Prospective Evaluation

Long-term Consequences of Acute Pain for Patients under Methadone or Buprenorphine Maintenance Treatment

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Background: Acute and chronic pains are reported to be highly prevalent in patients under opioid maintenance treatment (OMT). Lack of knowledge concerning the complex relationship between pain, opioid use, and their impact on OMT efficacy can account for the barriers encountered for pain management.

Objectives: To assess the impact of acute pain exposure on long-term OMT retention in a cohort of patients under buprenorphine or methadone followed up during 12 months.

Study Design: Prospective, multi-center observational cohort clinical study.

Setting: Emergency departments, surgery departments, and specialized addiction care centers in an outpatient setting in south-western France (Midi-Pyrénées area), from April 2008 to January 2010.

Methods: Patients aged 18 or more under OMT for at least 3 months, and followed up by a physician were recruited. Acute pain was assessed using the Visual Analog Scale (VAS) or the Verbal Rating Scale (VRS). Exposed patients were those with a pain score greater than 0 at the time of admission on any of the rating scales. The OMT rate after 12 months was compared among exposed and unexposed patients. OMT retention was also investigated after 3 and 6 months follow-up.

Results: A total of 151 patients, 81 exposed and 70 unexposed, were recruited; among them, respectively, 26 (32%) and 34 (49%) completed 12-months follow-up. Acute pain exposure appeared to be significantly and negatively associated with retention in treatment (crude OR: 0.44; 95% CI [0.22 – 0.87]; adjusted OR: 0.46; 95% CI [0.23 – 0.93]). Compared to methadone users, patients under buprenorphine were less likely to have their OMT maintained after 12 months (OR 0.37; 95% CI [0.18 – 0.75]; adjusted OR 0.38; 95% CI [0.18 – 0.80]).

Limitations: Follow-up rate was 40 % (60/151).

Conclusion: This study demonstrates the strong negative impact of acute pain on OMT in a population mainly composed of patients under buprenorphine, as well as differential response depending on the OMT medication. The findings highlight the need to consider the characteristics of pain in the population under OMT and to develop evidence-based guidelines for pain management.

Trial registration: The study was registered at www.clinical.trials.gov with the study identifier: NCT00738036. Ethics Committee approval was received on February 11, 2008. Participants' written consent was not required.

Key words: Analgesic drug, methadone, buprenorphine, opioid, opioid maintenance treatment, acute pain, long-term retention, pharmacodependence, pharmacoepidemiology

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Methadone and buprenorphine are approved for treatment of opioid addiction in France, with an increasing use of these drugs for this indication. The World Health Organization stated in 2008 that buprenorphine and methadone were available in 28% and 42% of the 144 surveyed countries, respectively (1). In France, 150,000 patients were under opioid maintenance treatment (OMT) in 2011, and more than 3 out of 4 were taking buprenorphine (2). After the initiation phase of the treatment, stabilized patients under methadone or buprenorphine are followed by either a specialist or primary care physician, or in specialized addiction centers in an outpatient setting.

The benefits of OMT on the reduction of illicit drug use and risk behaviors are recognized, but are strongly dependent on retention duration, which is a strong predictor of OMT success, as well as the gold standard to assess the effectiveness of these programs (3).

Acute and chronic pain are reported to be highly prevalent in patients under OMT, as described by Rosemblum et al for methadone (4). Lack of knowledge concerning the complex relationship between pain, opioid use, and their impact on OMT can account for the barriers encountered for pain management. Occurrence of opioid-induced hyperalgesia has been described in those patients, and could be involved in OMT failures (5). This led us to hypothesize that pain and pharmacological pain treatment in opioid-dependent patients could be associated with a shorter time of OMT retention.

Methods

This study intended to assess the impact of acute pain on long-term OMT retention in a cohort of patients under buprenorphine or methadone followed up for 12 months.

Study Design and Settings

This was a prospective, multicenter observational cohort study. Patients were recruited in 8 emergency departments, 2 surgery departments, and 3 specialized addiction care centers in south-western France (Midi-Pyrénées area), who agreed to participate, from April 2008 to January 2010. Patients were compared according to acute pain exposure at baseline and classified in exposed or unexposed groups.

Inclusion/Exclusion Criteria

Inclusion criteria were (i) patients aged 18 or more, (ii) under OMT for at least 3 months, (iii) followed up by a physician in ambulatory care or in a specialized center. The exclusion criteria applied were (i) patients substituted with a drug not approved for OMT, (ii) patients with chronic pain lasting more than 6 months, (iii) refusal of the patient to take part in the study, and (iv) lack of possible follow-up.

Exposure Definition and Measurement

A Visual Analog Scale (VAS) or Numerical Rating Scale (NRS) were used to assess and quantify the intensity of acute pain at the time of admission, after pain management, and just before hospital discharge. Acute pain scores rated from 0 to 10 were obtained indiscriminately from one or the other measurement tool. Acute pain exposure was defined as a pain score greater than 0 at the time of admission on any of the rating scales. Pain relief was defined in the exposed group as a pain decrease of 30% and more between admission and discharge.

Outcomes Studied

The retention rate under OMT was defined as the percentage of patients still under treatment at the time of follow-up. The main outcome studied was OMT after 12 months. The secondary outcomes were OMT after 3 and 6 months follow-up.

Other Variables Collected

Data collection was made on a paper-based questionnaire elaborated by an expert committee composed of addiction physicians, anesthesiologists, emergency physicians, pain specialists, and pharmacologists.

During baseline assessment, the following information was collected by recruiting physicians: patients demographics (age, gender), identification of the referring physician or center for the OMT, cause of consult, OMT characteristics (type, prescribed daily dose, route, timing, treatment duration), misuse of the OMT and type of misuse (injected, snorted, fractioned, overdose), complaints of chronic pain syndrome (lasting more than 3 months), usual management of chronic pain, illicit consumption of drugs and other substances (sedatives, stimulants, hallucinogens, cannabis), baseline prescribed drugs, and drugs prescribed during consult (including those prescribed for pain treatment and opioid maintenance). All the later information was based on self-reported data from face to face medical interviews.

Retention in treatment was assessed at 3, 6, and 12 months by contacting the identified referring phy-

sicians or specialized addiction care centers. Indeed, patients receiving OMT prescriptions had to visit their physicians every 14 days (for methadone) or 28 days (for buprenorphine) according to French rules of prescription for these drugs. Medical records from the most recent visit until the corresponding endpoints were used to collect the characteristics of OMT (retention, type, prescribed daily dose, route, and timing, misuse of the maintenance treatment and type of misuse), consumption of drugs and other substances, chronic or acute pain, and significant events (hospital stay and cause of admission).

Study Size

The OMT rate in buprenorphine-treated patients after 24 or 52 weeks has been estimated between 30 and 40%, and from 40 to 60% in patients under methadone OMT (6). A rate of 50% (all OMT) in unexposed patients was retained. Due to the scarce data in this area, it was difficult to provide an estimate of OMT rate in exposed patients after 12 months. It was hypothesized that acute pain exposure could lead to a 50% decrease in maintenance rate in the exposed group (OMT rate = 25%). A total of 65 patients per group was considered sufficient to detect a reduction from 50% to 25% in OMT rate with a 80% power (α = 0.05) in groups with equal size 1:1, whereas 50 exposed and 100 unexposed patients would be considered sufficient in an unbalanced design (1:2).

Statistical Methods

For patients followed up until the end of the study, the retention rate was the percentage of patients still under OMT. Lost of follow-up patients were analysed as OMT failure. A descriptive analysis was performed, comprising median and interquartile range (IQR) for continuous variables and frequency and percentages for qualitative variables. A binary logistic regression was performed with the 12 months OMT as the dependant variable. Univariate analyses on baseline variables derived from the literature as potential predictors for success or failure of OMT were performed using Chi-square statistics for categorical and Student t-test for continuous data. Variables with a *P*-value of < 0.2 after univariate analysis were entered into a multivariate logistic regression model. Crude and adjusted odds ratio (OR) and their confidence intervals were estimated. Interaction between variables was investigated using the log likelihood ratio test. The goodness-of-fit of the logistic models was assessed using the Hosmer–Lemeshow test and the Akaike information criteria. Collinearity was verified by Spearman correlation among explanatory variables. A significance level of 0.05 was used. Analyses were performed using the SAS LOGISTIC Procedure of SAS ® 9.2 software (SAS Institute Inc., Cary, NC, USA).

Ethical and Regulatory Issues

The study was registered at www.clinical.trials.gov with the study identifier: NCT00738036. The study protocol received approval from the Ethics Committee on February 11, 2008. Patients' written consent was not required for this noninterventional study.

Results

Baseline Characteristics of Study Patients

A total of 151 patients were included (in 9 active centers): 81 in the exposed group and 70 in the unexposed group. Among them, respectively 26 (32%) and 34 (49%) completed 12-months follow-up. The patient flow chart is presented in Fig. 1. Patients were almost exclusively recruited through emergency departments (n = 137; 91%). Characteristics of patients are detailed in Tables 1 and 2. Among the patients, men were 74% (n = 111). Age ranged from 20 to 54. There was no difference between exposed and unexposed patients regarding age (exposed: median 36; IQR 9, and unexposed: median 37; IQR 14) and gender (respectively, 58 [72%] women and 53 [76%] men).

Characteristics of OMT at Baseline

Among the 151 patients included, 104 (69%) were treated by buprenorphine and 47 (31%) by methadone (Table 1). Among patients receiving buprenorphine, the median daily baseline dose was 8mg [0.2 to 24 mg]. Among patients receiving methadone, the median daily baseline dose was 45 mg [10 to 120 mg]. Diversion or misuse of the OMT was found in 28% of patients (n = 43), and represented 38% of patients receiving buprenorphine (40/104 patients) and 6% of patients receiving methadone (3/47 patients).

Characteristics of Pain in Exposed Group

Existence of chronic pain lasting more than 3 months (but less than 6 months) was assessed in 107 patients: 21% of them (22/107) reported chronic pain at baseline (exposed 29% [16/55], unexposed 12% [6/52]).

Among exposed patients, median pain scores were 7 (IQR 3) at admission and 2 (IQR 2) at discharge. Pain

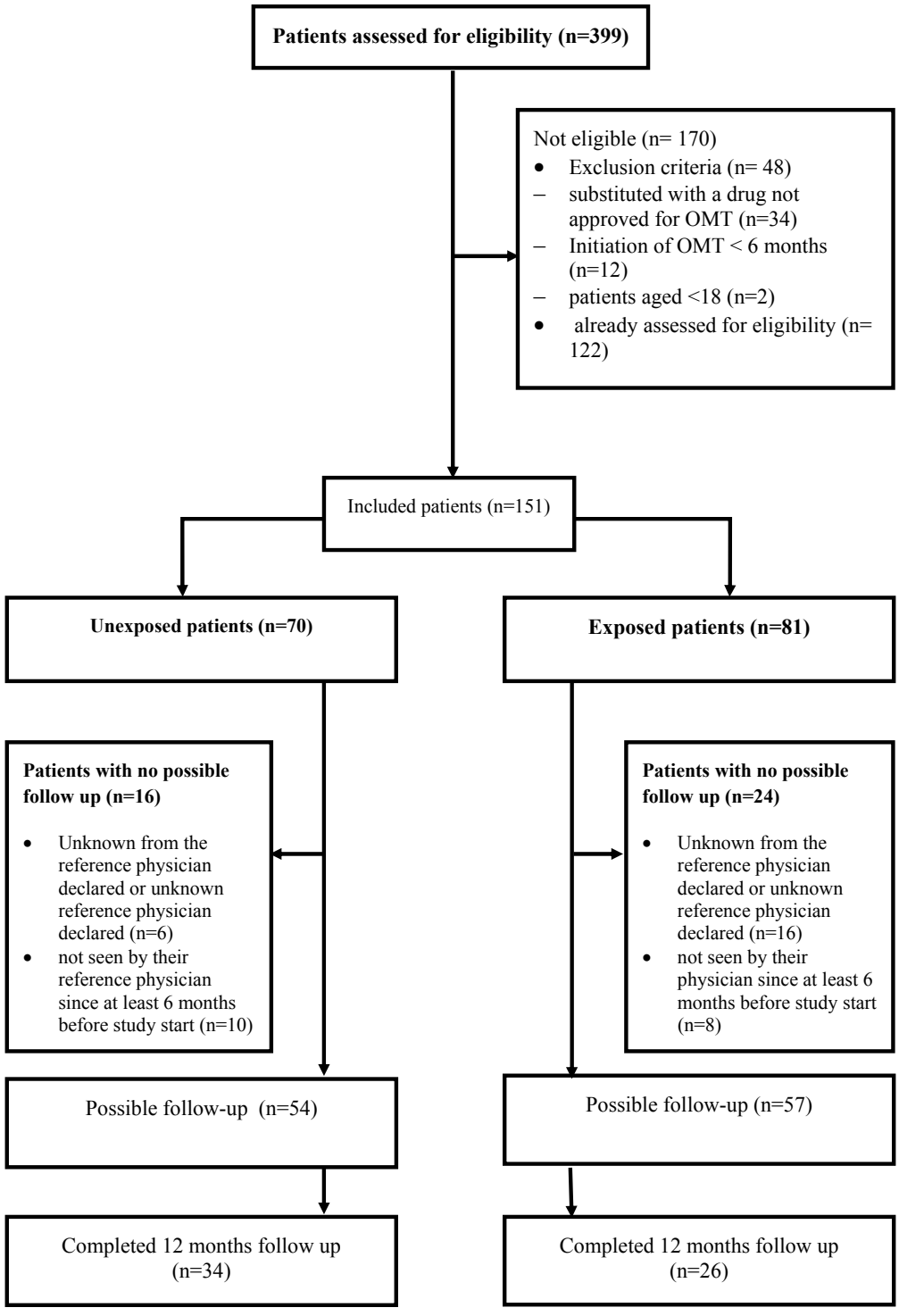

Fig. 1. Participant flow-chart.

Table 1. *Baseline characteristics of study participants: demographic and OMT.*

	Unexposed (n=70)	Exposed (n=81)	Total (n=151)
Median age [years (IQR)]	37 (14)	36 (9)	36 (11)
Men (%)	53 (76)	58 (72)	111 (74)
Buprenorphine users, n(%)	45 (64)	59 (73)	104 (69)
Daily dose [mg (IQR)]	8 (10)	12 (8)	8 (8)
Drug misuse at baseline	15 (21)	25 (31)	40 (27)
Injection	8 (11)	21(26)	29 (19)
Sniffing	2 (3)	0	2 (1)
Dose fractionation	0	1(1)	1(1)
Augmentation of prescribed doses	5 (7)	3 (4)	8 (5)
Methadone users, n(%)	25 (35)	22 (27)	47 (31)
Daily dose [mg (IQR)]	45 (30)	55 (40)	45 (35)
Drug misuse at baseline	2 (3)	1 (1)	3 (2)
Injection	1 (1)	1 (1)	2 (1)
Sniffing	0	0	0
Dose fractionation	0	0	0
Augmentation of prescribed doses	1 (1)	0	1 (1)
Baseline prescribed drugs (ATC pharmacological subgroup, 3rd level)			
opioids (N02A)	0	4 (5)	4 (3)
antipsychotics (N05A)	14 (20)	11 (14)	25 (17)
anxiolytics (N05B)	28 (40)	30 (37)	58 (38)
hypnotics and sedatives (N05C)	6 (9)	10 (12)	16 (11)
antidepressants (N06A)	11(16)	10 (12)	21 (14)
Stimulants			
Cocaine	16 (23)	16 (20)	32 (21)
Stimulants	0	3 (4)	3 (2)
Hallucinogens			
Hallucinogens	2 (3)	3 (4)	5 (3)
Other	1 (1)	1 (1)	2 (1)
Cannabis	15 (21)	28 (35)	43 (28)
Tobacco, n (%)	65 (93)	75 (93)	140 (93)

Table 2. *Baseline characteristics of study participants: medical conditions, main reasons for consult, and pain.*

	Unexposed (n=70)	Exposed (n=81)	Total (n=151)
Traumatic conditions [n (%)]	9 (13)	44 (54)	53 (35)
Top 3 reasons for consult			
Affray	3 (4)	10 (12)	13 (9)
Consequences of OMT injection	3 (4)	4 (5)	7 (5)
Head trauma	2 (3)	4 (5)	6 (4)
Non-traumatic conditions [n (%)]	61 (87)	37 (46)	98 (65)
Top 3 reasons for consult			
Drug or alcohol overdose	23 (33)	2 (3)	25 (17)
Neurological	7 (10)	4 (5)	11 (7)
Drug renewal	10 (14)	1 (1)	11 (7)
Median pain score (IQR) at inclusion, /10	0	7 (3)	-
Chronic pain at inclusion (> 3 months) [n (%)](107 patients assessed)	6 (9)	16 (20)	24 (16)

Table 3. *Pain relief (decrease of pain ≥ 30%) and 12 months OMT retention in exposed patients.*

12-months OMT retention	Pain relief reached (n=49)	Insufficient pain relief (n=17)	Total (n=66)*
Maintained, n(%)	16 (32.7)	1 (5.9)	17 (25.8)
Not maintained, n(%)	33 (67.3)	16 (94.1)	49 (74.2)

* Pain was not reassessed for 15 patients

Table 4. *12-months OMT retention rate among exposed and unexposed patients.*

	Unexposed (n=70)		Exposed (n=81)		Total (n=151)		*P*-value
"Intention to treat" approach: 12-months OMT retention *							
Maintained	30	(42.9)	20	(24.7)	50	(33.1)	0.018
Not maintained	40	(57.1)	61	(75.3)	101	(66.9)	
Analyses based on data available only: 12-months OMT retention**							
Maintained	30	(42.9)	20	(24.7)	50	(33.1)	
Not maintained	4	(5.7)	6	(7.4)	10	(6.6)	0.305
Lost patients	36	(51.4)	55	(67.9)	91	(60.3)	

* Chi square test
** Fisher test

relief was obtained for 49 patients (74%) out of 66 (15 patients were not reassessed). Among patients with insufficient pain relief, the OMT retention rate was 6% (n = 1) versus 33% (n = 16) for those with pain relief (OR = 0.132; IC 95% [0.029 – 1.002]). Those results are presented in Table 3.

Primary Outcome: 12-months OMT Retention

The follow-up rate was 40% (n = 60) and total retention rate was 33% (n = 50). Among patients included, respectively 26 (32%) exposed patients and 34 (49%) unexposed patients completed 12-months follow-up. The retention rate was 25% (20/81) for exposed patients versus 43% (n = 30) for unexposed ones, with a significant difference between groups (OR = 0.44 [0.22 – 0.87], $P < 0.02$), as presented in Table 4. When considering only patients with 12 months follow-up completed, no statistical difference was found for retention rate (20 patients out of 26 [77%] for the exposed group and 30 out of 34 [88%] for unexposed group, $P = 0.305$).

Factors Associated with 12-month OMT Retention

Bivariate analyses revealed 2 factors associated with retention in treatment after 12 months: exposure and type of OMT. Collinearity was found between traumatic conditions at inclusion and acute pain exposure. Therefore, the traumatic conditions variable was removed from multiple regression analyses. There was no significant interaction between the variables. As shown in Table 5, acute pain exposure appeared to be significantly and negatively associated with retention in treatment (crude OR: 0.44; 95% CI [0.22 – 0.87]; adjusted OR: 0.48; 95% CI [0.23 – 1.00]). Compared to methadone users, patients receiving buprenorphine OMT were less likely to have their OMT maintained after 12 months (crude OR: 0.37; 95% CI [0.18 – 0.75]; adjusted OR: 0.33; 95% CI [0.15 – 0.72]).

Discussion

This study aimed to investigate the impact of an acute painful phenomenon on long-term opioid maintenance rate. It revealed a significant drop in 12 months treatment retention in those exposed, compared to unexposed patients. Results on pain relief in exposed patients suggest an association between control of acute pain and long-term OMT retention. Relevant publications concerning the relationships between pain and OMT were focused on either pain management (7,8), chronic pain (4,9-12), or hyperalgesia (13-16), mostly in patients under methadone OMT (17). Chronic pain has been described to interfere with various domains of functioning (sleep, affect, physical activity, social relationships) (4). Some studies have shown a negative impact of chronic pain on heroin use (4,11). In a study of patients under methadone maintenance treatment (4), pain itself has been reported as increasing the risk

Table 5. *Binary logistic regression on factors associated with 12-months OMT retention.*

Factors		12-months		Univariate Analysis			Adjusted OR	Multivariate Analysis	
	total	n	%	Crude OR	95%CI	*P*-value		95%CI	*P*-value
Gender (Female vs. male)	111	39	35.1	**1.43**	[0.64-3.17]	0.380	**1.66**	0.71-3.87	**0.245**
Age (years)						0.729			**0.592**
< 30	35	12	34.3	**1**			1		
30-40	67	20	29.9	**0.82**	[0.34-1.95]		1.08	0.42-2.75	
> 40	49	18	36.7	**1.11**	[0.45-2.76]		1.56	0.59-4.18	
Acute pain exposure (exposed vs. unexposed)*	81	20	24.7	**0.44**	[0.22-0.87]	0.019	**0.48**	0.23-1.00	**0.050**
Chronic pain at baseline (exposed vs. unexposed)	22	8	36.4	**0.95**	[0.36- 2.5]	0.912			
Traumatic conditions (exposed vs. unexposed)*	53	13	24.5	**0.54**	[0.25-1.31]	0.102			
Type of OMT (buprenorphine vs. methadone)	104	27	26.0	**0.37**	[0.18-0.75]	0.006	**0.33**	0.15-0.72	**0.005**
OMT prescribed dose at baseline (high dose vs. low dose)	64	27	42.2	**1.48**	[0.64-3.44]	0.361			
OMT Injection or sniffing	50	9	18.0	**0.704**	[0.30-1.66]	0.422			
Prescribed drug at baseline (ATC pharmacological subgroup, 3rd level)									
antipsychotics (N05A)	25	8	32.0	**0.94**	[0.38-2.36]	0.897			
antidepressants (N06A)	21	7	0.33	**1.01**	[0.38-2.69]	0.892			
Associated consumption at baseline									
Sedatives									
anxiolytics and hypnotics	83	25	30.1	**0.66**	[0.33-1.31]	0.229			
opiates including heroin	46	19	41.3	**1.57**	[0.76-3.23]	0.224			
Alcohol	117	37	31.6	**0.75**	[0.34-1.65]	0.472			
Stimulants									
Cocaine	32	11	34.4	**1.01**	[0.44-2.30]	0.986			
Stimulants	3	1	33.3	**0.96**	[0.09-10.85]	0.973			
hallucinogens	5	2	40.0	**1.29**	[0.21-7.99]	0.783			
Other	2	0	0.0	**-**	-				
Cannabis	43	12	27.9	**0.66**	[0.30-1.44]	0.299			
Tobacco	140	47	33.6	**1.01**	[0.24-4.22]	0.988			

*collinearity between traumatic conditions and acute pain exposure

for patients to use illicit drugs, as well as alcohol, in order to treat their pain complaint. We hypothesize that poorly relieved significant acute pain at inclusion could become a chronic pain. This could explain the negative effect of acute pain on long-term OMT retention.

In our study, the focus on acute pain constituted an important asset for interpreting the result. In our study, the existence of a chronic pain at inclusion, lasting more than 3 months but less than 6, was not associated with long-term retention rate (chronic pain for more than 6 months was an exclusion criteria). However, only a few patients were concerned, which did not provide a definitive answer. Recruitment of patients undergoing painful phenomenon may avoid misinterpretation in relation with chronic pain, nevertheless chronic pain interference with outcome should be considered.

The one year maintenance rate was 3 times lower in patients receiving buprenorphine, compared to those receiving methadone. This result should also be interpreted with caution, as buprenorphine use in this

study is strongly associated with misuse (in particular injection).

Sample Representativeness (Demographics, Exposure, Patterns of Substance Use, Follow-up Rate)

Concerning demographics, the study sample appears to be representative of what is already reported in literature (18-20). The prevalence of chronic pain in the study population is consistent with previous studies, in which it has been estimated from 37% to 55% (4,21). Retention rate at 12 months was 33%, and was consistent with the literature (2,22), and studies performed in the same geographical area (19).

Data Collection, Quality, and Completeness

The consistency with previous findings concerning retention rate tends to confirm the practical difficulty of performing a long-term follow-up in OMT patients.

Quantification of pain exposure is based on self-assessment. The potential for information bias due to overestimation to obtain pain medication could not be entirely excluded and the magnitude could not be estimated in this study. However, the exposure variable was dichotomized, so overestimation in a pain patient would have no influence on the exposure assessment, and admission reasons were checked to ensure they were consistent with acute pain. Consumption of illegal opioids and other substances could have been dissimulated by the patients. However, some studies have demonstrated self-report of substance use could be considered as sufficiently reliable, including in an emergency context (23-25).

Bias and Confounding

Specialized addiction centers also had the opportunity to recruit patients. However, in contrast to emergency departments, they were more likely to recruit unexposed than exposed patients. So, an imbalance among patients' characteristics according to the settings could not be excluded. However, the potential for bias appears to be limited, as only a few patients were concerned (14 patients, 9% of the total sample). The large part of the exposed (n = 75, 94%) and unexposed patients (n = 62, 87%) have been recruited in emergency and other hospital settings.

The interest of research on usual care is that standard procedures are applied and the routine management is not affected by the research, leading theoretically to an unbiased, real life vision of the phenomenon. However, the possibility of influence of the research on pain management strategy in these patients should not be overlooked. In a previous study, initial pain assessment at the emergency department was performed in less than 10% of the cases (26). In the present study, pain assessment was necessary for including and classifying patients in the exposed or unexposed groups. It is well established that baseline assessment of pain is an important determinant for the success of analgesia (27,28). As a consequence, our patients should have benefited from improved pain management, and the quality of pain management in this population is potentially overestimated compared to what is routinely practiced.

Efforts were made to identify and to take into account relevant factors identified in the literature and known to be predictors of the success or failure of OMT. However, the potential for confounding due to not identified or unknown factors could not be excluded. This study could not discriminate the effect due to acute pain exposure from other related factors, such as administration of opioid analgesics; however, in the exposed group, insufficient pain relief is more frequent for patients with long-term retention failure. Finally, one important finding of our study is that acute pain concerning patients receiving methadone or buprenorphine maintenance treatment has to be aggressively treated to reach pain relief, as this may be a key for a better long-term outcome.

Conclusion

This study demonstrates the strong negative impact of acute pain exposure on OMT in a population mainly composed of patients receiving buprenorphine. It also revealed a differential response to this exposure depending on the OMT medication, with a lower maintenance rate among patients receiving buprenorphine in comparison to those receiving methadone. This study highlights the need to take account of the proper characteristics of pain and pain management in this population, which could be achieved by developing evidence-based guidelines for health professionals.

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