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Patient Preference and Adherence

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ORIGINAL RESEARCH

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Purpose: Extended-release buprenorphine (XR-BUP) covers a range of formulations of buprenorphine-based treatments for opioid use disorder (OUD) that release the medication over a period of one week, one month, or six months. OUD is particularly prevalent among incarcerated populations, and previous findings have shown that incarcerated subjects were not less interested in XR-BUP than non-incarcerated subjects. However, no study has ever investigated whether the factors of interest in XR-BUP were similar in incarcerated and non-incarcerated populations.

Patients and Methods: We carried out post-hoc analyses using data from the "AMBRE" survey, which was conducted among 366 individuals with OUD, that were recruited in 68 French addiction settings, including six prison medical centers. The reasons for interest in XR-BUP were compared between incarcerated and non-incarcerated interviewees, using logistic regressions models, which provided raw and adjusted odds ratios (aORs) and 95% confidence intervals (95% CI). Adjustment variables were gender, age category, level of education, and type of current medication for OUD, respectively.

Results: Data from 317 participants (ie, 221 non-incarcerated, and 96 incarcerated individuals) were included in the analyses. Adjusted comparisons found that "no longer taking a daily treatment" (aOR= 2.91; 95% CI= 1.21–6.98) and "having a more discreet medication" (aOR= 1.76; 95% CI= 1.01–3.10) were reasons that appealed more to incarcerated participants than to non-incarcerated ones. On the other hand, the potential reduction of withdrawal symptoms (aOR= 0.54; 95% CI= 0.29–0.99) or the risk of misuse (aOR= 0.56; 95% CI= 0.34–0.94) associated with XR-BUP treatment were considered more important by non-incarcerated individuals than by incarcerated ones.

Conclusion: Incarcerated interviewees were interested in XR-BUP for different reasons than those outside prison. In particular, incarcerated patients were more interested in practicability and discretion features, and less in improving recovery or reducing misuse than non-incarcerated patients.

Keywords: prison, opioid use disorder, buprenorphine, preferences

Introduction

Opioid use disorder (OUD) is the official term for opioid addiction. OUD is responsible for an important burden of disease, in part due to overdose, viral infection such as HIV or HCV, or severe psychosocial consequences.[1] Methadone and buprenorphine are the most common medications for opioid use disorder (MOUD) used in the pharmacotherapy of opioid use disorder (OUD). MOUDs

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allow to substantially improve the outcomes of uncontrolled opioid use, as well as recovery and quality of life among OUD subjects.[2] However, MOUDs also have some specific drawbacks. Methadone may significantly increase the risks of overdose, in particular during its initiation phase and if supervision is insufficient.[3] Sublingual buprenorphine can be misused if diverted for injection or intranasal use, which may lead to specific complications such as injection abscess, trauma, endocarditis.[1] Furthermore, the current forms of buprenorphine- and methadone-based treatments require daily intake, which may be a source of constraints, stigma and inconvenience.[4]

For all these reasons, new formulations of extended-release buprenorphine (XR-BUP) have recently been developed and commercialized, offering a one-week, one-month, or six-month treatment coverage to OUD subjects, through subcutaneous depot or implant formulations.[5] Two depot forms, ie Buvidal® (Camurus®, Sweden) and Sublocade® (Indivior®, USA), have been approved in different countries. Furthermore, an implant, Sixmo®, has been approved in the USA and in Europe. The efficacy of Buvidal® (one-week or one-month) has been explored in a double-blind double-dummy randomized clinical trial comparing Buvidal® versus sublingual buprenorphine/naloxone, during 24 weeks and among 428 subjects. This study found that Buvidal® was not inferior to sublingual buprenorphine/naloxone for supporting the cessation of non-therapeutic opioid use (35.1% and 28.4%, respectively).[6] In other study conducting during 48 weeks in 227 subjects, 82.8% of the participants who had switched from sublingual buprenorphine to Buvidal® maintained the cessation of non-therapeutic use of opioids.[7] Concerning Sublocade® (one-month), its efficacy has been investigated versus placebo for 6 months in 489 subjects. The main assessment criterion was reporting no opioid use and displaying a negative urine screen at the end of the study period (42.7% with Sublocade® versus 5.0% with placebo).[8] Finally, three efficacy studies were conducted on the implants (6-months formulation) in 627 subjects.[9–11] Efficacy was defined as a negative urine screen at the end of the study period, ie 24 weeks for 287 patients (31% efficacy for the implant, versus 13% for placebo and 33% for sublingual buprenorphine); 16 weeks for 163 patients (40% efficacy for the implant versus 28% for placebo); and six months for 177 subjects (approximately 96% were negative for heroin in the group receiving the active implant, versus 88% in the group receiving active sublingual buprenorphine). These new treatment options aim to improve treatment coverage, but also the reduction of withdrawal and craving, and the comfort and convenience features among treatment-seeking patients with OUD. Surveys among people using opioids or treatment-seeking OUD subjects have revealed that these new formulations raise interest for the reasons listed above. However, interviewees expressed some concerns: these new formulations can be perceived as coercive or as reducing the ability to stop MOUD and resume recreational opioid use, depending on individual preferences and treatment objectives.[12–14]

OUD is particularly prevalent among incarcerated persons. Though no prevalence rate has been estimated, it has been found that approximately one-third of individuals with OUD are incarcerated annually.[15] For these individuals, incarceration can constitute an opportunity to initiate treatment.[16] Compared with incarcerated subjects with OUD who are untreated, those who receive a MOUD show significant reductions in their overall opioid use during incarceration, as well as in the frequency of their injection behaviors, prison infractions, and suicide and overall mortality risk in prison.[17,18] Moreover, treated subjects are less likely to experience an overdose after prison release. Consequently, it has been deemed crucial to scale up OUD treatment and prevention strategies within a continuum of initiatives taking place before, during, and after incarceration.[18] However, the access to MOUDs remains globally insufficient in prison. This can be explained by a lack of resources and appropriate services, as well as negative perceptions among prison medical teams and penitentiary staff related to stigma, uncertainty of the effectiveness of MOUDs, and apprehension related to safety issues, such as overdose, diversion, or misuse of MOUDs.[19] Barriers may also come from the subjects' environment, as MOUD diversion is important in prison,[20] which can lead to bullying and violence, and thus prevent inmates with OUD from seeking treatment.[21] Justice-involved populations are largely disconnected from care, and offering on-demand, flexible, and de-stigmatizing treatment may be a first step in connecting high-risk populations with the healthcare system and interventions that reduce risks of overdose and related harms.[22,23]

Recent expert opinions and national guidelines have pointed out the interest of using XR-BUP in prison[4,24] to better ensure treatment coverage and discretion, as well as comfort of patients willing to receive these new forms of

MOUD.[4] However, until recently, the surveys investigating the interest for XR-BUP did not include incarcerated subjects. In the recent AMBRE study conducted in France in 366 treatment-seeking subjects with OUD, approximately one-third of the recruited sample consisted of incarcerated people.[25] This study found no difference in the number of people interested in being treated with XR-BUP between incarcerated and non-incarcerated participants. Nonetheless, respondents that reported experiencing situations in which taking their MOUD was impractical were significantly more interested in XR-BUP. However, the first series of analyses did not compare the reasons for which XR-BUP would be considered as an option between incarcerated and non-incarcerated subjects. Post-hoc analyses were thus required to examine this additional question.

Patients and Methods

This study is reported according to the "Strengthening the reporting of observational studies in epidemiology" (STROBE) statement.[26]

Study Design and Population

The "AMBRE" study was a cross-sectional survey conducted in 366 patients, recruited in 68 French addiction facilities prescribing MOUDs. Among them, 6 were prison medical centers. The survey took place between December 2, 2018 and May 31, 2019. Among them, 6 were prison medical centers. The survey took place between 12/02/2018 and 05/31/2019. Inclusion criteria were as follows: 1) being aged 18 years or more; 2) initiating or being currently treated with a MOUD; 3) providing written consent for participating in the survey; and 4) being capable of completing a self-administered questionnaire. Other features of the survey can be found in the parent publication.[25]

Study Questionnaire

The questionnaire (available in Supplemental Materials) was built by the authors and pre-tested on a small group of treatment-seeking OUD subjects, in order to ensure the acceptability and reproducibility of the collected data. It aimed to explore: 1) the main sociodemographic features and clinical history of participants, as well as characteristics regarding their use of MOUD; 2) the participants' objectives with respect to their OUD treatment; and 3) the perceptions of participants regarding the convenient or problematic aspects of MOUD in their daily life. Participants had to answer questions of a self-questionnaire, but they could be helped by a physician or a nurse if required. After this first series of questions, a quick standardized text, included in the questionnaire sheet and available in the Supplemental Materials, described what weekly and monthly XR-BUP consist of. After reading this text, participants were asked to assess their potential interest in such formulations of MOUD, using a 1–10 Likert scale. A last series of questions explored why participants would choose XR-BUP formulations, and what they would expect.

Data Transformation and Analysis

In the present study, only the following items of the questionnaire were integrated in the analyses: 1) sociodemographic features of participants; 2) type of current MOUD (ie, buprenorphine or methadone); and 3) possible factors of choice for changing their current mood for XR-BUP (as investigated in Q38). To simplify the analysis process and the interpretation of the results, the answers to questions offering multiple answer options were binarized. Answers to the different questions included in Q38 (eg, "In your opinion, what are the important factors that could lead you to choose this new treatment?") were binarized as follows: "very important" and "important" were merged into "important", while "not very important" and "not important at all" were regrouped into "not important". The four answer options to Q40 (ie "On a personal level, would you be prepared to change your current treatment in order to take this new treatment?") were also binarized as follows: "Yes, definitely", and "Yes, possibly", were merged into "Yes", while "I cannot say at this time", "No, probably not", and "No, certainly not", were defined as "No, or do not know".

Categorical parameters are presented as the number of subjects and percentage (n; %). Each variable of interest is presented for incarcerated participants, non-incarcerated ones, and both groups together. Comparisons were performed using bivariable tests, ie, chi-squared test or Fisher's exact test, when appropriate. Raw odds ratios and their 95% confidence interval (OR [95% CI%) are also displayed.

Subsequently, multivariable regression logistic regression models were built, with the answers to Q40 and Q38 as the dependent variables, incarcerated vs non-incarcerated status as the explanatory variable, and sex, age category, level of education, and housing status, as

adjustment variables. Results are provided as raw (ORs) and adjusted (aORs) odds ratios and their 95% confidence interval (95% CI). Subjects with missing values were not integrated in the models. Statistical analyses were performed using the XLSTAT2019 software (https://www.xlstat.com/en/).

Ethical Aspects

In accordance with the French law on clinical research (Loi Jardé), the study protocol was submitted to and approved by the CNIL (#2211988). All participants were informed about the purpose of the study, and that it was conducted in accordance with the Declaration of Helsinki.

Results

From the initial dataset of 366 participants, the data from 317 (ie, 221 non-incarcerated, and 96 incarcerated) interviewees were analyzed. The main sociodemographic and clinical features of the total sample, the responses to the readiness to change their current MOUD for XR-BUP (Q40) and the related factors of interest (Q38), are displayed in Table 1. This table also provides bivariable comparisons of the same parameters between incarcerated and non-incarcerated participants. Table 2 displays the ORs and aORs, and their 95% CI, regarding the comparisons in the different parameters between incarcerated and non-incarcerated participants, before and after adjusting for gender, age category, level of education, and type of MOUD.

Overall, multivariable comparisons found that, relative to non-incarcerated participants, incarcerated participants were readier to try XR-BUP than non-incarcerated ones (aOR= 1.80; 95% CI= 1.04 to 3.13). Significant reasons for a possible switch to XR- BUP were receiving a constant dose of MOUD (aOR= 2.91; 95% CI= 1.21 to 6.98), and taking a form of MOUD more discreet than oral or sublingual forms (aOR= 1.76; 95% CI= 1.01 to 3.10). By contrast, incarcerated subjects granted significantly less interest in the facts that a subcutaneous injection is involved (aOR= 0.24; 95% CI= 0.14 to to 0.43), that XB-BUP could reduce the risk of withdrawal, ie "No longer worrying about feeling ill if I forget my treatment" (aOR= 0.54; 95% CI= 0.29 to 0.99), or that, with XR-BUP, they can "no longer have the option of injecting, snorting or inhaling the MOUD" (aOR= 0.56; 95% CI= 0.34 to 0.94).

Discussion

Both expert opinions and national guidelines have pointed out that XR-BUP formulations could be of particular interest in prisons, for both convenience and efficacy reasons.[4,24] However, because some people with OUD were concerned about the concept of XR-BUP and more precisely with respect to a possible limitation of freedom and coercive treatment,[12,13] it was important to address whether incarcerated people with OUD were ready to try XR-BUP or reluctant to receive it, and what could be the factors of interest and the expectations about these new formulations. In the main results of the AMBRE survey, which were previously published in the parent study,[25] it was found that a majority of the participants was interested in the principle of XR-BUP, and that the average level of interest was similar in incarcerated and non-incarcerated interviewees. However, we did not explore whether the factors of interest and expectations about XR-BUP were different.

The first main finding of these post-hoc analyses was that almost two-thirds of incarcerated people with OUD declared themselves ready to change their current MOUD to XR-BUP, versus barely more than one-half of non-incarcerated subjects. This suggests a good level of acceptability of XR-BUP among subjects with OUD in a prison setting. In addition, we found that incarcerated interviewees were not interested in XR-BUP for the same reasons as those outside prison. More specifically, they less expected XR-BUP to help them improve outcomes of OUD, or to reduce safety issues related to MOUD, such as the occurrence of withdrawal, or the potential of misuse. By contrast, practical aspects such as no longer having to take their MOUD every day, or receiving a more discreet treatment, appealed to incarcerated participants. Buprenorphine diversion and misuse are widespread in prison[20] and thus recipients of daily medication can be subject to bullying and violence in this environment. This has been reported in France,[27] and in some other countries, such as the UK.[21] It will thus be important to assess whether the patients treated with a depot or implant form of buprenorphine will be exposed to the same harassment or extortion as those receiving sublingual buprenorphine. This may explain the patterns of responses found in the survey, although this would require further investigation. If the use of XR-BUP makes it possible to reduce diversion and trafficking, and incidentally the violence linked to

Table 1 Bivariable Comparisons in the Features of Incarcerated and Non-Incarcerated Interviewees

Parameter	Total n (%)	Incarcerated n (%)	Not Incarcerated n (%)	*p*-value
Sociodemographic features				
Gender				
Male	239 (75.4)	86 (89.6)	153 (69.2)	**< 0.001**
Female	78 (24.6)	10 (10.4)	68 (30.8)	
Housing status				
Unstable	117 (36.9)	61 (63.5)	56 (25.3)	**< 0.001**
Stable	200 (63.1)	35 (36.5)	165 (74.7)	
Level of education				
Primary	27 (8.5)	7 (7.3)	20 (9.0)	**0.005**
Secondary	223 (70.4)	79 (82.3)	144 (65.2)	
High school or higher	67 (21.1)	10 (10.4)	57 (25.8)	
Current MOUD type				
BUP or BUP/NAL	195 (61.5)	59 (61.5)	136 (61.5)	0.989
Methadone	122 (38.5)	37 (38.5)	85 (38.5)	
Binarized answer to Q40. "Would you be prepared to change your current treatment in order to take this new treatment (ie XR-BUP)?"				
No, or do not know	148 (46.7)	35 (36.5)	113 (51.1)	**0.016**
Yes	169 (53.3)	61 (63.5)	108 (48.9)	
Binarized answers to Q38. "In your opinion, what are the important points that could lead you to choose this new treatment (ie XR-BUP)?"				
No longer having to take any tablets (or capsules/syrup) every day				
Not important	86 (27.1)	19 (19.8)	67 (30.3)	0.053
Important	231 (72.9)	77 (80.2)	154 (69.7)	
No longer forgetting to take the tablets (or capsules/syrup)				
Not important	137 (43.2)	43 (44.8)	94 (42.5)	0.709
Important	180 (56.8)	53 (55.2)	127 (57.5)	
The option of taking the medication only once a week/month				
Not important	63 (19.9)	17 (17.7)	46 (20.8)	0.524
Important	254 (80.1)	79 (82.3)	175 (79.2)	
The fact that a subcutaneous injection is involved (only slightly painful)				
Not important	182 (57.4)	75 (78.1)	107 (48.4)	**< 0.001**
Important	135 (46.2)	21 (21.9)	114 (51.6)	
Being sure to receive a constant dose, always effective throughout the week/month				
Not important	44 (13.9)	6 (6.3)	38 (17.2)	**0.010**
Important	273 (86.1)	90 (93.7)	183 (82.8)	

(*Continued*)

Table 1 (Continued).

Parameter	Total n (%)	Incarcerated n (%)	Not Incarcerated n (%)	*p*-value
No longer having to use heroin/morphine				
Not important Important	67 (21.1) 250 (78.9)	24 (25.0) 72 (75.0)	43 (19.5) 178 (80.5)	0.267
Avoiding having to share (or resell) all or part of my prescribed treatment				
Not important Important	179 (56.5) 138 (43.5)	60 (62.5) 36 (37.5)	119 (53.8) 102 (46.2)	0.153
No longer worrying about feeling ill if I forget my treatment for a few hours, or if I am unable to take it at the usual time				
Not important Important	64 (20.2) 253 (79.8)	26 (27.1) 70 (72.9)	38 (17.2) 183 (82.8)	**0.044**
No longer feeling the effect of heroin/morphine if I take more of this treatment than I should				
Not important Important	148 (46.7) 169 (53.3)	53 (55.2) 43 (44.8)	95 (43.0) 126 (57.0)	**0.045**
No longer having the option of injecting, snorting or inhaling my treatment				
Not important Important	163 (51.4) 154 (48.6)	58 (60.4) 38 (39.6)	105 (47.5) 116 (52.5)	**0.035**
The option of a more "discreet" treatment (one injection a week/month by going to my doctor's/to the centre) as compared to tablets (or capsules, syrup) to be taken at home, with me, every day				
Not important Important	108 (34.1) 209 (66.9)	23 (24.0) 73 (76.0)	85 (38.5) 136 (61.5)	**0.012**

Note: Significant p-values are presented in bold.
Abbreviations: BUP, buprenorphine; BUP/NAL, buprenorphine/naloxone; MOUD, medications for opioid use disorder; XR-BUP, Extended-release buprenorphine.

trafficking in prison, it would be a shame to deprive incarcerated patients of this possibility. In addition, the access to MOUD in a prison setting can be impeded by insufficient time or insufficient training level of both health care and security staffs.[28] In this regard, the implementation of XR-BUP could reduce the overall time staff need to provide adequate access to MOUD for people with OUD. Though it would also require an additional, albeit limited, training of physicians and nurses on the injection procedure, the use of XR-BUP might be time-saving on the longer-term, which could facilitate its acceptance by security and health care staffs also.

This survey had some limitations that should be acknowledged. First, the study population was a small sample. Because these types of survey investigate people with illegal behaviors, it is usually very hard to build a "representative" sample of these populations with OUD. Nevertheless, the sample of the survey was consistent with the typical demographics of French people with OUD, including the proportion of males vs females and the proportion of subjects treated with buprenorphine or methadone.[27] A similar limitation was that the subjects compared were not paired with others from the second group, which could have generated biases, even if multivariable comparisons were adjusted on important sociodemographic and clinical features. Moreover, because XR-BUP formulations are not yet commercialized in France, this survey explored the intentions and representations of subjects with no practical experience with the products described. Thus, results may vary from those reported here if a comparable study is performed after XR-BUP formulations become available in France. Last, the analyses were not adjusted for multiple comparisons, but some authors deem that such adjustments are not required for exploratory observational studies.[29]

Table 2 Raw and Adjusted Comparisons of Factors of Interest for XR-BUP Between Incarcerated and Non-Incarcerated Subjects

Parameter	OR [95% CI]	aOR [95% CI] [a]
Binarized answers to Q.38. "In your opinion, what are the important points that could lead you to choosing this new treatment (ie XR-BUP)?"		
No longer having to take any tablets (or capsules/syrup) every day (nmv= 2)		
Incarcerated (n= 96; 30.1%) Not incarcerated (n= 223; 69.9%)	1.76 [0.99–3.14] † 1	1.81 [0.99–3.31] † 1
No longer forgetting to take the tablets (or capsules/syrup) (nmv= 5)		
Incarcerated (n= 96; 30.4%) Not incarcerated (n= 220; 69.6%)	0.91 [0.56–1.48] 1	0.87 [0.52–1.44] 1
The option of taking the medication only once a week/month (nmv= 6)		
Incarcerated (n= 95; 30.2%) Not incarcerated (n= 220; 69.8%)	1.22 [0.66–2.26] 1	1.25 [0.65–2.4] 1
The fact that a subcutaneous injection is involved (only slightly painful) (nmv= 3)		
Incarcerated (n= 96; 30.2%) Not incarcerated (n= 222; 69.8%)	**0.26 [0.15–0.46] **** 1	**0.24 [0.14–0.43] **** 1
Being sure to receive a constant dose, always effective throughout the week/month (nmv= 3)		
Incarcerated (n= 96; 30.2%) Not incarcerated (n= 222; 69.8%)	**3.11 [1.27–7.64] *** 1	**2.91 [1.21–6.98] *** 1
No longer having to use heroin/morphine (nmv= 3)		
Incarcerated (n= 96; 30.2%) Not incarcerated (n= 222; 69.8%)	0.72 [0.41–1.28] 1	0.67 [0.36–1.24] 1
Avoiding having to share (or resell) all or part of my prescribed treatment (nmv= 4)		
Incarcerated (n= 96; 30.3%) Not incarcerated (n= 221; 69.7%)	0.70 [0.43–1.14] 1	0.70 [0.42–1.17] 1
No longer worrying about feeling ill if I forget my treatment for a few hours, or if I am unable to take it at the usual time (nmv= 5)		
Incarcerated (n= 96; 30.4%) Not incarcerated (n= 220; 69.6%)	**0.56 [0.32–0.99] *** 1	**0.54 [0.29–0.99]*** 1
No longer feeling the effect of heroin/morphine if I take more of this treatment than I should (nmv= 10)		
Incarcerated (n= 93; 29.9%) Not incarcerated (n= 218; 70.1%)	**0.61 [0.38–0.99] *** 1	0.62 [0.37–1.03] † 1
No longer having the option of injecting, snorting or inhaling my treatment (nmv= 6)		
Incarcerated (n= 96; 30.5%) Not incarcerated (n= 219; 69.5%)	**0.59 [0.36–0.96] *** 1	**0.56 [0.34–0.94] *** 1
The option of a more "discreet" treatment (one injection a week/month by going to my doctor's/to the centre) as compared to tablets (or capsules, syrup) to be taken at home, with me, every day (nmv= 4)		
Incarcerated (n= 96; 30.3%) Not incarcerated (n= 221; 69.7%)	**1.98 [1.15–3.41] *** 1	**1.76 [1.01–3.10] *** 1

(*Continued*)

Table 2 (Continued).

Parameter	OR [95% CI]	aOR [95% CI] [a]
Binarized answers to Q.39. "Would you say that for you this new product (ie XR-BUP) involves"		
Fewer limitations compared to your current treatment (nmv= 3)		
Incarcerated (n= 96; 30.2%) Not incarcerated (n= 222; 69.8%)	1.54 [0.85–2.79] 1	1.44 [0.78–2.68] 1
The option of better following/adhering to my treatment, avoiding cravings and relapses (nmv= 3)		
Incarcerated (n= 96; 30.3%) Not incarcerated (n= 221; 69.7%)	1.29 [0.75–2.21] 1	1.42 [0.81–2.47] 1

Note: †p<0.1; *p<0.05; **p<0.0001. Significant OR or aOR (p-value) are presented in bold. ([a]adjusted for gender, age category, level of education, and type of OAT).
Abbreviations: OR, odds ratio; aOR, adjusted OR; 95% CI: 95% confidence interval; nmv, number of missing values; XR-BUP, extended-release buprenorphine.

Conclusion

Our post-hoc analyses found that the motivations for trying XR-BUP were different inside and outside prison. In particular, incarcerated subjects with OUD were more interested in the possible discretion and practicability aspects related to XR-BUP, and less in their potential effectiveness in improving recovery or safety by using long-acting treatment.

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Disclosure

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