REVIEW

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Opioid replacement therapy

The institutional and historical context of its introduction in France, and the situation in other comparable countries

Résumé

Dans quel contexte historique et institutionnel ont été mis en place les traitements de substitution aux opiacés en France, et comment notre pays se situe-t-il aujourd'hui dans ce domaine par rapport aux pays comparables ?
Les principales caractéristiques des traitements de substitution en France sont : 1) l'importance du nombre de patients, soit près de 100 000 ; 2) l'utilisation de la buprénorphine haut dosage ; 3) environ huit patients sur dix sont en médecine de ville. Le développement des traitements de substitution y a été à la fois très récent (1995, autorisation de mise sur le marché) et très rapide. Or, si l'on peut observer des détournements des médicaments (injection, revente sur le marché noir), une évaluation nationale démontre qu'au niveau national, le développement de ces traitements s'est accompagné d'une amélioration de la santé et de l'insertion (baisse de 80 % des overdoses mortelles, réduction du partage des seringues, baisse de 67 % des interpellations pour usage d'héroïne entre 1994 et 1999 – voir INVS, 2001). Ces bons résultats sont dus à un accès large aux soins, d'une part, aux bonnes pratiques cliniques d'une majorité des praticiens, d'autre part. Sur la base des études de suivi, environ les deux tiers des patients tirent bénéfice de ces traitements. Améliorer les résultats actuels exige une adaptation des prises en charge aux patients mal stabilisés, avec un élargissement de l'offre de soin, dont un accès plus aisé à la méthadone. Les pratiques erratiques doivent être combattues par la diffusion des bonnes pratiques, la formation des praticiens et l'amélioration de la qualité de la relation avec les patients.

Mots-clés

Évaluation – Buprénorphine haut dosage – Méthadone – Opiacé – Traitement de substitution – Pratique clinique – Réseau de soin – Accès aux soins.

Summary

The main characteristics of opioid replacement therapy in France are: 1) the large number of patients, almost 100,000 ; 2) the use of high-dose buprenorphine ; 3) about eight out of ten patients are treated by GPs. The development of opioid replacement therapy is both very recent (1995, Marketing Authorisation) and very rapid. Although cases of misuse have been observed (injection, resale on the black market), a national evaluation showed that development of these treatments has been accompanied by an improvement of health and social integration (80 % reduction of fatal overdoses, reduction of syringe sharing, 67% reduction of arrests for heroin use between 1994 and 1999 – see INVS, 2001). These good results are due to a large access to care and Good Clinical Practice by a majority of practitioners. On the basis of follow-up studies, about two-thirds of patients obtain a benefit from these treatments. An improvement of current results would require adaptation of the management of poorly stabilized patients, with a broader access to care, including easier access to methadone. Erratic practices must be controlled by publishing good clinical practice guidelines, training of practitioners and improvement of the quality of the relationship with patients.

Key words

Evaluation – High-dose buprenorphine – Methadone – Opioid – Replacement therapy – Clinical practice – Healthcare network - Access to care.

In 1989, the *Direction Générale de la Santé* (DGS, French Department of Health) ordered a study on the outcome of substance abusers, but how can the mortality of substance abusers be evaluated in the absence of any French studies or research? The epidemiologist asked to conduct this study reviewed the main international follow-up studies: mortality rates varied according to the cohort from 6.9 % to 30 %. According to an English study, the average mortality rate is ten deaths for a cohort of 100 substance abusers. This rate was adopted to evaluate the outcome of substance abusers in France. This approach assumes that substance abuse complies with an internal logic, the natural history of the disease, but such an assumption is clearly refuted by the 80 % reduction of fatal overdoses observed between 1994 and 1999. This demonstrates that the mortality of substance abusers is not due to a natural course, but is essentially due to the way in which substance abusers are treated.

If we try to discreetly cover up the errors of the past by claiming that "in the past, we have made mistakes, but now we know the truth", we would be very likely to repeat the same errors of judgement or symmetrical errors, according to a pendulum effect that has already been repeated several times in the history of substance abuse. We therefore need to examine, not the errors themselves, but their roots, *i.e.* our system of beliefs and the way in which they have been integrated into the institutional framework. From this point of view, we will discuss three questions by trying to explain how they are formulated in France, in view of our history, common beliefs and the French institutional framework:
- the question of the status of treatment of opiate dependence attributed to opioid replacement therapy;
- the question of Good Clinical Practice;
- large-scale prescription of high-dose buprenorphine (HDB, Subutex®) in general practice: a French specificity.

The status of treatment of opiate dependence attributed to opioid replacement therapy

For most practitioners, this status is self-evident, but this question has not been resolved either in terms of common beliefs nor in terms of the institutional status of these treatments. In the information booklet *Les dispositifs publics* published in 1999 by the *Mission Interministérielle de Lutte contre la Drogue et la Toxicomanie* (MILDT, Interministerial Drug and Durg Addiction Task Force) (1), healthcare and social responses to the problems of illicit substance users comprised three plans of action: specialized management of substance abuse, risk reduction in relation to infectious risks, and finally opioid replacement therapy.

Why did the MILDT add a special category, "opioid replacement therapy", in 1999, without integrating it into the substance abuse treatment system? It is possible that, as most treatments are prescribed in general practice, they do not exclusively correspond to units specialized in the treatment of substance abuse, but the same applies to outpatient withdrawal treatment, for which a study conducted in 1992 showed a much greater number of patients than that managed in specialized substance abuse treatment centres. The real reason lies elsewhere: integration of this special category of treatment does not correspond to a simple addition, but requires a review of the management of substance abusers, the objectives of this management, the various treatment strategies and various other questions such as the respective roles of specialists and general practitioners, and we believe that this constitutes one of the major challenges for this consensus conference.

This study was impossible for a long time because the French substance abuse management system is based on an essentially psychodynamic explanatory theory, with the exclusion of any other approach. The origin of the French consensus on the treatment of substance abuse is the 1970 law that makes a substance abuser either a patient or an offender. The French substance abuse treatment system was developed to protect the substance abuser from the treatment required by law, but which was not justified: "Substance abuse is not a disease, it must not be medicalized". This is the unifying principle of the substance abuse management system; it had to exclude any possibility of mandatory treatment. Although psychoanalytical concepts provided the theoretical basis for this approach, it remains primarily an ethical position: healthcare professionals must not be agents of social control. Also at this time – and the same is true today – substance abusers infringing the 1970 Law were essentially users of cannabis; however, according to the Pelletier report of 1978, cannabis users are neither criminals or patients, but rather present a deviant behaviour. What exactly does the term "*toxicomane* (addict)" used in the law mean: does it refer to a cannabis user or a heroin user? This is a good example of the type of question that cannot be raised according to the 1970 Law; according to this law, no distinction can be made between various substances; this question also does not concern specialists, who refer to a psychodynamic problem. In fact, the substance used has little importance if "substance abuse is a symptom of mental suffering" and if

treatment consists of analysing the origins of this suffering. However, integration of opioid replacement therapy into the substance abuse treatment system is not incompatible with a psychological interpretation of dependence, but we need to abandon the idea of unifying the approach to substance abuse on the basis of a unique theoretical problem. The dogmatic approach which led to the refusal to grant the status of treatment to therapeutic communities, such as strategies based on the approach adopted by *Narcotics Anonymous*, or to cognitive therapies, can therefore be very counter-productive and can lead, as in the case of opioid replacement therapy, to disqualification of current institutional responses. We now need to develop a peaceful coexistence of the various explanatory theories. This work is underway in the context of addiction medicine, which can adopt various explanatory theories, while integrating knowledge about neurobiological processes that were formerly radically excluded from clinical practice (see MILDT for a meta-analysis of studies (2)).

This clearly corresponds to a change of conceptual framework, but this change occurred without any formal discussion and healthcare professionals were not even necessarily informed and appropriately trained. On the contrary, these treatments were presented to specialists with the assurance that they were only added to the existing treatments and therefore did not fundamentally change the situation. Here is an example of this underground revolution. In 1994, a circular defined the conditions of use of methadone. For specialists and for the DGS, methadone is not "a treatment" of substance abuse, but "a management tool" and is designed to maintain the patient in treatment in order to undertake psychotherapy, which constitutes the only real treatment for substance abuse. The conceptual revolution took place in 1995, when the circular integrating HDB suddenly adopted a medical approach: "the therapeutic tool" became "medication" and "management" became "treatment", a term used 39 times in this circular. This appeared to be obvious to the general practitioners who were starting to prescribe HDB, but specialists, who gradually accepted to open up methadone programmes, did not necessarily modify their concept of addiction. They sometimes still used the terms of the 1994 circular on methadone, and this concept clearly resulted in a limitation of access to care. Moreover, this was its objective: at the time, people were saying that we must not "open the floodgates", but that is exactly what happened with HDB the following year. Considered to be an outcast of the healthcare system, since this "therapeutic tool" was not given the status of "treatment of substance abuse", HDB was left to general practitioners, although the circular did not specify the modalities of prescription. Control of methadone prescription was described in minute detail for 15 pages, while the circular concerning HDB, a new drug, consisted of three pages. While prescription of methadone was limited to seven days in the 1994 circular (14 days today), the 1995 circular authorized prescription of Subutex® every 28 days with, however, a simple recommendation: see the patient "more frequently" during initiation of treatment. For substance abuse specialists, this product was nothing more than an improved version of codeine, an over-the-counter product simply used as emergency palliative treatment of withdrawal. As there was no risk of overdose, doctors were able to use this product as they wished. This situation could have led to the catastrophe that the strict controls of methadone were intended to prevent. Fortunately, rather than prescribing wildly, the first prescribers worked in a network, they compared their practices, acquired missing pharmacological information and defined the principles of the clinical practice, which was tested and diffused via these networks (3, 4).

Prescribing the drug without worrying about the effects of prescription, limiting prescription to the lowest doses possible for the shortest duration possible, with the addition of benzodiazepines if the patient complains of anxiety are some of the possible consequences of the belief that "the product doesn't matter, as the real problem is elsewhere". For a long time, this belief was the basis for refusal of any form of prescription; it was subsequently used to justify erratic practices: as the only justification for prescription is to allow psychotherapy, the choice of drug and the modalities of prescription are of secondary importance. This conception also led to the idea that the only role of prescription was to supply an illicit substance, while not daring to make it available over-the-counter; in other words, the doctor, acting on behalf of the law, assumed the role of social control – this is still a widely held belief in intellectual circles –, due to the absence of a public debate on the objectives and effects of prescription (see *Le Monde Diplomatique* in 2001 (5)). Definition of Good Clinical Practice does not mean that we have to abandon a psychological theory of addiction, but it means that we need to take prescription seriously, as it constitutes a treatment *per se*.

Results obtained in France and Good Clinical Practice

All over the world, the question of Good Clinical Practice was at the centre of the debate over methadone throughout the 1980s. It may be useful to recall the context of this

debate in the United States. The excellent results obtained with methadone at the end of the 1960s led to an extensive development of methadone programmes from 1970 onwards; the number of patients treated by methadone increased from 6,000 in 1969 to about 120,000 in 1972. Politicians hoped that methadone would resolve the drug problem, but the results proved to be disappointing; deaths were observed with methadone and a black market started to develop. Restrictive measures were taken: dosages were defined by State regulations and substance abusers were closely monitored (daily attendance of treatment centres, etc.). However, budgets were cut, reflecting the disappointment of politicians. The virtuous cycle of the experimental phase was reversed. At the end of the 1970s, treatments with methadone appeared to be condemned to an increasingly marginal use; the debate on methadone treatment was re-opened with the appearance of AIDS, as patients treated with methadone had a lower contamination rate than street heroin users (11 % in one New York programme *versus* 45-55 % for street heroin users). Although not all patients had abandoned injection, as demonstrated by certain estimates, at least there was a significant reduction of intravenous drug use. The pioneer prescribers of methadone were convinced that the less and less convincing results were due to the dispensing constraints that completely altered the treatment. This was demonstrated by various evaluations, including a last study that definitively closed this debate: by comparing six programmes for four years, this study demonstrated that clinical practice determines the results, more than patient profile or motivation (6). These results constituted the basis for the international development of methadone. Several factors were associated with good results: high dosage; unlimited duration of treatment; individual dispensing modalities (*take home*); counselling; availability of medical, social, psychiatric and psychotherapy services.

These results led to the elaboration of guidelines which constitute the basis for training of practitioners in the United states (7). Many clinical practices identified in the study by Ball and Ross have been validated internationally, such as the dosage or the duration of treatment. Other practices must be interpreted as a function of the American prescribing context. For example, the study demonstrated that dispensing constraints must be adapted to each individual patient, but these constraints are necessarily essential. The same applies to the medico-psychosocial services associated with prescription. Budget restrictions have often forced American programmes to reduce the range of medico-psychosocial services provided; the study demonstrated that programmes must be able to provide the services that the substance user needs; counselling training must be systematic for all practitioners, but if the services provided to users improve the results, there is no evidence to suggest that they must be systematically imposed on all patients. The study was unable to distinguish between specialist and general practitioner programmes, which do not exist in the United states, but, in general, it argues in favour of individual adaptation of prescribing modalities.

This could constitute one of the reasons for the success of the French programme. Although the French programme is far from meeting all of the requirements, it has nevertheless achieved results comparable to international results, for example, those of the six American research programmes indicated above and the general practice study. Thus, in the patient cohorts studied, heroin consumption decreased by an average of 70 % with an equivalent reduction of injection, *i.e.* an improvement for 70 % of patients. The precise consequences of this improvement are sometimes difficult to identify or interpret in cohort studies due to the absence of before/after comparisons. It is especially difficult for non-stabilized patients (who continue injection for example) who may obtain benefit from this treatment, if only as a result of contact with the healthcare system, although such a result is a long way from the ideal model of success. Another problem concerns the interpretation of depression or mental disorders observed during follow-up. These disorders are sometimes attributed to the treatment itself due to a lack of data concerning the mental health of users outside the healthcare system.

Evaluation of social integration is also faced with similar difficulties: access to the *Revenu Minimum d'Insertion* (RMI, minimum income allowance) or *Allocation d'Adulte Handicapé* (adult disability allowance), and maintenance of employment are the main results. Once again, these results are disappointing compared to the ideal model of success, which would require employment for all, but what would have happened if these subjects had not received any treatment? The violence of social exclusion, and health threats weighing on substance abusers were invisible due to lack of follow-up. These questions were the subject of international debate for a long time, but have now been clarified by several studies comprising before/after comparisons, either for reduction of mortality or reduction of crime. Reduction of crime, for example, is reflected indirectly by a national indicator, *i.e.* the 67 % reduction of arrests for heroin use, but have not been studied directly. In reality, French practitioners do not like to emphasize crime reduc-

tion, as they are afraid of being accused of social control, *i.e.* of prescribing "*pour protéger le cœur des cités bourgeoises*" (to protect the centre of bourgeois cities), as claimed by the article of *Le Monde Diplomatique*, the only article published to date on the subject of replacement therapy in this newspaper (5).

Nevertheless, several indicators used in French follow-up studies directly or indirectly reflect improvements in various aspects of the patient's life: significant reduction of high-risk practices and improvement of health, and improvement of social integration, as reflected by affective, social and family relationships. These results are no longer contested and we now know that they depend on the quality of clinical practice. This highlights our responsibility in this conference, which must at least preserve access to care, the primary condition to obtain any form of result.

Broad access to care

This is the first characteristic of the French substance abuse treatment programme. Although cohort studies provide results that are not at all exceptional with respect to international studies, France is currently the only country which has been able to demonstrate, at the national level, the extraordinary efficacy of these treatments. From 1994 to 1999, French national evaluation obtained the following results: 80 % reduction of fatal overdoses, 67 % reduction of arrests for heroin use, 67 % reduction of AIDS mortality. Associated with these results, although more difficult to quantify, is the change of users' behaviour reflected by decreased HIV contamination (the current HIV contamination rate is 4 %, while it was as high as 30 % in the beginning of the 1990s). High-risk practices obviously continue to be observed, but who would have believed that these practices could be totally eradicated? Injection, performed by about 90 % of heroin addicts in the 1980s, is still performed, but although the percentage reduction of injection during treatment with HDB is controversial, it is at least 54 % (highest percentage obtained in studies), and there is every reason to believe that this percentage will improve with time and attentive follow-up of cohorts (see below), and that is a significant result.

All these results reflects a reduction of mortality, which is not limited to overdoses, and an improvement of health, which is not limited to AIDS: 80,000 patients treated with HDB and 12,000 treated with methadone are now managed clinically in the context of long-term follow-up. They therefore have access to care. Never before have so many drug users received treatment, which has an influence on users who are not currently under treatment, but who can be better informed by their friends about the effects of high-risk practices. This has also had an influence on the changing modes of consumption: the youngest heroin users are no longer initiated by heroin users of the 1980s... These results also reflect an improvement of social integration, associated with a reduction of crime: "addicts", who have become "patients like any others", have regained their place in society, although this process is not yet complete, in view of their legal situation. This new position is not always gratifying but it provides some improvement.

France has been able to demonstrate the efficacy of opioid replacement therapy in view of the sudden changes: from one day to the next, doctors started to see these patients in their offices and, once they were stabilized, they were better received in hospitals. Heroin users no longer die at the entry to these hospitals (or at least much less often). Have hospital departments that announced openly, without any doubt, that they did not accept drug addicts finally understood the fatal consequences of exclusion from care? Possibly not, as the results obtained – decreased mortality and decreased crime – are truly incredible, and this constitutes the major obstacle to their diffusion among health-care professionals, but also to the general public and politicians: senators have just discovered this fact. This is probably why the actors of this change, *i.e.* practitioners, drug users and user associations have considerable difficulty to obtain recognition of these results. In fact, they are also somewhat sceptical.

These results are in contradiction with commonly held beliefs, in contradiction with drug policies and even in contradiction with clinical experience: for example, it is difficult to believe in a real reduction of injection when every day so many intravenous drug users attend syringe exchange programmes and substance abuse treatment centres. It is difficult to believe that opioid replacement therapy improves social integration of drug users when, on the contrary, the patients attending substance abuse treatment centres appear to be increasingly precarious. The scepticism of clinicians may correspond to the impatience of users; stabilization with treatment does not automatically give access to satisfactory social integration and is also not sufficient to relieve the patient's mental suffering. Medication alone obviously cannot ensure the patient's happiness, but heroin users currently under treatment are survivors of a health catastrophe and they are still paying a high price, especially with the growth of hepatitis; for the moment, this threat is negligible compared to the morta-

lity, ranging from AIDS to suicide, and including septicaemias, that decimated their friends in the 1980s. This information has been under-used by the self-support press. It may also constitute a form of self-doubting, as the role of "victim" is not an easy role to play; nevertheless, it has been demonstrated by the facts.

Several contextual factors have contributed to these results. The age of heroin addicts, the duration of their dependence, the threat of AIDS, and the arrival of antiretroviral therapy all promoted a demand for treatment. The changing modes of consumption with decreased use of heroin in favour of psychostimulants also contributed to these results, but this decreased use was not sufficient on its own to reduce mortality or the number of arrests. According to the national evaluation, these two results can be attributed to access to HDB (8). However, this evaluation fails to identify the way in which these medications have been used. In the absence of an evaluation conducted specifically to identify clinical practices, this study suggests that the medication itself is sufficient to directly improve the patient's health and social integration.

This corresponds to the interpretation of positivist medicine, according to which opiate dependence is a chronic disease that can be treated by a drug in the same way that diabetes is treated by insulin. For anti-prohibitionists, this constitutes proof that access to the product should be legalized. Both sides have excellent arguments: heroin dependence is clearly a chronic disease and the illicit nature of heroin introduces a large number of health and social risks (adulterated product, clandestine injection with no possibility of hygiene, etc.). However, free access of the substance on the current market would not be sufficient to reduce risks. Experience shows that over-the-counter products (such as codeine in France) as well as prescription drugs (which apparently was the case with methadone in Spain in the late 1980s) can be added to illicit drugs, without appreciably modifying health and social risks. This was demonstrated by international evaluations of methadone, which attribute the variability of results to good or bad clinical practice.

The therapeutic alliance

One particular aspect of our clinical practice plays a decisive role, although it is difficult to demonstrate: the quality of the doctor-patient relationship. Pioneers in this field did not simply prescribe the drug; in addition to pharmacological treatment, they accepted patients as they were, and not as they would have liked them to be, *i.e.* using drugs, including by injection. They learned to talk and negotiate with these new patients. In turn, heroin users gradually accepted the logic of harm reduction, a rational logic that was not at all spontaneous, and in contradiction with the stereotype of junkies. Heroin users and doctors changed both their relationships and their behaviour, with the creation of networks of doctors on one side, and self-support associations on the other, that played a key role in experimentation and diffusion of these new behaviours (9).

These results certainly need to be further improved: diversion of opioid replacement therapy to the black market must be controlled as much as possible; practitioners require better training, more support must be given to isolated doctors; access to psychiatric care and social services must be improved; finally, minimal access to methadone must be improved. But first, the new measures must preserve what made these treatments so effective in France: broad and easy access to treatment in the context of a therapeutic alliance based on the patient's responsibility. One of the difficulties in this field is to clearly define the nature of the "therapeutic alliance", the word itself sounds like a slogan that everyone can claim. All practitioners are convinced of the quality of their relationships with their patients. The quality of this relationship is not systematically at stake; in practice, clinicians select their patients who always have the possibility to refuse the treatment proposed. During the debate on replacement therapy, specialists opposed to prescription emphasized their clinical experience; users reported that they no longer wanted to take drugs, that they wanted to start a new life and that they did not need methadone to achieve that goal. It must be remembered that drug abuse is stigmatized, that users in contact with healthcare professionals say that they want to stop taking drugs. It is not surprising that they refuse the status of "chronic disease" associated with methadone. The demand for opioid replacement therapy was therefore inaudible and invisible, but was nevertheless massive. This does not mean that we should ignore what our patients tell us: they certainly want to "get out of drugs", but various strategies can be employed to achieve this goal. The experience of users and the experience of clinicians must be correlated with each other; a consultation methodology must therefore be developed for users and clinicians.

To avoid a vague, theoretical discussion, we need to more clearly define the content of the therapeutic alliance. This is a clinical process not governed by regulations and legislation in general. Administrative measures must at least

preserve this process or, whenever possible, support it. This is not the case when "this patient just like any other patient" for practitioners is an offender in the eyes of the law, but this will be discussed later. Legal aspects and the clinical relationship must therefore be clearly distinguished. Here is an example to illustrate this principle: according to a study conducted on data from the Provence-Alpes-Côte d'Azur regional health insurance fund, less than 10 % of patients received more than 80 % of polyprescriptions in 2000 and 2002 (10). These patients' demands would appear to correspond to financial objectives that have nothing to do with clinical needs. Pharmacists and doctors can identify diversion of prescribed drugs, but neither can be held responsible for the fight against drug trafficking; these polyprescriptions must be subject to administrative control. It would be perfectly counterproductive to submit the remaining 90 % of users to a set of controls that make all patients suspects, while the real offenders manage to escape this control. These controls would also discourage doctors and pharmacists, who have both accepted to accompany these patients who, to say the least, had a bad reputation, precisely because they have acquired the status of "patient just like any other". However, these patients like any others can also suffer from mental disorders, they can be violent or rude; there is no reason to oblige the pharmacist to carry the weight of exclusion from care of difficult patients currently managed in general practice. The status of "patient just like any other" must be preserved, as it is a prerequisite for improvement.

Stabilization of patients, including giving up injection, cannot be obtained by administrative control; it can only be obtained progressively according to the patient's motivation, adaptation of treatment and the quality of the clinical relationship, which allows erratic practices that would be prohibited by punitive measures.

Large-scale prescription of HDB by general practitioners: a French specificity

For a long time, France was the European country most refractory to replacement therapy. With about 90,000 patients currently receiving treatment, France is now the leading prescriber in Europe, where the total number of patients was estimated to be 300,000 in 2000. With large-scale prescription by general practitioners, France started at the spearhead of the process, where the most experienced European countries were only cautiously advancing. Experience has shown that misuse, particularly diversion to the black market, constitutes a threat that must be taken seriously. General practice prescription in Switzerland, The Netherlands, Belgium, and Australia is authorized by specific regulations that may concern the general practitioner's qualifications, notification of patients or their numbers. Are these regulations effective? Could they discourage pharmacists and doctors? These two questions need to be evaluated with experts from the countries concerned before taking any measures; this should constitute one of the recommendations of this consensus conference.

Finally, we conducted a large-scale investigation of a new drug, Subutex® (HDB) at a time when it was contraindicated in combination with benzodiazepines or when the user is unable to forgo injection. It is generally estimated that one in every two heroin users are also dependent on benzodiazepines, while injection was performed by about 90% of heroin addicts in the 1980s. Methadone and HDB replacement therapy are also faced with these difficulties. It would be unrealistic to imagine that these difficulties are going to magically disappear, simply with the use of opioid replacement therapy. However, they can be more easily overcome when:

- the choice of treatment and medication is adapted;
- treatment is initiated very carefully (this is one of the conditions of adaptation of treatment to the patient);
- the dialogue with the practitioner is based on confidence (another condition of adaptation), which is not the case when injection requires implementation of strict control measures;
- associated disorders are taken into account;
- sufficient time is allowed, as demonstrated by the results obtained with methadone and HDB. The percentage of injectors among patients treated with HDB ranges from 12 % to 46 % (percentages reported in studies analysed by the ANAES); the 12 % rate was obtained in patients after two years of follow-up.

Injection, made visible by syringe exchange programmes, raises both legitimate concern on the part of healthcare professionals and horror of public opinion, but, from a clinical point of view, the decision to abandon injection must be left to the patient. This does not correspond to laxity, but good clinical practice. It is the patient's place, as far as possible, as treatments are not always accessible, to choose the treatment, the drug and the modalities of management, while the practitioner's role is to provide useful information. The practitioner must be informed that methadone facilitates withdrawal from injection and he must inform the patient about this effect; he must strongly

recommend methadone in the case of compulsive injection. However, be that as it may, the choice must always be left to the patient, otherwise the patient will be forced to either lie to the doctor or drop out of the programme, which can have dangerous consequences.

Patients should be given three options: methadone therapy when they want to abandon injection; maintenance of HDB therapy when they are not immediately able to forgo injection; and finally medicalized prescription of parenteral heroin for those patients who do not want to forego injection. Swiss and Dutch experiences show that this last group constitutes a minority, when good quality alternatives are available.

Diversion to the black market is also a subject of public indignation. It must be stressed that this diversion is inevitable in a context of large-scale prescription: if methadone is prescribed more widely, it will be more often diverted to the black market. Once again, we cannot stand by passively and let this happen, more effective measures must be implemented to control these diversions, but these measures must be defined in the light of their objectives, weighing up the efficacy against the harmful effects that they can induce. First of all, there is absolutely no reason why national health insurance (which reimburses treatments) should pay the price of these criminal practices, for HDB or for any other drugs diverted to the black market, such as anxiolytics. Control measures must be taken to curb polyprescription.

Diversion to the black market raises a major problem in terms of health protection, that of primo-dependence; the fact that the drug's reputation is tarnished also has a negative impact. Another question needs to be discussed with Afghan heroin on our doorstep: is heroin a better product for the black market than HDB in terms of health protection? Is multiple substance abuse, general practice on the streets, more dangerous with HDB or with heroin? We do not have a clearly defined opinion on this subject, we simply know that measures must be carefully developed and must not be taken hastily to satisfy the most repressive part of public opinion. They must take into account the context as well as the point of view of law enforcement, as the heroin black market and the prescription drug black market are radically different in terms of their mafia networks.

The effects of measures taken hastily in response to a scandal are well known and correspond to the cycle described above, composed successively of enthusiasm, disappointment, more restrictive regulations, even poorer results, budget restrictions, etc. It would be absurd to repeat with HDB the same errors committed with methadone. This cycle of events constitutes a real threat for several reasons. First of all, the debate on replacement therapy occurs in a political context that tends to be unfavourable to the development of health and social policies. As the demand for security measures increases, health and social welfare responses lose their credibility; healthcare professionals must preserve their tools, but, in response to a crisis which affects all institutions – hospital departments, the psychiatric sector, social services – the care of drug users tends to take second place. Another difficulty is that related to the changing modes of consumption, now marked by multiple substance dependence and the growth of psychostimulants. In the past, opioid replacement therapy managed to overcome the barrier of common beliefs, as the first prescribers observed for themselves the beneficial effects of prescription. However, in a context in which multiple substance dependence is much more prevalent, the effects of prescription are less immediate and therefore less convincing; the growing use of psychostimulants such as cocaine is a particularly unfavourable context for replacement therapy, and for harm reduction policies.

It fairly rapidly became apparent that access to methadone would have to be proposed to patients poorly stabilized by HDB (injection, depression, benzodiazepines taken erratically, etc.). The MILDT recommended this measure in 1999, but this recommendation had little impact, as more than two-thirds of the increased number of patients on general practice methadone treatment was due to the deliberate action of a few programmes including that of Émergence-Espace-Tolbiac (11). Following a recent report, the possibility of prescription has been extended to hospital practitioners, but no-one in France today envisages extension of methadone prescription to all practitioners. We would not risk such a recommendation, which runs counter to popular beliefs, that would not be welcomed by general practitioners, and which would require a policy of supportive care that could not be provided by public services. A more logical proposal would therefore be to refer patients poorly stabilized by HDB to specialized treatment centres, but such a referral encounters a number of obstacles.

When we set up the Émergence-Espace-Tolbiac project, we wanted, in practice, to answer the question: which patients require follow-up by a multidisciplinary team and which patients can achieve satisfactory stabilization in

general practice (in France, after the initial prescription of methadone, stabilized patients may be oriented toward general practitioners)? Very rapidly, the selection criteria became almost exclusively social: we kept the most socially outcast patients in our service and, therefore, we were obliged to direct more socially integrated patients to general practitioners because the coexistence was poorly tolerated by and could even be damaging to them. Socially integrated patients can be very dependent and can benefit from more or less daily follow-up during initiation of treatment or during crises, as well as long-term follow-up possibly associated with psychotherapy, for example such as that provided in Geneva in the programme directed by Dr Déglon in his private centre. This type of service could not be provided at Émergence-Espace-Tolbiac, as it was too difficult to ensure coexistence of these two types of populations. This difficulty must be discussed collectively in order to identify priorities, otherwise the tasks assigned to substance abuse treatment centres become impossible tasks.

Another problem, the most socially outcast patients, usually presenting behavioural disorders, require mobilization of the team that is difficult to maintain in the long term. It is not impossible, but sufficient resources must be allocated to valorize this complex work, by providing support and training, as well as social and psychiatric responses. Management in a collective context also has its limits; the place and other people, both professionals and patients, must be respected. Respect of the patient is usually sufficient to obtain respect of the centre, except in crisis situations or in the case of serious mental illness. We have had to refer patients with the most severe forms of psychiatric illness to a few experienced doctors, who have dealt as effectively as they can with the refusal of psychiatric departments to follow these patients who are "outcasts" from all institutions... except for prison. However, prison cannot replace treatment; it is not enough just to say that, useful measures must be taken: who should manage difficult patients and how?

Referral of difficult patients to specialized substance abuse treatment centres requires definition of the necessary skills; it requires close collaboration with the psychiatric sector and access to social services; finally, it requires a new approach to the very idea of treatment. When the proposed treatment is exclusively or essentially psychotherapy, patient motivation is essential. Patient motivation is certainly preferable regardless of the treatment modalities, but it plays a much less decisive role in the outcome of patients treated by opioid replacement therapy. On the contrary, we have observed several paradoxical outcomes in patients who were initially poorly motivated, convinced that they would not stop either injection or heroin use. However, most substance abuse treatment centres continue to make motivation the prerequisite for admission, which results in exclusion of the most difficult patients. In fact, the only requirements should be that treatment is voluntary, as required by law, and that the patient must respect the place and other people, practitioners and patients.

Fully accepting the logic of treatment means renouncing the idea that this treatment is a reward granted to "good patients", as is still often the case in programmes which do not hesitate to lower the doses in the case of heroin consumption or, even worse, which stop treatment after three positive opiate screens, as indicated in the regulations of one centre. Another consequence of the status of treatment attributed to opioid replacement therapy is to ensure continuity of care. The choice of treatment must take the patient's preferences into account; treatment provides opportunities for change that the patient is more likely to accept when the practitioner considers the patient to be just like any other patient, and therefore responsible for the choices concerning his or her lifestyle. Treatment corresponds to a strategy of defining an appropriate threshold. This strategy must be explicitly integrated into clinical practice and given a real meaning. Accepting the fact that a patient injects illicit drugs or even prescribed medicine does not mean that the clinician has given up and is letting the patient do whatever he likes, but simply that he is giving the patient time to change; *a priori* all patients, like everyone else, want to get better. When they are given a chance to change, they generally seize this chance; when they do not seize this chance, it is because they encounter obstacles (mental illness, social exclusion) in relation to which the therapeutic alliance must be reinforced and better adapted responses must be found.

Specialists were for a long time opposed to opioid replacement therapy, which they considered to represent abandonment of therapeutic ambitions. Medical prescription can have a dual aspect: it can become chronic or, on the contrary, open the way to progress; all depends on the significance given to prescription by the practitioner and the patient, all depends on the quality of care associated with the prescription. Adapted threshold responses require a great effort from healthcare professionals and little from patients. This is the clinical problem that must be taken into account to allow substance abuse treatment centres to manage patients who cannot be stabilized in general practice.

The improvement of clinical practice in specialized substance abuse treatment centres is therefore a prerequisite to patient referral, but, regardless of this improvement, it would be illusory to imagine that all patients will accept the constraints currently imposed by methadone programmes, which are difficult to support not only by the more fringe patients, but perhaps even more by socially integrated patients. Referral to a specialized centre can therefore be only one of the various options proposed to patients. New modalities of management must be tested so that patients followed in general practice can receive methadone treatment whenever it is indicated; moreover, this is the objective of prescription of this treatment by hospital practitioners. The development of methadone prescription implies the constitution of specialized teams comprising the most experienced practitioners. This was the role played by networks of general practitioners following the release of HDB; unfortunately, all too often, these networks gradually broke down when practitioners acquired the basic knowledge that they initially lacked. However, this knowledge is not sufficient to deal with changing modes of consumption; clinical practice requires continual updating, otherwise it becomes obsolete.

It is important to develop the work of networks, pharmacists and other healthcare professionals such as social workers, psychiatrists, and psychologists, must be directly involved in follow-up; hospital practitioners will not be able to prescribe effectively if they do not work in close collaboration with these networks. The same applies to specialists, as competence is acquired with comparison of practices. Finally, modalities of consultation with patients and self-support associations must be encouraged. This is the type of approach that must be adopted to constitute poles of excellence accessible to general practitioners and treatment centres.

Conclusion

In 1994, when Simone Veil, Minister of Social and Urban Affairs and Health, set up the infectious harm reduction programme, comprising access to opioid replacement therapy, she knew that these measures contravened the 1970 law which penalizes the use of illicit drugs. How can you distribute syringes and ban their use? How can you provide access to a narcotic (because methadone had this status at that time)? This last question was resolved the following year by giving methadone the status of medicinal product, although it first had to be recognized as a treatment, but this status of treatment was refused by specialists. The question of the 1970 law was submitted to the Henrion Commission, which failed to reach a consensus on depenalization of use, but recommended a public health policy. These measures were taken in the context of the threat of AIDS, but Simone Veil would not have obtained the support of her government if she had not complied with an implicit imperative: these measures must not change anything in the fight against drug addiction or the fight against illicit drugs. This programme was therefore given an experimental status.

In view of its results, this programme acquired an official status in 1999, but the implicit imperative not to make any changes to the existing legislation was not modified. The consequences are paradoxical: risk reduction is still officially limited to reduction of the infectious risk, but how did the fight against AIDS lead to a reduction of mortality from overdoses and a reduction of arrests for illicit drug use? Why has there never before been so many drug users in treatment, or even simply in contact with the healthcare system? These results extend well beyond reduction of the infectious risk! All health responses, both treatment and prevention, must be revised. Great Britain conducted this type of review in 1987 by formulating the principles of a new health policy, no longer limited to the urgent problem of AIDS (12). Prevention can no longer be limited to "no drugs", but must also integrate a logic of harm reduction, in common with licit or illicit psychotropic drugs. The same applies to treatment, which must no longer be limited to withdrawal from dependence, which does not mean that this objective must be abandoned.

This conceptual process has already started in the field of prevention (13) with integration of alcohol, tobacco and licit drugs (MILDT) (14). Progress in treatment must clearly consist of more than simple addition of this special category of opioid replacement therapy. However, these changes must not be limited to the healthcare system. There is obviously a contradiction between the status of "patients just like any others" that practitioners claim to give to substance users, and the status of offender in the eyes of the law. This contradiction is flagrant in prison where continuity of care is still not satisfactorily ensured. A call for responsibility, which must be the basis of clinical practice, implies recognition of citizenship. Penalization of use is theoretically justified by protection of public health. Healthcare professionals must therefore decide whether this status is justified. This analysis was conducted in the context of AIDS (*Conseil national du sida*, 2001) (15); practitioners of opioid replacement therapy must also define their position.

We now have about one decade of clinical experience with opioid replacement therapy; with the introduction of addiction medicine, a conceptual process has been initiated that could revolutionize our frames of reference. We also know how to put these measures into practice with pooling of knowledge and clinical experience in the context of networks. We therefore now need to:
- improve skills and qualifications, with the elaboration of poles of excellence accessible to practitioners;
- develop treatment networks and promote the creation of social resources networks;
- develop clinical research into new modes of consumption (multiple substance abuse, psychostimulants, etc.);
- develop clinical trials: medicalized heroin programmes, prescription of psychostimulants and, more generally, offer a broader range of treatment options;
- associate patients in clinical research, experimentation, evaluation of services; encourage patient associations and self-support associations;
- recognize the citizen status of users with depenalizaton of drug use;
- integrate opioid replacement therapy into non-specialist social welfare and health responses (hospitals, psychiatric sector, social services);
- inform the public, and more particularly social work and healthcare professionals as well as politicians about the results of these treatments. ■

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Opioid replacement therapy. The institutional and historical context of its introduction in France, and the situation in other comparable countries
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