



Risk assessment in morphine sulfate off-label use in non-painful opioid dependent patients

Célian Bertin

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DOCTORAT EN MÉDECINE
(Diplôme d'État)

par

BERTIN Célian

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**Risk assessment in morphine sulfate off-label use
in non-painful opioid dependent patients**

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Membres du jury :

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Professeur Nicolas Authier

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Professeur des Universités - Praticien Hospitalier en Pharmacologie Médicale
Chef de service de Pharmacologie Médicale, CHU Gabriel-Montpied, Clermont-Ferrand

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Service de Psychiatrie Adulte B - Pôle d'Addictologie, CHU Gabriel-Montpied,
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Maître de Conférences Universitaire – Praticien Hospitalier en Psychiatrie
d’Adultes-Addictologie
Responsable du Service Universitaire d’Addictologie – Pôle UP-MOPHA,
CH Le Vinatier, Bron

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté et de mes chers condisciples,
Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité
dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un
salaire au-dessus de mon travail.

Admis à l'intérieur des maisons, mes yeux ne verront pas ce qui s'y
passe, ma langue taira les secrets qui me seront confiés et mon état ne
servira pas à corrompre les mœurs ni favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs
enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes
promesses. Que je sois couvert d'Opprobre et Méprise de mes
confrères si j'y manque.

SERMENT D'HIPPOCRATE

(Conseil National de l'Ordre des Médecins)

Au moment d'être admis(e) à exercer la médecine, je promets et je jure
d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la
santé dans tous ses éléments, physiques et mentaux, individuels et
sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans
aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou
menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je
ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de
leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir
hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je
ne me laisserai pas influencer par la soif du gain ou la recherche de la
gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront
confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des
foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas
abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma
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entretiendrai et les perfectionnerai pour assurer au mieux les services qui
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Que les hommes et mes confrères m'accordent leur estime si je suis fidèle
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LIST OF ABBREVIATIONS

ATC: Anatomical Therapeutic Chemical

CMU-c: Couverture Maladie Universelle complémentaire

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HDB: High Dosage Buprenorphine

HIV: Human Immunodeficiency Virus

ICD-10: International Statistical Classification of Diseases, 10th Revision

LTD: Long-Term Disease

mg: milligram

MS: Morphine Sulfate

MTD: Methadone

PMSI: Programme de Médicalisation des Systèmes d'Information

OST: Opioid Substitution Treatment

SAMU: Service d'Aide Médicale Urgente

SNIIRAM: Système National d'Information Inter-Régimes de l'Assurance Maladie

SROM: Slow-Release Oral Morphine

1. Introduction

The off-label use of opioids in a context of addictive behavior is a major topical issue since 2015 in the international media, due to the massive increase of overdoses and deaths related. This phenomenon is particularly prevalent in North America, where health and government agencies now speak of ‘opioid crisis’ and ‘opioid epidemic’, and where this situation has just been decreed as ‘national health emergency’ [1,2]. Although in the United States (US) this crisis began with oxycodone, recent publications show that this preoccupying phenomenon tends to become worldwide, but carried by other opioids than oxycodone, such as morphine sulfate [3–5].

Morphine sulfate (MS) is available in France in rapid and slow-release oral forms. This treatment is indicated for severe acute or resistant chronic pain, especially cancer pain, and is marketed under the name of Skenan[®], Actiskenan[®], Moscontin[®], Sevredol[®] and Oramorph[®]. In some European countries, as Austria, Luxembourg, Slovenia, Bulgaria and Switzerland, a slow-release oral morphine (SROM) formulation got an indication for the treatment of opioid dependence.

In France, it can be sometimes used and prescribed as an opioid maintenance treatment for non-painful opioid dependent patients after failure or adverse effects onset with conventional treatment, such as methadone (MTD) or high dosage buprenorphine (HDB). In this case, the prescriber should first obtain the agreement of the medical adviser of the French health insurance system to provide treatment reimbursement.

Different agencies are in charge of the monitoring of drug abuse and dependence related to psychoactive medications [6]. Between 2003 and 2006, they show an increase of MS abuse from 3.2% to 9% among users attending harm reduction centres, while the use as opioid substitution treatment (OST) remains stable during this period [7]. This highlighting led to a greater vigilance of the health insurance funds and a reluctance of physicians to prescribe the MS, despite the users solicitations [8].

This limited availability has limited the MS misuse until 2011, when a shortage of heroin led to a reduction in the quality/price ratio and a report to the MS whose quality is constant [9]. Another hypothesis might be the search for another type of substitution in patients dissatisfied with buprenorphine or methadone. Indeed, morphine sulfate is considered by drug users as injectable, contrary to methadone, and causing a flash effect, unlike buprenorphine, which some patients cannot give up despite the maintenance treatment [10].

To date, no data are available in France for morphine recreative or maintenance use and shopping behavior. However, misusing of morphine sulfate remains a current public health problem in France. Indeed, first data of the first French supervised drug-injection facility in Paris shows that 47.6% of patients come to inject MS oral forms (Skenan[®]) [11].

Some studies were interested in slow-release oral forms of MS as OST, with heterogeneous results. Few of these studies were randomized, double blinded and controlled. In all studies that investigated morphine sulfate as opioid maintenance therapy, administration was orally. Though the retention rates were good with SROM maintenance, similar rates were obtained with methadone. Studies concluding to an improvement in quality of life, withdrawal symptoms, craving, and additional drug consumption with SROM than methadone. Two meta-analyses have not identified sufficient elements in the literature to assess the use of morphine sulfate as OST, due to the absence of sufficient quality studies [12,13]. No data were showed about risk associated to SROM, especially in case of a non-conventional way of administration. On the other hand, it appears that in France in most cases of off-label use in non-painful dependent-patients, MS is administered intravenously. According to the results of various surveys, 71 to 93% of off-label MS users inject it, including patients using it as OST [8,14]. According to a drug users survey, the effect of intravenous injections would be shorter than heroin leading to an increase of intakes and the risk of complications such as overdoses but also viral and bacterial infections, and thrombosis [15]. The occurrence of these complications is known to be reduced by initiation of opioid substitution treatment. However, when these complications are found, they occur preferentially in the months following initiation or the end of the substitutive treatment [16]. There is no data for morphine sulfate use on this point.

In France, the question of the oral morphine sulfate safety as an effective and secure opioid maintenance treatment and the risks related to its intravenous misuse remains unanswered. The main objective of this study was to compare the one-year incidence of unintentional opioid-related overdose hospitalisations in a non-painful opioid dependent population following the initiation of continuous use of morphine sulfate, compared to HDB and MTD maintained patients. Secondary objectives were to compare, between these 3 different opioid maintained groups, the one-year incidence of mortality, occurring diagnosis of Hepatitis C Virus (HCV), bacterial infections-related hospitalisations and thrombosis-related hospitalisations.

2. Methods

2.1. Study plan

This was a population-based retrospective cohort study of patients with morphine sulfate off-label use from 2012 to 2015 using exhaustive data from the French health insurance database.

2.2. Data source

Data were extracted from the French Health Insurance Information System (SNIIRAM). This database, widely used for public health and pharmaco-epidemiological purposes for many years, comprehensively covers the entire French population and contains exhaustive anonymous individual information on administrative, medical, and pharmacy data. An anonymous, unique patient identifier links SNIIRAM information to national hospital discharge database (Programme de Médicalisation des Systèmes d'Information [PMSI]), providing discharge diagnoses (using International Statistical Classification of Diseases, 10th Revision [ICD-10]).

Administrative data include individual anonymous information on the year of birth, long-term diseases, date of death and affiliation to free supplementary health insurance coverage (Couverture Maladie Universelle Complémentaire [CMU-c]). The attribution of the CMU-c is only based on the income, independently of the health status. Indeed, CMU-c is attributed to unemployed and low-income insured and can be consequently used as a proxy for low-income status. In the French healthcare system, 30 major chronic diseases have been designated as long-term diseases (LTD, Appendix – Table 1), i.e. chronic diseases such as diabetes mellitus, cancer or cardiovascular diseases. The information recorded includes the chronic disease code and the associated International Classification of Disease (ICD)-10 codes. These chronic conditions represent proxies for comorbidity assessment.

Pharmacy data comprise anonymous pharmacy identifier, exhaustive claims for all reimbursed drugs dispensed in retail pharmacies (including dates of prescription and dispensation and supplied quantities). Medications are identified by their Anatomical Therapeutic Chemical (ATC) class codes.

Medical data comprise anonymous doctor identifiers, ambulatory medicine consultation dates. Data on hospital admissions are also recorded during the patient's stay, principal and associated diagnoses are available and coded according to the ICD-10. The SNIIRAM database also

includes registration of the date of death, captured automatically from the National Institute for Statistics and Economic Studies and independently of use or not of healthcare resources.

Approval was obtained from IDS (Institut des Données de Santé - Health Data Institute) and the French data protection agency (Commission Nationale de l'Informatique et des Libertés - National Commission on Information Technology and Liberties).

2.3. Study data

Demographic information such as the year of birth, gender, date of death and low-income status were collected from this database.

2.3.1. Selection of exposure

All patients 15 years or older benefiting from oral morphine sulfate were identified by strong opioids ATC codes, 'N02AA01' and 'N02AA51', crossed with the galenic form used, namely 'capsule' for Skenan[®] and Actiskenan[®], 'tablet' for Moscontin[®] and Sevredol[®], 'Solution' for Oramorph[®].

All patients 15 years or older treated with HDB or MTD were identified by their ATC codes 'N07BC01' and 'N07BC02' respectively. Dates of each dispensation were collected to determine their regularity.

2.3.2. Selection of chronic pain patients

Patients suffering from cancer were identified either by a specific long-term disease code ('LTD-30') or on the basis of hospital discharge reports including 'C' codes (ICD-10 category: malignant neoplasms) and 'D0' codes (ICD-10 category: in situ tumours). Patients benefiting from palliative care ('Z515' ICD-10 code), and all patients identified by a specific ICD-10 code for chronic pain ('R521 and R522'), or for a rheumatologic condition for which morphine sulfate is recommended in France [17] ('M16, M17, M47, M50, M51, M431, M992, M993, M994, M995' ICD-10 codes), were considered as likely to receive morphine sulfate to treat their painful chronic condition.

Patients followed in pain clinics (Medical Unit: '61') and those who received a continuous prescription for 3 months of analgesic other than morphine sulfate were also considered as chronic pain patients.

2.3.3. Selection of opiate-dependent patients

Opiate-dependent patients were defined, 1 – either as having at least one dispensation of conventional opioid substitution treatment (HDB or MTD), or 2 – on the basis of hospital discharge reports or chronic condition with the 'F11' ICD-10 code (i.e. opioid-related disorder), or 3 – by the combination of a morphine sulfate dosage ≥ 550 mg/day and an age ≤ 37 years, according to published data from a previous French study. These thresholds were chosen because they correspond to the median daily dose of morphine sulfate and median age for patient abusing morphine sulfate or taking it as an OST [18].

2.3.4. Selection of infectious complications of injection drug use

Human immunodeficiency virus (HIV) ('B20, B21, B22, B23, B24, R75, Z21' ICD-10 codes), hepatitis B virus (HBV) ('B16, B180 and B181' ICD-10 codes) and hepatitis C virus (HCV) ('B182' and 'B171' ICD-10 codes) were identified through hospital discharge diagnoses or long-term diseases.

Similarly, the most specific and frequent infectious complications associated with injections in drug addicts, were selected according to literature data [19–21] and identified through hospital discharge diagnoses including cutaneous abscesses ('L02, L08, M65'), phlegmon and cellulitis ('L03'), nasal septum abscess ('J340'), infective endocarditis ('I330'), candidiasis (meningitis: 'B375', endocarditis: 'B376', and sepsis: 'B377'), other sepsis ('A41'), spondylodiskitis ('M463'), intracranial and intraspinal abscesses ('G06') and endophthalmitis ('H440').

2.3.5. Selection of thrombotic complications of injection drug use

The most specific and frequent thrombotic complications associated with injections in drug addicts were selected according to literature data [22–24] and identified through hospital discharge diagnoses. These codes concerned venous thrombotic complications, including phlebitis and thrombophlebitis ('I80'), post-thrombotic syndrome ('I870'), embolism and venous thrombosis (specified: 'I828', or not: 'I829') and venous disease (specified: 'I878', or not: 'I879'). Regarding arterial thrombotic complications, targeted codes were embolism and arterial thrombosis of the upper ('I742') and lower ('I743') limbs, of distal arteries ('I744'), and embolism and arterial thrombosis (specified: 'I748', or not: 'I749').

2.3.6. Selection of overdoses-related hospitalisations, psychiatric illness, alcohol dependence and co-prescription of benzodiazepines

In the same way, ICD-10 codes corresponding to unintentional opioid intoxication ('X42, T400, T401, T402, T403, T404, T406'), and long-term diseases for psychiatric conditions ('LTD-23') were extracted.

Alcohol-dependent patients were identified through either hospital discharge diagnoses and long-term diseases including the 'F10' ICD-10 code (alcohol-related disorders), or the dispensations of drugs specifically used in alcohol dependence: Disulfiram ('N07BB01'), Acamprosate ('N07BB03'), Naltrexone ('N07BB04') and Nalmefene ('N07BB05'). Dates of benzodiazepine (BZD) dispensations ('N05BA' ATC code) were collected in order to identify the potential concomitant prescription of 2 respiratory depressants.

2.4. Participants

All patients, male or female, aged 15 years and older, with at least one dispensation of the drug of interest between April 01, 2012, and December 31, 2014, with no dispensation in the 3 preceding months, were included. Each patient was followed until December 31, 2015, allowing at least 1 year of follow-up.

The index date was the date of the first dispensation of a continuous sequence of at least 90 days of treatment. A continuous sequence of treatment was defined as an interval between 2 consecutive dispensations inferior to 35 days. This threshold of 35 days was based on the fact that in France those drugs were prescribed and dispensed for a maximum of 28 days. Accordingly, drugs prescribed for 3 months will be dispensed in 3 distinct times. To be more specific, and not to detect wrongly a prescription discontinuation, 7 days were added to the maximum duration of prescriptions. The end date of this continuous period corresponds to the date of inclusion in the study, and is named D90.

A patient who meets this criterion of continuous dispensation for at least 3 months, with an interval of less than 35 days between 2 dispensations is considered to be 'regular'.

2.4.1. First cohort: non-chronic pain and opioid-dependent patients with regular morphine sulfate dispensations

This first cohort is constituted by all patients starting a continuous sequence of morphine sulfate between April 01, 2012, and December 31, 2014. Patients treated with morphine sulfate in the 3 months before the index date were excluded, in order to select incident morphine sulfate users.

All patients suffering from cancer or benefiting from palliative care were excluded over the whole period.

Then, patients suffering from chronic pain before D90, identified according to the selection procedure explained above, were excluded.

In order to recruit only opioid-dependent patients, we only keep those for whom we have a notion of opiate dependence, according to the procedure of selection detailed above.

2.4.2. Cohort 2: non-chronic pain and opioid-maintained patients with regular high dosage buprenorphine dispensations

The second cohort is constituted by all patients starting a continuous prescription of buprenorphine between April 01, 2012, and December 31, 2014. Patients treated with HDB in the 3 months before the index date were excluded, in order to select incident buprenorphine users.

As previously, patients suffering from cancer or benefiting from palliative care were excluded over the whole period, while chronic-pain patients were excluded before D90.

Patients with morphine sulfate dispensation within 3 months before the index date were also excluded.

2.4.3. Cohort 3: non-chronic pain and opioid-maintained patients with regular methadone dispensations

The third cohort is constituted like the second, but with patients starting a continuous prescription of methadone instead of buprenorphine.

2.5. Doctor Shopping

Doctor shopping is defined as seeking multiple physicians to obtain multiple prescriptions for the same drug in a short period of time, and is usually associated with a high level of misusing [25–28]. Pharmacy shopping and overlapping prescriptions are also associated with this high level of abuse and diversion [29,30]. Many definitions are available with different thresholds for the numbers of prescribers and/or pharmacies. The threshold of at least 1 day of overlap, by at least 2 different prescribers and filled in at least 3 different pharmacies was chosen because it has been used in previous research published mainly to assess analgesic opioids doctor shopping behavior [31,32].

2.1. Outcomes measurement

The primary outcome was the incidence of unintentional opioid overdose related hospitalisations in a non-painful opioid dependent population initiating a regular off-label use of morphine sulfate compared to HDB and MTD substituted patients, 12 months after the date of inclusion. Secondary outcomes were to assess the incidence of mortality, doctor shopping, and complications underlying by injection practice (HCV seroconversion, bacterial infections and thrombosis complications) a year after D90, compared to opioid maintained patients.

2.2. Statistical analysis

Data were expressed as frequencies and associated percentages for categorical data and as mean \pm standard deviation or as median and interquartile range for quantitative variables.

Date of the first dispensation of the considered substance was considered as the starting date. The date of unintentional opioid intoxication, or of the last information (i.e. end of treatment or of follow-up, or beginning a continuous OST for MS patients, or MS for OST patients, concomitantly or not) as the ending (or censoring) date to survival analyzes. Analysis of secondary outcomes used the same method, but the event considered was death, doctor shopping, HCV seroconversion, infectious or thrombotic complications and the ending date is defined by the end of the follow-up (December 31, 2015) or the date of death or of last information.

Crude mortality incidence with 95% confidence intervals were calculated for one year and for 100 000 persons.

Cox regression (conditional backward selection) was used to examine the association between MS exposure and OST for primary and secondary outcomes (opioid intoxication, mortality, doctor shopping, HCV seroconversion, bacterial infections and thrombotic complications). In order to reduce the risk of bias, an adjustment was made on certain variables: age, gender, socioeconomic status, chronic alcohol consumption, concomitant use of benzodiazepines, major chronic somatic and psychiatric comorbid disease (i.e. the 30 long-term diseases).

Each variable was tested in univariate association with the 2 conventional OST (p-value cut-off point of 0.20) and then, entered into a multifactorial model. The least significant variable was then removed step by step from the model, retaining only those with significant interaction (level of significance considered: $p < 0.05$) in the final multifactorial Cox model. Corresponding hazard ratios (HR) were shown with their 95% confidence intervals.

Survival curves of annual incidence rates of main and secondary objectives were estimated using the Kaplan – Meier method, adjusted on variables retained in the final multifactorial Cox model.

All statistical analyses were performed using SAS for Windows version 9.3 (SAS Institute, North Carolina, USA) and STATA for Windows version 14.1 (StataCorp, Texas, USA).

3. Results

1075 eligible non-painful opioid dependent patients were included in the continuous morphine sulfate cohort (Appendix – Figure 1A). During the same period, 20 834 HDB maintained patients and 9778 MTD maintained patients were included in the second and third cohorts, respectively (Appendix – Figure 1B).

3.1. Characterization of study populations (Appendix – Table 2)

3.1.1. First cohort: non-chronic pain and opioid-dependent patients with regular morphine sulfate dispensations

Among these patients (N=1075), the mean age was 34.7 ± 8.7 years, for a median of 33 years [28–41], with 76.6% of men and 44.3% of low-income status. The prevalence of HIV was 2.0%, 0.8% for HBV and 13.9% for HCV. Regarding psychiatric disorders, prevalence was 20.2% in this population, and 19.0% had a history of alcohol dependence. 22.1% of patients in this cohort received concomitant benzodiazepines prescriptions during the follow-up period. The prevalence of doctor shopping after one year of follow-up was 27.0%.

The median length of continuous treatment duration was 234.0 [142.0–436.0] days. The median daily dose of MS delivered was 553.0 mg [250.1–881.0].

Two trademarks were essentially concerned: Skenan[®] ranks first, with 97.6% (N=1049/1075) of patients, followed by Actiskenan[®] (22.1%–N=238/1075) and Moscontin[®] (2.6%–N=28/1075). For Skenan[®], most frequent dosage per tablet was 100 mg (72.7%), followed by 200 mg (59.2%), 60 mg (50.6%), 30 mg (48.8%) and 10 mg (42.6%). For Actiskenan[®], dosage per tablet was mainly 10 mg (68.5%), followed by 20 mg (47.1%), 30 mg (34.4%) and 5 mg (25.6%).

3.1.2. Cohort 2: non-chronic pain and opioid-maintained patients with regular high dosage buprenorphine dispensations

Among those patients treated by regular HDB (N=20 834), the mean age was 34.5 ± 9.1 years, for a median of 33 years [27–41]. The population was made up of three-quarters of men (79.0%), and 26.7% had a low-income status. The prevalence of HIV was 0.5%, HBV 0.2% and HCV 3.8%. Regarding psychiatric disorders, prevalence was 9.5% in this population, and 10.6% had a history of alcohol dependence. 28.6% of patients in this cohort received concomitant benzodiazepines and opioids, during the follow-up period. The prevalence of doctor shopping after one year of follow-up was 9.9%.

The median length of continuous treatment duration was 259.0 [148.0–503.0] days. The median daily dose of HDB delivered was 9.5 mg [5.4-16.6].

During the follow-up period, 82.8% of patients benefited from at least once the original drug (i.e. Subutex®), 62.3% buprenorphine generic and 13.4% Suboxone® (buprenorphine + naloxone). More precisely, over the entire follow-up period, 32.0% of patients benefited exclusively from Subutex®, 17.3% for buprenorphine generic and 2.6% for Suboxone®, whereas 48.1% of patients benefited from prescriptions of these 3 buprenorphine formulations.

3.1.3. Cohort 3: non-chronic pain and opioid-maintained patients with regular methadone dispensations

Among those patients treated by regular MTD (N=9778), the mean age was 33.5 ± 8.2 years, for a median of 32 years [27–39]. 71.8% were men and 24.2% had a low-income status. The prevalence of HIV was 0.7%, 0.3% for HBV and 5.4% for HCV. Regarding psychiatric disorders, prevalence was 10.4% in this population, and 8.2% had a history of alcohol dependence. 27.6% of patients in this cohort received concomitant benzodiazepines and opioids, during the follow-up period. The prevalence of doctor shopping after one year of follow-up was 0.5%.

The median length of continuous treatment duration was 451.5 [233.0–787.0] days. The median daily dose of MTD delivered was 46.7 mg [30.2-68.2].

During the follow-up period, 75.5% of patients benefited from at least once syrup formulation, and 70.2% from capsule formulation. More precisely, over the entire follow-up period, 29.8% of patients benefited exclusively from syrup formulation, 24.5% for capsule formulation and 45.7% of patients received alternatively both formulations.

3.1.4. Two-to-two comparisons

A two-to-two comparisons of the patient's characteristics between the different cohorts showed significant differences between the following criteria: low-income status, psychiatric comorbidities, alcohol dependence, prevalence of infectious viral disease and benzodiazepine co-prescription).

No significant difference was observed for age and sex criteria between MS and HDB patients (i.e. cohorts 1 and 2).

3.2. Unintentional opioid overdose-related hospitalisations (Appendix – Fig. 2A)

One-year crude opioid overdose incidence in MS cohort was 4.3 for 100 000 patient-year (/100 000 p-y) [95% CI: 2.5-7.2]). Regarding HDB maintained patients, incidence was 0.8/100 000 p-y [95% CI: 0.7-1.1], and 1.4/100 000 p-y [95% CI: 1.1-1.9] for MTD patients.

Adjusted (for alcohol dependence and ‘LTD-17’) and compared to buprenorphine patients, Hazard Ratio (HR) of non-painful opioid-dependent regular use morphine sulfate patients was 3.6 ($p<0.01$; [95% CI: 2.0-6.4]), and 1.9 ($p<0.01$; [95% CI: 1.3-2.7]) for MTD cohort.

Adjusted and compared to methadone patients, Hazard Ratio of non-painful opioid-dependent regular use morphine sulfate patients was 1.9 ($p=0.03$; [95% CI: 1.1-3.4]), and 0.5 ($p<0.01$; [95% CI: 0.4-0.8]) for BHD cohort.

3.3. Mortality (Appendix – Fig. 2B)

One-year crude mortality incidence in 1st cohort was 0.6/100 000 p-y [95% CI: 0.2–2.4]. Regarding HDB maintained patients, incidence was 0.01/100 000 p-y [95% CI: 0.002-0.1], and 0.05/100 000 p-y [95% CI: 0.01-0.2] for MTD patients.

Adjusted (for ‘LTD-10’) and compared to HDB cohort, Hazard Ratio of non-painful opioid dependent morphine regular use patients was 45.6 ($p<0.01$, [95% CI: 4.1-509.2]), and 2.0 ($p=0.6$; [95% CI: 0.2-26.9]) for MTD cohort.

Adjusted and compared to MTD cohort, HR of non-painful opioid dependent morphine regular use patients was 22.6 ($p<0.01$, [95% CI: 2.3-224.4]), and 0.5 ($p=0.6$; [95% CI: 0.04-6.6]) for BHD cohort.

3.4. Doctor Shopping (Appendix – Fig. 2C)

One-year crude Doctor Shopping incidence in MS cohort was 107.7/100 000 p-y [95% CI: 96.0-120.9]. Regarding HDB maintained patients, incidence was 29.8/100 000 p-y [95% CI: 29.8-32.5], and 1.2/100 000 p-y [95% CI: 0.9-1.6] for MTD patients.

Adjusted (for age, gender, low-income status, concomitant dispensation of benzodiazepines and opioids and ‘LTD-3 -7 -9 -14 -29’) and, Hazard Ratio of non-painful opioid dependent morphine regular use patients was 3.0 ($p<0.01$, [95% CI: 2.6-3.4]) compared to HDB patients and 68.3 ($p<0.01$, [95% CI: 49.7-93.9]) compared to MTD patients.

3.5. Complications underlying by MS intravenous injections

3.5.1. Infectious diseases

3.5.1.1. Hepatitis C Virus diagnosis (Appendix – Fig. 2D)

One-year HCV seroconversion incidence in MS cohort was 5.5/100 000 p-y [95% CI: 3.4-8.7]). Regarding HDB maintained patients, incidence was 2.5/100 000 p-y [95% CI: 2.1-2.9], and 3.1/100 000 p-y [95% CI: 2.6-3.7] for MTD patients.

Adjusted (for age, gender, alcohol dependence, low-income status, concomitant dispensation of benzodiazepines and opioids and ‘LTD-6’) and compared to buprenorphine patients, MS cohort had a Hazard Ratio = 1.7 (p=0.03; [95% CI: 1.1-2.7]), and 1.5 (p<0.01; [95% CI: 1.2-1.9]) for MTD cohort.

Adjusted and compared to MTD cohort, MS cohort had a HR = 1.2 (p=0.5; [95% CI: 0.7-1.9]), and 0.7 (p<0.01; [95% CI: 0.5-0.9]) for BHD cohort.

3.5.1.2. Bacterial infectious complications (Appendix – Fig. 2E)

One-year bacterial infectious-related hospitalisation incidence in MS cohort was 7.0/100 000 p-y [95% CI: 4.7-10.5]). Regarding HDB maintained patients, incidence was 2.2/100 000 p-y [95% CI: 1.8-2.5], and 1.6/100 000 p-y [95% CI: 1.2-2.0] for MTD patients.

Adjusted (for age, alcohol dependence, concomitant dispensation of benzodiazepines and opioids and ‘LTD-5 -6’) and compared to buprenorphine patients, MS cohort had a HR = 2.8 (p<0.01; [95% CI: 1.8-4.3]), and 0.8 (p=0.1; [95% CI: 0.6-1.1]) for MTD cohort.

Adjusted and compared to MTD cohort, MS cohort had a HR = 3.5 (p <0.01; [95% CI: 2.2-5.7]), and 1.3 (p=0.1; [95% CI: 0.9-1.7]) for HDB cohort.

3.5.2. Thrombotic complications (Appendix – Fig. 2F)

One-year thrombotic-related hospitalisations incidence in MS cohort was 13.2/100 000 p-y [95% CI: 9.8-17.9]). Regarding HDB maintained patients, incidence was 8.1/100 000 p-y [95% CI: 7.5-8.8], and 8.4/100 000 p-y [95% CI: 7.5-9.3] for MTD patients.

Adjusted (for alcohol dependence, concomitant dispensation of benzodiazepines and opioids and ‘LTD -9 -11 -23’) and compared to buprenorphine patients, 1st cohort had a Hazard Ratio = 1.3 (p=0.07; [95% CI: 1.0-1.8]), and 1.1 (p=0.4; [95% CI: 0.9-1.2]) for MTD cohort.

Adjusted and compared to MTD cohort, MS cohort had a HR = 1.3 (p=0.17; [95% CI: 0.9-1.7]), and 0.9 (p=0.4; [95% CI: 0.8-1.1]) for HDB cohort.

4. Discussion

To our knowledge, few studies had focused on this specific non-painful population who present a regular off-label use of morphine sulfate in a context of opioid dependence as an alternative to conventional opioid maintenance treatments. The size of this specific population, their socio-demographic characteristics and associated risks were only roughly estimated by French public health authorities, without accurate, comprehensive and reliable data.

4.1. Algorithm validity

To test the validity of our recruitment algorithm, we compared the socio-demographic characteristics of our different cohorts with those published in the literature, especially two previous French studies [14,18] which studied data compilation from the cross-referencing of different sources. In our study, socio-demographic characteristics of opioid-dependent regular MS users were close in ages, sex ratio, and daily dose to those found in Peyriere et al. studies [14,18]. These similar results confirm that our restrictive selection criteria made it possible to select the specific population of non-painful opioid-dependent MS users. Concerning socio-demographic characteristics found for patients treated by OST in cohorts 2 and 3, our results on ages and sex ratio agreed with those obtained in recent French pharmacoepidemiological study [33]. Ages and sex ratio found in the 3 opioid-dependent cohorts, whatever the treatment, are quite comparable.

The one-year incidence of shopping behavior in our OST cohorts are comparable to those published for HDB and MTD in a recent French study [34].

The high cumulative dosages found in MS cohort are comparable to the high dosages found in previous epidemiological studies evaluating MS as maintenance therapy versus methadone.

4.2. Unintentional opioid overdoses related hospitalisations incidence

Epidemiological data show a significant increase in the number of visits related to non-medical use of prescribed opioids in the United States emergency department in recent years, with a worldwide extension of the phenomenon. While the US record a tripling of mortality due to overdoses between 1990 and 2006, with major involvement of oxycodone abuse, in Austria deaths by overdose now exceed the number of road deaths since 2011 [35–37]. Recent data show a similar emergence of this opioid abuse in the United Kingdom [38].

This study is the first French nationally exhaustive population-based study that focuses on the incidence of overdoses in these non-painful opioid dependent off-label morphine sulfate use population. Our results show a significantly higher incidence of opioid overdoses requiring

hospitalization for these MS users. Hazard ratio shown that a non-painful MS regular user had an increased risk of 3.6 having an overdose in the year following the start of its consumption versus HDB patients, and 1.9 versus MTD. These results encourage continuing efforts recently made by distribution of opioid overdoses rescue kits containing Naloxone in the population of opioid-dependent patients [39].

The higher incidence of overdoses can be partly explained by the high prevalence of intravenous administration of MS and the high prevalence of benzodiazepine co-prescription use and alcohol use disorders. This association and its risks are well established in the literature [40,41]. Our results regarding this concomitant prescription of benzodiazepine are lower than US data, but consistent with European data [42]. The lower prevalence of benzodiazepine prescriptions in morphine sulfate cohorts versus HDB and MTD cohorts could be explained by the anxiolytic property of MS compared to OST especially HDB. This psychotropic effect of MS is attested by the score improvement of mood and anxiety, sleep quality, and general well-being scale in studies evaluating MS as OST [43–48].

4.3. Mortality

This study also displayed a significantly higher incidence of mortality in MS patients compared to opioids maintained patients (buprenorphine or methadone). The use of MS is therefore linked to an increased risk of death compared to these usual treatments, without any difference concerning mortality incidence between OST cohorts. These deaths frequently occur after unintentional intoxication, and frequently need appropriate urgent care with naloxone administration. It is now recognized that opioid maintenance therapy reduces the high mortality, 6 to 30 times higher than the general population of age and gender matched, particularly deaths linked to intoxication [49,50]. The low mortality rate found in the 2 cohorts of maintained patients compared to MS cohort reinforces the need to offer a suitable maintenance therapy for these patients to reduce the risk of death.

4.4. Doctor Shopping

The evaluation of the shopping behavior and its evolution makes it possible to reflect the misuse that is made of a substance. From 1999 to 2007, the United States recorded a parallel increase in the schedule II opioid prescription (approximately 150–280%) and opioid shopping behaviors (approximately 111–213%) [51]. Among drug-related deaths for controlled substances, 25.2% were doctor shoppers and 17.5% were pharmacy shoppers [27].

The results of our study highlight an increased shopping behavior incidence for morphine sulfate cohort compared to OST cohorts. Previous study found a one-year prevalence of shopping behavior of 8.4% for buprenorphine and 0% for methadone in France [34].

It is known that patients treated by methadone have low doctor shopping scores, whereas those treated by buprenorphine show an increased shopping behavior [34], due to a different permissiveness prescription framework with higher accessibility and a potential easy misuse by snorting or injecting buprenorphine versus methadone.

The significant shopping behavior incidence found in morphine sulfate cohort reflects a potential frequent abuse behavior and the need to obtain ever-increasing doses. This need for increasing doses raise the risk of unintentional intoxication. The high shopping scores obtained in our study should draw the prescribers and pharmacists attention to the misuse that is made of continuous morphine sulfate use in an opioid dependence context, and the associated risk of overdoses.

4.5. Intravenous administration related complications

The cohort of morphine sulfate users is more affected by viral infections compared to HDB and MTD patients. It is actually well established that injecting drug users are more infected by HIV, HBV and HCV than non-injecting drug users, with a greater prevalence for HCV. Opioid maintenance treatment is a reducing factor of this contamination risk by decreasing intravenous drug use [52–55]. However, it is also well established that, in France, morphine sulfate is mostly injected (71% to 80%), both in cases of abuse or OST [14,18], in a similar way to HDB maintained patients (20% to 46%) [56–61], while methadone is not considered to be injectable. Although, recent data from harm reduction centres showed that 16.4% of integrated OST patients still had injections in the last month [62].

HCV prevalence in MTD cohort is slightly higher than in HDB cohort whereas the seroconversion incidence observed during the follow-up is lower.

These findings in the methadone cohort could be correlated to a reduction in injection practice. In France, MTD is particularly prescribed in harm risk reduction objective more than abstinence one, and for the most socially disinserted users, especially when they were injectors. We can hypothesize that this higher prevalence of HCV in MTD patients is the result of past risk behavior, prior to the substitution, while the higher HCV incidence in HDB patients would result from unsafe practices (snorting and injection) that persist despite the opioid maintenance therapy.

The risk of reporting bacterial infections event after the onset of a regular consumption is significantly higher for MS users than OST cohorts. Our results do not show any difference when comparing BHD and MTD to each other.

Our results do not show any difference between the 3 cohorts of substituted patients for the occurrence of thrombotic comorbidities.

These results suggest that efforts to inform and prevent infection risk need to be strengthened, particularly among this population of morphine sulfate users. In view of harm reduction and because of the very high proportion of MS injectors, a free and wider availability of sterile injection equipment would be appropriate. In addition, routine screening for viral infectious diseases (HIV, HCV, HBV) should be performed at initiation of treatment and then periodically during the follow-up.

On the other hand, these results lead to a discussion in the interest of being able to propose an injectable opiate substitution treatment under medical supervision to this minority of patients not relieved by the conventional treatments and their route of administration.

These provisions would reduce healthcare costs associated with complications which patients are facing, as well as bringing some patients not relieved by conventional OST to specialized care.

4.6. Comorbid diseases and Socioeconomic status

The lower prevalence of benzodiazepine prescriptions in MS versus OST cohorts is confronted with a higher prevalence of patients suffering from mental health disorder and alcohol dependence. However, morphine sulfate could partly alleviate alcohol withdrawal syndrome and some psychiatric symptoms (like anxiety) [62].

Therefore, based on our findings on low-income status, opioid-dependent patients in morphine sulfate cohorts had a lower socioeconomic level than OST patients. It has been described for a long time that a low socioeconomic status is associated with a higher prevalence of some psychiatric disorder and alcohol dependence [63–66] while the comorbidities between these two disorders are also well described [67–69].

These results suggest that MS patients should be offered a global and multidisciplinary approach (medical, psychological and social), and should therefore be directed towards addiction centres and not to primary care facilities.

4.7. Product characteristics

Our results regarding the brand name and dosages of MS dispensed were consistent with those found in previous French studies with a strong predominance of high dosage Skenan[®] [14,18]. It can be explained by its capsular form, containing sustained-release pellets which can easily be crushed and dissolve to be injected with heroin-like effects. In comparison, Moscontin[®] is less misused, because this coated sustained-release formulation requires talcum powder, difficult to filter and impossible to dissolve for injectable homemade preparation.

Regarding Actiskenan[®], an immediate-release form of Morphine Sulfate, it appears to be used in almost 30% of regular MS users. This formulation is less known to be injected, as evidenced by users on internet harm reduction discussion forums. Indeed, Actiskenan[®] would be difficult to crush, which causes many deposits difficult to filter.

In several clinical studies, the morphine sulfate used was a 24h sustain-released form, as well as controlled delivery with oral administration, which limit risks of misuse [45,47,70–72]. In France, off-label use of morphine sulfate, especially prescribed in primary care, does not permit the control of prescription and dispensation in France.

A way to limit the intravenous misuse of morphine sulfate would be to modify its galenic and to develop abuse deterrent formulations, combining the active substance and its inactive oral antagonist, such as Embeda[®] (extend-release capsules of morphine sulfate associate to Naltrexone Hydrochloride) in order to limit the injection. These formulations are the subject of numerous recent studies particularly in the United States because of the rise of the oxycodone misuse [73–75]. However, although their effectiveness is now validated, alerts merge regarding the transfer of these abuse deterrent formulations towards other opioid treatments possible to misuse or to heroin use [76,77].

4.8. Limitations

One of the main limitations of our study is related to the utilization of health insurance database which implies to include only patients that benefiting from MS reimbursement. Indeed, several national surveys and previous study based on spontaneous addictovigilance notifications showed that 55 to 80% of morphine sulfate users sometimes bought in street markets [14,18,78] and do not appear in the health reimbursement database or irregularly. In the same way, patients benefiting from a MS dispensation in an addiction centres did not appear in the database.

Moreover, we have chosen to adopt very selective inclusion criteria in order to include only well-phenotyped patients. This choice implies to exclude the patients least integrated in care

networks, maybe the most at risk of complications. These most desocialized patients are probably not accessible to a database study but would require a field survey.

In addition, the health insurance reimbursement database includes only inpatient data. So, information on overdoses supported in emergency departments or by ‘SAMU’ (Emergency Medical Assistance Service) are not taken into account, which may underestimate our results.

Regarding mortality, the database does not yet contain the reason of the death. It is therefore not possible to know precisely whether death is directly related to the substance or the use that is made of it. The small number of events recorded during the follow-up may be explained by a small proportion of patients concerned by this problem and the relatively short follow-up period. This limit may affect the result of the Cox model for which it is recommended to have at least 10 events per variable. Nevertheless, this rule tends to be called into question [79] and the clear difference found between the MS cohort versus OST cohorts, whereas they are not significant between the 2 cohorts of substituted patients, incites to believe in their value.

Another limitation inherent to the use of databases is linked to missing data, due to lack of filling and although there has been a gradual improvement in recent years. Those missing data implies to delete some patients from the analyses.

All these limitations have the effect of underestimating the size of the morphine sulfate cohort for opioid dependence, and maybe the risks to which they are exposed.

5. Conclusion

This work is the first national pharmacoepidemiological study which provides exhaustive information on risk associated with off-label oral morphine sulfate use in France.

We highlighted that non-painful opioid dependent patients treated by morphine sulfate display a higher risk of overdose, death, shopping behavior and infections.

These new data provide new knowledge about this specific population and remind us that morphine sulfate should be a third-line treatment, only after failure or serious adverse effect with buprenorphine and methadone, and supervised by addiction centres. Off-label use of morphine sulfate, associated with an intravenous misuse and frequent psychiatric and other substance use (alcohol) disorders, should be a matter of specialized addiction centres and not of primary care physicians, in order to associate harm reduction (injection material) and a global management. Finally, searchers and authorities should consider prescribing an injectable form of morphine (chlorhydrate), associated with a take-home naloxone kit, which is already available in France. It would be more secure with regard to the main risks associated with intravenous misuse, i.e. overdoses and infections.

Monsieur le Doyen de la Faculté de Médecine,
Pierre CLAVELOU



Monsieur le Président du Jury,
Pierre-Michel LORCA

A black ink signature of Pierre-Michel LORCA, written in a stylized, cursive manner.

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Appendix

Table 1. List of Long-Term Disease

1	Cerebral vascular accidents
2	Marrow insufficiency and other chronic cytopenias
3	Chronic arteriopathies with ischemic manifestations
4	Complicated bilharziasis;
5	Severe heart failure, severe rhythm disorders, severe valvular heart disease; Congenital heart disease
6	Active Chronic Diseases of the Liver and Cirrhosis
7	Severe primary immune deficiency requiring prolonged treatment, infection with Human Immunodeficiency Virus
8	Type 1 and Type 2 Diabetes
9	Severe form of neurological and muscular disorders (including myopathy), severe epilepsy
10	Hemoglobinopathies, hemolysis, chronic constitutional and acquired severe
11	Hemophilia and constitutional affections of severe hemostasis
12	Severe hypertension
13	Coronary disease
14	Severe chronic respiratory insufficiency
15	Leprosy
16	Parkinson disease
17	Hereditary metabolic diseases requiring prolonged specialized treatment
18	Cystic fibrosis
19	Severe chronic nephropathy and primary nephrotic syndrome
20	Paraplegia
21	Periarteritis nodosa, acute disseminated lupus erythematosus, evolutive generalized scleroderma
22	Severe Rheumatoid arthritis
23	Psychosis, severe personality disorder, mental retardation
24	Evolutive Crohn's disease and haemorrhagic disease
25	Multiple Sclerosis
26	Scoliosis evolutionary until spinal maturation
27	Severe ankylosing spondylitis
28	Organ transplantation suites
29	Active Tuberculosis
30	Malignant tumor, malignant disease of lymphatic or haematopoietic tissue

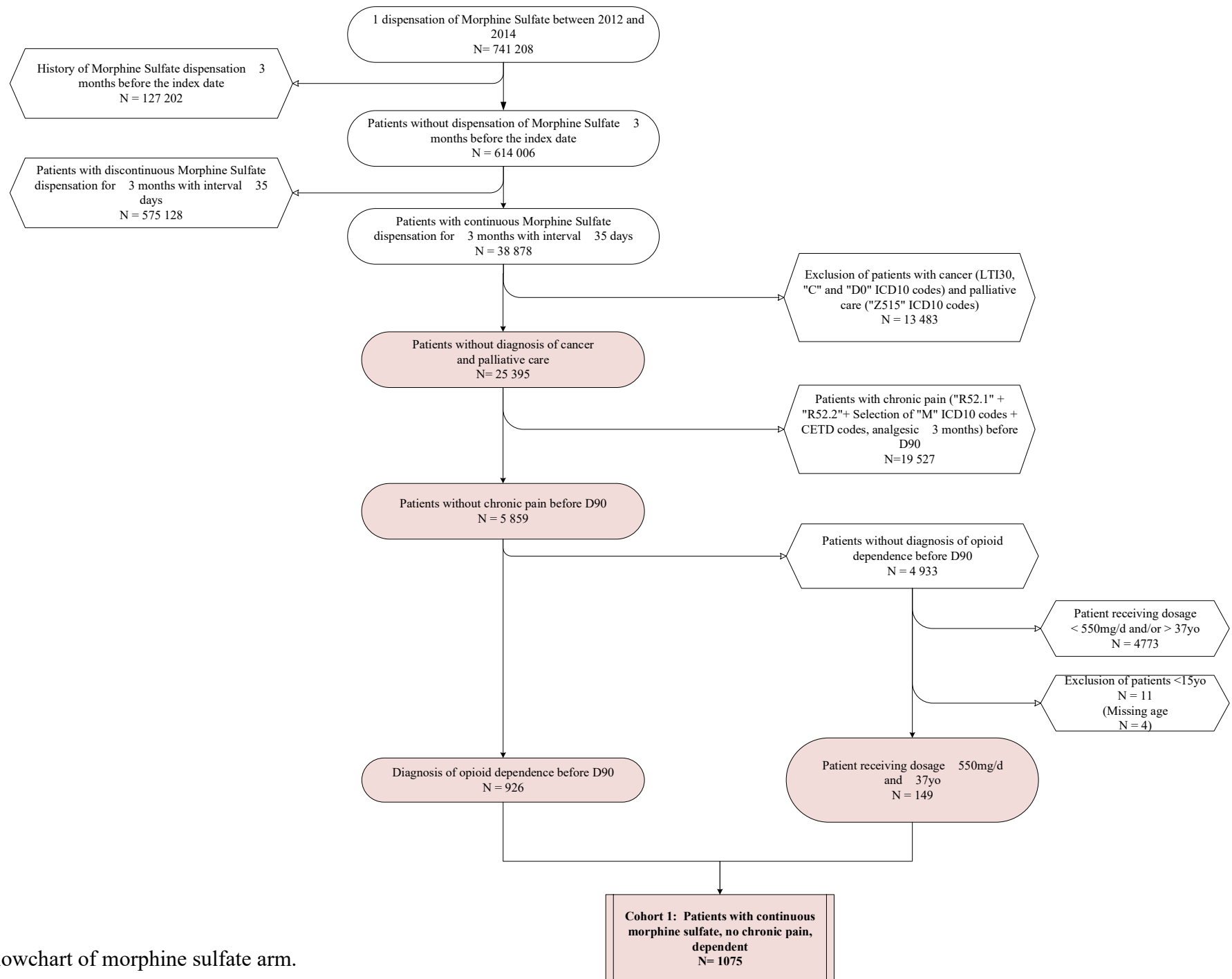


Fig. 1A: Flowchart of morphine sulfate arm.

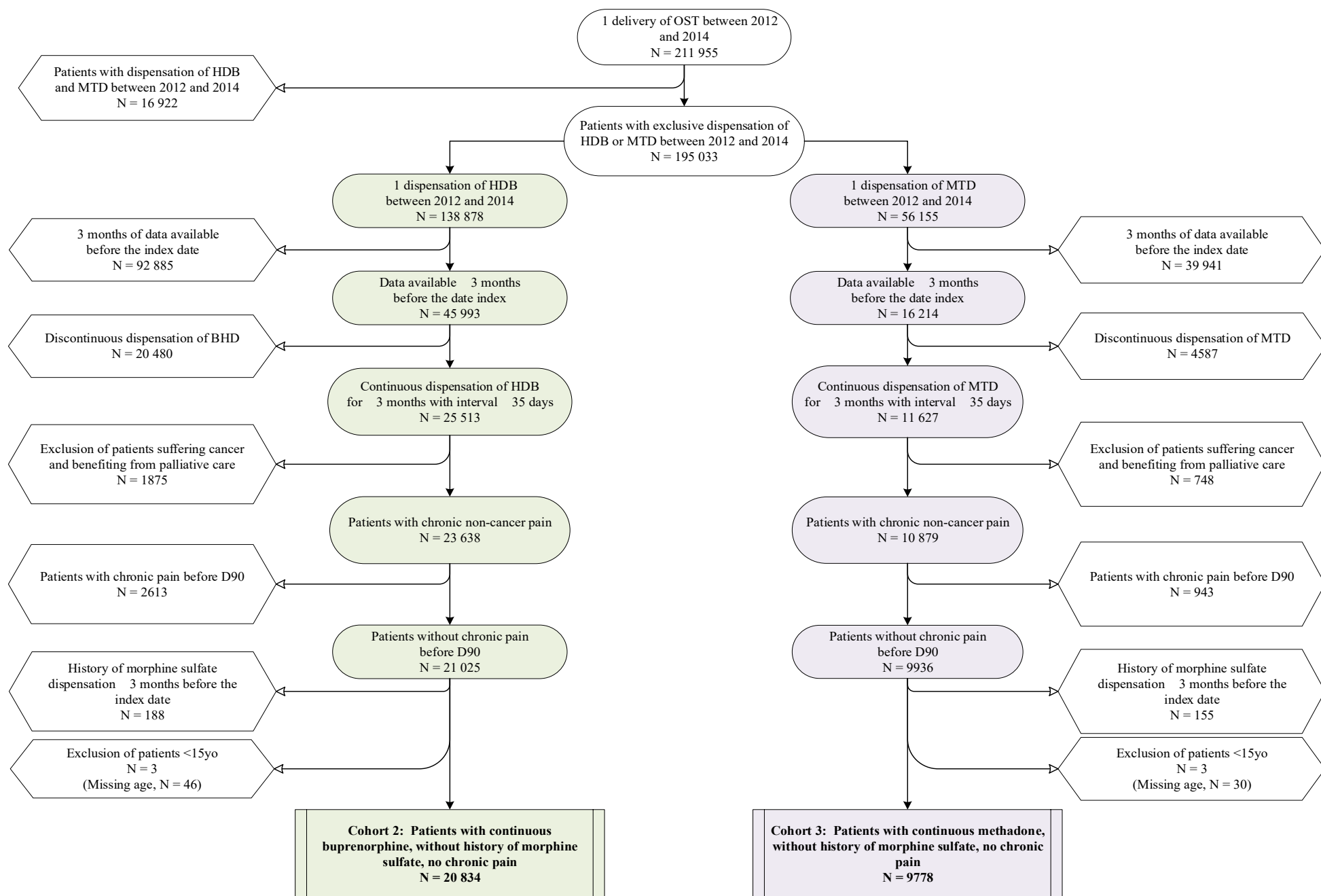


Fig. 1B: Flowchart of buprenorphine and methadone arms

Table 2. Characteristics of included Patients MS, and OST control cohort (HDB and MTD)

	<i>Cohort 1: Patients continuous morphine sulfate, non-chronic pain, dependent</i>	<i>Cohort 2: Patients continuous buprenorphine, without history of morphine sulfate, non-chronic pain</i>	<i>Cohort 3: Patients continuous methadone, without history of morphine sulfate, non-chronic pain</i>	<i>P-value</i>
	N= 1075	N= 20 834	N= 9778	
Age, year				
Mean \pm SD	34.7 \pm 8.7	34.5 \pm 9.1	33.5 \pm 8.2	<.0001
Median	33 [28-41]	33 [27-41]	32 [27-39]	
Gender, % (N)				
Male	76.6 (823)	79.0 (16 453)	71.8 (7018)	<.0001
Female	23.4 (252)	21.0 (4381)	28.2 (2759)	
Low-income status, % (N)	44.3 (476)	26.7 (5556)	24.2 (2361)	<.0001
History of HIV, % (N)	2.0 (22)	0.5 (110)	0.7 (69)	<.0001
History of HBV, % (N)	0.8 (9)	0.2 (51)	0.3 (26)	<.0001
History of HCV, % (N)	13.9 (149)	3.8 (787)	5.4 (524)	<.0001
Mental health disorders (ALD23), % (N)	20.2 (217)	9.5 (1974)	10.4 (1021)	<.0001
Alcohol dependence, % (N)	19.0 (204)	10.6 (2205)	8.2 (803)	<.0001
Coprescription BZD + opioid, % (N)	22.1 (238)	28.6 (5961)	27.6 (2698)	<.0001
Doctor Shopping at one-year, % (N)	27.0 (290)	9.9 (2056)	0.5 (47)	<.0001
Median daily dose, mg [IQR]	553.0 [250.1-881.0]	9.5 [5.4-16.6]	46.7 [30.2-68.2]	
Median length of treatment, day [IQR]	234.0 [142.0-436.0]	259.0 [148.0-503.0]	451.5 [233.0-787.0]	

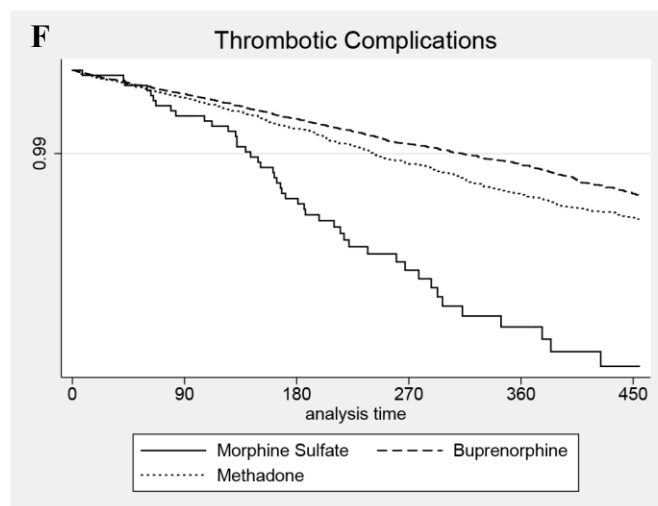
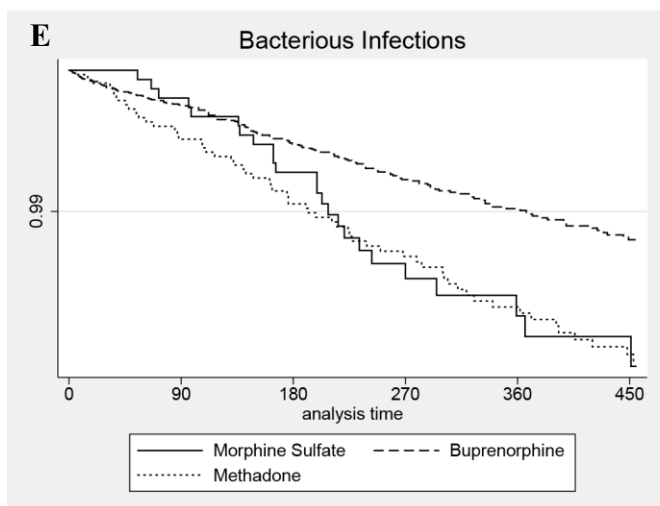
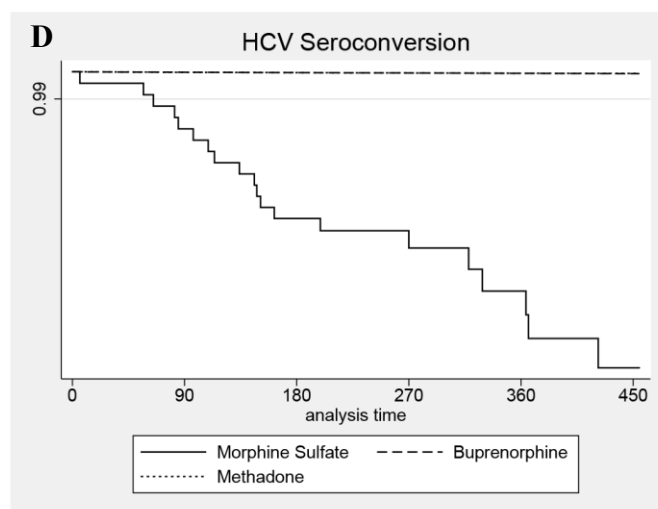
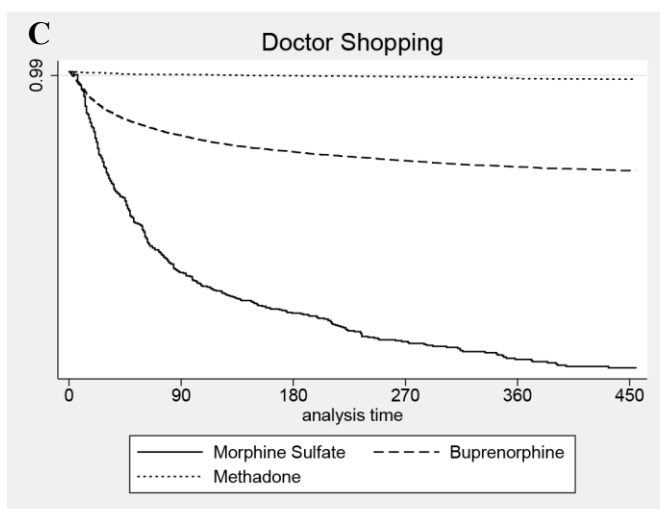
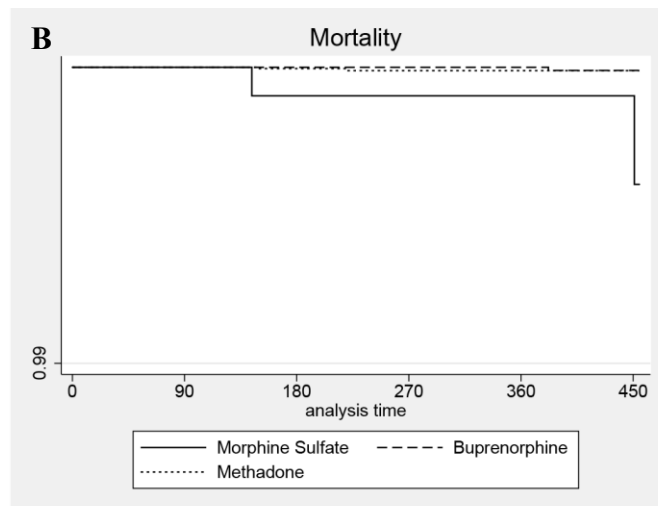
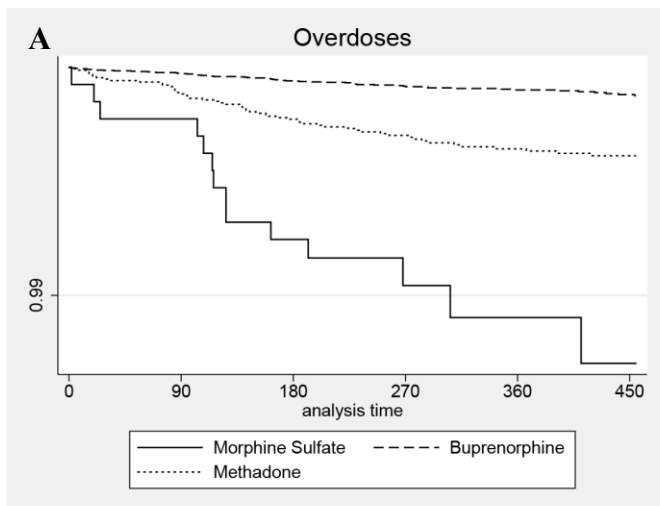


Fig. 2: Adjusted Kaplan-Meier survival curves for primary outcome (A- Overdoses), and secondary outcomes (B- Mortality; C- Doctor Shopping; D- HCV seroconversion; E- Bacterious infections; F- Thrombotic complications)

BERTIN Célian

Risk assessment in morphine sulfate off-label use in non-painful opioid dependent patients

Thèse de Médecine - Clermont-Ferrand - 2017

RESUME

Background: Some addictovigilance studies describe off-label use of morphine sulfate in non-chronic pain opioid-dependent patients for recreational purposes or as an alternative to conventional substitution treatments. The objective of this study is to provide comprehensive data on the risks associated with this off-label use.

Methods: A retrospective cohort of non-chronic pain patients who benefited from regular dispensation of morphine sulfate between April 1, 2012 and December 31, 2014 was based on the comprehensive health insurance database (SNIIRAM). Sociodemographic characteristics and prevalence of associated comorbidities were investigated. The incidence of overdoses, deaths, doctor shopping behavior and complications (i.e. viral and bacterial infections and thrombotic complications) related to the very frequent practice of intravenous administration were compared by the Cox regression method to those treated by opioid substitution therapy (OST): buprenorphine or methadone).

Results: 1075 non-chronic pain opioid-dependent patients were included (76.6% of men, median age: 33 years). Overdose incidences were significantly higher than OST patients. Except for thrombotic complications versus OST and hepatitis C virus versus methadone group, incidence of the other associated risks was significantly higher in morphine sulfate group.

Conclusion: This study is the first to assess the risks associated with off-label use of morphine sulfate at national level. It questions the relevance of these prescriptions as a secure opioid maintenance therapy.

MOTS-CLES

morphine, misuse, addiction, overdose, doctor shopping, opioid, substitution

JURY

Président : LLORCA Pierre-Michel, Professeur

Membres :

JALENQUES Isabelle, Professeur

AUTHIER Nicolas, Professeur

BROUSSE Georges, Professeur

ROLLAND Benjamin, Docteur

DATE DE LA SOUTENANCE

Vendredi 6 octobre 2017