolonged phase, possibly lasting over 50 hrs., during which the level of methadone in the blood gradually decreases. After a two-week period of administration, the raceme mixture's half-life is about 24 hrs.. In reality, methadone has two stereo-isomeric variants, D and L; L only possesses an intrinsic activity on μ -opioid receptors. The L isomer, has a steady state half-life as long as 36 hrs.. The raceme lasts for a shorter time, probably due to isomerism-dependent changes in metabolic rapidity. Methadone's absorption and bioavailability follow a linear pattern, which means they do not respond to any dose-related variation. This is why methadone's effect is always predictable and only depends on the subject's tolerance threshold. Methadone is metabolised by the liver enzymatic system known as cytochrome P450, subtype 3A4 (CYP3A4). Resulting metabolites do not possess any pharmacological activity. After the first few weeks of administration, methadone mildly enhances its own metabolism, which explains why kinetic balance is

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only achieved after at least 15 days, if dosages are left unchanged. Due to its long plasma half-life, a single administration of methadone is effective in preventing the onset of withdrawal for 24 hrs. in most subjects. A sharp difference separates heroin and methadone in terms of pharmacokinetics, whereas the pharmacodynamics of the two compounds are essentially similar. Unlike methadone, and like morphine, heroin is completely absorbed after oral administration, but undergoes a major first pass effect through the liver. Heroin is rapidly de-acetylated to monoacetyl-morphine and then morphine, by a variety of esterases, so that its plasmatic half-life after intravenous administration lasts no longer than 10 minutes. It cannot be excluded that its initial effect is partly due to its interaction with other specific opioid receptors. The effect produced by a single dose of either morphine or heroin lasts as long as 3 to 6 hrs. (1.5 to 3 hrs. is the plasma half-life of morphine). After intravenous administration, heroin elicits a 'rush', coinciding with a higher, fast-dwindling plasma peak. A phase of acute intoxication follows, which may vary in length according to the ratio between the subject's tolerance threshold and the dose administered. Afterwards, a period of subjective well-being or a neutral condition is experienced, lasting 2-3 hrs.. It may be that, when people administer heroin to themselves frequently and at a stable dose, the eventual phase starts immediately after the rush, with no intoxication interlude. For habitual users, withdrawal can be expected later; its intensity, as with somatic symptoms, depends on the tolerance level reached by subjects. On the other hand, withdrawal-related mood alterations are still excruciating for any addict. The continuous intravenous administration of heroin, when able to keep plasma levels in a range corresponding to normality/well-being, is effective in preventing withdrawal from setting in. The same result can be achieved by a μ -opioid agonist characterized by a long-lasting, stable effect, which is what methadone appears to be. Moreover, the differences in the kinetics of methadone and heroin have further implications. The intravenous administration of heroin and the subsequent peaking blood levels, make it unlikely that maximum tolerance levels are ever reached, so that heroin addicts, even if they inject themselves heavily and frequently, always run a risk of overdosing events. Apart from that, the administration of gradually increasing dosages of methadone makes it possible to achieve a maximum tolerance condition, where methadone blood receptors saturate still available receptors. Such a dose is referred to as "blocking dose"; it shields the addict from the toxic effect of the heaviest heroin (or other opiate) dose as far as possible. The shielding effect is equally strong in situations of opiate-induced euphoria and breath inhibition. In other words, the administration of methadone at blocking dosages separates heroin from its expected and sought-after pleasurable effect in the experience of the addict; this may lead to the gradual dwindling of self-administering behaviour, along with the disappearance of desired gratification. Maintaining patients on methadone doses at blocking values is often a crucial step towards stopping a severe drug-taking behaviour. Administering heroin does not change the individual's sensitivity to narcotic drugs, which can be shielded, as explained above, by the use of methadone within a range of 60-100 mg/day. With heroin, the craving (urgent desire) for narcotics is

continuous and it recurrently soars; by using methadone, it is usually suppressed. Withdrawal from heroin usually sets in within 3-6 hrs. after administration; it is intense and can be controlled by methadone. Withdrawal from methadone begins 24 hrs. after the latest administration, reaches a lower level of severity and lasts longer. When appropriate - that is, when methadone maintenance has been accomplished - slow, steady methadone tapering can be performed, under medical supervision and in a safe context, in such a way as to avoid the emergence of withdrawal symptoms. The risk of HIV or hepatitis infection is higher when heroin is self-administered by injection, using unsafe methods and without hygienic prophylaxis. Conversely, it appears to be lower for methadone-maintained patients. The immune system and endocrine functions of HIV-negative heroin addicts are usually abnormal, but tend to normalize as methadone treatment proceeds. HIV-positive patients run the risk of starting a rapid evolution towards AIDS, as long as they keep on using heroin, whereas the disease-free interval appears to be longer for methadone-maintained patients. As regards the hypothalamic-hypophysis-surreal axis, heroin addicts continue to swing between a state of overstimulation, during withdrawal, and one of suppression, during peak heroin stimulation. Sexual functioning and gratification are also discontinuous in heroin addicts of both sexes, and menstrual periods are often disturbed. All such abnormalities tend to become slighter as methadone maintenance develops. Ongoing heroin use during pregnancy implies severe risks both for the mother and the foetus. Peak-related hypoxia and withdrawal-related uterine spasms may cause damage to the placenta, especially at its roots within the endometrial layer, and may thus hamper, directly or indirectly, the development of the embryo and, later, of the foetus. On the other hand, methadone-maintained pregnant patients can benefit from medical, social and nursing interventions, and so be able to face any accident or critical decision. Moreover, the foetus does not undergo any stress; nor does it show growth abnormalities or retardation. The phenomenon of neonatal withdrawal, though expected, is predictable in its intensity, depending on how much methadone the mother is taking, and it is, anyway, easy to buffer pharmacologically. During heroin use, mood instability is the rule, affective and intellectual functioning are both severely disturbed, emotions and pain perception are enhanced, reactions are reckless, and interpersonal relationships and social adaptation are disrupted too. During methadone treatment, all affective and relational abnormalities tend to improve. This is especially true when counselling or psychotherapy facilities, and possibly Therapeutic Community in-treatments, are available, together with pharmacological interventions, in a way that does not interfere with the principles of methadone maintenance. Under the impact of heroin-induced dysphoria, educational activities and the achievement of working skills are quite likely to fail, and it may be difficult, in any case, for patients to keep a currently held job. On the other hand, when methadone maintenance is in place, educational and working areas are strongly favoured, so that any job may be done efficiently, including those involving the driving or supervision of machines. Heroin addicts with additional psychiatric diseases are awkward to treat, very often engage in polyabuse, and commit crimes. High

rates of criminal behaviour, drug-related deaths and disease-spreading must therefore be expected. Within a well-managed methadone programme, psychiatric comorbidity can be treated as well, polyabuse may be eliminated, and illegal acts can be expected to dwindle, often, to the point of extinction. Social safety is thus empowered, crime and death rates are sharply reduced and society's quality of life improves along with the treated patient's. To sum up, the therapeutic use of methadone does not produce or perpetuate any addictive condition; it is a cure for opiate addiction, meaning by "cure" a clinical check, of just the same kind as is observed when an anti-hypertensive drug is administered to a patient suffering from hypertension, or thyroxine is given to hypothyroid patients. So far no therapeutic approaches have been developed that are able to eradicate a chronic pathology, that is, cure it with no risk of relapse in treatment-free conditions. Medicines are now available, that are useful in alleviating pathologies previously regarded as untreatable. No medicine is equally effective on all patients who share the same diagnosis, and the best outcome such medicines can achieve is that of permitting the clinical control of symptoms, interference with the evolution of a pathological process, and the prevention of possible somatic complications. Methadone does exactly that: while it buffers withdrawal symptoms, it cuts the risk of infection and impulsive behaviours, in concomitance with which patients are likely to engage in law-breaking. In addition, it permits a condition of individual well-being, in terms of somatic comfort and mood stability, that is capable of restoring the individual's productive potential, when that has previously been hampered by longlasting heroin use. Indeed, the therapeutic effect of methadone does not fade as a result of tolerance through time; nor has any social impairment been observed to develop. The dangers to society mentioned above, together with the core addictive pathology, are just those accounted for by the DSM-IV in defining an addictive disease. In order to achieve the objectives just indicated, a methadone programme should be worked out on the basis of a schedule that defines the criteria for eligibility, achievable objectives and methodology through different phases that act as milestones along the therapeutic path to recovery.

Patient enrolment

The subjects who are supposed to benefit most from methadone maintenance identify with those heroin abusers who find it awkward or almost impossible, to stop using heroin in the short term. Such individuals are likely to have repeatedly tried to get off the substance, but relapsed into using it in the short term, despite intervening periods of stable abstinence of variable length. Such attempts demonstrate the intention to stop using heroin, and may have been made either on the patient's own initiative or under medical supervision; they may rely on opiate agonist tapering or on directly decreasing dosages of heroin itself, within natural environments or protected ones, such as hospitals or therapeutic communities. Methadone maintenance does not necessarily have to appeal to addicts with a long personal history of attachment to heroin, who are unable to handle their lives on their own. As to any kind of specific intervention, the earlier the phase of the targeted disease at the moment intervention starts, the greater its expected

effectiveness. The literature has not provided a great deal of evidence in support of this position, since cultural resistance to the spread of methadone treatment has strengthened the view that maintenance should be resorted to only in the case of patients who have “reached the bottom”. Concern over the AIDS epidemic and acknowledgements about viral hepatitis have by now discredited that slogan. The impact of early-intervention measures on infective pathologies has been so strong that no intervention-delaying policy appears to make sense any longer. Heroin addiction, as a disease, spontaneously tends to follow a chronic, relapsing course. A functional imbalance is set up, where the early withdrawal symptomatology - that is, the cluster of somatic vegetative alterations triggered by the absence of habitually consumed opiates - does not play a crucial role. In fact, other symptoms are also comprised within the opiate withdrawal phenomenon; these are masked in the early phase by overwhelming somatic alterations, but are bound to persist, and may recurrently and unpredictably intensify, so impairing most subjects’ ability to maintain abstinence, and pushing them towards a relapse into heroin use. These other symptoms comprise dysphoric mood, a heightened sensitivity to painful stimuli, and the incapacity to carry out tasks, even quite simple ones. These are subtle elements, but they can be intense enough to elicit relapses, and may escape recognition by clinicians; patients themselves are usually hardly aware of them. On grounds of diagnosis, a case of addiction is considered severe when repeated relapse into abuse of the same substance (heroin, in our case) is documented, despite an evident intention to stop using it, as demonstrated by repeated failures. Though any clinical treatment should meet the individual’s specific needs, most severely addicted patients, who happen to be the vast majority of heroin addicts, can best achieve recovery by a long-term methadone maintenance programme. Methadone maintenance guarantees a better outcome than no treatment at all, even when not associated with psychosocial support initiatives. Methadone is more effective in treating most heroin addicts than other therapeutic alternatives. More precisely, patients should be offered a well-structured programme, and be well informed about its mechanisms so as to best benefit from its advantages. The patient’s informed consent will actually correspond to a higher level of compliance as long as patients are aware of the aims and limitations of the approach chosen.

Objectives

A methadone maintenance treatment programme must pursue three fundamental objectives from the onset:

1. To free patients from their condition of suffering (resulting from a history of repeated failures, along with the consequent fear of being unable to achieve stable well-being at any time);
2. To block the effects of what may be self-administered heroin by the induction of a condition of tolerance to methadone (up to a full blocking dose, when necessary), which implies cross-tolerance to heroin. This second objective is crucial in achieving the third:
3. To suppress, rather than reduce, the craving for heroin, which may endure despite the

achievement of a stable opiate blockade.

If any craving, even if a minor one, is left, patients may resort to alcohol or psychotropics (depressants), as a surrogate for unavailable heroin, or for heroin made ineffective by a methadone-mediated opioid-blockade. Clinical experience has proved that these three objectives can easily be accomplished for most patients, so leading to the eradication of addictive practices and a resumption of patients' previous lives. An individual's potential and skills, which were progressively impaired as addiction developed, can be restored, partly as a direct result of addiction control, and partly as the outcome of rehabilitative intervention. Social and psychological remedies can be resorted to in order to optimize the results achieved by pharmacotherapy; they are especially useful for subjects who are afflicted with serious socio-environmental impairment. Behavioural changes witnessed in methadone-treated patients after the first few weeks are essentially due to the general, stable well-being made accessible by methadone itself - a state superseding the previous condition of affective and somatic instability. When tolerance to the administered methadone dosage has been achieved (so that there is no sign of narcosis, apart from a control of withdrawal that leads into a feeling of well-being), and when the patients show they have firmly broken away from addictive issues and environments, stabilization has been achieved.

Methodology

Early phase: Relief from global suffering

When patients ask for treatment, they are usually in a phase in which the only effect of daily heroin is that it buffers withdrawal, and surrogates such as sedatives and alcohol may as well be resorted to in order to soothe withdrawal-related discomfort. Addicts have learned that heroin is the best way to interrupt incipient withdrawal, and they have developed a stereotypical pattern of appetitive behaviour whose aim is that of finding the substance. As soon as withdrawal begins to escalate, when heroin is available in the environment, the addict's behaviour becomes a craving-led one, which leaves no room for self-control, and it intensifies until the sought-after substance is found. At later phases of the disease, or when independent psychopathology is present, craving may lose its primary adaptive function and may no longer support inappropriate behaviour, such as aspecific acting-outs. One of the reasons for a heroin addict has for applying for methadone treatment may simply be to achieve relief, even if transient, from a state of discomfort. When the therapeutic programme is managed competently and with respect for patients, they will have the chance to realize that, as long as they stay in treatment, they will have no need to resort to street opiates (i.e. heroin) as a means to buffer discomfort. On the first day of treatment, dosages of methadone of 20 to 30 mg should be administered at first, possibly followed by supplementary charges if withdrawal does not diminish within 2-3 hrs. Additional dosages of 20-30 mg will then be administered every 3-4 hrs. (methadone blood level peaks at the 4th hr.), as long as its previous

administration, apart from not causing sedation, was not followed by a thorough resolution of withdrawal. No further dosage supplement will be administered in the absence of persistent or residual withdrawal. The total amount administered on the first day will be administered as a single dose on the following days. First-day doses higher than 30 mg may only be administered to patients, whose tolerance threshold is already known as quite high.

Blockade of heroin effects and suppression of craving-related drug-seeking

After 4-5 day of treatment, the methadone dosage will be gradually increased by 5-20 mg every 1-4 days, up to a value that is presumed to be enough to block the effect of injected street heroin, usually at least 60-70 mg. Patients receiving these doses continue to use heroin, but are unable to feel its effects any longer. This dilemma is crucial: on one hand heroin is ineffective, but on the other it is still sought after and craved by the subject. Thus, patients may take methadone at dosages lower than prescribed, in order to be able to feel the effect of injected heroin, or else try to increase heroin dosages to overcome the methadone blockade. As a further alternative, alcohol or psychotropics (especially benzodiazepines) may be used to elicit a narcotic effect from methadone, or psychostimulants may be resorted to. A strong risk of polyaddiction must therefore be taken into account. It should be remembered too that in normal individuals, behaviours tend to disappear if there is no reward for them. Blocking dosages of methadone suppress heroin-induced reinforcement, so the self-administration of heroin goes unrewarded and usually disappears. If it persists, or is replaced by alcohol or benzodiazepine use, the methadone dosage should be increased, and precautions should be taken to ensure that methadone is, in fact, taken at the prescribed dosages. Even when the oral dosages administered to different individuals are the same, methadone blood levels vary over a wide range. At oral dosages ranging between 80 and 120 mg/day, the definitive therapeutic objective - the cessation of heroin use - is usually achieved. A minority of patients, however, continue to consume heroin, and these require higher methadone dosages. Clinicians should always clarify whether any independent psychopathological condition is involved. A number of studies have tried to assess whether a value for methadone blood level can be defined as a marker of effectiveness for oral dosages. Effective methadone blood levels have been reported varying between 100 and 600 mg/ml. No threshold value for methadone blood levels has been identified. It is not good clinical practice to treat any individual at a single rigidly fixed standard dose. So too, it is not reasonable to fix a termination date for treatment. Putting a limit to methadone dosage or excluding some categories of addicts from treatment actually means leaving patients tied to their uncontrollable craving, which implies increasing the risks they incur of overdose, unsafe injections, polyaddiction, and HIV infection. The suppression of craving, that is, the compulsive appetitive drive, is the crucial therapeutic issue in the treatment of heroin addiction. The pharmacological properties of heroin reinforce heroin-directed search behaviours to a level of paroxysm. Once addicts find that the

effects of heroin have been blocked, their commitment to heroin is supposed to gradually fade to the point of extinction. This hypothesis, originally formulated by Wikler, provided the rationale for the use of long-lasting opiate antagonists in the treatment of heroin addiction. Antagonist treatments, however, are likely to be abandoned in the short term by most enrolled patients; in their case relapse occurs long before craving disappears. Like heroin antagonists, methadone too prevents heroin from inducing its effects; but, unlike the former, it cannot be discontinued abruptly, due to the persistence of heightened opioid tolerance. This characteristic, which is shared by all known opioid agonists, can be regarded as a drawback. On the other hand, therapeutic aims (e.g. retention in treatment) are favoured if patients know they cannot discontinue their therapy, without facing unpleasant consequences. In fact, compliance and retention rates are much higher in methadone maintenance programmes than in any other kind of approach. The retention rate is the most reliable index in assessing the effectiveness of any treatment approach to heroin addiction.

Methadone treatment practice

Like any other treatment, methadone maintenance should be adapted at all time, according to the ongoing clinical situation. During the first few months of therapy, patients are usually monitored daily. This is the so-called induction phase, during which the optimum methadone dose is worked out. No standard lowest effective dose has yet been determined, nor has any maximum dose ever been defined. So, it is unreasonable to increase the dose if addictive behaviours have been stably eradicated, or to raise the dose over a certain threshold if the response has been unsatisfactory. Methadone dosage should be tailored to the needs of each individual patient. Although most clinicians agree that the lowest effective dose is as high as 60 mg/day, and the average optimum value ranges between 80 and 120 mg/day, that knowledge must be read in statistical terms, which have been assessed with respect to retention in treatment, and to urinalysis results over the previous month or over a six-month interval. As a rule, the higher the standard dose used in the study, the higher the rate of responders to treatment. This correlation does not mean that all patients should be treated with high doses without allowing for any other differences. It means, rather, that it is unreasonable to put a limit either on methadone doses or on duration of treatment, as long as optimum results are being aimed at. Once stabilization dosages are reached, and the incipient reversal of addictive behaviour, as reflected in the restoration of social adaptation, is observed, psychosocial initiatives can be resorted to, as long as the maintenance phase continues. When behavioural changes are satisfactory and stable, patients can be allowed to attend the structure less often (but at least once a week). At this point, the controversial issue of take-home methadone dosages looms. It must be pointed out here that the transition from stricter to less strict supervision marks a necessary step towards recovery; there is also the psychological advantage of showing a patient who had lost control over his or her self-administration of a substance that treatment has given them a new capacity to

handle the medication. The feasibility of a take-home follow-up gives objective proof of restored self-control that has been achieved by therapeutic means, after previous authentication by a regular attendance at appointments for administration and the persistent negativity of urinalyses. The decision to allow a patient take-home rights also provides feedback to him or her arising from previous good compliance with treatment; it is the instrument of what we may call “methadone-mediated indirect behavioural conditioning”. Take-home is unsuitable for patients who have failed to display a positive therapeutic response, as it will end up working to favour unhealthy therapeutic relationships. Of course, physicians are allowed to make exceptions, when there are objective impediments to a patient’s daily attendance of the structure, as in the case of constraints arising from work or study needs, when these are important on rehabilitative grounds, or in that of more directly medical issues. However, patients should be made aware that they are not being given a privilege, but are being relied on in terms of responsibility. At first sight, it may seem too strict to require patients to attend the structure daily, but it goes against therapeutic logic to be indulgent to patients who are unable to achieve or maintain any stable balance outside that mode. Frequent contact with operators is also a source of therapeutic support, besides creating a chance for patients to benefit from counselling or psycho-educational facilities. With help from psychosocial operators, patients may start new jobs, or resume activities they had given up. Also, when take-home is allowed, patients should take their daily dose face to face with the operator on the day of weekly dose delivery, so as to prove they have maintained their tolerance level. When patients are suspected of having let their tolerance fall, they should be observed for a couple of hours after the oral administration of their supposed dose. If sedation develops, it means the patient has not been taking the supposed take-home dose regularly. In these circumstances, the patient must be confronted and asked for an explanation. It is quite likely that patients who have been put on to a take-home mode, because they had previously displayed stable abstinence, will reduce their daily dose, or split it over the 24-hour cycle, without saying anything about this to their physicians, to avoid facing disapproval. In any case, the clinical situation is the parameter that should determine decisions about the take-home option. Some patients may be allowed to attend less often than daily after the first few months, while for others this may take six months or longer, according to the single patient’s clinical situation (stable continuous administration, control of substance use and psychopathological balance). It is not strictly necessary to pass from daily administration to an alternate-day mode and then a twice-a-week mode, before allowing weekly take-home: some patients may be allowed to proceed directly to a weekly take-home mode. Even if methadone can be prescribed by GPs and provided by chemists, that solution would make it awkward for operators to check whether the patient actually takes the prescribed dose, if any, and does not seem to meet the requirements of patient monitoring. Patients may be directly provided with methadone by their GPs only in a condition of stable psychopathological balance, when they have no need for any psychosocial intervention, so that they can be trusted to manage the administration of their therapy. Nevertheless, GPs play an

important role in the programme, either when directly managing the therapy, or when in charge of long-stabilized patients. It must also be pointed out that the provision of take-home methadone by chemists directly to patients implies a lack of privacy.

Subpopulations of heroin addicts who should be given priority for enrolment in methadone programmes

Some categories of heroin addicts should be given priority in entering methadone treatments:

- a) Pregnant addicts. Heroin addiction is unlikely to be compatible with healthy pregnancy. Methadone should be started without delay, and dosages should be reached that grant the mother a state of global well-being. Foetuses are just as much at risk as mothers by withdrawal, especially due to possible placenta disruption, and intoxication. It follows that no attempt to taper methadone, let alone interrupt its administration, should be performed during the last two months of pregnancy, when the placenta is losing its initial elasticity.
- b) Parents of minors. Parenthood does benefit from the behavioural stabilization achievable with methadone, partly due to the improvement of family relationships.
- c) HIV-positive/AIDS-affected heroin addicts or addicts with hepatitis. There is no incompatibility between methadone on one hand and antiviral therapies or therapy for the non-viral infective diseases of AIDS patients on the other. In addition, compliance with anti-infective therapies is far higher among methadone-maintained subjects. Special attention should be paid to the adjustment of methadone doses for patients who are also taking anti-retroviral drugs, due to the possibility of metabolic induction (e.g. nevirapine, efavirenz and lopinavir/ritonavir).
- d) Jailed addicts. Adequate methadone treatment reduces the occurrence of self-injurious or violence acts among jailed addicts. Methadone tapering must not be performed too fast or earlier than reasonable, and must be assessed according to the patients' symptomatology. Benzodiazepines should be avoided for as long as possible. If jailing is not expected to last long, it is reasonable to start a methadone maintenance programme, or at least maintain the dose previously administered. In this way, the risk of overdose after discharge from jail is minimized.
- e) Heroin addicts with dual diagnosis. Heroin addicts suffering from additional psychiatric syndromes usually need higher dosages, possibly combined with other psychotropics, and take longer to reach stabilization. For those who were successfully stabilized, the outcome, in terms of retention rate and abuse of non-prescribed drugs, is equivalent, if not superior, to that of uncomplicated heroin addicts. Methadone treatment also favours the patient's compliance with taking medications that target the associated psychopathology, and it improves their effectiveness.

The issue of programme monitoring

Within a well-conducted methadone programme, urinalyses should not be followed by sanctions, but should always be intended as a means to tailor treatment to each single patient's needs. Moreover, urinary controls are helpful in deciding dosage changes. The response to pharmacotherapy is usually mirrored by:

1. the absence of morphine at urinalysis;
2. the absence of other abused substances;
3. quiet behaviour while physically present in the structure;
4. compliance with the schedule of administration and the rules of the programme;
5. positive changes in behaviour, detachment from the street environment, improvement of social and family contexts and involvement in new activities.

It is crucial to check that tolerance to opiates is maintained and stable. Patients who are stably maintained at a high tolerance level, like that induced by methadone stabilization, have no chance to feel the effects of heroin, at least at standard market dosages. As a result, possibly self-administered heroin cannot produce its toxic effect upon the brain. Other recommendations are that urinalysis checks be performed at random, and that checking samples should be correctly collected, so as to allow access to reliable information about the patient's drug-taking behaviour. Other aspects should, however, also be taken into account, such as how a patient behaves while waiting for his or her turn at an administrative office or other facility, what relatives report about familial adaptation, information about school and work activities, and any other clues, circumstances or contexts which may help to spotlight behavioural changes. Whenever possible, physicians may directly ask patients questions about their knowledge of heroin abuse, especially when patients themselves report their personal experiences. In these circumstances, the physician in charge can directly weighup his decision while being acknowledged by the patient, so that adjustment, whether pharmacological or psychosocial, is granted immediately.

Medication tapering

Methadone tapering is the objective sought by everyone – patients, families and operators. Methadone maintenance actually aims to achieve tapering, but on time-scales and using modes which can be perceived as feasible and reasonable. Patients usually express their request for the completion of treatment after the first few months. It should be borne in mind that the reported condition of well-being, which supports the wish to terminate treatment, though genuine, is unlikely to correspond to an actual well-considered chance to remain abstinent in a drug-free condition. Follow-up studies on patients who had had their methadone tapered in the short term after stabilization have proved that treatment duration is crucial to making the treatment itself successful. Only after detachment from addictive behaviour has consolidated through time should any tapering be taken into consideration, let alone performed. A hypothesis of tapering

methadone should always take into account the clinical evaluation of the patient's probability to maintaining on-drug achieved results in a drug-free condition. Skilled operators should favour the acceptance by patients of the time-scales necessary for a successful methadone programme, and, as a trend, try to retain the patients in treatment for prolonged periods. "The longer the patient attends the programme, the sounder and the more substantial are the results that can be achieved at the end of the treatment". The tapering phase, to follow a long-term stabilization, is itself meant to last a long time, and tapering should not proceed, or be reversed, if the patient shows physical symptoms (e.g. somatization) or psychopathological ones. Tapering happens to be more awkward, and must be expected to last longer, in patients who have gone through repeated attempts at detoxification, rather than only one. Hence, a drug-free patient who underwent detoxification at some point in the past, and asks to be started again on methadone, should immediately be admitted to treatment.

Conclusions

At present, methadone treatment is regarded as the most effective and most popular treatment approach to heroin addiction. Administering an adequate dose of methadone may drastically improve the quality of life of subjects, who, due to the nature of their disease, have usually reached a high degree of somatic, psychic and social impairment. Methadone programmes must comprise a careful procedure involving increasing doses in order to achieve stabilization, which should then be maintained with a view to a long-lasting, slow tapering. In the meantime, other kinds of medical intervention, counselling and rehabilitative facilities should be provided.

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