Opioid substitution treatments in France: recent data

Nearly twenty years after they were first launched in France (1995), opioid substitution treatments (OSTs) remain a cornerstone of the country’s harm reduction policy. As part of medical, psychological and social treatment, OSTs promote access to care for opioid-dependent drug users and reduce morbidity, mortality and social harm [1]. While the relevant population continued to grow, the efficacy of OSTs is clearly recognised from a social health point of view. The latest 2013-2017 Government Plan for Combating Drugs and Addictive Behaviours, aims to improve the quality of patient treatment and enhance accessibility of these treatments (see box on page 5).

This analysis presents a summary of the latest OST data available. It is a follow-up to a series of studies initiated in 2002 of opioid substitution medication (OSM) reimbursement data1. Other sources (see page 6) are also used in this issue of Tendances, which begins with presenting an estimate of the number of people receiving OSTs in France and in Europe. Then, there is a description of the relevant population, distinguishing between approaches to follow-up and treatment dispensing as well as a discussion of the issue of misuse and diversion. There is also a discussion on the control measures put in place and OSM-related morbidity and mortality risks. Finally, there is a brief discussion on “the French model” of substitution therapy.

Relevant population size

High dose buprenorphine (HDB) and methadone have had marketing authorisations (MAs) since 1995 (see box on page 2). Initially commercialised alone as Subutex®, since 2012 HDB has also been available in combination with naloxone. Naloxone, sold under the trade name Suboxone®, is intended to prevent misuse by causing withdrawal symptoms in the event of use by the injectable route. Finally, although there is no MA for this indication, morphine sulphates (Skenan®, Moscontin®), which are major analgesics, are sometimes prescribed within the scope of opioid dependence. Prescribing these drugs for substitution is rare according to the available information; therefore, they have not been integrated into this analysis.

In France, the most frequently prescribed OSM is HDB. Its use rose sharply from 1996 to 2003, and then more gradually, but still steadily, from 2003 to 2013 (see Figure 1). The only year that saw a steeper rise was 2006; this was undoubtedly due to the introduction of HDB generics2. The quantities of HDB sold (alone and in combination with naloxone) continued to rise until 2013 without a clear change in trend, indicating a limit to the increase in prescriptions, as seemed to be the case in the early 2000s.

Methadone use initially developed slowly, and then picked up starting in 2004, the year of the Consensus Conference on Substitution Treatments [1], which advocated better accessibility to such treatments. The proportion of methadone used among OSMs in 2013 was 30% (see Figure 1). The data on people reimbursed by substance and dosage form provides additional information on the trends seen. For methadone, the number of people receiving the capsule form, which has been available since 2008, rose sharply. In the second half of 2013, for the first time there were more people treated with the capsule form than with the syrup form. The number of people taking HDB dropped slightly in 2008 with the introduction of methadone capsules, and then rose again the following year before stabilising from 2009 to 2013. The decrease in the number

1. The words “opioid substitution medication” refer to pharmaceutical products, while “opioid substitution treatments” refer not only to the prescription of OSMs but also to any accompanying treatment.
2. In 2014, six HDB generics are being commercialised in France: Buprenorphine Arrow®, Buprenorphine Biogaran®, Buprenorphine EG®, Buprenorphine Mylan®, Buprenorphine Sandoz® and Buprenorphine Teva®.
of people taking HDB only observed in 2012 was offset by the launch of HDB combined with naloxone (see Figure 2).

The comparison of the trends seen in Figures 1 and 2 reveals a discrepancy between the 2009-2013 variations in HDB quantities sold and the number of people prescribed this OSM. The former group increased by 7% while the latter group remained stable. This difference may first and foremost be due in part to the inaccuracy of the measurements. However, it may indicate a narrowing of the gap as well as a widening. Two other hypotheses can be mentioned: an upward trend in the number of prescribed doses and/or an increase in the prescription duration. Regardless of the reason, if the number of people receiving prescriptions remains stable in 2014, logically the quantities should also reach a limit.

In 2012, half of the patients treated with HDB received only the originalator drug (original reference form), one quarter received only the generic form and one quarter received both forms. The methadone capsule form, which was launched in 2008, was prescribed at least once in the last year to 47% of the people who were reimbursed for this medication.

As is demonstrated by the reimbursement data of the Exanthillon généraliste des bénéficiaires (EGB, a sample of French persons with social security coverage, see Methodological reference points), HDB is the most widely-prescribed OSM: 105,000 patients were prescribed HDB in 2012, and nearly 3,500 of them were prescribed Suboxone®. Approximately 47,000 individuals were reimbursed for a methadone prescription. In total, 150,000 people were dispensed an OSM in a retail pharmacy in 2012. However, this estimate does not cover all people who received an OSM prescription. To be exhaustive on this question, there must also be consideration for those people, albeit fewer in number, who are dispensed OSMs in a retail pharmacy who were not covered by one of the main health insurance schemes or who are not reimbursed for their treatment, as well as people who are only prescribed and dispensed methadone in a health establishment or a CSAPA (National Treatment and Prevention Centre for Addiction). In these two institution types, methadone prescriptions can be dispensed either in a retail pharmacy (occasionally or systematically for stable users) or in the institution itself. For HDB, the situation is easier since nearly all prescriptions are dispensed in a retail pharmacy. The data on population numbers for both of these groups (non-EGB or people not requesting reimbursement on the one hand, and those treated only in establishments on the other hand), not integrated into the French National Health Insurance Fund (CNAM-TS) information system, are inevitably incomplete. According to the data in their 2010 activity reports, CSAPAs prescribed methadone to 23,000 users and dispensed it to 18,000 [2]. However, it must be considered that some of these patients may already have been included in the CNAM-TS data through retail pharmacy dispensing.

In total, given the various sources of information, it can be reasonably estimated that 160,000 to 180,000 patients received prescriptions for OSTs in France in 2013. Data on CNAM-TS reimbursements, which are what was mainly used in this analysis, covers approximately 90% of these people. One third of patients taking an OST receive methadone (distributed equally between the capsule form and the syrup form) and the remaining two thirds receive HDB. The breakdown between the HDB originator drug, generics and the naloxone combination product is 73%, 24% and 3% respectively.

The most recent average estimate of the number of problem opioid users was 210,000 in 2011 with a high margin of uncertainty [95% CI: 145,000 – 275,000]. When comparing the number of people taking an OST to this estimate, 86% of problem opioid users allegedly take OST, which seems credible. The territorial breakdown of patients receiving OST reveals heterogeneity from one department to the next [3].

Two very different prescription frameworks

Methadone, which is classified as a narcotic, has a stricter prescription framework than HDB (alone or in combination with naloxone). HDB is a list I drug, but is regulated by narcotics prescription and dispensing rules. This difference is related to the lesser danger involved with HDB (a partial opioid receptor agonist) compared with methadone (a pure agonist), since HDB’s depressant, and particularly cardiopulmonary depressant, effects are limited.

Methadone treatments must be initiated by physicians practising in National Treatment and Prevention Centres for Addiction (CSAPAs) or hospitals. Primary care physicians may provide follow-up care once patients have been stabilised. Experimentation with initial methadone prescriptions in a primary care setting is part of the 2013-2017 Government Plan for Combating Drugs and Addictive Behaviours. The methadone capsule form, which is more discreet than the large-volume syrup bottles and does not contain sugar or ethanol, is not intended for treatment initiation. It can be prescribed to patients taking the syrup form once they have been stabilised. Initial methadone capsule prescriptions can only be written by CSAPA or hospital physicians specialised in treating drug users.

Any physician can initiate HDB treatment. The maximum duration of prescription is 14 days for methadone syrup, while it is 28 days for HDB and methadone capsules. Both of these treatments are subject to controlled prescriptions.

Figure 1 - Quantities of HDB and methadone used from 1995 to 2013

The quantities of HDB and methadone sold are expressed in number of daily doses per day. The daily dose is 8 mg for HDB and 60 mg for methadone and corresponds to the average recommended maintenance dosage.

Sources: SIAMOIS sales data (InVS), Medic’AM sales data (CNAM-TS), Bouchara-Recordati sales data, OFDT extrapolation. These data cover all quantities prescribed in a primary care setting, in hospitals or in CSAPAs.

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3. Medications dispensed via medical prescription only are either on list I drugs, list II drugs or on the narcotics list. Narcotics carry the risk of addiction with their use and are subject to controlled prescriptions. List I medications carry high risk and list II medications are considered less dangerous.

4. These patients are those followed in CSAPAs and receiving their methadone in a primary care setting and those who, in a given year, were followed both in a CSAPA setting and in a primary care setting. Therefore, it is certain that far fewer than 18,000 prescriptions are dispensed solely in CSAPAs in a given year. No source provides information on the number of people who had prescriptions dispensed only in non-CSAPA hospitals, but this figure is probably not higher than the CSAPA figure.

5. The accepted definition of opioid problem users is derived from the definition of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), i.e., any individual aged 15 to 64 stating last-month opioid use. These are mainly heroin and OSM users, including patients who are stable with their OST. The population number estimate comes from an extrapolation of the number of people seen in CSAPAs (RECAP scheme, OFDT).
The number of users treated with OSM per 10,000 inhabitants, estimated in 2011 using sales data (which does not take into consideration methadone dispensed in CSAPAs or hospitals) can vary by a factor of 1 to 7. Alsace and Lorraine, and certain other administrative departments in Eastern France that have a proportionately high rural population (Haute-Marne, Jura, Haute-Saône) have the highest OSM user prevalences. Although certain very urban departments (such as Paris, Gironde and Bouches-du-Rhône) have the highest number of patients taking OSMs, they rank among the thirtieth in terms of prevalence.

**European comparison**

First launched in the late 1960s in countries like the United Kingdom, the Netherlands and Denmark, OSTs were introduced later in France. France also stands out from other countries in that HDB is the main OSM, like in Greece, the Czech Republic, Cyprus and Turkey. Elsewhere in Europe, methadone is the most common OSM, except in Austria where sustained-release morphine is the most prescribed OSM. In total in Europe, nearly three quarters of patients receiving substitution treatment take methadone and the majority of other patients take HDB. Other substances used as OSMs, like sustained-release morphine or diacetylmorphine (heroin) represent less than 5% of all treatments dispensed.

The absence of standardised calculation methods limits the comparability of the data. However, it is certain that France is now one of the European countries with the highest number of OST patients for its 15- to 64-year-old population. The choice of HDB as the main OST and its regulatory framework provided tremendous prescription freedom to general practitioners and high availability of these treatments compared to other countries, while limiting the number of opioid-related overdoses, which are fewer in France than in other countries, like the United Kingdom or Germany.

**Relevant population characteristics**

Most of the figures presented in the following sections on OSM prescriptions come from the CNAM-TS information system (2012 EGB) on the 90% of OST-taking patients who have their treatment dispensed in retail pharmacies and are reimbursed for them. For the population whose methadone treatment is dispensed only in CSAPAs or hospitals, the data available are presented in parallel.

**Mainly primary care prescription and dispensing**

In total, of all patients reimbursed for an OSM in 2012, 72% obtained their prescriptions exclusively through primary care physicians, 10% only in a health establishment and 18% in one or the other in the last year. The proportion of hospital-only and CSAPA-only prescriptions is somewhat underestimated since these figures do not include the 10% of patients who not only had their prescriptions delivered but also dispensed in one of these institutions. The sharing of prescriptions between primary physicians and institutions differs according to the OST. In the case of HDB, 78% of patients receive their treatment prescription uniquely in a primary care setting, 16% both in primary care and in an institution and 6% only in an institution (see Figure 3). For methadone, only 54% of patients receive their treatment prescription in a primary care setting. The proportion of mixed prescriptions is higher for methadone (27%) than for HDB due to the importance of primary care follow-up for treatment initiated in institutions. The breakdown of Suboxone® prescribers is close to what is observed for methadone (see Figure 3).

OST-prescribing primary care physicians are almost all general practitioners. The Health Barometer survey of general practitioners (INPES) conducted in 2009 demonstrated that half of all general practitioners had seen at least one opioid-addicted drug user per month. The physicians who receive opioid addicts see an average of 3.6 drug users per month. Of these, 87% prescribe an OST, with HDB prescribed more often (77%) than methadone (38%) [4].

**A predominantly male population with long-term illness (ALD)**

Patients reimbursed for an OSM have an average age of 36.2 years. People receiving HDB are a bit older than those receiving methadone (an average age of 36.6 years versus 34.9 years). Men represent more than three quarters of people receiving OSM reimbursement, and are a little older than the women (36.5 years versus 35.0 years).

In CSAPAs, patients receiving OSTs have the same characteristics in terms of age and gender (RECAP scheme, OFDT).

OSMs dispensed in the primary care setting are reimbursed at a level of 65% by the Social Security scheme. The remaining 35% are covered by complementary health insurance, complementary medical insurance (CMU-C) or by long-term illness benefits (ALD) if the treatment is related to their condition. In CSAPAs, OSM dispensing and medical consultations are free and anonymous.

Of people being reimbursed for OSMs, 40% receive CMU-C coverage, and women more often than men (47% versus 38% respectively). Patients taking HDB are more often covered by CMU-C than patients taking methadone (41% versus 38%).

Nearly 40% of people reimbursed for an OSM are treated for an ALD, and more of these patients are being treated with methadone than with HDB (48% versus 36%). ALDs are usually justified by a psychiatric condition, especially mental and behavioural problems related to opioid use: 15% of people receiving OSMs are covered by long-term illness benefits, and this phenomenon occurs more frequently in people receiving methadone (22%) than in people receiving HDB (11%). Of people receiving OSMs, 9% receive their treatment under the French ALD scheme for chronic viral hepatitis or HIV infection. People reimbursed for an OSM in 2012 were frequently prescribed psychotropic medicines. Subsequently, 45% of them were reimbursed for anxiolytics, 31% for hypnotics, 23% for antidepressants.

**Figure 2 - Half-yearly trend in the number of people reimbursed for an OSM from 2004 to 2013**

Source: CNAM-TS data, General scheme strictly speaking, excluding local mutualist sections.
sants and 16% for antipsychotics. Nearly one quarter of people reimbursed for an OSM had been hospitalised in the last year.

The median of the average daily dose was 43 mg/d for methadone and 7.7 mg/d for HDB. Of people receiving HDB, 15% had average daily doses higher than 16 mg/d, which is the maximum effective dose (see Figure 4). Of those receiving methadone, 7% had average daily doses higher than 100 mg/d (see Figure 5).

Of patients reimbursed for HDB, nearly nine in ten (87%) received regular prescriptions (the time frame between prescriptions was no more than 30 days and could be slightly exceeded if it remained under 40 days on no more than three occasions per year). The lesser regularity of methadone prescriptions can be explained by dispensing in CSAPAs or by a doubling of prescribed doses to ensure less frequent consultations.

Nearly 37% of patients being followed in CSAPAs have been taking long-term therapy for over five years (RE- CAP scheme, OFDT). In contrast with retention in treatment, discontinuation of substitution is not a priority objective of the 2004 Consensus Conference recommendations [1]. However, many patients request discontinuation of their substitution treatment, leading health professionals to rethink their practices to determine strategies, indications and procedures that contribute to this discontinuation [7].

**Population seen in CAARUDs**

In 2012, 57% of people seen in low-threshold structures (ENa-CAARUD survey) stated taking an OST (with a prescription and medical surveillance). Their average age (35.7 years) was similar to what was observed for the entire population being reimbursed for an OSM in a primary care setting, with a slightly higher proportion of men (81%). HDB is the most common OST, especially among young people, with the exception of women (for whom methadone predominates). For these people, OSTs are mainly prescribed by a primary care general practitioner (54%) and secondly by a CSAPA physician (37%) [5].

**OSTs in prison settings**

OSTs were introduced into prison settings in 1995, at the same time as for the population in general. The procedures for initiating and renewing OSTs in prison settings are exactly the same as for outside of prisons. The proportion of inmates receiving substitution treatment was estimated to be 8% in 2010, or approximately 5,000 people, 69% of whom were receiving HDB. This proportion is on the rise compared with 1998 and 2004 (when it was 2% and 7% respectively). This trend is related to the fact that OSTs are now available in all penal establishments. Moreover, the PREVACAR survey conducted in a given month by the Institut de veille sanitaire (InVS, or the French Institute for Public Health Surveillance) and the Direction générale de la santé (DGS, or the French National Health Directorate) demonstrates that, for 31% of inmates taking OSTs, treatment was initiated during incarceration [6].

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6. The average equilibrium dose for methadone is between 60 and 100 mg/day; however, higher doses may be necessary for some people.

Misuse, diversion and control measures

With the more widespread use of these treatments comes diversion and use that does not comply with prescriptions. Such misuse and diversion is usually reported for HDB. The widespread accessibility of HDB, due to how it is prescribed and the fact that it can be injected, have promoted the misuse of the substance. Thus, according to the OPPIDUM survey (2012), which was conducted primarily in CSAPAs, 10% of people taking HDB had injected it in the last week and 10% had snorted it in 2012 [7]. The primary substance that most often leads users to consult for treatment is an OSM for 3% of CSAPA users, representing 7,000 people per year according to RECAP (OFDT). In CAARUDs, HDB is mentioned by 16% of users as the “primary substance used in the last 30 days”. For methadone, this proportion was 4% [5]. Established in 2004, the French National Health Insurance Fund’s 2004 plan for controlling and monitoring opioid substitution treatments involves individually identifying and monitoring people who are dispensed more than 32 mg of HDB per day, as those who have at least five prescribers or five dispensing pharmacies. Having several prescribers and frequenting several pharmacies may be a method for procuring OSMs for dealing purposes. In 2012, as in 2006, 2% of people being reimbursed for HDB had a daily dose of over 32 mg, whereas this proportion was 6% in 2002 [8]. In 2012, for HDB as well as for methadone, 1% to 2% of people being treated had five or more prescribers (10% had three or more) and 1% had five or more dispensing pharmacists (12% had three or more). Despite these control measures, there is still HDB diversion. Small-scale street dealing mainly by people who are selling part of their treatment has been reported by various OFDT TREND scheme sites [9]. More structured trafficking involving individuals seeing multiple physicians to receive prescriptions for high quantities of OSMs or people who steal prescriptions or health insurance cards seem to be rare given the limited number of such reported cases. The 2011 average price of an 8 mg tablet on the black market varied from €3 and €5, depending on the TREND scheme site. Only the originator drug (Subutex®) was present on the black market because generics have a reputation for being more difficult to inject or snort due to their excipients. The methadone syrup form has been misused as an occasional “spare supply” between users helping each other out. The capsule form is also used for these purposes. With increasing frequency, “self-treated” street methadone users end up consulting CSAPA physicians for treatment. Moreover, the Paris, Marseille and Rennes sites report cases in which precarious Eastern European populations inject diluted methadone syrup using large 10 ml syringes. This practice remains marginal. There have been no reports of methadone capsule injection [9].

Morbidity and mortality related to OSMs

The main risk of OSMs is that of fatal overdose, a risk that is heightened by concomitant benzodiazepine or alcohol use. In 2012, 60% of deaths by overdose were at least partially caused by OSMs; methadone was involved in 45% of these, while HDB was responsible for 15%, according to the results of the DRAMES survey (ANSM-Grenoble CEIP-A) [10]. In 2006, the ANSM implemented an opioid addiction and substitution treatment harm management plan with reinforced national pharmacovigilance and addiction vigilance. A report on the period from 2008 (when methadone was commercially launched) to 2013 concluded that there were still accidental paediatric intoxications (79 cases), although parents were responsive and helped limit the severity of such intoxication cases. The increase in the number of deaths involving methadone was compared in this report with the decrease in the number of deaths involving heroin and with the increase in the number of misuse cases (and especially those related to illegal procurement, capsule snorting, occasional use or intake by naive subjects) [11]. Like for the injection of other substances, HDB injection leads to circulatory complications (thromboses, phlebitis, “Puffy hand syndrome”) and infectious complications that can be viral (hepatitis B or C, HIV infection), bacterial or fungal (e.g., skin abscesses, septicemia, endocarditis or arthritis). Moreover, in 2011, the Centres d’évaluation et d’information sur la pharmacodépendance et d’addictologie (CEIP-A or French Network of the Regional Abuse and Dependence Monitoring Centres) was alerted by reports of skin lesions – evolving into necrosis in some cases – following the intravenous injection of crushed, diluted sublingual HDB tablets. The majority of reported cases had occurred with HDB generics containing excipients (such as talc and silica) that were not present in the originator drug. A new generic formulation will be available in late 2014. It will contain neither talc nor silica.

Other, less serious adverse reactions can change the quality of life of OSM-treated patients and be exacerbated by the poor hygiene seen more frequently in this population. Hence, OSMs, like all opioids, can generate reduced saliva production, dental and gingival problems, weight gain, excessive perspiration, constipation, libido disturbances and sleep disorders. Moreover, the frailty of people receiving an OST exposes them to other comorbidities, such as infection, psychiatric problems, accidents and suicide, etc.

Conclusions and outlook

Based on easy and widespread access to HDB, the French substitution model provides a second option, or for more precarious users, an opportunity to initiate methadone treatment. This system provides users with a smooth transition from a specialised environment to a primary care environment through the development of follow-up networks and practices. In the past 20 years, this OST organisation, associated with other harm reduction measures, has helped decrease the number of deaths by opioid overdose, control the HIV-AIDS epidemic among injecting drug users, and more generally, has improved the health and living conditions of opioid-addicted people. The
high prevalence of HCV remains troubling. Even when one considers a possible underestimation of their number, there are fewer fatal overdoses in France than in large neighboring countries, like the United Kingdom or Germany, where methadone is almost exclusively used for OST. This must be credited to the French model, at least in part. The flip side is a certain, apparent level of misuse. The French National Health Insurance Fund’s control policy, which seems to have been partially effective even though misuse persists, and the balance re-established with methadone are responses that attempt to correct the flaws of the French model and improve the situation and health of opioid-addicted drug users.

The quality of OST patient treatment and the surveillance of morbidity and mortality indicators in drug users remains a priority. Hence, expanding the range of therapies, initiating primary care methadone prescriptions [10], establishing programmes for distributing naloxone to opioid users and providing equal access to OSTs throughout France (including in rural areas) are evidence of actions taken.

In terms of observation, it is now possible to quantitatively analyze how people access OST in the general primary care setting (giving rise to reimbursements) and what their mortality is using longitudinal data from National Health Insurance Fund reimbursement information. This source enables nine in ten OST patients to be observed. A more detailed analysis of the treatment pathway of problem opioid users, both in specialised and in general settings, would require a qualitative approach to add useful information to reimbursement data. Finally, knowledge on OSTs in the prison setting needs to be updated.

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**bibliographie**


11. ANSM, Compte rendu de la séance n° 4 du 19 septembre 2013 de la Commission des stupéfiants et des psychotropes.

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**methodological reference points**

**Sources of information on the OST-taking population**

The population being dispensed an OSM in the primary care setting was studied using data on the French National Health Insurance Fund’s “EBG” general population sample from 2012. The EBG is a permanent representative sample of the population protected by the general health insurance scheme (excluding students and public servants), the agricultural worker health insurance scheme (MSA) and the independent worker health insurance scheme (RSI). It comprises 1/97 of the list of Social Security numbers, grouping more than 600,000 beneficiaries in 2012.

The database resulting from this sample contains some sociodemographic data and all reimbursed health services and treatments (e.g., medical consultations, medicines and laboratory work). There are also medical data on long-term illnesses (ALDs) as well as from the medicalised information system programms (PMSI) covering medicine, surgery and obstetrics. The CNAM-TS has made the EBG available to several health agencies, including the ANSM. The data presented here were extracted by the ANSM. Moreover, every six months since 2004, the CNAM-TS has been counting the number of people being reimbursed for OSMs.

The population receiving OST and followed in National Treatment and Prevention Centres for Addiction (CSAPAs) is analysed using two sources:

- CSAPA activity reports, of which the most recent to have been used by the OFDT and the DGS date back to 2010 [2].

- The Common Data Collection on Addictions and Treatments (RECAP), which continuously collects information on people seen in CSAPAs (current treatment, treatment follow-up, substances used and patient health), the most recent of which dates back to 2012.

The population treated with OSMs and followed in low-threshold structures (CAARUDs) is compared with that of the exhaustive biennial ENa-CAARUD survey for a given week on use, use behaviours, screening and the social situation of CAARUD users. The latest edition was conducted in 2012 [6].

Even though these three populations partially overlap, they each have specific characteristics. CAARUD users are characterised by active drug use and tend to be in more precarious situations, while CSAPA users more frequently request methadone prescription and treatment; finally, patients being dispensed treatments in a primary care setting are more stable in their treatment and are more frequently prescribed HDB.

OSM sales data come from the SIAMOIS scheme (InVS) and from Bouchara-Recordati for methadone. For HDB, 2012 and 2013 sales data are estimated using Medic’AM reimbursement data (CNAM-TS).

**Credits**

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