STIMULANT USE AND TREATMENT RETENTION AMONG INDIVIDUALS IN AN OPIOID MAINTENANCE TREATMENT PROGRAM

By

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CERTIFICATE OF APPROVAL

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Table of Contents

Tables

Abstract

Objectives: (1) Identify variables associated with retention in an opioid treatment program and (2) investigate the association between continued stimulant use and patient retention.

Methods: Patients (n = 153) in an opioid treatment program were enrolled in a clinical trial that randomized participants to six months of buprenorphine /naltrexone or methadone and assessed the measures of liver functioning. A secondary analysis of clinical data assessed patient and program influences on study retention. A Markov chain analysis compared methadone and buprenorphine study participants on the probability of positive urine drug screens for stimulant use.

Results: Superior retention time was found in patients on methadone, who began treatment halfway through the study, attended group meetings weekly, had longer periods of time without drug use in the last year, and who were not intravenous users. Buprenorphine was not found to be more effective at decreasing stimulant use than methadone.

Conclusions: In an opioid treatment program, methadone patients taking methadone and participating in counseling achieved better retention in care. Greater retention may improve patient outcomes. Counseling appears to help patients stay involved in their treatment. At this time there is no conclusion on the effectiveness of either buprenorphine or methadone on stimulant use for patients enrolled in an opioid treatment program.

Lay Summary

Illicit drug use in the United States remains high. Drug treatment programs aid substance abusers to quit and remain clean. Methadone and buprenorphine are used to treat opioid dependence. Regular use of stimulants with heroin occurs among the population of interest. This paper evaluated data from an opioid treatment program in Portland, Oregon, where 366 patients were randomized to either buprenorphine or methadone. The focus of study is on a subsample of 153 patients and their retention (how long they stayed in the study) and on continued stimulant use (measured by weekly urine tests).

Research Questions

(1) What factors are associated with patients completing or leaving the drug treatment program early?

(2) Is methadone or buprenorphine effective in reducing stimulant (cocaine, methamphetamine, and amphetamine) use?

Specific Aims

This project is a secondary analysis of clinical data abstracted from patient files. The patients were study participants in a clinical trial conducted by the National Drug Abuse Treatment Clinical Trials Network testing the effects of methadone and buprenorphine on liver functioning. Participants were randomized to six months of opioid agonist treatment with either methadone or buprenorphine/naloxone. All patients in the clinic participated in routine random urinary screening throughout their treatment. This project had two specific aims:

(1) Assess patient and program variables associated with the weeks of study retention.

(2) Analyze the urine screen results of the two different treatment groups, methadone and buprenorphine; and Inspect for an effect on cocaine and/or methamphetamine use.

Background and Significance

Methadone is a synthetic opioid agonist. It binds to mu opiate receptors on the surfaces of brain cells, which mediate the analgesic and other effects of opioids. A therapeutic dosage of methadone decreases the response to short-acting opioids (including heroin), thus suppressing withdrawal symptoms and opioid cravings as the short acting opioid is eliminated from the body. Methadone has been used since the early 1960s for opioid maintenance treatment (CSAT, 2006).

Buprenorphine is a synthetic opioid partial agonist. While it does bind to the mu receptors fully, it does not completely activate them. As a result, there is a ceiling effect that prevents greater doses of buprenorphine from producing greater agonist effects (Walsh et al., 1994). The drug Suboxone® is a combination of buprenorphine and naloxone, ratio 4mg to 1mg respectively. Naloxone inhibits intravenous use of buprenorphine because the naloxone in the Suboxone® triggers withdrawal symptoms if injected but is ineffective when taken sublingually (CSAT, 2006).

Methadone and buprenorphine are both used in medication-assisted treatment (MAT) for opioid addiction in opioid treatment programs (OTP). Methadone treatment is more prevalent; only an estimated 1.6% of OTP patients receive buprenorphine (SAMHSA, 2010). To be classified as an OTP, the program must be certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) to provide supervised assessment and MAT for opioid addicted patients. Generally methadone cannot be dispensed for MAT outside of an OTP, therefore in a primary care setting buprenorphine is offered for MAT. Unlike MAT in a physician's office, OTPs provide a more comprehensive, individually tailored program of medication therapy integrated with psychological and

medical treatment and support services that cater to the complex factors affecting each patient (CSAT, 2006). In 2008 there were 1,132 OTPs (SAMHSA, 2010) and the number of patients enrolled in OTPs had almost doubled since 1993 (CSAT, 2008).

Studies have shown a relationship between length of treatment stay in OTPs and superior treatment outcomes (Sees et al. 2000, Zhang et al. 2003, Hubbard et al. 1997, and Simpson et al. 1997). Treatment retention is a concern since early dropout can lead to relapse. Treatment dropout can lead to adverse effects such as overdose, HIV and Hepatitis C infection or transmission, criminal behavior, and premature mortality (Davoli et al. 1993, Caplehorn et al. 1996; and Zaric et al. 2000).

Different pre-treatment characteristics have been linked to OTP retention. Older age has been shown to increase retention (Villafranca et. al, 2006 and Neufeld et al., 2008 and Deck and Carlson, 2005). Female methadone patients have also been shown to have higher long-term retention rates (Schiff et al., 2007). Neufeld et al. (2008) found that patients referred to a methadone maintenance treatment through syringe exchange programs were less likely to complete one year of a program than were other referrals. However once adjusted for baseline characteristics, i.e. greater frequency of injection drug use, employment status, and age, this association was not significantly different. Employment status has also shown to be a predictor of retention in methadone patients (Gerra et al., 2004).

While all these studies results are useful, treatment facilities cannot choose patients based on demographic characteristics that lead to better retention and ultimately greater treatment outcomes. Controllable factors, like provider-related variables, should be

considered when looking to improve retention. The most commonly studied of these is dose. Strain et al. (1999) found no significant difference in treatment retention between higher (≥80mg/day) and moderate (40-50mg/day) methadone dosage; however the higher dosage was associated with lower rates of opioid-positive urine sample during treatment and detoxification. However, D'Ippoliti et al. (1998) found that patients receiving ≥60mg/day of methadone were 70% more likely to stay in treatment than patients receiving <30 mg/day of methadone. Higher dosage of buprenorphine was not found to be related to retention for buprenorphine patients (Gerra et al., 2004). This discrepancy between the two drugs can be expected by their pharmacology and buprenorphine's ceiling effect at high doses (Walsh et al., 1994).

There is a difference in the chemical makeup between buprenorphine and methadone. Many studies have examined their efficacy in treating opioid dependence. Negative urine samples were found to be associated with both buprenorphine and methadone therapy (Gerra et al. 2004, Strain et al. 1994, Mattick et al. 2003, and Amass et al. 2000). Additional findings showed that buprenorphine was more effective than methadone in patients affected by depressive symptoms, hypothesized to be a result of buprenorphine's antagonist action on κ-opioid receptors. Buprenorphine patients have been shown to have higher early (first 4-weeks) dropout rates but become comparable to those of methadone patients after this time (Gerra et al., 2004).

In 2008, an estimated 282,000 persons 12 years or older were dependent on or abused heroin and 1,716,000 were dependent or abusers of opioid pain relievers (SAMSHA, 2008). SAMSHA also estimated that 7.6 million people needed treatment for illicit drug use, of which 6.4 million did not receive treatment. Fortunately, methamphetamine use in the

United States has decreased by half between 2006 and 2008 (731,000 and 314,000 respectively), however cocaine users still comprise of 0.7 percent of the population, 1.9 million people (SAMSHA, 2008).

The co-abuse of stimulants with heroin is of increasing interest. The prevalence of baseline stimulant abuse has been reported in over half of OTP's patients (Grella et al. 1997, Hubbard et al. 1997 and Leri at al.). A meta-analysis of the efficacy of MAT for dual heroin and cocaine abuse showed that methadone was more efficacious than buprenorphine in the achievement of sustained cocaine abstinence and methadone was associated with an increased cocaine-free urinalysis (Castells et al., 2009).

There is emerging evidence that buprenorphine could be used to treat stimulant abuse. McCann (2008) argues that a buprenorphine/naltrexone combination should be studied for treatment of methamphetamine dependence because of evidence from a Zhao et al. (2003) study showing nociceptin's ability to block methamphetamine-conditioned place preference in rats and buprenorphine's ability to act as nociceptin, an endogenous agonist for ORL-1 receptor (Wnendt et al., 1999). Additional evidence in a rat model for the efficacy of buprenorphine in treating methamphetamines was provided by Pereira et al. (2009) who showed an alteration of dopaminergic response to methamphetamine as a result of buprenorphine.

Methods

This study was a secondary analysis of chart abstractions of 153 opiate dependent adults randomized to either buprenorphine or methadone at CODA Inc., a drug treatment clinic in Portland, Oregon, from 8/1/2006 to 7/1/2009.

Study Subjects/Selection Criteria

Study cohort members met the following inclusion criteria:

1. Age 18 years or older
2. Met DSM-IV criteria for opioid dependence
3. Females of childbearing potential agreed to use contraception throughout study
4. Able to read and verbalize understanding and voluntary sign the approved Informed Consent form

Study cohort members did not meet the following exclusion criteria:

1. AST or ALT values > 5 times the upper limit of normal
2. ALP > 3 times the upper limit of normal
3. Documentation of past or present history of ascites, presence of esophageal or gastric varices, hepatic encephalopathy or other signs of significant liver disease as indicated by a Model for Endstage Liver Disease score of ≥ 11
4. Total bilirubin >2.0 mg/dl
5. Prothrombin time more than 3 seconds prolonged
6. Albumin level less than 2.5 g/dL
7. Cardiopathy or other risk factors without evidence of a normal ECG
8. Acute medical condition that would cause participation medically hazardous
9. Allergy or sensitivity to Buprenorphine, naloxone, or methadone or to any inactive ingredient in study medication
10. Diagnosis of acute psychosis, severe depression or imminent suicide risk
11. DSM-IV diagnosis of dependence on benzodiazepines, alcohol, other depressant, or stimulants requiring medical attention
12. Participated in an investigational drug study within the past 30 days
13. Had a treatment with methadone, Buprenorphine/naloxone, or Buprenorphine for more than 15 of the past 30 days
14. Had pending legal action that could prohibit the study
15. Unable or unwilling to remain in the local area for duration of the treatment
16. Had poor venous access
17. Pregnant or lactating female

Measurement and Data Collection

In the fall of 2008, 153 patient charts were abstracted as a pilot study completed with support from the Methamphetamine Abuse Research Center (MARC). A trained research assistant collected patient data (e.g. age, gender, race/ethnicity) and medical provider related variables (e.g. medication and dose). The chart review collected data from

qualitative urine drug screens; this included date of test and presence or absence of seven substances (e.g. methamphetamines, alcohol, cocaine).

Variables

Time spent in the study is the outcome variable for retention. This was calculated from the date of the first dosing to the date of the last dosing. Typical treatment was to last six months; the maximum retention time recorded was 36 weeks.

Urinary analysis results were the outcome variables for stimulant use. CODA protocol called for a UA to be performed prior to first dosing and for random UAs to be given to each patient once a week after first dosing till the end of treatment or six months of clean UAs obtained. The routine CODA UA detects seven different substances: opiates, methadone, amphetamines, alcohol metabolites, benzodiazepines, cocaine, and THC (tetrahydrocannabinol: psychoactive substance present in marijuana). The UA results in this data set were qualitative and did not record the amount of substance in the urine. Using these UAs, a variable representing the percentage of UAs positive for illicit opiates was calculated per patient and used as a covariate in predicting retention.

Treatment medication, Suboxone® (buprenorphine/naloxone) or methadone, was the main predictor variable for stimulant use. The therapeutic treatment dosage of Suboxone® and methadone varied per patient. Adjustments were dependent on nurse and counselor evaluations of opioid withdrawal, UA toxicology showing the presence or absence of illicit opioids or opiates, opioid intoxication due to treatment drug, or patient craving for opioids.

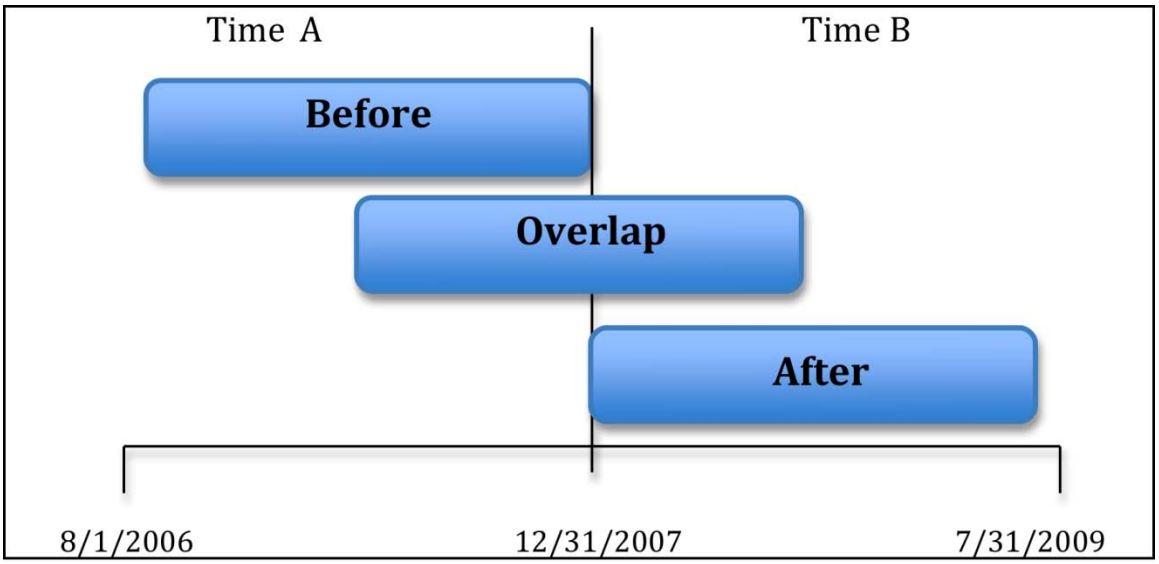
As noted previously, provider related variables are of interest since they can be controlled. Halfway through the study at CODA there were changes made to improve clinic recruitment and retention (Table 1). In this analysis a provider associated predictor is the

period prior to 12/31/07 and the period after, at which time the modifications were fully implemented. The study population was stratified into three groups according to their intervention status: before, overlap, and after (see Table 2).

Table 1: Changes made to study (fully implemented by 12/31/07)

Provided treatment and treatment services for free
Improved staff relations between clinic and research
Added research visit 24 hours after randomization
Dedicated a research assistant/counselor to study participants
Increased physician involvement
Participant reached a therapeutic dose of buprenorphine more quickly

Table 2: Groups for Intervention Status



Demographic and other patient variables were included as covariates in the model predicting study retention. Demographics measured at the beginning of the study included age, gender, ethnicity, children present in the home, smoking, employment and housing status. Additional drug related measurements were primary and secondary drug of use, route of drug use, age at first use, previous treatment and longest period of days without use in past year. Ordinal scaled measurements of emotional, behavioral, developmental conditions and complications (PPCEMOCO), readiness to change (PPCREADY), and

recovery environment (PPCENVIR) were assessed. These three variables were treated as factor variables; each having five levels with larger values signifying greater severity.

Regression Analysis

The primary objectives of this paper were to: (1) study the associations between patient and demographic variables and retention; (2) analyze intervention effects on retention. Univariate analysis was performed for all covariates, with treatment type and intervention status as the primary predictors of interest, using simple linear regression (SLR). A multivariate model was built using the results of the SLR. Intervention status and treatment type remained the main predictors and other covariates were added one at a time that met the SLR threshold *p*-value of 0.2. They were kept in the model if they remained significant at this level. Once removed, covariates were analyzed as possible confounders. After an optimal model was determined it was evaluated for goodness of fit using residual diagnostics.

Markov Chain Analysis

A secondary study evaluated the effect of buprenorphine and methadone on stimulant use. This examination utilized Markov chains. A Markov chain is a discrete random process with the property that the probability of passing into the next state is completely determined by the current state. For this paper's purposes, probabilities were computed that described the probability distribution of testing negative or positive for stimulants if the patient had tested negative or positive for the most recent UA test. This is referred to as the transition matrix and was calculated for each treatment group.

After this calculation, the limiting distribution property of Markov chains was employed. A transition matrix has a limiting distribution if, after many iterations, it comes to a steady state. This property can be used to describe the ultimate probability

distribution. For this study, the limiting distribution gives the probability distribution of final states of testing positive or negative for stimulants.

Results

Demographic information for the study population is shown in Table 3. Overall, patients were male (65%), white (84%), unemployed (62%), with a mean age of 34 years. Heroin was the primary drug of choice (74%). Stimulant use was reported by 44% of the study population as a secondary drug. Within the two different treatment groups, gender, mean age, ethnicity, and employment status were not significantly different (see Table 3 for demographics by treatment type). Homeless status though, for the buprenorphine group was 47% while the methadone group homeless percent was 65% (χ_1^2 =4.74, p=0.03), however this difference appeared to occur by chance and was not due to bias in the randomization process.

The first hypothesis tested for associations between treatment type and intervention status on study retention, measured as the amount of weeks patients stayed in treatment. The mean retention time for methadone patients (24 ± 11 weeks) was significantly different than buprenorphine patients (15 ± 12 weeks), t=-4.67, p<0.001. SLR analysis suggested that buprenorphine patients stayed in the study for less time than methadone patients, β=-8.75. Thus, a buprenorphine patient was likely to leave the study 8 weeks and 5 days before a methadone patient.

Table 3: Demographics for study population by study medication

	Total Patients N = 153	Buprenorphine N=85	Methadone N=68	Test for difference in treatment groups
Treatment type:				
Buprenorphine	85(56.6%)			
Methadone	68(44.4%)			
Retention in weeks	19.2 ± 12.3	15.3 ± 12.2	24.0 ± 10.7	$t_{(151)}$=-4.67, p=<0.001
Intervention Status:				
Before	56(36.6%)	30(35.3%)	26(38.2%)	$\chi^2_{(2)}$=9.93, p=0.007
Overlap	24(15.7%)	7(8.2%)	17(25.0%)	
After	73(47.7%)	48(56.5%)	25(36.8%)	
Gender:				
Male	99 (64.7%)	58(68.2%)	41(60.3%)	$\chi^2_{(1)}$=1.04, p=0.31
Female	54 (35.3%)	27(31.8%)	27(39.7%)	
Age	33.8 ± 10.7	34.6±11.2	32.8±10.1	$t_{(151)}$=1.03, p=0.30
Race/Ethnicity:				
White non-Hispanic	129(84%)	69(81.2%)	60(88.2%)	Fisher's exact, p=0.45
Black	6(4%)	5(5.9%)	1(1.5%)	
Hispanic	6(4%)	3(3.5%)	3(4.4%)	
Asian	2(1%)	2(2.3%)	0(0%)	
Other	10(7%)	6(7.1%)	4(5.9%)	
Housing:				
Homeless	83(54.2%)	39(45.9%)	44(64.7%)	$\chi^2_{(1)}$=4.74, p=0.03
Had Housing	68(44.4%)	44(51.8%)	24(35.3%)	
Employment:				
Unemployed	95(62.1%)	51(60.0%)	44(64.7%)	$\chi^2_{(1)}$=0.04, p=0.85
Employed	50(32.7%)	26(30.6%)	24(35.3%)	
Kids at Home:				
Yes	30(19.6%)	18(18.8%)	12(17.6%)	$\chi^2_{(1)}$=0.37, p=0.54
No	119(77.7%)	64(75.3%)	55(80.9%)	
Primary Drug:				
Heroin	113(73.9%)	64(75.3%)	49(72.1%)	
Prescription Opioids	40(26.1%)	21(24.7%)	19(27.9%)	$\chi^2_{(1)}$=1.04, p=0.31
Drug Route:				
IV	80(52.3%)	49(57.6%)	31(45.6%)	$\chi^2_{(3)}$=2.63, p=0.45
IM	13(8.5%)	7(8.2%)	6(8.8%)	
Oral	33(21.6%)	17(20.0%)	16(23.5%)	
Smoking/Inhaling	27(17.6%)	12(14.1%)	15(22.1%)	
Age at first use	21.3 ± 7.6	22.4 ± 8.0	20.1 ± 7.0	$t_{(151)}$=1.87, p=0.06
Amount of days without drug use in past 12 months	28.7 ± 52.2	24.3 ± 47.0	34.10 ± 57.9	$t_{(151)}$=-1.16, p=0.25

Mean retention time for the intervention status groups was 14 ±12 weeks for the before group, 29 ± 6 weeks for the overlap group, and 20 ± 12 weeks for the after group. SLR analysis indicated that patients in the study prior to the study intervention on 12/31/2007 stayed less time in the study than those who began the study after the intervention (β=-5.23, t=-2.58, p=0.011), while the group that overlapped the study intervention time had superior retention time than those who began completely after the intervention took place (β=9.19, t=3.42, p<0.001). Therefore the before group were in the study 5 weeks and 2 days less than the after group and the overlap group were in the study 9 weeks and 1 day longer than the after group.

Univariate analyses for the other covariates are summarized in Table 4. Group meeting attendance had a significant association with mean retention. Patients attending group meetings 1-3 times weekly stayed in the study longer. Drug route was significant, showing that IV users had decreased retention time compared to other users. Surprisingly neither gender nor age was significant in SLR, however employment status did predicted retention -- employed patients remained in care longer. Each month of abstinence from opiates in the year preceding the study improved mean study retention by 8 days.

Univariate analysis for the three ordinal measures patient readiness to change, environment, and mental health was performed treating them as factor variables. Recall that 1 represents the best-case scenario and 5 the worst. None of these factors were significant at the p=0.05 level, Table 5.

Table 4: Univariate Analysis Results

Predictor Variable	Mean Retention	
	β (95% CI)	*p*-value
Intervention Status:		
Before vs. After	-5.23(-9.24, -1.22)	0.011
Overlapping vs. After	9.19(3.88, 14.50)	<0.001
Treatment:		
Buprenorphine vs. Methadone	-8.75(-12.47, -6.03)	<0.001
Group Attendance:		
No attendance vs. Sporadic	-11.29(-16.24, -6.35)	<0.001
1-3 times per week vs. Sporadic	7.36 (2.20,12.52)	0.006
Gender:		
Female vs. Male	1.25 (-2.87, 5.38)	0.55
Age	0.07(-0.12,0.025)	0.47
Housing Status:	-0.35(-4.32, 3.62)	0.86
Homeless vs. Had housing		
Previous Treatment:		
No vs. Yes	-0.07(-4.90, 4.77)	0.98
Employment:		
Employed vs. Unemployed	4.78(.071, 8.85)	0.02
Smoking Status:		
Smoker vs. Nonsmoker	-0.87(-9.74, 8.00)	0.85
Kids at Home:		
Yes vs. No	4.05(-0.87, 8.97)	0.11
Primary Drug:		
Heroin vs. Prescription Opioids	-1.83(-6.32, 2.65)	0.42
Drug Route:		
IM vs. IV	7.53(0.39, 14.67)	0.04
Oral vs. IV	2.49(-2.44, 7.44)	0.32
Smoking/Inhaling vs. IV	6.89(1.58, 12.21)	0.01
Age at first use	0.03(-0.23, 0.30)	0.80
Race/Ethnicity:		
White non-Hispanic vs. Other	1.78(-6.19, 9.75)	0.66
Black vs. Other	-9.27(-21.80, 17.71)	0.15
Hispanic vs. Other	-1.43(-13.97, 11.10)	0.82
Asian vs. Other	-1.10(-19.91, 17.71)	0.66
Amount of days without drug use in past 12 months	0.04(0.003,0.08)	0.03
Percent of UAs Positive for Illicit Opiates	-10.22(-15.38, -5.06)	<0.001

Table 5: Univariate Analysis for PPC variables

Predictor Variable	Mean Retention	
	β (95% CI)	*p*-value
PPCEMOCO:		
1 vs. 5	-0.12(-18.40, 18.15)	0.99
2 vs. 5	0.84(-16.74, 18.41)	0.92
3 vs. 5	1.45(-16.14, 19.04)	0.87
4 vs. 5	-2.03(-19.77, 15.71)	0.82
PPCREADY:		
1 vs. 5	14.80(-10.39, 40.00)	0.25
2 vs. 5	-0.41(-10.36, 9.53)	0.93
3 vs. 5	5.62(-2.63, 13.87)	0.18
4 vs. 5	1.9(-6.22, 10.09)	0.64
PPCENVIR:		
1 vs. 5	No Data	-
2 vs. 5	1.06(-5.13, 7.26)	0.73
3 vs. 5	-0.99(-6.67, 4.69)	0.73
4 vs. 5	-5.87 (-11.95, 0.21)	0.06

After showing that treatment type and intervention status were significant predictors of retention time, multiple linear regression modeled retention time to assess the influence of treatment type and intervention status controlling for each measure of patient demographics and background variables. After these covariates were tested for association with study retention using simple linear regression, the significant predictors using a *p*-value threshold of 0.2 were kids in household, amount of days without drug use in past twelve months, route of drug use, employment status, recovery environment, group attendance, and percent of UAs positive for illicit opiates.

Model selection using treatment type and intervention status and the significant variables from univariate analysis yielded a model that included group attendance, drug route, and amount of days without drug use in past 12 months. Percent of UAs positive for illicit opiates was removed because of association with drug route (Anova F=6.28, $p<0.001$) and group attendance (Anova F=4.52, $p=0.013$).

The results for the final model are found in Table 6. Treatment type and intervention status continued to have similar outcomes after adjustment for the other three covariates. That is, there was a 6 week and 2 day mean retention reduction for buprenorphine patients compared to methadone patients. Compared to the after intervention group, the before intervention group had a 10 week and 4 day mean retention reduction and the overlapping group had a 2 week and 4 day increase.

Table 6: Regression Full Model Results

Predictor Variable	Mean Retention	
	β (95% CI)	*p*-value
Intercept	23.37(19.26, 27.47)	<0.001
Intervention Status:		
Before vs. After	-10.51(-14.84, -6.18)	<0.001
Overlapping vs. After	2.56(-1.89, 7.01)	0.26
Treatment:		
Buprenorphine vs. Methadone	-6.35(-9.79, -2.90)	<0.001
Group Attendance:		
No attendance vs. Sporadic	-10.11(-14.12, -6.11)	<0.001
1-3 times per week vs. Sporadic	5.41(1.20, 9.61)	0.01
Drug Route:		
IM vs. IV	6.34(0.40, 12.28)	0.04
Oral vs. IV	0.02 (-3.99, 4.04)	0.99
Smoking/Inhaling vs. IV	5.74 (0.75, 10.73)	0.03
Amount of days without drug use in past 12 months	0.04(0.01,0.06)	0.01

Another hypothesis this paper tested was if buprenorphine patients decreased their stimulant use more than methadone patients. The limiting distributions using Markov chains did not support this hypothesis. The distribution consisted of only those patients who tested positive for stimulants at least once during the study. Recall as described in the methods section, Markov chains are based on the probabilities of passing into the next

state based on the current state of the system. The probability of a patient being positive for stimulants on their next visit is based on their current stimulant status. Table 7 shows the limiting distributions for stimulant use for the two treatment groups; the distribution of patients testing negative for stimulants at the end of treatment was 58 percent for buprenorphine patients and 69 percent for methadone patients. Using the sample size of the 86 patients in this group (48 buprenorphine, 38 methadone) there was not a significant difference in this distribution ($\chi^2_{(1)}$ =0.924, p=0.336).

Table 7: Limiting Distribution for Stimulant Users* N=86

Treatment Type	Negative	Positive
Buprenorphine	0.58	0.42
Methadone	0.69	0.31

*$\chi^2_{(1)}$ =0.924, p=0.336

Stratifying the UA results into three different time periods (1 to 8 weeks, 9 to 18 weeks, and 19 to 24 weeks) the analysis was repeated to adjust for the effect of longer retention time for methadone patients. The resulting limiting distributions are displayed in Table 8. Using the sample of patients in each group there was not a significant difference in the distributions between buprenorphine and methadone patients for any of the time periods and the marginal association seen in the limiting distribution over the whole time period was weakened.

Table 8: Stimulant Group Limiting Distributions Stratified by Week

	1 to 8 weeks		9 to 18 weeks		19 to 24 weeks	
Treatment Type	Negative	Positive	Negative	Positive	Negative	Positive
Buprenorphine	0.52	0.48	0.66	0.34	0.73	0.27
Methadone	0.56	0.44	0.67	0.33	0.70	0.30
Bup N, Meth N, $\chi^2_{(1)}$, p-value	39,36, $\chi^2_{(1)}$=0.14, p=0.71		31,31, $\chi^2_{(1)}$=0.07, p =0.79		18,27, $\chi^2_{(1)}$=0.02, p =0.89	

The stimulant group was divided into two distinct drug groups, cocaine and methamphetamine/amphetamine users. The cocaine group consisted of 80 patients who tested positive at least once for cocaine. The methamphetamine group was 34 patients who tested positive at least once for methamphetamine or amphetamine. Therefore there were 28 patients who tested positive for cocaine and methamphetamines/amphetamines and 52 patients who tested positive only for cocaine and 6 patients who tested positive only for methamphetamine/amphetamines. The resulting limiting distributions for these groups are shown in Tables 9 and 10. Using the sample size of the 80 patients in the cocaine group (45 buprenorphine, 35 methadone) there was not a significant difference in this distribution, (χ_1^2=2.04, p=0.153). The methamphetamine/amphetamine group (14 buprenorphine, 20 methadone) also did not show a significant difference in the limiting distribution, Fisher's two sided exact (*p*=0.704).

Table 9: Limiting Distribution for Cocaine Users N=80*

Treatment Type	Negative	Positive
Buprenorphine	0.62	0.38
Methadone	0.79	0.21

* χ_1^2=2.04, p=0.153

Table 10: Limiting Distribution for Methamphetamine/Amphetamine Users N=34*

Treatment Type	Negative	Positive
Buprenorphine	0.67	0.33
Methadone	0.76	0.24

*Fisher's two sided exact *p*=0.704

Again the groups were stratified into time groups to adjust for the longer retention times for methadone patients. These results are found in Tables 11 and 12. Again we see

the trend of methadone having a stronger association with negative UAs weakened when separated into time groups.

Table 11: Cocaine Group Limiting Distributions Stratified by Week

	1 to 8 weeks		9 to 18 weeks		19 to 24 weeks	
Treatment Type	Negative	Positive	Negative	Positive	Negative	Positive
Buprenorphine	0.58	0.42	0.66	0.34	0.65	0.35
Methadone	0.67	0.33	0.79	0.21	0.75	0.25
Bup N, Meth N, $\chi^2_{(1)}$, *p*-value	36,33, $\chi^2_{(1)}$ =0.51, *p*=0.48		27,28, $\chi^2_{(1)}$=0.98, *p* =0.32		17,26, $\chi^2_{(1)}$=0.76, *p* =0.38	

Table 12: Methamphetamine Group Limiting Distributions Stratified by Week

	1 to 8 weeks		9 to 18 weeks		19 to 24 weeks	
Treatment Type	Negative	Positive	Negative	Positive	Negative	Positive
Buprenorphine	0.61	0.39	0.72	0.28	0.84	0.16
Methadone	0.66	0.34	0.73	0.26	0.81	0.19
Bup N, Meth N, Fisher's 2-sided exact *p* -value	12,18, *p* =0.71		11,18, *p* =1		6,15, *p* =1	

Discussion

Buprenorphine patients stayed in treatment for less time than methadone patients. This finding could be due to the chemical difference in the two drugs and buprenorphine's inability to produce a "high". Patients randomized to buprenorphine who had a desire to be placed on methadone may have prematurely dropped out of the study for this reason. Confirming Gerra et al. (2004) observation that buprenorphine patients' retention tends to improve after the first four weeks of treatment, i.e. those originally disappointed about the "non-effects" of buprenorphine leave the study early.

As stressed in this paper, retention of patients is key to successful outcomes in OTP. Simply put the longer one stays in an OTP, the more likely they are to stay off opiates.

Therefore when patient retention was below optimal at CODA, they moved to improve it by implementing the different strategies shown in Table 2. The results of both SLR and MLR showed that these interventions were successful in their target, patients in the after group had improved retention. However, the overlap group had the best mean retention time. Suggesting possibly an added value of treatment when one has to pay for it in the beginning and then it becomes free, or an overall appreciation for the improvements made.

Findings on the associations of demographic covariates with retention were different than found in the literature. Older age in this population was not found to significantly increase retention as Villafranca et al. (2006) and Deck and Carlson, 2005 found. However, the mean age of the CODA population was only 34 and the Villafranca et al. study population was older US veterans while Deck and Carlson's mean age of their study population was 39. Additionally females were not found in this study population to have improved retention for the population as a whole or within the two different treatment groups. Employment status was significant in univariate analysis, however it was not included in the final MLR model.

The urinary analysis data presented this study with an analytical challenge. Each patient provided a binary time series, testing either positive or negative for each week they were in the study. A simple calculation of the percentage of negative tests is informative, but it gives the same weight to each test. To account for previous tests' effects on the next, Markov chain methods were used. This process assumes that each test is only dependent on the previous. While it is likely that someone testing negative possibly tested negative on more than just the previous test, for this study the previous test is considered a good proxy of the past history of test results.

Currently there is no FDA approved drug therapy for stimulant (methamphetamine, amphetamine, or cocaine) abuse. Over 50 percent of this study population tested positive for stimulants at least once, confirming Grella et al. 1997, Hubbard et al. 1997, and Leri et al. findings of the high prevalence of stimulant abusers in OTP patients. Previous research showed methadone had greater outcomes in reducing stimulant use than buprenorphine (Castells et al., 2009). However, while in the results of this paper methadone patients had higher percentages of negative UAs for stimulants, it was not significantly different than buprenorphine. The separate stimulant groups (cocaine and methamphetamine/ amphetamine) revealed the cocaine group may have driven this trend. The limiting distributions of the cocaine group, even when stratified by weeks, showed methadone having a stronger association with negative cocaine UAs than the methamphetamine/ amphetamine group did with negative methamphetamine/ amphetamine UAs. Larger sample sizes could help increase the strength of the association.

This study had several limitations and drawbacks that should be noted. 1) This paper is a secondary analysis of clinical data from a chart abstraction that was not designed to specifically answer the research questions here. 2) As a result while the study protocol was for every patient to have a random UA every week, the data set indicates that this was not consistently done for all patients. 3) The short amount of time in which stimulants are detectable in the urine, led to imperfect measurement of a patient's stimulant use.

Conclusion

This analysis suggests that methadone treatment for a population in OTP has better retention results than buprenorphine treatment; which ideally leads to better treatment results. Additionally providing services free of charge improved retention outcomes, as did

enhancing various client services as CODA implemented. Stimulant use was high in this population but the evidence was not definitive on a difference in decreased use between the two treatments, methadone and buprenorphine. Further research on this topic is needed.

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