

# **Predictors of heroin abstinence in opiate substitution therapy in heroin-only users and dual users of heroin and crack**

F. Heidebrecht<sup>1</sup>, M.B. MacLeod<sup>2</sup>, L. Dawkins<sup>1</sup>

<sup>1</sup> London South Bank University, London, UK

<sup>2</sup> Walthamstow Drug Services, London, UK

Running head: Predictors of heroin abstinence

Word count: 3538 words

Declarations of competing interest: None

Key words: Heroin; crack; dual use; Opiate substitution therapy;  
Predictors; Abstinence

## Abstract

**Aims:** To analyse predictors of heroin abstinence in opiate substitution therapy (OST) based on frequency of crack use and its interactions with other predictors in a clinical non-experimental setting.

**Design:** Retrospective study.

**Setting:** A community drug service in London, UK.

**Participants:** 325 clients starting OST between 2010 and 2014 (197 methadone and 128 buprenorphine).

**Measurements:** Logistic regression models (a general model and separate models for methadone and buprenorphine) assessed demographic and clinical data as predictors of heroin abstinence at one year after treatment start (or at the date of transfer to another service).

**Findings:** For the general model participants choosing methadone were more likely to use heroin at follow up (OR=2.36, 95% CI: 1.40–3.17) as were daily crack users on methadone (OR=2.62, 95% CI: 0.96 – 7.16).

For the methadone model only daily crack use predicted heroin use at follow up (OR = 2.62, 95% CI: 0.96 – 7.16).

For buprenorphine, higher amounts of baseline heroin use, lower buprenorphine dose and daily drinking predicted heroin use at follow up (OR=0.85, 95% CI: 0.75–0.95; OR=1.31, 95% CI: 1.06–1.60 and OR=6.04, 95% CI: 1.26–28.92). Both use of cannabis and depression increased likelihood of heroin abstinence for clients not using crack compared to occasional (OR=6.68, 95% CI: 0.37–119.59; OR=106.31, 95% CI: 3.41–3313.30) and daily (OR=57.49 (95% CI: 2.37–1396.46; OR=170.99 (95% CI: 4.61–6339.47) users.

**Conclusions:** Most of the predictors in the general model were found significant only in the buprenorphine but not in the methadone model, suggesting that a general model has little predictive value. Crack use was a significant predictor of heroin abstinence at follow up in all models, however for buprenorphine only when depression or cannabis use was present. Further research is needed to assess effective treatment approaches for the growing population of dual users.

## Introduction

Opiate substitution therapy (OST) for heroin dependence is recognized across the world as effective for retention in treatment and reducing illicit drug use [1]. The most commonly used medications are methadone and buprenorphine [2], but sustained-release morphine [3,4] sulphate and diamorphine [4,5] are also sometimes used. The current UK drug strategy based on the recovery model has resulted in a shift in treatment aims from maintenance towards complete abstinence. OST is now considered a first step in achieving abstinence and is followed by detoxification and complemented by regular psychosocial support [2]. Abstinence from illicit drug use therefore becomes an equally relevant treatment outcome as retention.

Documented abstinence rates of heroin users receiving OST vary between 25% and 70% [6-9]. The impact of medication type and dose on treatment outcomes has been extensively researched, with higher doses of both methadone and buprenorphine being associated with heroin abstinence [1]. In terms of demographic and clinical predictors, the use of alcohol or other drugs, legal issues, mental health, younger age at drug use start and employment have all been found to correlate with heroin use at follow up [10-14].

Traditionally studies have focused on the treatment outcomes of heroin-only users. The high prevalence of crack/cocaine use among heroin users accessing OST in the UK however has been documented for over a decade [15], and British national statistics show an increase in the percentage of dual users (relative to all heroin users) starting treatment, from 34.7% in 2005-2006 to 42.6% 2013-2014 [16]. More recent studies have recognised that dual users are less likely than heroin-only users to reduce their heroin use or achieve abstinence on OST [7, 14, 17-19]. A review of treatment options for dual users concluded that methadone is better than buprenorphine for achieving abstinence of both heroin and cocaine, and that reduction in cocaine use can be additionally supported with indirect dopamine agonists and contingency management interventions reinforcing cocaine abstinence [20]. Despite this, apart from suggesting that dual users are more likely to benefit from an increase in psychosocial interventions, no specific recommendations are made in the UK guidelines on clinical management [2].

The need for systematic studies of the patterns of concurrent cocaine use alongside heroin has been recognised [21], however the majority of studies have considered dual users as a homogeneous group [14, 17, 22]. A very recent study which did segment dual users into regular and occasional users did so to identify predictors of future crack/cocaine frequency of use rather than to predict treatment outcomes [23].

The aim of the present retrospective study was to assess if a series of sample characteristics routinely collected at OST start (such as frequency of crack use, length of drug use, other drugs and alcohol use, route of administration of drugs, mental health, housing, employment) along with the substitution medication type and dose were predictive of heroin use in a clinical non-experimental setting.

## **Methods**

### ***Setting and Sample***

This naturalistic retrospective study was conducted at the community drug treatment service Lifeline in Hackney, London, UK and involved only analysis of already recorded data. A total of 325 service clients were included in the study (197 methadone and 127 buprenorphine) and were identified after reviewing 852 case files of clients who started treatment between April 2010 and September 2014. The inclusion criteria were: dependent (daily) heroin use, starting OST, and in treatment for at least one month if they were later transferred to another service. Before treatment start, a comprehensive general assessment is completed by a practitioner, followed by a medical assessment with a specialist doctor, where medication type is chosen in agreement with the client. In line with the UK guidelines encouraging flexible dosages, medication is titrated up to a dose perceived as comfortable by the client.

As part of their registration with the service, all clients routinely consent to their data being accessed for research/service improvement purposes.

### ***Data collection***

All data was extracted from electronic client records. Amount/frequency of drug and alcohol use, route of drug administration, mental health, housing situation, employment and age of first drug use are based on self-reports at initial and/or medical assessment. For heroin and crack, available results of urine drug screens were also considered.

### ***Measures***

#### **Outcome variable**

The outcome assessment was performed one year after treatment start, or at transfer date if a client was transferred to another service. The two states of the binary outcome variable *heroin use at follow up* were as follows: Heroin use was considered to take place either if a participant had dropped out of treatment or was still in treatment but using heroin alongside the prescribed medication. Treating drop-outs as treatment fails is the most conservative approach to take and consistent with the gold-standard intention to treat analysis. A participant

was considered heroin-free if either discharged from treatment as drug-free, or still in treatment but not using heroin.

Heroin use at the time of the outcome assessment for participants still in treatment was ascertained by self-reported drug use as stated in electronic case records of three consecutive appointments around the outcome assessment date and verified by drug screening records.

## Predictors

The following predictors were considered: length of drug use (years), heroin use (g/week), crack use (g/week), crack pattern (no use/occasional use/daily use), housing situation (stable/problematic), employment status (employed/unemployed), use of other drugs (yes/no), mental health problems (yes/no), route of heroin/crack administration (smokers only/current or previous injectors), alcohol use (units/week), alcohol pattern (no use/occasional use/daily use), medication type (methadone/buprenorphine) and medication dose after titration. All these predictors characterized the participants at the time of treatment start.

### Calculation of predictors

The values were assigned on the basis of client database entries as follows: Housing situation was considered problematic if the client reported any of the following: living on the streets, no fixed abode, squatting, housing problem, sleeping on different friend's floor each night, use of night hostels (night-by-night basis) or stay with friends/family as a short term guest. Clients were considered employed with the following database entries: 'regular employment', 'student', 'retired'. The mental health status was determined according to self-reported issues, prescribed psychiatric medication, and doctor's considerations at medical assessment.

The amount of alcohol use at treatment start was taken from the *Treatment Outcome Profile* (TOP) [24-25], a standardized questionnaire routinely used in all substance misuse services across the UK to record information on substance use and related issues over the past 28 days. Reported drug use has been validated against oral fluid drug tests (Cohen's  $\kappa$  between 0.69 and  $\kappa=0.88$  for different drugs) and yields good inter-rater reliability ( $\kappa$  between 0.59 to  $\kappa=0.88$ ). Because it is based on self-reported sensitive information, we complemented this data with the drug use as reported by each participant at the medical assessment. Amount of heroin, crack and other drug use were based on self-reports collected from both the TOP and medical assessment. If the reported amount of heroin and crack was not consistent, the higher value was considered. Clients usually report their drug use either in amount or the monetary

value spent. £ 10 heroin was considered in this study to correspond to 0.2g heroin, and £ 10 crack to 0.1g, as recommended by National Treatment Agency [25]. For crack and alcohol patterns a frequency of use less than daily was considered occasional use. Clients reporting no crack/cocaine use but testing positive at medical assessment were also classified as occasional users. The medication dose after titration was determined by reviewing the history of issued prescriptions. If two or more consecutive prescriptions included no further dose increase, the dose was considered stable. All categorical predictors were coded in SPSS using effect coding.

## ***Statistical analyses***

Comparisons between samples were performed with t tests, Mann-Whitney test for non-parametric variables, or Chi-Square test for categorical variables.

A general logistic regression model including all participants and separate models for methadone and buprenorphine were built in a backward stepwise method. All considered predictors and interactions between crack pattern and other categorical predictors were included in the first step. The predictor or interaction with the highest p value of the Wald test was then removed and the regression computed again. This procedure was repeated until all remaining interactions and independent predictors were significant or close to significance ( $p < .1$ ). A residual analysis was performed and data points with the analog of Cook's influence statistic  $> 1$  and/or normalised residuals  $> \pm 3$  were removed: 2 data points from the general model, 4 from the buprenorphine model and none from the methadone model. All predictors still having a p value  $> .05$  were removed. For the general model, the medication dose was normalized on the median value of the corresponding study population (45 mg for methadone and 8 mg for buprenorphine), as there is no direct equivalence between the two due to differences in their pharmacological properties [26-27]. For each model, the classification cut-off that provided an equal percentage of correct classifications in both category outcomes was chosen. This was 0.75 for the general and methadone model and 0.62 for the buprenorphine model.

All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA).

## Results

### *Demographic and clinical characteristics*

Sample characteristics are summarized and compared in Table 1: 77.5% (252/325) were dual users of heroin and crack. Clients choosing buprenorphine over methadone: used on average significantly less heroin ( $p<0.001$ ), smoked rather than injected drugs ( $p=0.03$ ), were employed ( $p<0.001$ ), and in stable accommodation ( $p=0.001$ ), and a significantly lower proportion were still using heroin at the one year follow up ( $p<0.001$ ).

*Table 1. Demographic and clinical characteristics of participants for total sample and stratified by medication type. Tests used: chi square, <sup>a</sup> Mann Whitney U-test, <sup>b</sup> independent samples t-test.*



Characteristic	Participant characteristics			p value
	Total sample (n=325)	Methadone (n=197)	Buprenorphine (n=128)	
Age (years: range, mean $\pm$ SD)	21-69 (37.80 $\pm$ 9.37)	22-69 (38.02 $\pm$ 9.48)	21-63 (37.46 $\pm$ 9.23)	0.603 <sup>p</sup>
Gender (% male)	76.6	74.6	79.7	0.187
Sexuality (%)				0.364
Heterosexual	89.5	90.9	87.4	
Homosexual	4.9	4	6.3	
Other or not stated	5.6	5.1	6.3	
Nationality (%)				0.813
United Kingdom	68	67.5	68.8	
Italy	10.5	10.7	10.2	
Poland	2.5	3	1.6	
Other	19	18.8	19.4	
Ethnicity (%)				0.707
White British	35.8	36.2	35.2	
White Other	35.2	33.7	37.5	
Black or Black British	12.7	13.8	11	
Other	16.3	16.3	16.3	
Employment status (% employed)	30.1	22.7	41.1	< 0.001
Housing situation (% stable)	71.4	65.5	80.5	< 0.001
Frequency of crack use (%)				0.828
none	22.5	22.3	22.7	
occasionally	42.5	41.6	43.8	
daily	35	36.1	33.5	
Frequency of alcohol use (%)				0.143
none	54	56.1	50.8	
occasionally	27.5	24.5	32	
daily	18.5	19.4	17.2	
Use of other drugs (%)	44.3	46.7	40.6	0.171
Mental health condition (%)	46.6	46.9	46.1	0.861
Crack use (g/week: range, mean $\pm$ SD)	0-21 (1.54 $\pm$ 2.66)	0-18 (1.61 $\pm$ 2.64)	0-21 (1.43 $\pm$ 2.70)	0.245 <sup>a</sup>
Alcohol use (units/week: range, mean $\pm$ SD)	0-420 (25.15 $\pm$ 56.23)	0-196 (19.36 $\pm$ 40.59)	0-420 (34.02 $\pm$ 73.34)	0.247 <sup>a</sup>
Heroin use (g/week: range, mean $\pm$ SD)	0.3-28 (5.06 $\pm$ 3.61)	0.3-21 (5.52 $\pm$ 3.46)	0.4-28 (4.35 $\pm$ 3.73)	< 0.001 <sup>a</sup>
Length of Drug use (years: range, mean $\pm$ SD)	0-40 (13.04 $\pm$ 8.74)	0-39 (13.39 $\pm$ 8.96)	0-40 (12.51 $\pm$ 8.41)	0.376 <sup>p</sup>
Route of administration (% smokers)	49.6	45.4	56.3	< 0.001
Normalized Medication Dose (dose/median dose: range, mean $\pm$ SD)	0.15-2.25 (1.09 $\pm$ 0.45)	N/A	N/A	
Medication Dose (mg: range, mean $\pm$ SD)	N/A	15-110 (47.99 $\pm$ 17.41)	1.2-22 (9.17 $\pm$ 4.33)	
Heroin use at follow up (%)	72	78.8	61.7	< 0.001

## *Differences in heroin use with crack use frequency*

78.8% of the methadone sample and 61.7% of the buprenorphine sample were still using heroin at the follow up. As can be seen in Table 2, the results stratified by the pattern of crack

use show that the proportion of participants using heroin at follow up increases with the frequency of crack use for both samples.

*Table 2: Number and percentage of participants still using heroin at the follow up for both medication types: Total samples and stratified by the frequency of crack use.*

	Methadone		Buprenorphine	
	Heroin use		Heroin use	
	N	%	N	%
total	197	78.7	128	61.7
Frequency of crack use				
none	33	75	12	41.4
occasionally	59	72	36	64.3
daily	63	88.7	31	72.1

## ***Predictors of heroin use***

### **General model**

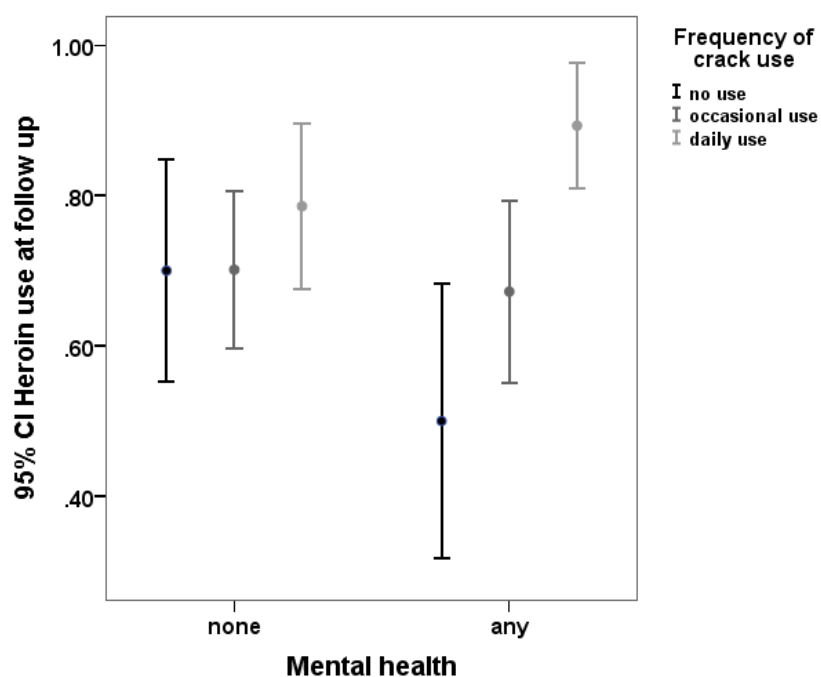
For the general model, medication type and dose, pattern of crack use and the interaction between mental health and the pattern of crack use significantly predicted heroin use at follow up. A test of the full model against an intercept-only model was statistically significant, indicating that collectively these predictors reliably distinguished between the two considered treatment outcomes (heroin use vs. no use) ( $\chi^2 = 35.1$ ,  $p < .001$  with  $df = 7$ ) and the model explained 15% of the variability in the outcomes (Nagelkerke's  $R^2 = 0.15$ ). Participants choosing methadone were more likely to still use heroin at follow up (OR = 2.36, 95% CI: 1.40–3.97; see Table 3) as were both occasional and daily crack users compared to heroin-only users (OR = 1.55, 95% CI: 0.83–2.88 and OR = 4.19, 95% CI: 1.98–8.85 respectively; see Table 3). Medication dose negatively correlated with the use of heroin at follow up (OR=0.54, 95% CI: 0.31–0.94).

*Table 3 General logistic regression model including significant factors associated with heroin use at follow up, n=325*

	B	S.E.	Wald	df	P	OR	95% CI for OR	
							Lower	Upper
Medication type	0.86	0.27	10.46	1	0	2.36	1.4	3.97
Medication dose (normalized)	-0.61	0.28	4.74	1	0.03	0.54	0.31	0.94
Mental health	-0.01	0.28	0	1	0.97	0.99	0.57	1.72
Frequency of crack use			14.73	2	0			
occasional use	0.44	0.32	1.89	1	0.17	1.55	0.83	2.88
daily use	1.43	0.38	14.1	1	0	4.19	1.98	8.85
Crack frequency x Mental health			4.73	2	0.09			
occasional use x Mental health	0.84	0.63	1.75	1	0.19	2.31	0.67	8.02
daily use x Mental health	1.63	0.75	4.7	1	0.03	5.08	1.17	22.08
Constant	1.62	0.35	20.82	1	0	5.05		

The effects of a mental health condition on heroin use at follow up depended on frequency of crack use (Figure 1): As the mental health condition changes from none to any, the odds of using heroin at follow up for a daily crack user compared to a heroin-only user were OR=5.08 (95% CI: 1.17–22.08). The effect was still significant for occasional crack users compared to heroin-only users, (OR=2.31, 95% CI: 0.67–8.02).

*Figure 1 Interaction between frequency of crack use and mental health in the general logistic regression model, n=325*



## Methadone Model

For the methadone model daily pattern of crack use significantly predicted use of heroin at follow up. A test of the full model against an intercept-only model was significant ( $\chi^2 = 7.36$ ,  $p = .025$  with  $df = 2$ ). Nagelkerke's  $R^2$  of .057 indicated that the pattern of crack use explains less than 6% of the variance. Daily crack users were more likely to still use heroin at follow up compared to heroin-only users (OR = 2.62, 95% CI: 0.96 – 7.16), although this fell short of statistical significance ( $p=.06$ , see Table 4).

*Table 4 Logistic regression model for methadone sample including factors associated with heroin use at follow up, n=197*

	B	S.E.	Wald	df	P	OR	95% CI for OR	
							Lower	Upper
Frequency of crack use			6.45	2	0.04			
occasional use	-0.16	0.43	0.13	1	0.71	0.86	0.37	1.97
daily use	0.97	0.51	3.55	1	0.06	2.62	0.96	7.16
Constant	1.37	0.19	52.23	1	0	3.93		

## Buprenorphine model

A test of the buprenorphine model against an intercept-only model was statistically significant, indicating that collectively these predictors reliably distinguished between heroin use and heroin abstinence at follow up ( $\chi^2 = 42.53$ ,  $p < .001$  with  $df = 12$ ). Nagelkerke's  $R^2$  of .392 indicated that the model explains 39% of the variation in the outcome.

In terms of main effects, buprenorphine dose correlated negatively with heroin use at follow up (OR = 0.85, 95% CI: 0.75–0.95). Amount of heroin used before treatment start and daily drinking correlated positively with heroin use at follow up (OR = 1.31, 95% CI: 1.06–

1.60 and OR = 6.04, 95% CI: 1.26–28.92 respectively, see Table 5). Main effects were also found for mental health condition, use of other drugs and frequency of crack use. These were driven by the interactions explained below.

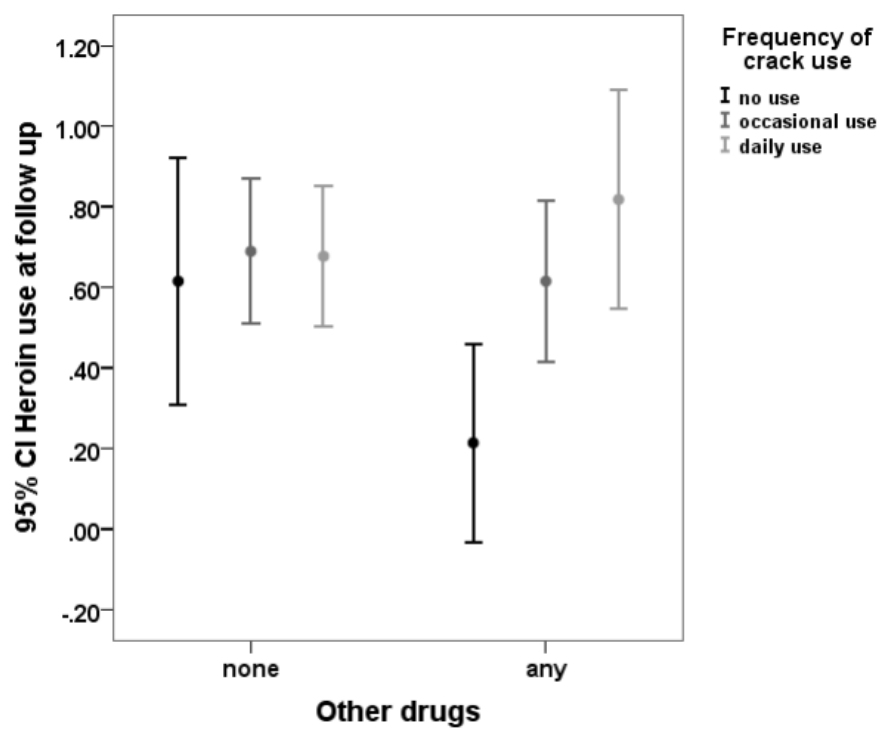
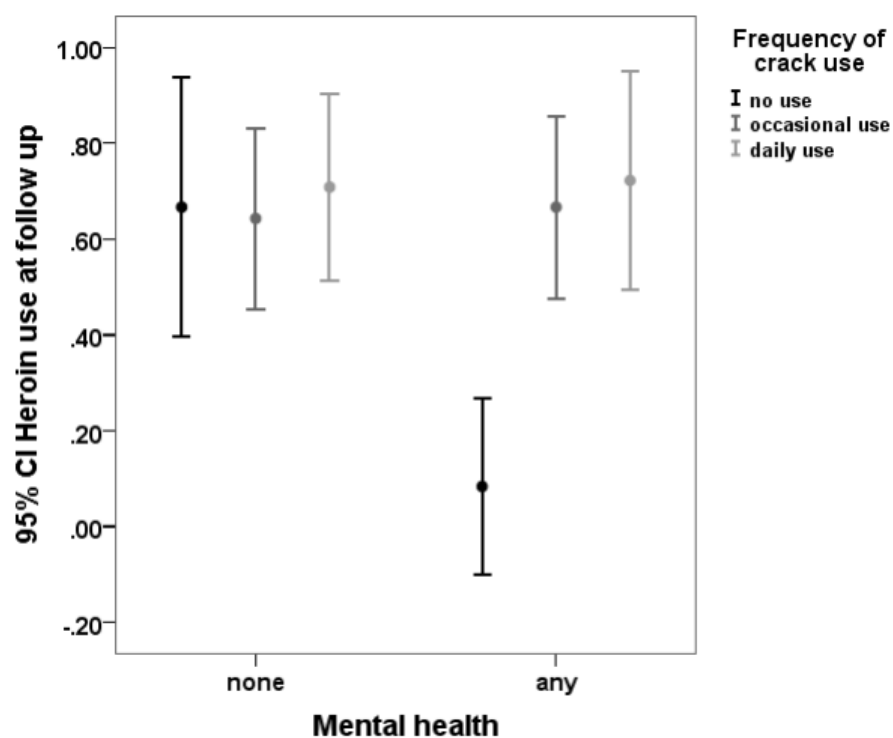
*Table 5 Logistic regression model for buprenorphine including significant factors associated with heroin use at the follow up, n=128*

	B	S.E.	Wald	df	P	OR	95% CI for OR	
							Lower	Upper
Medication dose	-0.17	0.06	7.49	1	0.01	0.85	0.75	0.95
Heroin use	0.27	0.1	6.47	1	0.01	1.31	1.06	1.6
Other drugs	-0.8	0.58	1.93	1	0.16	0.45	0.14	1.39
Mental health	-1.53	0.64	5.66	1	0.02	0.22	0.06	0.76
Frequency of crack use			10.77	2	0			
occasional use	2.22	0.83	7.1	1	0.01	9.17	1.8	46.78
daily use	3.14	0.96	10.76	1	0	23.02	3.53	149.98
Frequency of alcohol use			5.06	2	0.08			
occasional use	0.28	0.5	0.31	1	0.58	1.32	0.5	3.54
daily use	1.8	0.8	5.06	1	0.02	6.04	1.26	28.92
Crack frequency x Other drugs			6.74	2	0.03			
occasional use x Other drugs	1.9	1.47	1.66	1	0.2	6.68	0.37	119.59
daily use x Other drugs	4.05	1.63	6.2	1	0.01	57.49	2.37	1396
Crack frequency x Mental health			8.13	2	0.02			
occasional use x Mental health	4.67	1.75	7.07	1	0.01	106.31	3.41	3313
daily use x Mental health	5.14	1.84	7.78	1	0.01	170.99	4.61	6339
Constant	1.06	0.64	2.7	1	0.1	2.88		

There was a significant interaction between mental health and crack frequency. As the mental health condition changes from none to any, the odds of using heroin at follow up for daily and occasional crack users compared to heroin-only user were OR=170.99 (95% CI: 4.61–6339.47) and OR=106.31, 95% (CI: 3.41–3313.30) respectively. That is, those not using crack but who reported a mental health condition were less likely to be using heroin at follow up (see Figure 2A).

A similar interaction was found between the use of other drugs and crack frequency. As the use of other drugs changes from none to any, the odds of using heroin at follow up for daily and occasional crack users compared to a heroin-only user were OR=57.49 (95% CI: 2.37–1396.46) and OR=6.68, (95% CI: 0.37–119.59) respectively. That is, those not using crack but who reported using other drugs were less likely to be using heroin at follow up (see Figure 2B).

Figure 2 Interactions between: frequency of crack use and mental health (A) and frequency of crack use and use of other drugs (B) in the logistic regression model for buprenorphine,  $n=128$



## Discussion

This retrospective study analysed predictors of heroin use at one year follow up (or the time of transfer to another service) in individuals accessing pharmacological treatment for opiate dependency in a community drug service in London with a particular focus on frequency of crack use. Most of the significant predictors in the general model were found significant only in the buprenorphine but not in the methadone model, suggesting that a general model has little predictive value. For the methadone sub-sample, 78.8% of participants were using heroin at follow up, and none of the considered predictors were significant (with daily crack use being the closest at  $p=0.059$ ). Only 61.7% of the buprenorphine population still used heroin at follow up. Lower doses of buprenorphine, higher amounts of heroin at baseline and daily alcohol use increased the odds of heroin use at follow up, and no crack use predicted heroin abstinence at follow up only when occurring together with either a mental health condition or the use of other drugs.

In this study 38.3% of the clients on buprenorphine and 21.2% on methadone were heroin-free at the follow up. Some studies have shown an advantage of buprenorphine in reduction of heroin use [28,10], however the most recent Cochrane review concluded that these medications are equally efficient [1]. These findings are based on randomized studies, whereas our study was naturalistic and, as in the current treatment model, the client's free choice of the medication is encouraged. This implies that the differences found are unlikely due to the pharmacological properties of the two medications. More individuals choosing buprenorphine were employed, in stable housing, were smokers rather than injectors of heroin, and used on average significantly less heroin before starting treatment, suggesting better social and health status. A likely corollary of this is that they were more likely to be aiming for abstinence compared with those choosing methadone who may be seeking a harm reduction option. This is consistent with studies exploring client's experience with the two medication types suggesting that buprenorphine is preferred when aiming for fundamental behavioural change [29-30]. Thus clients' motivations for treatment are an important factor influencing outcomes.

Medication dose was a significant predictor in the buprenorphine but not in the methadone sample, with a higher dosage of medication predicting heroin abstinence. This is partially consistent with findings from randomized trials, where higher dosages of both medications correlated with reduction in illicit opiate use [1, 28-29, 31]. The UK guidelines

[2] recommend daily doses of buprenorphine above 12 mg and methadone between 60 and 120 mg, however, as the UK clinical practice supports client choice and flexible dosage [32], daily dose is generally established in agreement with the client. In the studied sample 33% and 17% of the buprenorphine and methadone sample respectively wished to be titrated up to a dose in these recommended ranges. This could explain why higher doses of methadone did not significantly predict heroin abstinence. The client's preference for lower doses of methadone could again indicate a motivation to only reduce and not eliminate illicit drug use.

Another relevant predictor of heroin use at follow up in the buprenorphine sample was daily alcohol use, which is consistent with Ferri et al (2014) [33]. Daily and occasional crack use generally predicted heroin use at follow up. This is consistent with findings from other studies showing worse outcomes for cocaine users in OST [7, 17-18, 23-24, 34]. Other studies found no difference in the outcomes of dual users in buprenorphine treatment [22], however outcomes were retention in treatment and reduction in heroin use rather than abstinence. For the methadone-only sample daily crack use fell short of significance, despite the higher sample size. However, methadone clients were more likely to use heroin at follow up so relative differences between the outcomes of crack frequency were smaller.

Whereas all crack users on buprenorphine were similarly likely to use heroin at follow up, the use of other drugs increased the likelihood of heroin abstinence for clients not using crack. The most commonly used drug apart from heroin and crack was cannabis. Elsewhere cannabis use did not predict opiate abstinence in buprenorphine-naloxone [35] or methadone treatment [36], but did predict a reduction in heroin use in methadone treatment [37]. A positive effect of cannabis use may reflect a self-medication attempt; people shift their psychological attachment from heroin to cannabis as the drug providing immediate emotional relief. For the crack-users in our study, no beneficial effect of cannabis on heroin use was observed. This could be due to the strong association between crack and heroin, which has already been proposed by others [38-39]. These findings suggest that addressing crack use with clients presenting to services for heroin dependency could improve treatment outcomes.

A similar interaction between crack pattern and mental health was observed in the buprenorphine model: the co-occurrence of a mental health condition increased significantly the likelihood of heroin abstinence only for clients not using crack. This is consistent with [40] who have shown that prescription-opioid dependent patients with co-occurring psychiatric disorder respond better to buprenorphine/naloxone treatment. In our sample depression was the most common mental health condition reported or diagnosed. Putative antidepressant properties of buprenorphine have been suggested in several other studies: [6,



41-42] and results were independent of cocaine use. However where this information was available, only up to 12% of the sample used cocaine, considerably lower than 77.5% in our sample. Cocaine use has been associated with depressive disorders [43-44], and cocaine dependence is strongly related to substance-induced depression [45]. These results suggest that cocaine use could both maintain and enhance depressive symptoms and is associated with a worse outcome. Thus for those suffering from depression, crack use may counteract any possible beneficial effects of buprenorphine.

This study has a number of limitations. Drug and alcohol use is based on self-report. Although several sources of information were considered, some of this information might still be imprecise. Crack pattern classes are not homogeneous in terms of frequency of use: no crack use and daily use are fairly clearly defined, but occasional crack use includes a broad definition from once a month to 4-5 times a week. It is also possible that some clients reporting relatively frequent weekly use are actually daily users under-reporting their use. These inaccuracies could explain why the confidence intervals crossed 1 for main effects and interactions involving occasional crack users.

The regression models here were built using a sample of drug users living in a single borough in London. The dual use of heroin and crack in this sample was much higher than national estimates of slightly over 40% for 2012-2013 [16]. However, about 20% of our study sample reported no crack or cocaine use when completing the TOP at treatment start, but tested positive for cocaine, so national statistics based on the TOP forms might be underestimates. Nonetheless, the sample might otherwise be unrepresentative of the entire population, so further studies are needed to assess whether the predictive effects of the pattern of dual use are generalizable to other drug user populations.

In conclusion, the findings of this study show that in a naturalistic setting: (1) For clients choosing methadone daily crack use predicted heroin use at follow up; (2) In the buprenorphine sample lower doses of medication, higher amounts of baseline heroin use and daily alcohol use increased the odds of heroin use at follow up; and (3) For buprenorphine sample, no crack use predicted heroin abstinence at follow up only when occurring either with a mental health condition or the use of other drugs.

## References

1. Mattick R. P., Breen C., Kimber J., Davoli, M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews* 2014; 2.
2. Department of Health (England) and the devolved administrations. Drug Misuse and Dependence: UK Guidelines on Clinical Management. 2007. Available at: [http://www.nta.nhs.uk/uploads/clinical\\_guidelines\\_2007.pdf](http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf) (accessed 13 June 2015)
3. Mitchell T. B., White J. M., Somogyi AA, Bochner F. Slow-release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. *Addiction* 2004; **99**: 940–5.
4. White J. M., Lopatko O. V. Opioid maintenance: a comparative review of pharmacological strategies. *Expert Opinion on Pharmacotherapy* 2007;**8**: 1–11.
5. Strang J., Metrebian N., Lintzeris N., Potts L., Carnwath T., Mayet S. *et al.* Supervised injectable heroin or injectable methadone versus optimized oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomized trial. *Lancet* 2010; **375**: 1885–95.
6. Gerra G., Borella F., Zaimovic A., Moia G., Bussandri M., Bubici C. *et al.* Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. *Drug and Alcohol Dependence* 2004; **75**: 37-45.
7. Marsden, J., Eastwood B., Bradbury C., Dale-Perera A., Farrell M., Hammond P., *et al.* Effectiveness of community treatments for heroin and crack cocaine addiction in England: a prospective, in-treatment cohort study, for the National Drug Treatment Monitoring System Outcomes Study Group. *Lancet* 2009; **374**: 1262–1270.
8. Kraft M. K., Rothbard A. B., Hadley T. R., McLellan A. T., Asch D. A. Are Supplementary Services Provided During Methadone Maintenance Really Cost-Effective? *Am J Psychiatry* 1997; **154**: 1214–1219.
9. Teesson M., Ross J., Darke S., Lynskey M., Ali R., Ritter A. *et al.* One year outcomes for heroin dependence: Findings from the Australian Treatment Outcome Study (ATOS). *Drug and Alcohol Dependence* 2006; **83**: 174–180
10. Saxon A. J., Wells E. A., Fleming C., Jackson T. R., Calsyn D. A. Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. *Addiction* 1996; **91**: 1197-1209.

11. Soyka M., Zingg C., Koller G., Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *International Journal of Neuropsychopharmacology* 2008; **11**: 641–653.
12. Marsch L. A., Chutuape Stephens M. A., Mudric T., Strain E. C., Bigelow G. E., Johnson R. E. Predictors of Outcome in LAAM, Buprenorphine, and Methadone Treatment for Opioid Dependence. *Experimental and Clinical Psychopharmacology* 2005; **13**: 293–302.
13. Darke S., Ross J., Teesson M., Ali R., Cooke R., Ritter A. *et al.* Factors associated with 12 months continuous heroin abstinence: findings from the Australian Treatment Outcome Study (ATOS). *Journal of Substance Abuse Treatment* 2005; **28**: 255– 263.
14. Lions C., Carrieri M. P., Michel L., Mora M., Marcellin F., Morel A. *et al.* Predictors of non-prescribed opioid use after one year of methadone treatment: an attributable-risk approach (ANRS-Methaville trial). *Drug Alcohol Depend.* 2014; **135**: 1-8.
15. Beswick, T., Best, D., Rees, S., Coomber, R., Gossop, M., Strang, J. Multiple drug use: patterns and practices of heroin and crack use in a population of opiate addicts in treatment. *Drug and Alcohol Review* 2001; **20**: 201-204.
16. PHE (Public Health England). Adult Drug Statistics from the National Drug Treatment Monitoring System (NDTMS) 1 April 2013 to 31 March 2014. 2014. Available at: <http://www.nta.nhs.uk/uploads/adult-drug-statistics-from-the-national-drug-treatment-monitoring-system-2013-14.pdf> (accessed 10 July 2015).
17. Sullivan L. E., Moore B. A., O'Connor P. G., Barry D. T., Chawarski M. C., Schottenfeld R. S. *et al.* The association between cocaine use and treatment outcomes in patients receiving office-based buprenorphine/naloxone for the treatment of opioid dependence. *Am J Addict.* 2010;**19**: 53–8.
18. Williamson A., Darke S., Ross J., Teesson M. The effect of persistence of cocaine use on 12-month outcomes for the treatment of heroin dependence. *Drug and Alcohol Dependence* 2006; **81**: 293–300.
19. Salamina G, Diecidue R, Vigna-Taglianti F, Jarre P, Schifano P, Bargagli AM, *et al.* Effectiveness of therapies for heroin addiction in retaining patients in treatment: results from the VEdeTTE study. *Subst Use Misuse.*2010; **45**: 2076–92.
20. Castells X., Kosten T. R., Capella D., Vidal X., Colom J., Casas M. Efficacy of Opiate Maintenance Therapy and Adjunctive Interventions for Opioid Dependence with Comorbid Cocaine Use Disorders: A Systematic Review and Meta-Analysis of Controlled Clinical Trials. *American Journal of Drug & Alcohol Abuse* 2009; **35**: 339-349.
21. Leri F., Bruneau J., Stewart J. Understanding polydrug use: review of heroin and cocaine co-use. *Addiction* 2003; **98**: 7–22.

22. Cunningham C. O., Giovanniello A., Kunins H. V., Roose R. J., Fox A. D., Sohler N. L. Buprenorphine Treatment Outcomes among Opioid-Dependent Cocaine Users and Non-users, *Am J Addict.* 2013; **22**: 352–357.
23. Roux P., Lions C., Vilotitch A., Michel L., Mora1 M., Maradan G *et al.* Correlates of cocaine use during methadone treatment: implications for screening and clinical management (ANRS Methaville study). *Harm Reduction Journal* 2016; **13**:12.
24. Marsden J, Farrell M, Bradbury C, Dale-Perera A, Eastwood B, Roxburgh M. *et al.* Development of the Treatment Outcomes Profile. *Addiction* 2008; **103**: 1450–60.
25. NTA (National Treatment Agency for Substance Misuse). The Treatment Outcomes Profile (TOP) A guide for keyworkers. 2007. Available at [http://www.nta.nhs.uk/uploads/top\\_keyworker\\_guide\\_270907.pdf](http://www.nta.nhs.uk/uploads/top_keyworker_guide_270907.pdf) (Accessed 6 August 2015).
26. Bell J. Pharmacological maintenance treatments of opiate addiction. *Br J Clin Pharmacol.* 2014; **77**: 253-63.
27. Saxon A. J., Hser Y. I., Woody G., Ling W. Medication-assisted treatment for opioid addiction: Methadone and buprenorphine. *Journal of food and drug analysis* 2013; **21**:69-72.
28. Hser Y. I., Saxon A. J., Huang D., Hasson A., Thomas C., Hillhouse M. *et al.* Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction* 2014; **109**: 79-87.
29. Pinto H., Maskrey V., Swift L., Rumball D., Wagle A., Holland R. The SUMMIT Trial: A field comparison of buprenorphine versus methadone maintenance treatment. *Journal of Substance Abuse Treatment* 2010; **39**: 340–352.
30. [Gryczynski J., Jaffe J. H., Schwartz R. P., Dušek K. A., Gugsá N., Monroe C. L. \*et al.\* Patient Perspectives on Choosing Buprenorphine over Methadone in an Urban Equal Access System. \*Am J Addict.\* 2013; \*\*22\*\*: 285–291.](#)
31. Garcia-Portilla M. P., Bobes-Bascaran M. T., Bascaran M. T., Saiz O. A., Bobes J. Long term outcomes of pharmacological treatments for opioid dependence: does methadone still lead the pack? *British Journal of Clinical Pharmacology* 2012; **77**: 272–284.
32. NICE. Technology appraisal guidance 114: Methadone and buprenorphine for the management of opioid dependence. 2007. Available at <https://www.nice.org.uk/guidance/ta114/resources/methadone-and-buprenorphine-for-the-management-of-opioid-dependence-82598072878789> (accessed 10 August 2015).
33. Ferri M., Finlayson A. J. R., Wang L., Martin P. R. Predictive Factors for Relapse in Patients on Buprenorphine Maintenance. *Am J Addict.* 2014; **23**: 62–67.

34. Hartel D. M., Schoenbaum E., Selwyn P. A., Kline J., Davenny K., Klein R. *et al.* Heroin Use during Methadone Maintenance Treatment: The Importance of Methadone Dose and Cocaine Use. *Am. J. Public Health* 1995; **85**: 83-88.
35. Hill K., Bennett H. E., Griffin M. L., Connery H. S., Fitzmaurice G. M., Subramaniam G. *et al.* Association of cannabis use with opioid outcomes among opioid-dependent youth. *Drug and Alcohol Dependence* 2013; **132**: 342–345.
36. Epstein D. H., Preston K. L. Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against. *Addiction* 2003; **98**: 269–279.
37. Best D., Gossop M., Greenwood J., Marsden J. Lehmann P., Strang J. Cannabis use in relation to illicit drug use and health problems among opiate misusers in treatment. *Drug and Alcohol Review* 1999; **18**: 31-38.
38. Bravo M. J., Llorens N., Barrio G., Brugal M. T., Santos S., Sordo L., *et al.* Methadone maintenance treatment: A protective factor for cocaine injection in a street-recruited cohort of heroin users. *Drug and Alcohol Dependence* 2010; **112**: 62–68.
39. Baumeister M., Vogel M., Dürsteler-MacFarland K. M., Gerhard U., Strasser J., Walter M. *et al.* Association between methadone dose and concomitant cocaine use in methadone maintenance treatment: a register-based study. *Substance Abuse Treatment, Prevention, and Policy*, 2014; **9**: 46.
40. Griffin M. L., Dodd D. R., Potter J. S., Rice L. S., Dickinson W., Sparenborg S. *et al.* Baseline characteristics and treatment outcomes in prescription opioid dependent patients with and without co-occurring psychiatric disorder. *Am J Drug Alcohol Abuse* 2014; **40**: 157–162.
41. Kosten T. R., Morgan C., Kosten T.A. Depressive symptoms during buprenorphine treatment of opioid abusers. *J Subst Abuse Treat.* 1990; **7**: 51-4.
42. [Dreifuss J. A., Griffin M.L., Frost K., Fitzmaurice G. M., Potter J. S., Fiellin D. A., et al.](#) Patient Characteristics Associated with Buprenorphine/Naloxone Treatment Outcome for Prescription Opioid Dependence: Results from a Multisite Study. *Drug Alcohol Depend.* 2013; **131**: 112–118.
43. Rounsaville B. J., Anton S. F., Carroll K., Budde D., Prusoff B. A., Gawin F. Psychiatric diagnoses of treatment-seeking cocaine abusers. *Arch Gen Psychiatry* 1991; **48**: 43–51.
44. López A., Becoña E. Depression and cocaine dependence. *Psychol Rep* 2007; **100**: 520–524.

45. Dakwar E., Nunes E. V., Bisaga A., Carpenter K. C., Mariani J. P., Sullivan M. A. *et al.* A Comparison of Independent Depression and Substance-Induced Depression in Cannabis-, Cocaine-, and Opioid-Dependent Treatment Seekers, *The American Journal on Addictions*, 2011; **20**: 441–446.