

Management of opioid addiction with buprenorphine: French history and current management

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Abstract: The way in which opioid addiction is managed in France is unique, as it is based on the prescription of buprenorphine by general practitioners and is dispensed by retail pharmacies. This policy has had a direct, positive impact on the number of deaths caused by heroin overdose, which was reduced by four-fifths between 1994 and 2002. In addition, certain associated comorbidities, such as infection with the human immunodeficiency virus, have also been reduced; the incidence of acquired immune deficiency syndrome in intravenous drug users fell from 25% in the mid-1990s to 6% in 2010. Since the implementation of this French model of opioid management, major scientific progress has been made, leading to a better understanding of the pathophysiologic mechanisms of addiction and of the management modalities required for its treatment. However, despite notable advances in scientific knowledge and in the implementation of devices, opioid addiction remains a major public health care issue in France, with 275,000–360,000 “problem drug users” being reported in 2011. The situation is still particularly worrying due to psychoactive substance use and misuse of opioid substitution treatments. Since 2003, there has been a persistent increase in the number of deaths and comorbidities related to opioid addiction, principally hepatitis C virus infection, which affects up to 40% of intravenous drug users. In France, the direct involvement of general practitioners in the management of opioid addiction is indisputable. Nevertheless, management could be optimized through better understanding of the pathophysiologic mechanisms of the disease, better knowledge of the pharmacology of opioid substitution treatments, and clear definition of short-, medium- and long-term treatment objectives. Data related to the management of opioid addiction by general practitioners in France have been published in 2005. Since then, the context has changed, other drugs were launched on the market such as generics of buprenorphine, methadone capsule, and Suboxone. Thus, an update seems necessary. This paper provides a description of opioid addiction management objectives and treatment modalities for general practitioners, based on currently available knowledge.

Keywords: opioid addiction, withdrawal, opioid substitution treatment, buprenorphine, naloxone, general medicine

Introduction

“Problem drug users” are defined by the European Monitoring Center for Drugs and Drug Addiction as intravenous drug users or long-duration/regular users of opioids, cocaine, and/or amphetamines over the past year, in people aged 15–64 years.¹

Of the 230,000 problem drug users recorded in France in 2006, 145,000 had used drugs intravenously at least once before, and 81,000 were still using this route of administration. The most frequently used drugs were opioids (heroin combined with opioid substitution treatments (OSTs)) 31%, cocaine 41%, hypnotics/sedatives

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and tranquilizers 29%. One-third of such drug users also misuse alcohol,² and there is a constantly increasing number of codeine and tramadol users, who should be included in these figures.

Opioid addiction management in France is unique in that it is based on the prescription of buprenorphine by general practitioners and is dispensed by retail pharmacies. In the first half of 2010, buprenorphine still accounted for nearly 75% of all nonhospital prescriptions; the total number of beneficiaries of buprenorphine reimbursements (Subutex® [Schering-Plough, Kenilworth, NJ, USA] generic buprenorphine) was 103,014 compared with 40,595 for methadone (in syrup and capsule forms) over the same period.¹

This policy has had a direct and positive impact on the number of deaths caused by heroin overdose, which was reduced by four-fifths between 1994 and 2002.³ In addition, certain associated comorbidities, such as human immunodeficiency virus (HIV) infection, have also been reduced; the incidence of acquired immune deficiency syndrome (AIDS) in intravenous drug users fell from 25% in the mid-1990s to 6% in 2010.¹

Although the implementation of this mode of management in ambulatory medicine allowed the users wide access to buprenorphine, the situation remains a serious concern. A total of 392 deaths due to heroin overdose were recorded in France in 2010.⁴ According to the 2012 report from the French Monitoring Center for Drugs and Drug Addiction, the number of deaths by overdose increased between 2006 and 2009, partly due to the increased presence of heroin and to methadone overdose.¹

In 2010, the prevalence of HIV in intravenous drug users was 7.2% (39 AIDS-related deaths in 2009), whereas the prevalence of hepatitis C virus was approximately 40%.² In countries such as France, where the prevalence of HIV is low, the death rate for opioid-dependent persons is 13 times higher than for nonusers. The quality of life of users is significantly impaired due to a high level of comorbid psychiatric disorders, particularly depression, and also because users spend the majority of their time looking for more drugs.⁵

Some of the OSTs prescribed are diverted from their intended use, particularly buprenorphine, which is not always used therapeutically. Buprenorphine is misused in three different ways: it is either injected, inhaled or, more rarely, “smoked”. The predominant route of administration when a medicine is diverted from its therapeutic use is the injection route. Inhaling seems to be used by people who have been injecting for a long time. It enables them to overcome the

problem of damaged veins and to avoid the health problems associated with the injection of drugs.¹

Opioid dependence is, therefore, a significant public health problem. In France, the health policy for opioid addiction, which is characterized by risk prevention measures and users having easy access to OSTs, has significantly reduced addiction-related disorders. Nevertheless, data related to the management of opioid addiction by general practitioners in France have been published in 2005. However, an update is necessary, as the context has changed since then; other drugs were launched on the market, such as generics of buprenorphine, methadone capsule, and Suboxone (Reckitt Benckiser Pharmaceuticals, Richmond, VA, USA).⁶

Certain aspects, such as the quality of care, should be reconsidered by practitioners in order to optimize the management of opioid addiction. In this paper, we will present the information used to analyze the context (this study focuses on prescriptions from French general practitioners who cannot start a treatment with methadone [primary prescription] and who have significant experience of buprenorphine) and the available tools and then propose methods for improving opioid addiction management.

Definition of the disease

Our understanding of addiction is not yet complete and, with the abundance of neurobiological publications now available, it has become less common to refer to psychodynamic theories. For more than 20 years, numerous authors have corroborated the dopamine theory of addiction, whereby most addictive substances activate the reward circuit by increasing the release of dopamine in certain parts of the brain, particularly in the accumbens nucleus.^{7,8} Opioids lift the inhibition of dopaminergic neurons in the ventral tegmental area, which leads to an increase in the release of dopamine in the accumbens nucleus, where the cells project their axons.⁹

The increased release of dopamine gives rise to sensations of pleasure and euphoria, but the long-term consumption of opioids induces progressive adaptations, which could involve the cyclic adenosine monophosphate (cAMP) response element binding protein and lead to partial inhibition of the pleasure circuit.¹⁰ As a consequence, the drug user requires increasingly frequent doses to feel the same effects. This phenomenon, known as tolerance,¹¹ is related to dependence – that is, a need (“lack”) expressed by psychological distress and physical pain, which will only be relieved by taking the drug.

Substance use disorder is therefore a syndrome that has biological, psychological, and social characteristics. The product becomes a central part of the user’s life (loss of

control of use, compulsive need, dose increase, etc). The term “craving” refers to an irrepressible and violent need for the drug. This urge can drive treated patients to reuse or misuse drugs and to increase their dose of OSTs, or to use them in combination with other legal or illegal substances.

The purpose of management

The discovery of biological perturbations associated with addiction and opioid receptors has opened the way for the use of OSTs, the efficiency of which is now well established. A meta-analysis of eleven randomized studies, including 1,969 subjects, assessed the effectiveness of OSTs compared to placebo or nonpharmacological management of addiction. The meta-analysis showed that OSTs are significantly more effective than placebo and nonpharmacological methods for the endpoint “maintenance of patients in a heroin withdrawal and suppression program” (relative risk =0.66; 95% confidence interval 0.56–0.78).¹²

However, pharmacological treatment alone is insufficient. It is now well known that therapeutic regimens integrating psychosocial measures – such as regular, structured counseling sessions on drug abuse – produce better results in terms of decreased drug use than the prescription of OSTs alone. All current recommendations are based on this approach.^{5,13,14}

Management programs aim to reintegrate patients into society and improve their quality of life in a step-by-step process.¹⁵ Opioid addictions should be managed globally, and treatment programs should include pharmacological therapy, social support, and the dispensing of psychotherapeutic advice.

Opioid substitution treatment

Opioid addiction can be pharmacologically managed by buprenorphine and methadone; the molecules act by binding to endogenous opioid receptors. They are administered by the sublingual (buprenorphine) or oral (methadone) routes and are characterized by a long duration of action with no peak effect (“euphoric effect”). Consequently, they suppress or prevent the effects of need and have no reinforcing effects.^{16,17} Buprenorphine and methadone can be distinguished by the way in which they act on the opioid receptors: methadone is a full μ -opioid receptor agonist, whereas buprenorphine is a partial μ -opioid agonist and a κ -opioid receptor antagonist.¹⁸ The risk of respiratory depression at high doses is therefore reduced with buprenorphine, making it safer to use on an out-patient basis.¹⁹ Nevertheless, it is important to remind users that combining OSTs with benzodiazepines exposes them to a risk of death by central respiratory depression, particularly in cases of intravenous diversion of buprenorphine.²⁰

In order to limit the known risks of buprenorphine misuse, a treatment has been developed that combines two active ingredients, buprenorphine and naloxone, which is an opioid receptor antagonist.

With sublingual administration, the pharmacodynamic effect of the buprenorphine-naloxone combination is comparable to that of buprenorphine alone, because naloxone is only minimally absorbed by that route, or not at all. However, when the combination is administered by the intravenous or nasal routes, naloxone binds to the opioid receptors more rapidly than buprenorphine. The effects of naloxone are therefore felt first, which leads to a lessening, from a clinical perspective, of the reinforcing effect of buprenorphine and even of the feelings of craving.

Treatment objectives

The management of opioid dependence should be structured around short-, medium-, and long-term objectives that should be discussed with the patient when the health care project is established.

Short-term objectives

In the short-term, the aim of treatment is to relieve the suffering associated with withdrawal, so that the user may decrease or even stop the use of illicit opioids and remain in the health care program.

Opioid withdrawal symptoms include gastrointestinal disorders, abdominal and lumbar pain, hyperhidrosis, fatigue, irritability, and mydriasis. The symptoms start between 4–6 hours after the last administration of the opioid, and cause the patients to start looking for drugs. The symptoms peak after 36–72 hours, and then start decreasing.

A meta-analysis of five randomized studies has established that use of OST is useful during this phase. The symptoms disappear more rapidly with buprenorphine.²¹

Priorities need to be established when instituting treatment, and the first of these priorities is that the patient needs to have access to care and must agree to be treated. The first days of management are key to maintaining the patient in the treatment program. Decisive factors include establishing a dialogue and taking the patient's needs into account. The treatment dose must be adapted to the clinical situation: the faster a user's suffering is relieved, the higher the chances are that he/she will remain in the treatment program.

Medium-term objectives

The medium-term objectives are to control the user's cravings and to help them stop using drugs altogether, break the

cycle of addictive behavior, prevent the risk of misuse, and put a stop to the use of alcohol or other drugs.

Studies comparing maintenance treatment with placebo are indisputably in favor of the active treatment. In a randomized study including 40 opioid-dependent persons, according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria,²² subjects were given either buprenorphine (fixed dose of 16 mg/day for 12 months) or buprenorphine at decreasing doses over 6 days, followed by placebo. All the patients were given cognitive behavioral support. The rate of retention in the substitution program at 12 months was 75% for the buprenorphine group and 0% for the placebo group ($P=0.0001$; relative risk =58.7).²³

A study conducted under “real-world conditions” and including 266 patients managed by their family physician, showed similar rates of retention of the patients in the buprenorphine substitution program at 6 months (56.8%) and 12 months (61.6%).²⁴

OSTs should be administered as part of a global management strategy, and the management program should not only be limited to the prescription of an OST. A retrospective American study on 168 patients treated with buprenorphine in a primary care clinic showed that 73% of patients had no attending physician, and 68% of the 215 comorbid disorders that were diagnosed at the initial visit were not actively treated.²⁵

In addition to the medical aspect (treatment of dependence and related diseases), the management should also have psychological and social dimensions. The psychological dimension involves preventing relapse and identifying the problems that caused the user to become addicted in the first place.⁵ The social aspect of management involves helping patients to move out of the environment associated with drug abuse, helping them to regain a place in society and to recover their rights (social security, income, housing, etc), to find an occupation (occupational workshops or professional activity, etc), and to develop their social and relational abilities (through sports or art, or exercises such as managing a budget). The follow-up visits must be regular and closely spaced at this point, and the role of the attending physician is crucial. Physicians should regularly remind patients about risk prevention measures and treatment administration modalities and regularly reassess the dose. In best-case scenarios, the physicians are part of a network or belong to a medical microstructure.²⁶

Long-term objectives

It has been shown that maintenance treatment is associated with significant improvement in quality of life, and this in turn

contributes to the treatment being successful.²⁷ According to published recommendations, OSTs should be maintained for as long as required, and even indefinitely if necessary.³

A study conducted in opioid-dependent patients showed that treatment for 9 months with buprenorphine led to a significant and constant decrease in drug use, but that the trend was reversed when treatment was discontinued. The authors concluded that treatment should be continued until the patients themselves request it to be discontinued and, in such cases, very close monitoring of the patients is required.²⁸

If treatment discontinuation is envisaged, it is important, as with any chronic treatment, to monitor patients for the onset of a “somatic” rebound effect caused by receptor sensitization, and to identify and act on the psychological and social factors that increase the risk of relapse.

Treatment modalities

The duration of the different treatment phases is determined based on reaching the objectives of each of the phases.²⁹ At the end of the first phase of treatment, patients should no longer feel a physical or psychological need, and their use of illicit opioids should decrease. The basic requirements of the treatment program established during the first phase must be met. At the end of the second phase, patients should be able to cope with the main problems that cause them to use drugs/alcohol, and they should be able to resolve their problems of misuse of psychoactive substances and set themselves long-term objectives. The OST dose should be stabilized, even if dose adjustments may still be required from time to time. During the third phase, the patients should form part of the normal community again, and have an income and a certain amount of family stability.³⁰

From a pharmacological perspective, the most suitable dose is one that eliminates cravings and makes the patient feel relatively comfortable, thereby reducing the risk of relapse associated with too small a dose or the onset of undesirable effects caused by doses that are too high.

Guidelines for the initiation and follow-up of the OST have been discussed.^{3,5,20,30} It has been shown that rapid buprenorphine induction with doses that eliminate withdrawal symptoms is key to the patient remaining in the treatment program.³¹

Conclusion

Opioid addiction is a major health and social problem worldwide. Addicts find it difficult to stop taking the drug for long periods or to change their behavior despite the accumulation of adverse consequences (comorbid somatic

and psychiatric disorders, rejection of social or family ties). User requests to general practitioners vary across countries: in France, these doctors are often the first recourse, and they remain highly involved throughout the user's itinerary. One feature of opioid addiction is that specific and effective pharmacological treatments are available for it, especially if they are administered as part of a global medical, psychological, and social treatment strategy. The aim of the strategy is to progressively help patients stop using drugs without suffering, and to help them reintegrate into society by setting clear short-, medium-, and long-term objectives.

During treatment, patients may go through phases of intense craving, which may result in relapse, misuse, or excessive consumption of alcohol, benzodiazepines, or other psychoactive substances, and therefore expose them to potentially serious risks. Should this be the case, physicians should check for potential treatment underdosing and predisposing factors, such as a comorbid psychiatric disorder and/or social or family problems. When stabilization is difficult to achieve, or in times of crisis and destabilization, the physician should seek the advice of an addiction specialist or psychiatrist, or refer the patient to a specialized center.³

Any doctor is, however, able to provide this support, by using available treatments and staying informed about possible incidents and by following the developments in knowledge and treatment. Opioid addiction is an "open door" to many other addictions and public health problems, and its management cannot be reserved for specialists. The development of the health network and some new support recommendations are necessary.

Disclosure

Pierre Poloméni has participated in specific interventions (counseling activities, conferences, seminars, training activities) for Reckitt Benckiser Pharmaceuticals.

Raymund Schwan reports being involved in counseling and training activities for Reckitt Benckiser Pharmaceuticals. The authors report no other conflicts of interest in this work.

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