

# Why Buprenorphine Is So Successful in Treating Opiate Addiction in France

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In France, all registered medical doctors have been allowed to prescribe buprenorphine without any special education or licensing since 1995. This has led to a rapidly increasing number of opiate-dependent users under buprenorphine treatment in primary care. French physician compensation mechanisms, pharmacy services, and medical insurance funding all have contributed to minimizing barriers to buprenorphine treatment. Approximately 20% of all physicians in France are prescribing buprenorphine to treat more than one half of the estimated 180,000 problem heroin users. Intravenous diversion of buprenorphine may occur in up to 20% of buprenorphine patients and has led to relatively rare overdoses in combination with sedatives, whereas total opiate overdose deaths have declined substantially. In France, buprenorphine maintenance treatment for problem opiate users was feasible and safe through office-based prescriptions in a relaxed regulatory environment.

## Introduction

Opiate-agonist pharmacotherapy increased in popularity in Europe during the 1990s, and for the most part, the medication of choice for clinicians was methadone, mostly in center-based treatment settings in the context of somewhat tight regulations [1]. The fear of fatal methadone overdose among both patients and opiate users who might obtain methadone through diversion has been one rationale for restrictive methadone regulations worldwide. Except for a few limited European metropolitan areas such as in the Netherlands (Amsterdam) and Switzerland (Geneva), for most European countries, the average number of methadone-treated opiate problem users represents only 20% to 30% of those estimated in need of treatment [1–3].

In Europe, buprenorphine for the treatment of opiate addiction was first registered in France and by the year 2000

was available in eight Member States. However, its availability to most potential patients continued to be limited in comparison with methadone treatment [4]. In contrast, in France, buprenorphine treatment for opiate dependence has spread out quite rapidly since the mid 1990s. It was estimated in 2003 that 77% (83,000 of 107,000) of the buprenorphine-treated patients in Europe were in France [5•]. Another important change in France, in contrast to other European countries, is that most buprenorphine-treated patients receive their buprenorphine prescriptions from general practitioners (GPs) in primary care or office-based settings, with dispensing in community-based pharmacies happening in a relaxed regulatory context.

In 1986, after an initial experience with opium tincture, our group began using buprenorphine for opioid dependence, with dispensing in community pharmacies [6,7]. Based on our experience and that of others, by 1996, buprenorphine treatment was a registered medication, and this treatment could be prescribed by all registered medical doctors without a requirement for any supplementary educational program or special licensing, exactly as for any other medication. Indeed, the large majority of buprenorphine prescribers in France are office-based GPs with no initial specialty certification in addiction or psychiatry. The French experience since 1996 in using buprenorphine and training and regulating family physicians is informative for worldwide efforts to facilitate problem opiate users' access to treatment [8].

The French approach has potential advantages and drawbacks. On one hand, making treatment easier to access could increase the number of individuals in treatment; on the other hand, a lack of regulation could increase the occurrence of buprenorphine side effects or diversion to clinically inappropriate patients and thus limit the overall benefit of this medication.

In this paper, the reasons for the increased popularity of buprenorphine for the treatment of opiate dependence in France and its consequences are documented.

## What Does “Buprenorphine Treatment” Mean in the French Context: Hidden Contributing Factors (GPs, Office-based Settings, Funding)

Before the availability of buprenorphine as a registered medication in 1996, GPs were discouraged from getting

involved with problem opiate users, who were oriented to specialized treatment centers, many of which offered strong psychosocial support with little access to medical services. It was estimated then that only 15% to 30% of the estimated 150,000 to 200,000 problem heroin users had contact with specialized settings. In parallel to the introduction of buprenorphine in 1996, GPs were encouraged to treat opiate-dependent individuals in the office setting. By the late 1990s, it was estimated that GPs were treating 65,000 patients per year with buprenorphine and another 6000 patients with methadone. In 2003, it was estimated that 83,000 patients were being treated with buprenorphine: 13,000 in specialized centers and 70,000 in office-based practice. A year before the introduction of buprenorphine in France, methadone treatment, until then restricted to three treatment centers, was extended to all opiate addiction treatment centers on a regulatory basis similar to that in most countries in which it was available [9]. In addition, efforts were made to increase access to medical services within these centers. By 2003, it was estimated that 17,000 patients were being treated with methadone. Hence, the total coverage for opiate agonist treatment in France in 2003 was estimated to be more than 55% [10], way up from less than 3% in 1995. A little more than 80% of these patients were in buprenorphine treatment, and the large majority were treated by office-based family physicians and had treatment dispensed in community pharmacies. The most recent data (Daulouede, Personal communication) report that there were 95,000 buprenorphine patients and 26,000 methadone patients in 2006, meaning that more than 67% of opiate problem users were in pharmacologically assisted treatment.

Buprenorphine is provided mainly by GPs—91% to 99% of all prescriptions according to the geographic area [11]. However, 26% of overall French physicians prescribed buprenorphine to 75% of overall patients in buprenorphine maintenance treatment. These physicians are more often members of a health care network and trained in drug maintenance treatments, which may reflect special motivation and involvement in management of opiate-dependent subjects [12]. Although there is no regulatory training required of physicians prior to them prescribing buprenorphine, the majority of patients are receiving prescriptions from physicians who have had extra training in addiction medicine and who are involved in community-based treatment networks.

Many contextual factors contribute to buprenorphine treatment in France and have to be taken into consideration to understand the overall outcomes and possible generalization to other regions of the world. These include the role of buprenorphine's pharmacology versus that of methadone, the involvement of GPs over specialist practitioners, the importance of office-based setting versus center-based settings, and issues of funding and health insurance.

All these play a role in the overall outcome of "buprenorphine treatment in France."

### **Pharmacologic profile of buprenorphine**

Studies have shown that buprenorphine can be effective in treating opiate dependence and that buprenorphine's effectiveness was similar to that of methadone in terms of retention rates and reduction in drug use when controlling for early dropout [13,14]. In addition, it has been argued that the pharmacology of buprenorphine provides a number of benefits [15]. Like methadone, buprenorphine is a long-acting oral medication used to stabilize opiate-addicted patients and reduce or prevent craving. Unlike methadone, this long duration of action is not due to a long plasma half-life, but rather to its high affinity for the  $\mu$  receptor. However, buprenorphine differs from methadone in that it is a partial agonist at the  $\mu$  receptor, making overdose unlikely. Drug cessation is associated with milder levels of withdrawal distress, and the long duration of its action permits more flexible dispensing options such as every other day administration. Buprenorphine's pharmacology makes it theoretically unlikely to be a substance of abuse among regular opiate users because of its mixed agonist-antagonist action, slow onset, and ability to precipitate withdrawal among users of pure  $\mu$  opiates.

### **Methadone and buprenorphine prescription regulations in France**

It is clear in France that the difference in regulation of buprenorphine and methadone treatment contributes to the different prevalence of use of these two medications and to the increased number of buprenorphine-maintained patients in comparison to methadone-maintained patients.

Only physicians working in state-licensed substance abuse clinics or hospitals can initiate a methadone prescription that is initially dispensed only on site. Urine testing is compulsory. Once the initial prescriber has determined that the patient is stabilized, clinical management of the patient and methadone prescription may be transferred to any medical doctor. At that point, dispensing may be done from any pharmacy in the same manner as for buprenorphine. Buprenorphine's regulation is very different. Any physician working in office-based settings can prescribe buprenorphine, and any pharmacy can dispense it. No specific training is required. The maximum duration of a buprenorphine prescription is 28 days, and the maximum number of take-home doses is seven. However, a physician can override this rule either by requesting that the pharmacist provide daily, supervised dosing of buprenorphine or dispense up to 28 days of take-home doses. There is no regulatory requirement for urine testing.

### **Characteristics of French health organization**

Another explanation for the dramatic and safe increase in the number of opiate-dependent patients being treated might be found in the overall organization of the health care system [16]. The French health care system is orga-

nized on a pay-per-service basis, with universal medical coverage. The Social Security system acts as a universal medical insurance that covers more than 90% of the population, regardless of their economic situation, legal status, or nationality. This facilitates the treatment of marginalized individuals. A GP is paid 21 euros for an office visit, regardless of duration or frequency. Ordinary consultations are reimbursed at a 65% replacement level. However, if the patient has a chronic illness, reimbursement covers 100%, and the payment can be made directly from Social Security to the GP. Because opiate dependence qualifies as a chronic illness in the French health care system, payment is fully covered by Social Security. In addition, there is a dense psychosocial support service funded by local authorities at no charge to those in need. Further, patients with opiate dependence can be treated in special substance abuse treatment centers supported by Social Security funds. French pharmacies provide a range of clinical services. For example, the medication itself can be dispensed and taken at the pharmacy under the pharmacist's supervision daily, if required. In this context, pharmacists play a crucial role in the dispensing of treatment, in monitoring clinical improvement of subjects, and in informing the prescriber about any difficulties. Overall, the French health care system supports a substantial amount of care within primary care settings through medical and social support and through the possibility of supervised dispensing through pharmacy services.

Taken together, these different factors have contributed to the success of buprenorphine treatment in France. Accessible psychosocial and medical services, supported by the organization of French health care system, have particularly enhanced the management of opiate addiction through office-based settings. This office-based primary care model increased the number of heroin problem users accessing treatment, far exceeding treatment access to methadone programs in specialist centers. This impact was parallel to low-cost actions. Currently, treatment dispensed in French primary care settings appears to be a cost-effective strategy for treating opiate-dependent subjects compared with specialized centers [17].

### What are the Main Outcomes of Buprenorphine Treatment in France?

Buprenorphine maintenance treatment for problem heroin users in France has been associated with consistent public health, social, individual, and economic benefits [18].

Studies have reported a significant decrease of heroin use and injection practice and an improvement in the social conditions of those in treatment [19,20]. Data also suggested among those who inject a decrease of risk-taking behavior related to injection, such as needle and paraphernalia sharing [11,21]. Similarly, De Ducla et al. [22,23], in a retrospective study carried out among drug-dependent outpatients treated by GPs, collected data concerning the initial prescription, the first stabilization prescription, and

the most recent prescription for the period between June and December 1997. Results indicated a decrease of close to 50% in both heroin and benzodiazepine use over time in treatment. The authors also showed that persistent benzodiazepine use among buprenorphine-treated individuals was related to less supervised dispensing and lower buprenorphine dosage. In a prospective study [20,24] comparing patients at baseline and 2 years later, other authors found that 80% of those still in contact with the health care system (typically a GP) were still being prescribed buprenorphine and had reduced significantly heroin use and also polydrug use (including benzodiazepines). Measures of social adaptation also showed improvement. Another study documented in particular the positive impact of buprenorphine on the social conditions of patients [19], indicating that all markers of social vulnerability assessed through standardized questionnaires (employment, housing, social insurance, days of in-patient treatment related to drug consumption, and number of convictions) were improved after a 6-month period with buprenorphine.

Another consistent impact is the dramatic decrease in the reported overdose deaths since the development of drug substitution, buprenorphine in particular. In France, overdose deaths are registered by police [25]. The causes of such deaths are determined on the basis of on-site evidence. This source of information is, as in most countries, considered to be an under-representation of true involvement of all drug involvement. As country-specific methodological, legal, and political issues affect this reporting, the data cannot be compared among different countries. But as the monitoring system has been unchanged for many years, it is appropriate to compare the development of overdoses from year to year within France [26]. In this regard, the French overdose mortality monitoring system shows a consistent decrease in overdose deaths from the peak recording in 1994 to the present. From 1995 to 1999, the number of overdose deaths declined by 79%, whereas the overall number of opiate-abusing individuals in either buprenorphine (80%) or methadone (20%) treatment increased by more than 95% (from < 2000/y to > 60,000/y). Some authors suggested that the increase in buprenorphine-treated individuals is a major cause for the decline in overdose deaths [27]. However, it should be acknowledged that during this same time, there was a development of syringe exchange programs and a possible change in attitude toward intravenous drug users by health providers [28•].

### What are the Problems Related to Buprenorphine in France?

#### Mortality related to buprenorphine

Deaths due to buprenorphine misuse are very rare, and it is thought that the risk of overdose is lower with buprenorphine than with other opiates because of its agonist-antagonist pharmacologic characteristics (ie, beyond a certain dose, a further increase does not result in any

further increase in effect) and because its usual administration is sublingual.

Despite this, buprenorphine-related deaths from France and other European countries have been reported [29,30]. However, data are very limited, and in most cases, buprenorphine is detected in the blood together with other substances, often benzodiazepines or alcohol. Several authors have reported deaths in which buprenorphine was considered as a contributing or causal factor [31–35]. From 1996 to 2000, a total of 137 such deaths in France were reported. In all of these cases, buprenorphine was found by systematic analytical toxicology regardless of clinical context, information that was very often lacking. Benzodiazepines and other central nervous system respiratory depressants were identified in addition to buprenorphine in all but one of those cases. On average, more than three psychotropic medications were mentioned in these deaths by the following frequency: benzodiazepines (78%), cannabis (50%), neuroleptics (32%), alcohol (29%), other psychotropics (21%), and other narcotics (21%). Among the 137 case reports, only one did not have other possible explanations. Hence, a causal role for buprenorphine in most of these deaths is questionable. Overdose risk is thought to be highest with intravenous injection and concomitant use of alcohol and sedatives.

Perhaps it is most relevant to compare overdoses between buprenorphine treatment and methadone treatment over the same time frame [26], as the alternative to buprenorphine is not no treatment, but rather methadone treatment. For 1995 to 1998, the risk of death attributed to methadone was more than 10 times higher than that attributed to buprenorphine. Extrapolating from the death rate that would be expected from methadone (0.002 methadone-related annual deaths per patient treated with methadone), the number of expected buprenorphine-related deaths should have been 67 per year, or a total of 268 buprenorphine-related deaths expected from 1995 to 1998. Yet the number of buprenorphine-related deaths was only 27. In 2003, eight deaths related to buprenorphine were reported out of 72,000 to 85,000 people receiving buprenorphine treatment; by comparison, there were also eight deaths related to methadone—out of a total of 11,000 to 17,000 people receiving methadone treatment [36]. Comparing data on the number of deaths related to methadone misuse and the number of deaths related to buprenorphine misuse, buprenorphine appears to be associated with a lower risk than methadone.

#### **Diversion and abuse related to buprenorphine**

In 2004, of the 17 European countries in which buprenorphine treatment was available, 12 reported some misuse of buprenorphine, albeit often extremely rare [5•].

Diversion and abuse of buprenorphine reported in France may be due partly to its important availability. Diversion of buprenorphine to the black market is likely to concern marginalized populations, who may obtain

it from multiple providers. French surveys from medical insurance databases indicate that approximately 10% to 20% of patients collect prescriptions from more than one provider and/or filled prescriptions in several pharmacies. In contrast, 80% of patients in treatment only see one prescriber on a regular basis and went only to one pharmacy [37–39]. Several factors might be involved in the practice of “doctor shopping.” First, the French health care system and insurance policy make it easier by allowing people, regardless of the medication, to receive care and treatment from different GPs. Another factor potentially involved is subtherapeutic buprenorphine dosing, as data suggest that “doctor shopping” is less common when physicians prescribe 8 mg/d or more of buprenorphine [40,41•].

Diversion of buprenorphine via the intravenous route concerned 11% of outpatients in treatment in one study [11]. Diversion poses the problem of the risk-taking behaviors related to injection, medical complications (particularly an increased risk of liver toxicity), and the association with other substances (with possible increased risk of overdose). Studies carried out among specific populations have revealed that the proportion of buprenorphine misusers is higher among patients of low-threshold services (up to 41%) [5•]. Misuse of buprenorphine also is reported to be quite common among homeless people living in urban regions [42]. Overall, factors associated with injecting buprenorphine while in treatment are to be a polydrug user in precarious economic conditions and to have an insufficient dose of buprenorphine prescribed by a GP unwilling to respond to individual patient requests [40,43]. Nevertheless, indications of a decrease in buprenorphine injection in recent years are reported [5•]. However, the main limitation of data assessing the prevalence of buprenorphine misuse is the heterogeneity of recruited subjects. This is especially true for studies from the OPPIDUM survey [44,45]. Although data from this annual survey are of great interest, generalization is particularly difficult on the issues of buprenorphine abuse and misuse. This is because specialty treatment centers mainly (if not only) participate in that survey. These centers see only a minority of the total number of buprenorphine-treated patients. They are likely to have an over-representation of the more difficult patients referred to these centers by a GP because they needed more specialized or intensive care. Most buprenorphine patients who only see their GPs and are doing well are not represented in the survey. Hence, the OPPIDUM survey maximizes the likelihood of finding buprenorphine abuse and misuse and is therefore a very good surveillance outreach system. However, it is somewhat limited in its ability to estimate true buprenorphine misuse prevalence.

Among regular opiate users, buprenorphine’s pharmacology makes it theoretically unlikely to be a substance of abuse, and indeed, from some reports, it appears that out-of-treatment opiate users are not interested in buprenorphine. For example, in one report, 49 urine

samples were analyzed for 50 drug abusers admitted for inpatient detoxification. Nine had buprenorphine-positive urine (18% of the sample), and the majority tested positive for heroin (80%) and benzodiazepines (72%). Thus, despite the relatively easy access to buprenorphine, it appears that the large majority of French out-of-treatment opiate users are not interested in buprenorphine. One study [46,47] reported on the use of buprenorphine by individuals who were interviewed while they were accessing clean syringes from syringe exchange programs, vending machines, or community pharmacies. In this intravenous drug-using population, 57% reported that they injected buprenorphine at least once over the past 6 months. However, the majority (60% of those having used buprenorphine intravenously at least once and 34% of the total sample) reported being regular injectors of heroin and cocaine, but injecting buprenorphine only occasionally. The remaining 40% of buprenorphine injectors (24% of the total sample) declared having used only buprenorphine over the past 6 months; interestingly, the majority of those declared that they were in buprenorphine treatment. This group of in-treatment buprenorphine injectors (compared with occasional out-of-treatment buprenorphine injectors) reported less needle-sharing activities and polydrug use. The confusing factor preventing us from drawing a clear conclusion from this study's data is the heterogeneity of the studied population. The majority of patients were out of treatment, and they injected primarily heroin and cocaine, as well as buprenorphine. A significant minority was in buprenorphine treatment and only injected buprenorphine. On all variables, this latter group had better adjustment: more employment, less needle sharing, and less polydrug use. Thus, the simple prevalence of intravenous diversion may not be the best indication of the overall effectiveness of buprenorphine. This study only documents the existence of buprenorphine abuse, but even this population of regular buprenorphine intravenous abusers appears to be doing better than those who use less or no buprenorphine. Similar results with similarly limited information were found in a study focusing only on syringe exchange programs [48]. Two studies [49,50] have compared the use of the intravenous route in both methadone- and buprenorphine-treated individuals. Interestingly, the prevalence of use of the intravenous route was similar in both populations, approximately 20%. However, the buprenorphine patients were more likely to inject their own prescribed buprenorphine, whereas those methadone patients who injected were more likely to inject heroin and cocaine.

Finally, cases of buprenorphine use as first drug of abuse or dependence have been reported in France [51] in low-threshold programs. In these settings, buprenorphine as first opiate used concerned 6% of subjects, and buprenorphine as first opiate used with a diagnosis of dependence concerned 12% of subjects. These buprenorphine-dependent subjects were more likely to have a problem associated

use of alcohol or benzodiazepines and reported more often to use buprenorphine for its anxiolytic or psychotropic effect in order to relieve social or psychological difficulties.

### How to Do Better

There should always be a drive to do better, and there often is room for increasing quality of services and decreasing collateral damage. However, it is important when attempting to do better to keep an overall perspective so as to avoid unexpected adverse consequences from measures intended to do better. This balance currently is an important issue in the French situation for the treatment of opiate-addicted patients with office-based buprenorphine treatment and center-based methadone treatment. From a public health perspective, it is difficult to imagine doing any better when comparing with other regions in Europe, North America, and Australia. In a very cost-effective manner, two thirds or more of the total number of problem opiate users are either in buprenorphine or methadone treatment, and the large majority of these receive treatment from a GP. Since these important changes were implemented, over the past 10 years, opiate-related overdose mortality, HIV-drug-related prevalence, and drug-related crime have dropped dramatically [28•]. From this perspective, major changes in regulations are not easy to imagine. However, from an individual clinical perspective, cases of misuse of buprenorphine by the intravenous or intranasal routes and associated damage are of legitimate concern, as are issues related to the leaking of buprenorphine to the black market and possible clinically inappropriate use. Understanding some of the determinants of these individual behaviors can give insight as to how to do better.

Within the French treatment system, an important variable that may influence office-based treatment efficacy could be the frequency with which supervised—as opposed to take-home—doses of buprenorphine are administered. In a recent study, 202 patients were assigned quasi-randomly to daily supervised dosing for 2 weeks, 3 months, or 6 months, after which dosing was on a weekly schedule [52]. Results from this study showed that retention in treatment at the 6-month follow-up was highest for those patients in the 6-month daily supervised dosing group (80%) and lowest for those patients in the 2-week daily supervised dosing group (46%). Rates of opiate-positive urine samples were lowest for the 6-month daily supervised dosing group (14%) compared with the 3-month daily supervised (22%) and 2-week daily supervised (18%) groups. Finally, average daily doses at the 6-month assessment were similar for the three groups (7.9, 8.7, and 8.5 mg/d for the 6-month, 3-month, and 2-week groups, respectively). These results suggest that initial efficacy for office-based buprenorphine treatment may be enhanced by a more closely supervised dispensing of medication.

Finally, data suggest that the prescription of buprenorphine as a single daily dose, individually titrated for each

patient, optimizes the outcome and reduces misuse. In a retrospective study [22] carried out among GPs, the prescription of buprenorphine at a daily dose of less than 6.2 mg was associated with a higher rate of benzodiazepine use, and prescription of several daily doses of buprenorphine was associated with a higher percentage of injecting patients. This retrospective study provides evidence of a correlation between prescription practices and patient behavior.

## Conclusions

The evidence shows that allowing opiate users to acquire buprenorphine via office-based prescriptions is possible and safe. It also is true that some of the public health benefits seen during the time of buprenorphine expansion in France might be contingent upon characteristics of the French health care and social services systems and not necessarily transferable to other countries.

The French model is unparalleled in its rapid growth, and even though there was some level of diversion and continued intravenous use, it also is fair to report that there were very significant societal and individual benefits. In addition, some physicians might favor diversion. Particularly buprenorphine under-dosage, the lack of urine monitoring of drug use, and the lack of supervised dispensing in pharmacies have been shown to represent risk factors for diversion and misuse. Nevertheless, possible strategies to reduce buprenorphine diversion have to be enhanced. Among these strategies, helping health professionals, especially GPs, to be involved in health networks [53] may play a crucial role, allowing specific training in addiction treatment and facilitating interactions between primary care settings and specialized facilities.

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- Of importance
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