

## Research Paper

## Profile, risk practices and needs of people who inject morphine sulfate: Results from the ANRS-AERLI study



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## ABSTRACT

**Aims:** In France, a non-negligible proportion of opioid-dependent individuals inject morphine sulfate. Although it has not yet been officially approved as an opioid substitution treatment (OST), some physicians can prescribe its use for people in methadone or buprenorphine treatment failure. Longitudinal data from the ANRS-AERLI study, which evaluated an educational intervention for safer injection called AERLI, provided us the opportunity to better characterize the profile, risk practices and needs of people who inject morphine sulfate (MSI), through comparison with other injectors, and to identify correlates of HIV/HCV risk practices in this group.

**Methods:** The national multisite ANRS-AERLI study assessed the impact of AERLI offered in volunteer harm reduction (HR) centers (“with intervention”) (n = 113) through comparison with standard HR centers (“without intervention”) (n = 127). All participants were scheduled to be followed up for 12 months and have 3 telephone interviews: at baseline, 6 months and 12 months. We compared MSI (n = 79) with other opioid injectors (n = 161) and then used a mixed logistic model to identify factors associated with HIV/HCV risk practices among MSI.

**Findings:** Of the 240 eligible participants, 79 were regular MSI. They were less likely to use cocaine, crack or buprenorphine and to receive OST than other participants. Conversely, MSI were more likely to inject drugs more than three times a day and to report HIV/HCV risk practices. Among MSI, multivariate analysis showed that those receiving morphine sulfate as an OST were less likely to report such practices than other participants (aOR [95%CI] = 0.11 [0.02-0.61]).

**Conclusion:** Our results show that while MSI use fewer stimulants, they have more HIV/HCV risk practices than other injectors. However, when MSI are prescribed morphine sulfate as a treatment, these practices tend to decrease. Our findings suggest the importance of increasing access to morphine sulfate as a new OST in France.

## Introduction

Although Opioid Substitution Treatment (OST) (oral methadone and buprenorphine) is widely available in France, some people who use drugs (PWUD) continue to inject opioids, mainly diverted buprenorphine (Roux et al., 2008). Thanks to its safety profile (Auriacombe et al., 2004; Carrieri et al., 2006), buprenorphine has been available as an oral OST in primary care since 1996. In contrast, methadone induction in France is possible only in specialized centers caring for

addiction (Carrieri et al., 2014). Western countries are facing the growing problem of diversion of prescription opioids (PO) through injection (Delorme et al., 2016; Lake et al., 2015). In France, this is especially true for oral buprenorphine (Roux et al., 2008) due to its easier access through primary care physicians (Thirion et al., 2002). People who inject drugs (PWID) risk serious health issues related to the injection of illicit or prescription opioids in a non-medical context, as it promotes blood-borne transmission of pathogens, such as HIV and Hepatitis viruses (Yokell, Zaller, Green, & Rich, 2011), and leads to

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local complications at the injection site, including skin infections and vascular injuries (Dwyer et al., 2009; Gordon & Lowy, 2005). In PWID, these complications are particularly prevalent, and can lead to life-threatening situations requiring emergency care and hospitalization (Kerr et al., 2005; Larney, Peacock, Mathers, Hickman, & Degenhardt, 2017). With respect to the injection of drugs intended for oral use, some studies have reported local complications as well as pulmonary and cardiovascular complications (Lamb & Roberts, 1972; Shlomi et al., 2008; Waller, Brownlee, & Roberts, 1980) associated with the diversion of buprenorphine tablets (Del Giudice, 2004) and morphine sulfate capsules (Diot et al., 2014).

In France, morphine sulfate, better known under its brand name Skenan®, is mainly authorized and prescribed to relieve pain in patients with terminal illnesses such as cancer (Teoh & Camm, 2012). In an increasing number of countries (EMCDDA, 2012) it is also available as an alternative to standard methadone and buprenorphine OST. In France, although Skenan® is prescribed for pain, it has not yet been approved as an OST. Nevertheless, it can be prescribed by some doctors when methadone or buprenorphine treatment failure occurs (CCMSA, 1996). The growing IDU demand for morphine sulfate seems to be linked, in part, to their desire for an alternative to buprenorphine and methadone (Cadet-Taïrou & Gandilhon, 2014; Chappard, 2009). Indeed, a non-negligible proportion of opioid-dependent individuals already self-medicate with morphine sulfate as an OST. Easily found on the street, many PWID choose to inject it, as it provides an immediate and positive effect (Peyriere et al., 2016). To date, few studies have investigated the profile of people who inject morphine sulfate (MSI). Longitudinal data from the ANRS-AERLI study, which aimed to evaluate an educational intervention for safer injection called AERLI, provided us the opportunity to better characterize the profile, risk practices and needs of MSI, with respect to injectors of other opioids, and to identify correlates of HIV/HCV risk practices in this group.

**Methods**

*Study design*

The ANRS-AERLI study was designed to validate the effectiveness of an innovative community-based face-to-face intervention (entitled AERLI), which provided education about safer injection on HIV and HCV infectious risk reduction, and also about the reduction of local complications at injection sites (Roux et al., 2016). This national, clustered, multisite intervention study was conducted in 17 low-

threshold drug-user harm reduction (HR) centers in France between 2011 and 2013. It enrolled 271 PWID seeking support for their injection practices, including 144 people recruited in 8 HR centers implementing the intervention (hereafter “intervention group”) and 127 people in 9 HR centers not providing the intervention (hereafter “control group”). HR centers were not randomly assigned, because not all HR centers had a dedicated space or trained staff/volunteers. The study enrolled PWID attending HR centers who spontaneously asked for help or information related to injection and who could be reached by phone. Each participant received a small monetary incentive for each questionnaire completed during the study’s scheduled 3 telephone interviews. All PWID who agreed to participate in the study provided written informed consent. ANRS-AERLI was approved by the National scientific research ethics committee in Paris. Further details of the study are described elsewhere (Roux et al., 2016).

AERLI consisted in providing training and education about HIV and HCV transmission risk reduction, with a focus on drug-injecting practices, other injection-related complications, and access to HIV and HCV testing and care. It was organized as a series of participant-centered face-to-face educational sessions, taking place in a dedicated room in each intervention group HR centers. Intervention group participants had to receive at least one educational session over the first 6 months after study enrolment.

*Data collection*

Data were collected using computer-assisted telephone interviews (CATI) conducted by a trained, non-judgmental interviewer not involved in the AERLI sessions. These interviews, performed at baseline, at 6 months and at 12 months, collected data on socio-demographic characteristics (gender, age, education level, living in a couple or not, employment status, housing situation) and behavioral data on the following variables: history of drug use (age at first drug injection), drug use in the previous month (frequency of drug sniffing and/or drug injection using the Opiate Treatment Index (OTI (Darke, Hall, Wodak, Heather, & Ward, 1992))), alcohol use (AUDIT-C questionnaire (Bradley et al., 2007)) and HCV-HIV risk practices (BBV-TRAQ-SV questionnaire (Fry & Lintzeris, 2003))).

The variable “Morphine Sulfate Injector” (MSI) was defined as a PWID who reported to have injected morphine sulfate at least 3 times during the previous 5 days (yes/no). Information about whether morphine sulfate was prescribed as an OST or not was also recorded for this variable. The variable “on OST” was defined as being on OST at the

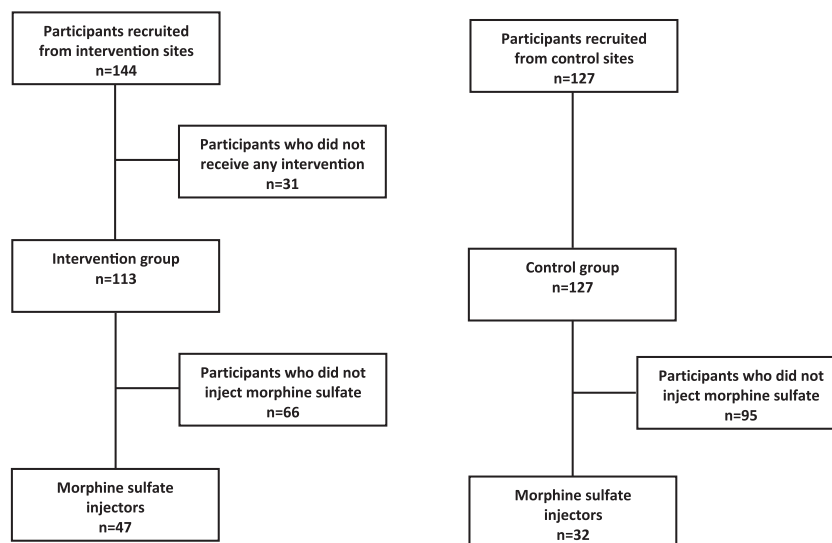


Fig. 1. Flow chart ANRS-AERLI (n = 271).

**Table 1**  
Baseline characteristics (n (%) or median [IQR]), ANRS-AERLI study (n = 240).

	Morphine sulfate injectors <sup>a</sup>		P-value	Total (n = 240)
	No (n = 161)	Yes (n = 79)		
Gender			0.07	
Male	131 (81)	56 (71)		187 (78)
Female	30 (19)	23 (29)		53 (22)
Age (years) <sup>b</sup>	30 (25-37)	31 (26-38)	0.13	30 [26-37]
Education			0.60	
< High School Certificate	122 (76)	57 (73)		179 (75)
≥ High School Certificate	38 (24)	21 (27)		59 (25)
Living in a couple			0.75	
No	120 (75)	57 (73)		177 (74)
Yes	40 (25)	21 (27)		61 (26)
Employment (paid activity)			0.84	
No	82 (60)	35 (61)		117 (60)
Yes	55 (40)	22 (39)		77 (40)
Precarious housing			0.67	
No	114 (71)	58 (73)		191 (80)
Yes	47 (29)	21 (27)		49 (20)
Age at first drug injection <sup>b</sup>	19 (17-22)	19 (17-25)	0.72	19 [17-23]
Harmful alcohol consumption <sup>c</sup>			0.71	
No	73 (46)	34 (43)		107 (45)
Yes	87 (54)	45 (57)		132 (55)
Heroin injection <sup>d</sup>			0.05	
No	102 (63)	60 (76)		162 (67)
Yes	59 (37)	19 (24)		78 (33)
Cocaine/crack injection <sup>d</sup>			0.01	
No	81 (50)	54 (68)		135 (56)
Yes	80 (50)	25 (32)		105 (44)
Buprenorphine injection <sup>d</sup>			< 0.001	
No	69 (43)	74 (94)		143 (60)
Yes	92 (57)	5 (6)		97 (40)
Frequent daily injection <sup>e</sup>			< 0.001	
No	94 (58)	27 (34)		121 (50)
Yes	67 (42)	52 (66)		119 (50)
Polydrug use <sup>f</sup>			0.98	
No	122 (76)	60 (76)		182 (76)
Yes	39 (24)	19 (24)		58 (24)
HCV screening			0.68	
No	31 (19)	17 (22)		48 (20)
Yes	130 (81)	62 (78)		192 (80)
Unsafe HIV-HCV transmission practices <sup>g</sup>			0.09	
No	110 (69)	45 (58)		155 (65)
Yes	50 (31)	33 (42)		83 (35)
Complications at the injection site <sup>h</sup>			0.77	
No	62 (39)	32 (41)		94 (39)
Yes	99 (61)	47 (59)		146 (61)
Opioid substitution treatment			< 0.001	
No	16 (10)	19 (24)		35 (15)
Morphine sulfate	0 (0)	27 (34)		27 (11)
Others <sup>i</sup>	145 (90)	33 (42)		178 (74)

<sup>a</sup>At least 3 injections during the previous 5 days. <sup>b</sup>In years. <sup>c</sup>Alcohol Use Disorders Identification Test (AUDIT)-C ≥ 3 for women and ≥ 4 for men. <sup>d</sup>During the previous 4 weeks. <sup>e</sup>More than three times a day. <sup>f</sup>≥ 2drugs. <sup>g</sup>At least one HIV – HCV risk practice during the previous month. <sup>h</sup>At least one complication at the injection site during the previous month. <sup>i</sup>Methadone or buprenorphine.

time of the interview. The type of OST was also recorded for this variable (No OST, Morphine sulfate as OST, Other drug as OST).

The primary outcome was HIV – HCV risk practices, defined as reporting at least one HIV – HCV risk practice during the previous month (sharing of syringes/needles, sharing of other injecting equipment (filter, swab, water, cup, etc.)).

### Study population

Among the 271 participants included in the study, 31 were removed from the intervention group because they had not received any educational session. Of the remaining 240 participants, regular MSI were identified. After careful examination of discordant answers, we reclassified 4 participants as MSI (n = 79) [Fig. 1].

### Statistical analyses

First, we compared the population of MSI (n = 79) with the others (n = 161) at baseline, using a Chi-square or exact Fisher test for discrete variables, and a t-Student or Wilcoxon test for continuous variables. Second, we compared MSI who received the drug as a prescribed OST (n = 23) with those who did not (n = 52). In order to identify factors associated with unsafe HIV – HCV transmission practices in MSI, we used a mixed logistic regression model. A threshold P-value < 0.20 was employed in univariate analyses to identify the variables eligible to enter the multivariable mixed logistic model. A backward procedure was then used to select the explanatory variables for the final multivariable model, with a P-value < 0.05. We also created a variable which combined both the interaction effect between follow-up time and

**Table 2**

Factors associated with HIV–HCV risk practices: logit mixed model, univariate and multivariate analyses, ANRS-AERLI study, morphine sulfate injectors (n = 79 individuals, n = 171 visits).

	Univariate analysis		Multivariate analysis	
	OR [95% CI]	P-value	aOR [95% CI]	P-value
Gender				
Male	1			
Female	1.03 [0.36-2.94]	0.96		
Age – years <sup>a</sup>	0.89 [0.83-0.96]	0.001	0.87 [0.79-0.96]	< 0.003
Education				
< High School Certificate	1			
≥ High School Certificate	1.52 [0.48-4.79]	0.47		
Living in a couple				
No	1			
Yes	1.72 [0.70-4.20]	0.23		
Employment (paid activity)				
No	1			
Yes	1.15 [0.39-3.39]	0.80		
Precarious housing				
No	1			
Yes	1.39 [0.49-3.91]	0.53		
Age at first drug injection <sup>a</sup>	0.98 (0.90-1.06)	0.62		
Harmful alcohol consumption <sup>b</sup>				
No	1			
Yes	2.83 [1.06-7.55]	0.04		
Heroin injection <sup>c</sup>				
No	1			
Yes	2.26 [0.76-6.74]	0.14		
Cocaine/crack injection <sup>c</sup>				
No	1		1	
Yes	7.44 [2.32-23.79]	0.001	12.57 [2.81-56.30]	0.001
Buprenorphine injection <sup>c</sup>				
No	1			
Yes	0.62 [0.11-3.52]	0.59		
Frequent daily injection <sup>d</sup>				
No	1			
Yes	1.66 [0.73-3.78]	0.23		
Polydrug use <sup>e</sup>				
No	1			
Yes	3.82 [1.30-11.20]	0.01		
Opioid substitution treatment				
No	1		1	
Morphine sulfate	0.30 [0.09-1.04]	0.06	0.12 [0.02-0.61]	0.01
Others <sup>f</sup>	0.68 [0.23-1.96]	0.47	0.31 [0.08-1.25]	0.10
Intervention				
No	1		1	
Yes	0.82 [0.31-2.20]	0.70	1.46 [0.33-6.40]	0.61
Follow-up time				
M0	1		1	
M6 or M12	0.42 [0.19-0.94]	0.03	1.08 [0.29-4.00]	0.91
Interaction effect <sup>g</sup>				
Intervention group at M0			1	
Intervention group at M6 or M12			0.11 [0.01-0.87]	0.04

<sup>a</sup>In years. <sup>b</sup>Alcohol Use Disorders Identification Test (AUDIT)-C ≥ 3 for women and ≥ 4 for men. <sup>c</sup>During the previous 4 weeks. <sup>d</sup>More than three times a day. <sup>e</sup>≥ 2 drugs. <sup>f</sup>Methadone or buprenorphine. <sup>g</sup>between Intervention and follow-up time variables.

receiving the intervention, in order to measure the impact of both on HIV–HCV risk practices.

## Results

### Characteristics of MSI

The characteristics of the study sample are described in Table 1. Of the 79 MSI, 29% were female and median age [interquartile range (IQR)] was 31 [26–38] years. Seventy-three per cent had a high school certificate, 39% were employed and 27% were living in a couple. At baseline, more than half (57%) had harmful alcohol consumption. Twenty-four per cent reported heroin use, 32% cocaine and/or crack use, and 6% buprenorphine use during the previous month. With respect to treatment status for opioid dependence, 34% were currently on morphine sulfate-based OST and 42% were receiving methadone or

buprenorphine.

After comparing participants' baseline characteristics between MSI and others, we found that the former were less likely to use cocaine, crack and buprenorphine and to receive OST. Conversely, they were more likely to inject drugs more than three times a day and tend to report more unsafe HIV–HCV transmission practices.

Of the 79 MSI, 27 (34%) reported receiving the drug as a prescribed OST. We found no difference between MSI who received the drug as an OST and those who did not at baseline [Supplementary Table].

### Impact of morphine sulfate as an OST on HIV–HCV risk practices

The univariate and multivariate analyses, described in Table 2, show the factors associated with HIV–HCV risk practices among MSI (n = 79). After adjusting for two other factors associated with such practices (age and cocaine/crack use), and for the interaction effect

between the intervention group and follow-up, we found that receiving morphine sulfate as an OST was independently and negatively associated with HIV – HCV risk practices (adjusted odds ratio (aOR) = 0.12, 95% confidence interval (95%CI) = 0.02 – 0.61). We also found that MSI who received AERLI were less likely to have HIV – HCV risk practices than the control group (aOR [95%CI] = 0.11 [0.01; 0.87]).

## Discussion

The results of this secondary analysis focusing on people who inject morphine sulfate (MSI), showed that one third of all PWID of the study sample reported regularly injecting morphine sulfate. These people constituted a specific population, as they used fewer stimulants but had more HCV-HIV risk practices. Among them, we also found a high proportion of MSI who were prescribed the drug. The main finding of our study is that the latter population tended to report fewer HIV – HCV risk practices than their counterparts not prescribed morphine sulfate. This is an important result in the French context, where the drug has not yet been officially licensed as an OST. More generally, this result shows that a large proportion of people who inject opioids self-medicate with morphine sulfate for their opioid dependence. As has been already suggested, “the needs of drug users for substitution therapy and drug-use-related care can vary greatly” (Chappard, 2009). It is very probable that oral OST, be it methadone or buprenorphine, does not fully meet the self-medication needs of these people. In a previous article, Khantzian suggested that “there is a considerable degree of preference/specificity for an individual’s drug-of-choice” (Khantzian, 2013). In his opinion, drug addictive behaviors stem from self-medication “to relieve human psychological suffering”. In general, self-medication is known to be efficient in some contexts, but to a lesser extent in participants who are very socially and medically vulnerable (da Rocha et al., 2016; Raynaud, 2008). Khantzian’s drug-related self-medication hypothesis, together with our findings, underline the importance of developing treatment for addiction reflecting the specific needs of drug users.

MSI had a higher frequency of daily injection than PWID who injected other drugs. This could be explained by morphine sulfate having a shorter half-life than other opioids (Rook, Huitema, van den Brink, van Ree, & Beijnen, 2006). Although a non-negligible proportion of MSI (34%) received morphine sulfate through prescription, this drug was prescribed less often than other OST, which is not surprising given its current legal status in France (Peyriere et al., 2013). MSI were also less likely to use cocaine or crack which corroborates previous findings (Fischer et al., 1999; Kraigher et al., 2005). This may be correlated to the pharmacological difference between morphine sulfate and other opioids, especially buprenorphine, which has a lower intrinsic activity than morphine (Jasinski, Pevnick, & Griffith, 1978) and lower abuse liability (Lofwall & Walsh, 2014; Walsh, Nuzzo, Lofwall, & Holtman, 2008). Therefore, the desired effect which morphine sulfate users seek may be different from that of buprenorphine users (Peyriere et al., 2016; Roux et al., 2017). Finally, the higher rate of HIV/HCV risk practices in MSI in our study may be explained by their higher frequency of daily injection. However, those prescribed morphine sulfate were 90% less likely to report HIV – HCV risk practices than those who injected non-prescribed morphine sulfate. In a context where this opioid has not yet been approved for opioid dependence in France, this result is of paramount importance.

In Austria, morphine has been prescribed to treat opioid dependence since 1998 and many studies have demonstrated its efficacy (Beck et al., 2014; Eder et al., 2005; Mitchell, White, Somogyi, & Bochner, 2004). In particular, several studies evaluating slow-release morphine sulfate have suggested that this OST option is clinically more effective than methadone in reducing craving for heroin (Falcato, Beck, Reimer, & Verthein, 2015), in improving well-being (Eder et al., 2005), reducing symptoms of mental-health problems and increasing treatment satisfaction (Verthein, Beck, Haasen, & Reimer, 2015). We also found that the AERLI intervention have a positive impact on HIV/HCV

risk practices among MSI (Roux et al., 2016). AERLI could be provided to users in harm reduction programs and to patients who inject morphine sulfate as part of therapeutic education programs.

With respect to injection-related complications, we did not find any differences between those who injected prescribed and non-prescribed morphine sulfate. Furthermore, the AERLI intervention had no impact on MSI in general, in terms of injection-related complications. This is important to note as the injection of a tablet, even in the context of prescribed treatment, has many negative consequences for patients (Diot et al., 2014; Peyriere et al., 2013). These findings highlight two important issues. The first is the need to develop injectable treatment for opioid-dependent individuals refractory to oral OST (Strang et al., 2015). The second is the necessity to adapt the AERLI intervention to MSI.

In this perspective, some interesting findings have been reported recently regarding the safety profile of injectable hydromorphone when monitored by health professionals (Oviedo-Joekes et al., 2017). All these findings suggest that further clinical studies are needed to enlarge the therapeutic arsenal for opioid-dependent people who inject drugs. More particularly, as heroin-assisted treatment is not easily accepted in some countries, morphine sulfate or hydromorphone should be considered.

Some study limitations must be acknowledged. First, drug and alcohol use data were collected through self-reports and could be subject to social desirability bias. However, it has been already shown that self-reported drug use data in this population is reliable (Darke, 1998). Second, the ANRS-AERLI study was not designed to specifically investigate morphine sulfate injection among opioid injectors and accordingly, no information could be collected regarding the reasons why individuals chose to inject this drug instead of buprenorphine (Roux et al., 2017).

In conclusion, MSI are a sub-group of PWID with specific needs in terms of OST and education about safer injection. Our results show that they use fewer stimulants but have more HIV/HCV risk practices than other injectors. However, when morphine sulfate is prescribed (versus non-prescribed), these risk practices tend to decrease. This hugely important finding underlines the need to adapt available harm reduction tools to MSI, and to provide comprehensive education about safer injection and injecting materials. Our results shed light not only on the importance of increasing access to prescribed oral morphine sulfate as a treatment for opioid dependence, but also on the potential of developing a groundbreaking injectable OST.

## Authors’ contributions

PC, MD, PR, CP, GM and DRC designed the study and wrote the protocol. PR and SM managed the literature searches, and formulated the research questions. PR wrote the first draft of the manuscript. CP and GM participated in the data collection, and CP, KN, SM and PR undertook the statistical analyses. All authors contributed to and approved the final manuscript.

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## Conflict of interest declaration

The Authors taking part in this study declare they have nothing to disclose regarding funding or conflict of interest with respect to this manuscript.

## Declaration of interests

None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugpo.2018.06.013>.

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