# PART B: SELECTED ISSUES

## 11. Buprenorphine, treatment, misuse and prescription practices

During the 1970's, the policy for fighting drug addiction did not consider any therapeutic objective other than withdrawal. As the HIV/AIDS epidemic among injecting drug users grew during the 80's, risk reduction methods (free sale of syringes in 1987, development of syringe exchange programmes) were progressively developed. Substitution treatments for opiates have only developed in any significant way in France since 1996 and are mostly based on prescription of high dose buprenorphine (HDB) and, to a lesser extent, of methadone.

Since 1993, methadone treatments have lost their experimental status, but are still governed by strict prescription rules: they can only be initiated by doctors practising in a specialised centre for drug addicts[28] (CSST). Referral to a general practitioner can only be done once the patient is stabilised (Ministère des Affaires Sociales de la Santé et de la Ville, 1995). At the start of treatment, the product must be dispensed daily under medical supervision, with urinary analyses carried out to check progress of the treatment. The prescription may then be given for a period of 14 days, dispensed in two 7-day lots[29]. Conditions for access to "methadone" programmes and remaining within these programmes are more or less strict, depending on the centre. They can sometimes be very selective.

Because of the conditions for access, the fact that there are too few places and that the centres are unequally distributed over the national territory, the availability of treatment has clearly been insufficient in comparison with needs. In addition, some professionals who are rather set on the psychotherapeutic approach to dependence seemed reluctant to use medication treatments for opiate dependence.

So, an additional therapeutic treatment was introduced in France at the beginning of 1996 which was based on high dose buprenorphine with an initial prescription which could be given by any doctor. The choice of HDB by the health authorities was based partly on previous experience of activist doctors who used an analgesic form of buprenorphine (Temgesic®) for substitution in opiate-dependent people and partly on the absence of risk of overdose[30] (contrary to methadone) where HDB is used without any other psychotropic molecule.

### Prescription framework

The legislation (Ministère des Affaires Sociales de la Santé et de la Ville, 1995) states that the prescription is part of an overall treatment, both psychological and social, but does not set out the treatment procedures. In the same way, working in a network of specialised centres, doctors and local pharmacists is recommended but is not obligatory. The prescription procedures stated in the MA (marketing authorisation) are also more flexible than those for methadone: prescription is based on a legally-controlled prescription for a maximum period of 28 days, dispensed in 7-day lots unless expressly stated otherwise by the doctor[31]. It is specified that treatment is reserved for voluntary patients aged over 15. The only criterion for selection of patients is the existence of a confirmed drug dependency on opiates.

[28] And since 2002 by doctors in health institutions.

[29] Order of 8th February 2000, relating to split dispensing of methadone-based medicines.

[30] High dose buprenorphine is a morphinic agonist-antagonist. The partial agonist action limits the depressive effects, particularly the cardio-respiratory effects.

[31] Order of 20th September 1999 relating to split dispensing of certain buprenorphine-based medicines.

In the years following the marketing authorisation for HDB, considerable effort has gone into training doctors. The training is mainly provided by the producing laboratory using documents written by professionals in the sector. Training is also given within the networks and within continuous training organisations supported by public subsidies. Finally, university training about drug addiction now incorporates these new treatment options.

The practice of prescribing HDB is fairly widespread among GPs, who are the principal prescribers. Office-based doctors prescribed 93.2% of the HDB dispensed in 2002 (Assurance Maladie (Health Insurance), 2003).

On the basis of a study involving thirteen cities or districts in metropolitan France it can be estimated that in 2002, 35% of GPs prescribed treatment with high dose buprenorphine. However, there are considerable variations between one city and another (from 23% to 60%). The number of prescribing GPs continues to increase and grew by 11% between the first half of 2001 and the second half of 2002 (A. Cadet-Taïrou and Cholley, 2004).

However, prescription is frequently concentrated in a limited number of doctors. During the second half of 2002, 20% of the doctors who were the greatest prescribers of substitution treatments carried out 73% of the treatments. In 2001, only 10% of the GPs belonged to a "drug addiction" network and these doctors would, on average, monitor 32 addict patients per year, compared to 6 for non-network doctors (Coulomb *et al.*, 2002). The proportion of practitioners who have prescribed a substitution treatment for only one or two patients in 6 months is 59% of prescribers. Although prescription of substitution treatment by HDB seems to be a widespread practice, a significant proportion of doctors have little experience of these treatments. This may be linked to a lack of training since 81% of those who see fewer than 10 patients per year consider themselves to be insufficiently trained or not trained (Coulomb *et al.*, 2002).

Within this prescription framework, it is difficult to estimate the proportion of patients who receive support together with the substitution treatment. Seventy-two percent of GPs say that they offer psychological support along with treatment (Coulomb *et al.*, 2002). However, many experience difficulties in getting their patients registered for psychological or psychiatric treatment in specialist centres or at a hospital.

## Treated patients

### *How many of them are there?*

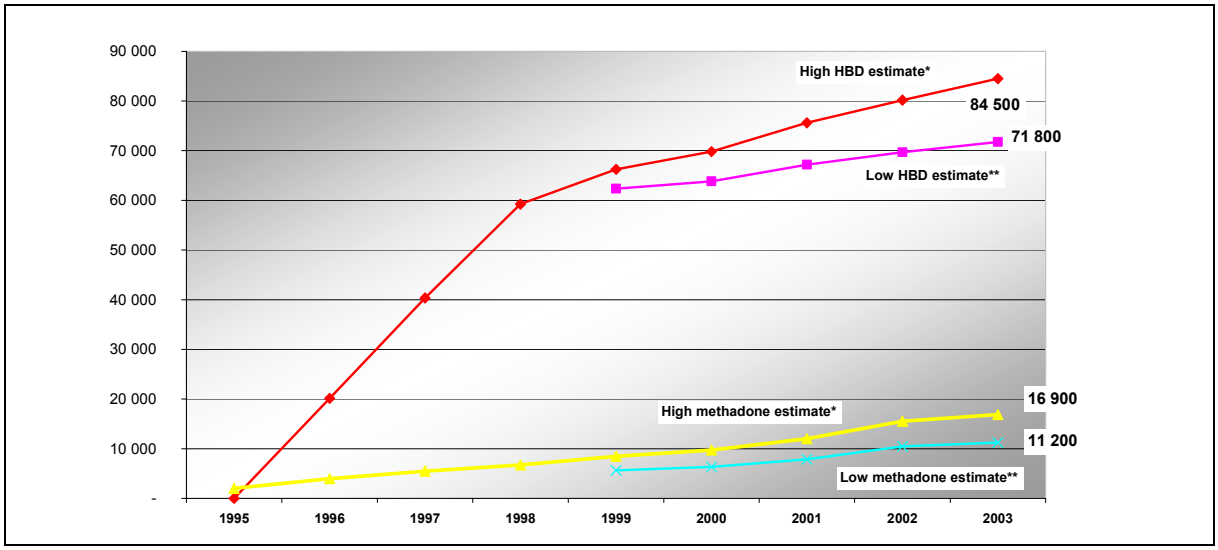
The growth in distribution of Subutex among opiate-dependent people is usually monitored by dividing sold quantities by the average estimated therapeutic doses. This theoretical number of treated patients was between **71,600 and 84,500** in 2003[32], which is slightly less than half the number of problem users of opiates in France (Graph 8). After significant growth, the trend now is towards stagnation in the number of patients receiving HDB and even towards a decrease over the areas where the practice of substitution has been widespread and long-standing (A. Cadet-Taïrou and Cholley, 2004).

However, after HDB came onto the market in 1996, it rapidly became, quantitatively, the main treatment for opiate-dependence in France. The relaxed framework adopted in France for HDB made this product highly available, whether via medical prescription or on the parallel market. In addition to patients involved in a medium or long term treatment protocol, people have been identified who receive intermittent prescriptions, once or twice in six months, or who experience multiple treatment interruptions (**at least 22,000 people** at the

[32] OFDT estimates using SIAMOIS/InVS and CNAMTS data. The high value is based on a theoretical average dose of 8 mg, the low value is based on the projection of a series of median doses dispensed to patients and observed in 13 cities.

end of 2002, according to OFDT[33] estimates). As well as these users, there are slightly less than 5000 people who consult many doctors to obtain drugs for trafficking.

**Graph 8: Estimated number of users of substitution treatment**




*Sources: SIAMOIS InVS data and OFDT estimates*

In addition to these "total or partial prescription" users there are "non-prescription" users who are difficult to quantify (Figure 1). In the TREND[34] "2003 low-treshold" survey, 24% of Subutex® users in the past month, had acquired it exclusively on the black market and 25% had acquired some of it from that source (Bello *et al.*, 2004).

So, the number of ***patients on HDB actually undergoing a treatment process*** in 2002 was not more than **52,000.** By comparison, the number of patients treated with methadone in June 2003 was almost 11,000.

*Who are they?*

The majority (76% to 79%) of HDB users are men. According to the sources, the average age of users is between 30 years 6 months (2003) and 34 years 5 months (2002) (A. Cadet-Taïrou and Cholley, 2004; Bello *et al.*, 2004; Claroux-Bellocq *et al.*, 2003; Thirion, 2003). The trend is for the age to increase, probably linked to a cohort effect: the patients age as they are being treated.

Significant variations can be seen in the average age of the patients, and this is partly explained by variations in the length of time for which substitution practices have been in use in the different urban agglomerations studied (A. Cadet-Taïrou and Cholley, 2004). These differences are also a reflection of age variations between population groups. Patients using buprenorphine under medical supervision are older than patients using non-protocol Subutex® with no protocol (31.7 compared to 29.2) (CEIP de Marseille, 2003).

The women are on average younger than the men (0.7 year difference between men and women for all the patients who received a Subutex® prescription (A. Cadet-Taïrou and Cholley, 2004), 1.8 years in low-threshold facilities) (Bello *et al.*, 2004). This may be linked to the fact that women begin the treatment process at an earlier stage than men.

[33] OFDT estimates using Health Insurance refund data: this data gave an estimate for the number of French people who had received refunds over 3 months (2000 projected to 2002) and was used to study the doses dispensed and the consultation habits of patients (doctor shopping, irregular prescriptions) for each half-year between 1999 and 2002, over 13 cities.

[34] The TREND network information system is concerned with users attending low-threshold facilities (syringe exchange programmes, drop-ins etc.). Many are still active users. Some use Subutex® under medical supervision (protocol) but others do not.

The patients on Subutex® are frequently in insecure situations: 56% of patients who received a prescription in the second half of 2002 had CMU (couverture maladie universelle – universal health cover[35]) compared to 7% of the French population as a whole (A. Cadet-Taïrou and Cholley, 2004; Claroux-Bellocq *et al.*, 2003). Among users of the low-threshold facilities, the youngest [aged 15 – 24] more often have no fixed address (64%) than do older users (45%) and absolutely no social security cover (17%) (Bello *et al.*, 2004).

The patients receiving methadone, who represent between 12% and 18% of patients on substitution treatment, are two years older on average and are slightly more often women than patients on Subutex® (24% compared to 21% among patients on a treatment protocol attending the specialised centres for drug addicts) (CEIP de Marseille, 2003). However, local data show that variations in sex ratios between the two populations are not constant (A. Cadet-Taïrou and Cholley, 2004). Nor do the differences in ages follow any pattern. The trend is towards homogenisation of the populations on buprenorphine and methadone (A. Cadet-Taïrou and Cholley, 2004).

### The positive effects of high dose buprenorphine treatments

All the available information, although patchy, whether recorded in relation to individuals or groups, points to a positive assessment of substitution treatment strategies for opiates addicts. Some studies, mostly carried out on the second part of the 90s, provided a longitudinal individual follow-up of patients by GPs involved in the treatment of drug addicts, practising privately or in the specialised centres for drug addicts: for example, SPESUB (1996) (Duburcq *et al.*, 2000), ARES 92 (1996) (Barbier and Lert, 2001), ANISSE (2000) (Batel *et al.*, 2001). The follow-ups relate to periods from 6 months to 2 years. As with any longitudinal analysis, the evaluations only concern subjects who remained in the original treatment system, but these studies alone are able to observe the actual effects of substitution treatments in regard to individuals. Two retrospective studies supplement their results, that of Bilal (1999) (Bilal *et al.*, 2003) and the AIDES survey (2001) (AIDES, 2002), carried out from the point of view of the patients.

In terms of use, we note a progressive movement away from the drug-taking culture. The use of illicit substances is decreasing, as are injection practices. It is becoming less common to share equipment and syringes. Substitution treatment is also, for the patient, an opportunity for improved treatment, even if it does not solve everything. In particular, it provides better access to anti-retroviral treatments (Carrieri *et al.*, 1999). Finally, the positive results of HDB administered during pregnancy on the condition of the mother and child leave no room for doubt (Lejeune *et al.*, 2003). These different follow-up studies of users undergoing substitution treatment or the qualitative studies carried out among users (Milhet, 2002), provide evidence of the assistance given by substitution in the process of social reintegration. Housing conditions tend to improve, as do employment situations and access to social security cover. The fabric of relationships shifts away from the "network" linked to drug addiction. Finally patients feel better about their quality of life. In addition, undergoing substitution treatment during a period of imprisonment appears to limit the number of subsequent prison sentences (Levasseur L. et al, 2002).

In regard to public health, the most noteworthy element lies in the significant drop in deaths from overdoses, on which several sources agree (Lopez *et al.*, 2004b), although the benefit can not be attributed solely to substitution treatments. The epidemic linked to HIV, which was particularly strong among injecting drug addicts, has also slowed considerably. The decrease in frequency of injection may have contributed to this.

Attempts to compare treatment by HDB and methadone in France are hindered by the significant differences in conditions for prescribing these two substances and the treatment

[35] Coverage of health costs without payment of contributions, for people on very low incomes.

system offered. Because of this, the populations treated within one system or another are quite different so that it is not possible to compare like with like.

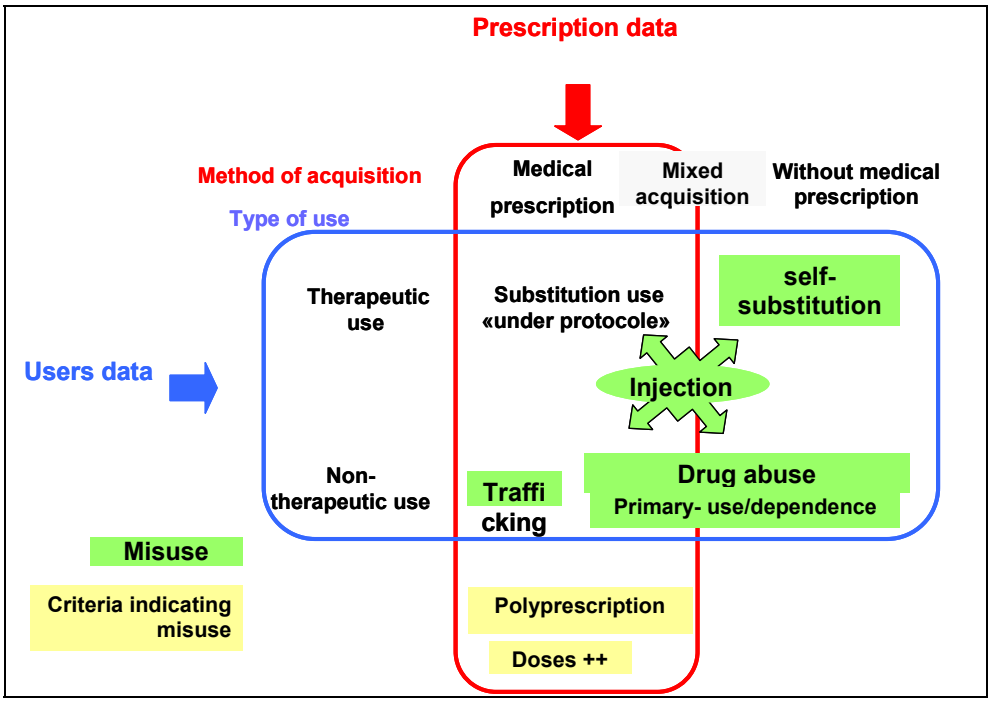
## Misuse

The development of HDB treatments has led to numerous improvements in the status and living conditions of people dependent on opiates, but this has also brought undesirable consequences. Recorded misuse relates to the method of obtaining the medicine (bought in the street from a dealer) and the use made of it.

Concerning undesirable uses, a distinction must be made between:

- **"Non-protocol therapeutic use"** or **self-substitution** (by opiate-dependent patients, using Subutex® as a substitute without medical supervision)
- **"Drug abuse"**: For others, use of HDB is not for the purpose of stopping heroin use. It is a way of managing opiate use. So there is a continuum of situations between use of HDB as any other drug to control heroin use, as a breakdown product or as a maintenance product, and self-substitution.
- A **non-substitution use** (**primary use** and **primary dependence)** has been clearly highlighted for 3 or 4 years by the TREND facility. This use is not attributable to a pre-existing drug dependence: it is **a drug abuse** or with a its purpose of controling various problems.

**Figure 1: Practices of Subutex® users according to use of the method of acquisition**




*Source : OFDT*

Procurement for non-therapeutic use is from doctors and from the black market.

Moreover, whether as part of a substitution treatment or not, **buprenorphine injection** (buprenorphine is theoretically not injectable) has developed, which limits the impact of substitution treatments on injection but also leads to worrying health consequences. Finally, its use by some users as a drug, either for substitution or not, leads to **dangerous combinations,** particularly with benzodiazepines, which can entail potentially lethal overdoses.

It seems to be very difficult, even impossible, to mark a clear boundary between self-substitution use (therapeutic) and drug abuse (non-therapeutic), since both can be in play alternately. In the low-treshold facilities (2003), which most often receive users who are still following their drug abuse career, 41% of people had used Subutex® in the past month. Of these, 13% used it exclusively for drug abuse, while 34% mixed therapeutic and drug abuse. The oldest patients are most frequently undergoing a treatment procedure (Table 23).

Although it is not possible to include everyone's experience within a general picture, it seems nevertheless that some of the opiate-dependent users are gradually changing: buprenorphine is at first considered as an occasional substitute, then as a means of self-controlled maintenance, and may then be incorporated into a treatment process (Milhet, 2002). Non-protocol use of buprenorphine has preceded prescribed use for many users: 28 % of them in the AIDES survey (2001) said that they were regularly using their substitution product several months before it was prescribed for them by a doctor (AIDES, 2002).

**Table 23: Frequency of reasons for use of HDB in the past month, in 2003, among participants in the "2003 low-threshold" survey by age group**

| | 15-24 years | 25-34 years | 35 years and over | All |
|---|---|---|---|---|
| As treatment | 47% | 50% | 66% | 54% |
| To "get high" | 20% | 10% | 13% | 13% |
| Both | 33% | 40% | 21% | 34% |
| Total | 100% (n=80) | 100% (n=209) | 100% (n=100) | 100% (n=389) |

*Source: TREND/OFDT (Bello et al., 2004)*

## Self-substitution

Several studies confirm the existence of self-controlled substitution (Reynaud-Maurupt and Verchère, 2002; Escots and Fahet, 2003; Bello *et al.*, 2004). There are many reasons for this “street substitution”, but they seem linked in particular to social insecurity. So in 2001 the TREND facility highlighted the existence of users in very vulnerable circumstances or on the street, young people and adolescents, and people who may have begun to use HDB in prison. In 2002, the facility also noted "the existence of a very marginalised population, particularly migrants who do not have, or do not wish to have, anything to do with the treatment system" (Bello *et al.*, 2003).

The 202 users of HDB without a medical prescription encountered in the ASUD/OFDT (2000) study (Bello, 2001) mentioned first and foremost the great accessibility of the product (35%) as a reason for their use of diverted HDB. The majority of users who gave this reason stated that they did not have adequate social security cover and considered street Subutex® to be cheaper than in a pharmacy. The insufficiency of the doses prescribed by doctors compared to what they felt they needed was mentioned by 29% of users. The other reasons were the fact that they were injecting (greater number of doses needed), the need for anonymity (9%), particularly among minors or young adults still benefiting from their parents' social security and not wishing the latter to be informed of their use. Finally, 6% were intermittent users and 5% got supplies in the street because their doctor refused to prescribe it.

Other data show that this "unauthorised substitution" is done by opiate users who are still active and is accompanied by risk behaviour more frequently than it is for patients under the treatment protocol: their injection rates, including HDB (Table 25) and their use of licit and illicit products are greater (Bello *et al.*, 2003; CEIP de Marseille, 2003).

## Drug abuse and non-substitution use

In drug abuse in heroin-dependent patients, HDB is considered to be a drug like other drugs and is used as an alternative to heroin when heroin can not be obtained, if the heroin available is insufficient or to control use of other substances. Procurement in these situations is largely unlawful (Table 26).

For some years now, it has seemed that HDB represented for some a vehicle for entry or relapse into drug abuse (**non-substitution use**). This phenomenon was the subject in 2002 and 2003 within the TREND network of a specific study which included a quantitative and a qualitative section (Escots and Fahet, 2003). Three use situations were found which were not the result of heroin dependence:

- the user who uses Subutex® without ever having previously used other opiates (**primary user**). In 2003 these represented 6% of users of low-threshold facilities;
- the user for whom HDB is the cause of a first drug dependency on opiates (**primary drug dependency,** 11%) ;
- the former heroin addict who, after long-term stoppage of his or her heroin dependency begins a dependency on HDB which is not continuous with his or her previous addiction (**non-consecutive use,** 10%).

All these users represent around a quarter of the HDB users encountered in the low-threshold facilities in 2002.

**Table 24: Frequency of methods of obtaining HDB in the past month, in 2003, among participants in the "2003 low-threshold" survey according to intentionality of use**

| | As treatment | To "get high" | Both | All |
|---|---|---|---|---|
| Prescription only | 69% | 22% | 35% | 51% |
| Black market only | 18% | 54% | 23% | 24% |
| Both | 13% | 24% | 42% | 25% |
| Total | 100% (n=196) | 100% (n=46) | 100% (n=126) | 100% (n=368) |

*Source: TREND/OFDT (Bello et al., 2004)*

Non-substitution use of HDB involved groups with quite a wide age range (from 15 to 51 years) (Escots and Fahet, 2003) and varied socio-demographic profiles. The main part of this group is composed of very vulnerable young people who are more or less living on the streets. But non-substitution use of HDB also involves older users who had not developed opiate-dependence; subjects at times not involved in any way with drug use; users of the techno party scene who regulate their use of psychostimulants or use them to get high; delinquents who are not addicts at the time of their imprisonment; very vulnerable people, living on the streets, in squats or in institutions, who include, among others, immigrants of uncertain or illegal status. In Guyana, young Creoles use it to regulate their crack use. Non-substitution use of HDB is also seen in better-integrated socio-professional groups or those on their way to that status, since the qualitative survey also covered students, trainees undergoing professional training, salaried workers from various economic sectors and craftsmen (Escots and Fahet, 2003). The user profiles vary considerably from one city to another (Escots and Fahet, 2003; Bello *et al.*, 2004).

The reasons for use of HDB in a non-substitution way fall into three major categories as shown by the research; the categories sometimes overlap within the same subject (Escots and Fahet, 2003).

- In a subject who is not opiate-dependent, to get high, like any other product, because of its effectiveness, its cost and ease of access;

- For others, HDB provides a way of operating. In terms of performance, Subutex® allows the subject to meet others, talk to them or perform activities such as busking, studying, working etc. Some users find that using HDB helps to improve their sexual relations.
- The tranquillising effect of Subutex® is a means of soothing tensions, limiting aggression and reducing anxiety.

A proportion of the users who had become dependent on HDB without ever having developed previous opiate-dependence were already problem users of other substances, particularly benzodiazepines and alcohol, but almost half of them had never used heroin or cocaine before HDB.

Non-substitution use frequently leads to drug dependency which is difficult to break, according to the evidence of users.

Finally, the method of use, as already mentioned, does not affect the method of procurement. Of "non-substitution users" of HDB, 58% obtain it only by medical prescription (Escots and Fahet, 2003) and 17% only on the black market, with the rest mixing these two sources of supply.

Subutex® is a substance which has a negative image with users who use it outside substitution treatment for heroin (Bello *et al.*, 2004). Several combined elements are the reason for this.

- High dose buprenorphine is considered as a very addictogenic substance which makes attempts at withdrawal painful and difficult;
- Buprenorphine appears to be perceived among users more and more as causing injuries occurring at the time of injection;
- The phenomenon of assimilation of Subutex® as a simple street drug (already begun in previous years) appears to be continuing, leading to growing discreditation and devaluation of its users in their own view and that of other users.

Because of this, at the same time as this movement towards the use of Subutex®, we may observe a movement in the opposite direction away from this use towards other opiates, particularly heroin.

### Injection of HDB and its consequences

The use of HDB by injection involves all groups of HDB users (under medical supervision or not, substitution or not) in different proportions. The prevalence varies, for instance, with populations. The practice seems to be more important among the most desocialised users encountered in low-threshold facilities and/or the prison environment (Table 25 and Table 26) (Lert, 1999; Vidal-Trécan and Boissonnas, 2001; Stambul, 1999). It seems to be more current in subjects monitored in private medicine than in those treated in specialised drug treatment centres (22% compared to 6% in the OPPIDUM 2002 survey). Injection also seems to be more frequent when HDB is used to "get high" (Table 26).

It seems to diminish with duration of treatment and with degrees of integration into a treatment process (Courty, 2003).

However, the observations of the TREND network mention both a decrease in the practice of injection and a growth in sniffing, particularly among the youngest users. Of participants in the low-threshold survey, 64% injected HDB in 2001 and 47% in 2003. Over the same period sniffing was used by 10% of them in 2001 and 25% in 2003.

**Table 25: Method of administration of substitution treatments in patients attending specialised drug treatment centres (CSST)**

| | Buprenorphine protocol | | | Buprenorphine without protocol | | |
|---|---|---|---|---|---|---|
| | 1999 | 2000 | 2002 | 1999 | 2000 | 2002 |
| Oral | 85% | 88% | 87% | 39% | 49% | 53% |
| Injection | 15% | 14% | 11% | 43% | 32% | 27% |
| Sniffing | 6% | 6% | 7% | 22% | 30% | 29% |
| Inhalation | | | 1% | | | 6% |

*NB: there are several possible methods of use*

*Sources: OPPIDUM/CEIPs/AFSSAPS*

**Table 26: Frequency of methods of administration of HDB in the past month, in 2003, among participants in the "2003 low-threshold" survey by intentionality of use**

| | As treatment | To "get high" | Both | All |
|---|---|---|---|---|
| Oral | 66% | 33% | 64% | 61% |
| Injection | 41% | 50% | 55% | 47% |
| Sniffing | 17% | 33% | 33% | 25% |
| Total | 100 % (n=205) | 100 % (n=48) | 100 % (n=126) | 100 % (n=379) |

*NB there are several possible methods of use*

*Source: TREND/OFDT (Bello et al., 2004)*

In addition to the risk of viral contamination, injection of HDB amplifies the risk of respiratory depression and overdose, particularly when it is associated with the use of benzodiazepines or alcohol (Pirnay *et al.*, 2002) and this seems especially to be linked to the use of supra-therapeutic doses.

In particular, the injection of tablets of Subutex®, which contain HDB but also various excipients, is the cause of abscesses, significant and persistent oedema of the hands and forearms (boxing glove and Popeye syndrome) deep-vein thrombosis and necrotic ulcerations of the skin. They can also cause systemic candida infections with secondary locations in the prostate, bones, joints or skin (Bello *et al.*, 2002).

The data collected from users of low-threshold facilities show that the probability of the presence of abscesses or swelling of the hands or forearms is twice as high in Subutex® injectors than in injectors who said that they had not used Subutex® in the past month (Table 27).

**Table 27: Frequencies and odds ratios (OR) of problems linked to injection in injectors during the past month depending on whether or not they had injected Subutex®**

| | Subutex® injectors | Injectors of other substances | OR and confidence interval of 95% | |
|---|---|---|---|---|
| Abscess | 31% | 19% | 1.9 | [1.2 – 3.1] |
| Injection difficulties | 68% | 55% | 1.7 | [1.1 –2,-6] |
| Blocked vein, thrombosis, phlebitis | 42% | 30% | 1.7 | [1.1 – 2.5] |
| Swelling of hands or forearms | 44% | 26% | 2.3 | [1.5 - 3.5] |
| Febrile episodes | 27% | 22% | 1.4 | [0.9 – 2.1] |
| Haematoma | 44% | 36% | 1.4 | [0.9 – 2.1] |

*Source: TREND/OFDT (Bello et al., 2004)*

## Polydrug use in subjects on HDB

As for subjects treated with methadone, patients treated with HDB are also seen to use other psychoactive products in parallel with the treatment (Bello *et al.*, 2004; CEIP de Marseille, 2003). This use is, however, greater in users who are not under medical supervision that in those who are (Table 28).It has been noted in fact that users of low-threshold facilities who are on HDB are much more likely to use more than one drug: 53% use benzodiazepines, 48% cocaine, 32% ecstasy, 26% heroin, 25% Flunitrazepam (Rohypnol®), 23% crack, 21% amphetamines etc.

**Table 28: Use of psychoactive substances by users of specialised drug treatment centres (CSST) according to whether or not they are taking part in a treatment protocol**

| Substances used | Methadone protocol | HDB protocol | HDB without protocol |
|---|---|---|---|
| Heroin | 13% | 8% | 27% |
| Cocaine | 10% | 6% | 19% |
| Alcohol dependence | 20% | 17% | 22% |
| Codeine | 1% | 1% | 0% |
| Benzodiazepines | 22% | 21% | 37% |
| Antidepressants | 9% | 8% | 1% |
| Tranquillisers | 7% | 7% | 4% |
| Average number of substances | 2.2 | 2.0 | 2.0 % |

*Sources: OPPIDUM/CEIPs/AFSSAPS*

The use of illicit drugs decreases as treatment progresses (Duburcq *et al.*, 2000; Fhima *et al.*, 2001b). On the other hand, these data raise the question of alcoholisation of patients undergoing substitution treatment and the persistence of significant use of benzodiazepines. For instance, the AIDES survey (AIDES, 2002) carried out in 2001 among patients receiving substitution treatment at treatment centres or in general practice shows that 26% used benzodiazepines and 72% used alcohol. In the same way, the SPESUB survey showed that alcohol dependence originally declared by 20% of patients involved 32% of them 2 years later (Tracqui *et al.*, 1998).

Health insurance (Assurance Maladie) data confirm the existence of significant prescription of benzodiazepines with substitution treatments: in the second half of 2002, over 13 cities (A. Cadet-Taïrou and Cholley, 2004), 47% of patients who had acquired HDB received a prescription for benzodiazepines. Some patients may receive a substitution treatment and benzodiazepines by doctor shopping (since a patient may obtain different products from several different prescribers). However, combined prescriptions from a single doctor are frequent (56% of GPs in a study in the Marseilles district (Ronflé *et al.*, 2001) which showed that HDB/benzodiazepines combination is also a practice of doctors for some patients).

Deaths associated with the presence of HDB were reported by several sources (M. Reynaud *et al.*, 1998; Tracqui *et al.*, 1998; Kintz, 2001). HDB is, in almost all cases, found in association with other substances, particularly benzodiazepines. It is not at present possible to quantify the phenomenon exactly as there have been no systematic samplings. Out of 119 cases of death with presence of buprenorphine (Kintz, 2001) which occurred between 1996 and 2001 and in which it was possible to carry out toxicological analyses, other psychoactive medicines were found to be present in 113 cases (Benzodiazepines, antidepressants, tranquillisers).

The risk of death also seems to be associated particularly with intra-venous injection (Baud, 2000; M. Reynaud *et al.*, 1998; Tracqui *et al.*, 1998) and could be greater in the case of *occasional* combination of substances.

The data available, although patchy, tend however to confirm the existence of a greater risk with methadone than with Subutex® (Auriacombes *et al.*, 2001).

## Doctor shopping and parallel market for HDB

In terms of value, HDB is eleventh in the list of medicines refunded in France, at 110 million Euros in 2002 (Assurance Maladie, 2003), and a considerable proportion of the refunds seem to correspond to prescriptions which are not for therapeutic use.

Doctor shopping is when a patient consults several different doctors at the same time for the purpose of obtaining a greater daily dose of medicines than prescribed by a single doctor. It can be linked, to the need felt by the patient for larger doses than prescribed by the reference doctor if he *or she considers this dose to be* too low, especially if he or she is injecting or and multiplying the doses over the day. It can also be a way of obtaining more of the substance in order to resell some of it.

There has been evidence of doctor shopping for several years from data from Assurance Maladie (Cholley and Weill, 1999; Fumeau *et al.*, 2000; Damon *et al.*, 2001; V. Pradel, 2003; Claroux-Bellocq *et al.*, 2003; A. Cadet-Taïrou and Cholley, 2004). The use of doctor shopping for trafficking purposes seems to involve between 6% and 10% of the people who receive an HDB prescription (around 5,000, assumed to be users).

This activity seems to be concentrated in some cities. A study of the 2002 data from 13 cities showed that Paris and its northern suburbs, Marseilles and Toulouse are the places where trafficking is most frequent, while other sites are practically free from it (Table 29). The use of an indicator representing the proportion of HDB potentially dispensed and diverted locally to the black market suggests that the quantities involved are far from negligible in the concerned areas (V. Pradel *et al.*, 2003; A. Cadet-Taïrou and Cholley, 2004). From 21% to 25% of the quantities sold annually in France may be diverted towards the parallel market.

**Table 29: Classification of 13 cities according to three indicators showing doctor shopping and diversion activity**

| | Lille<br>Rennes<br>Metz and Dijon | Nice,<br>Bordeaux,<br>Lyon,<br>Grenoble,<br>Montpellier | Bobigny,<br>Toulouse<br>and Marseilles | Paris |
|---|---|---|---|---|
| average % of patients who had consulted at least 5 different prescribers | 2% | 4% | 8% | 11% |
| average % of patients receiving more than 32 mg per day | 1% | 3% | 8% | 12% |
| Proportion of HDB potentially diverted | 7% | 12% | 25% | 40% |

*Source: CNAMTS data, OFDT processing (A. Cadet-Taïrou and Cholley, 2004)*

The numerous indicators attest to the existence of a parallel market and to easy accessibility. In the specialised drug treatment centres, 10% of patients on buprenorphine in 2002 obtained the treatment illegally (CEIP de Marseille, 2003). In the low-threshold facilities in 2003, 24% of users obtained their supplies exclusively on the parallel market and 25% mixed lawful (prescriptions) and unlawful supplies.

The price of the 8 mg tablet on the black market seems very modest (median price 3 Euros in 2003 (Bello *et al.*, 2004)). It varies depending on the city, from 1 Euro (Paris) to 4 Euros

(Dijon, Bordeaux), according to the intensity of the local market (the pharmacy price is 24.2 Euros for 7 tablets, i.e. around 3.5 Euros per tablet).

The changes in the different indicators over the 2000-2002 period show a significant growth in the phenomenon of diversion (A. Cadet-Taïrou and Cholley, 2004). In 2002, observations by the TREND network showed an increase in the presence of Subutex® on the parallel market, mostly in cities (Bello *et al.*, 2003). Its median price dropped by 50% between 2000 and 2003, which is evidence of the increased availability of Subutex® on the black market over the last few years. These figures led Assurance Maladie to set out a plan in April 2004 which was aimed at reducing polyprescriptions for HDB.

## Conclusion: observations which lead to questions

After eight years of important development in substitution treatments in France for methadone and HDB, the current situation appears to be one of contrast.

Compared to the situation which already existed in 1996, the life of very many users has been transformed by the inrush of substitution treatments and the breaking of the vicious circle of dependence, heroin-taking, withdrawal syndrome. Breaking this circle gave both users and those treating them time to seek answers to the social, medical and psychological problems caused by use of substances. So we note with satisfaction that it has enabled opiate-dependent people to have better access to treatment and to improve their social situation, although it can not solve all the problems. For instance, in spite of the shortening of the drug abuse career and greater closeness between users and the treatment system, contamination by hepatitis C persists at a significant level.

At the same time, we note that HDB is the object of significant, increasing trafficking and is extremely available on the black market, that injection of HDB is frequent and is accompanied by injuries which are sometimes dramatic, that addictions to HDB are developing and that deaths have been described which are associated with HDB.

Because the background to its appearance was the struggle between supporters of risk reduction and some specialist workers, HDB is still passionately debated in France. Eight years later, however, we need to find an equilibrium which will enable users who need it to benefit from the positive results, while limiting the negative consequences.

The great availability of HDB on the black market is linked to the relative ease with which several prescriptions can be obtained. Limiting trafficking involves the responsibility of all the actors (patient, doctor, pharmacist, Assurance Maladie). The extent of HDB injection, sometimes by people who are part of a treatment system, poses the question of diversifying the forms of substitution on offer which, in 2004, are still exclusively provided orally. In counterpoint to the almost complete absence of misuse of methadone because of the system under which it is prescribed and its galenic form (syrup), is the role of the HDB prescription treatment system or systems in the misuse recorded.

All these points will certainly be dealt with at the national consensus conference on treatment strategies for opiate-dependent persons, to be held in June 2004.

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