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► To cite this version:

Margaux Poireau, Virgile Clergue-Duval, Angéline Maillard, Romain Icick, J. Azuara, et al.. Predictors of abstinence maintenance after cocaine inpatient detoxification: A prospective study. *American Journal on Addictions*, 2024, 33 (5), pp.576-582. 10.1111/ajad.13571 . hal-04686049

HAL Id: hal-04686049

<https://hal.science/hal-04686049v1>

Submitted on 8 Nov 2024




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Predictors of abstinence maintenance after cocaine inpatient detoxification: A prospective study

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Abstract

Background and Objectives: Cocaine is a highly addictive substance, and with no approved medication for cocaine use disorder (CUD), leading to a heavy burden. Despite validated psychosocial treatments, relapse rates after detoxification are very high in CUD. Few consistent factors can predict abstinence after detoxification. Our study, therefore, aimed at identifying factors predicting abstinence among CUD patients after inpatient detoxification.

Methods: Eighty-one CUD inpatients were included during detoxification and characterized for clinical and sociodemographic data at baseline and at a follow-up of 3 months after discharge, including a standard measure of their abstinence duration from cocaine. We performed Cox univariate analyzes to determine the factors associated with abstinence maintenance, followed by a multivariate Cox regression to identify independent predictors.

Results: Abstinence maintenance was shorter in patients injecting cocaine (hazard ratio [HR] = 5.16, 95% confidence interval [CI]: 2.01–13.27, $p < .001$) and using cocaine heavily in the month before inclusion (HR = 1.03, 95% CI: 1.00–1.06, $p = .046$). Conversely, abstinence maintenance was longer in patients with longer inpatient detoxification stays (HR = 0.96, 95% CI: 0.94–0.99, $p = .015$) and prescribed with selective serotonin reuptake inhibitors (SSRIs) (HR = 0.30, 95% CI: 0.16–0.56, $p < .001$).

Discussion and Conclusions: Patients with severe CUD may require longer inpatient stays to achieve abstinence. Regarding SSRI prescription, more specific studies are needed to provide stronger recommendations about their use in clinical practice.

Scientific Significance: Our findings suggest several modifiable factors to improve inpatient treatment response in CUD. As there are no specific recommendations about the optimal duration of inpatient stay, our results could pave the way for evidence-based guidelines.

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INTRODUCTION

According to the World Drug Report 2022 of the United Nations Office on Drugs and Crime (UNODC),¹ roughly 21.5 million people used cocaine at least once in 2020 (i.e., 0.4% of the global population aged 15–64). The number of cocaine users has also increased by 32% since 2010.

Cocaine is a highly addictive substance, insofar as 15% of cocaine users develop dependence within 10 years of first cocaine use.² Cocaine dependence (DSM-IV), or severe cocaine use disorder (CUD, DSM-5), was the motive for entering specialized addiction treatment for 32,000 cocaine users entering treatment in 2020.³

CUD is a major health problem with a high mortality⁴ and leads to several medical morbidities. According to the Global Burden of Disease, 12,779 users died worldwide in 2019 because of their CUD.⁵

No approved pharmacological medication is available for CUD. Currently, treatment of CUD mainly relies on psychotherapeutic approaches, including 12-step therapy, Cognitive-Behavioral Therapy and contingency management.^{6,7}

According to the *Practice Guideline For The Treatment of Patients With Substance Use Disorders* (Second Edition) published by the American Psychiatric Association in 2007,⁸ the care of a patient with CUD does not necessarily require an inpatient setting, insofar as several studies highlighted that intensive outpatient treatment is efficient for cocaine abuse.^{9,10}

In France, the most recent version of guidelines about CUD treatment programs were published in February 2010 by the Haute Autorité de Santé (HAS).¹¹ In this report, the recommended care includes psychotherapies and psychosocial support. However, there are no indications about the setting where this treatment should take place (outpatient or inpatient setting), nor about the optimal duration for hospitalization in case of inpatient stay.

Usually, patients whose care objective is to reach abstinence are offered an inpatient stay after a previous relapse during an outpatient intensive care program. Inpatient stays can also be indicated to explore and manage complications of CUD (pulmonary, cardiovascular, psychiatric, nasal, etc.).

Previous studies have identified clinical markers of severity, such as frequency and quantity of cocaine use per month, craving scores, or number of DSM-5 criteria met, as predicting factors for treatment retention or abstinence maintenance.¹² However, the inclusion criteria as well as the characteristics of detoxification were heterogeneous between studies, making it difficult to replicate the results. These studies are not always conducted in an inpatient setting, and sometimes contain restrictive exclusion criteria such as other substance use disorders (SUDs) or medication. Nevertheless, as relapse is common in patients with CUD, it is important to identify factors that may influence relapse in patients aiming for abstinence. Identifying validated predictive factors for abstinence maintenance, after a cocaine inpatient detoxification and among patients without strict exclusion criteria, would therefore, help

adapt the detoxification program and the withdrawal care to each patients' profile, to achieve abstinence maintenance.

This is why we decided to perform a prospective study assessing clinical factors of abstinence maintenance after cocaine inpatient cessation in patients with CUD.

METHODS

Patients' recruitment

This multicentric study collected data from CUD inpatients through clinical practice in two different hospitals: Hôpital Fernand Widal (Paris) ($n = 84$) and Clinique du Château (Garches) ($n = 2$) between 2015 and 2021. Inclusion criteria were: patients aged ≥ 18 years old, with a diagnosed CUD (according to DSM-5), attempting an inpatient cocaine detoxification program as a primary objective, agreeing to be contacted for follow-up visits, being insured under the French social security system, and giving informed written consent to participate in the study. Patients were excluded if they were aged < 18 , pregnant or nursing, under guardianship, receiving court-mandated care, or had any contraindication to magnetic resonance imaging (MRI). The specific results from the imaging study will be published elsewhere.

Funding and ethics

The study was funded by the French Ministry of Health (PHRC-N AOM12390). The relevant ethics committee (Comité de Protection des Personnes Ile de France IV 15/01/2015 and Agence Nationale de Sécurité du Médicament 10/10/2014) approved the protocol ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT02416050).

Study design

This was a prospective, observational study of CUD patients recruited during inpatient detoxification.

The baseline visit was conducted within 2 days of patients admission to the hospital for cocaine detoxification, scheduled by their referring clinician as part of their usual care. During this visit, we collected sociodemographic data and characterized CUD, patterns of recent cocaine use, comorbid SUDs, and current medication regimen. Patients also completed standardized scales and questionnaires about craving: the Obsessive Compulsive Cocaine Scale,¹³ a Visual Analog Scale for craving,¹⁴ and a questionnaire about their insight of CUD (Insight Q8).¹⁵ They were also assessed with the Montreal Cognitive Assessment (MOCA)¹⁶ to detect the presence of early withdrawal-associated cognitive symptoms.

The inpatient detoxification program typically lasts 10–14 days, depending on the referral and inpatient clinicians' advice and the patient's will. Longer stays could thus occur—depending on the global

clinical project, the need of the patient to consolidate the detoxification, or even the potential need to treat somatic complications—and could be followed. Indeed, patients could ask for a prolonged stay in another residential facility for 3 weeks to 6 months if they choosed aftercare.

Due to the naturalistic nature of the study, other addictive substances could be part of the detoxification project, and all medications were allowed, according to the physicians' evaluation. The inpatient treatment also included the ability to attend health education and relapse prevention group sessions, but attendance was not compulsory and left to each patient's discretion.

After discharge from the inpatient detoxification, patients were followed for up to 3 months. We prospectively documented relapse through self-declared cocaine use by the timeline follow-back method¹⁷ at 2 weeks, 1 month, and 3 months after discharge. In case of a relapse, we determined the day of relapse to measure the total days of abstinence maintenance after discharge. Post-inpatient treatment visits were designed to be conducted by phone.

Statistical analysis

Patients' characteristics are described using counts, percentages, means and standard deviations, or medians. They are presented for 81 patients, representing the patients included in this study for whom we collected the days of abstinence.

As normality assumptions were not always met, we applied non-parametric tests.

To take account that we study a censored outcome, we decided to use survival analysis. Indeed, univariate associations between abstinence maintenance (in days) and continuous or categorical variables were analyzed with Cox survival analysis. Then, two criteria were used for selecting variables to enter a multivariate Cox regression (stepwise): missing subjects <10% of the sample, and significant univariate association with abstinence ($p < .05$).

The descriptive analysis were carried out with JASP,¹⁸ and we performed univariate and multivariate survival analysis using R.¹⁹ The statistical significance threshold was set at $p < .05$.

RESULTS

Description of the sample

Demographic characteristics

The CUD patients ($n = 81$) sample had a mean age of 40 (± 8.7) years and comprised 18 (22%) females, with a mean level of education of 12 years (equivalent to the end of high school degree in France). A total of 56% patients were unemployed, 61% were single, and 25% were homeless or living in emergency or long-term social shelters at the time of their inclusion in the study.

CUD characteristics

The sample characteristics are described in Table 1. A more detailed presentation of the patients characteristics is proposed as a Table S1.

Among the sample, 48% used cocaine through the intranasal route, 42% through smoking, and 10% intravenously. Thus, 53% used rapid routes of administration (comprising smoking and injection routes of use). The mean cocaine intake was 1.26 (± 1.1) grams per

TABLE 1 Clinical characteristics of CUD patients.

	CUD patients ($n = 81$) Mean (SD; median), or n (%)	Number of available observations
Sociodemographic data		
Age (years)	40 (± 8.7 ; 41)	81
Female	18 (22%)	81
Cocaine use disorder		
Cocaine use		
Cocaine hydrochloride	41 (53%)	78
Crack-cocaine	37 (47%)	78
Usual route of cocaine administration		
Intranasal	37 (48%)	78
Smoking	33 (42%)	78
Intravenous	8 (10%)	78
Current use through a rapid route		
Smoking and IV	41 (53%)	78
Amount of cocaine use (g/day)	1.26 (± 1.1 ; 1)	75
Days of use in the prior month	19 (± 9.2 ; 20)	76
MOCA	24.76 (± 4.7 ; 26)	63
Current medications 80		
Benzodiazepines	56 (70%)	
Antipsychotics	46 (61%)	80
OAT	33 (41%)	
SSRI	29 (36%)	80
Mood stabilizers	8 (10%)	
Lithium	1 (1%)	
Hospitalization and abstinence		
Duration of hospitalization (days), mean	16 (± 9 ; 14)	80
Aftercare	23 (28%)	81
Relapse before 3 months	66 (82%)	81
Days of abstinence	31 (± 34 ; 15)	81

Abbreviations: CUD, cocaine use disorder; IV, intravenous; MoCA, montreal cognitive assessment; OAT, opioid agonist treatment; SSRI, selective serotonin reuptake inhibitor.

day, and the mean current number of days of use was 19 (±9.2) days per month. On average, the first use of cocaine occurred at 25 (±8.9) years old, with a reported Age at Onset of CUD at 30 (±10.1) years old i.e., 5 years after the first use.

The vast majority, 97% (n = 74) of the patients, met 6 or more DSM-5 criteria for CUD, thus defining a severe use disorder.

Comorbid SUDs and medications

Other current SUDs prevalence were as follows: 89% (n = 71) for tobacco, 60% (n = 48) for alcohol, 34% (n = 27) for opioids, 31% (n = 25) for cannabis and 19% (n = 15) for benzodiazepines.

The majority of patient's medication at the baseline included benzodiazepines (70%, n = 56) and antipsychotics (61%, n = 49). Moreover, 41% (n = 33) of patients received Opioid Agonist Treatments (OATs) and 36% (n = 29) selective serotonin reuptake inhibitors (SSRIs).

Hospitalization and relapse

The observed mean duration of hospital stay was 16 days (±9). We applied the following post hoc categorization: premature discharge (less than 7 days, 11%, n = 9); typical stay (between 7 and 14 days,

31%, n = 25), prolonged stay (more than 14 days, 29%, n = 23), and chose to attend a residential aftercare treatment (29%, n = 23).

Among the 81 participants, 82% (n = 66) relapsed within 3 months following discharge. The mean duration of abstinence was 31 days (±34, median: 15).

Factors associated with abstinence maintenance

Univariate analysis showed that abstinence maintenance (in days) after discharge was shorter in patients with more days of cocaine use in the prior month (hazard ratio [HR] = 1.04, 95% confidence interval [CI]: 1.01–1.06, p < .01), as well as in patients smoking cocaine (HR = 1.74, 95% CI: 1.03–2.94, p = .039) and injecting it (HR = 2.45, 95% CI: 1.06–5.67, p = .037). Conversely, abstinence duration after discharge was longer in patients with higher MoCA scores at baseline (HR = 0.93, 95% CI: 0.88–0.98, p = .019), patients who consumed cocaine-hydrochloride only rather than crack-cocaine (HR = 0.54, 95% CI: 0.33–0.89, p = .015), and patients currently prescribed with SSRIs (HR = 0.50, 95% CI: 0.29–0.87, p < .01). Finally, patients with more days of hospitalization (HR = 0.97, 95% CI: 0.94–0.99, p = .016) and attending aftercare (HR = 0.57, 95% CI: 0.33–0.99, p = .041) maintained abstinence for longer within the 3-month follow-up. Those results are presented in Table 2 (left column).

TABLE 2 Multivariate model (N = 75): univariate and multivariate association results.

	Days of abstinence (med [Q1–Q3]) ^a	Univariate analysis				Multivariate analysis			
		HR	95% CI		p-value	HR	95% CI		p-value
Days of use in the prior month	-	1.04	1.01	1.06	<.01	1.03	1.00	1.06	.046
Type of cocaine use									
Crack-cocaine	8 [1–30]	ref	ref	ref					
Cocaine hydrochloride	30 [9–90]	0.54	0.33	0.89	.015	-	-	-	-
Route of cocaine use									
Intranasal	30 [10–90]	ref	ref	ref		ref	ref	ref	
Smoking	10 [1–35]	1.74	1.03	2.94	.039	1.56	0.87	2.78	.132
Intravenous	4.50 [2.25–10.25]	2.45	1.06	5.67	.037	5.16	2.01	13.27	<.001
Use of "rapid route"	8 [1–30]	1.84	1.11	3.04	.016	-	-	-	-
SSRI									
No	10 [1.50–40]	ref	ref	ref		ref	ref	ref	
Yes	29 [5–90]	0.50	0.29	0.87	<.01	0.30	0.16	0.56	<.001
Days of hospitalization									
Aftercare	10 [2–30.75]	0.57	0.33	0.99	.041	-	-	-	-

Note: β: Cox regression coefficient.

Abbreviations: 95% CI, 95% confidence interval; CUD, cocaine use disorder; HR, hazard ratio; OCCS, Obsessive Compulsive Cocaine Scale; Q1, first quartile; Q3, third quartile; SSRI, selective serotonin reuptake inhibitor; VAS, Visual Analog Scale.

^aTheoretical min–max is 0–90 days. For univariate analysis, other variables were also tested but not significant: age, sex, years of education, socioeconomic status (marital status, employment, housing, resources), amount of cocaine use, years of CUD, number of DSM-5 criteria, craving VAS, craving OCCS scores, insight, codependencies, current medications. Significant p-value: <.05.

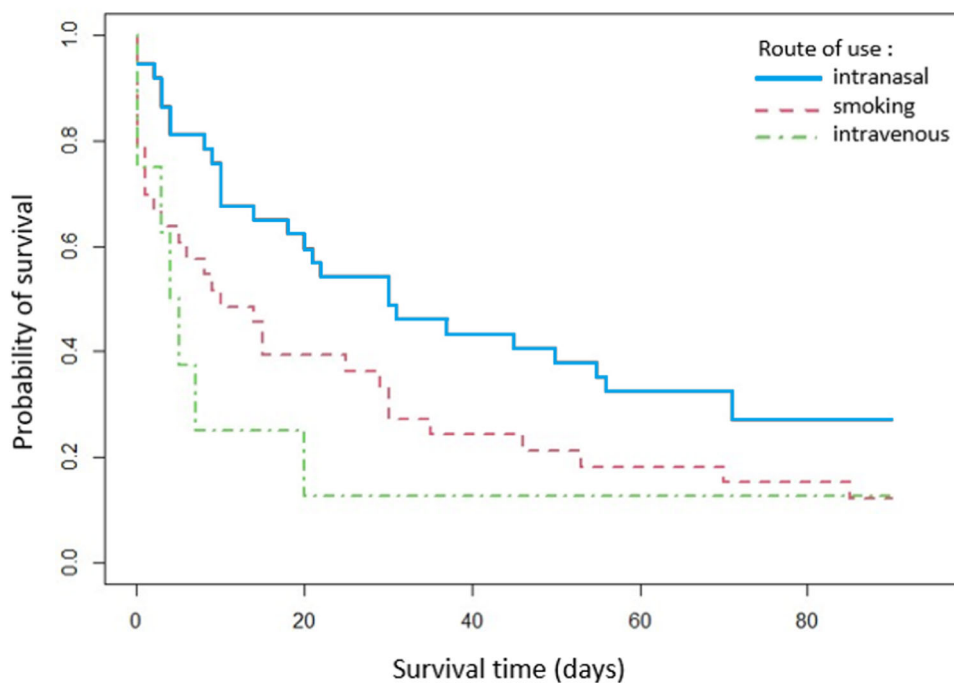


FIGURE 1 Survival curves as a function of the route of administration. The probability of survival represent the percentage of patients who did not relapse at one time. For example: at 20 days after discharge, approx. 60% of patients using cocaine intranasal did not relapsed (vs. 40% for smoking and 15% for intravenous).

Survival curves were modeled regarding the four categorical variables (route of administration, SSRI prescription, use of rapid route and aftercare) (example for route of administration in Figure 1).

All variables which showed a significant effect in univariate analysis were entered in the multivariate model, except the MoCA score ($N = 67$, missing 22%).

This Cox regression model has been obtained for 75 patients, including 60 relapsers and 15 patients with a documented 90 days of abstinence (last available information). This model could significantly predict abstinence duration ($p = 8 \times 10^{-6}$). This model and the variables retained using stepwise procedure are presented in Table 2 (right column).

In this multivariate Cox regression model, four retained variables were significantly associated with the duration of abstinence after discharge. Patients injecting versus snorting (HR = 5.16, 95% CI: 2.01–13.27, $p < .001$) and patients consuming cocaine heavily in the prior month of inclusion (HR = 1.03, 95% CI: 1.00–1.06, $p = .046$) maintained shorter abstinence at discharge after inpatient detoxification. Conversely, abstinence maintenance was longer in patients prescribed with SSRIs during hospitalization (HR = 0.30, 95% CI: 0.16–0.56, $p < .001$) and with a longer duration of inpatient detoxification (in days) (HR = 0.96, 95% CI: 0.94–0.99, $p = .015$).

DISCUSSION

This study aimed at prospectively identifying factors associated with longer abstinence maintenance after an inpatient detoxification program for patients with CUD. We observed that 15 patients

(18%) could maintain a documented abstinence for the 3-month follow-up period. This relapse rate is in line with previous findings from the literature.²⁰ This seemingly low rate can be related to the severity criteria of this sample: indeed, these patients had suffered from CUD for an average of 10 years, and 53% used rapid routes of administration. Furthermore, we observed a high prevalence of co-occurring other SUDs and that these patients face many social difficulties.

We identified four independent clinical predictors of abstinence duration. Patients using intravenous administration and consuming heavily in the prior month maintained a shorter abstinence. Conversely, abstinence was maintained for longer by patients prescribed with SSRIs and staying longer for their inpatient detoxification.

These results confirm previous studies identifying heavy cocaine use as a predictor of rapid relapse, measured either as higher frequency or larger doses of cocaine intake.^{12,21} In fact, in our study, patients consuming more days in the month before inclusion relapsed earlier. However, this result must be interpreted with caution, as the significance was close to the limit. It may, therefore, be necessary to replicate this finding in a larger sample.

In our study, patients using injecting and smoking routes of administration are those reporting more days of use in the prior month. Injecting cocaine has already been associated with an early age of onset of cocaine use²² as well as greater physical and psychological consequences of cocaine use.²³ Contrary to other studies,²¹ we did not identify craving assessed at baseline as a predictor of relapse after discharge. In this sense, our results are in line with an experimental study of cue-induced craving using

EEG-record, which showed that higher craving scores occurred at 1 and 6 months of abstinence, suggesting that patients may be more vulnerable to relapse at these times.²⁴

Conversely, SSRI prescription had not previously been associated with better treatment response in CUD. This observation could be a chance finding, a confounding factor for a specific patient group (already in a psychiatric care circuit before the inpatient stay, or specifically presenting with depressive or anxiety symptoms co-occurring with their CUD), or for another reason. The previous clinical trials that have been assessing the efficacy of SSRIs such as fluoxetine²⁵ or venlafaxine²⁶ in dose reduction or abstinence from cocaine produced negative results, although another study suggested better treatment retention in the fluoxetine group in crack-cocaine users, despite the absence of efficacy on cocaine use reduction.²⁷

Nevertheless, we can hypothesize that in this sample of patients with severe CUD entering an inpatient detoxification program, the occurrence of cocaine withdrawal symptoms is frequent and could lead to depressive symptoms. Indeed, patients using high doses and having high dopaminergic signs of cocaine intoxication are highly vulnerable to depression-like withdrawal symptoms.²⁸ While we could not identify published studies showing an improvement of cocaine withdrawal symptoms with SSRI antidepressants in patients currently using cocaine, it is common in clinical practice to prescribe them to attenuate the “downs” occurring some hours or days after each cocaine use. The role of CUD in triggering depressive episodes and the role of SSRI prescription in alleviating cocaine-induced “downs”, as well as the consequences for abstinence maintenance, needs further investigation.

Regarding the inpatient detoxification duration, there are no clinical practice guideline on this topic to the best of our knowledge. Conducting such studies is difficult because of an indication bias: more severe patients are more frequently offered inpatient treatment. However, at least one randomized study has shown that inpatient detoxification is significantly associated with likelihood of abstinence after 3 months.²⁹ Our results suggest that patients suffering from severe CUD should be offered a longer inpatient stay, as long as they are willing.

There are several limitations to our study. First, the small sample size increases the risk of overfitting the data, possibly leading to highly significant results. Also, as this study was exploratory, we did not perform multiple testing corrections for univariate analysis. Furthermore, we cannot exclude that our identified factors may be confounding factors. In addition, the choice to include patients with severe CUD is associated with a high relapse rate and treatment dropout, which limits the statistical power of the study. Furthermore, 30% of the discharged patients attended an aftercare, potentially introducing a bias in abstinence prediction. Indeed, these patients received support in a controlled environment, which may shield them from situations triggering craving and leading to relapse. Of note, the most severe patients may not agree to attend an aftercare, and even ask for a shortened detoxification stay, which could represent a self-indication bias. Further well-designed prospective randomized controlled trials are needed to definitively assess the optimal length of inpatient stay and the impact of aftercare programs. These studies should carefully

balance the patient's severity across all groups, to ensure generalizable results. Nevertheless, our results are closer to the current clinical practice and easier to translate to the bedside, as patients included presented severe CUD, with fewer exclusion criteria as possible. Indeed, the number of users suffering from a severe CUD and requesting treatment is increasing significantly in France.³⁰ However, while the characteristics of cocaine users in French treatment centers provide valuable insights, it is important to recognize that this specific population is not fully representative of the global picture of CUD patients. The demographic landscape of CUD patients has diversified among the years,¹ necessitating further research efforts to understand the factors influencing relapse across the different users profiles encountered in different healthcare systems. Finally, the MRI data from this study are not yet available. They may provide interesting information on the intricate brain changes associated with clinical factors in predicting treatment outcome.

CONCLUSION

In this prospective study investigating inpatient detoxification for severe CUD, we identified four clinical predictors of abstinence maintenance: longer inpatient stay and SRI prescriptions were associated with longer abstinence, while injecting and heavier cocaine use in the previous month were associated with shorter abstinence. Those results can inform harm reduction interventions and encourage medical professionals to offer prolonged inpatient stays to patients aiming towards cocaine abstinence. Furthermore, the indications and clinical or biological targets of SSRIs prescription in patients with severe CUD deserves specific studies.

AUTHOR CONTRIBUTIONS

All authors contributed to this manuscript. Florence Vorspan, Vanessa Bloch, Emmanuelle Volle and, Christine Delmaire conceived the study. VCD, RI, JA, PS, and Margaux Poireau collected the data. Margaux Poireau, Florence Vorspan, and Virgile Clergue-Duval conducted statistical analyzes. Romain Icick provided statistical consultation. Margaux Poireau and Florence Vorspan were principally responsible for writing the manuscript. Angéline Maillard, Mathieu Faurent, Virgile Clergue-Duval, Romain Icick, Emmanuelle Volle, Julien Cabé, and Vanessa Bloch provided feedback. PS carried out English editing. All authors approved the final version of the manuscript.

ACKNOWLEDGMENTS

The study was funded by the French Ministry of Health Programme Hospitalier de Recherche Clinique PHRC N AOM12390. The relevant ethic committee (Comité de Protection des Personnes Ile de France IV 15/01/2015 and Agence Nationale de Sécurité du Médicament 10/10/2014) approved the protocol (ClinicalTrials.gov Identifier: NCT02416050).

The authors would like to thank Dr Gael Dupuy who supervised patients inclusions at the Clinique du Château de Garches,

Nightingale Hospitals, as well as the Direction de la Recherche Clinique et de l'Innovation (DRCI) and l'Unité de Recherche Clinique (URC) Saint-Louis Lariboisière Fernand Widal for their help in the methodology and management of this protocol.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Poireau M, Clergue-Duval V, Maillard A, et al. Predictors of abstinence maintenance after cocaine inpatient detoxification: a prospective study. *Am J Addict*. 2024;33:576-582. doi:10.1111/ajad.13571