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EDITORIAL

Novel forms of injectable buprenorphine and French model of opioid use disorder treatment

Abbreviations

COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
GP	general practitioners
OMT	opioid maintenance treatments

Opioid dependence is a severe addictive disorder with an important health and social burden of disease and with increased risks of death and disabilities due to several consequences of opioid dependence, including overdose, HIV or HCV infection, suicide, and the concurrent use and misuse of several other licit and illicit drugs. The number of patients treated by opioid maintenance treatments (OMT) in the European Union with the estimated number of problematic opioid users suggests a treatment coverage rate of approximately 50%, with considerable variation between countries (from 10 to 70%). In France, the OMT coverage rate of 80% is one of the highest in Europe [1]. Pharmacological options for opioid dependence [2] should be integrated within a global therapeutic approach, which includes psychosocial support, and which should focus on the individual's functional recovery. In this respect, OMT represent the gold standard medication for opioid dependence. In France, it has been decided in the 1990s to facilitate the specific access to buprenorphine for subjects with opioid dependence [3—6]. While the initial prescription and dispensing of methadone remains restrained to specialized addiction settings, buprenorphine can be started by any physician, including general practitioners (GP), with no need for a prior training or waiver. Similarly, community pharmacists

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under coordination of the prescribing physician can perform buprenorphine dispensing. Twenty-four mg per day of buprenorphine was the maximum dose approved, with maximum prescription duration of 28 days. For methadone, taking into account the full agonist nature of the drug, and therefore the major risk of overdose compared with buprenorphine, the maximum prescription duration has been limited to 14 days [7,8], and urine screens are compulsory only for methadone [9,10]. All of this has contributed to durably shaping the French landscape of opioid dependence treatment, which has been largely dominated by GP-based prescription of buprenorphine [1,4]. Most patients with opioid use disorders in France are thus treated with buprenorphine prescribed by GP in private practice, with buprenorphine exclusively dispensed in community pharmacies [6,11,12]. This ''French model'' contrasts with other countries worldwide where methadone is predominantly used [13]. Community pharmacies are outpatient facilities supplying medicines and are the first line and the most accessible to the public, contrary to pharmacies of specialised addiction centres or hospital pharmacies. Their collaboration with GPs guarantees the performance of this model [4].

Buprenorphine was first commercialized in France with the brand name ''Subutex®'', which became very popular in the early 2000s with a marginal proportion of patients misusing (through diverted routes, nasal, intravenous, snorted...) and abusing a high quantity of the highest dosage of sublingual tablets, with marked behaviours of doctor shopping [14] and/or falsified prescriptions [15]. This behaviour was associated with the emergence of serious and frequent unfavourable outcomes [16,17]. Generics of buprenorphine were available from 2006, with several concerns regarding their safety profile in case of diverted use (through intravenous route), explaining its low acceptance of generic substitution by pharmacists, and degradation of the product's image, initially considered as a remarkable drug, then evolving towards the image of a second-class drug (in the patients and prescribers' mind) [18—20]. The European approval of the fixed combination buprenorphine + naloxone by the European Medicines Agency (EMA) in 2006 did not change the situation, the medication being marketed some years after the initial approval in France, with a very low level of exposure (less than 5% of buprenorphine treated patients). During the last decade, with the introduction of solid oral forms of methadone and the possibility for any GP to renew an initial prescription from an addiction care structure or a hospital prescriber, the relative proportion of buprenorphine-methadone in OMT changed from 80—20% in the mid-2000s to 60—40% in the mid-2010s, with around 62,000 patients treated by methadone and 99,000 by buprenorphine in 2017 in France, according to health insurance system data [1].

In the present Therapies's issue, Chappuy et al. present the future and expected new forms of injectable prolonged release buprenorphine [21]. Actually, the three new galenic formulations of buprenorphine have been recently approved (or will be approved) through European procedure, as hybrid drug. A prolonged released injectable formulation appears very attractive for stabilized patients and/or for patients for whom brutal interruption in opioid maintenance must be avoided. One can regret that, because of the hybrid status of these new drugs, bioequivalence studies were not performed (these new formulations are not generic), and the comparator was often a placebo. Considering the well-known benefit of buprenorphine maintenance treatment, a relevant study evaluating how these newer forms could reduce the risk of opioid misuse (compared to sub-lingual buprenorphine or methadone) would have been very useful, rather than a short-term intermediate criterion for negative urine. Moreover, considering the French model (with buprenorphine mainly prescribed by GP), the constraints related to the implant's form and the unknowns on the median-term evolution suggest difficult diffusion of this drug. As underlined by Chappuy et al., the reception that GP will have with regard to prolonged-release buprenorphine formulations remains largely unknown [21]. This question is of main importance, since GP are the most frequent prescribers of OMT in France, but only 5% initiated buprenorphine in 2015 compared to 10% in 2009 [1].

Management of opioid use disorders driven by buprenorphine maintenance treatment in general practice has been found to be highly protective against mortality [22]. Dupouy et al. have shown in a population-based cohort of buprenorphine treated patients, that being in treatment versus being out of treatment was associated with a reduction of at least 10-fold in the risk of death. These findings should encourage physicians to avoid interrupting buprenorphine treatment and encourage patients to continue treatment as long as it is needed. The possibility of offering certain patients and under certain conditions a prolonged-release injectable form of buprenorphine could be a promising approach to put into perspective the benefit-risk profile of buprenorphine, which in absolute terms, at least on the harm side, remains always more favourable than that of methadone [23]. The addictovigilance activities during the recent coronavirus disease 2019 (COVID-19) epidemic with the global population lockdown have shown an increase in cases of overdose during lockdown, with deaths reported with methadone (and not buprenorphine) more frequently than with illicit drugs such as heroin [24].

Disclosure of interest

The author declares that she has no competing interest.

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