Title: Medications for Opioid Use Disorder in People who inject substances: reflection on the potential place of Morphine Sulfate as substitution treatment? Results of COSINUS Cohort Study

Running title: Morphine Sulfate use as Substitution treatment?

Abstract

Background: Opioid Use Disorder (OUD) often provokes dramatic consequences in terms of increased morbi-mortality. Two medications have mainly been worldwide used for OUD (MOUD), buprenorphine and methadone. Recently, however, some reports have highlighted the use of Morphine Sulfate (MS) mainly obtained without a prescription but used as MOUD by opioid users and especially People Who Inject Substances (PWIS). We propose to characterise the prevalence and distribution of MOUD and MS use in PWIS.

Methods: This study examines the use of MOUD and MS amongst French PWIS recruited in harm reduction facilities and drug consumption rooms in the context of the COSINUS (Cohort to assess structural and individual factors in drug use) study.

Results: MOUD are prescribed, respectively, to one-third and one-fifth of PWIS, whereas a half of them declared MS consumption without prescription. MS users live with higher precariousness and are younger than non-users. MS is associated with salt cocaine and heroin use. It is often consumed with methadone and more rarely with buprenorphine and we hypothesized that this is probably linked to buprenorphine's pharmacological antagonism.

Discussion: Our results show the high prevalence of MS consumption and highlight the importance of considering the highly restricted possibility of prescribing MS as MOUD. Its association with methadone raises the question of their synergistic action on craving and mental disorders. The profiles of opioid users who could benefit from MS with or without methadone must be examined to improve their care but with the utmost caution, given the risk of overdose.

Keywords: opioid use disorder, morphine sulphate, methadone, buprenorphine, people who inject substances, drug consumption room

Abbreviations:

COSINUS cohort: cohort to identify structural and individual factors associated with drug use

DCR: drug consumption room

MOUD: medications for opioid use disorder

MS: morphine sulfate

OUD: opioid use disorder

PWIS: people who inject substances

1. Introduction

Opioid use disorder (OUD) is defined by problematic opioid use (Hasin et al., 2013) and induces psychological distress as well as deficits in interpersonal and social functioning. OUD can cause dramatic consequences in terms of increased morbi-mortality, with a life expectancy decreased by more than 10 years due to infections, overdoses, psychiatric comorbidities, and suicidal risk (Degenhardt et al., 2019). In North America, the crisis of opioid overdose has led more than one million deaths, is a cause of life-expectancy decrease (Hedegaard et al., 2015; The Lancet Regional Health-Americas, 2023), and recently emerged in European countries (EMCDDA. 2022). In France, the large coverage by Medications for Opioid Use Disorder (MOUD), which is the most efficient strategy to stabilise OUD patients, which can only be delivered with counselling (Durpoix et al., 2024), and limit the risk of overdose (Sordo et al., 2017), is high compared with other countries (87% compared to 20% in the US for example) (Weill-Barillet et al., 2016; Englander 2024). Consequently, France has lower overdose risks due to its increased use of MOUD combined with a public-funded integrated medical-social approach (Nguemeni et al., 2022). The two types of MOUD recommended in France and many other countries are methadone and buprenorphine, along with their derived products. Pharmacologically, these treatments replace the opioid substance dependency through their action on mu-opioid-receptor; they act differently on others delta and kappa opioid system receptors (Darcq & Kieffer, 2018; Lutz & Kieffer, 2013).

Methadone is a synthetic compound which functions as an opioid receptor agonist. In opioid users, methadone acts on both the positive and negative reinforcing effects and replaces short-acting opiates by reducing craving and drug-related activities. Methadone has a long

and highly variable half-life of 7–150 hours, average 25h, and its dosages range from 60 to 120 mg and more (Lynch, 2005).

Clinically, there is a correlation between levels of methadone in the blood and its effect on mood (Ball, 1991). Consequently, a low dosage is associated with a bad mood, but an adequate dosage is associated with antidepressant effects (Kreek, 2000, 2019). Moreover, methadone acts physiologically on stress by decreasing the secretion of ACTH (adrenocorticotropic hormone) and cortisol, two factors which contribute to addiction relapse (Kreek, 2000, 2019). This action combined with mood and reward alleviation is crucial to decrease the risk of relapse and to maintain patients' use of methadone (Kakko etal., 2019).

Buprenorphine is a high-affinity and mu-opioid-receptor partial agonist with moderate efficiency; it displaces other high-efficacy opiates, if present, and induces withdrawal symptoms (Kumar et al., 2024). Compared with other full opioid agonists, buprenorphine is safer concerning respiratory suppression and overdoses except for in case of association with benzodiazepines and alcohol (Walsh et al., 1994; Park et al., 2020; Kumar et al., 2024). Buprenorphine's half-life is long, and there is considerable variation in reported values (mean values ranging from 3 to 44 hours (Elkader & Sproule 2005). The range of clinical efficiency for opioid treatment substitution is between 12 and 16 mg (Walsh et al. 1994), and in certain countries, the maximal authorised dose is either 16 mg or 32 mg but in France is 24 mg. Concerning neurobiological and associated behavioural effects, the literature indicates that buprenorphine has antidepressant effects related to its kappa inverse agonist action (Lalanne et al., 2014; Klein, 2016, Serafini et al., 2018). It suppresses stress responses which contribute to relapse.

Although methadone is by far the most prescribed substitution in many countries (Whelan, P.J., & Remski K., 2012), in France, buprenorphine has been significantly the more prescribed of the two treatments for a long time (Emmanuelli et al. 2005) but has been recently rebalanced with 43% of people on methadone compared to 57% on buprenorphine (Ndiaye 2023). Moreover, clinical observations of opioid users' habits have shown that MOUD authorised for prescription are not always adapted to stabilise cravings and withdrawals; thus, **Morphine Sulfate (MS)** is sometimes used as an MOUD and the form most sought by users in the community in France is SKENAN ® LP, and others derivate products (Bertin et al., 2023).

The use of MS outside its intended therapeutic context is not a new phenomenon in France. During the 2000s, it appeared relatively controlled, geographically localised, and fluctuating over time (Cadet-Taïrou & Gandilhon, 2014). Since around 2011, there has been an increase in demand, which is far from homogeneous and is spreading geographically in France. According to a TREND (Recent Trends and New Drugs) study coordinated by OFDT (Observatoire français des drogues et des tendances addictives/ French Observatory of Drugs and Addictive Tendencies), MS was used in the month prior to the ENa-CAARUD survey (National survey of low-threshold structures (CAARUDs)) in 2012 by 17% of harm reduction facilities users (it was 15% in 2008 and 2010) (Cadet-Taïrou & Gandilhon, 2014). In a survey conducted between 2011 and 2013, 49% of active injecting users declared having taken MS in the previous month in a representative survey conducted amongst people attending harm reduction services and drug treatment centres at the same time period (Jauffret-Roustide et al.2018) ; the level of MS was also high (34%) in another non representative survey conducted between 2011 and 2013 in low-threshold services (Roux et al., 2018).

MS is a μ-opioid receptor agonist which relieves pain. It produces analgesia by binding to opioid receptors in the central nervous system. The form most sought by users in the community is SKENAN® LP capsules, at 100 mg or 200 mg depending on the site. Lower doses (30 mg, 60 mg) are sometimes used for lack of anything better, as is MOSCONTIN® LP or ACTISKENAN®. The half-life of morphine is between 20 minutes and 15 hours, with an average of 6h (Berkowitz, 1976, Herman et al., 1994), and depends on its immediate or long-term release.

People who inject substances (PWIS) may increase their use of MS and methadone/buprenorphine, in France (Cadet-Taïrou & Gandilhon, 2014) and the United States (Dart et al., 2021) compared to those who do not inject substances. To understand this trend, we aimed to characterise the prevalence and distribution of MOUD/MS amongst PWIS who have access to harm reduction facilities and drug consumption rooms (DCRs) (harm reduction facilities and DCRs are places in which people have access to programs aimed at reduction negative consequences associated with substances use like sterile material of injection, access to social and medical cares and to MOUD prescription; the main difference between the two devices is the possibility pour PWIS to inject substances under supervision only in DCRs) (EMCDDA 2018). To this purpose, we use data from the COSINUS cohort to identify structural and individual factors associated with drug use (Auriacombe et al, 2019).

2. Materials and Methods

This prospective, multisite cohort study enrolled 665 PWIS in four cities—Bordeaux, Marseille, Paris, and Strasbourg—from November 2016 to May 2018 and completed follow-up questionnaires with them until 2019. In Paris and Strasbourg, PWIS were recruited in DCRs opened at the beginning of the study, whilst in Bordeaux and Marseille, people were recruited

in harm reduction facilities. Therefore, two groups of PWIS were recruited, those exposed versus non-exposed to DCR (those who frequent versus those who don't frequent DCRs). The study protocol was approved by the Institutional Review Board (IRB00003888) of the French Institute of Medical Research and Health (opinion number: 14-166).

2.1 Population

Participants were eligible if they reported having injected illegal substances or prescribed medications (e.g., methadone, buprenorphine, benzodiazepines, MS, oxycodone) at least once during the previous month. They were recruited in either DCRs or in harm reduction facilities after providing informed consent. Additional inclusion criteria were to be over 18 years old and French-speaking. Participants were compensated for the time spent with 10 euros' worth of service vouchers (securities redeemable for services; in our study, compensation for answering questionnaires and taking biological samples, in accordance with the ethics committee) after each interview.

2.2 Data Collection

PWIS were interviewed face to face by trained interviewers. The questionnaire collected information with an electronic survey form on informatic tablets about sociodemographic and socioeconomic characteristics (sex, age, educational level, country of birth, employment, housing, parenthood, city of recruitment), information about access to care (past overdoses, past suicidality, consultations with a general practitioner or specialist, use of DCRs and harm reduction material), and their behaviour towards MOUD/MS consumption prescribed or not (prescribed versus not, taken different MOUD in association, taken methadone or buprenorphine in association with MS or all together). Data we used in this study were provided by PWIS responses at the recruitment stage.

2.3 Outcome and Explanatory Variables

In this study, we examine the use MS amongst PWIS that is outcome variable. For this, several groups of explanatory variables are included: first, sociodemographic and socioeconomic characteristics, second, category of information about health and access to care and harm reduction programmes, third, the use of MOUD and other substance use in the previous month (for more information see supplemental material and data).

2.4 Statistical Analysis

A univariate analysis consisted of a statistical description of the repartition of the variables and production of Venn diagrams for the cross-uses amongst MS, buprenorphine, and methadone in the month.

A bivariate analysis was performed on the outcome (MS use in the month) for all explanatory variables using Chi-2 tests ($p > .005$).

Further analysis was conducted with a binomial logistic regression on the outcome variable, including sociodemographic and socioeconomic characteristics as well as information about health and access to care and harm reduction risk programmes.

3. Results

3.1 Description of Population

<Insert Table 1>

Table 1—Description of Study Population

The PWIS were mostly male, over 30 years old, unemployed and living in precarious conditions. More than one-third of the PWIS use DCRs, and more than two-thirds often visit other harm reduction facilities (i.e. not DCR). About a half of PWIS declared MS use without

prescription and very few with a prescription. Use of methadone was most often prescribed, similarly for buprenorphine[1].

3.2 Venn Diagram Analysis and Cross-Table for MS Use in the Month

The Venn diagram analysis shows the type of poly-use amongst buprenorphine, methadone, and MS (considering uses with or without prescriptions). Whilst most of the people who used buprenorphine did not take methadone or MS (n = 142), use of methadone and MS was common in the last month (n = 176).

<Insert Figure 1>

Figure 1: The Venn diagram analysis shows the type of poly-use amongst buprenorphine, methadone, and MS (considering uses with or without prescriptions).

We specifically analysed the link between MS use in the month and several explanatory sociodemographic and substance use variables (see methods), employing a Chi-2 test ($p < .05$).

Concerning sociodemographic variables, results are significant at the threshold of 5% for the Chi Square Test for age, housing conditions, city, having children or not, general practitioner visit within six months, and use of DCRs and other harm reduction facilities.

MS was less frequently used in the last month amongst PWIS over 45 years old (39.5% versus 52.5% for all PWIS, $p < .001$). Precarious housing is also strongly linked with substance use—65% of PWIS living in very precarious conditions (living on the street, or in a car) reported MS

[1] PWIS could declare using both morphine with and without prescription. It has to be noted that the sum of medicines is not equal to the sum of prescribed and non-prescribed for these medicines given.

use compared with only 42.9% amongst PWIS living in a stable house ($p < .001$)—as well as the experience of sleeping on the street at least once in the month (60.8% of MS use amongst PWIS who reported this versus 43.4%, $p < .001$). This is coherent with the fact that amongst people who inject in public spaces, MS use is more often reported (56.6% versus 42.3% in private spaces, $p < .001$). Finally, PWIS who have not had any appointments with general practitioners in the six previous months reported more frequent MS use during the month (60.1%, $p < .001$) compared with PWIS who visited them at least once (46.3%, $p < .001$).

Strong differences are observed according to the cities of residence of PWIS ($p < .001$). Parisian PWIS use MS more often (78.3%), whilst less use was declared in Strasbourg (32.5%), and Marseille (28.6%). Bordeaux shows an average use of MS (53.4%, $p < .001$).

Results in table 2 finally indicate that people who use salt cocaine (the powdered form of cocaine that can be taken intravenously or intranasally) more often used MS in the month as well (68.8%, $p < .001$) compared with people who do not use salt cocaine (35.9%, $p < .001$). This association is not observed with cocaine, where, on the opposite hand, less MS use was reported (43.3% compared with 68.9% for cocaine non-users in the month, $p < .001$).

<Insert Table 2>

Table 2—Cross-Table of MS Use in the Month with Chi-2 and overall difference. Legends signification: * p<0.05 ; ** p<0.01 ; *** p<0.001

3.3 Binomial Logistic Regression with MS Use in the Month as Variable of Interest (see Table 3 in Supplemental Material and Data)

Finally, we conducted a binomial logistic regression on the variable of interest (MS use during the month with or without a prescription), applying sociodemographic variables in the model.

These analyses provided information on the odds ratio of MS use amongst PWIS, all other variables in the model being equal.

Age, educational level, housing conditions, nationality, city of residence, and attendance to a DCR were found to be predictors of MS use during the month ($p < .05$).

All other variables being equal, PWIS over 45 years old are 2.2 times less likely to use MS than PWIS under 30 (OR = 0.452, $p < .05$). PWIS with their high school certification (baccalaureate) or upper levels are 59% more likely to use MS than undergraduates (OR = 1.589, $p < .05$).

The analysis reinforces the importance of the city in the likelihood of MS consumption in the month. Living in Strasbourg (OR = 0.079, $p < .001$) or Marseille (OR = 0.22, $p < 0.001$) is associated with less of a chance of using this substance compared with living in Paris. French PWIS are also 2.08 times more likely to use MS compared with foreigners (OR = 0.390, $p < 0.001$).

4. Discussion

Our study characterises the prevalence and distribution of MOUD/MS amongst PWIS who have access to harm reduction facilities and drug consumption rooms (DCRs). Our results show that PWIS are mostly males over 30 years old, unemployed (80.9%), and living in precarious conditions. More than a half uses cocaine and more than one-quarter uses heroin the previous month. This result confirms the importance of polydrug use found in the literature in PWIS who use harm reduction facilities (Cadet-Taïrou & Gandilhon, 2014, Valente et al., 2020) and highlights its importance in PWIS who use DCR (Schulte et al., 2016).

The model reveals a link between attending a DCR and MS use. PWIS who attend DCRs are 2.5 times more likely to report this substance use compared with people who do not go to DCRs

(OR = 2.51, $p < 0.05$) and attendance at DCRs was associated with higher odds of MS use, even after adjusting for city." MS use is also associated with the cities of Paris and Bordeaux. Our analyses depict a specific portrait of MS users amongst PWIS. They are more often younger and living in precarious conditions including living on the street. They appear to be closer to and more likely to attend DCRs than other PWIS. The majority of them use methadone as a substitution treatment, and a significant portion of them are also regular salt cocaine users. Our results confirm those of a previous study in France (Cadet-Taïrou & Gandilhon, 2014). About half of PWIS declared MS use without a prescription and very few with a prescription, which is not surprising as there is no prescription authorisation for MS in this substitution context but only for pain relief in France (Teoh & Camm, 2012). However, when conventional treatments fail, addiction specialists can prescribe off-label MS as MOUD (according to the French circular n°54, 1996 also called Girard circular). One-third of PWIS declared using methadone with a prescription (234/665) and only 20% use buprenorphine with a prescription (135/665), but less are on MOUD without a prescription (84 for unprescribed methadone and 89 for unprescribed buprenorphine). These results show the importance of methadone and MS consumption in harm reduction facilities and in DCR and the less importance of buprenorphine consumption, whose is known to decrease between 2008 and 2023 (Brisacier, A-C., 2020, Ndiane, 2023). In our study, the association of MS and methadone is frequent compared to the association of MS and buprenorphine. As the literature reported it, its partial agonist action at the mu-opioid receptor with high receptor affinity can displace opioid agonists of lower receptor affinity (e.g. heroin, Methadone) from the receptors without full activation (partial agonism), leading to a 'precipitated' opioid withdrawal (Mannelli et al., 2012, Lintzeris et al., 2018). Therefore, the weak association between Buprenorphine and MS could be due to its pharmacological action. Alternatively, it could suggest that buprenorphine

discourages MS use more effectively than methadone and in this way, might be an interesting treatment in PWIS who use MS (Gerra et al., 2004).

We also showed that MS is more frequently used amongst younger PWIS (under 30) with upper educational levels and high precariousness conditions (living in the street or in a car) who inject in public spaces. These results are partly consistent with findings from another French survey on MS use reported from harm reduction facilities. While in this survey, people who use MS are, on the whole, slightly younger than other opioid users, their average level of precariousness and their education level were not significantly different from those of people who use other opioids (Cadet-Taïrou & Gandilhon, 2014).

Finally, our results showed that people who use MS are more likely to attend DCRs compared with other PWIS . They also had fewer appointments with general practitioners in the previous six months, and unstable accommodation was independently associated with MS use. These findings highlight that people who use MS are often in highly precarious situations and may be seeking solutions to decrease the risks related to their substance use by visiting DCRs which offer access to harm reduction services as well as social and medical care. One such solution for some PWIS is access to an MS prescription when methadone and buprenorphine are not tolerated or failed (Cadet-Taïrou & Gandilhon, 2014, Roux et al., 2018). For instance, MS prescription has been evaluated in several studies which demonstrated the effects of specific long-term actions of MS. One study has shown that slower release of MS seems to reduce the craving for heroin better than methadone (Falcato et al., 2015) with additional impacts on well-being and mental health symptoms such as phobic (social and agora), dysphoric, and depressive (Verthein et al., 2015). In Austria, slower-release MS has been prescribed with efficacy since 1998 (Beck et al., 2014; Eder et al., 2005, Mitchel et al., 2004). A meta-analysis

of existing randomised trials has further suggested that slow-release oral MS may generally be equal to methadone in retaining patients in treatment and reducing heroin use whilst potentially lessening craving (Klimas et al., 2019).

Nonetheless, what is original about the current results is that they highlight the higher complexity of substance association. Indeed, a lot of the PWIS surveyed seem to take both methadone and MS. Whilst the half-life of MS is longer than that of heroin, the half-lives of methadone and buprenorphine are generally longer than the half-life of MS (Berkowitz, 1976, Herman et al., 1994, Elkader & Sproule 2005, Lynch, 2005). Thus, the association between MS and methadone might help some opioid users decrease cravings and better maintain their heroin abstinence. However, it remains to determine precisely the profile of candidates for MS prescriptions and whether or not it should be associated with methadone, especially as the risk of overdose is an important concern when associating two opioid agonists. Moreover, as shown in this study, MS users are specific and their profile often involves a high level of precariousness and a young age, but in terms of the psychiatric severity of PWIS who require such treatment, studies must precisely determine their profile. All in all, whereas the ratio between effectiveness and lethality of association between methadone and MS seems to be low due to the high risks of overdoses, future studies have to determine the strict indication of this association. Indeed, MS might be considerate as MOUD when other treatments failed or in association with MOUD in strict indication.

Overall, given that a large proportion of patients on methadone use MS, it is very important for clinicians to ask patients on methadone about their co-use of MS. In general population, opioid crisis highlighted the necessity to engage a dialogue between clinicians and their patients about their poly-substance use especially in pain context or after a surgery (Dart et

al., 2021). These results highlight the possibility that MS could be considered as on official MOUD, and consequently the determinants of the profile of opioid users who could benefit from this therapeutic action should be investigated. In a recent publication, it has been showed that MS use can increase the risk of overdose, especially among occasional MS users compared to regular MS users (Bertin et al, 2022). This publication makes the hypothesis that when MS is used more regularly under medical supervision, the risk of overdose decreases, that advocates for having MS as on official MOUD with strong medical supervision for a minority of users profiles for which other MOUD are ineffective. More globally, other countries, such as Switzerland, Germany, the Netherlands or Canada have implemented heroin-assisted treatment that are well-tolerated and effective within medical supervision (EMCDDA 2012, Uchtenhagen, 2017). DCRs may be considered as adequate settings to implement these type of alternative treatments (MS and heroin treatments as MOUD) in collaboration with trained medical practitioners, as the majority of users who attend these facilities are already on MS without any supervision that put them more at a risk of overdose. In the US context of the opioid overdose crisis with people addicted to fentanyl (a very high-potent opioid compared to heroin or morphine), it is very crucial to disseminate MOUD including methadone and buprenorphine as well as slow-release oral MS, in a environment that takes into account the needs of patients in a continuous dialogue with care practionners (Englander et al. 2024, Nguenemi et al. 2022). Our recommendation to get further in the prescription of slow-release oral MS is to conduct a comparative and randomized study to explore the effects of MS compared to buprenorphine and methadone in terms of efficacy and safety. The recruitment of individuals with OUD and psychosocial difficulties at variable severity will allow determining the characteristics of opioid users who should benefit from MS use.

However, several limitations must be acknowledged in our study. First, substance consumption was self-declared and not assessed by urine tests but by non-biological measures. Although we may consider that consumption can be underestimated, surveys about the reliability on declared measures showed that there is a strong correlation between declaration and real consumption in substance users (Darke, 1998). Furthermore, substance use was evaluated by different interviewers in various cities, which might have resulted in interview bias, according to cities. However, this bias was limited due to consistent written guidelines provided to all interviewers to conduct the study.

5. Conclusion

The results show a high prevalence of MS consumption and highlight the necessity of considerate the possibility to prescribe MS as MOUD but with strict regulations rules and supervision in France. Its association with methadone raises questions about their synergistic action on cravings but questions the risk of overdose. The profiles of opioid users who could benefit from MS must also be examined concerning psychiatric comorbidities and levels of precariousness. It is possible that opioid users with more severe psychiatric disorders and highly precarious conditions require different medications than other users. It is also crucial to be aware of the risk of overdose induced by the combination of two opioid agonists and thus to precisely select amongst responder patient profiles and to supervise the prescription of MS in a multidisciplinary environment that combines care and harm reduction.

Competing Interests: Laurence Lalanne, Davalos Ricardo, Martin Audran, Naomi Hamelin, Carole Chauvin, Laelia Briand-Madrid, Charlotte Kervran, Sébastien Kirchherr, Marc

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Contributors

The four investigators (Marc Auriacombe, Marie Jauffret-Roustide, Laurence Lalanne and Perrine Roux) designed the survey and supervised the data collection of the Cosinus cohort. For this paper, statistical analyses were realized by Ricardo Davalos and Martin Audran under the supervision of Marie Jauffret-Roustide and Laurence Lalanne. Laurence Lalanne wrote the first version of the paper, which was firstly discussed with Marie Jauffret-Roustide and reviewed after by all the authors. All authors contributed to this paper, critically reviewed its content, and approved the final version.

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Declaration of generative AI in scientific writing

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Characteristic	**Overall** (665 obs.)[12]
Gender	
Female	20.2% (134 obs.) [17.2%, 23.4%]
Male	79.8% (531 obs.) [76.6%, 82.8%]
Age	
18-29	19.1% (127 obs.) [16.2%, 22.3%]
30-44	48.6% (323 obs.) [44.7%, 52.4%]
>45	32.3% (215 obs.) [28.8%, 36.1%]
Study level	
Lower to highschool	70.4% (468 obs.) [66.7%, 73.8%]
High school and upper	29.6% (197 obs.) [26.2%, 33.3%]
City	
Bordeaux	22.0% (146 obs.) [18.9%, 25.3%]
Marseille	29.9% (199 obs.) [26.5%, 33.6%]
Paris	36.1% (240 obs.) [32.5%, 39.9%]
Strasbourg	12.0% (80 obs.) [9.7%, 14.8%]
Country	
France	82.7% (550 obs.) [79.6%, 85.5%]
Foreigner (Nationality declared)	17.3% (115 obs.) [14.5%, 20.4%]
Employment	
Unemployed	80.9% (538 obs.) [77.7%, 83.8%]
Employed	19.1% (127 obs.) [16.2%, 22.3%]
Housing	
Very stable	35.0% (233 obs.) [31.4%, 38.8%]
Precarious/unstable	22.4% (149 obs.) [19.3%, 25.8%]
Very precarious	42.6% (283 obs.) [38.8%, 46.4%]
Sleeping over the street in the month	52.2% (347 obs.) [48.3%, 56.0%]
Children	48.3% (321 obs.) [44.4%, 52.1%]
Place of injection	
Private space	47.6% (312 obs.) [43.7%, 51.5%]

Characteristic	**Overall** (665 obs.)[12]
Public space	34.8% (228 obs.) [31.1%, 38.6%]
Semi-public space	4.9% (32 obs.) [3.4%, 6.9%]
SIS	12.8% (84 obs.) [10.4%, 15.7%]
Unknown	9
DCR frequentation	40.0% (265 obs.) [36.2%, 43.8%]
Unknown	2
Overdose over the last 6 months	6.2% (41 obs.) [4.5%, 8.4%]
Unknown	1
Suicide attempt over the last 6 month	5.2% (34 obs.) [3.7%, 7.3%]
Unknown	11
General practitioner over the last 6 months	
Never	44.5% (296 obs.) [40.7%, 48.4%]
At least once	55.5% (369 obs.) [51.6%, 59.3%]
Specialized practionner over the last 6 months	
Never	71.0% (472 obs.) [67.3%, 74.4%]
At least once	29.0% (193 obs.) [25.6%, 32.7%]
Harm reduction services frequentation	
Not often	29.2% (193 obs.) [25.8%, 32.9%]
Often	70.8% (468 obs.) [67.1%, 74.2%]
Unknown	4
Deliquency events	25.4% (169 obs.) [22.2%, 28.9%]
Lended injection equipment in month	12.7% (84 obs.) [10.3%, 15.5%]
Unknown	1
Borrowed injection equipment in month	11.0% (73 obs.) [8.8%, 13.7%]
Morphine in the month (without prescription)	47.8% (318 obs.) [44.0%, 51.7%]
Methadone in the month (without prescription)	12.6% (84 obs.) [10.3%, 15.5%]
Buprenorphine in the month (without prescription)	13.4% (89 obs.) [10.9%, 16.3%]
Buprenorphine in the month (with prescription)	20.3% (135 obs.) [17.3%, 23.6%]
Methadone in the month (with prescription)	35.2% (234 obs.) [31.6%, 39.0%]

Characteristic	**Overall** (665 obs.)[12]
Morphine in the month (with prescription)	7.8% (52 obs.) [5.9%, 10.2%]
No opiates (mor,bup,metha)	8.9% (59 obs.) [6.9%, 11.4%]
Cocaine in month	64.2% (427 obs.) [60.4%, 67.8%]
Crack cocaine in the month	50.5% (336 obs.) [46.7%, 54.4%]
Heroin in the month	26.9% (179 obs.) [23.6%, 30.5%]
Cannabis in the month	61.4% (408 obs.) [57.5%, 65.1%]
Benzodiazepine in the month	17.3% (115 obs.) [14.5%, 20.4%]

[1]% (n obs.)

[2]CI = Confidence Interval

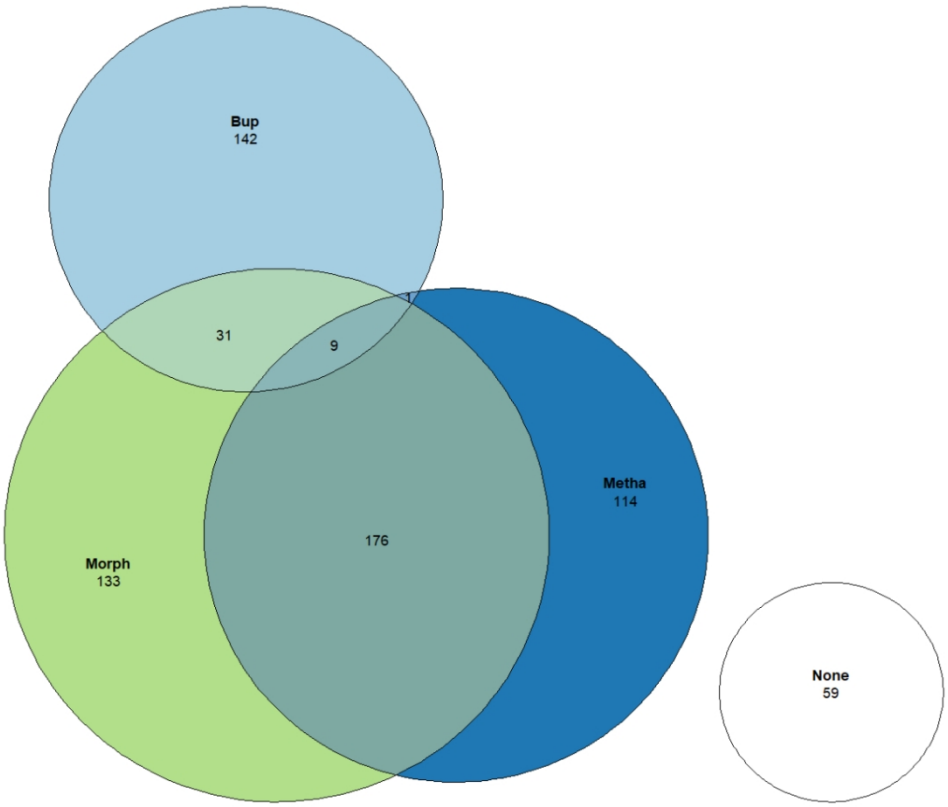

Figure 1: The Venn diagram analysis shows the type of poly-use amongst buprenorphine, methadone, and MS (considering uses with or without prescriptions).

810x654mm (38 x 38 DPI)

Variable	Modality	Morphine	Khi2	Diff.Overall
	Overall	52.5	-	-
Gender	Femme	59,7	0.076	7,2
	Homme	50,7	0.076	-1,8
Age	**18-29**	**59,8**	**2.2e-05**	**7,3**
	30-44	**58,2**	**2.2e-05**	**5,7**
	>45	**39,5**	**2.2e-05**	**-13**
Study level	Lower to high school	50	0.059	-2,5
	High school or upper	58,4	0.059	5,9
Employment	Unemployed	52,2	0.87	-0,3
	Employed	53,5	0.87	1
Housing	**Very stable**	**42,9**	**1.8e-07**	**-9,6**
	Precarious/unstable	**43,6**	**1.8e-07**	**-8,9**
	Very precarious	**65**	**1.8e-07**	**12,5**
Sleeping in the street in the month	**Yes**	**60,8**	**1e-05**	**8,3**
City	**Bordeaux**	**53,4**	**2.2e-26**	**0,9**
	Marseille	**28,6**	**2.2e-26**	**-23,9**
	Paris	**78,3**	**2.2e-26**	**25,8**
	Strasbourg	**32,5**	**2.2e-26**	**-20**
Country of birth	France	54,2	0.069	1,7
	Foreigner	44,3	0.069	-8,2
Children	**Yes**	**47,4**	**0.013**	**-5,1**
Place of injection	**Private space**	**42,3**	**1.3e-08**	**-10,2**
	Public space	**56,6**	**1.3e-08**	**4,1**
	Semi-public space	**53,1**	**1.3e-08**	**0,6**
	SIS	**79,8**	**1.3e-08**	**27,3**
SIS	**Yes**	**73,2**	**3.3e-18**	**20,7**
Overdose in the last 6 months	Yes	46,3	0.52	-6,2
Suicide attempt in the 6 last months	Yes	55,9	0.86	3,4
General practitioner visits in 6 months	**Never**	**60,1**	**5.4e-04**	**7,6**
	At least once	**46,3**	**5.4e-04**	**-6,2**
Harm reductions services frequentation in the month	**Not often**	**44**	**0.0067**	**-8,5**
	Often	**56**	**0.0067**	**3,5**
Delicts	Yes	56,8	0.22	4,3
Methadone in month	**Yes**	**61,7**	**2.4e-05**	**9,2**
Buprenorphine in the month	**Yes**	**21,9**	**4.6e-22**	**-30,6**
Heroin in the month	Yes	58,7	0.065	6,2
Cocaine in month	**Yes**	**43,3**	**4.1e-10**	**-9,2**
Crack in the month	**Yes**	**68,8**	**4e-17**	**16,3**
Benzodiazepine in the month	Yes	59,1	0.14	6,6

Supplemental Material and Data

Material and Method section

2.3 O**utcome and Explanatory Variables**:

« - A first group of sociodemographic and socioeconomic characteristics were analysed: age, gender, education level (lower to highschool versus High school and upper), country of birth, parenthood, city of recruitment, type of housing (very stable [living in one's own house, in a rented home, or at family's home], unstable or precarious [living in a hostel, at a friend's], very precarious [living on the street, in a car]), employment status, and delinquency events (the question put to users was: "In the past month, have you done any of the following? robbery, shoplifting, prescription theft, car theft, theft from a car, handling stolen goods, resale of illegal drugs or medicines, purchase of diverted drugs or medicines, social security scams, other scams, use of violence during a robbery, armed robbery, assault, prostitution or soliciting").

- A second category of information about health and access to care and harm reduction programmes: suicide attempts in the past six months, overdose attempt in the past six months, use of harm reduction facilities in the past six months (less than often versus often or always), at least one visit to a physician (general or specialist) in the past six months, access to harm reduction material, use of DCRs, place of injection (public, private, semi-private, in DCRs).
- A third group concerns MOUD and MS use during the previous month (prescribed and unprescribed buprenorphine, prescribed and unprescribed methadone, prescribed and unprescribed MS).
- A fourth category involves other substance use in the previous month (e.g. cocaine, salt cocaine, heroin, and benzodiazepine)."

Results

Table 3

	OR	**2.5 %**	**97.5 %**	**p**	
(Intercept)	1,42654493	0,30057137	6,87721315	0,655681722	
30-44	0,79075318	0,47366932	1,31476047	0,366598739	
45 and more	0,45196867	0,24284625	0,83586135	0,011652604	*
High school or upper	1,58855884	1,02767652	2,46827838	0,038090663	*
Employed	1,44265865	0,88223955	2,37172479	0,145562757	
Precarious/unstable	1,22050679	0,70398443	2,11902373	0,477649306	
Very precarious	2,56029083	1,4818956	4,45878618	0,000804442	***
No sleeping in the street during month	0,67435374	0,41907953	1,08389409	0,103541231	
Marseille	0,22605031	0,10493448	0,48251509	0,000126424	***
Bordeaux	0,3555132	0,1552812	0,79970896	0,013115103	*
Strasbourg	0,07971854	0,03906533	0,15745523	1,02148E-12	***
Foreign country	0,38996521	0,22516713	0,66412905	0,000625471	***
Children yes	1,43183348	0,95089256	2,16109675	0,086106028	

Public space injection	0,75967411	0,45644181	1,25595349	0,286373245	
Semi-public space injection	0,87974292	0,35731579	2,14360471	0,778104375	
DCR	1,58789501	0,76622242	3,38269119	0,220363786	
DCR frequentation	2,51471924	1,21551429	5,28557502	0,013590552	*
No overdose over the last 6 months	1,71928086	0,77568001	3,89540987	0,185724829	
No suicide attempt over the last 6 months	0,81621948	0,34575256	1,90797574	0,639120459	
At least one visit over the last 6 months general practitioner	0,94656289	0,63614505	1,41241782	0,786975586	
Harm reductions frequentation: Often	1,4311424	0,94200269	2,17926325	0,093413961	
No delict reported	0,79125999	0,5064124	1,23220416	0,301263339	

Table 3—Binomial Logistic Regression on Morphine Use during Last Month (Odds Ratio). Legends signification: * p<0.05 ; ** p<0.01 ; *** p<0.001

	OR	2.5 %	97.5 %	p	
(Intercept)	1,42654493	0,30057137	6,87721315	0,655681722	
30-44	0,79075318	0,47366932	1,31476047	0,366598739	
45 and more	0,45196867	0,24284625	0,83586135	0,011652604	*
High school or upper	1,58855884	1,02767652	2,46827838	0,038090663	*
Employed	1,44265865	0,88223955	2,37172479	0,145562757	
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Marseille	0,22605031	0,10493448	0,48251509	0,000126424	***
Bordeaux	0,3555132	0,1552812	0,79970896	0,013115103	*
Strasbourg	0,07971854	0,03906533	0,15745523	1,02148E-12	***
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