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EUROPEAN 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 object of EUROPAD is to promote, in the EU and elsewhere, the effective treatment of drug addiction, especially heroin addiction, in particular, but without prejudice to the generality of the foregoing:

- (1) to promote the development and acceptance of treatment with methadone and other prescribed medicaments (buprenorphine, LAAM, heroin, naltrexone) including long-term prescribing;
- (2) to enhance the provision and quality of services to drug abusers and their families, especially heroin addicts;
- (3) to promote a better understanding of methadone treatment by the general public and its elected representatives and officials;
- (4) to promote collaborative research and to provide a European research centre;
- (5) to work with the American Methadone Treatment Association to promote support for methadone treatment worldwide;
- (6) to promote good will and cooperation among the staff of methadone and other medical treatment services in Europe and elsewhere,

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HEROIN ADDICTION AND RELATED CLINICAL PROBLEMS

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Treating Heroin Addicts, i.e. “Breaking through a Wall of Prejudices”

Icro Maremmani

Summary

The medical, psychiatric, psychological and social manifestations of heroin addiction require more than an integrated intervention. To effectively treat addiction, rehabilitation and/or prevention is necessary but we must also treat the patients according to the phase of illness. In other words, it is often necessary to adapt the intervention to the clinical phase of illness, by trying to raise the programme “retention rate”. This condition is indispensable in the rehabilitative process. The nature of drug addiction will often make it necessary for patients to be contacted in the street, so that they can benefit from counselling and “harm reduction”. Finally, primary or secondary prevention cannot be separated from a global intervention philosophy.

Key words: Different level of intervention - Prevention - Harm Reduction - Diagnosis and Treatment of Associated Pathologies - Specific Treatments - Rehabilitation and Social Integration - Prevention and Treatment of Relapse

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

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

Presently, almost all researchers in the field of drug addiction agree that the “retention rate” is a fundamental requisite for the successful outcome of any program (2). This is obvious if one considers the official definition of drug addiction as a chronic

illness involving relapses. Thus therapeutic planning must be adapted to the patient and not vice versa.

If, as systematic observations reveal, many drug addicts stay addicted over a long period, some for the rest of their lives, attempts to treat this large group of subjects must not be abandoned. Priority should be given to long-term treatment by giving the drug addict the chance to gradually recuperate his or her bio-psycho-social functioning. This could be defined as clinical improvement, even if “restitutio ad integrum” has not been achieved. It is the main goal of adequate pharmacotherapy and psychosocial treatment (12).

Achieving this limited goal may be the best possible result for some, while for others it may open the door to being able to function well, in an opioid-free state, over the long term. In both cases, however, these subjects have a right to a normal life, personal gratification, social respectability, and physical and mental well-being (7).

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

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

While comprehensive treatment programs attempt to deal with many of the problems associated with addiction, we feel that Therapeutic Community re-educational programmes (TCps), when based on segregation and accusation, must not be utilized. Examples of this kind of treatment were common in Italy and in other European countries in the 1970's and 1980's, when the stigma experienced by heroin addicts was severe and treatment with opioid agonists was strictly regulated but not accepted by politicians. The re-educational programmes on which most of Italian TCps are based are highly selective, and have proved to be beneficial to only a very small number of addicts, when pharmacological support is denied. My personal experience allowed me to note the cognitive disorganization of patients who followed TCps; this tended to reinforce guilt and convey the idea that drug addiction is an acquired vice caused by deviant behaviour. In this way patients found themselves defenseless and unprepared for relapses, which they interpreted as being an explicit sign that they could never recover. In these programmes the refusal of the biological basis of addiction or the withdrawal of family counseling is a very harsh measure; it often means cutting ties with the patient,

who is described as "lacking in will and motivation". For heroin addicts, "reaching the bottom", the most famous slogan of some Italian TCs (CEIS group), very often meant dying of an overdose, contracting AIDS, or the refusal of all types of treatment (9).

Comprehensive treatments need a new philosophy of intervention. Staff must know the various levels of the treatment programme, and the policies adopted at different levels must not be contradictory.

Our theory of comprehensive treatment includes different levels of intervention, as follows:

Level 0: prevention. Level 1: harm reduction. Level 2: diagnosis and treatment of associated diseases. Level 3: specific treatments. Level 4: rehabilitation and social integration. Level 5: prevention and treatment of relapses. These levels can be implemented individually or in groups in a coordinated manner, depending on the needs and willingness of the patient.

LEVEL 0 (Prevention)

Currently, no effective primary prevention model is operative. Educational models based on particular cultural backgrounds are rarely acceptable to all.

Although drug dependence may have its roots in societal organization, or in consumerism, educational models alone are not effective preventive measures, and may cause diametrically opposite results in social groups with different cultural backgrounds. Research has not yet identified specific educational impairments or temperamental types associated with drug addiction. A large number of subjects begin using drugs recreationally or to facilitate socialization without knowledge of the real risks or consequences of drug abuse.

As a primary prevention model, we suggest a public health education programme, on the various psychoactive substances that are targeted during abuse, and the effects and consequences of use and abuse. This programme should be free from ideological and moralistic interpretations, which often do no more than leave an attractive mythical or mysterious image (13, 14).

Health education constitutes a valid primary prevention policy, but secondary prevention (harm reduction, therapy, prevention and treatment of relapses) should not be overlooked.

Research indicates that the spread of heroin use is correlated with precise market interests which are kept alive in certain well-defined conditions such as clandestineness, which implies high cost, consumer-pusher phenomena and the unavailability of any effective therapy. Within this framework, the depenalization of drug use, and the treatment of drug addicts are essential preconditions for the elimination of this problem (1, 7).

LEVEL I (Harm Reduction)

The aims of level 1 may be summarized as follows:

- a) reduce the social and the medical consequences related to addiction, such as: criminal activity, spread of AIDS, consumer-pusher phenomena, the clandestine

nature of the market partly responsible for the high numbers of heroin users, and the high level of risk for the general population.

- b) protect heroin addicts from syringe-related pathologies (HIV, hepatitis, vascular damage, endocarditis, overdose, etc.) and from withdrawal syndrome; this will be an advantage for the patient, and will reduce social costs.
- c) more accessible public health services for the heroin addict population (11). Establishing the first contact between medical staff and addicts means (1) reaching a larger number of subjects; and (2) offering accurate information about physical and mental well-being and therapeutic prospects. These measures have not yet been implemented, especially in Italy and most other parts of Europe.
- d) the possibility of an early diagnosis; this aim is currently unattainable because drug addicts live in clandestineness. The patient usually seeks help when the situation is no longer bearable, and the course of addiction is far advanced.

Suitable interventions at level 1 include:

- a) expansion of agonist substitution therapy programmes based on methadone or other substitutive compounds (LAAM, Buprenorphine). The Swiss experiments with heroin do not provide conclusive evidence. They did not have a good control group, and the heroin patients received much more psychosocial treatment than the methadone patients. Also, the heroin clinics were much more expensive to run than methadone programmes, and it is unclear how heroin clinics fit into the overall framework of treatment programmes.
- b) free distribution of disposable syringes.
- c) instructions on the self-administration of medications.
- d) information about first aid in the case of an overdose or a withdrawal syndrome.
- e) information about the risks and consequences of the continued use of illegal drugs, and about types of treatment and rehabilitation.
- f) health education of HIV subjects

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

The effectiveness of a pragmatic approach has been convincingly demonstrated in the experience of countries such as England and Holland, which have succeeded in limiting the spread of heroin addiction (e.g. in 1991 in the United Kingdom 8,000 heroin addicts were officially registered, the spread of AIDS was limited and restricted to subjects at risk, mainly homosexuals). During the same period in Italy, due to moralistic and repressive attitudes, there were more than 320,000 heroin addicts, 1,200 deaths by overdose, and a high incidence of HIV; 70% of heroin addicts were seropositive.

The drawback of this first level is that it is not an actual form of treatment, so it cannot help patients recuperate bio-psycho-social functioning. In order to achieve this goal we must pass to the next level of our programme, which includes services and personnel with better qualifications.

LEVEL 2 (diagnosis and treatment of associated pathologies)

This level marks the beginning of specific treatment for drug addiction. The patient is examined by a medical specialist and other professional staff in order to decide on a diagnosis and devise a therapeutic plan appropriate for that subject. The scientific literature shows broad agreement in defining heroin addiction as an illness, and experience shows that it is the patient's degree of impairment, together with other factors, that determine if a particular intervention will work or not at that time. The principal task of specialized staff at this stage is to define a diagnosis and identify potential resources (personal attributes, family members or social skills), that may help in rehabilitating the patient. This will be possible if interviewing techniques reactivate two-way communication, in so allowing the needs of the patient to be identified, and concrete proposals to be formulated. Special attention should be given to unsuccessful attempts, which are often indicative of errors in the interventions proposed or in the monitoring of the patient.

This level requires more qualified personnel and specialized services than are currently available. Specialized centres for the diagnosis and treatment of addiction are needed. These centres should be equipped to carry out research, in collaboration with Ph. D. Research Programmes in Drug Addiction, and specialized personnel must be educated and trained.

Once a diagnosis has been made, the patient undergoes the appropriate form of therapy. The initial choices should not be restrictive or rigid but open and interchangeable with other treatment modalities. Staff will only be able to verify the choices made if the patient acquires and stays in a functional state.

At the same time associated pathologies and psychiatric disorders should be diagnosed and treated (4, 8).

LEVEL 3 (specific treatments)

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

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

A. Patients who do not require opioid agonists

The patients included in the first group should satisfy the following requisites: they should meet DSM-IV or ICD-10 criteria for a substance use disorder; they should have a low level of craving, good social adjustment, and good family support, with the availability of a referring family member; these subjects are reliable, and have good interpersonal relationships with staff (3).

It is important to stress that methods based on a "drug-free state" are highly selective, and are applicable to a very small number of patients (5, 6, 10); some antisocial and very resistant addicts, however, make good progress in these programmes, while not responding to anything else. Understandably, caution is needed before detoxifying patients, and there is also a need for attention in checking behaviour at risk, and

immediately admitting the patient to an agonist treatment programme if difficulties arise.

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

1. Abstinence is controlled by psychotherapeutic support, with or without opioid antagonists.
2. Self-help groups which encourage social reintegration during treatment. Antagonists may also be used in this case.
3. We propose TCps comprising greater flexibility and research in selecting participants, as compared with the rigorous ones that currently dominate the scene. NIDA is supporting studies on more “flexible” TCps (those that use medications and treat dual diagnosis patients).

B. Patients who require opioid agonist long-term therapy

This group includes the large majority of drug addicts who seek help. They do not meet requisites for “drug-free” programmes, which would be detrimental for these subjects.

The first task staff must face is that of redefining the patient’s expectations by suggesting the form of long-term treatment that promises to be the safest and the most successful.

One should aim to set up services that are able to support and be integrated with a long-term agonist therapy.

1. Basic counselling. Many patients on methadone or other substitutive therapies who have obtained metabolic stabilization experience a return to normality; they become socially reintegrated, especially if they have personal resources, with help from family members (home, work, hobbies, etc). For these patients therapeutic success may be attained through specific information and treatment counselling.
2. Treatment of psychiatric disorders with psychotherapy and/or pharmacotherapy, along with drug counselling for patients with psychiatric disorders.
3. Self-help groups could provide solid support for subjects who lack rehabilitative resources. Greater attention should now be focused on these groups, because they cost little, and have been shown to be effective in other areas (alcohol abuse, psychiatric pathologies, etc.), while many subjects can be treated simultaneously.
4. Residential Communities. These communities would help especially very young patients or subjects who need specialized social structures in addition to pharmacotherapy; these comprise drug addicts with serious psychiatric disorders, and those who find themselves jobless and homeless.

In concluding we would like to stress the following:

1. The therapeutic communities would be linked to social agencies and other health services. They would no longer be reclusive structures that isolate the patient from his or her family, or cut social ties. They must not create an artificial world in which recovery is obtained but quickly lost when the patient is released. Contrary to what happens in Italy, in the US many TCs work very hard to integrate patients back into the real world prior to discharge. It is important to have a transition phase, so as to help patients overcome the problems associated with the artificial environment.

2. The primacy of "drug-free" programmes should be abolished. Recovery cannot be strictly associated with a "drug-free" state; it should be related to psychological and social functioning.

LEVEL 4 (rehabilitation and social integration)

This level foresees the complete rehabilitation of drug addicts, independently of the kinds of treatment mode being used. The achievement of this goal varies (in terms of mode and length of treatment), according to the needs and the severity of illness of each individual. The forms of intervention which allow the patient to achieve this status may, for example, comprise: getting a job, the return to family life; the use of methadone, LAAM, and buprenorphine detoxication.

We would like to focus on the needs of patients who cannot be deprived of agonist therapy due to biological determinants. A substantial part of the drug addict population – who have good social and psychological adjustment – require agonist therapy, but not social support services. We consider these patients to be capable of complete recuperation, and feel that they should be allowed to manage their pharmacotherapy in the way diabetics do. For these subjects agonist availability should be convenient, and interfere as little as possible with daily life, work or leisure time. The patient could be entrusted with dosages that cover a longer period of time; family doctors would be able to prescribe methadone or other substitutive compounds. Any community health service could dispense methadone or other substitutive compounds under certification, so as to help the patient. On the international level contacts could be set up between the health services of different countries, so permitting the patient to travel freely. The organization of a health service network would be an advantage for the patient, who would not need to travel great distances to reach specialized centres. At the same time these centres would not be overloaded with work such as dispensing methadone or other substitutive compounds to patients who have been rehabilitated, so reducing social costs.

LEVEL 5 (prevention and treatment of relapses)

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

In conclusion, we have attempted to outline a rather complex strategy for the treatment of heroin addiction, on the grounds that it has a scientific and pragmatic basis. Obstacles to the realization of this project are political interference and cultural prejudices. It may be hoped that education of the public will help to correct current misconceptions about the problem of drug dependence.

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Heroin Addiction as a Normal Illness

Alessandro Tagliamonte

Summary

History teaches us how difficult it is to challenge some axioms that are rooted in common culture, even when they are not supported by scientifically indisputable evidence. The two most famous examples of controversial scientific novelty were the Copernican theory and the theory of evolution. Do analogous mechanisms underlie the refusal of behaviour disorder, i.e. psychiatric disease or drug addiction, as a biological phenomenon? Man, it is said, was created by God in his own image and likeness, and God gave him a soul; according to this view, it must be the soul that is responsible for his behaviour. With increasing precision, modern psychobiology is succeeding in correlating specific aspects of animal and human behaviour with definite brain areas, and with the neurotransmitters that are located in them. Various behaviours have a clear genetic basis, but particular genes take part in organizing each behaviour; similarly, various neurotransmitters in specific brain areas interact, so causing a given form of behaviour. Psychiatric disturbances, including drug addiction, are leaving the limbo of approximation or even of utopianism, to enter into the scientific dimension of medical empiricism.

Key words: Heroin Addiction - Psychiatry - Drug Addiction
Psychobiology

In 1991 the University of Cagliari conferred an honorary degree on Prof. Vincent Dole for his scientific merits. On that occasion, a reporter from the local daily paper interviewed him, and I was the translator. The reporter was evidently puzzled when confronted by the clarity of Prof. Dole's argumentations and by the simplicity with which the indisputable statistical data on the effectiveness of methadone in treating chronic heroin addiction were presented (1- 4). At a certain point he could not refrain from asking an emotional but provocative question: "Well then, why are the mass media, politicians, public opinion, and even many physicians so decidedly against the use of methadone?" Dole looked at him with a gentle smile, then looked away, and, almost

disconsolately, answered: "I have been asking myself that question for 25 years, but I haven't yet found an answer."

Methadone was first used almost by chance, as a substitute for morphine, in chronic heroin addicts, who were admitted to clinics. Its effectiveness in controlling withdrawal symptoms over long periods, and in bringing stability to the patient's mood was immediately evident to the earliest observers. It is therefore logical that they continue to wonder why what has been evident to them for over 30 years is still refused even by those who have the social position and the institutional duty to provide medical assistance.

The easiest explanation must be found in the fear of novelty, which affects both the individual, and, especially, larger groups of people, who, taken together, help to form opinion. History teaches us how difficult is to challenge some axioms that are rooted in common culture, even if not supported by scientifically undeniable evidences; I am not referring to religious principles or acts of faith, for which objective evidence is not required.

The two most famous examples of controversial scientific novelty were the Copernican theory and the theory of evolution. Firstly, man had been told that he lived at the centre of the universe, and that everything, including the sun, revolved round the world he inhabited. Secondly, it has been stated that he was created by God as the last of the living creatures, after plants and animals, in his own image and likeness. But a scientist appeared who claimed that the Earth not only is not the centre of the universe, but a small planet revolving round the sun. Finally, a few centuries later, Charles Darwin stated that man was not created as such, but is the result of a natural process of evolution which, through simple organisms and the chance appearance in them of new transmissible characters, passed through the stages of reptile, bird, mammal, up to the primates; so, from now on he should consider himself a well-developed form of monkey (5).

The two axioms, which were called into question by the new discoveries, continued to be supported by religions, which considered them as principles of faith and had enfatically proclaimed them in the Holy Writings as truth revealed by a god. According to them, acceptance of the new truths, even if scientifically demonstrated, could be considered a sin or heresy.

Do analogous mechanisms underlie the refusal of behaviour disorder, i.e. psychiatric disease, as a biological phenomenon? The dynamics leading to that refusal are analogous: on one hand a minority of operators, who set up a methodology based on experimental findings and who utilize that methodology to improve the quality of the life of psychiatric patients; on the other, public opinion which is opposed to that methodology and to those who use it, considering specialists to be greedy, inscrupulous individuals, and including in its criticism patients who have clearly benefited from the new treatments.

What axiom, then, is undermined by the use of methadone or EKS or imipramine? Man, it is said, was created by God in his own image and likeness, and God gave him a soul: it must therefore be the soul that is responsible for his behaviour. Trasgressive behaviour leads to the loss of the soul and to the punishment of the sinner, who should

make a decision to choose the right path. Such reasoning may be valid in an ethical vision of society when it is applied to sane people, if they are willing to accept it. But it has no meaning when applied to people who are not sane, and who suffer from a psychiatric disease (that is a disease of the mind, meant as an organ that is part of the central nervous system).

To overcome the obstacle of psychiatric disease, various methods have been tried, ranging from accusations of witchery and possession by evil spirits, to the intervention of exorcists who are able supposedly to defeat devilry. These methods were followed by theories based on the ancient observation that experiences modify behaviour. Starting from this principle, which is included in the definition of memory, some misrepresentations were made, and though it was difficult to identify the single negative experiences responsible for a pathological modification of behaviour, the importance of forgotten events began to be evoked; this led to the concept of the “repression” of forgotten events as an etiopathogenetic factor in the induced disorder.

The belief that the psychiatric disorder could be cured by a return to its origins, through a heightened consciousness of the causal traumatic event, represented a wonderful invention, which was taken up by unforgettable novels and films; but it also strengthened the illusion and superstition that mental disease has external causes only, and that it can only be eradicated by means of processes of refined exorcism (6, 7).

In reality, psychiatric disease has a biological basis, whether genetic or acquired as a result of a physical or emotional trauma, an infectious disease, or a substance toxic to the central nervous system. Once the psychiatric disorder has become stable, it is not necessarily useful to go back to its cause, which is often insignificant; returning to that cause may even be harmful. With increasing precision, modern psychobiology is succeeding in correlating specific aspects of animal and human behaviour with definite brain areas, and with the neurotransmitters that are located in them. Various behaviours have a clear genetic basis, but particular genes take part in organizing each behaviour; similarly, various neurotransmitters in specific brain areas interact, so causing a given form of behaviour. A small dysfunction in the structure, such as a single neurotransmitter alteration, may, theoretically, also modify the regular pattern of a behaviour, in the sense of a set of responses to a certain kind of stimulus. Thus, we should not be surprised if a medication, by strengthening or decreasing the response to serotonin, is able to restore a psychiatric patient to his or her normal reactivity. Psychiatric disturbances are leaving the limbo of approximation, or even of utopianism, to enter into the scientific dimension of medical empiricism. The cultural shift is as important as that caused by Galileo. In some schools in the northern states of the USA it is still forbidden to teach the theory of evolution, so we should not be surprised at the resistance encountered by these new ideas on brain functions, considering their ethical and political implications.

Some generations will be needed, and then the heroin addict will be free of restrictions in receiving the most suitable medication from his or her physician, and everybody will accept this intervention as naturally as in the case of a patient taking tablets for hypertension.

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Methadone Maintenance. Comes of Age

Vincent P. Dole

Summary

Methadone maintenance treatment in the United States is reaching maturity. During the past three decades it has progressed from an innocent childhood, through a turbulent adolescence, to recognition as an essential medical procedure. At present approximately 115,000 former heroin addicts in the United States are being treated in 750 clinics located in 40 of the 50 states. The treatment has survived challenge by professional sceptics, by ideologically hostile agencies, by competitive modalities, and even by well-intentioned clinicians in methadone programmes who have prescribed inadequate doses of the medication.

Key words: Methadone Maintenance

The simple fact is that it works. When given to a heroin addict once daily in adequate dose, methadone abolishes the compulsive narcotic hunger of addicts without producing euphoria. The transformation of apparently hopeless narcotic users into normally functioning individuals seemed miraculous to the original research team – Marie Nyswander, Mary Jeanne Kreek and me – three decades ago. How could the administration of a narcotic medicine normalize persons whose dependence on narcotics had been characterized by psychiatrists as immature, degenerate, sociopathic, etc?

The phenomenon obviously demanded verification and further study under different conditions to determine its potential as a large-scale treatment. A talented group of clinicians, nurses, administrators, ex-addicts, vocational specialists, epidemiologists and lawyers joined us in studying the question. The list of persons who participated in the work during the first decade is too long for proper acknowledgement here, but the

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critically important involvement of persons closest to the early work must be mentioned: Drs. Joyce Lowinson, Ray Trussell, Robert Newman, Lars Gunne, Robert Millman, Elizabeth Khuri (physicians); Maurice Bachrach (administrator); Leo Vono (vocational specialist); Frances Gearing, Herman Joseph (epidemiologists); Donal O'Brien, Manny Guerrero (lawyers); and a team of ex-addicts who must remain anonymous. Systematic studies were initiated with financial support from New York City's Health Research Council and Department of Hospitals with endorsement by civic leaders.

The work moved forward rapidly. Over the next ten years treatment programmes utilizing methadone were established in Beth Israel Medical Center and Bronx State Hospital, with other major hospitals of New York City serving as administrative and medical backup centres supporting a network of satellite clinics that served all of the city's boroughs. Physical examinations on admission and periodically thereafter defined the medical needs of all patients, and were established as a routine to detect any ill effects of the medication. None were found. A comprehensive, computerized data system was developed to record the progress and problems of every person admitted, with repeated analyses of urine for drugs to provide objective data on response to treatment. An independently appointed evaluation committee was empowered to inspect records, interview patients and publish independent reports, subject only to the requirement that the names of the patients be kept confidential. Professionals in the field of drug abuse were welcomed as visitors to the clinics, and a series of National Conferences on Methadone Treatment was inaugurated in 1968 to provide a forum for reporting experience in other cities.

The first decade culminated in the admission (during 1970-74) of over 20,000 heroin addicts into a diversified system of clinics in many hospitals of New York City, directed by Robert Newman and supported by the city's Health Services Administration. The public health impact of this major programme was reflected in statistics showing a significant reduction in arrests for drug related crimes and a reduction in reported cases of hepatitis (presumably due to a decrease in intravenous drug abuse).

Thus by the end of the first decade, after the small experimental beginnings in a metabolic ward, a successful model for large-scale treatment of heroin addicts was in place. Maintenance treatment had been proven to be medically safe, feasible to administer on a large scale and generally successful in rehabilitation of addicts. Needless to say, throughout this period the treatment had been under continuous attack by supporters of the old regime – the lockup and punish school of therapists – and by bureaucrats whose authority was threatened by the new programme. Complicating matters, the State of New York at the same time was funding a hugely expensive and unsuccessful lockup programme that had been advertized in political campaigns as a definitive answer to the addiction problem.

Opposition from vested interests did not block progress in developing the methadone programme (in fact it contributed to the unity of the staff), but we were surprised by the indifference of the medical profession and the failure of public health officials to provide strong support for expansion of a treatment that had proven successful. In the second decade, instead of expansion, the objectives of treatment were reversed by Federal

agencies and the authority of physicians was limited by these agencies on political and philosophical grounds: abstinence rather than rehabilitation was restored as the goal of treatment; doses were lowered to levels that were frequently inadequate; administrators became punitive and often contemptuous of the patients (now called “clients”); termination of maintenance was encouraged despite an 80% relapse rate. The punitive attitude of moralists hardened into regulatory law, subjecting clinics to an unprecedented degree of control over every detail of their operation. In New York, in 1976 at the peak of this folly, a survey revealed that methadone clinics were subject to regulation by 11 uncoordinated agencies of Federal, State, City and Community, and that a physician working in the clinic would need to spend 185% of his time in paperwork to provide the redundant reports and documentation required by these different agencies.

The quality of treatment deteriorated during this period. Underfunded, crowded, operating in poor quarters, prevented from moving to more adequate facilities by hostile communities, harassed by teams of inspectors who criticized their deficiencies without providing money or political support for improvement, with a negative image fuelled by disinformation in the media, the methadone clinics nevertheless survived, thanks to the dedication of their overworked staffs. While under this pressure methadone clinics were providing more than 90% of all the long-term rehabilitation services available to heroin addicts in New York City.

This turbulent phase has not ended, but the third decade brought a change in political attitude. The onset of the AIDS epidemic in the late 1970s alerted public health officials to the fact that needle-sharing addicts are a major vector in transmission of the deadly virus (as well as other blood-borne infections), and that AIDS patients, with impaired immunity, constitute a large susceptible population into which drug-resistant tuberculosis is spreading.

Even the opponents of maintenance treatment have been obliged to concede that no alternative treatment has sufficient capacity and proven efficacy to play a significant role in curbing transmission of the virus by addicts. Today there is a new generation of clinicians with knowledge of recent developments in neurophysiology. Younger physicians with more training in neurophysiology are prepared to recognize drug craving as a symptom of a neurochemical imbalance, and therefore to accept maintenance treatment as rational chemotherapy. The field of addiction medicine has emerged from the rigid dogma of descriptive psychiatry (“character defect”, “sociopathic personality”, etc.) into the modern world of neurophysiology. Methadone maintenance is part of this new field – indeed it might qualify as one of the founding members – but its role is transitional. In time, with enough effort and luck, the neurochemical disorders responsible for the pathological craving will be identified, and other medications for treatment of addictions will be developed that are simpler to use, and perhaps even curative.

We enter the fourth decade of maintenance treatment with new and difficult challenges but with more knowledge. The explosive spread of AIDS – a disease so far without effective immunization or treatment – has amplified the problem of drug abuse, and made effective treatment of addicts a critical priority. Needle-using addicts have become a threat to the health of the general population, first spreading infection among

themselves and subsequently to others by sexual activity and contamination of the blood supply. In effect, addiction makes AIDS a highly contagious disease.

The challenge for the immediate future is to make effective use of what we have learned about addictions in the past few decades. Of course, it would be easier if we had a vaccine or other medication that would eliminate the susceptibility of all potential addicts – not an impossible hope since only a minority of person become chronically addicted to narcotics or alcohol when exposed – and a definitive cure for established addiction is a dream worth pursuing, but as a practical matter we are confronted at present with serious public health problems requiring immediate responses. A person with responsibility for health of a community must work with the tools that are available.

They are considerable. If the lessons of the past are learned, large-scale programmes providing adequate doses of methadone, and social support as needed can rehabilitate heroin addicts. They do not need to be coercive since chronic heroin addiction is not pleasant, but they must be readily available and have outreach to alienated, homeless addicts. Although methadone has only a specific and limited effect, the therapeutic environment of a good clinic provides a favourable setting for treatment of complicating addictions and infections.

Termination of needle use by addicts reduces the transmission of AIDS. Social rehabilitation of addicts reduces crime and improves neighbourhoods, thus reducing the availability of addictive drugs in the area. Rehabilitated ex-addicts, having escaped the slavery of heroin addiction, can become highly motivated and effective agents of prevention in a community susceptible to adolescents.

This sounds straightforward, but the practical difficulties of developing large-scale treatment facilities should not be minimized. To be effective as a public health response, maintenance clinics must have a capacity that is comparable to the size of the addict population and yet continue to be as effective in rehabilitation as they were when small. Expansion of services will face prejudice, denial, hostility and indifference – but with informed medical leadership the nature of the addiction problem can be explained to politicians and the public. The process of developing an effective response to the many problems of addiction starts with discussion among specialists in meetings such as this, then expands to inform the general medical profession and the public.

I am reminded of a parallel situation in 1955 when the co-founder of Alcoholics Anonymous, Bill W., spoke on the occasion of the twentieth anniversary of the Fellowship and saluted the “Coming of Age of AA” . Like Bill on that occasion, I look to the future of the Methadone Maintenance Programme with confidence, knowing that it too, has “Come of Age” .

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Pharmacokinetics and Pharmacogenetics of Methadone: Clinical Relevance

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Summary

Recent data on the pharmacokinetics and pharmacogenetics of methadone, taking into account its enantiomers, have been collected. In particular, it has been demonstrated that isozymes belonging to the cytochrome P450 superfamily play a major role in the metabolism of methadone. During the past ten years, a large amount of information has been collected on this enzymatic system. In particular it is now well known that these isozymes can be inhibited or induced by specific compounds. Marked variability in the activities of these isozymes has been demonstrated; that variability is both genetically and environmentally controlled. These data allow us to explain and, possibly, avoid the majority of metabolic interactions involving methadone, and to understand the interindividual variability of methadone pharmacokinetics. This latter point is of major clinical relevance, and stresses the importance of individualizing methadone treatment.

Key words: Methadone - Pharmacokinetics - Pharmacogenetics
- Clinical Implications

Introduction

Methadone is a synthetic analgesic drug used as a maintenance treatment for opioid addicts and in the treatment of pain. The effectiveness of orally delivered methadone for opiate dependence has been demonstrated in many studies, i.e. it reduces illicit drug use, risk of HIV infection, mortality, crime, and unemployment (13, 21, 28), provided it is administered at an adequate dosage. As with morphine, methadone's mechanism of action is mediated by the activation of the opioid receptors (principally of the μ type).

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However, unlike morphine, methadone has some special features which make it an effective drug for the maintenance treatment of opioid dependence. Firstly, methadone taken orally generally has a high bioavailability when (around 80%, compared with 30% for morphine (59, 70)), this allows it to be administered orally. Secondly, the long elimination half-life of methadone (mean values 28 hours, compared with 2 hours for morphine (59, 70)) allows a single daily administration. Thirdly, it undergoes extended, reversible absorption into tissues (in particular, the liver (20)) and steady-state concentrations can be obtained after multiple administrations. It should, however, be noted that large interindividual variations in bioavailability and elimination half-life have been measured (70): this important point will be discussed later on in this paper.

Methadone is a racemic drug, i.e. it is a 50:50 mixture of two enantiomers called (R)- or (l)- and (S)- or (d)-methadone. (R)-methadone accounts for the majority, if not the totality, of the opioid effect of racemic methadone (29, 46). During the past few years, new data on the pharmacokinetics and pharmacogenetics (i.e. the study of the genetically determined variations in drug response) of methadone, taking account of its enantiomers, have been collected. These data provide a better understanding of the biochemical mechanisms involved in methadone metabolism, the aim being to explain and, if possible, avoid most of the metabolic interactions involving methadone, by more effectively taking the individual needs of the patient into account.

Stereospecificity

Due to its chemical structure, methadone exists in two enantiomeric forms, i.e. two forms with the same chemical composition but with two different spatial arrangements. Methadone is marketed in almost all countries as a racemic mixture, i.e. a 50:50 mixture of two enantiomers called (R)- or levo- or l-methadone and (S)- or dextro- or d-methadone. The stereospecificity of most opiates to μ receptors is well known, but for methadone the difference between the two isomers is less dramatic, probably owing to a greater conformational mobility of the molecule (57). Nevertheless, *in vitro* binding experiments have shown that the necessary concentration of (R)-MET to inhibit by 50% the binding of [3H]-naloxone to whole rat brain homogenate is 10 times less than that of (S)-MET (57). In humans, (R)-MET is about 50 times as analgesically potent as the (S)-form (62).

It has also been shown that the effects of 7.5 mg per os of (S)-MET did not significantly differ from the placebo response involving respiratory and pupillary effects, while 7.5 mg of (R)-MET and 15 mg of (R,S)-MET induced intense and sustained respiratory depression and miosis (55). It should be mentioned that (S)-MET administered at high doses (650 mg to 1000 mg/day) also induces morphine-like subjective effects, partially suppresses symptoms of abstinence from morphine, and creates a mild degree of physical dependence (29). Although morphine-like effects were observed at such high doses, patients consistently denied that they experienced satisfying subjective opiate-like sensations and disliked the effects (29). Lastly, in another study, Dole and collaborators switched the daily dose of (R,S)-methadone in 6 patients to (S)-methadone. To the patients this switch was blind, but it was followed by

the gradual appearance of abstinence symptoms (20). Altogether, these results show that (R)-MET accounted for the large majority, if not all, of the opioid effects attributable to racemic methadone.

Pharmacokinetics

Methadone is rapidly absorbed after an oral administration, the maximum plasma concentration being reached after around 3 hours (51). Like the majority of basic drugs, methadone is strongly bound to plasma proteins, in particular to alpha₁-acid glycoprotein (25). There is a slight binding difference between the two enantiomers, and a mean free fraction of 10% and 14% was found for (S)- and for (R)-methadone, respectively (25). Interestingly, there is a genetic polymorphism of alpha₁-acid glycoprotein in the population. Within each individual, alpha₁-acid glycoprotein consists of two major forms (ORM1 and ORM2), encoded by two separate genes (67). There are two major variants of the ORM1 locus (ORM1 F1 and ORM1 S), while the ORM2 locus is mainly monomorphic (ORM2 A) (24). We have demonstrated that methadone significantly binds to the so-called ORM2 A variant but not to the ORM1 F variant (25). Theoretically, the binding of drugs to plasma proteins is an important pharmacokinetic parameter, as only free drugs are able to reach their site of action (i.e. the central nervous system, when considering psychotropic drugs); in addition, this binding may influence the clearance of these drugs by the liver and kidneys. However, it remains to be demonstrated whether the pharmacogenetics of methadone binding to alpha₁-acid glycoprotein does have any significant clinical implications.

A mean value of 28 hours has been found for methadone elimination half-life, with a very large interindividual range (from 9 to 47 hours in one study (51), but values as low as 4 hours and as high as 91 hours have been reported (70)). (R)-methadone was found to have a significantly longer elimination half-life than (S)-methadone (38 versus 29 hours, respectively) (45). Following the chronic administration of methadone, a shortening of methadone half-life has been measured (from 55 hours to 22 hours) due to an induction of methadone metabolism (69) (see also the paragraph on cytochrome P4503A4). The rate of clearance of methadone from the body has been reported to vary by a factor of almost 100! (from 23 to 2100 ml/min) (70), and significant differences in the mean clearance between the two enantiomers are seen (158 ml/min versus 129 ml/min for (R)- and (S)-methadone, respectively (45)). The apparent volumes of distribution were found to be relatively variable, with values ranging from 2.1 to 5.6 l/kg (mean values: 3.9 l/kg) (51), with larger values for (R)- than for (S)-methadone (45).

Methadone is extensively metabolised in the body, mainly at the level of the liver, and the elimination rate of methadone is mostly attributable to metabolic clearance (54). Bioavailabilities were found to range from 65 to 100% (45) and from 41 to 99% (51). No statistically significant differences in bioavailabilities were found between the two enantiomers (45). Methadone's main metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) is inactive: it is formed by N-demethylation and subsequent spontaneous cyclisation (65). Studies by us and by other groups have demonstrated the involvement of enzymes from the cytochrome P450 superfamily in the metabolism of

methadone, which is of major importance for the understanding of the clinical pharmacology of methadone.

Cytochrome P450

Cytochrome P450 enzymes are heme-containing proteins that are responsible for the oxidative metabolism of many endogenous substances as well as foreign chemicals. It is believed that the ancestral gene of cytochrome P450 already existed 3.5 billion years ago, i.e. before the divergence of procaryotes and eukaryotes. However, the number of new isozymes of this superfamily within eukaryotes has considerably increased during the past 800 million years, and this is considered to be the consequence of what several authors have called «plant-animal warfare » (31). As animals began to diverge from plants and to ingest them, plants developed toxins which protected them. In their turn, animals with new isoforms of cytochromes P450 were favoured by being able to metabolize and detoxify those substances. It should be mentioned that many drugs presently on the market are either extracted from plants or are derivatives of plant products. The classification of cytochrome P450 enzymes is based on gene similarity (cytochromes within families have more than 40% homology in their protein sequence) (19). CYP1, CYP2 and CYP3 are the major families of the CYP system involved in drug metabolism. Studies performed during the past few years have shown that CYP450 isoforms belonging to each of these major families (namely CYP3A4 and CYP2D6, and possibly also, but to a smaller extent, CYP1A2) are involved in methadone metabolism. The involvement of these CYP enzymes explains the majority of cases of metabolic interaction, or enzymatic induction, with methadone, which have been described in the literature. Furthermore, the activities of these CYP enzymes are genetically and environmentally determined, leading to large interindividual variations. Taking account of this point is thus of major importance, as it explains the large interindividual variations in methadone pharmacokinetics. It most probably also explains the so-called methadone rapid metabolizers, whose typical complaints are « methadone does not support me ».

Cytochrome P4502D6

A genetic polymorphism has been described for CYP2D6: this enzyme is absent in about 5 to 10 % of the European population (16). As a result, these people are unable to metabolize drugs which are biotransformed by this enzyme, and are, therefore, called poor metabolizers, while those who have CYP2D6 activity are called extensive metabolizers. There are currently more than 80 drugs whose metabolism partly or mainly depends on this enzyme (some of these drugs are listed in Table 1; for a more complete list see (47)). CYP2D6 is not inducible, but its activity can be strongly inhibited by several drugs (see Table 1) (16, 34). Determination of poor or extensive metabolizer status can be performed by phenotyping or by genotyping. The phenotyping test consists of the oral intake of a test drug (e.g. 25 mg dextromethorphan, an over-the-counter antitussive drug), the 8-hour urine is collected, and the parent drug/metabolite (i.e. dextromethorphan/dextrorphan) ratio is determined (6). One can also genotype

Table 1. Substates, inhibitors and some features of cytochrome P4502D6

| | |
|---|--|
| Substrates: | Antidepressants: mianserine, nortriptyline, paroxetine, venlafaxine Neuroleptics: levomepromazine, perphenazine, risperidone, thioridazine Antiarrhythmics: encainide, flecainide, propafenone, sparteine Beta-blockers: bufuralol, metoprolol, propranolol, timolol Anti-hypertensives: debrisoquine, indoramine, guanoxan Antianginal: perhexiline Antitussives: dextromethorphan Analgesics: codeine |
| Inhibitors | quinidine, fluoxetine, paroxetine, levomepromazine |
| Prototype substrate | debrisoquine, sparteine, dextromethorphan |
| Inducibility | No |
| Genetic polymorphism | Yes 5 to 10 % of poor metabolizers in Europe 1 to 10 % of ultrarapid metabolizers in Europe |
| Interindividual variability of activity | More than 1 to 100 |

subjects by directly analysing the main mutations leading to the loss of CYP2D6 expression in the DNA extracted from leucocytes (36).

Several studies strongly suggest that CYP2D6 is involved in the methadone metabolism. We studied seven addicts treated with racemic methadone who were comedicated with fluoxetine, an antidepressant and a strong CYP2D6 inhibitor. The plasma concentrations of (R)-methadone (but not (S)-methadone) were increased by the addition of fluoxetine (23). This suggests that CYP2D6 is involved in the methadone metabolism, with a stereoselectivity towards the (R)-enantiomer. This is in agreement with the results of another study showing a decreased partial metabolic clearance of (R)-methadone in four poor as compared with four extensive metabolizers (73). Amitriptyline, a CYP2D6 substrate, has also been found to decrease methadone clearance (58), and it has also been shown that methadone increases concentrations of desipramine (50), a typical CYP2D6 substrate (16), probably by an inhibition of CYP2D6 activity. This is confirmed by the results of another study showing significantly lower 2-hydroxylation of desipramine, which is mediated by CYP2D6, in a group of 11 patients receiving methadone, compared with another group of 61 patients not maintained on methadone (44). The inhibition of CYP2D6 by methadone was confirmed by two studies showing that methadone is a potent inhibitor of codeine O-demethylation (52) and dextromethorphan O-demethylation (72), 2 enzymatic pathways involving mainly, if not exclusively, CYP2D6. It should be mentioned that in an in vitro study with human liver microsomes, a minor involvement of CYP2D6 in the methadone metabolism has been found (40). However, this study used (R,S)-methadone, but not the enantiomers separately, and, as shown above, CYP2D6 seems to exhibit a stereoselectivity towards the (R)-enantiomer.

Several studies have previously shown that a CYP2D6 poor metabolizer status, or

the administration of CYP2D6 inhibitory drugs, may result in increased concentrations of drugs metabolized by this enzyme, and in the occurrence of important side-effects (27). In most cases, this should not result in a dramatic increase in methadone concentrations, as other CYP enzymes are also involved in its metabolism. To our knowledge, no cases of toxicity resulting either from a genetically inherited inability to metabolize methadone (i.e. in a CYP2D6 poor metabolizer), or from the inhibition of the CYP2D6-mediated methadone metabolism by a comedication, have been described in patients undergoing methadone-maintenance treatment, i.e. in subjects who tolerate opioid effects. Such cases cannot, however, be excluded, especially when subjects start methadone treatment, i.e. subjects who may not tolerate opioid effects, or patients under maintenance treatment who receive comedications which simultaneously block all CYP enzymes.

Very recent studies show that a proportion of the population has a very high CYP2D6 activity due to the duplication and/or multiduplication of the CYP2D6 gene, resulting in increased CYP2D6 activity (41). The proportion of these so-called ultrarapid metabolizers is variable, being around 1.5% in Germany (33), 7 % in Spain (1) and as high as 29% in Ethiopia (2). Determination of an ultrarapid metabolizer status can be performed by genotyping, i.e. by determining the presence of CYP2D6 gene duplication or multiduplication in the DNA extracted from the leucocytes (41). Our group, and others, have already demonstrated that a very rapid metabolism of drugs, such as clozapine (10), clomipramine (5) and nortriptyline (12), may lead to therapeutic failure. A study conducted by our group on the importance of the CYP2D6 ultrarapid metabolizer status on the outcome of a methadone maintenance treatment is nearly complete, and the final results will be ready within the next few months.

Cytochrome P4501A2

Cytochrome P4501A2 is involved in the metabolism of several drugs such as clozapine, olanzapine and tacrine (see Table 2). No genetic polymorphism has been described for CYP1A2, but there is a more than 40-fold variability in its activity (61). Several phenotyping tests can be used to measure CYP1A2 activity, but probably the most widely used is the caffeine test, which requires the determination of urine or plasma metabolic ratios after the oral administration of various doses of caffeine (around 200 mg, or approximately two cups of coffee) (11). In addition, CYP1A2 activity can be induced by compounds present in smoke. It can also be inhibited by several drugs (see Table 2).

We studied six addicts treated with racemic methadone who were comedicated with fluvoxamine, a strong CYP1A2 inhibitor (14, 23). The plasma concentrations of both (R)- and (S)-methadone were raised by fluvoxamine, which suggests that CYP1A2 is involved in the metabolism of both enantiomers. Interestingly, among the six patients who received fluvoxamine, one clear and one possible case of withdrawal symptoms were reported when fluvoxamine was stopped. This was most probably due to a relatively rapid decrease in fluvoxamine concentration, resulting in a decrease of

Table 2. Substrates, inhibitors and some features of cytochrome P4501A2

| | |
|---|---|
| Substrates: | acetaminophen, caffeine, clomipramine, clozapine, imipramine, olanzapine, tacrine, theophylline |
| Inhibitors | fluvoxamine, furafylline, quinolones |
| Prototype substrate | caffeine |
| Inducibility | Yes |
| Inducing agents | omeprazole, smoking, polycyclic aromatic hydrocarbons, broccoli |
| Genetic polymorphism | No |
| Interindividual variability of activity | About 1 to 40 |

methadone metabolism inhibition and a decrease in methadone concentrations. On the other hand, such cases were not found in the group of patients receiving fluoxetine: this is most likely due to the very long half-life of fluoxetine (1-2 day) and of its metabolite, norfluoxetine (7-14 days), resulting in a very slow decrease in their concentrations when interrupting administration of this drug. We have also observed strong withdrawal symptoms in patients receiving methadone when they stopped taking moclobemide (J.J. Déglon, unpublished observations), an antidepressant belonging to the group of selective inhibitors of the monoamine oxidase. This is very probably due to the fact that moclobemide is an inhibitor of CYP2D6 and CYP1A2 (32), and that it has a short elimination half-life (1 to 4 hours).

The involvement of CYP1A2 in the methadone metabolism has also been suggested in a study showing a higher (R)- and (S)-methadone plasma clearance in four smokers as compared with four non-smokers (73) (as mentioned above, CYP1A2 is induced by smoke). However, in an *in vitro* study using human liver microsomes, CYP1A2 did not seem to be involved in the methadone metabolism. No explanations can at present be given for this discrepancy.

Cytochrome P4503A4

CYP3A4 is the most abundant CYP form in the liver, but this enzyme is also expressed in the gut. It is involved in the metabolism of a large number of drugs, including benzodiazepines such as alprazolam, antidepressants such as sertraline, calcium channel blockers such as nifedipine, or immunosuppressants such as cyclosporine (Table 3, see also (43)). No genetic polymorphism has been described for CYP3A4, but a marked interindividual variability in the expression of this enzyme has been noted (up to 30-fold in liver and up to 11-fold in gut) (43). Several phenotyping tests have been proposed for the determination of CYP3A4 activity, but probably one of the most accurate of these relies on the oral administration of midazolam and on the metabolic ratio determination in blood (18).

CYP3A4 is inducible, and this is the likeliest explanation for the induction of the methadone metabolism at the beginning of a maintenance treatment. Thus, a decrease in steady-state plasma levels of MET is observed during maintenance treatment with racemic methadone (53, 69), which could require modification of the dose. This may

Table 3. Substates, inhibitors and some features of cytochrome P4503A4

| | |
|---|--|
| Substrates: | Antiarrhythmics: amiodarone, disopyramide, lidocaine, quinidine Anticonvulsants: carbamazepine, ethosuximide Antidepressants: amitriptyline, imipramine, sertraline Benzodiazepines: alprazolam, clonazepam, diazepam, midazolam Calcium channel blockers: felodipine, nicardipine, nifedipine, verapamil Macrolide antibiotics: clarithromycin, erythromycin, triacetyloleandomycin Steroids: androstendione, cortisol, dexamethasone, progesterone, testosterone |
| Inhibitors | erythromycin, itraconazole, ketoconazole, grapefruit juice (furanocoumarin, bergamottin) |
| Prototype substrate | midazolam |
| Inducibility | Yes |
| Inducing agents | Anticonvulsants: carbamazepine, phenobarbital, phenytoin Steroids: dexamethasone, progesterone Others: benzoflavone, rifampicin, naphthoflavone, phenylbutazone, sulfadimidine, sulfipyrazone |
| Genetic polymorphism | No |
| Interindividual variability of activity | About 1 to 30 (liver), about 1 to 11 (gut) |

party be due to an increase in MET demethylation (3, 69), as shown by higher values for the ratios between the main metabolite, EDDP, and methadone (3, 69). In this case, a substrate (methadone) induces its own metabolism - a phenomenon that has been shown for other drugs (for example, carbamazepine is a strong CYP3A4 inducer, and it induces its own metabolism, which is mediated by CYP3A4 (43)). The inducibility of CYP3A4 probably also explains the decrease in mean (R)-methadone concentrations observed by us in a group of 22 patients in Germany, whose (R)-methadone dose was replaced by a double dose of (R,S)-methadone (26). Up to the mid-nineties, Germany was one of the few countries in the world where methadone was marketed as the pure (R)-enantiomer. Due to the higher costs of (R)-methadone compared with the racemic form, (R)-methadone has progressively been replaced by (R,S)-methadone (e.g. 50 mg (R)-methadone were replaced by 100 mg (R,S)-methadone). This change, however, was not welcome by addicts, and a journal printed for and by addicts reported some cases of withdrawal symptoms after the switch. Although the mean decrease in (R)-methadone serum concentration/dose ratios measured in our study was of small magnitude (15%) (26), this may explain the withdrawal symptoms reported by some patients.

Several substances are strong CYP3A4 inducers; rifampicine is an example. The administration of rifampicine for the treatment of pulmonary tuberculosis in addicted

patients led to withdrawal symptoms in a large proportion (as much as 70%) of patients; a third of these were considered severe (15). In this case, the methadone dose should be increased, and the dosage should itself, if necessary, be split until these withdrawal symptoms disappear completely, or until methadone blood concentrations return to their pre-rifampicine level. This approach, however, is not possible in many centres due to their dose policy. Drugs other than rifampicine can be used: it seems that rifabutine is less likely to influence methadone kinetics, although an increase in methadone dose seems to be necessary in some patients (15). Other drugs, such as phenobarbital, phenytoin and carbamazepine, are classic CYP3A4 inducers, and can induce withdrawal symptoms by enhancing the methadone metabolism. For the treatment of epilepsy, valproic acid can be used instead of the antiepileptics just mentioned, as it does not possess inducing properties (on the other hand, it is not clear whether this drug has any inhibitory activity). Some steroids, such as dexamethasone, a synthetic glucocorticoid, or spironolactone, a semi-synthetic steroid which is an antagonist of aldosterone and is used as a diuretic, are CYP3A4 inducers. This explains the results of a study showing that steroids and spironolactone increase methadone clearance (58). It has recently been shown that the addition of ritonavir and nelfinavir, two HIV protease inhibitors, when patients were on steady-state therapy with methadone and nucleosides analogues, led to a decrease of methadone steady-state concentrations by 40 to 50% (7). On the other hand, indinavir or saquinavir did not affect methadone concentrations (7). Although the exact mechanism by which ritonavir and nelfinavir decrease methadone concentrations is not known, an induction of CYP3A4 (and, possibly, of other enzymes) by these drugs is probable, considering that both substances are CYP3A4 substrates (4), and that a 30% reduction in the area under the curve for ritonavir has been shown after three to four weeks of continued therapy with this drug, suggesting enzyme induction following initial enzyme inhibition (4).

Several drugs, such as ketoconazole or erythromycin, are known to be strong CYP3A4 inhibitors (43) (see Table 3). Even if, to our knowledge, no cases of metabolic inhibition involving these substances have been described with methadone (ketoconazole, an antimycotic drug, is also administered per os), such an interaction can be expected. Diazepam, a CYP3A4 substrate (43), is an *in vitro* inhibitor of methadone N-demethylation (63). Methadone concentrations increased when coadministered with diazepam and nifedipine (7), the latter drug is also a CYP3A4 substrate (43). One last point that should be mentioned is the probable inhibition of methadone by grapefruit juice. Now, it is very well known that grapefruit juice, through the inhibitory activity of some of its components, such as furanocoumarin and/or bergamottin (30, 35), strongly inhibits CYP3A4 at the level of the intestines. Thus, several studies have shown a strong reduction in the clearance of several benzodiazepines, such as triazolam (39), whose metabolism is mediated by this isozyme. These changes in the pharmacokinetic parameters resulted in increased pharmacodynamic effects, such as increased drowsiness (39). One case of death was reported in the literature, involving grapefruit juice and terfenadine (an antihistaminic drug) attributed to a probable inhibition of the terfenadine metabolism by grapefruit juice, resulting in fatal arrhythmias caused by an increase in

terfenadine concentrations (64). We therefore raise the question whether some patients on methadone maintenance treatment (in particular, in centres with a low-dose policy) may be tempted to drink grapefruit juice to increase their methadone blood levels. Such attempts, without any supervision, should be strongly discouraged, as there are no data about the increase of methadone that can be expected (published data on other drugs suggest that the increase varies between individuals, probably depending on the amount of intestine CYP3A4 (60)).

Interindividual variability of Methadone Metabolism and Methadone Dose

Since the early work of Dole and Nyswander, who recommended a methadone dose of 80 to 120 mg/day (21), other studies have consistently shown that methadone must be provided at adequate dosages. Thus, a clear inverse correlation has been found between increasing dose and the risk of interrupting treatment (17), and there is general agreement on the fact that an insufficient dose of methadone is a major cause of therapeutic failure. Variable concentrations of (R,S)-methadone are measured for a given dose of racemic methadone (37, 66). Using an enantioselective method, in a study on 50 patients, we recently found that, for a given dose of racemic methadone corrected for body weight, concentrations of (R)-methadone can vary 1- to 7-fold (22). An even larger range was found in another study comprising a larger number of subjects (Eap et al., submitted). Several studies have aimed to find a minimum methadone blood level which can reliably support effective methadone maintenance therapy (8, 9, 37, 38, 42, 48, 66, 68). In some studies, no such threshold was found (8, 38, 68), while a range of values, between 50 to 600 ng/ml of (R,S)-methadone, was found in other studies (9, 20, 37, 42, 48, 71). A concentration of 400 ng/ml is now often considered to be necessary in providing stabilized maintenance (49, 56); it is used as a reference value when performing the therapeutic drug monitoring of methadone. To our knowledge, however, no study so far has clearly demonstrated the existence of such a threshold.

As there is marked interindividual variability in the (R)/(S) ratios of methadone measured in blood (range 0.63-2.4) (26), this suggests that measuring methadone enantiomers could be more reliable than determining total concentrations, when one tries to correlate methadone blood levels and therapeutic outcome. In one such study with 180 patients, we found a significant association of an (R)-methadone plasma concentration with therapeutic response, as determined by the absence of illicit opiates in the urine samples collected during a 2-month period prior to blood sampling (Eap et al., submitted). This supports the use of the therapeutic monitoring of (R)-methadone, when there is a continued intake of illicit drugs. Interestingly, to obtain any (R)-methadone concentrations, theoretical doses of racemic methadone could vary within a 1- to 17-fold range!

Conclusions

Recent data on the pharmacokinetics and pharmacogenetics of methadone will, hopefully, allow a better prescription of this drug. Most metabolic interactions involving methadone can be explained, as well as the interindividual variability of methadone pharmacokinetics – a variability which is genetically and environmentally controlled. This point is of major clinical relevance, considering the low-dose policy implemented in many centres; it stresses the need to individualize methadone doses, by taking account of the interindividual variability of the methadone metabolism – not to mention possible variability at the level of the receptors.

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Integrating Methadone Treatment in the Slovenian Public Health System

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Summary

In this article on the quality of service in the methadone maintenance programme the authors wished to determine whether the establishment of the network of centres for the prevention and treatment of dependence on illegal drugs was made possible higher quality professional services in carrying out the methadone maintenance programme, greater effectiveness in the programme and greater satisfaction on the part of those involved.

According to new directives originating in the Spring of 1995, the Methadone Maintenance Program is operating as one of the services of the eleven Centres for the Prevention and Treatment of Drug Dependency in the Republic of Slovenia. In 1995 the authors collected data on the quality of the programme by using a questionnaire, and they repeated this inquiry in April 1997.

The 1995 questionnaire was completed by 267 patients on the maintenance programme (51% of all participants in the programme), and the 1997 questionnaire was answered by 729 patients (71.8% of all participants in the programme).

The authors interpreted the results of the survey on the basis of five criteria.

Key words: Methadone maintenance programme - drug dependence prevention and treatment centre - network of centers - integral treatment of addicts - satisfaction of person on maintenance with the programme

Introduction

The methadone maintenance programme provides basic treatment, and is supported by the harm reduction programmes included in current drug policy, which aims to protect the users of illegal drugs by increasing the number of users who make contact with the medical service. These users remain on treatment or join higher threshold programmes.

It was therefore very helpful to assess the level of satisfaction amongst those enrolled in the programme, and use the results to further increase acceptability for its users.

National guidelines for the management of drug addicts, including the strategy for methadone maintenance harm reduction have been adopted by the Health Council at the Ministry of Health in 1994, and methadone maintenance programme policies were confirmed at a consensus Symposium on Methadone Maintenance, with participants from the Ministry of Health, the Ministry of Internal Affairs, the Ministry of Labour, Family and Social Affairs and the Ministry of Justice.

With the opening of the Centre for Treatment of Drug Addiction at the Mental Health Centre in Ljubljana, and considering the fact that some of the specialist outpatient clinics for drug dependence treatment were not operating very well, the need has arisen to establish a more efficient network of drug prevention and rehabilitation centres in Slovenia which will provide treatment, and will be computer-linked and financially supported by the Health Insurance Institute of Slovenia.

Eleven regional Centres for the Prevention and Treatment of Drug Addictions have been set up, and the training of professional staff at the Centres has been organized.

a) Medical basis

The recommendations adopted for the treatment of drug addiction comprised instructions for general practitioners, for emergency procedures, the hospitalization of addicts for diseases connected or unconnected with drug dependence, for psychiatrists, territorial defense doctors and those dealing with prisoners, and for other situations in which medical personnel come across unauthorized drug taking.

The recommendations give instructions on the identification of drug use, on diagnostic and therapeutic methods to be used in hospitals and outpatient clinics and the recommendations for the methadone maintenance programme. Support is provided not only for opiate addicts, but also for the abusers of sedatives, hypnotics, stimulants, hallucinogens etc., whether they experiment with or are addicted to them.

The recommendations also provide guidance on the abstinence syndrome, the application of medicaments, the stabilization of opiate addicts, outpatient treatment, detoxification and a detailed description of the methadone maintenance program.

b) Network of Centres for prevention and treatment of drug addiction

A network of six Centres of type "A" and five Centres of type "B" has been confirmed by the Health Council.

The main difference between the two Centres is, that in the Centre of type "A" criteria for the application of the methadone maintenance programme are being drawn up, and the Centres also supervise the methadone maintenance programme.

The drug prevention and rehabilitation centres provide:

- counselling services for addicts, relatives and educators;
- individual, group and family therapy;
- preparation for hospital treatment;
- aid towards rehabilitation and social reintegration;

- consultations for health and social services;
- determination, on the basis of case history, clinical examination, laborator tests and welfare service reports, of criteria of the methadone maintenance program;
- supervision of the methadone maintenance programme;
- practical implementation of methadone maintenance programme;
- community-health nursing services;
- linkage with therapeutic and self-help groups;
- research work.

In view of the complex nature of drug dependence treatment, the normal operation of a drug prevention and rehabilitation centre requires a multidisciplinary team of specialists including: a general medicine or social medicine specialist, a college-graduate nurse, a consulting or permanently employed psychiatrist, a psychologist, a social worker, a laboratory technician, and an administrative worker.

c) Methadone maintenance programme

The final decision on whether to enrol an addict on the methadone programme is made by the programme manager after consultation with the team.

The minimum requirements for placing an addict on the methadone maintenance programme (MMP) are:

- opiate addiction lasting at least one year and current physical dependence;
- previous detoxification attempts;
- written consent for inclusion on the MMP;
- minimum age of 18 years;
- permanent residence in the region where a drug prevention and rehabilitation centre is located;
- addict's own choice of his or her doctor;
- health insurance.

The addict must meet with her or his counsellor (chief consultant) at least once a week and/or receive one of the forms of psychosociotherapy.

Methadone dispensing units are outpatient clinics with a general practitioner or pharmacies. They need not be situated within Centres for drug prevention or the treatment of drug addicts.

Methadone may only be prescribed by the addict's chosen doctor who receives the corresponding license from a Centre for the Prevention and Treatment of Drug Addiction after completing an educational programme organized by the Ministry of Health.

Other doctors may only prescribe methadone to the addict in the absence of his doctor and in agreement with him.

The addict's doctor may authorize a doctor at a drug prevention and rehabilitation centre, or his colleague at the community health centre, to prescribe and dispense methadone to the addict and to apply other necessary therapeutic measures if that arrangement is more effective for the addict on the programme or for the organization of work.

Methadone is administered in the form of a solution mixed with fruit juice, and is taken daily in the presence of a nurse, preferably a graduate from nursing college. The addict may take methadone at home only over weekends and during national holidays, but after three months this is permitted for two days if he or she is not using any illegal drug; after the next three months it is allowed for three days, and after the next three months for a whole week.

The formation of the network of Centres for the Prevention and Treatment of Drug Addiction is considered a significant advance in the inclusion of dependent persons in the assistance programmes.

The evaluation of the methadone maintenance programme was a study whose aim was to establish whether the formation of the basic network of centres facilitated a more rational implementation of the methadone support programme, and to discover the level of satisfaction among participants in the programme.

Methods

In 1995 the authors collected data on the quality of the programme using a questionnaire; this inquiry was repeated in April 1997.

Criteria for more efficient treatment included:

- more people making contact with the medical service;
- non-use of other drugs by patients;
- participation of patients in a psychosociotherapeutic programme;
- cessation of sales of the drug;
- cessation of abuse of methadone;
- motivation for detoxification;
- the patient should be feeling better and more socialized, and should have a job.

Results and discussion

The 1995 questionnaire was completed by 267 patients on the maintenance programme (51% of all participants in the programme), while the 1997 questionnaire was completed by 729 clients (71.8% of all participants in the programme).

Among those included in the programme the number of male participants increased from 77.7% to 80.0%. There was also an increase in the number of young people aged up to 20 years included in the programme – from 16.4% to 21%, and a decrease in the percentage of those between 30 and 40 years of age – from 19.3% to 16.4%. A slight change in the educational level of the participants was also noted.

The number of participants who were regularly employed increased from 21.8% to 28%, while the number of those who worked part time decreased from 34.2% to 25.5%.

The average age of the clients when first taking drugs increased from 16.6 to 17.3 years. There was also a rise in the number of patients who had started taking drugs at the age of 18.

The average interval between the first use of an illegal drug (in 87% of all cases, marihuana) by the participants in the maintenance programme and the use of heroin fell from 4.4 years to 3.9 years.

Previously patients used heroin for an average of 3.9 years before beginning the methadone maintenance programme, while the current average is 3.0 years. The proportion of those who would like to stop using illegal drugs immediately rose from 22.8% to 48.6%.

In the first phase the structured implementation of the programme met the needs of 40% of the clients. That number has now grown to 70%. In addition, the programme appeared as useful and beneficial to 86.5% of all patients in 1995, and to 90.7% in 1997.

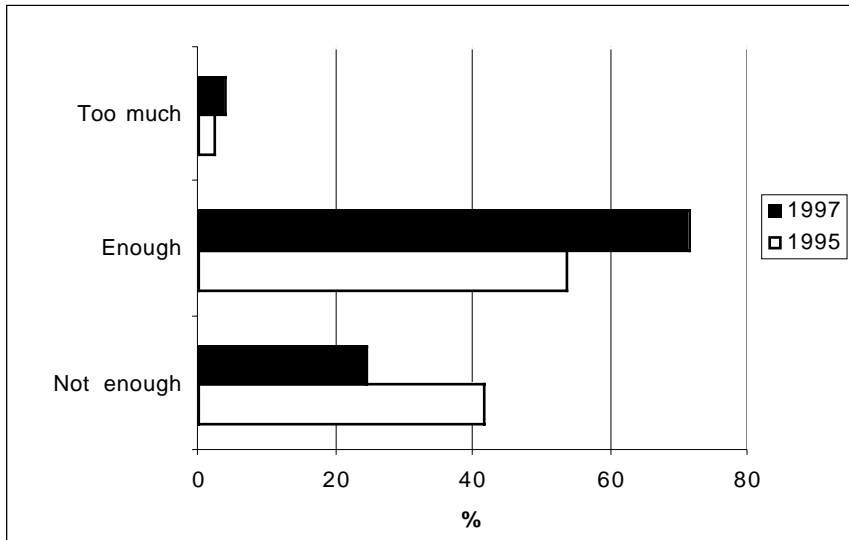


Figure 1: Amount of psychosocial therapy received

Conclusions

A low public self-image in the eyes of patients and their relatives, and also of many therapists contributing to the methadone maintenance programme, together with a lack of sufficient information, led the majority of patients taking part in the methadone maintenance programme in Slovenia to request a low or unduly low dose. Half of them regularly take heroin at least once a month, and another fourth occasionally. 75% of them also drink alcohol (20% regularly), and 26% occasionally take cocaine. But three-fourths are satisfied with the dose of methadone they take, and report satisfaction because they are able to influence the dose.

In 28% of these cases, taking heroin leads to overdoses that are, fortunately, non-fatal; only 4% involve fatal doses. The majority of them continue to share the injecting equipment. There is, therefore, no reduction in risk behavior.

Psychological counselling, and the education of such patients to become therapists, by teaching them counselling skills, can normalize the use of methadone as a medication.

In these cases urine tests and the drinking of methadone solution under the supervision of a therapist should only be necessary at the beginning of the programme.

However, with stable patients it is possible to make the transition to a tablet prescribed by the treating physician. This is a very important step in restoring the status of the patient, with the aim social cohesion.

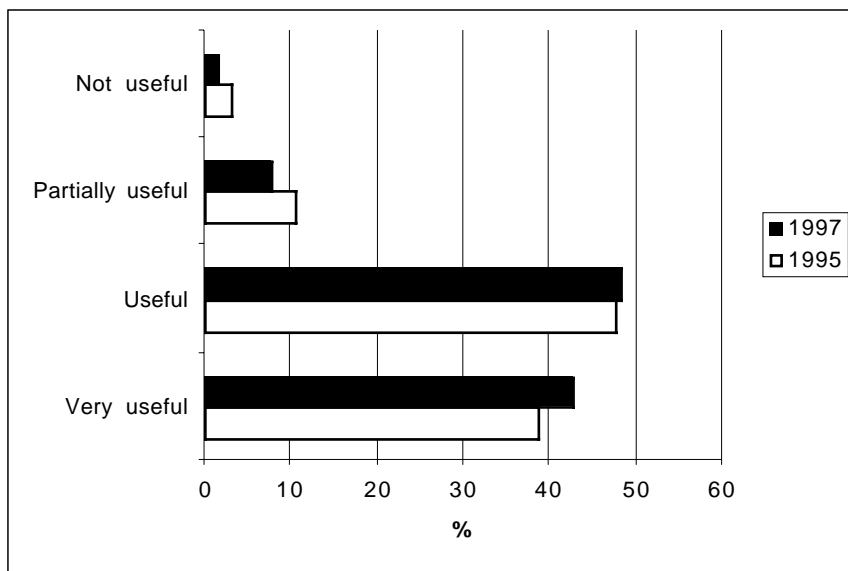


Figure 2: Opinion regarding usefulness of the methadone maintenance program

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Treatment of Opiate Dependency: a Comment

Peter Vossenber

TO THE EDITOR:

It would seem logical that comprehensive treatment, that addresses all aspects of substance dependence, would be standard treatment. Much treatment for medical disorders is based on research and experience. If, somewhere in Europe, you have hypertension, you will probably get (more or less) the same treatment, with an adequate dosage of medication. If you are unfortunate enough to be dependent on, say, heroin, the treatment given, and, indeed, the diagnosis, will differ between countries, even between cities. Even though research shows that comprehensive treatment – which, in my opinion, includes everything from proper diagnosis to relapse prevention – works, it is still under discussion and, in some cases, under attack. This journal may help, not only to spread scientific information, but also to strengthen cooperation and, hopefully, remove some of the arbitrary differences in treatment.

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Methadone as a Mood Stabilizer

Pier Paolo Pani¹, Alessandro Agus¹, Gian Luigi Gessa²

TO THE EDITOR: The positive effect of opioid agonists in psychotic disorders has repeatedly been hypothesized. Methadone has been noted as interfering positively with depressive affects and psychotic rage (3); buprenorphine has been considered for its antidepressant activity (2).

We report a case in which methadone seems to have a role in the treatment of a bipolar mood disorder.

Mr. A was admitted to a methadone maintenance treatment program (MMTP) at age 26, after three years of heroin addiction. Upon intake he exhibited major depression (according with DSM-III-R), with anxiety, guilt and suicidal thinking, which subsided within 10 days of treatment with methadone (50 mg/day). The MMTP, lasting three years, was interrupted because of six months' incarceration for old crimes. Mr. A was readmitted to a MMTP two months after release, relating his heroin-relapse to a new depressive episode begun while in prison. Major depression was again ascertained, subsiding only with methadone treatment (40 mg/day).

After four years of heroin-free MMTP (morphinuria-results confirmed), Mr. A requested detoxification, as he had the chance to commute impending imprisonment for a therapeutic community programme. After a complete medical and psychiatric evaluation, detoxification was started and accomplished within 7 days of in-patient treatment with clonidine and benzodiazepines. At discharge, the patient started feeling extraordinarily well, attractive and successful. This status evolved rapidly into mania (according to DSM-IV), with euphoria, insomnia, delusions and hallucinations. Over the next two months the patient was repeatedly hospitalized and treated with neuroleptics and benzodiazepines. While euphoria, delusions and hallucinations subsided, restlessness, nervousness and insomnia increased. There were rapid mood shifts from dysphoria to depression, and suicidal thoughts appeared. Mr. A started stating that only methadone could give him relief. A mixed status was diagnosed (according to DSM-IV), and treatment started with lithium and carbamazepine (serum concentration were 0.70 mEq/L and 9.5 µg/mL, respectively), as well as clonazepam and clotiapine (6 and 80 mg/day, respectively). After one month without improvement, Mr. A came to the service,

claiming heroin use in the preceding three days in order to be allowed to re-enter the MMTP. After toxicological urinalysis confirmation, he was re-accepted into the programme and medicated with methadone (30 mg/day). In a few days his mood improved, and anxiety, insomnia and dysphoria subsided. This improvement continued with the increase of the daily dose to 50 mg. Upon follow-up, two months later, his mood was stable and the urine samples were consistently morphine-free. The patient was still taking methadone (50 mg/day), clotiapine (40 mg/day), lithium and carbamazepine (serum concentrations were 0.65 mEq/L and 9.4 µg/mL, respectively).

The improvement of depression and psychotic symptoms in patients on methadone has been previously reported (3), as has the existence of psychosis during methadone detoxification (1); thus methadone appears to share some characteristics of mood stabilizers like lithium or carbamazepine.

Our case seems to confirm the mood-stabilizing effect of methadone. Our patient spent a total of seven years in methadone maintenance and only one year out of it, both polarities of mood disorder being concentrated within this short period of time and resolved rapidly on re-entering the MMTP. Thus methadone may have played some role in preventing mood disorder relapses.

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