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How to improve ambulatory care of opioid-addicted patients?

A pharmacoepidemiological approach

assessing the value of urine drug screening tests.

This manuscript is fully written in English.

Ce manuscrit étant entièrement écrit en anglais, un résumé en français est placé en début de chaque partie, encadré, sous cette mise en forme.

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ABBREVIATIONS

AFSSAPS: *Agence Française de Sécurité Sanitaire des Produits de Santé*

ALD: *Affection de Longue Durée*

AMM: *Autorisation de Mise sur le Marché*

CNAM-TS: *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés*

CSAPA: *Centre de Soins d'Accompagnement et de Prévention en Addictologie*

CNIL: *Commission Nationale Informatique et Libertés*

DCIR: *Données de Consommation Inter-Régimes*

DGS: *Direction Générale de la Santé*

DHOS: *Direction de l'Hospitalisation et de l'Offre de Soins*

DSM: Diagnostic and Statistical Manual of Mental Disorders

EGB: *Echantillon Généraliste des Bénéficiaires*

EGBS: *Echantillon Généraliste des Bénéficiaires Simplifié*

EMCDDA: European Monitoring Center for Drugs and Drug Addiction

ERASME *: Extraction, Recherches, Analyses pour un Suivi Médico-Economique*

GP: General Practitioner

HAS: *Haute Autorité de Santé*

ICD10: International Classification of Diseases – 10th version

IDS: *Institut des Données de Santé*

INSEE: *Institut National de la Statistique et des Etudes Economiques*

INSERM: *Institut National de la Santé et de la Recherche Médicale*

MILDT: *Mission Interministérielle de Lutte contre les Drogues et les Toxicomanies*

NIDA: National Institute on Drug Abuse

OFDT: *Observatoire Français des Drogues et des Toxicomanies*

OMT: Opioid maintenance treatment

OS-UDT: On-Site Urine Drug screening Test

PMSI: *Programme de Médicalisation des Systèmes d'Information*

PMSI MCO: PMSI *Médecine Chirurgie Obstétrique*

RG: *Régime Général des travailleurs salariés*

RSA: *Régime Social Agricole*

RSI: *Régime Social des Indépendants*

SAMSHA: Substance Abuse and Mental Health Administration

SNIIR-AM: *Système National d'Information Inter-Régime de l'Assurance Maladie*

UDT: Urine Drug screening Test

WHO: World Health Organization

WONCA: World Organization of National Colleges, Academies and academic associations of general practice/family physicians

ABSTRACT

Since the recognition of addiction as a mental disease, specific treatments have been developed. For opioid-addicted patients, opioid maintenance drugs (methadone, buprenorphine and buprenorphine/naloxone) have been showed to decrease opioid use, related diseases (HIV, hepatitis C), to improve social outcomes and to decrease mortality. In France, because buprenorphine is easily accessible, most of opioid-addicted patients are mainly managed by general practitioners (GPs). Nevertheless, the assessment of psychoactive substance use by the physician, thanks to self-report and clinical examination, is known to underestimate the use of psychoactive substances. The implementation of urine drug screening tests should improve this assessment. These tests enable a qualitative detection of psychoactive substances in the urine.

The objective of this thesis is to assess the value of urine drug screening in opioid addicted patients managed in ambulatory care. This assessment has been conducted in three parts. The first one aimed to summarize the knowledge concerning drug tests in the literature and of French GPs. The second one aimed to assess the effectiveness of drug tests in managing opioid-addicted patients using observational cohorts conducted from French health insurance system databases. Finally, the last part aimed to confirm the value of urine drug screening tests in real life and thus, to assess their efficacy planning a pragmatic cluster randomized controlled trial in general practice.

In the first part, we first investigated French GPs' knowledge and practices concerning drug tests. We conducted a descriptive cross-sectional study by postal questionnaires sent to a random sample of GPs in the Midi-Pyrénées area of France. Many French GPs treating opioid-addicted patients regularly did not perform drug tests and lacked knowledge of them. Secondly, we summarize the evidence pertaining to the efficacy of urine drug screening for medical management. A systematic review of clinical trials, quasi-randomized and observational studies was performed. The value of urine drug screening in managing patients was not clearly indicated in these studies.

The first work of the second part aimed to assess the effectiveness of drug tests for treatment retention in outpatients starting opioid substitution therapy. A retrospective cohort of patients starting opioid substitution treatment was created from the data of the French health insurance system database for the Midi-Pyrenees region. Use of a drug test in follow-up of opioid substitution treatment, although rarely prescribed, significantly improved treatment retention. The second work assessed the effectiveness of drug tests on mortality using a national database: the "Echantillon Généraliste des Bénéficiaires" (permanent beneficiaries sample). This work confirmed the association between drug tests and retention in treatment but did not find an association with mortality.

All these results were used to plan the third part: a pragmatic cluster randomized controlled trial (the ESUB-MG study). We present the protocol of this study aiming to assess the impact of on-site urine drug screening tests in general practice compared to routine medical care on opioid maintenance treatment retention at six months in patients initiating buprenorphine.

To conclude, this thesis has shown that urine drug screening tests were rarely done in France for managing opioid-addicted patients and that few studies had assessed their value. Nevertheless, drug tests seem to have a positive effect on opioid maintenance treatment retention. The on-going pragmatic randomized trial we proposed should bring sufficient level of evidence to assess effectiveness of on-site urine drug screening in general practice for patients treated by buprenorphine.

INTRODUCTION: OPIOID-ADDICTION MANAGEMENT IN PRIMARY CARE

Introduction : prise en charge des patients ayant une addiction aux opiacés en soins primaires

L'addiction aux opiacés est une pathologie chronique classée dans les pathologies mentales. Les traitements de maintenance aux opiacés associés à des interventions psychosociales sont les traitements les plus efficaces pour ces patients. Les médicaments que sont la méthadone et la buprénorphine ont montré leur efficacité sur plusieurs critères de jugement cliniques dont la mortalité. Leur efficacité est néanmoins limitée par des ruptures de traitements qui sont fréquentes et précoces.

La prise en charge de ces patients en Europe est partagée entre les centres spécialisés, les médecins généralistes et les structures de bas seuil. La prise en charge en médecine générale serait, selon certaines études, aussi efficace voir plus efficace, que la prise en charge en centre spécialisé. Néanmoins, entre les différents pays européens, les réglementations permettant aux médecins généralistes de prescrire ces traitements diffèrent. La méthadone est le médicament le plus souvent prescrit (75 à 80% des patients à l'échelle européenne).

En France, la situation est assez différente puisque les conditions de prescription et de délivrance de la buprénorphine sont plus souples que celles de la méthadone. Les patients français sont donc majoritairement traités par buprénorphine et ce, en médecine générale. La médecine générale, de par ces caractéristiques, est adaptée à la prise en charge de ces patients.

Pour autant, l'offre de soins reste hétérogène pour ces patients et les médecins généralistes impliqués dans leur prise en charge font face à certaines difficultés parmi lesquelles la sous évaluation fréquente, par l'interrogatoire et l'examen clinique, des substances consommées par les patients. Pour pallier à cette difficulté, l'utilisation de tests de dépistage des substances psycho actives a été proposée. Ils auraient d'autant de valeur que leur résultat se lit en quelques minutes (ce qui semble adapté au contexte de la médecine générale : prise de décision généralement rapide, dans le temps de la consultation) ; et que plusieurs études ont montré la validité de leur utilisation au lit du malade, et notamment au cabinet du médecin généraliste.

Ces tests donnent des résultats qualitatifs par une technique immunochimique qui peuvent être confirmés par un dosage en laboratoire à l'aide de la méthode de référence : la chromatographie couplée à la spectrométrie de masse. Leurs limites doivent être connues par les cliniciens pour bien interpréter leurs résultats.

Ces tests sont recommandés en France : un premier avant la mise sous médicament (avec un caractère obligatoire avant l'initiation de méthadone), et d'autres pendant le suivi selon le jugement du médecin. Les

tests pourraient permettre d'évaluer les consommations du patient tout au long de la prise en charge et donc permettre indirectement une évaluation du craving.

Les valeurs diagnostiques de ces tests sont bien établies mais leurs conséquences sur la prise en charge des patients sont mal connues. Pour autant, les programmes de surveillance ont montré leur efficacité sur des critères de jugement cliniques.

L'objectif de cette thèse est d'évaluer l'intérêt des tests urinaires de dépistage pour les patients dépendants aux opiacés pris en charge en médecine ambulatoire. Cette évaluation a été conduite en 3 parties : 1) une synthèse des connaissances des tests dans la littérature, et par les médecins généralistes français ; 2) une évaluation de l'efficacité des tests pour la prise en charge des patients dépendants aux opiacés par des études observationnelles de cohorte sur les bases de données de l'Assurance Maladie ; 3) la confirmation de leur intérêt en médecine générale en planifiant la mise en place d'un essai pragmatique contrôlé randomisé en médecine générale.

OPIOID-ADDICTION AND ITS TREATMENT

Opioid addiction is currently defined as a "chronic, relapsing disorder" (Dole & Nyswander, 1967; Nyswander & Dole, 1967). As all addiction, this disease is classified as a mental disease in the Diagnostic and Statistical Manual of Mental Disorders DSM (with different terminologies from DSM III to DSM V). Mortality of untreated heroin dependence is consistently estimated at 1–3% per year, at least half of which because of heroin overdose (Darke & Hall, 2003). Beyond mortality and morbidity, heroin dependence inflicts enormous social and economic costs due to crime, unemployment, relationship breakdown, and the costs of law enforcement.

Opioid maintenance treatment (OMT), combined with psychosocial interventions, was found to be the most effective treatment option for opioid users. In comparison with detoxification or no treatment at all, methadone or buprenorphine treatments show significantly better outcomes regarding drug use, criminal activity, risk behaviours and HIV-transmission, overdoses and overall mortality, as well as better rates of retention in treatment (WHO, 2009). Data from systematic reviews show that methadone maintenance is the most effective treatment in retaining patients in treatment and suppressing heroin use (Amato et al., 2005; Mattick, Kimber, Breen, & Davoli, 2008). The systematic review by Mattick et al. demonstrated the efficacy of buprenorphine maintenance treatment, with a lower retention rate than methadone but giving a similar decrease in opiate consumption (Mattick et al., 2008). The combination of buprenorphine and naloxone (marketed as Suboxone®) was created to prevent the injection of buprenorphine. Nevertheless, its

effectiveness in preventing intravenous use of buprenorphine is not yet clear (Bruce, Govindasamy, Sylla, Kamarulzaman, & Altice, 2009; Simojoki, Vorma, & Alho, 2008).

Effectiveness of opiate maintenance treatment is mainly limited by drop-outs. Early drop-outs are frequent (Stein, Cioe, & Friedmann, 2005) and are often under estimated in studies (Encrenaz, Rondeau, Messiah, & Auriacombe, 2005). Rate of drop-outs would be close to 50% in the first 6 months in Germany (Soyka, Zingg, Koller, & Kuefner, 2008). In France, early drop-outs are frequent and occur often in the first year of treatment (Batel et al., 2004; Duburcq, Charpak, Blin, & Madec, 2000). Treatment interruptions exist also and must concern more than 50% of patients in France (Pradel et al., 2004). This is an important issue as the end of OMT was associated with a higher somatic morbidity in the first year after leaving OMT (Skeie et al., 2013) and with a three-fold higher mortality (particularly the fifteen days immediately after stopping the treatment) in 5577 patients from the United Kingdom General Practice Research Database (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010).

No consensus exists in OMT withdrawal. In an Australian study, 62% of the patients were worried about the end of OMT (Winstock, Lintzeris, & Lea, 2011).

OPIOID-ADDICTED PATIENTS' MANAGEMENT IN EUROPE

In the European Union during 2012, 1.3 million people received treatment for illicit drug use. In Germany, Spain, France, Italy and the United Kingdom, 80 % of drug users were in contact with treatment (EMCDDA, 2014).

The average annual prevalence of problematic opioid use among adults (from 15 to 64 years old) is estimated at around 0.4 %, representing 1.3 million opioid users in Europe in 2012 (EMCDDA, 2014). Patients using mainly heroin, as their primary drug, represented 46 % of all drug users who entered specialized treatment in 2012 in Europe (180 000 patients). They represented also around 26 % of those entering treatment for the first time, of whom more than 10% misused opioids other than heroin (EMCDDA, 2014).

Patients entering outpatient treatment for primary opioid use have a mean age of 36 years, with a more than three quarters of men (EMCDDA, 2014). Almost all countries report an increase in the mean age of their opioid patients since 2003 (EMCDDA, 2010). An average time lag of about 10 years is reported between first use of opioids and first contact with drug treatment (EMCDDA, 2010). Opioid users entering treatment have higher rates of unemployment, lower levels of educational attainment and higher levels of psychiatric disorders than patients reporting other primary drugs (EMCDDA, 2010).

The two main modalities of outpatient treatment in Europe are psychosocial interventions and opioid maintenance treatment (OMT). For opioid users, they are often provided in combination.

OMT is the predominant treatment option for opioid users in Europe and is mostly conducted in outpatient settings, which can include specialist centres, general practitioners' surgeries and low-threshold facilities. OMT, generally integrated with psychosocial care, is provided at specialized outpatient centres but can be also provided by general practitioners (GPs), usually under shared care arrangements with specialized treatment centres. A 12-month naturalistic study of 2 694 patients in OMT in Germany showed that GPs can achieve better results than specialized centres in terms of retention in treatment, abstinence rates and co-consumption of other drugs (Wittchen et al., 2008). Other studies have shown that the implementation of OMT in general practice is cost-effective (Gossop, Stewart, Browne, & Marsden, 2003; Hutchinson et al., 2000).

A comparison of the number of patients treated by OMT in the European Union with the estimated number of problematic opioid users suggests a treatment coverage rate of about 50%, with considerable variation between countries (from 10 to 60%), represented in Figure 1. In Belgium, Czech Republic, Denmark, France, Italy, Cyprus, Netherlands, Portugal, United Kingdom, Croatia, all GPs are allowed to prescribe OMT. In Germany, Ireland, Luxembourg, Austria, Slovenia, Norway, only those who have been specifically trained or accredited are allowed to prescribe it. In Bulgaria, Estonia, Greece, Spain, Lithuania, Hungary, Poland, Romania, Slovakia, Finland, Sweden, only specialists in treatment centres can provide OMT. More than the authorization to prescribe, the legal regulation framework can be a barrier for OMT supplying if administrative tasks are numerous as, for example, in Germany (Schulte et al., 2013).

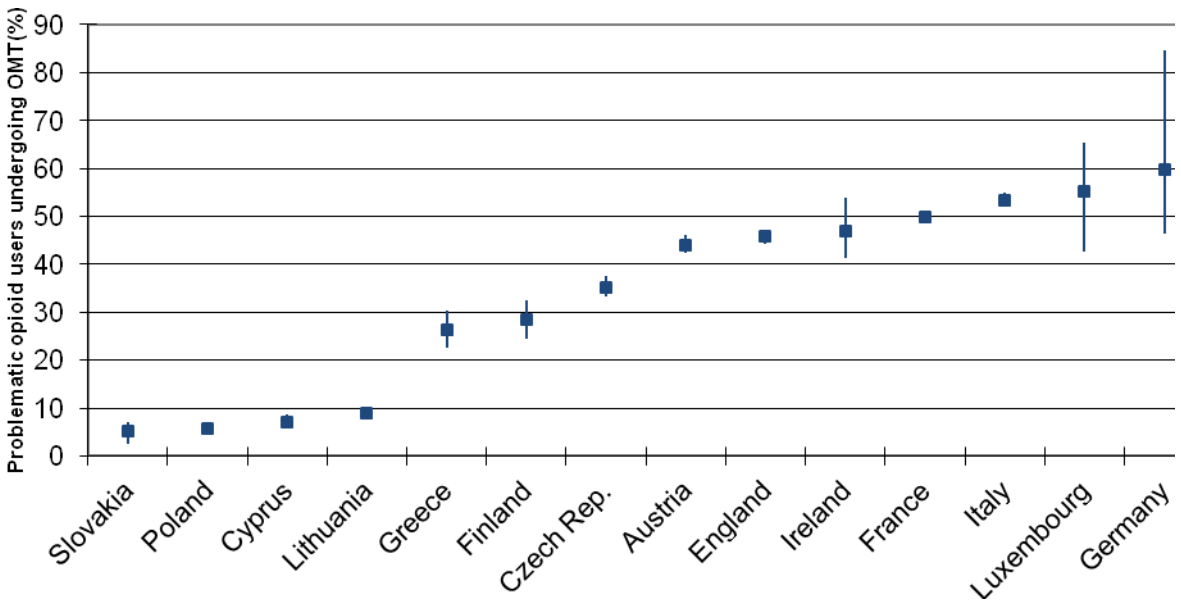

Figure 1 : Estimated proportion of problematic opioid users undergoing maintenance treatment in some European countries (EMCDDA, 2010)

Most patients treated by OMT in Europe receive methadone (75 - 80 %), and buprenorphine is used in 20–25 % of all OMT provided in Europe and in more than 50 % in some countries (of which France, see Figure 2). The buprenorphine–naloxone combination, approved by the European Medicines Agency in 2006, has been introduced in most of the European countries. Other options, which represent a small percentage of all OMT, include slow-release morphine, codeine and diacetylmorphine (heroin).

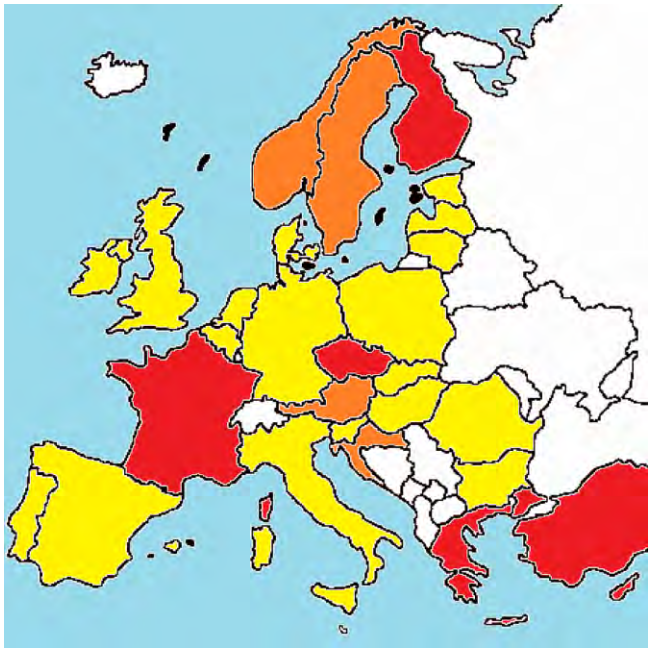

Figure 2 : Predominant OMT at national level (EMCDDA, 2014): buprenorphine in red, methadone in yellow, and both equally in orange.

Buprenorphine is, thus, more widespread in France than in other countries; but, the efficacy and the safety of this drug are well known (Lee, Grossman, DiRocco, & Gourevitch, 2009; Simoens, Matheson, Bond, Inkster, & Ludbrook, 2005). Its use tends to be more common; for example, British GPs are favourable to its widespread (Strang et al., 2007).

OPIOID-ADDICTED PATIENTS' MANAGEMENT IN FRANCE

More recent data estimates that near 150 000 patients are treated, in France, by an opioid maintenance treatment (OMT) (Commission Nationales des stupéfiants et des psychotropes, 2010). Methadone, buprenorphine and buprenorphine-naloxone received marketing authorization in 1995, 1996 and 2006 respectively, for maintenance treatment for major opiate dependence as part of overall medical, social and psychological therapeutic management. These drugs are prescribed and delivered according to two different, very strict guidelines. Methadone, a pure μ agonist, is a listed narcotic and can be prescribed for a maximum of 14 days and delivered for a maximum of 7 days. Primary prescription of methadone is restricted to physicians in specialized units and to hospital physicians. When the patient is stabilized, treatment may be continued in an outpatient setting and followed up by any physician, whether specialist or generalist practitioner (GP). Buprenorphine, a partial μ agonist, is a class I psychotropic drug (Schedule III of the 1988 Convention) and can be prescribed for maximum periods of 28 days and delivered for periods of 7 days. It can be prescribed by any physician, whether specialist or GP, and can be delivered in any local pharmacy. In summary, in France, methadone must be started in a specialized unit or a hospital and can be continued, after the patient is stabilized, in an outpatient setting, whereas buprenorphine is easily accessible as it can be started in a specialized unit, a hospital or an outpatient setting. The physician can prescribe methadone for a maximum of 14 days and buprenorphine for 28 days, but the pharmacist must deliver the medication only for 7-day periods unless otherwise indicated by the prescriber.

In ambulatory practice, GPs are involved in initiating treatment by buprenorphine and follow-up of treatment by buprenorphine and methadone. Because buprenorphine is easily obtainable (Fatseas & Auriacombe, 2007), more than three-quarters of patients treated for opioid addiction receive buprenorphine (Auriacombe, Fatséas, Dubernet, Daulouède, & Tignol, 2004; Fatseas & Auriacombe, 2007; Thirion et al., 2001) and most of them are treated in general practice using this drug (Fatseas & Auriacombe, 2007; Thirion et al., 2002). The number of people receiving opiate maintenance treatment (OMT) was estimated at around 100,000 for buprenorphine and around 35,000 for methadone in 2009 (Commission Nationales des stupéfiants et des psychotropes, 2010).

Maintenance on OS is requisite for successful treatment. Buprenorphine retention is associated with a decrease of drug consumptions (heroin, cocaine, benzodiazepines) (De Ducla, Gagnon, Mucchielli, Robinet, & Vellay, 2000; Thirion et al., 2001), of morbidity and mortality, with an improvement of social insertion (Lavignasse et al., 2002), and also, with a decrease of infectious risks related to injection (Human Immunodeficiency Virus HIV, hepatitis C and B) and with a best compliance with antiretroviral drugs (Moatti et al., 2000). Retention on OS (methadone in the cited study) was beneficial for patients, were they discharged involuntary or not and against medical advice or not (Wang et al., 2012). Opiate substitutive drug benefits are applicable whatever the motivations of the patient to take the treatment.

French guidelines stipulate that stopping OMT can be suggested after a period of patient's stabilization if the patient wants it (HAS, 2004). This little-known modality may have concerned 6.7% patients treated with buprenorphine in Haute-Garonne (south-western France area) in 2010 (Porcher, Poutrain, Lapeyre-Mestre, & Persil, 2012).

AN APPRAISAL TO MAXIMIZE: HETEROGENEITY OF CARE ACCESS, BARRIERS FOR GENERAL PRACTITIONERS

The management of opiate-dependent patients in France is shared among specialized centres and general practitioners (GPs). As previously cited, management in general practice may offer advantages (Gossop, Stewart, Browne, & Marsden, 2003; Hutchinson et al., 2000; Wittchen et al., 2008). Despite that, heterogeneity of care access was highlighted in the 2004 clarification on therapeutic strategy for managing opioid-addicted patients (HAS, 2004), such as inequality in this care access according to geographic area. These heterogeneity and inequality exist in terms of choice of opioid maintenance treatment and of number of prescribers and pharmacists dispending OS (HAS, 2004).

Today, even if GPs are concerned like health caregivers, often primary care providers, a minor part of them is engaged in the management of opioid-addicted patients. Twenty percent of GPs used to manage these patients in 2001/2002 (Feroni et al., 2004), which is a stable number compared to 1999, with most of them having one or two maintained patients (Thirion et al., 2002).

Several GPs are afraid of drug trafficking which keeps growing (Michel, 2009), particularly with the reported frequent resale of buprenorphine (Frauger et al., 2012) and its misuse for recreational purpose, even though this misuse is limited in the US (Cicero, Surratt, & Inciardi, 2007) and in France (buprenorphine misuse concerns around 10% of patients treated with buprenorphine) (Nordmann et al., 2012). Opiate maintenance treatments are, always in 2008, within the two first drugs the most illegally obtained in France (by 'street market', 'gift', 'theft', 'forged prescription', and 'internet') (Frauger et al.,

2012). Buprenorphine was one of the drugs for which prescriptions were the most forged between 2001 and 2004 (Boeuf & Lapeyre-Mestre, 2007).

Buprenorphine trafficking is also supported by the « doctor-shopping » phenomenon (i.e. patients consulting several physicians in the order to have prescriptions for the same drug) (Pradel et al., 2004). Doctor-shopping is considered by several authors as one of the most common way to illegally obtain drugs (Inciardi, Surratt, Cicero, & Beard, 2009; Winther & Bramness, 2009). And, actually, since the beginning of OMT in France, non-rational behaviours have been shown (Lapeyre-Mestre et al., 2003). It would concern 25% to 40% of these patients (Pradel et al., 2004). No lower retention rate was shown for these patients (Lapeyre-Mestre et al., 2003). The aim of polyprescription remains unclear (to sustain black market, to increase dose, to misuse buprenorphine, etc.) as studies assessing for the best this issue are performed in reimbursement databases.

To struggle against street market of buprenorphine, the Summary of Product Characteristic and the *Haute Autorité de Santé* (HAS) guidelines (HAS, 2004) recommend that the physician and the pharmacist act systematically in concert. This collaboration is actually not always performed (54% of the physicians concerned in Bouches-du-Rhône in 2002). Predictive factors are physician's training in addictology care, being in touch with a network, having a favourable opinion of buprenorphine prescription in ambulatory care, and early moving into the patient management. This collaboration is associated with positive outcomes for the patient's management (Feroni et al., 2005).

Whatever it be, these behaviors of certain patients cause damage to opioid-addicted patients who are suffering from stigmatization from the general public as well as health professionals, of whom the GPs. In a study performed by the *Observatoire Français des*

Drogues et des Toxicomanies OFDT, two over three GPs reported their refusal to manage some opioid-addicted patients consulting them (OFDT, 2002). A medical thesis about difficulties experienced by the GPs in prescribing OMT highlighted relational difficulties reported by GPs in front of these patients (Laleu, 2013). More generally, high levels of stigmatization toward psychiatric patients have been shown by studies conducted in health professionals or medical students (Ay, Save, & Fidanoglu, 2006; Li, Li, Thornicroft, & Huang, 2014; Mukherjee, Fialho, Wijetunge, Checinski, & Surgenor, 2002). Stigmatization restricts care access, treatment quality and life quality of patients suffering from psychiatric disorders (Livingston & Boyd, 2010; Thornicroft, 2008). The representation of addiction as a disease is not the rule, and for GPs less than for psychiatrists (Lawrence, Rasinski, Yoon, & Curlin, 2013). Representations and stigmatization can be decreased by medical education and training (Balhara, Yadav, Arya, & Kataria, 2012; Mas & Hatim, 2002). Moving attitudes by this way seems essential but takes time.

Finally, one of the difficulties for physicians involved in treating opioid-addicted patients is to evaluate the concordance between the patient's word and his drug use (OMT and other illicit drugs) (Lavie et al., 2008) while associated drug use is frequent (at least one or two thirds of patients under OMT would also consume alcohol and benzodiazepines (Lapeyre-Mestre et al., 2003)).

In the field of addiction, assessment of substances consumption is crucial for diagnosis and, even more, for medical management. Nevertheless, this assessment is often difficult as self-reports use to under estimate psychoactive substances' consumption (Galletly, Field, & Prior, 1993; Kilpatrick, Howlett, Sedgwick, & Ghodse, 2000; Lundy et al., 1997; Olshaker, Browne, Jerrard, Prendergast, & Stair, 1997; Perrone, De Roos,

Jayaraman, & Hollander, 2001). One Scandinavian study in 2009 (Mordal, Holm, Mørland, & Bramness, 2010) compared the assessment by the psychiatrist of drug consumption in an emergency setting to that obtained by a urine drug screening test (UDT); the reference method being chromatography-tandem mass spectrometry. The physician had correctly assessed the consumption of alcohol but the assessment for illicit substances was not so good for others psychoactive substances. The value of urine drug screening was assessed comparing urine screening tests' results and chromatography. At the same time, urine drug screening presented a better sensitivity for benzodiazepines, opiates and for cannabis. This study clearly showed that physicians' assessment of psychoactive drug use lead to underestimate the true consumptions, and UDT would be useful in making decisions about treatment.

By contrary, in certain context, patients can overestimate their use of psychoactive substances notably when entering a detoxification program (Zullino, Krenz, Eap, Benguettat, & Khan, 2008).

Despite advances during these thirty last years in managing and treating patients with abuse or addiction, addiction management consists always in a difficult practice (Governmental Plan 2008-2011 (MILDT, 2008)) exposing the GP by contrast to the multidisciplinary team of a specialized centre (called *Centre de Soins d'Accompagnement et de Prévention en Addictologie* CSAPA in France) or to an hospital addiction care unit team.

The characteristics of general practice according to the World Organization of National Colleges, Academies and academic associations of general practice/family physicians (WONCA) are that it:

a) is normally the point of first medical contact within the health care system, providing open and unlimited access to its users, dealing with all health problems regardless of the age, sex, or any other characteristic of the person concerned.

b) makes efficient use of health care resources through coordinating care, working with other professionals in the primary care setting, and by managing the interface with other specialties taking an advocacy role for the patient when needed.

c) develops a person-centered approach, orientated to the individual, his/her family, and their community.

d) promotes patient empowerment.

e) has a unique consultation process, which establishes a relationship over time, through effective communication between doctor and patient.

f) is responsible for the provision of longitudinal continuity of care as determined by the needs of the patient.

g) has a specific decision making process determined by the prevalence and incidence of illness in the community.

h) manages simultaneously both acute and chronic health problems of individual patients.

i) manages illness which presents in an undifferentiated way at an early stage in its development, which may require urgent intervention.

j) promotes health and well-being both by appropriate and effective intervention.

k) has a specific responsibility for the health of the community.

l) deals with health problems in their physical, psychological, social, cultural and existential dimensions (WONCA, 2011).

Thus, the practice of general practice is completely adapted to the management of addicted patients. Furthermore, the practice of general practice is characterized by managing complex situations.

Nevertheless, decision making may be in a short term (mean time of consultation is 18 minutes for psychiatric disorders (DREES, 2006)) and without the support of a multidisciplinary team. These characteristics have to be taken into account before to offer a help to GPs.

In other medical domains, tools adapted for ambulatory care demonstrated their value in making decision about treatment like the rapid diagnostic test of sore throat (Portier et al., 2001). One study directed by the *Direction de la Recherche, des Etudes, de l'Evaluation et des Statistiques* DRESS about general practice highlighted that the good practice guidelines are the first help tool for prescription and patients' management (DREES, 2007).

In this context, UDT would be useful in making decisions about treatment in opiate addicted patients and would help GPs engaged in the management of opioid-addicted patients.

CHARACTERISTICS OF URINE DRUG SCREENING TESTS

Drug tests can be carried out by immunochemical methods, either by automated analyzers in the biology laboratory or by drug screening kits in the surgery of the physician. Screening can be done during the patient's visit, in either a specialized addiction centre or the physician's office with an immediate lecture of results. These tests (whether on a laboratory automat or using a commercial kit) are qualitative and have defined thresholds. Results can be confirmed by the reference method, liquid or gas phase chromatography with mass spectrometry, which gives quantitative measurements (Bagøien, Morken, Zahlsen, Aamo, & Spigset, 2009). Laboratory tests, regardless of the method or the biological medium, are reimbursed by the French health insurance system with no limit on their number or time period. On-site urine drug screening (OS-UDT) by commercial kits is not reimbursed by the French health insurance system but some specialized addiction networks in France provide them to their members.

It is possible to observe differences in sensitivity and specificity between available commercial tests for which detection thresholds can vary; fields covered by each test are, themselves, also variable. These tests have limits which need to be recognized to ensure pertinent treatment. In addition, it is essential to ensure that they propose a qualitative determination to be able to interpret the significance.

Positivity threshold are generally in accordance with the recommendation of the National Institute on Drug Abuse (NIDA) (NIDA, 1986) and the Substance Abuse and Mental Health Administration (SAMSHA) (SAMSHA, 2008) (See Table 1). These recommendations are from the working world in which urine drug screening tests are only performed for controlling. The SAMSHA increased the threshold for screening opiates in 2008 (2000ng/mL instead of 300ng/mL) to avoid false positive to ingestion of poppy-seeds. Nevertheless, many laboratories maintained the threshold of 300 ng/mL to preserve the opiates screening sensibility (Moeller, Lee, & Kissack, 2008). Thus, most commercial kits always use the threshold of 300 ng/mL.

Table 1 : Cutoff values used in workplace (Moeller et al., 2008)

Substance	**Initial drug test level** (immunoassay) (ng/mL)	**Confirmatory drug test level** (gas chromatography-mass spectrometry) (ng/mL)
Marijuana metabolites	50	15
Cocaine metabolites	300	150
Opiate metabolites	2000	2000
Amphetamines	1000	500

Positivity thresholds currently used are (NIDA, 2008):

- buprenorphine: 10 ng/mL
- methadone: 300 ng/mL (or the metabolite 2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine EDDP: 100 ng/mL)
- opiates: 300ng/mL
- cocaine: 300 ng/mL

Urine drug screening tests deter opiates, in particular morphine and codeine, but not fentanyl nor oxycodone (specific immunoassays can be used for these substances). Urine drug screening tests for alcohol are not validated and those for benzodiazepines are not testing all benzodiazepines (Z-drugs are not detected: zopiclone and zolpidem).

The physician must take into account detection time windows for interpreting the given results. Table 2 describes these time windows.

Table 2: Time windows for the detection of drugs of abuse in urine (Moeller et al., 2008)

Drug	Time
Alcohol	7 - 12 h
Amphetamine/Metamphetamine	48 h
Benzodiazepine	
Short-acting	3 d
Long-acting	30 d
Cocaine metabolites	2 - 4 d
Marijuana	
Single use	3 d
Moderate use (4times/wk)	5 -7 d
Daily use	10 -15 d
Long term heavy smoker	>30 d
Opioids	
Codeine	48 h
Heroin	48 h
Hydromophone	2 - 4 h
Methadone	3 d
Morphine	48 - 72 h
Oxycodone	2 - 4 d
Propoxyphene	6 - 48 h

The physician must also be watchful about interactions. Numerous false negatives exist, notably for cocaine and benzodiazepines; the tests have better intrinsic qualities for the detection of opiates (1.9% false negatives) (Table 3) (Pesce et al., 2010). False positive exits also, mainly with psychotropic drugs (Table 4).

Table 3: Percent of false negatives obtained by urine drug screening test (in the consulting rooms of physicians) in chronic pain patients (Pesce et al., 2010)

Drug	Total tested	Percent false negative
Amphetamine	2792	9.3%
Benzodiazepines	3301	22%
Cannabinoid	2921	10.6%
Cocaine	2840	50%
Methadone	2735	6.1%
Opiates	3414	1.9%

Table 4: Agents leading to false positive results (Brahm, Yeager, Fox, Farmer, & Palmer, 2010; Moeller et al., 2008)

Substance tested	Agents leading to false positive results
Amphetamine or Methamphetamine	**Amphetamines derivates** (benzphetamine, chlobenzorex, *l*-Deprenyl, dextroamphetamine, fenproporex, MDMA, methylphenidate, phentermine) **Antihistamines/decongestants** (brompheniramine, ephedrine, pseudoephedrine phenylpropanolamine, phenylephrine, phenylpropanolamine) **Antidepressants** (bupropion, trazodone, desipramine, trimipramine) **Antipsychotics** (chlorpromazine, promethazine, thioridazine) **Other agents** (amantadine, isomethepthene, isoxsuprine, labetalol, ranitidine, ritodrine, selegiline, trimethobenzamide)
Methadone	**Antihistamines/decongestants** (diphenhydramine, doxylamine) **Antidepressants** (clomipramine) **Antipsychotics** (chlorpromazine, quetiapine, thiorizadine) **Other agents** (verapamil)
Opioids, opiates and heroin	**Opiate derivates** (dextrometorphan, heroin, opiates – codeine, hydromorphone, hydrocodone, morphine -, poppy seeds) **Antihistamines** (diphenhydramine) **Antibiotics** (quinolones, rifampin) **Other agents** (quinine, verapamil and metabolites)
Benzodiazepines	**Antidepressants** (sertraline) **NSAIDS** (oxaprozin)
Cannabinoids	**Cannabinoids derivates** (dronabinol, hemp-containing food) **NSAIDS** (ibuprofen, naproxen, tolmetin) **Proton pum inhibitors** **Other agents** (efavirenz)
Cocaine	**Coca leaf tea** **Topical anesthesics** containing cocaine
Tricyclic antidepressants	**Antiepileptics** (carbamazepine) **Antihistamines** (cyproheptadine, diphenhydramine, hydroxyzine) **Antipsychotics** (quetiapine) **Other agents** (cyclobenzaprine)

In the Scandinavian study previously cited (Mordal et al., 2010), the assessment by the psychiatrist of drug consumption in an emergency setting was less efficient than the assessment obtained by a urine drug screening test. The reference method was chromatography-tandem mass spectrometry. The physician had correctly assessed the consumption of alcohol but the assessment for illicit substances was not so good: 76% sensitivity for amphetamines, 61% for benzodiazepines, 57% for opiates, 55% for cannabis and only 50% for cocaine. Specificity rates varied from 94 to 99% for the various classes of substances. At the same time, UDT presented a sensitivity of 76% for amphetamines, 83% for benzodiazepines, 80% for opiates and 97% for cannabis. The specificity rates varied from 82 to 100% for the various classes of substances.

Table 5: Physician's assessment of recent substance intake (n = 325) and on-site urine screening tests results (n = 92) compared with urine laboratory findings serving as the reference standard (Mordal et al., 2010)

	Physician assessment		On-site screening test	
	Sensitivity (95%CI), %	Specificity (95%CI), %	Sensitivity (95%CI), %	Specificity (95%CI), %
Benzodiazepines	61 (53 – 68)	94 (90 – 97)	83 (71 – 94)	84 (74 – 94)
Opiates	57 (37 – 75)	96 (92 – 98)	80 (55 – 100)	99 (96 – 100)
Amphetamine	76 (64 – 88)	96 (93 – 98)	76 (58 – 94)	99 (96 – 100)
Cannabis	55 (42 – 68)	96 (93 – 98)	97 (91 – 100)	82 (72 – 92)
Cocaine	50 (10 – 90)	99 (98 – 100)	-	100 (100)
Ecstasy	-	-	-	100 (100)

In another study, sensibility for buprenorphine with 3 different OS-UDT varied from 88 to 100% and specificity from 91 to 100 % (Leino & Loo, 2007).

A recent study in the Netherlands compared UDT results performed by physicians and nurses in an emergency setting and not specifically trained to their use versus UDT results analyzed by the same immunochemical technique but in a laboratory by trained technicians. The sensitivity of three different commercial kits (screening for opiates, methadone, cocaine, tricyclic antidepressants and barbiturates) was assessed (considering tests performing in the laboratory as the gold standard) and ranged from 80 to 100% and specificity from 93 to 100% with no difference between the tests performed in the emergency setting than in the laboratory (Attema-de Jonge, Peeters, & Franssen, 2011).

As far as we know, no study reported positive and negative predictive values. Furthermore, studies cited above concerned mainly chronic pain patients treated by opioids. If sensitivity and specificity can be extrapolated to a population of opioid-addicted patients because of their intrinsic value, positive and negative predictive values depend on the prevalence of the studied phenomenon and, thus, should be assessed in this specific population to be discussed.

In medical offices, immunoassays have been shown to be reliable (Manchikanti, Malla, Wargo, & Fellows, 2011a, 2011b). Performing UDT at the physician office seems, thus, to be an appropriated answer to the requirements and questions for optimizing the management quality. Whatever it be, prudence is recommended for managers of clinical laboratories and good quality information is therefore required for clinicians in the field (Melanson et al., 2010).

GUIDELINES ABOUT URINE DRUG SCREENING TESTS VERSUS PRACTICES IN FRANCE

In France, summaries of product characteristics of methadone and buprenorphine (which govern the legal aspects of their prescription), such as circulars of the *Direction Générale de la Santé* DGS n°14 (7 March 1994) and n°4 (11 January) and n°29 (31 March 1995) reminded conditions of the marketing authorization (*Autorisation de mise sur le marché* AMM) and detail the recommendations about urine tests. Methadone prescription guidelines detail the recommended urine tests: a first, obligatory test before starting methadone treatment and later control tests. The first urine test confirms current drug consumption and the absence of methadone intake. Tests are subsequently done once or twice a week during the first 3 months of treatment, then twice monthly. When the patient has been transferred to an outpatient setting, tests can be done if the physician considers it necessary. Tests are not obligatory for buprenorphine. The circular of the *Direction de l'Hospitalisation et de l'Offre de Soins* DHOS of the 29th April 2002 took over the elements of 1994 and 1995 and detailed that urine tests have to be continued once a month without time limit. In 2004, updated French guidelines on optimal opiate addict care reinforced these recommendations and advised a standardized screening test schedule in the initiation of buprenorphine treatment (HAS, 2004). This biological analysis can also be proposed for the follow-up with the patient's consent. The OMT group from the addiction commission of the French health ministry highlighted the value of urine monitoring to improve therapeutic management quality and specified that performing these analyses must not weigh care ask and it accessibility. Lead-time of laboratory results actually are a barrier to a good management of patients addicted to opioids. Moreover, all patients do not perform these analyses as agreed with the physician. These analyses are, besides,

expensive leading the DGS to interview their utility. A clarification was published in October 2011 by the French agency of medicinal products, called *Agence Française de Sécurité Sanitaire des Produits de Santé* AFSSAPS at this time (AFSSAPS, 2011). The need for urine testing was reminded before starting an OS with the patient's consent; and the possibility of urine testing after that.

Some physicians, using regularly UDT, specifically in specialized centres or in hospital report that they bring a help to the dialogue, in addition to enable drug use monitoring. On the other hand, others argue that the use of these tests will be in opposition with the confident patient-doctor relationship. Nevertheless, a freedom of the speech could be trigger after talking with the patient of the results of the urine drug screening test. The addicted patient is extremely self under evaluated; the declaration of a drug use to his physician (but also to himself) is often difficult and could be as difficult as the relationship with the physician is of quality. The opioid-addicted patient process is difficult and deterring sooner relapses enables to talk about consumptions and craving and to reinforce therapeutic management.

Urine screening would so have two goals:

- A "technically" first one when starting treatment to check the absence of an anterior treatment by methadone before prescribing it and to assess associated consumptions to start buprenorphine or methadone.

- A second one in the follow-up to assess consumptions and to facilitate the dialogue about craving by the way of this assessment. The value would be then to repeat them more frequently than monthly: weekly with contingent

take-homes would be a condition with better outcomes in heroin use (Chutuape, Silverman, & Stitzer, 2001). This assessment could of course be associated with other assessment tools (craving calendar for example).

Guidelines highlight the use of the first "technically" test when starting treatment and advised tests for the follow-up in an optional manner without explaining their potential value at this stage. However, when you consider addiction as a chronic relapsing disease, the potential value of the second test seems obvious.

Practices may differ from guidelines and from the above defined framework. In specialized centres (CSAPA), practices are heterogeneous between health professionals of a same CSAPA as well as between different CSAPA (Saura, 2011).

IMPACT OF URINE DRUG SCREENING TESTS

For opioid maintenance treatments, these tests are used to assess the achievement of abstinence and the intake of the drug used for opioid maintenance as well as for the assessment of others consumptions. Their place could be, before starting OMT, to complete the initial assessment and to decide to prescribe the OMT: or in the follow-up, to monitor the consumptions and the craving, to evidence with the patient the achievement of abstinence, to have a positive reinforcement when results are negative and to deter as soon as possible the use of the substance to talk about it with the patient and reinforce the therapeutic management if necessary. UDT should be of significant use for GPs treating opioid-addicted patients by promoting dialogue, further educating patients in treatment-related issues and network-based work.

The value of drug tests for the diagnosis of substance abuse has been demonstrated: many studies agree that drug tests are more sensitive than self-reports (Galletly et al., 1993; Kilpatrick et al., 2000; Lundy et al., 1997; Olshaker et al., 1997; Perrone et al., 2001) or physician clinical evaluation (Mordal et al., 2010). Nevertheless while diagnostic value of these tests is well demonstrated, the consequences of carrying out these tests on management of treatment have not been established.

In school programs (Roche, Bywood, Pidd, Freeman, & Steenson, 2009) and in occupational drivers (Cashman, Ruotsalainen, Greiner, Beirne, & Verbeek, 2009), drug tests are known to be effective respectively on the illicit drug use and injuries. In emergency settings, a recent review found that drug tests may have no influence on

therapeutic management (Tenenbein, 2009). In chronic non-cancer pain patients, the effectiveness of urine testing to reduce opioid misuse is still debated (Starrels et al., 2010).

In the field of algology, these tests are frequently used to reduce the risk of misuse of opioids prescribed over the long term for chronic non cancer pain. The American recommendations advocate, before initiating treatment, the collection of written consent from the patient, and urine drug screening tests to identify any risk of misuse (Chou et al., 2009). These recommendations are also applied in the whole North-America (Gourlay, Heit, & Almahrezi, 2005). Procedures for urine drug testing are well described in this field (Christo et al., 2011; Owen, Burton, Schade, & Passik, 2012). Urine drug screening tests are also used for adolescents, generally at the request of the parents, but there is a great lack of training in correctly carrying out and analysing these tests correctly (Levy, Harris, Sherritt, Angulo, & Knight, 2006).

Few studies explored the consequences of carrying out these tests on medical management whereas they should have a particular value in primary care while outpatients care is developing (Walley et al., 2008). Since few years, actually, the use of these tests has been increasing in general practice. American general practitioners question the possibility of using these tests in their daily practice (Standridge, Adams, & Zotos, 2010), at a time when, in some countries, the use of rapid blood tests as a therapeutic aid is becoming common practice (glycosylated haemoglobin, cholesterol, INR, etc.) (Blattner, Nixon, Dovey, Jaye, & Wigglesworth, 2010; Laurence et al., 2008).

Some addiction network used performing these tests: the « Passage » network in Toulouse conducted a pilot study to assess drug use: 17.7% of the first prescriptions have

been questioned, many associated consumptions were shown, particularly of benzodiazepines (*unpublished data*).

Besides, monitoring procedures have been shown useful and effective to control behaviours of patients treated with an OMT. A first study, in France, suggested that the behaviours of patients treated with OMT depended less on the nature of the maintenance drug than the nature of the delivery and monitoring practices (Barrau et al., 2001). Efficacy of prescription monitoring programs has been shown in the US to decrease opioid analgesics consumptions (Chakravarthy, Shah, & Lotfipour, 2012; Simoni-Wastila & Qian, 2012). In France, they are associated with a decrease of doctor-shopping indicators (Pradel et al., 2009). Consumptions' monitoring by OS-UDT should decrease doctor-shopping behaviours and improve compliance of patients.

Compliance of patients on OMT could be improved by a monitoring procedure such as on-site urine drug screening test (OS-UDT). Patients may be self-motivated by the negativity of OS-UDT. Testing will urge GPs to be more attentive to substances' consumptions of their patients. This higher attention from GP will be beneficial for patients.

All these data highlight the importance of monitoring in OMT programs. Monitoring in OMT programmes should be beneficial for GPs and patients modifying their behaviours. As reminded above, available treatments are effective. To help GPs assessing consumptions with a basic tool like OS-UDT should help them to be more at ease with addictive diagnoses and should promote their involvement in opioid-patients management. This can only have beneficial outcomes for patients in terms of care access but also in terms of a decrease of morbidity and mortality thanks to a longer OMT retention.

OBJECTIVE

The objective of this thesis is to assess the value of urine drug screening in opioid-addicted patients managed in ambulatory care.

This assessment has been conducted in three parts:

- The first one aimed to summarize the knowledge concerning urine drug screening tests in the literature and of French GPs.
- The second one aimed to assess the effectiveness of drug tests in managing opioid-addicted patients using observational cohorts conducted from French health insurance system databases.
- Finally, the last part aimed to confirm the value of urine drug screening test in real life and thus, to assess their efficacy planning a pragmatic cluster randomized controlled trial in general practice.

PART 1: KNOWLEDGE CONCERNING URINE DRUG SCREENING TESTS

This first part aimed to summarize the knowledge concerning drug tests in the literature and of French GPs. As few studies assessed the prevalence of performing drug tests and the knowledge of UDT outside the North America, we aimed to investigate these issues in France by a transversal descriptive study. Besides, while the diagnostic value of UDT was clearly established and studies demonstrating their value on the therapeutic management were sparse, we aimed to summarize the evidence on this issue with a systematic review.

Partie 1 : Connaissance des tests urinaires de dépistage

Synthèse des connaissances des tests dans la littérature et par les médecins généralistes français

Première publication :

Cette étude descriptive menée en Midi Pyrénées avait pour objectif d'évaluer les connaissances et l'utilisation des tests urinaires de dépistage des médecins généralistes prenant en charge des patients dépendants aux opiacés. Un questionnaire a été envoyé par courrier postal à 1340 médecins généralistes tirés au sort à partir des bases de données de l'Union Régionale des Médecins Libéraux. Le taux de réponse était de 37% (n=496), 482 questionnaires ont été inclus. Parmi ceux-ci, 24,1% des médecins prenaient en charge régulièrement des patients dépendants. Concernant les tests urinaires de dépistage, 3,4% des médecins en réalisaient au cabinet médical à l'initiation et au suivi d'un traitement substitutif. Ces médecins manquaient d'information sur l'existence de ces tests, leur fiabilité, les moyens de se les procurer.

Deuxième publication :

Une revue systématique de la littérature a été réalisée selon les recommandations internationales PRISMA avec pour objectif d'évaluer si la réalisation de test urinaire de dépistage modifiait la prise en charge médicale et ses conséquences pour les patients abuseurs ou dépendants (ou à risque de l'être). La recherche a été effectuée le 26 octobre 2011 sur plusieurs bases de données : PubMed, ISI Web of Science, PsycINFO, Cochrane database of systematic reviews, Cochrane central register of controlled trials, Cochrane Drugs and Alcohol group et National Institute of Drug Abuse (NIDA). Deux relecteurs ont sélectionné indépendamment les articles selon des critères d'inclusion précis ; leur accord a été évalué par le coefficient κ de concordance inter évaluateur. Les données des articles inclus ont été extraites à l'aide d'une grille

standardisée. Leur qualité a été évaluée par des échelles validées (score de Starrels, GRADE, CONSORT et STROBE). Une synthèse qualitative a été menée. Sur 6046 articles identifiés, 8 ont été inclus : 1 essai clinique randomisé, 2 études quasi-expérimentales type avant/après, 1 étude de cohorte, et 4 études transversales descriptives. Ces études de qualité faible à moyenne ont montré que la réalisation de tests urinaires de dépistage entrainait peu ou pas de modification de prise en charge dans des populations de patients en centre anticancéreux, en centre antidouleur, en service de médecine, et aux urgences psychiatriques ou médicales. Les critères de jugement de ces études étaient hétérogènes et subjectifs.

STUDY 1: ON-SITE DRUGS OF ABUSE URINARY SCREENING TESTS FOR THE MANAGEMENT OF OPIATE-ADDICTED PATIENTS: A SURVEY AMONG FRENCH GENERAL PRACTITIONERS

PRESENTATION OF THE STUDY

Dupouy J, Bismuth S, Oustric S, Lapeyre-Mestre M

On-Site Drugs of Abuse Urinary Screening Tests for the Management of Opiate-Addicted Patients: A Survey among French General Practitioners

European Addiction Research 2012; 18: 175-83 (Dupouy, Bismuth, Oustric, & Lapeyre-Mestre, 2012)

OBJECTIVE

The objective of this first study was to investigate French GPs' knowledge and practices concerning drug tests with a focus on OS-UDTs.

METHOD

To perform an overview on this topic, we conducted a descriptive cross-sectional study in ambulatory practice. A random sample of 1340 GPs (i.e. one third of all GPs in the database) was selected from the *Union Régionale des Médecins Libéraux*'s (URML) computerized database of all GPs working in ambulatory practice in the Midi-Pyrénées area of France (region of south-western France, 3 million inhabitants). GPs with a nonexclusively ambulatory family practice were excluded. Postal questionnaires were sent in December 2009.

RESULTS

Of the 1340 send questionnaires, 496 were returned (37.0%) and 482 (36.0%) were included in the analysis. Of the 482 GPs in the sample, 116 (24.1%) regularly treated opiate-addicted patients. Only 31 of them (26.7%) used drug tests and 4 of them (3.4%) performed OS-UDT

in their consultation rooms. The main reason for not performing UDT was a lack of knowledge about screening test: most of the GPs did not perform OS-UDT because they were unaware of whether such tests were reliable or available. Among the few GPs using tests, the consequence they reported was mainly reinforcing dialogue with the patient.

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On-Site Drugs of Abuse Urinary Screening Tests for the Management of Opiate-Addicted Patients: A Survey among French General Practitioners

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Key Words
Opioid-related disorders · Substance abuse detection · Family practice · Immunoassay · Opiate substitution treatment

Abstract
In France, opiate-addicted patients are mainly managed by general practitioners (GPs). Because on-site abuse drugs urinary screening tests (ODUTs) are now on the market, we investigated French GPs' knowledge and practices concerning drug tests with a focus on ODUTs. We conducted a descriptive cross-sectional study in ambulatory practice. Postal questionnaires were sent to a random sample of GPs in the Midi-Pyrénées area of France in December 2009. Of the 482 GPs in the sample, 116 (24.1%) regularly treated opiate-addicted patients. Only 31 of them (26.7%) used drug tests and 4 of them (3.4%) performed ODUTs in their consultation rooms. Most of the GPs did not perform ODUTs because they were unaware of whether such tests were reliable or available. Many French GPs treating opiate-addicted patients regularly did not perform ODUTs and lacked knowledge of them.
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Introduction

Since 1996, two drugs have been approved in France for the treatment of opiate addiction: methadone, a long-acting agonist at the μ receptor, and buprenorphine, a long-acting partial agonist at the μ receptor. The rules of prescription for these two drugs differ widely and they are both delivered in different ways. Methadone use is governed by the regulations on the application of narcotics in France [1]. Initial methadone prescription is restricted to specialized addiction centers and usually requires strict patient compliance with a supervised daily intake, as well as urinary tests. Psychosocial support and follow-up is also usual. When patients are stable, a higher amount of methadone can be given for take-home treatment. Switching from treatment centre to general practitioner (GP) prescription is also possible. Methadone must be prescribed on a special form for controlled substances and for no more than 14 days. It must be dispensed by the pharmacist named on the prescription. As of January 2002, the initial prescription of methadone can be made by any hospital practitioner in order to make access to it easier. In contrast, buprenorphine, a psychotropic medicine in Schedule III of the 1988 Convention [1], is not clas-

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sified as a narcotic in France and can be prescribed by any physician and dispensed by any community pharmacist. Prescription must be on a special form for controlled substances and may be for a maximum of 28 days. Since September 1999, buprenorphine has had to be dispensed in multiples of 7 days. The Summary Product Characteristics of buprenorphine mention that maintenance treatment with buprenorphine has to be included in a global programme of medical, social and psychological care. The recommended daily dose ranges from 4 to 10 mg, with a maximum of 16 mg. Health authorities have also encouraged training programmes on addiction and the formation of informal networks of GPs, pharmacists and specialized centers.

In ambulatory practice, GPs can be involved in initiating treatment by buprenorphine and follow-up of treatment by buprenorphine and methadone. Because buprenorphine is easily obtainable [2], most opiate-addicted patients are treated in general practice using this drug [3]. The number of people receiving opiate maintenance treatment (OMT) was estimated at around 100,000 for buprenorphine and around 35,000 for methadone in 2009 [4]. The proportion of French GPs involved in these patients' treatment is around 20% [3].

The Summary of Product Characteristics of methadone specifies that an initial urinary analysis has to be performed to assess opiate addiction and to confirm the absence of methadone before initiating methadone prescription. Then, urinary analyses have to be performed once or twice a week during the first 3 months of treatment, and twice a month after this period. Substances tested for will be methadone, opiate, alcohol, cocaine, amphetamines, cannabis and LSD. After the patient has been transferred from a specialized center to a GP, urinary analyses can be used at the GP's discretion. If a patient is treated with buprenorphine, there is no regulatory requirement for urine testing. In 2004, French guidelines [5, 6] reasserted the compulsory need for urinary analyses to initiate methadone prescription and recommend them before buprenorphine prescription and during the follow-up of both treatments. These guidelines highlight the need to establish consistent regulations on urinary analyses. GPs who began prescribing OMT after 2004 might be more informed on drug tests than GPs who prescribed OMT since a long time.

Screening assays based on immunoassay procedures [7] are used to assess the consumption of substances. Confirmatory procedures with the gold standard for drug testing (liquid or gas chromatography-mass spectrometry) can then be performed. Recently, on-site urinary screening tests have become available in France, granting GPs the opportunity to use them in their consulting rooms. For the following, we will use DTs for drug tests and ODUTs for on-site drug of abuse urinary screening tests. The term DT will refer to all techniques performed in order to search for drugs of abuse in a biological liquid (urine or blood). It will include screening assays by immunoassay procedures, performed in the consulting room or in a laboratory, and confirmatory testing by chromatography-mass spectrometry. The term ODUT will be reserved for urine screening assays by immunoassay procedures performed on-site, that is to say in the consulting room.

The aim of this work was to investigate GPs' knowledge and use of DTs with a focus on ODUTs according to their involvement in opiate-addicted patients' treatment in an area of south-western France.

Materials and Methods

This study was conducted in the Midi-Pyrénées area, a region of south-western France with 3 million inhabitants. A random sample of 1340 GPs (i.e. one third of all GPs in the database) was selected from the Union Régionale des Médecins Libéraux's (URML) computerized database of all GPs working in this area in ambulatory practice. A postal questionnaire was sent out in December 2009, with a prepaid envelope enclosed to return the questionnaire. GPs with a nonexclusively ambulatory family practice were excluded.

The questionnaire included the following items: demographic and professional characteristics and GPs' level of involvement in the domain of drug abuse (for online supplementary material, see www.karger.com/doi/10.1159/000336540). One question assessed addictology training, which is acquired in continuous self-training in France. Performing DTs or ODUTs was assessed at buprenorphine treatment initiation and during follow-up for buprenorphine or methadone treatment. We also considered the impact of these tests on patient management and reasons for not using them. Finally, a number of questions sought to assess GPs' interest in ODUTs.

The deadline for returning the questionnaire was 28 February 2010. Data capture and analysis were performed with EPIDATA Entry® and Analysis®. Two groups of GPs were defined: GPs who regularly treated opiate-addicted patients (more than once a month) and those who infrequently (less than once a month) or never did. A descriptive analysis was performed with a univariate analysis by χ^2 test to compare demographic and professional characteristics between the two groups. Use of DTs was assessed in the group of GPs regularly treating opiate-addicted patients. A χ^2 test was performed to compare if GPs who had been practicing for less than 5 years (implementation of national guidelines) used more DTs than other GPs (who had been practicing between 5 and 15 years or more than 15 years). Use and knowledge of ODUTs was assessed in the group of GPs regularly treating opiate-addicted patients. For that, two subgroup analyses were per-

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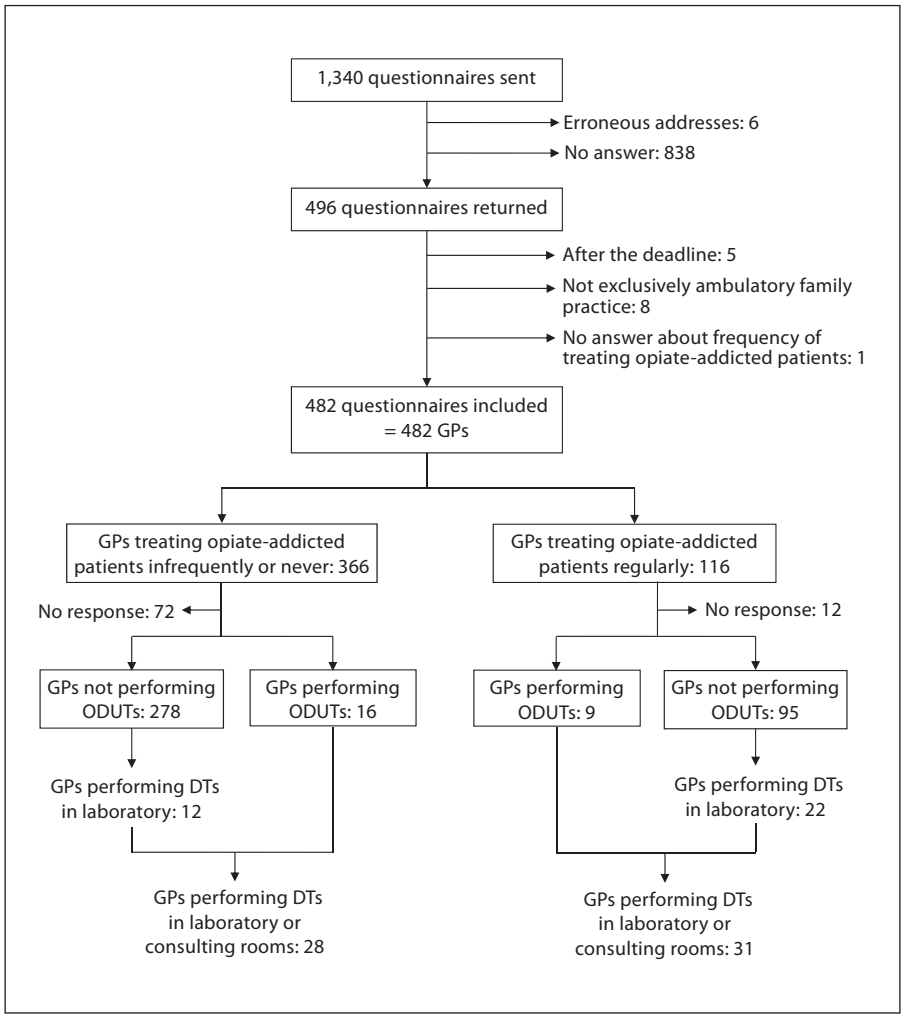

Fig. 1. Groups and subgroups of GPs included. Main results. ODUTs = On-site drugs of abuse urinary screening tests; DTs = drug tests.

formed: the first subgroup included GPs who performed DTs (be they blood or urinary tests in laboratories or at the site of consultation) in order to know how performing DTs affected patient management; the second analysis included GPs who did not perform ODUTs, and aimed to ascertain their reasons for not performing them.

Results

Six questionnaires were sent back because of erroneous addresses. Four hundred and ninety-six questionnaires were returned filled in, which constitutes a response rate of 37%, although five arrived after the deadline and were not included (fig. 1). Of the remaining questionnaires, eight were excluded because physicians did not engage exclusively in ambulatory family practice (five were angiologists, two were retired and one worked exclusively in a health-care facility). One GP was excluded because he did not answer the question investigating his involvement in the treatment of opiate-addicted patients. This left 482 questionnaires which were included in the analysis. Table 1 shows the demographic and professional characteristics of the GPs included.

One hundred and sixteen physicians (24.1%) regularly treated opiate-addicted patients, 248 (51.4%) managed them rarely (less than once a month), and 118 (24.5%) never did so (fig. 1). Forty-nine physicians (10.2%) had addictology training and 33 (6.8%) belonged to an addictology care network. One hundred and forty-five physicians (30.1%) had prescribed OMT at least once.

GPs regularly treating opiate-addicted patients were more frequently trained in addictology, participated more frequently in an addictology network, prescribed OMT more frequently (univariate $p < 0.001$) and were

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Table 1. Demographic and professional characteristics of all GPs in the sample and broken down by treatment of opiate-addicted patients

Characteristics of GPs	All GPs (n = 482)	GPs treating opiate-addicted patients regularly (n = 116)	GPs treating opiate-addicted patients infrequently or never (n = 366)	p value[1]
Sex				
Man	328 (68.0%)	85 (73.3%)	243 (66.4%)	0.143
Woman	138 (28.6%)	27 (23.3%)	111 (30.3%)	
No response	16 (3.3%)	4 (3.4%)	12 (3.3%)	
Location				
Town centers	180 (37.3%)	62 (53.5%)	118 (32.2%)	<0.001
Suburbs	133 (27.6%)	23 (19.8%)	110 (30.1%)	
Rural areas	169 (35.1%)	31 (26.7%)	138 (37.7%)	
Duration of practice				
Less than 5 years	40 (8.3%)	14 (12.1%)	26 (7.1%)	0.242
5 to 15 years	89 (18.5%)	21 (18.1%)	68 (18.6%)	
More than 15 years	352 (73.0%)	81 (69.8%)	271 (74.0%)	
No response	1 (0.2%)	0 (0.0%)	1 (0.3%)	
Type of practice				
Sole	192 (39.8%)	40 (34.5%)	152 (41.5%)	0.177
Group practice	290 (60.2%)	76 (65.5%)	214 (58.5%)	
Distance from a laboratory				
Nearby (less than 10 km)	384 (79.7%)	99 (85.5%)	285 (77.9%)	0.041
Further away but used to work with this facility	93 (19.3%)	15 (13.0%)	78 (21.3%)	
No easy access to a laboratory	2 (0.4%)	0 (0.0%)	2 (0.5%)	
No response	3 (0.6%)	2 (0.5%)	1 (0.3%)	
Addictology training				
Yes	49 (10.2%)	31 (26.7%)	18 (4.9%)	<0.001
No	426 (88.4%)	84 (72.4%)	342 (93.5%)	
No response	7 (1.4%)	1 (0.9%)	6 (1.6%)	
Participation in addictology network				
Yes	33 (6.8%)	30 (25.8%)	3 (0.8%)	<0.001
No	441 (91.5%)	85 (73.3%)	356 (97.3%)	
No response	8 (1.7%)	1 (0.9)	7 (1.9%)	
Prescription of OMT				
Yes	145 (30.1%)	86 (74.1%)	59 (16.1%)	<0.001
No	327 (67.8%)	27 (23.3%)	300 (82.0%)	
No response	10 (2.1%)	3 (2.6%)	7 (1.9%)	

[1]Univariate analysis by χ^2 test between GPs regularly treating opiate-addicted patients and GPs rarely or never treating opiate-addicted patients.

located nearer to a laboratory (p = 0.041). By contrast, they were not significantly different in gender (p = 0.143), duration of practice (p = 0.242) or type of practice (p = 0.177) (table 1).

Of the 116 GPs regularly treating opiate-addicted patients, 31 physicians (26.7% of GPs regularly treating opiate-addicted patients) reported using DTs (fig. 1). Twenty-seven (23.3%) reported using them for the initiation or follow-up of OMT: 7 only for initiation, 11 only for follow-up and 9 for both situations (table 2). GPs who had been practicing for less than 5 years did not use DTs more than other GPS (p = 0.347). Only four physicians (3.4%) re-

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Table 2. Use of DTs (many answers possible) in the group of GPs regularly treating opiate-addicted patients (n = 116)

Kind of screening tests	Yes (n = 31)	No (n = 85)	No response
Blood tests at laboratory			
For initiating OMT	2 (1.7%)	110 (94.8%)	4 (3.4%)
For follow-up OMT	6 (5.2%)	104 (89.7%)	6 (5.2%)
Urinary tests at laboratory			
For initiating OMT	11 (9.5%)	103 (88.8%)	2 (1.7%)
For follow-up OMT	15 (12.9%)	94 (81.0%)	7 (6.0%)
Urinary tests at practice (ODUTs)			
For initiating OMT	4 (3.4%)	111 (95.7%)	1 (0.9%)
For follow-up OMT	4 (3.4%)	110 (94.8%)	2 (1.7%)
For other reasons	6 (5.2%)	97 (83.6%)	13 (11.2%)

Table 3. Change in addicted patients' management because tests were performed (many answers possible) in the subgroup of GPs regularly treating opiate-addicted patients and performing DTs (n = 31)

Patients' management	Yes	No	No response
Nonprescription of OMT	9 (29.0%)	16 (51.6%)	6 (19.4%)
Reinforcement of therapeutic education	22 (71.0%)	5 (16.1%)	4 (12.9%)
Referral to a specialised consultation	15 (48.4%)	12 (38.7%)	4 (12.9%)
Other	2 (6.5%)	10 (32.3%)	19 (61.3%)

Table 4. Reasons for not performing ODUTs in the subgroup of GPs regularly treating opiate-addicted patients and not using ODUTs (n = 95)

Reasons for not performing ODUTs	Yes	No	No response
Utility considered insufficient	13 (13.7%)	46 (48.6%)	36 (37.9%)
Cost judged too expensive	13 (13.7%)	34 (35.8%)	48 (50.5%)
Tests considered too long or difficult	9 (9.5%)	38 (40.0%)	48 (50.5%)
Tests' reliability unknown	42 (44.2%)	20 (21.1%)	33 (34.7%)
Tests' existence unknown	50 (52.6%)	26 (27.4%)	19 (20.0%)
How to procure tests unknown	59 (62.8%)	16 (17.0%)	19 (20.2%)
Other	7 (7.4%)	34 (35.8%)	54 (56.8%)

ported performing ODUTs initially and during follow-up. Six physicians reported using ODUTs in other contexts, namely uncovering illicit drug consumption in patients denying this practice for two GPs; requisitioning by the French police force for one GP; screening for illicit drugs such as cannabis in minors at parents' request for one GP, and follow-up of cannabis addiction for one GP. The remaining GP did not specify his reason for carrying out these tests.

These 31 GPs reported that performing DTs led them to change their management of opiate-addicted patients (table 3): 9 (29.0%) did not prescribe any treatment following the test; 22 (71.0%) reinforced therapeutic education; 15 (48.4%) referred their patients to a specialist, and two

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Table 5. Interest in ODUTs in the group of GPs regularly treating opiate-addicted patients (n = 116)

Questions on interest of GPs	Yes	No	No response
Interest in ODUTs?			
For initiating OMT	65 (56%)	23 (19.8%)	28 (24.1%)
For follow-up of OMT	73 (62.9%)	16 (13.8%)	27 (23.3%)
Would it be possible to manage more opiate-addicted patients and prescribe more OMT if ODUTs were available at the practice?	44 (37.9%)	53 (45.7%)	19 (16.4%)

confirmed that they had made other changes (many answers possible).

Of the 116 GPs regularly treating opiate-addicted patients, 95 (81.9%) reported that they did not perform ODUTs. The reasons reported included (table 4) a lack of knowledge about ODUTs – 50 GPs (52.6%) were unaware of their existence – and the constraints of ODUTs – 59 GPs (62.8%) were unaware of how to obtain them. Seven GPs reported other reasons: two said that they lacked training, and one thought that doing urinary screening tests would be considered as a lack of trust in patients and might reveal interpersonal problems. The remaining four cited reasons mentioned above. The rate of nonresponse ranged from 20% to 56.8% for this question.

In the group of GPs regularly treating opiate-addicted patients, the use of ODUTs seemed useful for 65 physicians (56%) at the initiation of OMT and 73 (62.5%) during follow-up (table 5). Forty-four physicians (37.9%) thought that performing these tests would allow them to treat more opiate-addicted patients and to prescribe more OMT (table 5). The rate of nonresponse ranged from 16.4% to 24.1%.

Discussion

This observational study investigated GPs' knowledge and use of ODUTs. Some limitations must be acknowledged. First of all, we performed an anonymous postal survey among a sample of GPs randomly selected from the whole population of GPs working in the Midi-Pyrénées area. One third of GPs were selected and we obtained a global response rate of 37%, excluding erroneous addresses and questionnaires which went astray in the post. This response rate is low but similar to response rates obtained from recent French surveys using electronic or postal questionnaires to investigate GPs' practices (from 23 to 35%) [8–11]. We did not issue a reminder. Thus, we cannot exclude a selection bias in respondents. Unfortunately, we could not compare characteristics between GPs included and GPs who did not reply (the URML database did not allow this). However, the characteristics of our sample of participating GPs were similar to those of the whole population of GPs working in the Midi-Pyrénées area, particularly where gender, mean age and duration of practice were concerned, as can be seen from the regional demographic data made available by the French General Medical Council [12]. By contrast, GPs working in rural areas and suburbs were overrepresented in our sample, whereas GPs working in town centers were underrepresented. In 2008, in the Midi-Pyrénées area, 58.3% of GPs worked in town centers, 12.7% in the suburbs and 29.1% in rural areas (data provided by the regional monitoring center for public health, Observatoire Régional de la Santé-Midi-Pyrénées).

In this study, 24.1% of GPs treated opiate-addicted patients regularly and 30.1% prescribed OST. These figures were probably inflated due to selection bias, as physicians involved in addictology were more inclined than the others to offer a response. However, other French data identified that 20% of GPs treated 73% of opiate-addicted patients and 35% of GPs had prescribed OST at least once [3]. Considering GPs who were used to treat opiate-addicted patients more than once a month like GPs regularly treating opiate-addicted patients was a choice we made to identify GPs involved in treatment of opiate addiction and who could be, thus, concerned by DTs. As expected, GPs who regularly treated these patients were working mainly in town centres and were more frequently trained in addictology in the Midi-Pyrénées area. The involvement of French GPs in the management of drug addicts is lower than that of GPs in other countries: in a national survey in England, 51% of GPs had seen opiate addicts over the course of the preceding four weeks [13].

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This could be partly explained by the differences between the health-care systems in the two countries. In England, being treated by GPs rather than in drug clinics seems to offer the advantage of decreasing consumption practices associated with OMT and the occurrence of psychological disorders [14]. By contrast, 24.1% is high compared to other countries: in a study carried out in Australia in 2008, around 1% of all GPs in some jurisdictions prescribed OMT [15]. In our study, the small number of GPs regularly treating opiate-addicted patients can be explained by the generally low level of addictology training observed in the GP population and by the GPs' low rate of participation in specialized addiction networks. These low levels of training and involvement were also observed in a French study in 2005, which reported that 32% of GPs were trained in addictology and 21% were in touch with a specialized addictology network [16]. One explanation of this low level of involvement should be that GPs struggle to assess the extent of patients' honesty about their use of substances (OMT and other illicit drugs) [17]. In reality, one to two thirds of patients on OMT are reported to consume alcohol and benzodiazepines [18, 19]. Furthermore, many French GPs are afraid of bolstering drug trafficking [20], particularly with the resale of buprenorphine and the increasingly widespread nature of OMT. Performing DTs might be an appropriate response to these barriers.

Our results suggest that, in the Midi-Pyrénées area, GPs who regularly treat opiate-addicted patients do not usually perform screening tests in line with national recommendations on DTs. Only 23.3% of GPs regularly treating opiate-addicted patients reported performing DTs for OMT initiation and follow-up. This practice is not related to implementation of national guidelines, which asked about knowledge of these guidelines. Actually, GPs who began prescribing OST after implementation of guidelines (for less than 5 years) were not likely to use DTs more than other GPs. For a few GPs using DTs, the consequence was mainly increased dialogue with the patient. Carrying out ODUTs at the consultation site remained a rarity. This is doubtless unrelated to difficulties in accessing a laboratory (none of these GPs reported that they could not easily access such a facility). This could probably be explained by GPs' lack of knowledge about ODUTs, which was undoubtedly more significant than the observations suggested given the nonresponse rate for questions on reasons for not using ODUTs and interest in them. Around half of GPs claimed that they lacked knowledge about ODUTs, and the other half did not respond, making it impossible to establish whether they lacked knowledge or not. This suggests that the actual level of unawareness of ODUTs is higher than that observed. As regards the last question on GPs' interest about ODUTs, a quarter of GPs did not respond; this is unsurprising given that they did not know of the existence of ODUTs. Indeed, use of DTs is a known practice in the US by GPs involved in opiate-addicted patients' treatment: in 2008 it was practiced by 82% of practice-based physicians authorized to prescribe buprenorphine in Massachusetts [21].

The main finding to have emerged from this study, in spite of its limits, is that GPs lacked information concerning the existence and reliability of ODUTs and ways to obtain them. This lack of awareness also reflects the lack of data in the literature on the topic. A study performed by an addictology network in the capital city of the Midi-Pyrénées area (Réseau Passages) reported that carrying out ODUTs made it possible to reconsider 17.7% of OMT first prescriptions [unpubl. results]. As far as we know, few studies have assessed the consequences of performing ODUTs in order to manage addicted patients. We have identified systematic reviews in schools [22] and for occupational drivers [23]: ODUTs seemed to be an effective tool on clinical outcomes. ODUTs' effectiveness in limiting abuse in chronic pain patients seems to be real [24, 25], but needs to be confirmed by further studies. We also identified studies evaluating ODUTs in an emergency context, and these studies did not demonstrate ODUTs' effectiveness [26, 27]. As far as we know, no study assessed ODUTs' effectiveness in ambulatory settings or for the management of opiate addicts. Various studies looked at the inherent characteristics of ODUTs and showed that they are less efficient than liquid chromatography-mass spectrometry [28]. This is due to the high number of false-negative results, mainly for cocaine and benzodiazepines. By contrast, the performance of ODUTs seemed to be more efficient in identifying opiate drugs [29]. A recent Norwegian study [30] revealed satisfactory levels of sensitivity and specificity on the part of ODUTs; these levels were, respectively, 76–97% and 82–100% compared to liquid chromatography-mass spectrometry. This study compared the physician's assessment of patients' current intake with the combined results of blood and urine laboratory analyses in the psychiatric emergency context; physicians were rather successful in assessing alcoholic consumption but less so in evaluating illicit drug consumption (76% for amphetamines, 57% for opiates and 50% for cocaine). All of these results are encouraging and suggest that ODUTs could be useful in family practice. However, as far as we

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know, the usefulness and reliability of ODUTs have not been evaluated in ambulatory general practice. Further studies are needed for such assessments to be carried out. ODUTs should be of significant use for GPs treating opiate-addicted patients by promoting dialogue, further educating patients in treatment-related issues and network-based work.

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Disclosure Statement

None of the authors have any conflict of interest to declare in relation with this study.

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STUDY 2: DOES URINE DRUG ABUSE SCREENING HELP FOR MANAGING PATIENTS? A SYSTEMATIC REVIEW

PRESENTATION OF THE STUDY

Dupouy J, Mémier V, Catala H, Lavit M, Oustric S, Lapeyre-Mestre M.

Does urine drug abuse screening help for managing patients? A systematic review.

Drug and Alcohol Dependence 2014; 136: 11-20 (Dupouy, Mémier, et al., 2013)

OBJECTIVE

In front of the lack of significant evidence of efficacy for managing patients, we conducted a systematic review to summarize the evidence pertaining to the efficacy of drug abuse urinary screening test for the medical management of patients.

METHOD

A systematic review of clinical trials, quasi-randomized and observational studies was performed using PubMed, Cochrane database of systematic review, Cochrane central register of controlled trials, PsycINFO, National Institute on Drug Abuse, ISI Web of Science. The methodological quality was assessed with the score developed by Starrels *et al*.; the report quality using the CONSORT and the STROBE checklists. The main outcome was medical management or consequences of management for patients in terms of psychoactive substance consumption and its complications, be they medical, social or professional.

RESULTS

In this evaluation, a total of 8 studies met the inclusion criteria: one randomized clinical trial in psychiatric emergency settings, two quasi-randomized studies in emergency settings and pain centre, one cohort in adolescent ambulatory care, and four descriptive transversal studies

in cancer centre, emergency settings and family medicine. The quality of the methodology of these studies was judged to be poor, with the exception of the randomized clinical trial where the quality was judged to be fair. The value of the urine drug screening in managing patients was not clearly indicated in these studies.

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Review

Does urine drug abuse screening help for managing patients? A systematic review☆

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ABSTRACT

Background: In the field of addiction, assessment of psychoactive substance use is a key element. Nevertheless, self-reports and clinical examination underestimate the use of psychoactive substances. The implementation of urine drug screening tests (UDS) should improve this assessment. While the diagnostic value of UDS is well demonstrated, the consequences of carrying out UDS on medical management have not been established. Our aim was to summarize the evidence pertaining to the efficacy of UDS for medical management.
Methods: A systematic review of clinical trials, quasi-randomized and observational studies was performed using PubMed, Cochrane database of systematic review, Cochrane central register of controlled trials, PsycINFO, National Institute on Drug Abuse, ISI Web of Science. The methodological quality was assessed with the score developed by Starrels et al.; the report quality using the CONSORT and the STROBE checklists. The main outcome was medical management or consequences of management for patients in terms of psychoactive substance consumption and its complications, be they medical, social or professional.
Results: Eight studies met the inclusion criteria: one randomized clinical trial, two quasi-randomized studies, one cohort, and four cross-sectional studies. The methodological quality was judged to be poor, with the exception of the randomized clinical trial (fair quality). The value of UDS in managing patients was not clearly indicated in these studies.
Conclusions: Few studies, with poor quality, have assessed the value of UDS in managing patients using psychoactive substances; though with insufficiency to demonstrate the interest of carrying out UDS. Therefore, pragmatic intervention studies are necessary.
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Contents

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1. Background

In the field of addiction, assessment of psychoactive substance use is a key element for diagnosis and medical management. Nevertheless, this assessment is often difficult as self-reports underestimate the use of psychoactive substances (Galletly et al., 1993; Kilpatrick et al., 2000; Lundy et al., 1997; Olshaker et al., 1997; Perrone et al., 2001). One Scandinavian study compared the performance of psychiatrists versus the use of urine drug screening tests (UDS) in the context of emergency settings for the assessment of drug use, using chromatography–tandem mass spectrometry as the reference (Mordal et al., 2010). The sensitivity of the physicians' assessment was 76% for amphetamines, 61% for benzodiazepines, 57% for opiates, 55% for cannabis and only 50% for cocaine. The specificity varied from 94 to 99% for the various classes of substances. By contrast, the sensitivity of UDS was 76% for amphetamines, 83% for benzodiazepines, 80% for opiates and 97% for cannabis. The specificity ranged from 82 to 100% for the various classes of substances. Actually, physicians' assessment of psychoactive drug use lead to underestimate the true consumptions, and UDS should improve this assessment.

UDS are based on immunoassay techniques and enable a qualitative and non-quantitative analysis with detection-based on designated thresholds. It is essential to ensure their proposition of qualitative determination, in order to be able to interpret their significance. In addition, their limits need to be recognized to guarantee pertinent interpretation. Numerous false negatives exist, notably for cocaine and benzodiazepines (Pesce et al., 2010); the tests provide better intrinsic qualities for the detection of opiates (1.9% false negatives). UDS can be performed in physicians' consulting rooms or at the patient's bedside, thanks to commercial kits as well as by an automaton at the laboratory. In the physician's office, immunoassays have been shown to be reliable (Manchikanti et al., 2011a,b). Whatever the method, caution is recommended for managers of clinical laboratories and good quality information is, therefore, required for clinicians in the field (Melanson et al., 2010).

While the diagnostic value of UDS is well demonstrated (Galletly et al., 1993; Kilpatrick et al., 2000; Lundy et al., 1997; Olshaker et al., 1997; Perrone et al., 2001), the consequences of carrying out these tests on medical management have not been established. Nevertheless, UDS are widely used. American general practitioners question the possibility of using these tests in their daily practice (Standridge et al., 2010) at a time when, in some countries, the implementation of rapid blood tests as a therapeutic aid is becoming common practice (i.e., glycosylated hemoglobin, cholesterol, INR, etc.; Blattner et al., 2010; Laurence et al., 2008).

In the field of pain management, UDS are utilized to reduce the risk of misuse of opioids, prescribed over the long term for chronic non cancer pain. The American recommendations advocate, before initiating treatment, the collection of written consent from the patient, and UDS to identify any risk of abuse (Chou et al., 2009). The same recommendations are also given in Canada (Gourlay et al., 2005). Procedures for urine drug testing are well described in this field (Christo et al., 2011; Owen et al., 2012). UDS are also used for adolescents, generally at the request of their parents, however there is a great lack of training in carrying out and analyzing these tests correctly (Levy et al., 2006a). For opioid maintenance treatments, these tests should be applied to assess the achievement of abstinence and the intake of opioid maintenance drugs as well as for the assessment of other addictions.

On the basis of the current literature, it could be expected that carrying out UDS would provide an improvement in the management of patients with addictive behavior. UDS would be helpful, particularly in community office-based settings, as office-based management of opioid dependence grows up (Walley et al., 2008). Despite the lack of significant evidence of efficacy, UDS are recommended to assess the use of psychoactive substances when abuse or addiction is suspected. Thus, this systematic review is undertaken to summarize the evidence pertaining to the efficacy of UDS for medical management of patients.

The aim was to assess whether carrying out UDS changes the management of patients using psychoactive substances and the consequences of this management for these patients.

2. Methods

This review was realized according to a systematic review process derived from the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009; Moher et al., 2009).

2.1. Inclusion criteria

2.1.1. Types of studies.

Clinical trials: randomized or not, blind or not, controlled or not.

Quasi-randomized studies: before/after, here/elsewhere.
Observational studies: prospective or historic cohort, case-control, nested case-control.
Series of cases.

2.1.2. Types of participants.

Participants of interest were patients treated as outpatients or inpatients.
Using psychoactive substances.
Users or abusers or addicted (or suspected to be).

2.1.3. Types of interventions.

Carrying out UDS using the enzyme immunoassay technique.
At the patient's bedside, in consulting rooms or in the laboratory.
Possibly completed by a confirmation technique (chromatography).
If the test technique was not indicated in the article, the authors of the article were contacted to collect this information.
Comparison arm had to be the absence of UDS but studies without comparator were also included.

2.1.4. Types of outcome measures.

Medical management: medical treatment reassessment, request for specialist opinion, prescription of additional tests, prescription of medicinal products, hospitalization, duration of hospital stay, orientation toward a hospital department or another participant whether medical or not (i.e., paramedical, psychosocial, etc.).
Or consequences of management for patients in terms of psychoactive substance consumption and their complications (i.e., medical, social or professional).
The link between carrying out a urine test and the medical management achieved, or its consequences, needed to be clearly identified as such in the article.

2.2. Exclusion criteria

2.2.1. Types of participants. Studies dealing with pregnancy or perinatal period, with drug intoxications, voluntary or not (overdoses) or seen in connection with occupational health or medical jurisprudence were excluded.

2.2.2. Types of interventions. If the procedure was a test different than enzyme immunoassay screening techniques or biological tests other than urine or was focusing on the frequency of carrying out tests (scheduled, at random, close together or not, etc.), or if another intervention was following the test results, studies were excluded. In the latter case, not the test itself was assessed, more precisely the test was the eligibility criterion for the scheduled procedure measured (reward, scheduled consultation, etc.).

2.2.3. Types of outcome measures. If the assessment criterion was economic (if this was the only criterion assessed) or intrinsic performance of the tests (if it was the only criterion assessed) or characteristics of population or prognosis (predictive factor) depending on the result of the test, studies were also excluded. In this last case, the test only has a descriptive role by identifying distinct populations.

2.3. Literature search

The search for articles was carried out by two authors (J.D. and V.M.) on several databases: PubMed, Cochrane database of systematic review, Cochrane central register of controlled trials, PsycINFO, National Institute on Drug Abuse (NIDA), ISI Web of Science on October 26th 2011. Table 1 indicates the databases and the retrieval formula used for each one.

Table 1
Databases and retrieval formula used.

Databases	Retrieval formula
PubMed	((“Substance-Related Disorders”[Mesh]) OR “Central Nervous System Agents”[Mesh]) AND “Substance Abuse Detection”[Mesh]
Cochrane database of systematic reviews	drug abuse AND screening test*
Cochrane central register of controlled trials	drug abuse AND screening test*
Cochrane Drugs and Alcohol group	–
PsycINFO	drug abuse AND screening test*
NIDA	drug abuse AND screening test
ISI Web of Science	drug abuse AND screening test*

Previous literature reviews on the same topic were examined to identify manually potential eligible articles.

2.4. Search strategy

The search strategy included two notions: drug abuse first and, secondly, screening test. The Medical Subject Heading (MeSH) and keywords used are listed in Table 1. Keywords on the topic are not very specific and leading to a too high number of references to screen. Therefore, MeSH terms were applied for PubMed. In Cochrane databases, MeSH terms led to few results, we decided not to use them. In other databases, searching by MeSH terms was unavailable; consequently our strategy included pre-listed keywords. Keywords and MeSH terms were chosen to be sensitive rather than specific. The choice of keywords was done according to keywords more often present in papers of the field. Only articles reporting an original study in English, French, German or Spanish were included.

2.5. Data collection and analysis

Two authors (J.D. and V.M.) in a blinded standardized manner collected and analyzed independently the data. Disagreements were resolved by discussion between the two authors; if no agreement could be reached, a third author (M.L.-M.) decided.

2.5.1. Selection of studies. The two authors selected independently the articles. An initial selection was completed on the title and/or the abstract. After, a second reading of the full text was done for further selection. The κ coefficient of inter-raters concordance was calculated.

All possibly relevant articles were retrieved in full text. With regard to conference proceedings, the authors were contacted to obtain access to the full data (whether in the form of published article, or not).

2.5.2. Methodological quality assessment. A methodological quality assessment of the studies confirming our inclusion criteria was carried out independently by the two authors with the score applied by Starrels et al., 2010) in a systematic review similar to our subject (i.e., treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain).

The overall score applied by Starrels et al. is based on a quality assessment checklist derived from the Emergency Care Research Institute (ECRI) Institute (Noble et al., 2008), Downs and Black (1998), and Jadad et al. (1996) and includes a quality assessment

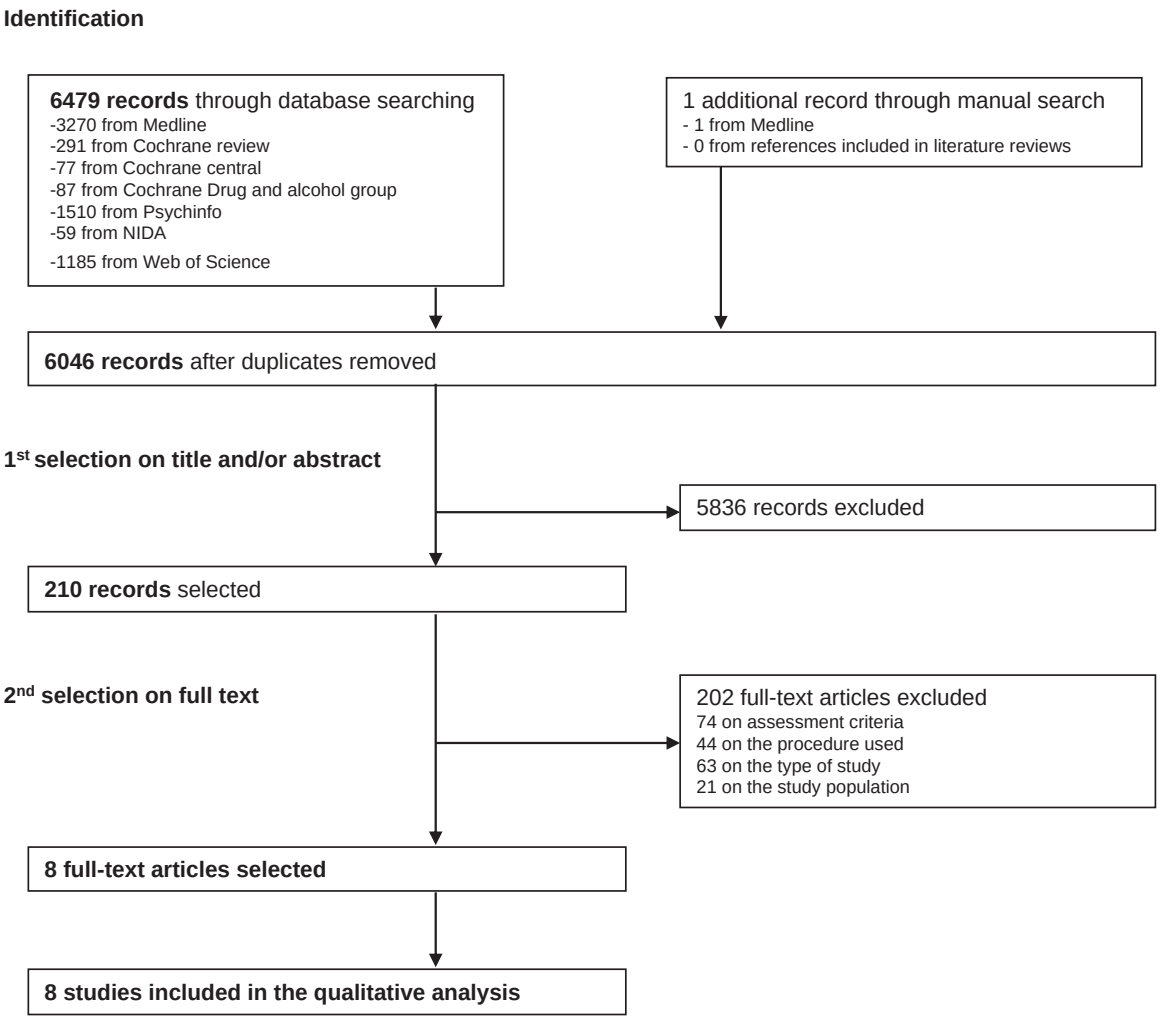

Fig. 1. Flow diagram of literature search.

by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) grid (Atkins et al., 2005).

- The quality checklist consists of 15 criteria spread over 2 domains: sample and design.
  - o The population included in the study is assessed on 3 points; 1 point is given if the sample consisted of persons with diverse types of chronic pain conditions, persons with history of substance abuse, persons with mental health disorders.
  - o With regard to the type of study, a total of 12 points is attributed if one of the following criteria was found: prospective design, control group included, control participants from a similar population, intervention described clearly, intervention consistent among groups, outcome described clearly, objective outcome, completion or response rate ≥ 85%, distribution of potential confounders provided, multivariate analysis conducted, adequate adjustment for confounding, results clearly presented.
- The GRADE grid (Atkins et al., 2005) enabled a global assessment of the articles based on the rigor of the chosen design, its bias, and its limits. This quality scale comprises 4 levels: 4, high if the study was a randomized clinical trial; 3, moderate if the study was virtually experimental; 2, low if it was an observational study; 1, very low if it was another type of study, not previously mentioned. After, levels are moderated assessing bias of the study.

On the basis of scores on the quality checklist and the GRADE grid, one of the following ratings was assigned to each study: excellent (score ≥ 11 and GRADE ≥ 3), good (score ≥ 11 and GRADE ≥ 2), fair (score = 6–10 and GRADE ≥ 2), or poor (score ≤ 5 or GRADE = 1).

2.5.3. Report quality assessment. We also assessed the report quality of the studies using the CONSORT (CONsolidated Standards of Reporting Trials) checklist for clinical trials and the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist for cross-sectional, observational or cohort studies, scoring the number of items followed by the articles selected. The results were expressed in percentages in relation to the total of possible recommendations.

2.5.4. Data extraction and management. Data were extracted from the included studies by two authors independently using a pre-established standard list. The assessment sheet included: Author/year, type of study (study design), settings, characteristics of the sample (population), management strategy (intervention), reference group (comparator), follow-up, measuring the study (outcome), results and quality assessed by the GRADE grid (Atkins et al., 2005), the overall score proposed by Starrels et al. (2010), and the CONSORT or STROBE checklist.

2.5.5. Qualitative analysis. Qualitative analysis was divided into two parts: the main analysis concerning the studies where the

Table 2
Methodological quality assessment score used by Starrels (Starrels et al., 2010).

	Passik et al. (2000)	Eisen et al. (2004)	Schiller et al. (2000)	Murnion et al. (2007)	Dupouy et al. (2012)	Manchikanti et al. (2006)	Tennant (1994)	Levy et al. (2006b)
Sample domain								
Persons with diverse pain types included	√	0	0	0	0	√	0	0
Persons with history of substance abuse included[a]	0	0	0	0	0	√	0	0
Persons with mental health disorders included[a]	0	0	√	0	0	√	0	0
Score (maximum 3 points)								
Design domain								
Prospective	0	√	√	0	0	√	√	0
Control group included	0	√	√	0	0	√	0	0
Control participants from a similar population	NA	NA	√	NA	NA	0	NA	NA
Intervention described clearly	√	√	√	√	NA	√	√	NA
Intervention consistent among groups	NA	NA	√	NA	NA	0	NA	NA
Outcome described clearly	√	√	√	√	NA	√	√	NA
Outcome objective	0	0	√	0	NA	√	√	NA
Completion or response rate ≥ 85%	NA	NA	NA	NA	0	√	NA	0
Distribution of potential confounders provided	0	0	0	0	0	0	NA	√
Multivariate analysis conducted	0	0	0	0	0	0	NA	√
Adequate adjustment for confounding	0	0	0	0	0	0	NA	√
Results clearly presented	√	√	√	√	√	√	√	√
Score (maximum 12 points)								
Sample + design score (maximum 15 points)	**4**	**5**	**9**	**3**	**1**	**10**	**5**	**4**
Global assessment based on the GRADE (26) algorithm								
Initial GRADE score[b]	2	3	4	2	2	2	2	2
Adjustment[c]	−1	−1	-	−1	−1	−1	−1	−1
Reason for adjustment	Design and limits[d]	Design[e]	-	Design[f]	Limits[g]	Selection bias[h]	Limits[i]	Limits[g]
Final **GRADE score (maximum 4 points)**	**1**	**2**	**4**	**1**	**1**	**1**	**1**	**1**
Quality rating	**Poor**	**Poor**	**Fair**	**Poor**	**Poor**	**Poor**	**Poor**	**Poor**

GRADE: Grading of recommendations assessment, development, and evaluation.
[a] Studies were scored with a check if patients with substance abuse or mental health disorders were not explicitly excluded.
[b] The initial grade score was based on study design: 4, randomized trial; 3, quasi-randomized trial; 2, observational study; 1, any other evidence.
[c] GRADE score was decreased for quality limitations or increased for strong association.
[d] No control group, Indication bias, Changes in management subjectively assessed.
[e] Before/after study in the same population, interview of the ordering physician regarding management changes just after the communication of UDS results compared to planned management before knowing the results: more an observational study than a real before/after study (i.e.,: after implementation of a urine drug screening program).
[f] No control group, Changes in management subjectively assessed.
[g] Changes in management assessed only by declarative data.
[h] Comparison with a historical control group that was not well described and differed from the intervention group in inclusion criteria and in exposure to contaminating co-interventions.
[i] Changes planned in the method, no control group.

assessment criterion was medical management and secondary analysis regarding the articles where the assessment criteria were the consequences of management for the patients (psychoactive substances use and its complications; i.e., medical, social or professional).

Heterogeneity of studies based on methodological design, type of population, and setting did not allow a quantitative analysis.

3. Results

3.1. Study selection

Fig. 1 shows a flow diagram of the study selection as recommended by the PRISMA statement (Liberati et al., 2009). Six thousand and forty-six titles (± abstracts) were reviewed from the initial database search. Two hundred and ten full text articles were reviewed and screened. After the exclusion of studies not meeting the inclusion criteria, 8 articles were identified for methodological quality assessment (Dupouy et al., 2012; Eisen et al., 2004; Levy et al., 2006b; Manchikanti et al., 2006; Murnion et al., 2007; Passik et al., 2000; Schiller et al., 2000; Tennant, 1994). The observed agreement between reviewers was 99.9% ($\kappa = 0.75$).

3.2. Methodological quality assessment

The quality of the 8 included studies (Dupouy et al., 2012; Eisen et al., 2004; Levy et al., 2006b; Manchikanti et al., 2006; Murnion et al., 2007; Passik et al., 2000; Schiller et al., 2000; Tennant, 1994) was assessed through the Starrels' score (Starrels et al., 2010) as shown in Table 2.

The 8 selected studies consisted of: 1 double-blind randomized clinical trial (Schiller et al., 2000), 2 quasi-randomized studies (Eisen et al., 2004; Manchikanti et al., 2006), 1 observational cohort (Tennant, 1994) and 4 cross-sectional studies (Dupouy et al., 2012; Levy et al., 2006b; Murnion et al., 2007; Passik et al., 2000). The randomized clinical trial (Schiller et al., 2000) was assessed as "fair" while the other studies were assessed as "poor" (Dupouy et al.,

Table 3
Qualitative analysis of the studies covering the main assessment criterion (medical management).

Study (year)	Study design	Setting	Sample characteristics[a]	Urine drug screening	Control condition	Follow-up	Screening effect measure	Results	Limitations	Quality[b]
Passik et al. (2000)	CSS	Cancer center USA	111 cancer patients (82%), mainly hospitalized (91%); mean age, 43 y	Urine drug screening test (the first one for patients having multiple UDS)	None	Chart review consisting of only the admissions in which the UDS was obtained for inpatients and including 1 month before and 1 month after the test for outpatients	Medical management modification assessed thanks to chart review	8 (7.2%) patients had documentation that the UDS led to a change in clinical management	Subjective unexplained assessment of outcome criteria (change: yes/no)	Poor; strobe = 13/32
Schiller et al. (2000)	RCT	Psychiatric emergency setting USA	198 inpatients in the mandatory-drug-screen group, 67% of patients from 25 to 45 y	Standard immunoassay and confirmatory tests performed for positive screens	194 inpatients in the usual-care group; Psychiatrists ordered urine drug screens for patients in both groups if a screen was needed in their clinical judgment	During hospitalization; data collected from hospital records and databases	Dispositions after emergency settings. Duration of hospitalization in psychiatric ward	No significant difference in dispositions or duration of hospitalization between the two groups. Difference in dispositions of patients for whom a drug screen was ordered by a physician with dispositions of patients for whom no drug screen was ordered	Test results often not always available to psychiatrists before patients were discharged from the emergency service	Fair; consort = 17/37
Murnion et al. (2007)	CSS	Emergency settings or medical wards Australia	171 patients; 121 presenting via the accident and emergency center and 50 inpatients in medical wards; mean age, 36 y	Immunoassay followed by confirmatory test (thin-layer chromatography)	None	During hospitalization; review of case histories by 2 trained assessors in a blinded manner	Test utility (categorized in diagnostic, prognostic, "management" and scored with a visual analog scale) by the 2 trained assessor	86 tests of utility (50%): 47(38.8%) requested from accident and emergency center and 38 (76%) from medical ward; more likely that a test will be of utility if it was requested from a medical ward than from the accident and emergency center	Subjective assessment of test utility	Poor; strobe = 16/32
Tennant (1994)	PCS	Outpatient clinics USA	100 adolescents whom parents request UDS; mean age, 16 y	Urine screening by polarized fluorescent immunoassay (confirmatory method not used)	None	Weekly follow-up urine screening (up to 8 weeks)	Clinical purposes	29 patients entered outpatient counseling. 8 were judged to be dependent and received outpatient medical detoxification or inpatient treatment	Clinical purposes planned in the method, urine screening follow-up at request of the parents, no medical intervention	Fair; strobe = 8/32

Dupouy et al. (2012)	CSS	Family medicine (ambulatory setting) France	482 PCPs of whom 31 regularly managing opioid-addicted patients and using drug tests	Urinary or blood test, immunoassay or chromatography	None	None	Changes in medical management following drug testing reported by PCPs using drug test in self-administrated questionnaire (ended-questions)	Nonprescription of opiate substitutive treatment: 29.0%. Increasing counseling: 71.0%. Referral to a consultant: 48.4%	Low response rate. Changes reported by GPs but not assessed in their practice	Poor; strobe = 24/32
Levy et al. (2006b)	CSS	Primary care USA	359 primary care providers (122 pediatricians, 126 adolescent specialists, and 103 family physicians)	Urine drug testing (in general medical clinics, in school and at home)	None	None	Steps following a positive urine drug test as declared by physicians	48%: share results with parents. 70%: assess in the office. 61%: mental health referral. 27%: begin treatment in the office	Outcome reported by physicians but not assessed in their practice	Poor; strobe = 22/32
Eisen et al. (2004)	QRS	Emergency settings Canada	110 inpatients; mean age 39 y	Immuno assay confirmed by chromatography	Same population but before results of the UDS having been communicated to the ordering physician	Interview of physicians about medical management of the patient before test result and after	Medical management assessed by telephone interview + chart review; assessment changes in medical management and in changes' reasons by an independent expert reviewer	4 over 110 tests led to management changes; changes judged not substantive (3/4) and unjustified (4/4) by the independent expert reviewer	Subjective unexplained assessment of management changes by the independent expert reviewer	Poor; strobe = 18/32

CSS, cross-sectional study; PCP, primary care provider; PCS, prospective cohort study; QRS, quasi-randomized study; and RCT, randomized clinical trial.

[a] Sample characteristics provided, as available.

[b] Quality rating: excellent (score ≥ 11 and GRADE ≥ 3), good (score ≥ 11 and GRADE ≥ 2), fair (score = 6–10 and GRADE ≥ 2), or poor (score ≤ 5 or GRADE = 1).

Table 4
Qualitative analysis of the studies covering secondary assessment criteria (consequences of management for the patients: psychoactive substances use and its complications, be they medical, social or professional).

Study (year)	Study design	Setting	Sample characteristics[a]	Urine drug screening	Control condition	Follow-up	Screening effect measure	Results	Limitations	Quality[b]
Manchikanti et al. (2006)	QRS	Pain center USA	500 chronic-pain patients having given consent for randomly screening; mean age 48.6 y	Randomly screening by immunoassay ± followed by confirmatory method (chromatography)	400 chronic-pain patients included in a previous study (42)	Prospective from consent to screening; review of the chart	Prevalence of illicit drug use (measured on urine test results)	Decreasing of total prevalence from 22% [18–27] to 16% [13–20] and THC prevalence from 18% [8–14] to 11% [14–22], significant differences	Control group non described	Poor; strobe = 17/32

QRS, quasi-randomized study; THC, tetrahydrocannabinoid.
[a] Sample characteristics provided, as available.
[b] Quality rating: excellent (score ≥ 11 and GRADE ≥ 3), good (score ≥ 11 and GRADE ≥ 2), fair (score = 6–10 and GRADE ≥ 2), or poor (score ≤ 5 or GRADE = 1).

2012; Eisen et al., 2004; Levy et al., 2006b; Manchikanti et al., 2006; Murnion et al., 2007; Passik et al., 2000; Tennant, 1994).

Three studies took place in emergency settings (Eisen et al., 2004; Murnion et al., 2007), whereby one of them was in a psychiatric emergency setting (Schiller et al., 2000). Two were conducted in specialized pain centers (Manchikanti et al., 2006) or cancer centers (Passik et al., 2000), one in outpatient clinics (Tennant, 1994), and two in primary care (Dupouy et al., 2012; Levy et al., 2006b).

3.3. Report quality assessment

Details of the CONSORT, STROBE (cohort), and STROBE (cross-sectional study) checklists are presented in Supplementary Material.[1]

3.4. Study Characteristics

Seven studies evaluated the main assessment criterion of the present review: medical management (Dupouy et al., 2012; Eisen et al., 2004; Levy et al., 2006b; Murnion et al., 2007; Passik et al., 2000; Schiller et al., 2000; Tennant, 1994); one evaluated the secondary assessment criteria (Manchikanti et al., 2006): use of substances or drugs with abuse or addiction potential and associated comorbidities.

3.4.1. Analysis on main assessment criterion. The analysis of the 7 studies (Table 3) indicates a modest efficacy of the tests.

In cancer centers, changes in management were rare: 8 patients over 111 included (7.2%) provided documentation on changes in clinical management related to UDS: ordering psychiatric or pain management consultations, placing restrictions on the patient, discharge of patient or postponement of treatment or procedures, medication changes, or referral for substance abuse treatment (Passik et al., 2000). All changes were presented in the group with positive UDS results, defined as the detection of one or more illicit drugs, prescription medications not documented as ordered or given, or alcohol (blood alcohol level was also taken into account).

In a randomized controlled trial aiming to test whether dispositions from a psychiatric emergency service would differ between patients receiving a routine mandatory UDS ($n = 198$) compared to those with an administered UDS only if psychiatrists' clinical judgment deemed it as useful (usual care, $n = 194$), no significant differences in dispositions or duration of hospitalization was found between these two groups (Schiller et al., 2000). Nevertheless, there was a significant difference in the dispositions of patients with an ordered drug screen by a physician compared to the dispositions of patients without ordered drug screen (analysis limited to the mandatory-drug-screen group). This difference was attributable to the referral of a larger proportion of patients for whom drug screens were not ordered to an inpatient unit at a county hospital (29.9% versus 15.3%, $p = 0.014$).

In 50 patients hospitalized in medical wards, 38 UDS (76.0%) were judged of utility; it was more likely that a test would be of utility if it was requested from a medical ward than from the accident and emergency center (Murnion et al., 2007). In this Australian study, presentations including psychosis, confusion, and behavioral disturbances were associated with a likelihood of UDS as important diagnostically, in management, and for prognosis.

UDS of adolescents on request of parents facilitated the entry to treatment (Tennant, 1994). In two outpatient clinics, UDS led to outpatient counseling in 29 adolescents over 100. Eight of them had repeated positive follow-up tests, confided their unability to

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org/10.1016/j.drugalcdep.2013.12.009.

cease drug use and desired help for their problem. They were judged to be dependent and received outpatient medical detoxification or inpatient treatment.

Two cross-sectional studies were in primary care settings (Dupouy et al., 2012; Levy et al., 2006b). The first one in France described that, in consequence of drug testing, changes in management reported by 482 primary care practitioners (PCPs), managing opioid-addicted patients and using drug tests, were mainly an increase of counseling (71.0%), secondly, the referral to a consultant (48.4%), and finally, the non-prescription of opiate substitutive treatment (29.0%). The second one in the United States presented that, follow-up practices with drug test results testified by 359 physicians (pediatricians, adolescent specialists, and family physicians) were mainly assessment in the office (70%), mental health referral (61%), sharing results with parents (48%) and beginning treatment in the office (27%). After controlling for physician age and gender, pediatricians, and family, physicians were more likely to share results with parents than adolescent providers (OR 2.4 [1.4–4.0] and 3.4 [1.9–6.1] respectively). Pediatricians presented a higher probability to refer to mental health services (OR 2.4 [1.4–4.2]); same trend existed, however was not significant for family physicians. Pediatricians were less likely to assess in the office and to begin treatment in the office (OR 0.25 [0.14–0.46] and 0.29 [0.13–0.54] respectively); same trends existed nevertheless it revealed insignificant for family physicians.

On the other hand, the efficacy of UDS was not demonstrated in emergency departments (Eisen et al., 2004; Murnion et al., 2007). In a Canadian emergency department, in 110 patients tested, 4 UDS (3.6%) led to management changes arranged by the ordering physician (Eisen et al., 2004). These changes concerned the cancelation of a planned head CT scan (for presentation of bizarre behavior), a consult to internal medicine changed to psychiatry (for presentation of "neurologic symptoms" *sic*), a medicine consult in a case where the physician was unsure which consultant was required (presentation of new onset psychosis), and a psychiatry referral cancelation due to the patient's confrontation with tetra-hydrocannabinoid (THC) use admitted by the patient and observed in the emergency department (for presentation of confusion; fell in a lake). Only one of these changes was viewed as substantive by an independent expert reviewer (the last change cited above) and all of them were judged unjustified. This study confirmed a diagnostic value of UDS as of the 110 UDS ordered, the ordering physician was able to completely predict the result in 48 cases (43.6%). The efficacy of urine tests was not demonstrated in psychiatric emergency units, in terms of duration of hospitalization (Schiller et al., 2000).

3.4.2. Analysis on secondary assessment criteria. An analysis of the included quasi-randomized study in an interventional pain management practice (Table 4) indicated a modest efficacy of the tests for patients with chronic pain ($n = 500$) for the consequences of management with a decrease of the total prevalence of drug use from 22% [18–27] to 16% [13–20], and a decrease of the THC prevalence from 18% [8–14] to 11% [14–22]; these differences were significant (Manchikanti et al., 2006).

4. Discussion

This systematic review evaluating the value of UDS in managing patients showed poor evidence. In this review, a total of 8 studies met the inclusion criteria: one randomized clinical trial, two quasi-randomized studies, one cohort, and four descriptive cross-sectional studies. The methodological quality of these studies was judged to be poor, with the exception of the randomized clinical trial where the quality was judged to be fair. Nevertheless, there is no evidence of the value for UDS in managing patients through these studies.

This review brought to light one of the first American study (published in 1981) investigating the impact of monitoring patients on methadone by urine tests (Havassy and Hall, 1981). However, this study was not eligible to be included due to the tests applied, a chromatographic technique (most certainly related to the time at which the study was conducted). It showed that subjects having been monitored by tests were more likely to terminate their treatment than others. Two hypotheses were raised by the authors: the tests could help patients trying to stop the habit of using methadone (recovery?), or the tests represented a supplementary cost for patients causing them to abandon treatment (probable relapse).

Most of the included studies took place in emergency settings. A systematic review of the literature (Tenenbein, 2009) did not show any interest in carrying out UDS in emergency rooms, whereby the review included mostly articles studying patients in acute intoxication. This is a very different clinical situation compared to patients who are chronic users, thus we chose to exclude this type of population in our review. Only one randomized clinical trial in a psychiatric emergency setting (Schiller et al., 2000) showed an impact of UDS on the patients' management if the physician had found it suitable to carry them out. However, this was a secondary analysis, independently from the primary objective of this study where no impact on the group systematically tested compared to the untested was found. This result is nevertheless interesting and supports a reasoned use of UDS depending on the context and the physician's opinion. The survey of the French General Practitioners' reporting seemed also to be in accordance with that (Dupouy et al., 2012).

Two studies were in specialized centers: a pain center (Manchikanti et al., 2006) and a cancer center (Passik et al., 2000). A review in patients with chronic pain found only a low level of evidence supporting urine tests in these patients with a view to decreasing opioid abuse (Starrels et al., 2010).

Some excluded studies often concluded on the interest of the tests (Bast et al., 2000; Buchfuhrer and Radecki, 1996; Claasen et al., 1997). However, these studies described two different populations according to the result of the screening (traditionally differentiated into two groups: positive or negative) in terms of socio-demographic characteristics, medical data and treatment process. It can be concluded that patients having used psychoactive substances are different but in no way that the results of the tests affect their treatment process, thus we excluded these studies.

Our review is limited by the considerable variation of settings and patients included. We chose not to limit them, to have the ability to offer an overview of the value of UDS. Another limitation was the difficulty to define medical management and to find studies of which outcome was medical management rather than diagnostic criteria. Moreover, the implementation of urine drug testing interventions (e.g., frequency, or type of assays) varied among studies and was reported inconsistently. All of these reasons contributed to the heterogeneity of the studies included and the difficulty to synthesize their results. Again, our objective was to synthesize the evidence supporting the use of UDS for the management of patients. This explains that we chose a broad retrieval formula and databases both general and specific on the topic, increasing the sensitivity of our search strategy whereby not specificity. Finally, publication bias and language bias may have limited the evidence available for this review.

Our systematic review reveals that weak evidence supports the use of UDS in settings where abusers or addicted patients are managed (i.e., psychiatric settings, primary care, pain clinics, outpatient clinics. . .).

In conclusion, few studies have assessed the value of UDS in managing patients using psychoactive substances; due to their poor

quality, these studies are not sufficient to demonstrate the interest of carrying out these tests. Pragmatic intervention studies with objective assessment criteria are necessary to underpin the implementation of these tests in daily practice to improve the treatment and health of these patients.

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Contributors

Julie Dupouy was involved in all stages of the project from design, writing of the protocol, through study selection, data extraction, quality assessment, analysis and synthesis. Vincent Mémier designed and conducted the searches for the review, was involved in study selection, data extraction, quality assessment, analysis and synthesis. Hélène Catala contributed to design and study selection. Michel Lavit contributed to quality assessment, analysis and synthesis. Stéphane Oustric and Maryse Lapeyre-Mestre shared responsibility for the overall management of the project and contributed to the design. Julie Dupouy wrote the first draft of the manuscript, and all authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2013.12.009.

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PART 2: A PHARMACOEPIDEMIOLOGICAL APPROACH

After informing the poor use of urine drug screening tests in France and the lack of evidence of their efficacy, the second part aimed to assess the effectiveness of drug tests in managing opioid-addicted patients. For that, we used observational cohorts conducted from French health insurance system databases. In front of the difficulty to find financial support to conduct a clinical trial, we choose to use one existing tool available for academic researchers in France: French health insurance system databases.

Partie 2 : approche pharmacoépidémiologique

Evaluation de l'efficacité des tests pour la prise en charge des patients dépendants aux opiacés par des études observationnelles de cohorte sur les bases de données de l'Assurance Maladie

Bases de données de l'Assurance Maladie :

Toute la population française étant couverte par un système public d'Assurance Maladie, toutes les données de remboursement sont collectées dans une énorme base de données appelée Système National d'Information Inter-Régime de l'Assurance Maladie SNIIR-AM. Ces données de remboursement sont reliées avec les données d'hospitalisation et les données de décès. Afin d'avoir un suivi prolongé, un échantillon randomisé au 1/97ème a été construit : l'Echantillon Généraliste des Bénéficiaires EGB. Celui-ci est accessible pour les chercheurs affiliés à un organisme de recherche public après une formation spécifique et permet de faire des études descriptives sur les patients et les médecins ainsi que des études de cohortes pour étudier des associations.

Troisième publication :

L'objectif de cette étude était d'évaluer l'impact de la réalisation de tests de recherche de substances psycho actives sur le maintien sous Médicament Substitutif aux Opiacés (MSO) en médecine ambulatoire en constituant une cohorte de patients ayant débuté un traitement par MSO à partir de juin 2009 et suivis 18 à 30 mois à partir de la base de données de la Caisse Nationale d'Assurance Maladie des Travailleurs Salariés en Midi Pyrénées. Deux groupes de patients ont été définis : le groupe biologie (ayant eu au moins un remboursement de test de recherche de substances psycho actives) et le groupe témoin (n'en ayant pas eu). Le maintien sous MSO a été analysé dans un modèle de Cox ajusté sur les potentiels facteurs de

confusion ; l'exposition au test biologique étant considérée comme une variable dépendante du temps. Cette cohorte comprenait 1507 patients dont 39 (2,6%) dans le groupe biologie. La durée moyenne de maintien sous MSO était de 207 jours dans le groupe témoin versus 411 jours pour le groupe biologie, p<0,0001. Dans le modèle de Cox, la réalisation d'un test de recherche de toxiques favorisait le maintien sous MSO : Risque Relatif RR = 0,55 [IC95% : 0,38 – 0,80]. La réalisation de test de recherche, bien que rare, améliorait le maintien sous MSO.

Quatrième travail :

L'objectif de cette étude était d'évaluer l'impact de la réalisation de tests de recherche de substances psychoactives sur la mortalité en constituant une cohorte de patients ayant débuté un traitement par MSO à partir de janvier 2007 et suivis jusqu'à décembre 2013 à partir de l'EGB. Deux groupes de patients ont été définis : le groupe biologie (ayant eu au moins un remboursement de tests de recherche de substances psycho actives) et le groupe témoin (n'en ayant pas eu). Une analyse de survie (modèle de Cox) a permis d'étudier les facteurs associés à la mortalité. Dans cette étude, plus de 15% des patients appartenaient au groupe biologie. Avoir eu un test n'était pas associé à la mortalité en univarié : RR = 0,60 [IC95% : 0,21 – 1,69]. Néanmoins la mortalité était supérieure hors traitement que sous traitement. Les autres facteurs associés à la mortalité étaient des facteurs indiquant la sévérité de la pathologie addictive.

FRENCH HEALTH INSURANCE SYSTEM DATABASES

All the French population is covered by a publicly funded health system. The French health insurance reimbursement databases gather information concerning these individuals. For some years, French health insurance system databases have been widely used for public health and pharmacoepidemiological purposes (Blin et al., 2012; Bongue et al., 2011; Fournier & Zureik, 2012; Frauger et al., 2011; Pariente et al., 2010), particularly in the field of addiction (Lapeyre-Mestre et al., 2003; Thirion et al., 2002).

The first used database (*Extraction, Recherches, Analyses pour un Suivi Médico-Economique* ERASME) is the database of the main French health insurance system (*Régime Général des travailleurs salariés* RG) for the Midi-Pyrenees area. This health insurance system covers 87% of the French general population: salaried workers and their families, and patients with universal coverage (attributed to the unemployed and low income insurees) (Martin-Latry & Bégaud, 2010).

This database includes locally and prospectively collected reimbursement data. Available data are those from the last 24 months. They comprise demographic data of the beneficiaries of the main health insurance system, out-hospital reimbursement data (drug, laboratory, radiology, medical acts) and medical data (costly long-term diseases called *Affections de Longue Durée* ALD – all acts concerning the concerned disease are reimbursed at 100% -, occupational diseases, and sick leaves). Other kinds of data are computerized in this database: characteristics of health professionals, data concerning health facilities. Concerning drug dispensing, the database contains information on the date of dispensing, quantity dispensed, and prescriber. Drugs are classified according to the

Anatomical Therapeutic Chemical system. The access to this database mainly depends on the relationship with the local physician of the health insurance system.

The validity of the ERASME database of the health insurance system has been confirmed (Latry, Molimard, Bégaud, & Martin-Latry, 2010). It has been shown in the Three-Cities (3C) cohort that the reimbursement data of the health insurance system agreed with consumption data with an acceptable concordance between drug consumption estimated through health insurance system databases and self-reported drug consumption (Noize et al., 2009). Although, as for all prescription or reimbursement databases, we cannot exclude that, even if the drug is prescribed and reimbursed, it is not consumed by the patient.

Local databases are united at a national level in a big database comprising also data from other health insurance systems; the two other systems are the *Régime Social des Indépendants* RSI (for self-employed) and the *Régime Social Agricole* RSA (for agricultural workers, farmers, and their employees) (other systems cover specific populations such as soldiers, railway workers, *etc*). All these data are organized since 2003 into a huge digital data warehouse, the *Système National d'Information Inter-Régime de l'Assurance Maladie* SNIIR-AM. It covers the entire French population (65 million inhabitants).

The SNIIR-AM includes demographic, out-hospital reimbursement (including drug dispensing), medical (costly long-term diseases, occupational diseases, sick-leaves…), and in-hospital data. In-hospital data of the *Programme de Médicalisation des Systèmes d'Information* PMSI are linked with the out-hospital reimbursement database *Données de Consommation Inter-Régimes* DCIR. In-hospital data in the SNIIR-AM include the PMSI

Médecine Chirurgie Obstétrique MCO (medicine, surgery and obstetrics), the PMSI of psychiatric wards, of hospital-in-the-home care, and of rehabilitation wards. Death data are also comprised thank to a linkage with the data of the *Institut National de la Statistique et des Etudes Economiques* INSEE. All these data are prospectively recorded, individualized, made anonymous and linkable. All consumers of medical services are recorded.

The access to the SNIIR-AM is conditioned by a request to the *Institut des Données de Santé* IDS and then to the *Commision Nationale Informatique et Libertés* CNIL. Mean time to have the data is 13 months and can be, in some cases, more than 24 months (IDS, 2013). Available data are data of the three last years plus the on-going year.

In order to facilitate studies on more frequent conditions, a random sample of 1/97th of national health system beneficiaries has been built since 2005, called the *Echantillon Généraliste de Bénéficiaires* (EGB) or the permanent beneficiaries sample (Tuppin, de Roquefeuil, Weill, Ricordeau, & Merlière, 2010). EGB is a permanent representative sample of subjects affiliated with the French health insurance system. It is obtained by 1/97th national random sampling with control for distribution of age, and gender. The EGB database includes approximately 660,000 beneficiaries from the national health insurance scheme (Tuppin et al., 2010). The value of EGB is to have a long follow-up (20 years of which 8 years available).

Available data are almost the same as in the SNIIR-AM with the exception that only the PMSI MCO has been included for now. All consumers and non-consumers are recorded.

EGB has been used for 5 years for pharmacoepidemiological purposes (Blin et al., 2012; Bongue et al., 2011; Dupouy, Fournier, et al., 2013; Fournier & Zureik, 2012;

Frauger et al., 2011; Pariente et al., 2010). The access is possible for academic researchers affiliated to a partner institution (for example the *Institut National de la Santé et de la Recherche Médicale* INSERM). The access to EGB required a specific training for all researchers and professionals of the health insurance: one first one-day training about the architecture of SNIIR-AM and one second three-day training about the EGB. The second formation is now about the EGBS (*EGB simplifié*) which is a simplified version of the EGB. In this EGBS, data are less raw than in the EGB, that means that data have been a little bit worked on to be more easily used. For researchers affiliated to INSERM, the access is easy: the synopsis has to be submitted to one person in charge of INSERM; after it is approved, the researcher can begin his work on the EGB. The person in charge of INSERM is responsible of the communication with the IDS. No other specific authorization is needed as data are anonymous (Journal Officiel de la République Française, 2012). Nevertheless, one restriction is that the researcher has to choose between one of four profiles to be connected to data. These different profiles give access to data according to the access to sensitive data that cannot be matched: date of birth (in month, year), date of death (in day, month, year), date of the act (in day, month, year) and the home town.

For the academic researcher, data access is simple. After a connection on the server of the *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* CNAM-TS, data are directly available online via the Citrix software®. Communication is facilitated between researchers thanks to documentation and a forum in the server.

The EGB is a new tool for researchers, evolving and progressing. The CNAM-TS is attentive to suggestions expressed by researchers using this database and a national club of users as well as local clubs enable researchers to progress by helping one another.

Limits of these databases are the lack of medical data: few medical data are available and the use of proxies is common to identify a disease. Proxies are sensitive and specific when they use drugs specifically used in one disease but can be less efficient when drugs are not specific for one disease. Data from costly long-term diseases are also useful but identify severe diseases (as ALD is given for severe chronic disease requiring a 100% reimbursement). The validity of these ALD codes is debated. More precisions can be obtained using codes of the International Classification of Diseases 10th version ICD10, these codes are recorded by physician of the health insurance system when they record ALD codes. They are more precise than ALD codes (a restrictive list of 33 codes) but their validity is also poorly known. For these reasons, identifying a population by the prescription of a drug is much more comfortable than identifying a population by a disease. Nevertheless, more and more research teams are working in defining algorithms to identify specific diseases.

To conclude, these databases are useful for all researchers and, specifically, for researchers in primary care, to:

- Describe
    - characteristics of patients
    - characteristics of prescribers and patterns of prescriptions
    - at a specific time or to describe the evolution on several years

- Analyze association and causality using retrospective cohorts and nested case-control studies
- Probabilistically match these data with clinical data of observational studies or randomized clinical trials.

STUDY 3: EFFECTIVENESS OF DRUG TESTS IN OUTPATIENTS STARTING OPIOID SUBSTITUTION THERAPY

PRESENTATION OF THE STUDY

Dupouy J, Dassieu L, Bourrel R, Poutrain J-C, Bismuth S, Oustric S, et al.

Effectiveness of drug tests in outpatients starting opioid substitution therapy.

Journal of Substance Abuse Treatment 2013; 44: 515-21 (Dupouy, Dassieu, et al., 2013)

OBJECTIVE

We aimed to assess the effectiveness of drug tests for treatment retention in outpatients starting opioid substitution therapy.

METHOD

A retrospective cohort was created from the data of the French health insurance system database for the Midi-Pyrenees region. Patients starting OMT were included and followed for 18 to 30 months. Two groups of patients were defined: the drug test group (at least one drug test reimbursement) and a control group (no drug test reimbursement). Survival analyses were performed.

RESULTS

The cohort included 1,507 patients. During follow-up, 39 subjects (2.6%) had at least one drug test reimbursement. Mean treatment retention was 207 days in the control group and 411 days in the drug test group ($P < 0.001$). Kaplan-Meyer curves showed a higher opiate substitutive treatment retention for drug tested patients. With a multivariate Cox model, drug tests were

associated with treatment retention: hazard ratio 0.55 [95% CI: 0.38 – 0.80]. Use of a drug test in follow-up of opioid substitution treatment, although rarely prescribed, significantly improved treatment retention. Nevertheless, persistent confounding related to the use of an administrative reimbursement database limited the significance of our results.

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Effectiveness of drug tests in outpatients starting opioid substitution therapy

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ABSTRACT

We aimed to assess the effectiveness of drug tests for treatment retention in outpatients starting opioid substitution therapy. A retrospective cohort was created from the data of the French health insurance system database for the Midi-Pyrenees region. Patients starting opioid substitution treatment (OST) were included and followed for 18 to 30 months. Two groups of patients were defined: the drug test group (at least one drug test reimbursement) and a control group (no drug test reimbursement). The cohort included 1507 patients. During follow-up, 39 subjects (2.6%) had at least one drug test reimbursement. Mean treatment retention was 207 days in the control group and 411 days in the drug test group ($p<0.001$). With a multivariate Cox model, drug tests were associated with treatment retention: hazard ratio 0.55 (95% CI: 0.38–0.80). Use of a drug test in follow-up of opioid substitution treatment, although rarely prescribed, significantly improved treatment retention.

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1. Introduction

In 2009, nearly 140,000 patients were treated in France with an opioid substitute (OS) (Commission Nationale des Stupéfiants et des Psychotropes, 2010). Methadone and buprenorphine received marketing authorization in 1995 and 1996, respectively, for substitution treatment for major opiate dependence as part of overall medical, social and psychological therapeutic management. These two drugs are prescribed and delivered according to two different, very strict guidelines. Methadone, a pure μ agonist, is a listed narcotic and can be prescribed for a maximum of 14 days and delivered for a maximum of 7 days. Primary prescription of methadone is restricted to physicians in specialized units and to hospital physicians. When the patient is stabilized, treatment may be continued in an outpatient setting and followed up by any physician, whether specialist or primary care physician (PCP). Buprenorphine, a partial μ agonist, is a class I psychotropic drug (Schedule III of the 1988 Convention) and can be prescribed for maximum periods of 28 days and delivered for periods of 7 days. It is widely used in France as it can be prescribed by any physician, whether specialist or PCP, and can be delivered in any local pharmacy, so in this country more than three-quarters of patients treated for opioid addiction receive buprenorphine (Auriacombe, Fatséas, Dubernet, Daulouède, & Tignol, 2004; Fatseas & Auriacombe, 2007). In summary, in France, methadone must be started in a specialized unit or a hospital and can be continued, after the patient is stabilized, in an outpatient setting, whereas buprenorphine is easily accessible as it can be started in a specialized unit, a hospital or an outpatient setting. The physician can prescribe methadone for a maximum of 14 days and buprenorphine for 28 days, but the pharmacist must deliver the medication only for 7-day periods unless otherwise indicated by the prescriber. The systematic review by Mattick, Kimber, Breen, and Davoli (2008) demonstrated the efficacy of buprenorphine maintenance treatment, with a lower retention rate than methadone but giving a similar decrease in opiate consumption. Maintenance on OS is requisite for successful treatment.

Methadone prescription guidelines detail the recommended urine tests: a first, obligatory test before starting methadone treatment and later control tests. The first urine test confirms current drug consumption and the absence of methadone intake. Tests are subsequently done once or twice a week during the first 3 months of treatment, then twice monthly. When the patient has transferred to an outpatient setting, tests can be done if the physician considers it necessary. Tests are not obligatory for buprenorphine. In 2004, updated French guidelines on optimal opiate addict care reinforced these recommendations and advised a standardized screening test

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schedule in the initiation and follow-up of methadone and buprenorphine treatment (Haute Autorité de Santé, 2004).

The drug tests can be carried out by immunochemical methods, either by automated analyzers in the biology laboratory or by drug screening kits. Screening can be done during the patient's visit, in either a specialized addiction center or the physician's office. These tests (whether on a laboratory automat or using a commercial kit) are qualitative and have defined thresholds. False negatives exist for cocaine and benzodiazepines in particular, but test quality is intrinsically better for opiate detection (1.9% false negatives) (Pesce et al., 2010). Results can be confirmed by the reference method, liquid or gas phase chromatography with mass spectrometry, which gives quantitative measurements (Bagøien, Morken, Zahlsen, Aamo, & Spigset, 2009). Laboratory tests, regardless of the method or the biological medium, are reimbursed by the French health insurance system with no limit on their number or time period. A recent study has shown that PCPs rarely used these tests and that most had limited knowledge of the subject (Dupouy, Bismuth, Oustric, & Lapeyre-Mestre, 2012).

The value of drug tests for the diagnosis of substance abuse has been demonstrated: many studies agreed that drug tests were more sensitive than self-reports (Galletly, Field, & Prior, 1993; Kilpatrick, Howlett, Sedgwick, & Ghodse, 2000; Lundy et al., 1997; Olshaker, Browne, Jerrard, Prendergast, & Stair, 1997; Perrone, De Roos, Jayaraman, & Hollander, 2001) or physician clinical evaluation (Mordal, Holm, Mørland, & Bramness, 2010). The value of drug testing for clinical management and patient outcomes has been further assessed in several settings: in school programmes (Roche, Bywood, Pidd, Freeman, & Steenson, 2009) and in occupational drivers (Cashman, Ruotsalainen, Greiner, Beirne, & Verbeek, 2009), drug tests are known to be effective. In emergency settings, a recent review found that drug tests had no influence on therapeutic management (Tenenbein, 2009). In chronic non-cancer pain patients, the effectiveness of urine testing to reduce opioid misuse is still debated (Starrels et al., 2010).

As far as we are aware, no study has yet assessed the effectiveness of these tests in ambulatory care in opioid-dependent patients, although they are recommended and they could help to improve therapeutic management when opiate substitutes are used. Our aim was to assess the effectiveness of drug tests for treatment retention in outpatients starting opioid substitution therapy.

2. Materials and methods

Data were extracted from the database of the main French health insurance system (Extraction, Recherches, Analyses pour un Suivi Médico-Economique, ERASME) for the Midi-Pyrenees region from January 1, 2009 to December 31, 2011 in order to build a cohort of patients who were starting opioid substitution therapy (Appendix Fig. 1). This health insurance system covers 87% of the French general population (other systems cover specific populations such as farmers, soldiers and railway workers) (Martin-Latry & Bégaud, 2010). Patients with universal coverage (coverage for the unemployed and low income insurees) are automatically registered in this system. Inclusion criteria for the study were absence of reimbursement for OS between January 1, 2009 and June 30, 2009 and at least one recorded reimbursement for OS between July 1, 2009 and June 30, 2010. These patients had therefore started an OS between July 1, 2009 and June 30, 2010 and were followed for 18 to 30 months. The reference date was defined as the first OS delivery. The period of 30 days before the first delivery of the first OS prescribed to the end of opioid substitution treatment (OST) was considered as the addiction treatment period.

The study was approved by the French Data Protection Authority (Commission Nationale Informatique et Libertés, CNIL), authorization for evaluation of health care practices n°1516745.

2.1. Definition of exposure

The exposure studied was prescription of a drug test during the addiction treatment period. Exposure was considered as a time-dependent variable with a single change, and the period of exposure to a drug test was defined as the period extending 30 days before the first test was carried out until occurrence of the event or censoring (Appendix Fig. 1). Laboratory tests were identified and described by the laboratory classification codes used for reimbursement by the health insurance system (Appendix Table 1). Tests for analgesics, narcotics and psychotropic drugs were taken into account, whatever the biological medium.

2.2. Definition of the event

The primary outcome measure was OST retention, defined as regular delivery of an OS (delivery every 35 days maximum for buprenorphine and 18 days for methadone). A period of more than 35 days between two deliveries of buprenorphine (or more than 18 days for methadone) was considered as treatment interruption and has been validated as such in other studies (Pradel et al., 2004, 2009). This definition of OST retention takes into account the particular conditions of prescription and delivery of these drugs. A patient who interrupted treatment was considered as having discontinued treatment (any later reinitiation was considered a new treatment cycle and was not analyzed here). Data were right-censored at the end of the study period (administrative censoring at December 31, 2011), at the patient's death or loss to follow-up. For patients who presented the event “treatment discontinuation” before death, the event was taken into account if it occurred more than 30 days before death. If the date of the last reimbursed act or the last reimbursed drug was prior to the date of treatment discontinuation by the patient, he/she was considered as lost to follow-up.

2.3. Definition of co-variables

The doctor-shopping indicator, proposed by Pradel et al. (2004, 2009), was used to take into account simultaneous use of several physicians by a patient in order to obtain prescriptions. To determine the doses of methadone and buprenorphine delivered, we used defined daily doses according to the World Health Organization guidelines (WHO Collaborating Centre for Drug Statistics Methodology). The dose delivered corresponded to the daily dose delivered to the patient. The dose prescribed corresponded to the daily dose that would have been delivered to the patient if he/she had only one physician. The doctor-shopping dose corresponded to the daily dose obtained by the prescriptions of several physicians in a same period of time. The doctor-shopping indicator was obtained by dividing the doctor-shopping dose by the dose delivered. If the doctor-shopping indicator was greater than zero, we considered that the patient exhibited doctor-shopping behavior (binary variable).

We used other reimbursed drugs as indicators of associated comorbidities. These drugs were identified by their anatomical therapeutic chemical classification code (ATC code) throughout the study period (Appendix Table 2). The variables taken into account during the addiction treatment period were hospital admission, status of the beneficiary (insured person or their dependent), health insurance coverage for a chronic disease (100% reimbursement of health care for the disease in question), complementary private insurance, universal coverage (coverage for the unemployed and low income insurees), state medical aid (coverage for foreigners not legally resident in France), and pregnancy (identified through maternity benefit).

2.4. Statistical analysis

Qualitative variables were expressed in numbers and percentages and compared between the drug test group (patients prescribed at

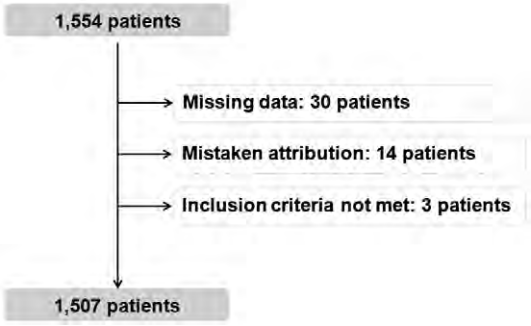

Fig. 1. Flow diagram of patient inclusion.

least one drug test) and the control group (patients with no drug test prescription) using the chi-square test or Fisher test. Quantitative variables were expressed as means and standard deviations, and were compared between the two groups using the Wilcoxon rank test. The primary outcome measure in both groups was survival analysis by Kaplan-Meier curves. A Cox proportional hazards model was constructed to assess treatment retention in the two groups. The Cox model tested the different variables and adjusted for potential confounding factors. The alpha risk threshold was set at 0.20 for selection of variables entered in the multivariate model. The definition of time-dependent exposure was tested using the Cox model in univariate and multivariate analysis (backward procedure, $\alpha = 5\%$). Data analysis was carried out using SAS 9.2 software (SAS Inst., Cary, North Carolina, USA).

3. Results

The data collected concerned 1554 patients. Thirty patients were excluded because of missing demographic data (Fig. 1). Following a check by the medical officer of the health insurance system, 14 patients aged less than 16 years were excluded due to mistaken attribution as their parents were the consumers. Lastly, three patients did not meet the inclusion criteria as they had been reimbursed for an OS before July 1, 2009. Finally, 1507 patients were analyzed.

In the cohort of 1507 patients, 39 (2.6%) had at least one reimbursement for a drug test during the addiction treatment period (mean 1.2, SD 0.4). These tests (68 tests) consisted of measurement of analgesics or narcotics in a biological fluid other than blood (38 tests, 55.9%), testing for benzodiazepines in a biological fluid other than blood (12 tests, 17.6%), testing and measurement in a biological fluid other than blood of a psychotropic agent not otherwise categorized (8 tests, 11.8%), measurement of analgesics or narcotics in blood (7 tests, 10.3%), testing and measurement of a psychotropic drug in blood (2 tests, 2.9%) and testing for benzodiazepines in blood (1 test, 1.5%).

Regarding the physicians of the patients in the drug test group, 137 had prescribed an OS and 41 of these physicians had started OST in these patients. Thirty physicians (25 PCPs, 5 psychiatrists) had prescribed drug tests.

Regarding PCPs of the Midi-Pyrenees region, 841 had prescribed OS. A total of 2620 PCPs were shown in our database to have prescribed a drug or carried out a medical act.

The social and demographic characteristics of the patients of the whole cohort, the drug test group and the control group are given in Table 1. Of the 384 women of the cohort, 14 (3.7%) were pregnant during follow-up (all in the control group, $p = 1.00$). During follow-up, 37 (2.5%) subjects died (none in the drug test group, $p = 0.62$). Two hundred forty five subjects were considered as lost to follow-up: 234 (15.9%) in the control group and 11 (28.2%) in the drug test group ($p = 0.041$).

Type of OS, durations of treatment retention, retention rates, characteristics of primary prescriber of an OS and doctor-shopping indicators are given in Table 2. Three hundred twenty-four patients (21.5%) exhibited doctor-shopping behavior: 19 (48.7%) in the drug test group and 305 (20.8%) in the control group ($p < 0.001$).

Reimbursements of medications according to class are given in Table 3. Few hospital admissions were observed during the addiction treatment period (mean 2.1, SD 9.3) with no difference between the two groups ($p = 0.25$).

Overall, 1252 (83.1%) patients discontinued OST: 1224 (83.4%) in the control group and 28 (71.8%) in the drug test group. Kaplan–Meier curves revealed differences in OST retention between the two groups (Fig. 2). This difference was significant in the log rank test ($p < 0.001$).

In univariate analysis, the variables associated with treatment retention included age, doctor-shopping behavior, drug tests, one or more hospital admissions, zolpidem reimbursements, morphine sulfate reimbursements, antidepressants reimbursements, alcohol abstinence drugs reimbursements, the type of OS prescribed (buprenorphine or methadone), the primary prescriber speciality and primary prescriber previously known to patient. Table 4 shows the results of multivariate analysis in a Cox model. In the multivariate Cox model, a drug test was independently associated with OST retention with an HR of 0.55 (95% CI, 0.38–0.80) ($p = 0.002$).

4. Discussion

Of the 1507 patients who had started OST, only 39 had been reimbursed for a drug screening test during the medical management

Table 1
Demographic characteristics and type of health insurance cover in the whole cohort, the drug test group and the control group.

	All patients ($N = 1507$)		Drug test group ($n = 39$)		Control group ($n = 1468$)		p value
Gender n (%)							
Male	1123	(74.5)	29	(74.4)	1094	(74.5)	0.98
Female	384	(25.5)	10	(25.6)	374	(25.5)	
Mean age (SD) in years	33.2	(9.3)	31.5	(8.9)	33.3	(9.3)	0.182
Status of beneficiary (dependent versus insured) n (%)	73	(4.8)	0	(0.0)	73	(5.0)	0.26
Health insurance coverage for a chronic disease n (%)	282	(18.7)	5	(12.8)	277	(18.9)	0.34
Complementary insurance n (%)							
No	43	(2.9)	0	(0.0)	43	(2.9)	0.68
Yes	364	(24.2)	9	(23.1)	355	(24.2)	
Universal coverage	605	(40.1)	14	(35.9)	591	(40.3)	
Not specified	495	(32.8)	16	(41.0)	479	(32.6)	
State medical aid n (%)							
No	1460	(96.9)	39	(100.0)	1421	(96.8)	1.00
Yes	18	(1.2)	0	(0.0)	18	(1.2)	
Not specified	29	(1.9)	0	(0.0)	29	(2.0)	

Table 2
Characteristics of opioid substitution treatment (OST) in the whole cohort, the drug test group and the control group.

	All patients ($N=1507$)		Drug test group ($n=39$)		Control group ($n=1468$)		p value
OST *n* (%)							
Buprenorphine	1053	(69.9)	23	(59.0)	1030	(70.2)	0.089
Methadone	344	(22.8)	10	(25.6)	334	(22.8)	
Buprenorphine and/or methadone	110	(7.3)	6	(15.4)	104	(7.1)	
Mean duration of treatment retention (SD)	212	(241)	411	(267)	207	(238)	<0.001
Retention rate at 6 months *n* (%)	547	(36.3)	27	(69.2)	520	(35.4)	<0.001
Retention rate at 12 months *n* (%)	321	(21.3)	21	(53.9)	300	(20.4)	<0.001
Retention rate at 18 months *n* (%)	224	(14.9)	16	(41.0)	208	(14.2)	<0.001
Primary prescriber of an OS							
Specialty *n* (%)							
Primary care physician	1422	(94.3)	38	(97.4)	1384	(94.3)	0.78
Specialist	75	(5.0)	1	(2.6)	74	(5.0)	
Not known	10	(0.7)	0	(0.0)	10	(0.7)	
Hospital physician *n* (%)	285	(18.9)	7	(18.0)	278	(18.9)	0.88
Physician previously known to patient *n* (%)							
No	1190	(79.0)	30	(76.9)	1160	(79.0)	0.75
Yes	317	(21.0)	9	(23.1)	308	(21.0)	
Doctor-shopping indicators							
Mean dose delivered (SD)[a]	1.6	(1.8)	2.0	(1.0)	1.5	(1.9)	<0.001
Mean dose prescribed (SD)[a]	1.5	(1.8)	1.8	(0.9)	1.5	(1.8)	<0.001
Mean doctor-shopping dose (SD)[a]	0.1	(0.3)	0.1	(0.3)	0.1	(0.3)	<0.001
Mean doctor-shopping indicator (SD)	0.04	(0.09)	0.05	(0.12)	0.03	(0.09)	<0.001

[a] In defined daily dose (DDD), dose delivered = daily dose delivered to the patient, dose prescribed = daily dose that would have been delivered to the patient if he/she had only one physician; doctor-shopping dose = daily dose obtained by the prescriptions of several physicians in a same period of time, doctor-shopping indicator = doctor-shopping dose/dose delivered.

of their addiction. Their treatment retention was significantly longer. The association between drug tests and OST retention was confirmed by multivariate analysis.

This observational study is based on the data of the French health insurance system. Use of such databases has become generalized in France for more than 10 years, particularly in the field of addiction (Lapeyre-Mestre et al., 2003; Thirion et al., 2002), and the validity of the ERASME database of the health insurance system has been confirmed (Latry, Molimard, Bégaud, & Martin-Latry, 2010). It has been shown in the Three-Cities (3C) cohort that the reimbursement data of the health insurance system agreed with consumption data (Noize et al., 2009).

Incident status was defined as non-reimbursement for an OS during the first 6 months of the study period. It can be assumed that the absence of a prescription for an OS over a 6-month period indicates that there was no previous treatment, or at least a prolonged interruption of treatment so that the patient can again be considered as starting treatment. Nevertheless, this raises the problem of the first delivery of methadone, which must be prescribed in a specialized center or in a hospital setting. Data concerning drugs delivered in hospital settings are not available in the database. For some subjects receiving methadone, the duration of treatment retention has in fact probably been underestimated.

We studied the influence on therapeutic management of the use of drug tests, whether in blood or urine, in the physician's office or in the laboratory. These tests can be used in various clinical situations, but in our selected population of patients starting OST and during the defined period of medical addiction treatment, we may assume that they were prescribed in connection with the management of opiate addiction. As PCPs seldom carry out such tests (Dupouy et al., 2012), we may consider that differences in practice do not limit the validity

Table 3
Drugs reimbursed for patients in the whole cohort, the drug test group and the control group.

	All patients ($N=1507$)		Drug test group ($n=39$)		Control group ($n=1468$)		p value
Class of drugs reimbursed							
Cardiovascular system *n* (%)	232	(15.4)	8	(20.5)	224	(15.3)	0.37
Platelet antiaggregants *n* (%)	37	(2.5)	1	(2.6)	36	(2.5)	1.00
Lipid-lowering agents *n* (%)	45	(3.0)	1	(2.6)	44	(3.0)	1.00
Statins *n* (%)	36	(2.4)	1	(2.6)	35	(2.6)	0.62
Hepatitis C treatment *n* (%)	30	(2.0)	0	(0.0)	30	(2.0)	1.00
HIV treatment *n* (%)	23	(1.5)	0	(0.0)	23	(1.6)	1.00
Alcohol abstinence drugs *n* (%)	112	(7.4)	5	(12.8)	107	(7.3)	0.21
Psychotropic agents *n* (%)	1058	(70.2)	29	(74.4)	1029	(70.1)	0.57
Antipsychotics *n* (%)	391	(26.0)	18	(46.2)	373	(25.4)	0.004
Benzodiazepines *n* (%)	1031	(68.4)	29	(74.4)	1002	(68.3)	0.42
Antidepressants *n* (%)	536	(35.6)	23	(59.0)	513	(35.0)	0.002
Potential drugs of abuse							
Flunitrazepam *n* (%)	23	(1.5)	1	(2.6)	22	(1.5)	0.46
Clonazepam *n* (%)	145	(9.6)	8	(20.5)	137	(9.3)	0.047
Diazepam *n* (%)	236	(15.7)	9	(23.1)	227	(15.5)	0.20
Bromazepam *n* (%)	305	(20.2)	6	(15.4)	299	(20.4)	0.45
Oxazepam *n* (%)	319	(21.2)	15	(38.5)	304	(20.7)	0.007
Alprazolam *n* (%)	215	(14.3)	5	(12.8)	210	(14.3)	0.79
Zolpidem *n* (%)	362	(24.0)	13	(33.3)	349	(23.8)	0.17
Methylphenidate *n* (%)	1	(0.1)	0	(0.0)	1	(0.1)	1.00
Morphine sulphate *n* (%)	80	(5.3)	2	(5.1)	78	(5.1)	1.00

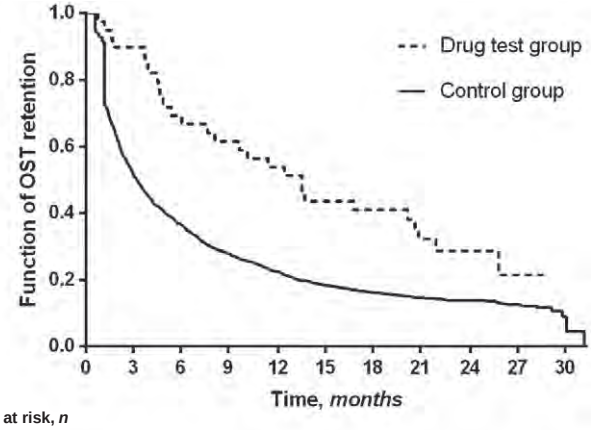

Fig. 2. Kaplan–Meier curves comparing opioid substitution treatment (OST) retention in the two groups (drug test group and control group), log rank test $p<0.001$.

of the drug test codes selected. This was confirmed by our findings, since only six laboratory test codes were in fact recorded out of the eight codes initially selected. Also, the majority of codes corresponded to tests in a biological fluid other than blood, probably urine tests. Adding 30 days before the first delivery of the first OS to define the addiction treatment period was justified because a drug test could be prescribed earlier and could, therefore, influence patient behavior.

This study is subject to several sources of bias. Affiliation to the main French health insurance system is dependent on occupation; part of the population, with a different social and economic profile, is not included in our analysis. This leads to a selection bias. This bias was limited by the fact that we were able to access the data of student health insurance organizations and by the fact that persons in difficulty were included.

Some patients possibly had drug tests in a specialized center or a hospital. Nevertheless, data concerning tests performed in hospital settings are not available in the database. Furthermore, some patients possibly had urine tests with commercial strips or kits. As these tests are not covered by the health insurance system, we had no trace of them and some patients were probably wrongly included in the control group, leading to underestimation of the hazard risk of drug screening. Use of a time-dependent variable to study exposure to a drug screening test avoided immortal time bias.

Only a small number of subjects were tested by physicians. This highlights that physicians seldom carry out such tests, which is in agreement with declarative data (Dupouy et al., 2012) but raises concerns about selection of patients tested. Two different hypotheses with opposite effects can be imagined. First, patients tested may be more compliant patients and may be self-selected on their motivation. However, this hypothesis is not in agreement with exposure of tested patients to certain drugs of abuse (benzodiazepines in particular) and doctor-shopping behavior which was more frequent in tested patients. The second hypothesis is that tested patients may be more heavily addicted patients, as physicians need to test them to assess their consumption.

Lastly, residual confounding factors are another bias in this work. Personal history, addiction severity, parallel drug consumption (Duburcq, Charpak, Blin, & Madec, 2000), injection profile, family support and the occupational (Stein, Cioe, & Friedmann, 2005), and social context (Batel et al., 2004) are variables that have a strong impact on OST retention in these patients, but these factors are not available in the database. The population that underwent drug tests was possibly more severely addicted, as suggested by exposure to certain drugs of abuse.

Demographic data of included patients were similar to demographic data of a French cohort in the same area (Lapeyre-Mestre et al., 2003). The primary care physicians who had issued a prescription or performed any medical act in this patient population represented 68.7% of PCPs in regular practice in the Midi-Pyrenees region on January 1, 2010 according to the data of the national order of physicians, the Ordre National des Médecins (Conseil National de l'Ordre des Médecins, 2010). This high proportion suggests that our data are exhaustive. Of these PCPs, 32.1% prescribed OST. This is in agreement with the declarative data we collected during a previous survey in the same area (Dupouy et al., 2012). Of the physicians treating patients in the drug test group, 30 had prescribed a test. This indicates that the differences between the two groups were not due only to differences in practice or training of some physicians.

Drug tests appeared to be associated with better OST retention. This can be explained by better assessment of drug consumption and easier dialogue between patient and practitioner. Drug tests are known to be effective in school programmes (Roche et al., 2009) and in screening of occupational drivers (Cashman et al., 2009). In an emergency setting, a recent review found no influence of drug tests on therapeutic management (Tenenbein, 2009). The effectiveness of urine testing to reduce opioid misuse in chronic non-cancer pain patients is still debated (Starrels et al., 2010).

Doctor-shopping appeared to be independently associated with better OST retention. This may simply be explained by the fact that doctor-shopping results in bias in the measurement of treatment retention time. Patients who see several prescribers are more likely to have a shorter time between two prescription deliveries and so to remain in treatment longer, leading to a non-differential information bias.

In conclusion, our study increased our knowledge of the value of drug tests in treatment of opioid addiction in an outpatient setting. In a cohort of 1507 patients starting OS treatment and followed for 18 to 30 months, only 39 (2.6%) had at least one reimbursement for a drug test. Treatment retention was longer in these patients, after taking the available confounding factors into account. These findings deserve to be confirmed by more detailed study.

Table 4
Analysis of opioid substitution treatment retention using the multivariate Cox model.[a]

	Adjusted hazard ratio (95% CI)	*p* value
Drug test	0.55 (0.38–0.80)	0.002
Doctor-shopping behavior	0.36 (0.31–0.41)	<0.001
Primary prescriber specialist versus PCP	0.69 (0.53–0.90)	0.007
Age (years)		
25–30 (versus <25)	0.88 (0.75–1.05)	0.153
30–40 (versus <25)	0.78 (0.67–0.91)	0.002
>40 (versus <25)	0.75 (0.63–0.89)	<0.001
1 or more hospital admission	1.14 (1.01–1.28)	0.036
Morphine sulfate	1.35 (1.06–1.71)	0.014
Alcohol abstinence drugs	1.38 (1.11–1.70)	0.004

PCP = primary care physician.

[a] Variables initially included in the model were age, gender, status of beneficiary, health insurance coverage for a chronic disease, universal coverage, complementary insurance, state medical aid, pregnancy, being hospitalized at least once, OST, specialty of primary prescriber, primary prescriber being an hospital physician, primary prescriber previously known to patient, dose delivered, doctor-shopping behavior, other drugs reimbursed and potential drugs of abuse reimbursed.

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Appendix Table 1

Medical laboratory classification codes used to identify drug screening tests in the French health insurance system database.

Medical laboratory code	Label of corresponding analysis
1659	Measurement in blood of analgesics or narcotics not otherwise categorized
0659	Measurement in a biological fluid other than blood of analgesics or narcotics not otherwise categorized
1662	Testing and measurement in blood for a psychotropic agent not otherwise categorized
0662	Testing and measurement in a biological fluid other than blood of a psychotropic agent not otherwise categorized
1667	Testing in blood for benzodiazepines (not for treatment follow-up)
0667	Testing for benzodiazepines in a biological fluid other than blood (not for treatment follow-up)
1668	Diazepam and its metabolite (measurement)
1669	Clonazepam (measurement)

Appendix Table 2

Anatomical Therapeutic Chemical (ATC) codes used to identify drugs in the French health insurance system database.

Class of drugs reimbursed	ATC code	Label of corresponding drugs
Cardiovascular system drugs	C	Cardiovascular system
Platelet antiaggregants	B01AC	Platelet aggregation inhibitors excluding heparin
Statins	C10AA	HMG-CoA reductase inhibitors
	C10B	Lipid modifying agents, combinations
Hepatitis C drugs	J05AB04	Ribavirin
	L03AB01	Natural interferon α
	L03AB04	Interferon α-2A
	L03AB05	Interferon α-2B
	L03AB06	Interferon α-N1
	L03AB09	Interferon alfacon-1
	L03AB10	Peginterferon α-2B
	L03AB11	Peginterferon α-2A
	L03AB12	Albinterferon α-2B
	L03AB60	Peginterferon α-2B, combinations
	L03AB61	Peginterferon α-2A, combinations
Antiretroviral drugs (HIV)	J05AE	Protease inhibitors
	J05AF	Nucleoside and nucleotide reverse transcriptase inhibitors
	J05AG	Non-nucleoside reverse transcriptase inhibitors
	J05AR	Antivirals for treatment of HIV infections, combinations
Alcohol abstinence drugs	N07BB	Drugs used in alcohol dependence
Psychotropic drugs	N05	Psycholeptics
Antipsychotics	N05A	Antipsychotics
Benzodiazepines	N05B	Anxiolytics
	N05C	Hypnotics or sedatives
	N03E	Benzodiazepine derivatives (clonazepam)
Antidepressants	N06A	Antidepressants
Drugs with known abuse potential[a] (monitored by the French addictovigilance system)	N05CD03	Flunitrazepam
	N03AE01	Clonazepam
	N05BA08	Bromazepam
	N05BA12	Alprazolam
	N05BA01	Diazepam
	N05BA04	Oxazepam
	N05CF02	Zolpidem
	N06BA04	Methyphenidate
	N02AA01	Morphine sulphate

[a] These drugs were taken from the last report of the OSIAP survey (Agence française de sécurité sanitaire des produits de santé, 2011). We selected the first 5 drugs cited (excluding buprenorphine): zolpidem, bromazepam, clonazepam, alprazolam, morphine. Methylphenidate abuse has recently been reported in France (Frauger et al., 2011). Diazepam is also known for its high potential for abuse (Pradel, Delga, Rouby, Micallef, & Lapeyre-Mestre, 2010). Oxazepam was selected as it is widely prescribed (Rosman, Marc, & Nathalie, 2011).

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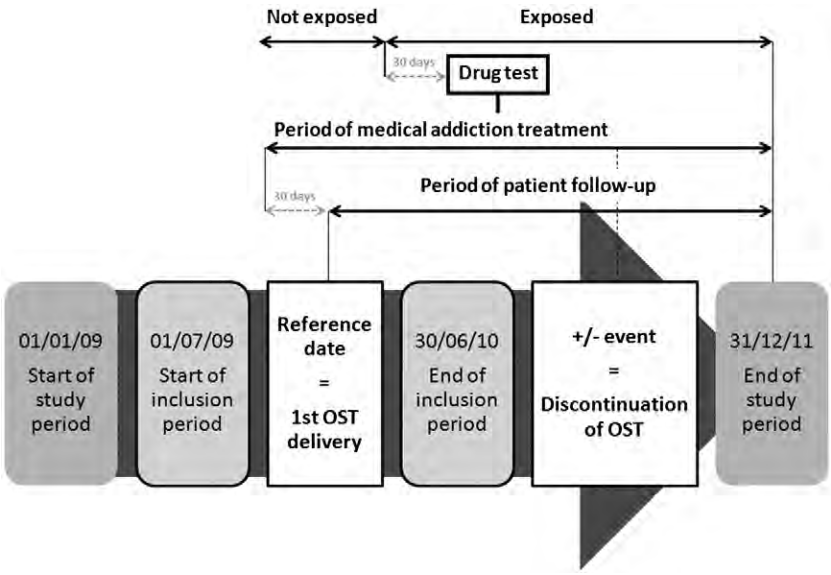

Appendix Fig. 1. Flow diagram of the cohort with principal timepoints and time-dependent definition of exposure to a drug screening test (OST: opioid substitution treatment).

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STUDY 4: EFFECTIVENESS OF DRUG TESTS FOR ALL-CAUSE MORTALITY IN OUTPATIENTS STARTING OPIOID SUBSTITUTION THERAPY

PRESENTATION OF THE STUDY

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Effectiveness of drug tests for all-cause mortality in outpatients starting opioid substitution therapy.

Manuscript in preparation.

A recent study has shown that UDT was a protective factor for mortality (McCowan, Kidd, & Fahey, 2009). This retrospective cohort study performed through data obtained from a primary care prescription registry in Tayside, Scotland aimed to assess predictors of mortality in a population of 2378 people prescribed methadone. A history of involvement in urine testing programmes (irrespective of the result) was associated with a reduced risk of all-cause mortality with a reduction of 70% of risk of death (adjusted hazard ratio of 0.33 [0.22 to 0.49]). The magnitude of the estimated risk ratio was similar to the hazard ratio observed in our previous presented study. Thanks to the previous conducted study and to this Scottish cohort, we could hypothesize that the benefit to perform UDT was found in several studies and is stable.

OBJECTIVE

This study aimed to assess the effectiveness of UDT on all-cause mortality in patients treated by OMT.

METHOD

We performed a pharmacoepidemiological retrospective cohort study on patients newly treated with OMT, using the database EGB. We used data from 01/01/2006 to 31/12/2013. As data for agricultural workers, farmers and self-employed were added in EGB in 2011, we decided to include only the population of the main French health insurance system (*ie.* salaried workers, retirees and patients with the universal coverage representing 86% of the French population) in order to work on the same population throughout the follow-up. We included patients who had a first dispensation of OMT between 01/01/2007 and 31/12/2011 and who were never exposed during the previous twelve months. Patients were followed-up at least one year until the end of the study period or censoring (death or drop out). Reimbursements of drug tests were identified and patients classified in two groups according to it. Survival analyses on all-cause mortality were conducted.

RESULTS

In this study, among patients starting OMT, more than 15% had a reimbursement for a drug test. Having been drug tested was not associated with mortality, HR 0.60 [95%CI 0.21 – 1.69]. Nevertheless, mortality risk was higher off treatment than on treatment. Factors associated with mortality were covariates representing the severity of the disease.

In front of this non-significant result concerning drug tests, we did not perform a multivariate analysis. The first analysis of these data showed that around 15% of patients had been drug tested and that this practice was quite heterogeneous with a first test happening 680 +/- 603 days after the first reimbursement of OMT (median: 583 [144 – 1063]; minimum -30, maximum 2263 days). These data will be more precisely analyzed distinguishing drug tests occurring in the initiation of opioid addiction management and

drug tests occurring in the follow-up. We will then valorize this work not only on drug tests but more globally on factors associated with mortality.

WORKING DRAFT

Effectiveness of drug tests for all-cause mortality in outpatients starting opioid substitution therapy

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Abstract

We aimed to assess the effectiveness of drug tests for all-cause mortality in outpatients starting opioid substitution therapy. A retrospective cohort was created from the data of a French health insurance system database called EGB. Patients starting opioid maintenance treatment were included and followed up for 2 to 7 years. Two groups of patients were defined: the drug test group (at least one drug test reimbursement) and a control group (no drug test reimbursement). The cohort included 1,076 patients. During follow-up, 177 subjects (16.4%) had at least one drug test reimbursement. Crude mortality rate was 0.53/100 person-year [95%CI 0.36 – 0.70]. Thirty-seven patients (3.4%) deceased during the follow-up: 4 (2.3%) in the drug test group and 33 (3.7%) in the control group (P = 0.346). Drug tests were not associated with all-cause mortality: hazard ratio 0.60 [95%CI 0.21 – 1.69]. Use of a drug test in follow-up of opioid substitution treatment, did not significantly improved all-cause mortality.

Keywords:

Opioid-related disorders

Substance abuse detection

Opiate substitution treatment

Mortality

Ambulatory care

Cohort studies

1. Introduction

Opioid addiction is currently defined as a “chronic, relapsing disorder” (1,2). Mortality of untreated heroin dependence is consistently estimated at 1–3% per year, at least half of which because of heroin overdose (3). Data from systematic reviews show that methadone maintenance is the most effective treatment in retaining patients in treatment and suppressing heroin use (4,5).

More recent data estimates that near 150 000 patients are treated, in France, by an opioid substitute (OS) (6). In France, methadone must be started in a specialized unit or a hospital and can be continued, after the patient is stabilized, in an outpatient setting, whereas buprenorphine can be started in a specialized unit, a hospital or an outpatient setting. The physician can prescribe methadone for a maximum of 14 days and buprenorphine for 28 days. Because buprenorphine is easily obtainable (7), more than three-quarters of patients treated for opioid addiction receive buprenorphine (7–9) and most of them are treated in general practice using this drug (7,10). The number of people receiving opiate maintenance treatment (OMT) was estimated at around 100,000 for buprenorphine and around 35,000 for methadone in 2009 (6).

One difficulty of physicians involved in treating opioid-addicted patients is to evaluate the concordance between the patient's word and his drug use (OMT and other illicit drugs) (11) as self-reports and clinical examination use to under estimate psychoactive substances’ consumption (12–17). By contrary, in certain context, patients can overestimate their use of psychoactive substances notably when entering a detoxification program (18).

Urine drug testing (UDT) can improve this assessment (17). Drug tests can be carried out by immunochemical methods, either by automated analyzers in the biology laboratory or by drug screening kits in the surgery of the physician. These tests are qualitative and have defined

thresholds. Results can be confirmed by the reference method, liquid or gas phase chromatography with mass spectrometry, which gives quantitative measurements (19). Laboratory tests, regardless of the method or the biological medium, are reimbursed by the French health insurance system with no limit on their number or time period. On-site urine drug screening by commercial kits is not reimbursed by the French health insurance system but some specialized addiction networks in France provide them to their members.

Methadone prescription guidelines detail the recommended urine tests: a first, obligatory test before starting methadone treatment and later control tests. When the patient has been transferred to an outpatient setting, tests can be done if the physician considers it necessary. Tests are not obligatory for buprenorphine but advised in the initiation of buprenorphine treatment and for the follow-up with the patient's consent (20).

The value of these tests could be to complete the initial assessment before prescribing OMT; and for the follow-up, to monitor the consumptions and the craving, to evidence with the patient the achievement of abstinence, to have a positive reinforcement when results are negative and to deter as soon as possible the use of the substance to reinforce the therapeutic management.

But, while diagnostic value of these tests is well demonstrated (12–17), the consequences of carrying out these tests on management of treatment have not been established. A recent systematic review reveals that weak evidence supports the use of UDS in settings where abusers or addicted patients are managed (i.e., psychiatric settings, primary care, pain clinics, outpatient clinics…). Few studies, with poor quality, have assessed the value of UDS in managing patients using psychoactive substances; though with insufficiency to demonstrate the interest of carrying out UDS (21).

Nevertheless, in a cohort of 1,507 patients starting OS treatment and followed for 18 to 30 months, of whom 39 (2.6%) had at least one reimbursement for a drug test, treatment retention was longer in these patients, after taking the available confounding factors into account (22).

Furthermore, a recent study has shown that UDT was a protective factor for mortality (23). This retrospective cohort study performed through data obtained from a primary care prescription registry in Tayside, Scotland aimed to assess predictors of mortality in a population of 2378 people prescribed methadone. A history of involvement in urine testing programmes (irrespective of the result) was associated with a reduced risk of all-cause mortality with a reduction of 70% of risk of death (adjusted hazard ratio of 0.33 [0.22 to 0.49]).

Thus, we could hypothesize that the benefit to perform UDT was found in several studies and is stable. This study aimed to assess the effectiveness of UDT on all-cause mortality in patient treated by OMT.

2. Material and methods

We performed a pharmacoepidemiological retrospective cohort study on patients newly treated with OMT, using the database EGB (24). EGB is a permanent representative sample of subjects affiliated with the French Health Insurance System. It is obtained by 1/97th national random sampling with control for distribution of age and gender. The EGB database includes approximately 660,000 beneficiaries (24). For some years, French Health Insurance System databases have been widely used for public health and pharmacoepidemiological purposes (25–30).

We used data from 01/01/2006 to 31/12/2013. As data for agricultural workers, farmers and self-employed were added in EGB in 2011, we decided to include only the population of the main French health insurance system (*ie.* salaried workers, retirees and patients with the universal coverage representing 86% of the French population) in order to work on the same population throughout the follow-up.

We included patients who had a first dispensation of OMT between 01/01/2007 and 31/12/2011 and who were never exposed during the previous twelve months. OMT were identifies by the ATC codes: N07BC (including N07BC01: buprenorphine, N07BC02: methadone, N07BC52: buprenorphine-naloxone). Patients were followed-up at least two years until the end of the study period or censoring (death or drop out). Patients were defined incidents if they had a first reimbursement between the age of 16 and 60 when starting OMT.

The exposure to drug tests was prescription of a drug test during the OMT period. Laboratory tests were identified and described by the laboratory classification codes used for reimbursement by the health insurance system (Appendix Table 1). Tests for analgesics, narcotics and psychotropic drugs were taken into account, whatever the biological medium.

The outcome was all-cause death. The date of death without the reason is encoded in the EGB from the national death register of the *Institut National de la Statistique et des Etudes Economiques* INSEE. Data were right-censored at the end of the study period (administrative censoring at December 31, 2013).

The exposure to OMT (buprenorphine, methadone, or buprenorphine-naloxone) was considered as a time-dependent covariate. To define different OMT exposure periods, OMT retention was defined as regular reimbursements of an OS with two definitions of treatment interruption: 1) reimbursement every 35 days maximum for buprenorphine and 18 days for methadone; 2) reimbursement every 70 days maximum for buprenorphine and 35 days for methadone. A period of more than 35 or 70 days between two reimbursements of buprenorphine (or more than 35 or 18 days for methadone) was considered as treatment interruption (any later reinitiation was considered a new OMT period). The first definition of OST retention takes into account the particular conditions of prescription and dispensing of these drugs. The period of more than 35 days between two reimbursements of buprenorphine (or more than 18 days for methadone) has been validated as such in other studies to identify doctor-shopping (31,32). As we disposed of a long follow-up (until seven years), we chose in a second definition to double this delay to increase specificity and sensitivity of the detection of OMT interruption, as we had already experienced in another study (33).

To determine the doses of methadone and buprenorphine dispensed, we used defined daily doses according to the World Health Organization guidelines (34). OMT period duration was the duration between the first and the last reimbursement of the period plus the number of reimbursed DDD of the last reimbursement. We defined patients as being “on treatment” on all the OMT period duration and “off treatment” the remaining time.

The doctor-shopping indicator, proposed by Pradel et al., was used to take into account

simultaneous use of several physicians by a patient in order to obtain prescriptions (31,32). The dose prescribed corresponded to the daily dose that would have been dispensed to the patient if he/she had only one physician. The doctor-shopping dose corresponded to the daily dose obtained by the prescriptions of several physicians in a same period of time. The doctor-shopping indicator was obtained by dividing the doctor-shopping dose by the dose dispensed. If the doctor-shopping indicator was greater than zero, we considered that the patient exhibited doctor-shopping behavior (binary variable).

We used other reimbursed drugs as indicators of associated comorbidities. These drugs were identified by their anatomical therapeutic chemical classification code (ATC code) throughout the study period (ATC codes N05A for antipsychotics, N06A for antidepressants, N03A for antiepileptics, N07BB for alcohol maintenance drugs). The co morbidity score of Charlson was calculated using codes defined by Quan (35). The variables taken into account during the addiction treatment period were complementary private insurance, universal coverage (coverage for the unemployed and low income insurees); status of the beneficiary (insured person or their dependent), psychiatric diseases identified by health insurance coverage for a chronic psychiatric disease (ALD code 23) and associated ICD10 codes (Appendix Table 2), hospital admission for a psychoactive substance use or for a psychiatric disease (GHS and ICD10 codes in Appendix Table 3).

Qualitative variables were expressed in numbers and percentages and compared between the drug test group (patients prescribed at least one drug test) and the control group (patients with no drug test prescription) using the chi-square test or Fisher test. Quantitative variables were expressed as means and standard deviations, and were compared between the two groups using the Wilcoxon rank test. The primary outcome measure in both groups was survival analysis by Kaplan-Meier curves. A Cox proportional hazards model was constructed to assess mortality in the two groups. The Cox model tested the different variables (and will

adjust for potential confounding factors). The alpha risk threshold was set at 0.20 for selection of variables entered in the multivariate model. The definition of time-dependent OMT exposure was tested using the Cox model in univariate (and multivariate) analysis (backward procedure, $\alpha = 5\%$). Data analysis was carried out using SAS Guide43 ® software (SAS Inst., Cary, North Carolina, USA).

We performed an observational study on anonymous data. Thus, considering the French legislation, it did not need to be approved by a regulatory structure or an ethic committee (36). The use of EGB for research teams is, thus, authorized by law and does not require the submission of a request to the National data protection commissions (CNIL and CCTIRS), but the study synopsis including source of funding was submitted to INSERM which approved the project.

3. Results

Between 2007 and 2013, 654 816 were in the EGB database. Among them, 543 576 (83.0%) were affiliated to the main French health insurance system. Among the beneficiaries of this scheme, 1076 (0.2%) began an OMT between the age of 16 and 60.

During the follow-up of these 1076 patients, 177 (16.4%) had at least one reimbursement for a drug test with a mean number of drug tests of 3.6 (+/- 6.7) per patient, median of 2 [1 – 3], maximum: 57 tests. The first test happened 680.0 +/- 603.0 days after the first reimbursement of OMT (median: 583 [144 – 1063]; minimum -30, maximum 2263 days). Table 1 described reimbursed drug tests. Most of them were the measurement in a biological fluid other than blood of analgesics or narcotics not otherwise categorized.

Table 1. Nature of the first urine test performed

Nature of the first urine test performed	n = 177
Measurement in a biological fluid other than blood of analgesics or narcotics not otherwise categorized	143 (80.8)
Testing and measurement in a biological fluid other than blood of a psychotropic agent not otherwise categorized	9 (5,2)
Testing for benzodiazepines in a biological fluid other than blood (not for treatment follow-up)	2 (1,1)
Measurement in blood of analgesics or narcotics not otherwise categorized	20 (11,3)
Testing and measurement in blood for a psychotropic agent not otherwise categorized	3 (1,7)

Included patients were mostly young men (75.3% of men, 32.4 years +/- 8.8 at the first OMT reimbursement). Table 2 described the characteristics of included patients.

Table 2. Sociodemographic characteristics of patients according to their group.

	Overall (n = 1076)	**Drug test group** (n = 177)	**Control group** (n = 899)	P-value
Gender				0.885
Male	810 (75.3)	134 (75.7)	676 (75.2)	
Female	266 (24.7)	43 (24.3)	223 (24.8)	

	Overall (n = 1076)	**Drug test group** (n = 177)	**Control group** (n = 899)	P-value
Age at the first OS reimbursement				<0.001
Mean +/- SD	32.4 +/- 8.80	29.1 +/- 7.16	33.0 +/- 8.96	
Median [Q1 – Q3]	31 [26 - 38.5]	28 [24 - 33]	32 [26 - 39]	
Status of beneficiary				0.660
Insured	1028 (95.5)	168 (94.9)	860 (95.7)	
Dependent	48 (4.5)	9 (5.1)	39 (4.3)	
Universal coverage	400 (37.2)	56 (31.6)	344 (38.3)	0.095
First OS ATC class				0.094
buprenorphine N07BC01	875 (81.3)	136 (76.8)	739 (82.2)	
methadone N07BC02	201 (18.7)	41 (23.2)	160 (17.8)	
Specialty of the first OS prescriber *				0.876
General Practice	1021 (94.9)	173 (97.7)	848 (94.3)	
Unknown	23 (2.1)	3 (1.7)	20 (2.2)	
Psychiatry	16 (1.5)		16 (1.8)	
Gastroenterology	3 (0.3)	1 (0.6)	2 (0.2)	
Activity of first OS prescriber				0.040
Private practice	828 (77.0)	148 (83.6)	680 (75.6)	
Salaried in a private establishment	212 (19.7)	27 (15.3)	185 (20.6)	
Unknown	36 (3.3)	2 (1.1)	34 (3.8)	
Deprivation index (Fdep09)				<.001
Mean +/- SD	0.4 +/- 1.50	1.0 +/- 1.32	0.3 +/- 1.52	
Median [Q1 – Q3]	0.5 [-0.5 ; 1.4]	0.9 [0.1 ; 1.7]	0.4 [-0.6 ; 1.3]	
Charlson score				0.053
Mean +/- SD	0.2 +/- 0.82	0.0 +/- 0.21	0.2 +/- 0.89	
Median [Q1 – Q3]	0 [0 ; 0]	0 [0 ; 0]	0 [0 ; 0]	
Maximum	9	1	9	
Health insurance coverage for a psychiatric disorder	85 (7.9)	10 (5.6)	75 (8.3)	0.225
Addictive disorders	25 (2.3)	6 (3.4)	19 (2.1)	0.303
Depressive or recurrent depressive disorder	10 (0.9)	3 (1.7)	7 (0.8)	0.246
Anxiety disorders	0 (0.0)	0 (0.0)	0 (0.0)	
Schizophrenia, schizotypal and delusional disorders	20 (1.9)	3 (1.7)	17 (1.9)	0.860
Manic episode and bipolar affective disorders	7 (0.7)	1 (0.6)	6 (0.7)	0.877
Specific personality disorder	29 (2.7)	2 (1.1)	27 (3.0)	0.159
Epilepsy	2 (0.2)	1 (0.6)	1 (0.1)	0.194
Number of consultations and visits				0.761
Mean +/- SD	7.3 +/- 12.12	7.0 +/- 11.74	7.3 +/- 12.20	
Median [Q1 – Q3]	4 [1 ; 8]	3 [2 ; 7]	4 [1 ; 9]	
Maximum	157	80	157	
Hospitalization for a psychiatric disorder	38 (3.5)	11 (6.2)	27 (3.0)	0.034
Hospitalization for an addictive disorder	2 (0.2)	2 (1.1)	0 (0.0)	0.001
Hospitalization for another disorder	156 (14.5)	29 (16.4)	127 (14.1)	0.436
Number of nervous system drugs (ATC class N)				0.903

	Overall (n = 1076)	**Drug test group** (n = 177)	**Control group** (n = 899)	P-value
Mean +/- SD	2.5 +/- 3.31	2.4 +/- 3.31	2.5 +/- 3.31	
Median [Q1 – Q3]	1 [0 ; 4]	1 [0 ; 3]	1 [0 ; 4]	
Maximum	25.0	18.0	25.0	
Antipsychotics	352 (32.7)	61 (34.5)	291 (32.4)	0.587
Antidepressants	487 (45.3)	85 (48.0)	402 (44.7)	0.419
Antiepileptics	234 (21.7)	28 (15.8)	206 (22.9)	0.046
Alcohol abstinence drugs	101 (9.4)	15 (8.5)	86 (9.6)	0.649

* Specialties for which n ≥ 3 are represented (overall patients)

Table 3 describes characteristics of OMT periods with the second definition of OMT periods (long definition). Patients were treated 1190.2 +/- 798.28 days by OMT and had 2.4 +/- 1.95 periods of OMT. Total duration under OMT was longer for patient of drug test group than for those of the control group (P <0.001). Characteristics of OMT periods with the first definition of OMT periods (short definition) are in Appendix Table 4. Seventy-seven patients (43.5%) of the drug test group experienced doctor-shopping versus 288 patients (32.0%) of the control group (P = 0.003).

Table 3. Characteristics of OMT periods (long definition).

	Overall (n = 1076)	**Drug test group** (n = 177)	**Control group** (n = 899)	P-value
Total duration under OMT				<0.001
Mean +/- SD	1190.2 +/- 798.28	1438.9 +/- 684.19	1141.2 +/- 810.26	
Median [Q1 – Q3]	1235 [454. 8 ; 1851.1]	1506 [1069.5 ; 1984.8]	1171.8 [336; 1814]	
Number of OMT periods				0.198
Mean +/- SD	2.4 +/- 1.95	2.6 +/- 1.93	2.4+/- 1.93	
Median [Q1 – Q3]	2 [1 ; 3]	2 [1 ; 3]	2 [1 ; 3]	
Maximum	26	13	26	
Mean duration of OMT periods				0.001
Mean +/- SD	610.9 +/- 552.28	747.6 +/- 558.49	584.0 +/- 547.35	
Median [Q1 – Q3]	466.5 [221.1; 818.8]	600.8 [346.6 ; 1056.8]	438.9 [201.8 ; 777.5]	
Mean daily dose of OMT periods (DDD)				0.845
Mean +/- SD	1.1 +/- 1.47	1.1 +/- 1.04	1.1 +/- 1.55	

Median [Q1 – Q3]	0.7 [0.4 ; 1.4]	0.8 [0.5 ; 1.6]	0.7 [0.4 ; 1.3]	
Maximum	28.0	8.3	28.0	
Duration of the first OMT period				0.091
Mean +/- SD	459.9 +/- 612.84	531.0 +/- 643.69	445.9 +/- 605.97	
Median [Q1 – Q3]	157.1 [28.0 ; 695.2]	234.8 [39.5 ; 846.0]	151.0 [28.0 ; 621.0]	
Daily dose of the first OMT period (DDD)				0.700
Mean +/- SD	1.5 +/- 1.93	1.4 +/- 1.54	1.5 +/- 2.01	
Median [Q1 – Q3]	1 [0.5; 1.8]	0.9 [0.5 ; 1.9]	1 [0.5 ; 1.8]	
Maximum	28.0	10.5	28.0	
Doctor-shopping indicator in the first OMT period				0.332
N	836	143	693	
Mean +/- SD	0.0 +/- 0.09	0.0 +/- 0.07	0.0 +/- 0.10	
Median [Q1 – Q3]	0 [0 ; 0]	0 [0 ; 0]	0 [0 ; 0]	
Maximum	0.7	0.6	0.7	
Having doctor-shopping behavior	365 (33.9)	77 (43.5)	288 (32.0)	0.003
Reimbursed OMT in the first OMT period				0.039
buprenorphine	835 (77.6)	127 (71.8)	708 (78.8)	
methadone	195 (18.1)	37 (20.9)	158 (17.6)	
buprenorphine et méthadone	46 (4.3)	13 (7.3)	33 (3.7)	
Summary of OS of OMT periods*				0.062
bup1	359 (33.4)	45 (25.4)	314 (34.9)	
bup1/met1	23 (2.1)	5 (2.8)	18 (2.0)	
bup1/met9	138 (12.8)	22 (12,6)	116 (12.9)	
bup1/mix1/bup1	20 (1,9)	4 (2,3)	16 (1,8)	
bup13	99 (9.2)	13 (7.3)	86 (9.6)	
bup17	54 (5.0)	8 (4.5)	46 (5.1)	
bup2/met17	76 (7.1)	6 (3,4)	20 (2.2)	
bup2/met5	75 (7,0)	10 (5.6)	66 (7.3)	
bup22	46 (4.3)	15 (8.5)	31 (3.4)	
bup3/b+n1	27 (2.5)	5 (2.8)	22 (2.4)	
bup4	27 (2.5)	8 (4.5)	19 (2.1)	

* OMT periods for which n ≥ 20 (overall patients are represented); bup1 = 1 period with only buprenorphine reimbursed; bup1/met9 = 1 period with only buprénorphine reimbursed then 9 periods with only methadone reimbursed; mix = 1 period with reimbursements of buprenorphine and methadone together ; b+n = buprenorphine + naloxone

Thirty-seven patients (3.4%) died during the follow-up: 4 (2.3%) in the drug test group and 33 (3.7%) in the control group (P = 0.346). Death occurred 879.2 +/- 585.4 days after the first

reimbursement of OMT (833 [392 – 1361]); this delay was 1014.5 +/- 586.7 in the drug test group (1186 [633 – 1396]) and 862.8 +/- 592.2 in the control group (775 (392 – 1361]). Among those who died, 13 died while "on treatment": 1 in the drug test group and 12 in the control group (P = 1.0). Six died in the 2 weeks after interrupting their treatment (1 in the drug test group and 5 in the control group, P = 0.524); 3 died in the week 3 and 4 after interrupting their treatment (1 in the drug test group and 2 in the control group (P = 0.298); and 16 died while off treatment (in the remaining time): 1 in the drug test group and 14 in the control group (P = 0.618). Crude mortality rate was 0.53/100 person-year [95%CI 0.36 – 0.70]. In the general population of EGB (subjects with same inclusion criteria: age from 16 to 60 from 2007 to 2011), crude mortality rate was 0.24/100 person-year [0.24 – 0.25].

Survival analysis did not show difference between the drug test and the control group on all-cause mortality (P = 0.327). Figure 1 represents Kaplan-Meyer curves.

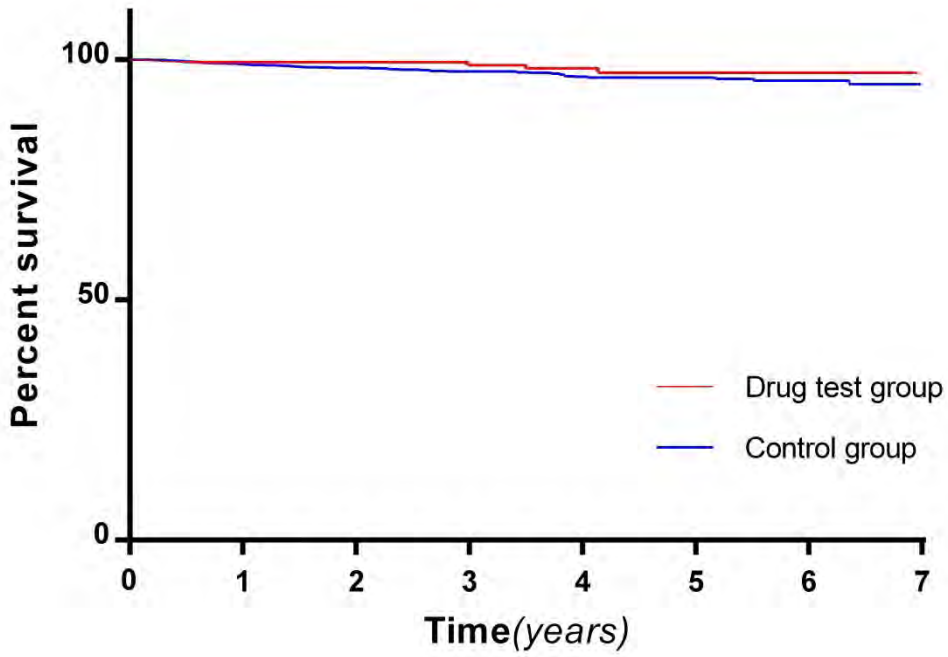

Figure 1. Descriptive survival analysis of all-cause mortality according to the group (drug test or control group) using Kaplan Meyer curves.

In an univariate Cox model, drug tests were not associated with all-cause mortality: hazard ratio HR 0.60 [95%CI 0.21 – 1.69]. By contrast, being “off treatment” versus “on treatment” was associated with an HR of 3.33 [1.75 – 6.35] using the first definition of OMT periods (short definition) and with an HR of 11.51 [5.85 – 22.64] using the second definition (long definition). Total duration of OMT and number of OMT periods were also associated with mortality. Table 4 describes covariates associated in univariate with mortality.

Table 4. Covariates associated with mortality in an univariate Cox model.

	Crude hazard ratio [95%CI]	**P**
Off treatment (versus on treatment)	11.51 [5.85 – 22.64]	<0.001
Total duration under OMT (long definition)	0.999 [0.998 - 0.999]	<0.001
Age	1.10 [1.06 - 1.14]	<0.001
Number of OMT periods (long definition)	0.68 [0.50 - 0.90]	0.010
Antiepileptics	2.33 [1.21 - 4.49]	0.012
Heath insurance coverage for a psychiatric disorder	2.86 [1.26 - 6.52]	0.012
Charslon score	1.37 [1.06 – 1.76]	0.016
Number of consultations	1.02 [1.00 - 1.03]	0.031
Hospitalization for another disorder than a psychiatric one	2.20 [1.07 – 4.55]	0.033
Number of nervous system drugs (ATC class N)	1.08 [1.00 - 1.16]	0.037

4. Discussion

Among patients starting OMT, more than 15% had a reimbursement for a drug test. While drug tests were not associated with mortality, mortality risk was higher off treatment than on treatment. Factors associated with mortality were covariates representing the severity of the disease.

This observational study is based on the data of the French health insurance system. Use of such databases has become generalized in France for more than 10 years and, specifically, EGB has been used for 5 years for pharmacoepidemiological purposes (25–30). Some studies have shown an acceptable concordance between drug consumption estimated through Health Insurance System databases and self-reported drug consumption (37). Although, we cannot exclude that, even if the drug is prescribed and reimbursed, it is not consumed by the patient.

Incident status was defined as non-reimbursement for an OS during the first 12 months of the study period. Nevertheless, the first delivery of methadone must be prescribed in a specialized center or in a hospital setting. Data concerning drugs delivered in hospital settings are not available in the database. For some subjects receiving methadone, the duration of treatment retention has in fact probably been underestimated.

We studied drug tests, whether in blood or urine, in the physician's office or in the laboratory. These tests can be used in various clinical situations, but in our selected population of patients starting OMT, we may assume that they were prescribed in connection with the management of opiate addiction. This was confirmed by our findings, since the majority of codes corresponded to tests in a biological fluid other than blood, probably urine tests. Some patients possibly had drug tests in a specialized center or a hospital and some patients possibly had urine tests with commercial kits. As data concerning tests performed in hospital settings are not available in the database and as on-site drug tests are not covered by the health

insurance system, we had no trace of them and some patients were probably wrongly included in the control group.

The proportion of patients having drug tests was more important than in another French regional study (22) which might highlight heterogeneous practices even if this result is influenced by the longer time of follow-up in our present study. Whatever it is, drug tests are rarely done and when they are, they are performed occasionally for each patient. We can imagine that drug tests are not seen like a repeated evaluation of consumptions and thus craving but as "safeguard" for patients younger and with a more severe disease as our results suggest (more hospitalizations, more nervous system drugs, and more doctor-shopping in drug tested patients). This, and the low number of events, could explain that we did not find an association between drug tests and mortality as shown in another study (23). Drug tests were associated with longer OMT retention as we had already found in a south-western France area (22).

The protective role of OMT for mortality has been confirmed with an off treatment HR between 3 and 11 according to the chosen definition of OMT retention. As far as we know, it is the first French study showing this protective effect, while French context is quite particular with the widespread of buprenorphine. Another finding was that longer was OMT, less patients died. Patients had around two periods of OMT representing a little bit than three years of OMT. Over seven years, it represents limited therapeutic managements in time while the protective effect of OMT for mortality has been demonstrated in larger studies in Scotland (23) and in the United Kingdom (38).

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Appendix. Table 1.

Medical laboratory classification codes used to identify drug screening tests in the EGB database.

Medical laboratory code	Label of corresponding analysis
1659	measurement in blood of analgesics or narcotics not otherwise categorized
0659	measurement in a biological fluid other than blood of analgesics or narcotics not otherwise categorized
1662	testing and measurement in blood for a psychotropic agent not otherwise categorized
0662	testing and measurement in a biological fluid other than blood of a psychotropic agent not otherwise categorized
1667	testing in blood for benzodiazepines (not for treatment follow-up)
0667	testing for benzodiazepines in a biological fluid other than blood (not for treatment follow-up)
1668	diazepam and its metabolite (measurement)
1669	clonazepam (measurement)

Appendix. Table 2.

ICD10 codes associated to costly long–term diseases (*Affections de longue durée* ALD) used to identify for diseases in the EGB database.

Identified disease	ICD10 codes
dementia	F01, F02, F03
addictive disorder	F10, F11, F12, F13, F14, F15, F16, F17, F18, F19
schizophrenia, schizotypal and delusional disorders	F20, F21, F22, F23, F24, F25, F28, F29
manic episode and bipolar affective disorders	F30, F31
depressive or recurrent depressive disorder	F32, F33
anxiety disorders	F40, F41, F42, F43, F44, F45, F48
specific personality disorder	F60
mixed disorder of conducts and emotions	F92
epilepsy	G40, G41

Appendix. Table 3.

GHS and ICD10 codes used to identify hospitalization for psychiatric disorders in the EGB database.

Hospital admission	GHS codes	PMSI
For a psychoactive substance use	7250, 7251, 7252, 7253, 7254, 7255, 7256, 7257, 7258, 7259, 7260, 7261, 7262, 7263, 7264, 7265, 7266, 7267, 7268, 7269, 7270, 7271, 7272, 7273, 7274, 7275, 7276, 7277, 7278, 7279, 7280, 7281, 7282, 7283, 7284, 7285, 7286, 7287, 7288, 8315, 8316	none
For a psychiatric disease	7000, 7001, 7002, 7003, 7004, 7050, 7051, 7052, 7053, 7054, 7055, 7056, 7057, 7058, 7059, 7060, 7061, 7062, 7063, 7064, 7065, 7066, 7067, 7068, 7069, 7070, 7071, 7072, 7073, 7074, 7075, 7076, 7077, 7078, 7079, 7080, 7081, 7082, 7083, 7084, 7085, 7086, 7087, 7088, 7089, 7090, 7091, 7092, 7093, 7094, 7095, 7096, 7097, 7098, 7099, 7100, 7101, 7102, 7103, 7104, 7105, 7106, 7107, 7108, 7109, 7110, 7111, 7113, 7114, 7115, 7116, 7117, 7118, 7119, 7120, 7121, 7122, 7123, 7124, 7125, 7126, 7127, 7128, 7129, 7130, 7131, 7132, 7133, 7134, 7135, 8034, 8291, 8292	principal or associated diagnoses of the ICD10 class F

Appendix. Table 4.

Characteristics of OMT periods (short definition)

	Overall (n = 1073)	**Drug test group** (n = 174)	**Control group** (n = 899)	P-value
Total duration under OMT				<.001
Mean +/- SD	1261.0 +/- 860.63	1506.1 +/- 724.88	1212.7 +/- 877.23	
Median [Q1 – Q3]	1296.9 [473.1 ; 1963.0]	1576.0 [1091.0 ; 2068.8]	1235.0 [357.0 ; 1911.2]	
Number of OMT periods				0.656
Mean +/- SD	5.5 +/- 5.67	5.6 +/- 4.90	5.4 +/- 5.82	
Median [Q1 – Q3]	2 [4 ; 7]	2 [4 ; 8]	3 [2 ; 7]	
Maximum	56	28	56	
Mean duration of OMT periods				0.006
Mean +/- SD	330.8 +/- 359.09	398.0 +/- 357.66	317.6 +/- 358.09	
Median [Q1 – Q3]	221.1 [108.4 ; 420.8]	309.5 [174.3 ; 535.0]	206.8 [99.5 ; 401.7]	
Mean daily dose of OMT periods (DDD)				0.823
Mean +/- SD	1.0 +/- 1.72	1.0 +/- 0.98	1.1 +/- 1.84	
Median [Q1 – Q3]	0.7 [0.3 ; 1.2]	0.7 [0.4 ; 1.3]	0.6 [0.3 ; 1.2]	
Maximum	28.0	8.3	28.0	
Duration of the first OMT period				0.298
Mean +/- SD	222.3 +/- 389.33	250.1 +/- 397.10	216.8 +/- 387.78	
Median [Q1 – Q3]	59.6 [21.0 ; 232.0]	76.0 [21.0 ; 290.5]	57.0 [21.0 ; 216.0]	
Daily dose of the first OMT period (DDD)				0.453
Mean +/- SD	2.0 +/- 6.34	1.6 +/- 1.65	2.1 +/- 6.94	
Median [Q1 – Q3]	1.1 [0.6 ; 2.0]	1.0 [0.7 ; 2.1]	1.1 [0.6 ; 2.0]	
Maximum	151.2	10.5	151.2	
Doctor-shopping indicator in the first OMT period				0.195
N	762	133	629	
Mean +/- SD	0.0 +/- 0.09	0.0 +/- 0.07	0.0 +/- 0.10	
Median [Q1 – Q3]	0 [0 ; 0]	0 [0 ; 0]	0 [0 ; 0]	
Maximum	0.7	0.7	0.7	
Having doctor-shopping behavior	365 (33.9)	77 (43.5)	288 (32.0)	0.003
Reimbursed OMT in the first OMT period				0.039
buprenorphine	859 (79.8)	131 (74.0)	708 (78.8)	
methadone	200 (18.6)	40 (22.6)	158 (17.6)	
buprenorphine et méthadone	17 (1.6)	6 (3.4)	33 (3.7)	
Summary of OS of OMT periods*				0.004
bup1	208 (19.3)	16 (9.0)	192 (21.4)	

bup2	127 (11.8)	20 (11.3)	107 (11.9)
bup3	73 (6.8)	9 (5.1)	64 (7.1)
bup4	48 (4.5)	14 (7.9)	34 (3.8)
bup5	58 (5.4)	9 (5.1)	49 (5.5)
bup6	33 (3.1)	6 (3.4)	27 (3.0)
bup7	36 (3.3)	5 (2.8)	31 (3.4)
bup8	26 (2.4)	3 (1.7)	23 (2.6)
bup9	20 (1.9)	4 (2.3)	16 (1.8)
met1	31 (2.9)	4 (2.3)	27 (3.0)
met2	25 (2.3)	7 (4.0)	18 (2.0)
met3	20 (1.9)	7 (4.0)	13 (1.4)

* OMT periods for which n ≥ 20 (overall patients are represented); bup1 = 1 period with only buprenorphine reimbursed; bup1/met9 = 1 period with only buprénorphine reimbursed then 9 periods with only methadone reimbursed; mix = 1 period with reimbursements of buprenorphine and methadone together ; b+n = buprenorphine + naloxone

PART 3: PROTOCOL OF AN INTERVENTION STUDY (STUDY 5)

Finally, the last part aimed to confirm the value of urine drug screening test in real life and thus, to assess their efficacy planning a pragmatic cluster randomized controlled trial in general practice.

Partie 3 : Protocole d'une étude d'intervention

La dernière partie a pour objectif la confirmation de l'intérêt des tests urinaires de dépistage en médecine générale en planifiant la mise en place d'un essai pragmatique contrôlé randomisé.
L'objectif principal de cet essai clinique randomisé ouvert en cluster est d'évaluer l'impact des tests urinaires de dépistage des toxiques en médecine générale chez des patients initiant un traitement par buprénorphine ou buprénorphine/naloxone sur le maintien sous MSO à 6 mois.
L'intervention consistera en : 1) Une formation spécifique des MG (sur comment réaliser les tests urinaires et comment les interpréter) 2) La mise à disposition des tests urinaires dans les cabinets médicaux des MG, les MG seront libres de réaliser les tests urinaires pour le suivi s'ils le jugent nécessaire 3) La réalisation d'un test urinaire avant la première prescription de buprénorphine ou buprénorphine/naloxone. Le bras témoin correspondra à la stratégie médicale standard pour évaluer les consommations de substances psychoactives.
Le critère de jugement principal est le maintien sous MSO à 6 mois.
Six centres, représentés par un binôme département de médecine générale – centre d'évaluation et d'information sur la pharmacodépendance-addictovigilance (Clermont-Ferrand, Grenoble, Marseille, Nancy, Poitiers, Toulouse), seront responsables d'inclure 200 médecins généralistes (exerçant dans un cabinet médical de ville en secteur 1 et prenant en charge régulièrement des patients traités par buprénorphine ou buprénorphine/naloxone) pour un total 400 patients (âgés d'au moins 18 ans et consultant pour une initiation de buprénorphine ou buprénorphine/naloxone) à inclure.
Cet essai devrait avoir un niveau de preuve suffisant pour évaluer l'efficacité des tests en médecine générale pour les patients traités par buprénorphine.

PRESENTATION OF THE STUDY

Dupouy J.

Impact of urine drug screening on opiate maintenance in general practice in France: the ESUB-MG pragmatic cluster randomized trial.

Manuscript ready for submission.

OBJECTIVE

The main objective will be to assess the impact of on-site urine drug screening tests in general practice compared to routine medical care on OMT retention at six months in opioid-dependent patients initiating buprenorphine.

METHOD

The ESUB-MG study uses a pragmatic, cluster randomized controlled trial design. GPs regularly managing patients treated with buprenorphine and consenting for participating to the trial will be invited to participate. GPs will be randomly assigned to one of two groups for 6 to 24 months: (a) control group (usual care: standard medical strategy for assessing drug use); (b) intervention (including 1/ a training session on practice and interpretation of OS-UDS; 2/ the supply of OS-UDS at GPs' medical offices; 3/ performing an OS-UDS before the first prescription of buprénorphine). GPs will have to include 1 to 10 patients aged 18 years-old or more, consulting for starting treatment by buprenorphine, not opposed to participate. The primary outcome will be OMT retention at 6 months.

RESULTS

This randomized intervention trial should bring sufficient level of evidence to assess effectiveness of performing OS-UDS in general practice for patients treated by buprenorphine.

MANUSCRIPT READY TO SUBMIT

Impact of urine drug screening on opiate maintenance in general practice in France: the ESUB-MG pragmatic cluster randomized trial

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Running head: the ESUB-MG pragmatic cluster randomized trial

Word count: 4105

ABSTRACT

Background and aims In addiction care, urine drug screening tests are recommended to be used to assess psychoactive substances use as self-reports underestimate their use. While intrinsic diagnostic value of these tests is already demonstrated, the consequences of carrying out these tests on opiate maintenance treatment (OMT) have not been clearly established. The main objective will be to assess the impact of on-site urine drug screening tests in general practice compared to routine medical care on OMT retention at six months in opioid-dependent patients initiating buprenorphine. **Methods** The ESUB-MG study uses a pragmatic, cluster randomized controlled trial design. GPs regularly managing patients treated with buprenorphine and consenting for participating to the trial will be invited to participate. GPs will be randomly assigned to one of two groups for 6 to 24 months: (a) control group (usual care: standard medical strategy for assessing drug use); (b) intervention (including 1/ a training session on practice and interpretation of OS-UDS; 2/ the supply of OS-UDS at GPs' medical offices; 3/ performing an OS-UDS before the first prescription of buprénorphine). GPs will have to include 1 to 10 patients aged 18 years-old or more, consulting for starting treatment by buprenorphine, not opposed to participate. The primary outcome will be OMT retention at 6 months. **Discussion** This randomized intervention trial should bring sufficient level of evidence to assess effectiveness of performing OS-UDS in general practice for patients treated by buprenorphine. Training GPs to drug tests and supplying them in their office should lead to an improvement of opioid-addicted patients' care through helping decision.

Trial registration: Clinical Trials (n°)

Keywords: opioid related disorder, opiate substitutive treatment, buprenorphine, substance abuse detection, urine drug screening test, outpatient, general practitioner, maintenance

BACKGROUND

Opioid addiction is currently defined as a "chronic, relapsing disorder" (1,2). Mortality of untreated heroin dependence is consistently estimated at 1–3% per year, at least half of which is because of heroin overdose (3). Beyond mortality and morbidity, heroin dependence inflicts enormous social and economic costs due to crime, unemployment, relationship breakdown, and the cost of law enforcement. Data from systematic reviews show that methadone maintenance is the most effective treatment in retaining patients in treatment and suppressing heroin use when compared with buprenorphine (4,5).

The management of opiate-dependent patients in France is shared among specialized centres and general practitioners (GPs). Three drugs are available for the maintenance treatment methadone, buprenorphine (approved since 1995) and buprenorphine-naloxone (approved since 2006). Methadone must be initially prescribed by practitioners in specialized centers, whereas buprenorphine and buprenorphine-naloxone should be prescribed by any general practitioner and available through community pharmacies. The number of people receiving maintenance treatment was estimated around 100,000 for high-dose buprenorphine and around 40,000 for methadone in 2010 (6). Because the availability and the easy access to buprenorphine (7) most of opiate-dependent patients are managed in general practice (8). Actually, few GPs take care of these patients: they were only 24% in 2009 to regularly take care of patients under opiate maintenance treatment (OMT) (9). One of their difficulties is to evaluate the concordance between the patient's word and his drug use (OMT and other illicit drugs) (10). Indeed, one or two thirds of patients under OMT would also consume alcohol and benzodiazepines (11). Several GPs are afraid of drug trafficking which keeps growing (12), particularly with the reported frequent resale of buprenorphine (13,14).

The assessment of psychoactive substance use is often difficult as patients' self-reports under estimate the use of psychoactive substances (15–19). One Scandinavian study

compared the performance of the psychiatrist versus the use of urine drug screening test (UDS) in the context of emergency setting for the assessment of drug use, using chromatography-tandem mass spectrometry as the reference (20). The sensitivity of the physician assessment was 57% for opiates, when it was 80% for opiates: this study clearly showed that physicians' assessment of psychoactive drug use lead to underestimate the true consumptions, and UDS should improve this assessment.

French guidelines highlight the need to assess opiate dependence for the management of patients taking OMT: screening tests have to be performed before introducing methadone; they are recommended before starting treatment with buprenorphine and during the follow up of both treatments. Methadone prescription guidelines detail the recommended urine tests: a first, mandatory test before starting methadone treatment and later control tests. The first urine test confirms current drug consumption and the absence of methadone intake. Tests are subsequently done once or twice a week during the first 3 months of treatment, then twice monthly. When the patient has transferred to an outpatient setting, tests can be done if the physician considers it necessary. Tests are not obligatory for buprenorphine, but highly recommended. In 2004, updated French guidelines on optimal opiate addict care advised a standardized screening test schedule in the initiation and follow-up of methadone and buprenorphine treatment (22).

The drug tests can be carried out by immunochemical methods, either by automated analyzers in the biology laboratory or by drug screening kits. These tests (whether on a laboratory automat or using a commercial kit) are qualitative and have defined thresholds. False negatives exist for cocaine and benzodiazepines in particular, but test quality is intrinsically better for opiate detection (1.9% false negatives) (23). Results can be confirmed by the reference method, liquid or gas phase chromatography with mass spectrometry, which gives quantitative measurements (24). Screening can be done during the patient's visit, in

either a specialized addiction centre or the physician's office. Laboratory tests, regardless of the method or the biological medium, are reimbursed by the French health insurance system with no limit on their number or time period. In medical offices, immunoassays have been shown to be reliable (25,26); nevertheless, on-site urine drug screening (OS-UDS) by commercial kits are not reimbursed by the French health insurance system but some specialized addiction networks in France provide them to their members.

In a recent study performed among a sample of French GPs, only 12.2% of GPs reported to perform urinary screening tests and in this proportion were counted GPs who reported to use them for other reasons than initiation and follow up of OMT (9). The main reason for not performing UDS was a lack of knowledge about screening test (9). Among the few GPs using tests, the consequence they reported was mainly reinforcing dialogue with the patient. In another study performed in the same area among 1,507 patients initiating an OMT with buprenorphine or methadone, only 2.6% had at least a drug test reimbursed by the Health Insurance System during their addiction treatment period (27).

Few studies explored the consequences of carrying out these tests on medical management. In the previous cited study, having been drug tested was associated with a better opiate substitution maintenance, with 45% decrease of drop-outs (95% CI: 0.38–0.80) (27). In a retrospective cohort study of methadone users performed through data obtained from a primary care prescription registry in Tayside, Scotland, a history of having urine tested was a protective factor in relation to all-cause mortality with a reduction of 70% of risk of death (HR 0.33, 0.22 to 0.49) (28). On the basis of the literature, one would suppose that carrying out UDS would provide an improvement in the management of patients with opioid addiction and positive outcomes for patients such as longer opiate substitution maintenance and its clinical consequences in which a decrease in mortality. However, this hypothesis relies only on observational data, and we cannot rule out confusion bias.

In order to provide more consolidated data on the interest of using UDT in the context of general practice, we propose an interventional trial, which the main objective is to assess the impact of on-site urine drug screening tests in general practice compared to routine medical care on OMT retention at six months in opioid-dependent patients initiating buprenorphine. Second objectives are to assess the acceptability of OS-UDS by patients and GPs, to assess patient adherence to buprenorphine and to assess associated consumptions (decrease in using psychoactive substances).

METHODS

Study design

The ESUB-MG study is a pragmatic, cluster randomized controlled trial design. Clustering is at the level of the GP. A cluster design is needed as the intervention concerns the GP and as the evaluation concerns the patient. Furthermore, patients of a same GP are more correlated than patients of different GPs.

Research objectives

This study is designed to assess the impact of on-site urine drug screening tests in general practice compared to routine medical care on OMT retention at six months in opioid-dependent patients initiating buprenorphine.

Study population

GP inclusion criteria

Professional criteria: to practice as a GP, to be in activity, to practice in general ambulatory practice (in a medical office)

patients' characteristics: to regularly manage patients treated with buprenorphine

legal characteristic: to be registered in sector 1

consent for participating to the trial

GPs exclusion criteria

to practice in a group medical office in which another GP has been included in the trial

Patients inclusion criteria

Aged 18 years-old or more

to consult for starting buprenorphine or OMT

affiliated to a health insurance scheme

not opposed to participate

Exclusion criteria

Patients exclusion criteria

to consult for continuing buprenorphine or for another complain related to opiate substitution treatment

to be known and yet managed by the GP for an opiate substitutive treatment

to have started buprenorphine in a specialized centre or in a hospital

to be treated with methadone

to be treated with methadone and asking a switch toward buprenorphine

not consenting to participate to the study

Recruitment

GPs recruitment

Six academic general medicine department and six centers for evaluation and information on pharmacodependence-addictovigilance (CEIP-A) will work in pairs to recruit voluntary GPs within their network of working GPs and through regional addiction networks.

Recently, in France, general medicine was recognised as a specialty with a specific training. Consecutively, academic general medicine departments were developed in each faculty. In 2008, an academic pathway of general medicine was created.

In order to assist the French Committee for Narcotics and Psychotropic Drugs, in charge of the monitoring and the scheduling of psychoactive substances with abuse potential, a monitoring system for psychoactive medications abuse consisting of a network of 13 centers for evaluation and information on pharmacodependence-addictovigilance (CEIP-A) was created in 1999.

In both sources for selection, GP will be contacted by postal mail comprising a questionnaire for validating inclusion criteria for the GP, and an agreement form for participating to the ESUB-MG study. A pre-stamped return envelope will be included. Monetary compensation is planned for participating GPs as compensation for the time and contribution to the study.

GPs in both groups will receive both oral and written information about study design and conduct (patients' recruitment, inclusion criteria). Material for data collection will comprise a GP questionnaire on basic demographic information and location, GP information notice (detail on recruitment and study conduct), questionnaire for the inclusion and follow up visit.

GPs agreeing to participate to the study will be randomly assigned to one of two groups: one group with intervention, one control group.

Patients' recruitment

GPs will be requested to include all consecutive patients that would be eligible. Each GP have to include at least 2 patients within 18 months.

Participant recruitment will commence in March 2015, and patient participation will be completed by August 2017. The planned end date for the trial is December 2018.

Consent

GPs will inform eligible patients of their involvement in the study and that their medical data will be used for the purpose of the research. As a research on standard care GPs will have to ensure that patient are not opposed to take part to the research.

Patients that would explicitly express their opposition will not be included. Patients who are not opposed to participate but refusing to submit to one or several OS-UDS will be maintained in their group defined by their cluster.

Randomization

Randomization will be undertaken at the cluster (GP) level. Based on the procedure allocated to GP, all patients within a cluster will be assigned to either intervention or control group.

Randomization of participating GP will be performed after obtaining consent of GP and collecting complete questionnaire including basic demographic information and their location. The randomization list will be generated by an independent biostatistician in the clinical research methodological support unit (Unité de Soutien Méthodologique à la Recherche Clinique USMR) of the University hospital (Centre Hospitalier Universitaire CHU) of Toulouse, France. Clusters will not be randomized all at once (first patients inclusion need to begin whereas GPs' recruitment will be on-going), thus the allocation for each consecutive participating GP will be obtained from the USMR through a specific website. To avoid contamination bias, no more than one GP could be included in a given medical practice.

Intervention

Intervention will consist in: 1) a training session for GPs on use and interpretation of OS-UDS; 2) the supply of OS-UDS at GPs' medical offices; 3) performing an OS-UDS before the first prescription of buprenorphine. GPs will be let free to perform OS-UDS for the follow-up if they judge it necessary.

GP assigned to the intervention group will be visited by a clinical research assistant (CRA) to be trained on the methods for performing test (urinary sample collection and reading of the test results). The training session is expected to last about 1 hour, and a written

guidance will be provided. Material for testing (OS-UDS) will also be supplied during this session. OS-UDSs will be centrally bought by the CHU de Toulouse and will be provided by the CRA in charge of the training session.

During the consult, GPs of the intervention group will dedicate an average 5 minutes to perform OS-UDS. Patients will be asked to collect a urine sample at the GP's medical office. GP will read and communicate the results immediately to the patients. GPs will keep free of their management according to OS-UDS results.

OS-UDS characteristics

OS-UDS will be in accordance with positivity threshold recommended by the National Institute on Drug Abuse (NIDA) (29) and the Substance Abuse and Mental Health Administration (SAMSHA) (30). The SAMSHA increase the threshold for screening opiates in 2008 (2000ng/mL instead of 300ng/mL) to avoid false positive to ingestion of poppy-seeds. Nevertheless, many laboratories maintained the threshold of 300 ng/mL to preserve the opiates screening sensibility (31). Thus, we will use the threshold of 300 ng/mL.

Several substances will be screened through the OS-UDS in our study: buprenorphine, methadone (or its metabolite, 2-ethylidine-1,5-dimethyl-3,3 diphenylpyrrolidine (EDDP)), opiates, and cocaine. Opiate substitutes should be systematically screened before starting buprenorphine, according to guidelines. Buprenorphine screening is intended to assess adherence to OMT after initiation, whereas opiates are screened to monitor concomitant consumptions over the course of OMT, or to confirm an opiate addiction before the first prescription (which confirms the indication of OMT). Methadone screening is intended to rule out an ongoing treatment by methadone. Cocaine is often consumed with opiates. In France, at least 10% of patients would be concerned by cocaine consumption while they are treated with an opioid substitute (32,33), and it is associated with negative outcome. Some patients

could request for an OMT being unaware of the indication of these drugs and believing they could be offered such treatment.

Positivity thresholds currently used (29,30) and that we will use are: buprenorphine: 10 ng/mL ; EDDP (the metabolite of methadone): 100ng/mL ; opiates: 300ng/mL ; cocaine: 300 ng/mL.

At these thresholds, sensibility was 80% (IC95%: 55 - 100) and specificity 99% [96 – 100] for opiates, sensibility not calculable and specificity 100% [100 -100] for cocaine (20). In another study, sensibility for buprenorphine with 3 different OS-UDS varied from 88 to 100% and specificity from 91 to 100 % (34).

Controlled group

Controlled arm will correspond to standard medical strategy for assessing consumptions while prescribing OMT. Excluding OS-UDS, there will be no prohibited procedure. In particular, GPs of the controlled harm are authorized to implement any biological test to ascertain associated substances use, including for instance laboratory testing. However, according to previous data, we can expected that few drug tests should be performed in this control group: 1 to 3% (9,27).

Outcome measures

The primary outcome will be OMT retention at 6 months. Secondary outcomes will be patient adherence to buprenorphine, associated psychoactive substances use, acceptability of OS-UDS reported by the patient, acceptability of OS-UDS reported by the GP.

Primary outcome

Retention in treatment at 6 months will be the main judgment criterion. Actually, a review on all Cochrane systematic reviews performed by the Cochrane Review Group on Drugs and Alcohol highlighted that the main outcomes used in studies assessing effectiveness

of opiate maintenance treatment were retention in treatment and illicit use of heroin (4). Whatever the treatments compared, the retention in treatment was the most constant and the most reproducible outcome used over the different clinical trials because heroin use (assessed through different ways, self-reported or through urinary analysis) is rarely reported in a standardized way. This outcome could be considered as intermediate steps of treatment for heroin-addicted patients. Because observational studies showed high rates of mortality in heroin-addicted patients (35), especially early after discharge from treatment, the ability of a treatment in retaining people in treatment should be reported as a proxy of effectiveness (36).

Retention in treatment will be defined as patients remaining under opiate maintenance treatment at 6 months in a context of medical care (i.e. drug prescribed by a physician, not diverted or obtained through an illegal way, whatever the drug considered, buprenorphine; buprenorphine/naloxone, methadone) and assessed by the general practitioner at the end of the follow-up. Patients switching from buprenorphine to methadone or to buprenorphine/naloxone during study follow-up will be considered as remaining under opiate maintenance treatment.

The patient will be defined as retained in treatment if he will be prescribed by the same GP a legal opiate maintenance drug, or if the drug will be prescribed by another practitioner in connection with the treating physician. In case of loss of follow-up or diverted use of drug (intravenous or nasal route or illegal acquisition of the OMT drug), the patient will be considered as not retained. In case of death, the patient will be considered as maintained until the date of death, and censored after this date. Buprenorphine must be prescribed under strict conditions for a maximum of 28 days (methadone for a maximum of 14 days). Consequently, a patient not attending a medical visit for more than 56 days (2 months) should be considered as not remaining under opiate maintenance treatment.

Retention in treatment has to be recorded at 6 months (time window tolerated of +/- 14 days) as there is no scheduled or mandatory visit for the patient.

Secondary outcomes

The secondary judgment criteria will allow answering secondary objectives of the study: adherence to buprenorphine associated psychoactive substances use, acceptability of OS-UDS reported by the patient, the GP.

We will specifically collect for both groups: characteristics of buprenorphine utilization (dose, duration), exposure to opiate or other illegal substances (heroin, morphine, cannabis, cocaine, benzodiazepines, amphetamines, other…) during the follow-up (self-reported during medical examination and/or biologically assessed) ; for the intervention group: number of OS-UDS performed by GP and by patient acceptability reported by the patient and by the GP (self-reported questionnaires).

Cross-link data

To ensure completeness in prescription drug record, significant medical event and death occurring during follow up, additional information on medical care will also be obtained through the database of the health insurance scheme. A query into the information system from the national health insurance scheme (SNIIRAM) and national mortality registry will be done to complete follow-up. Data collected will not be included in the main analysis.

Sample size calculation

Comparisons between groups will be performed taking into account clustering which the unity will be the GP. Thus the sample size must be corrected by an inflation factor according to guidelines on clustered analyses (37–40). According to the results of a previous study performed by our group on patients initiating buprenorphine in ambulatory care in the Midi-

Pyrénées area (27), we were able to identify clusters of GPs and calculated the intra-cluster correlation coefficient (CCI = 2.79%) and the mean cluster size (m=2), giving an inflation factor (IF = 1.03).

According to the literature, the retention rate with buprenorphine at 6 months is generally around 40%, with 60% in specialized centers with urinary testing and supervision (4,5). In studies performed in our area, observed retention rates were similar (11). Using reimbursement data from the French Health Insurance system at the regional level, we compared retention rate of patients newly treated by buprenorphine according to performing or not urinary testing (27). In this study including 1,507subjects followed-up over 30 months, the retention rate in patients with urinary testing was significantly better than the reference group, with an adjusted Hazard Ratio of 0.55 (95% CI: 0.38–0.80).

Thus, considering a retention rate in the reference group of 36%, and an expected retention rate of 50% in the intervention group, if mean cluster size (m) = 2, α risk = 0.05 and β risk = 0.20, the theoretical formula of Hayes and Moulton gives 100 clusters by group, i.e. 100 GPs in each group, corresponding to 200 patients in each group, i.e. 400 patients in all (Hayes and Moulton 2009).

Recruiting 2 patients by GPs over a period of 18 months seems realistic, even if these GPs are not working in an addiction specialized network. Hypothesizing that the expected retention rate will be 50% in the intervention group is very conservative. Actually, with an expected retention rate of 60% (as observed in our previous study) or with an expected relative risk of 0.3-0.4 in favour of the intervention group (as observed in the McCowan study (28), with a benefit of performing urinary testing -whatever the results- on mortality in patients treated by methadone in UK). With this retention rate, only 34 clusters should be needed, corresponding to 34 GPs in each group, 68 in the all sample, and consecutively 136 patients. This hypothesis should be probably optimistic but not completely unrealistic.

This strategy will allow to overcome the proper effect of each GP, to get enough clusters for the analysis and to regroup clusters (on the basis of the same geographic area (in French “Bassins de santé”) giving a sufficient number of individuals in each cluster (5 subjects).

Statistical analysis

Patients, will be analyzed according to the intervention assigned to their GP, whether being exposed to OS-UDS during their participation or not, in accordance with the intention-to-treat principle.

For patients followed up until the end of the study, the retention rate will be the percentage of patients still under OMT (complete data). For loss of follow up patients, an intention to treat approach will be used and loss of follow will be analyzed as failure.

A description of the baseline characteristics of the group will be performed, comprising mean ± SD for continuous variables and frequency and percentages for qualitative variables. Baseline characteristics and secondary outcomes will be compared among groups using the Chi2 test of independency or Fisher test for categorical variables and the Student t test or the Wilcoxon test for continuous variables. A significance threshold of 5 % will be applied for all the statistical analyses.

Retention at 6 months will be computed as an individual binary variable, and will be analyzed using mixed effect logistic regression, including General practitioners as a random effect parameter. Potential confounders or explanatory variables at individual and cluster level will be included. An alternative way for analysis would consist in applying generalized estimating equation (GEE). These models are appropriate in the study design as the number of cluster will be higher than 15 (38).

Univariate analyses on baseline variables as potential predictors for success or failure of OMT maintenance will be performed using Chi-square statistics for categorical and Student t-test for continuous data. Variables with a P-value of <0.2 after univariate analysis will be entered into a multivariate logistic regression model. Crude and adjusted Odds Ratio (OR) and their confidence intervals will be estimated. The main analysis will be completed by univariate and multivariate clustered survival analyses.

Analyses will be performed using the SAS ® 9.3 software (SAS Institute Inc., Cary, NC, USA).

DISCUSSION

This randomized intervention trial in primary care context should bring sufficient level of evidence to assess effectiveness of performing OS-UDS in general practice for patients treated by buprenorphine. The aim is to assess the impact of a global intervention, including a better knowledge of UDS (through a specific GP's training to perform UDS and interpret their results), and giving the opportunity to perform OS-UDS for any patient consulting for an OMT initiation in the medical office by the GP. The better way to assess this impact with a sufficient level of evidence is to perform a randomized intervention trial in primary care context, comparing OMT retention at 6 months in patients cared by GPs randomly assigned to having on-site UDS, compared to patients cared by GPs randomly assigned to performing standard care.

Most of OMT patients in France are managed in the context of primary care, whereas most of OMT clinical assessments have been done in the context of specialized centers. UDS should be used in this context of primary care, but are rarely done. Commercial kits are giving the possibility to perform UDS extemporarily in the medical office. The limits of these tests in terms of sensitivity and specificity are well-known, and this project does not aim to assess the intrinsic validity of these tests, assuming that they present a sufficient quality to be licensed in France, but to assess effectiveness of performing OS-UDS in general practice for patients treated by buprenorphine.

The widespread use of UDS is already a reality for some (few) GPs working in specialized addiction networks and in centers without laboratories inside. However, outside this context, urine testing is rare and knowledge of GPs remains scarce. Demonstrating the positive impact of OS-UDS on GPs' practice (in managing patients) and behaviors of patients treated with buprenorphine in general practice (adherence) would be an important issue in the field of opioid addiction care.

Training GPs to drug tests and supplying OS-UDS in their office should lead to an improvement of opioid-addicted patients' care through helping decision making in the GP medical office, improving GPs' practices, improving adherence of treated patients, and consequently, improving short and long term outcomes of OMT.

Governance and ethical considerations

The study will be done in the French regulatory context of standard care (in French “Soins Courants”), all the procedures used in the study being in the standard care of opiate addicts. Thus, the study will not modify the standard follow-up of patients newly treated by an OMT and all the medical visits and/or other interventions will be done as needed.

This study has been approved by Persons’ Protection Committee (CPP) of Bordeaux, France (n°2014-A00393-44) and the Consultative Committee on Data Processing in Research in the Area of Health (CCTIRS) (n°14.356bis). The protocol is submitted to the National Commission for Computing and Civil Liberties (CNIL).

Clinical trial registration

Trials registration:

Declaration of interests

The authors declare that they have no competing interests.

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GENERAL CONCLUSION

This thesis presented an overview of opioid maintenance treatment in France and investigated the potential value of urine drug screening in primary care. The first survey has demonstrated that few French GPs prescribed drug tests, the mean reason being that they did not know their existence. Then, the systematic review found that weak evidence supported the impact of drug tests in managing patients. Specifically, few studies have been performed about it in ambulatory care.

The pharmacoepidemiological approach assessed the effectiveness of drug tests in France for opioid substitution retention and all-cause mortality. Drug tests were associated with opioid substitution retention but not with mortality. However, in this last study about mortality, few events were counted, limiting its power. Furthermore, these cohort studies using real life data demonstrated that drug tests are rarely done. When they are, they are occasional and for a specific, more severe, population. This can also explain this last non-significant result on mortality.

The pharmacoepidemiological approach illustrated the value of French health system insurance reimbursement databases for the researcher in primary care. The regional ERASME database and the EGB have been interesting tools for exploring the value of drug tests in patients treated by OMT and provided first useful results to plan the intervention study.

Finally, the pragmatic randomized controlled trial that we will soon conduct, will investigate with better evidence the impact of urine drug screening in general practice for patients starting buprenorphine.

Conclusion générale :

Cette thèse a présenté un état des lieux des traitements de maintenance aux opiacés en France et a évalué l'intérêt des tests urinaires de dépistage en ambulatoire.

La première étude a montré que les médecins généralistes étaient peu nombreux à utiliser ces tests ; la principale raison étant une méconnaissance de leur existence. La revue systématique a ensuite montré que peu d'études soutenaient l'efficacité des tests pour la prise en charge des patients dépendants aux opiacés, notamment en ambulatoire, et que ces études avaient une qualité méthodologique faible.

L'approche pharmacoépidémiologique a montré que la réalisation des tests de recherche de substances psychoactives, quoique rare, était associée avec un maintien sous médicament de substitution aux opiacés plus long mais pas à une baisse de la mortalité. Néanmoins, un manque de puissance peut avoir affecté les résultats de cette dernière étude. Cette approche a illustré l'intérêt de l'utilisation des bases de données de l'Assurance Maladie (et particulièrement de l'EGB) pour les chercheurs en soins primaires.

Pour finir, un essai pragmatique randomisé a été mis en place et évaluera avec un meilleur niveau de preuve l'intérêt des tests urinaires de dépistage pour les patients débutant un traitement par buprénorphine.

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APPENDIX. SUPPLEMENTARY MATERIAL OF STUDY 2

Supplementary Material for the article

Does urine drug abuse screening help for managing patients? A systematic review

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This material supplements, but does not replace, the peer-reviewed article in *Drug and Alcohol Dependence*,

CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Schiller et al., 2000 Checked (Y/N)
Title and abstract			
	1a	Identification as a randomised trial in the title	N
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Y
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Y
	2b	Specific objectives or hypotheses	Y
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	N
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N
Participants	4a	Eligibility criteria for participants	Y
	4b	Settings and locations where the data were collected	Y
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Y
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Y
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Y
Sample size	7a	How sample size was determined	N
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Y
	11b	If relevant, description of the similarity of interventions	Y
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Y
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Y
	13b	For each group, losses and exclusions after randomisation, together with reasons	N
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Y
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Y
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Y
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Y
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N
Other information			
Registration	23	Registration number and name of trial registry	N
Protocol	24	Where the full trial protocol can be accessed, if available	N
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	N

NA: Non applicable

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Tennant, 1994 Checked (Y/N)	Eisen et al, 2004 Checked (Y/N)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	N	N
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y	Y
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y	Y
Methods				
Study design	4	Present key elements of study design early in the paper	N	N
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	N	Y
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Y	Y
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	N	Y
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	N	Y
Bias	9	Describe any efforts to address potential sources of bias	N	N
Study size	10	Explain how the study size was arrived at	N	N
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N	Y
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	N	Y
		(*b*) Describe any methods used to examine subgroups and interactions	N	Y
		(*c*) Explain how missing data were addressed	N	N
		(*d*) If applicable, explain how loss to follow-up was addressed	N	NA
		(*e*) Describe any sensitivity analyses	N	N
Results				

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y	Y
		(b) Give reasons for non-participation at each stage	N	Y
		(c) Consider use of a flow diagram	N	Y
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y	Y
		(b) Indicate number of participants with missing data for each variable of interest	N	Y
		(c) Summarise follow-up time (eg, average and total amount)	N	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	Y	Y
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA	Y
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N	N
Discussion				
Key results	18	Summarise key results with reference to study objectives	Y	Y
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N	Y
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	N	Y
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N	N

NA: Non applicable

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Passik et al., 2000 Checked (Y/N)	Murnion et al., 2007 Checked (Y/N)	Dupouy et al., 2012 Checked (Y/N)	Levy et al., 2006 Checked (Y/N)	Manchikanti et al., 2006 Checked (Y/N)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y	Y	Y	Y	N
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y	Y	Y	Y	Y
Introduction							
Background /rationale	2	Explain the scientific background and rationale for the investigation being reported	Y	N	Y	Y	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y	Y	Y	Y	Y
Methods							
Study design	4	Present key elements of study design early in the paper	Y	Y	N	Y	N
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y	Y	Y	Y	Y
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Y	Y	Y	Y	Y
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	N	Y	Y	Y	Y
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	N	Y	Y	Y	N
Bias	9	Describe any efforts to address potential sources of bias	N	N	N	N	N
Study size	10	Explain how the study size was arrived at	N	N	N	Y	Y
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y	Y	NA	Y	NA

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y	Y	Y	Y	Y
		(*b*) Describe any methods used to examine subgroups and interactions	N	N	Y	Y	NA
		(*c*) Explain how missing data were addressed	N	N	Y	N	N
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA	NA	N	N	N
		(*e*) Describe any sensitivity analyses	N	N	N	N	N
Results							
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y	N	Y	Y	Y
		(b) Give reasons for non-participation at each stage	NA	N	Y	Y	Y
		(c) Consider use of a flow diagram	N	N	Y	N	N
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y	N	Y	Y	Y
		(b) Indicate number of participants with missing data for each variable of interest	N	N	Y	N	Y
Outcome data	15*	Report numbers of outcome events or summary measures	Y	Y	Y	Y	Y
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N	Y	N	Y	Y
		(*b*) Report category boundaries when continuous variables were categorized	N	NA	Y	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA	NA	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity	N	Y	Y	N	NA

		analyses					
Discussion							
Key results	18	Summarise key results with reference to study objectives	N	Y	Y	Y	Y
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y	Y	Y	Y	N
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y	Y	Y	Y	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	N	Y	Y	N	N
Other information							
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N	N	Y	Y	Y

NA: Non applicable

AUTEUR : Julie DUPOUY

TITRE : **Comment améliorer la prise en charge ambulatoire des patients dépendants aux opiacés ? Approche pharmaco épidémiologique de l'intérêt des tests urinaires de dépistage des substances psychoactives.**

DIRECTEURS DE THESE : Dr Maryse LAPEYRE-MESTRE, Pr Stéphane OUSTRIC

LIEU ET DATE DE SOUTENANCE : 08/01/2014, Faculté de Médecine, allées Jules Guesde, 31000 Toulouse

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Depuis la reconnaissance de l'addiction comme maladie mentale, des médicaments spécifiques ont été développés. Les médicaments de substitution de la dépendance aux opiacés (méthadone, buprénorphine et buprénorphine/naloxone) ont montré leur efficacité en diminuant les consommations de drogues, les risques infectieux (VIH, hépatite C), en améliorant l'insertion sociale, et en diminuant la morbidité. En France, les conditions de prescription et de délivrance de la buprénorphine ont permis de prendre en charge une grande partie de ces patients en médecine générale. Néanmoins, l'évaluation des consommations par l'interrogatoire et l'examen clinique est connue pour sous-estimer l'usage de substances psychoactives. Proposer un outil d'évaluation tel que les tests urinaires de dépistage des substances psychoactives (proposant une évaluation qualitative des substances détectées dans les urines du patient) pourrait aider les médecins à identifier les consommations et avoir un impact sur la prise en charge.

L'objectif de cette thèse est d'évaluer l'intérêt des tests urinaires de dépistage pour la prise en charge des patients dépendants aux opiacés en médecine ambulatoire. Cette évaluation a été conduite en trois parties. Dans la première, les connaissances des tests à partir de la littérature et à partir des déclarations des médecins généralistes (MG) français a été décrite. Dans la seconde, l'efficacité des tests sur la prise en charge des patients dépendants aux opiacés a été étudiée par des études de cohortes observationnelles à partir des bases de données de l'Assurance Maladie. Pour finir, la dernière partie propose de confirmer l'impact des tests urinaires dans la vraie vie, en évaluant leur efficacité dans un essai pragmatique randomisé en cluster en médecine générale.

Dans la première partie, nous avons évalué les connaissances et pratiques des tests par les Médecins Généralistes de Midi Pyrénées par une étude transversale descriptive. La plupart des MG prenant en charge régulièrement des patients dépendants aux opiacés ne réalisaient pas de tests et ne les connaissaient pas. Dans un second temps, pour évaluer l'efficacité des tests urinaires de dépistage pour la prise en charge des patients, nous avons conduit une revue systématique de la littérature des essais cliniques, études pragmatiques et études observationnelles. L'intérêt des tests urinaires n'était pas clairement démontré dans les études incluses.

Le premier travail de la seconde partie a évalué l'impact des tests urinaires tests sur le maintien sous traitement substitutif aux opiacés. Une cohorte rétrospective a été créée à partir de la base Extraction, Recherches, Analyses pour un Suivi Médico-Economique ERASME pour la région Midi Pyrénées. L'utilisation des tests urinaires, quoique rare, augmentait significativement le maintien sous traitement. Le deuxième travail a évalué l'intérêt des tests sur la mortalité des patients sur une base nationale : l'échantillon des généralistes bénéficiaires (EGB). Ce travail a confirmé l'association entre les tests et le maintien sous traitement mais n'a pas retrouvé d'association avec la mortalité.

Les résultats obtenus ont été utilisés pour planifier la troisième partie : la mise en place d'un essai pragmatique randomisé en cluster en médecine générale. Nous présentons le protocole de cette étude qui a pour objectif d'évaluer l'efficacité d'une intervention (tests urinaires de dépistage au cabinet du médecin généraliste) sur le maintien sous traitement de patients débutant la buprénorphine.

Pour conclure, cette thèse a montré que les tests urinaires étaient peu réalisés en France chez les patients dépendants aux opiacés et que peu d'études ont évalué leur intérêt. Néanmoins, les tests semblent avoir un effet protecteur sur le maintien sous traitement substitutif aux opiacés. L'essai pragmatique randomisé en cours que nous proposons devrait permettre d'apporter des preuves suffisantes de leur intérêt en médecine générale.

MOTS CLES : Addiction aux opiacés, Médecine générale, buprénorphine, méthadone

DISCIPLINE ADMINISTRATIVE : Ecole doctorale BSB, Pharmacologie

LABORATOIRE DE RATTACHEMENT : UMR 1027 Inserm-UPS, équipe de pharmacoépidémiologie