
Buprenorphine in the Treatment of Opioid Addiction: The French Experience

29

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Contents

29.1	Introduction	502
29.2	The French Experience	503
29.2.1	“Buprenorphine Treatment” in the French Context	503
29.2.2	Main Outcomes of Buprenorphine Treatment in France	504
29.2.3	Problems Related to Buprenorphine Treatment in France	505
29.2.4	What Is Next?	507
29.3	Conclusion	508
	References	509

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Abstract

Buprenorphine provides a number of benefits and was registered as a medication for opiate addiction treatment by the French health authorities as early as 1995. All registered medical doctors may prescribe this treatment without requiring any supplementary educational program or special licensing. The French health organizations enable a substantial care within primary care settings through medical and social support and through the possibility of supervised dispensing through pharmacy services. Overall, 26 % of French physicians prescribe buprenorphine to 75 % of overall patients in buprenorphine maintenance treatment. Buprenorphine maintenance treatment for problem heroin users has been associated in France to consistent public health, social, individual and economic benefits; might be contingent upon characteristics of the French health and social services system; and may not necessarily be generalizable as is to other areas of the world.

29.1 Introduction

It has been argued that the pharmacology of buprenorphine provides a number of benefits (Cowan and Lewis 1995). Like methadone, buprenorphine is a long-acting oral medication used to stabilize patients with opiate addiction and reduce or prevent craving. Unlike methadone its long duration of action is not due to a long plasma half-life but to its high affinity for the mu receptor. Buprenorphine also differs from methadone in that it is a partial agonist at the mu receptor, making overdose less likely. Cessation of the drug 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. Based on our experience of using buprenorphine for opioid dependence with dispensing in community pharmacies in France since 1986 (Auriacombe et al. 1992, 1994) and that of others, buprenorphine was registered as a medication for opiate addiction treatment by the French health authorities as early as 1995. All registered medical doctors may prescribe this treatment without requiring any supplementary educational program or special licensing, exactly as for most medications. The French experience since 1995 in using buprenorphine and training and regulating family physicians is informative for worldwide efforts to facilitate opiate problem users' access to treatment (Auriacombe et al. 2004). Many contextual factors contribute to buprenorphine treatment in France and have to be taken in consideration to understand the overall outcomes and possible generalization to other regions of the world. These include the role of buprenorphine's pharmacology vs. that of methadone, the involvement of GPs over specialist practitioners, the importance of office-based settings vs. center-based settings, and issues of funding and health insurance. All these play a role in the overall outcome of "buprenorphine treatment in France" (Fatseas and Auriacombe 2007).

29.2 The French Experience

29.2.1 “Buprenorphine Treatment” in the French Context

29.2.1.1 General Characteristics of the French Health System

The overall organization of the healthcare system is an important possible contributor to buprenorphine treatment in France. The social security system acts as a universal medical insurance that covers over 90 % of the population, regardless of their economic situation, legal status, or nationality (Fielding and Lancry 1993). This facilitates the treatment of marginalized individuals. A general practitioner is paid a fixed price 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 general practitioner. Because opiate dependence may qualify as a chronic illness in the French healthcare 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. The medication itself can be dispensed and ingested at the pharmacy under the supervision of the pharmacist daily, if prescribed. In this context, pharmacists play a crucial role in dispensing of treatment, in monitoring clinical improvement of patients, and in informing the prescriber about any difficulties. Overall, the French health organizations enable a substantial care within primary care settings through medical and social support and through the possibility of supervised dispensing through pharmacy services.

29.2.1.2 Methadone and Buprenorphine Prescription Regulations in France

The difference in regulation contributes to the specific French increased number of buprenorphine-maintained patients in comparison to methadone-maintained patients in contrast to most other countries worldwide. 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. In contrast, buprenorphine’s regulation is very different. Any physician working in office-based settings can prescribe buprenorphine, and any pharmacy can provide the medication. There is no requirement for any type of specific training. 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 by requesting that the pharmacist either provide daily supervised dosing of buprenorphine or dispense up to 28 days of take-home doses. There is no regulatory requirement for urine testing.

Overall, 26 % of French physicians prescribe buprenorphine to 75 % of overall patients in buprenorphine maintenance treatment (Cadet-Taïrou and Chollet 2004). These physicians are more often members of a healthcare network, trained for drug maintenance treatments, which may reflect special motivation and involvement in management of opiate-dependent subjects (Feroni et al. 2004). Hence, although there are no regulatory training requirements prior prescribing buprenorphine, the majority of patients are receiving prescriptions from physicians that have had extra training in addiction medicine and are involved in community-based treatment networks.

29.2.2 Main Outcomes of Buprenorphine Treatment in France

Buprenorphine maintenance treatment for problem heroin users has been associated in France to consistent public health, social, individual, and economic benefits (Fédération française d'addictologie 2004).

Studies have reported a significant decrease of heroin use and injection practice and an improvement in the social conditions of those in treatment (Duburcq et al. 2000; Bilal et al. 2003). Data also suggest among those that inject a decrease of risk-taking behavior related to injection, such as needle and paraphernalia sharing (Cadet-Taïrou and Chollet 2004). Similarly, in both retrospective and prospective studies (De Ducla et al. 2000; Duburcq et al. 2000; Fhima et al. 2001) carried out among drug-dependent outpatients treated by general practitioners, results indicate a significant decrease of both heroin and benzodiazepine use over time in treatment and that persistent benzodiazepine use among buprenorphine-treated individuals was related to less supervised dispensing and lower buprenorphine dosage. A study documented particularly the positive impact of buprenorphine on the social conditions of patients (Bilal et al. 2003), 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 of the reported overdose deaths since the development of buprenorphine treatment. In France, overdose deaths are registered by the police (Office Central pour la Répression du Trafic Illicite des Stupéfiants 1999). 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 underrepresentation of true overdoses. Since country-specific methodological, legal, and political issues affect this reporting, the data cannot be compared between different countries. But since the monitoring system has been unchanged for many years, it is appropriate to compare the development of overdoses from year to year within France (Auriacombe et al. 2001). In this regard, the French overdose mortality monitoring system shows a consistent decrease in overdose deaths since the introduction of buprenorphine. The number of overdose deaths declined by 79 %, while the overall number of opiate-abusing individuals in either buprenorphine (80 %)

or methadone (20 %) treatment increased by over 95 % (from less than 2,000 per year to over 60,000 per year) within the 5 years following the introduction of buprenorphine and the involvement of general practitioners. Some authors have suggested that the increase in buprenorphine-treated individuals is the major cause for the decline in overdose deaths (Lepere et al. 2001). However, it should be acknowledged that during this same time, there was a development of syringe exchange programs, an increased availability of center-based methadone treatment, and a possible overall change in attitude toward intravenous drug users by health providers (Emmanuelli and Desenclos 2005).

29.2.3 Problems Related to Buprenorphine Treatment in France

29.2.3.1 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 pharmacological characteristics and because its usual administration is sublingual.

However, some authors have reported deaths in which buprenorphine was considered as a contributing or causal factor (Tracqui et al. 1997, 1998; Reynaud et al. 1998a, b; Kintz 2001). In all of these cases, buprenorphine was found by systematic analytical toxicology regardless of clinical context information very often lacking. Benzodiazepines and other central nervous system respiratory depressants were almost all the time identified in addition to buprenorphine: benzodiazepines, cannabis, neuroleptics, and alcohol. A causal role for buprenorphine in most of these deaths is questionable. It is thought that the risk of overdose is highest with intravenous injection and concomitant use of alcohol and sedatives.

Perhaps what is most relevant is to compare overdoses between buprenorphine treatment and methadone treatment over the same time frame (Auriacombe et al. 2001), as the alternative to buprenorphine is not no treatment but methadone treatment. For the 1995–1998 period, the risk of death attributed to methadone was considerably higher than that attributed to buprenorphine – in fact, over ten times higher during the same 4-year period. 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 (Observatoire français des drogues et des toxicomanies 2005). Noteworthy, this has now been reported in other countries (Bell et al. 2009; Soyka et al. 2011).

29.2.3.2 Diversion and Abuse Related to Buprenorphine

The 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 database indicated that around 10–20 % of patients collect prescription from more than one provider and/or filled prescriptions in several

pharmacies, whereas 80 % of patients in treatment only see one prescriber on a regular basis and go to only one pharmacy (Damon et al. 2001; Vignau et al. 2001; Thirion et al. 2002). Several factors might be involved in the practice of “doctor shopping.” First, the French health system and insurance policy make it easier by allowing people whatever the medication to receive care and treatment from different general practitioners. Indeed, the French healthcare system is centered on the patient who determines when, where, and how frequently to attend health providers. Another factor potentially involved is subtherapeutic buprenorphine dosing as data suggest that doctor shopping is less common when physicians prescribe 8 mg/day of buprenorphine or more (Feroni et al. 2005; Carrieri et al. 2006).

The diversion of buprenorphine via the intravenous route varies widely between studies. Diversion poses the problem of the risk-taking behaviors related to injection, medical complications (particularly an increased risk of liver toxicity), and the association to other substances (with possible increased risk of overdose). Some studies report that 11 % or less of outpatients in treatment have used buprenorphine intravenously (Cadet-Taïrou and Chollet 2004). 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 %) (EMCDDA 2005). Misuse of buprenorphine is also reported to be quite common among homeless people living in urban regions (Blanchon et al. 2003). Specific risk factors for buprenorphine injection in treatment settings may be as follows: being a polydrug user, being in precarious economic conditions, and having an insufficient dose of buprenorphine (Blanchon et al. 2003). Interestingly, since 2005, a consistent decrease in buprenorphine injection is reported (EMCDDA 2005; Cadet-Taïrou et al. 2010). This seems to be parallel to shared concerns by health regulatory authorities and individual clinicians.

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 as a recreational drug. Despite the relatively easy access to buprenorphine, it appears that the large majority of French out-of-treatment opiate users are not interested by buprenorphine and prefer heroin when available. One study (Moatti et al. 2001; Obadia et al. 2001) 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 being in buprenorphine treatment. This group of in-treatment buprenorphine injectors (compared to occasional out-of-treatment buprenorphine injectors) declared less needle-sharing activities and polydrug use. The confusing factor preventing 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 treatment. 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 that use less or no buprenorphine. Similar results with similarly limited information were found in a study focusing only on syringe exchange programs (Valenciano et al. 2001). Two studies (Fontaa and Bronner 2001; Franques et al. 2003) 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, about 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 but not methadone, which is only available as a difficult-to-inject syrup at the time.

Finally, cases of buprenorphine use as first drug of abuse or dependence have been reported in France (Escot and Fahet 2004) in low-threshold programs. In these settings, buprenorphine as the first opiate used concerned 6 % of the subjects, and buprenorphine as the first opiate used with a diagnosis of dependence, 12 % of the subjects. These buprenorphine-dependent subjects were more likely to have a problematic 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 than just as a recreational alternative.

29.2.4 What Is Next?

Increasing quality of treatment services and decreasing collateral damage related to such services are important challenges for health authorities and individual clinicians. It is currently an important issue in the French situation for the treatment of opiate-addicted patients with buprenorphine office-based treatment and methadone center-based treatment. From a public health perspective, it is likely difficult to imagine doing any better when comparing with other regions in Europe, North America, and Australia. In a very cost-effective manner (Kopp et al. 2000), more than two-third of the total estimated number of opiate problem users are in either buprenorphine or methadone treatment, and the large majority of these receive treatment from a general practitioner. Since these important changes, over the past 10 years, opiate-related overdose mortality, HIV drug-related prevalence, and drug-related crime have dropped dramatically (Emmanuelli and Desenclos 2005). From this public health and societal 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 well as 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, such as patient motivation for use, can give insight as to how to do better (Fatseas et al. 2009).

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 study, 202 patients were assigned quasi-randomly to daily supervised dosing for either 2 weeks, 3 months, or 6 months, after which dosing was on a weekly schedule (Auriacombe et al. 2002). 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, compared to the 3-month daily supervised and 2-week daily supervised groups. Finally, average daily buprenorphine doses at the 6-month assessment were similar for the three groups. These results suggest that initial efficacy for office-based buprenorphine treatment may be enhanced by a more closely supervised dispensing of medication and that this may be acceptable to patients.

Finally, data strongly suggest that prescription practices (single daily and individually titrated dosing) and prescribers' attitudes and beliefs about drug-dependent patients are closely associated to general treatment outcomes and patient compliance and behavior (De Ducla et al. 2000; Feroni et al. 2005).

29.3 Conclusion

As evidenced by the French example, buprenorphine maintenance treatment for problem opiate users can be feasible and safe through office-based prescriptions. This “French experience” is unparalleled in its rapid growth, and even though there is some level of diversion and continued intravenous use, it is also fair to say there are very significant societal and individual benefits. In addition there is evidence that some clinical attitudes of physicians might favor diversion more than patient characteristics. Particularly buprenorphine underdosage, the lack of toxicological monitoring of drug use, and the lack of supervised dispensing in pharmacies have been shown to represent risk factors for diversion and misuse. In the current context of the French experience, strategies to reduce buprenorphine diversion and misuse should focus on quality of treatment provision more than on regulatory changes. Among these strategies, helping health professionals, especially general practitioners, may play a crucial role allowing specific training in addiction treatment and facilitating interactions between primary care settings and specialized facilities. Finally, it is important to keep in mind that some of the public health benefits seen during the time of buprenorphine expansion in France might be contingent upon the characteristics of the French health and social services system and may not necessarily be generalizable as is to other areas of the world.

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