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The Association between Cocaine Use and Treatment Outcomes in Patients Receiving Office-Based Buprenorphine/Naloxone for the Treatment of Opioid Dependence

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Abstract

Cocaine use in patients receiving methadone is associated with worse treatment outcomes. The association between cocaine use and office-based buprenorphine/naloxone treatment outcomes is not known. We evaluated the association between baseline and in-treatment cocaine use, treatment retention and urine toxicology results in 162 patients enrolled in a 24-week trial of primary care office-based buprenorphine/naloxone maintenance. Patients with baseline cocaine metabolite-negative urine toxicology tests compared with those with cocaine metabolite-positive tests had more mean weeks of treatment retention (18.3 vs. 15.8, p=.04), a greater percentage completed 24 weeks of treatment (50% vs. 33%, p=.04) and had a greater percentage of opioid-negative urines (47% vs. 34%, p=.02). Patients with in- treatment cocaine metabolite-negative urine toxicology tests compared with cocaine metabolite-positive patients had more mean weeks of treatment retention (19.0 vs. 16.5, p=.003), a greater percentage completed 24 weeks of treatment (60% vs. 30%, p<.001), and had a greater percentage of opioid-negative urines (51% vs. 35%, p=.001). We conclude that both baseline and in-treatment cocaine use is associated with worse treatment outcomes in patients receiving office-based buprenorphine/naloxone and may benefit from targeted interventions.

Introduction

Cocaine use is prevalent among patients entering treatment for opioid dependence.[1] In one study of individuals entering methadone treatment, 42% reported cocaine use.[2] Cocaine use at the time of entry into and during methadone treatment is associated with increased rates of psychiatric disorders, HIV risk, criminal activity and negative social interactions [3–7] and can predict shorter treatment retention and poorer treatment outcomes.[7–9] While the data on cocaine use in patients entering or receiving methadone treatment is substantial and compelling, there is little data on the association between cocaine use and treatment outcomes in patients receiving buprenorphine/naloxone treatment, particularly office-based treatment.

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The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Buprenorphine/naloxone, is an effective for the treatment of opioid dependence and is approved in the United States for provision in office-based and primary care settings.[10–12] These settings, however, may have limited capacity to provide the psychosocial services that can be successful in addressing cocaine abuse and dependence. Cocaine metabolite-positive urine samples have been observed in 40–46% of patients entering treatment with buprenorphine/naloxone.[13,14] New cocaine use can also develop during opioid agonist treatment with one study reporting cocaine use in 20% of subjects who did not report previous cocaine use.[8] The purpose of the current study is to evaluate the associations between baseline and in-treatment cocaine use and treatment retention and opioid abstinence, and to examine new cocaine use during treatment in patients receiving office-based buprenorphine/naloxone treatment.

Methods

Study Design

We performed a secondary analysis of 162 patients enrolled in a 24 week randomized clinical trial of psychosocial counseling in conjunction with buprenorphine/naloxone maintenance in the primary care center of a large urban, academic medical clinic from August 2000 through February 2004.[15] We stratified patients by urine toxicology evidence of baseline or any in-treatment cocaine use. We also examined the incidence of new cocaine use during the treatment period in patients who had no evidence of recent use. Therefore, the groups we examined were individuals with urine toxicology evidence of; 1) cocaine use at baseline; 2) cocaine use while in-treatment; and 3) new cocaine use that emerged during treatment.

Subjects

Subjects met the following eligibility criteria; age >18, DSM-IV criteria for opioid dependence, opioid positive urine, no dependence on cocaine, alcohol, benzodiazepines or sedatives, no acute medical or psychiatric conditions, able to understand English, and agreeing to adequate contraception and pregnancy monitoring. The study was approved by the Yale University Human Investigations Committee and written informed consent was obtained.

Measures

We collected self-reported demographic and clinical characteristics and weekly urine toxicology analyses for opioids and cocaine. Supervised urine samples were collected at baseline, three times per week during the two-week induction and stabilization period and then weekly following randomization. Urine samples were analyzed using the Abbott Tdx system to test for opiates, methadone, oxycodone, cocaine metabolite (benzoylecognine), and benzodiazepines. Cut-off points, established by the manufacturer, were > 200 ng/ml for opiates and benzodiazepines, > 300 ng/ml for benzoylecognine and methadone, and >100 ng/ml for oxycodone.

We defined baseline cocaine use as any cocaine metabolite-positive urine toxicology at entry into treatment or during the induction period (first two weeks of buprenorphine/naloxone treatment); in-treatment cocaine use as any cocaine metabolite-positive urine toxicology during maintenance treatment (weeks 3 through 24); and new cocaine use as any cocaine metabolite-positive urine toxicology tests during maintenance treatment in patients reporting no cocaine use in the 30 days prior to start of induction and with cocaine metabolite-free urine toxicology tests prior to entry into treatment and during induction.

Given the association between treatment discontinuation and the relapse to illicit opioid use, we coded missing urine specimens as positive for opioids in our analysis. The pattern of results did not differ significantly in additional analyses that used other assumptions regarding missing urine specimens (e.g., coding them as missing, coding them as positive only when patients were still receiving treatment, or carrying the last result forward).[15]

Data Analyses

Analysis of baseline characteristics included descriptive statistics, chi-square for categorical data, and t-tests for continuous measures. Outcome variables controlled for treatment group assignment and interaction with treatment group. We evaluated the association between cocaine and benzodiazepine use at baseline using Cohen's kappa. Retention was analyzed using Cox regression, treatment completion using logistic regression, and continuous measures using Analysis of Variance (ANOVA).

Because patients in the original trial who engaged in unremitting illicit opioid and/or cocaine use were protectively transferred to other treatment modalities, ongoing cocaine use could be highly correlated with poor treatment retention. In order to prevent this from impacting our results, we identified the 14/164 (9%) patients who were protectively transferred during the study. We determined that only two patients met criteria for protective transfer because of unremitting cocaine use (the remainder met criteria for protective transfer due to persistent opioid use, opioid/cocaine use, psychiatric illness, or pregnancy). We subsequently removed these two patients from our analyses. This allowed us to determine the association between cocaine use and buprenorphine/naloxone treatment outcomes over the entire 24 week period of the study. All analyses used 2-tailed tests of significance and were performed using SPSS 15.0 (SPSS Inc., Chicago, Ill.). P-values <.05 were considered statistically significant.

Results

Characteristics

Of the 162 patients, the mean age was 36 years (18–56), 78% were male, 76% were white, and 82% had greater than or equal to a high school education (Table 1). Their mean years of opioid dependence was 8.1 (1–35), the majority of patients reported primarily using heroin (78%), and 31% reported current injection drug use at treatment entry. Thirty-seven percent (N=55) of patients had baseline cocaine use. Baseline non-cocaine users (N=107) were more likely to be white (p = .046) and less likely to have a positive urine toxicology test for benzodiazepines during induction (p = .01) compared with the baseline cocaine users (N=55). Of the 84 (52%) patients who reported no cocaine use in the 30 days prior to entry into treatment and had no urine toxicology evidence of cocaine use at baseline or during the first two weeks of treatment, 26 (31%) had a new cocaine metabolite-positive urine toxicology test during treatment.

Treatment Retention

Patients with a baseline cocaine metabolite-negative urine test compared with those with a cocaine metabolite-positive urine test were retained in treatment longer (mean of 18.3 vs. 15.8 weeks, p= .04), and a greater percentage completed the 24 weeks of treatment (50% vs. 33%, p= .04) (Table 2). In-treatment cocaine metabolite-negative patients compared with cocaine metabolite-positive patients were retained in treatment longer (mean of 19.0 vs. 16.5 weeks, p=.003) and a greater percentage completed 24 weeks of treatment (60% vs. 30%, p<.001) (Table 3 and Figure 1).

Illicit drug use

Patients with a baseline cocaine metabolite-negative urine tests compared with those with a baseline cocaine metabolite-positive urine test had had a higher percentage of opioid-negative urine tests (47% vs. 34%, p= .02), and more weeks of continuous opioid abstinence (p= .03) (Table 2). We evaluated the association between baseline cocaine and benzodiazepine use and found a modest, but significant agreement between cocaine and benzodiazepine use at baseline (kappa = .17, p = .01). In-treatment cocaine metabolite-negative patients compared with cocaine metabolite-positive patients had a higher mean percentage of opioid-negative urines (51.4 vs. 34.8, p=.001), and more weeks of continuous opioid abstinence (p= .001) (Table 3).

Discussion

Baseline and in-treatment cocaine use are associated with adverse treatment outcomes in patients receiving either methadone or buprenorphine/naloxone treatment in drug treatment programs. To our knowledge, our study is the first to examine the association between cocaine use and opioid dependence treatment outcomes in patients receiving buprenorphine/naloxone in a primary care office-based setting. We found that patients who were using cocaine prior to initiating buprenorphine/naloxone treatment and those who used cocaine while engaged in treatment, were less likely to be retained in treatment and had fewer weeks of continuous opioid-negative urine toxicology tests. In addition, over 30% of patients who had no evidence of cocaine use in the 30 days prior to entry into treatment and had no evidence of cocaine use during the beginning of treatment were found to use cocaine during treatment. Finally, while the number of subjects who used benzodiazepines was small we did find a modest but significant correlation between cocaine and benzodiazepine use at baseline highlighting the need to investigate this relationship in a future study that does not exclude patients who are using benzodiazepines.

These findings are similar to those in the literature for patients receiving methadone or buprenorphine/naloxone in drug abuse treatment settings. In prior work it has been noted that patients receiving buprenorphine/naloxone treatment through a drug treatment program who had ongoing cocaine use had more drug use, legal and psychiatric problems.[16] One study found that cocaine use tended to increase over time.[17] In a study of patients receiving methadone maintenance, 20% of those with no cocaine use in the month prior to treatment were found to be using cocaine during treatment.[8] In turn, it should be stated that there are a number of studies in which patients retained in opioid maintenance treatment, either with methadone or buprenorphine, experience significant reductions in their cocaine use.[7,18]

The precipitant for cocaine use among patients receiving opioid agonist treatment is not clear. One possibility is that this use develops or persists because the opioid receptors are blocked by pharmacologic agents. The impact on treatment retention and opioid use could be explained by the fact that patients who continue to use one illicit drug (cocaine) are more likely to continue using another illicit drug (opioids). In turn, as suggested by the findings of research examining the effect of cocaine use on buprenorphine pharmacokinetics, another possibility is that cocaine metabolite-induced vasoconstriction might reduce buprenorphine/naloxone absorption sublingually or increase buprenorphine metabolism.[19]

Our study has limitations that should be considered. First, the study was a secondary analysis and the original study was not specifically designed to examine the effects of baseline and in-treatment cocaine use on outcomes in buprenorphine/naloxone treatment of opioid dependence. Therefore, the samples may have differed in ways that we did not evaluate that may have affected our results. Secondly, patients did receive varying levels of counseling that may have influenced cocaine use. However, the counseling did not

specifically address cocaine use and cocaine use did not differ by counseling condition in the original trial.[15] In our evaluation of cocaine use that emerged during treatment, lack of use during the 30 days prior to initiating treatment was based exclusively on self-report and could not be verified by urine toxicology analyses. Finally, given this is predominately a white, male, educated population and since the eligibility criteria for the original study excluded individuals with dependence on cocaine, sedatives, benzodiazepines, or alcohol severe or co-occurring untreated psychiatric conditions,[15] the generalizability of our findings to all patients receiving office-based buprenorphine/naloxone treatment may be limited.

While the original study was not specifically designed to investigate the association between cocaine use and outcomes in primary care office-based buprenorphine/naloxone treatment, the findings were both statistically and clinically significant and consistent with results of previous studies of buprenorphine treatment that have been conducted in drug treatment programs.[2,8,11–13,17] Given the prevalence of cocaine use and its association with worse treatment outcomes, interventions that target cocaine may improve buprenorphine/naloxone treatment results in these patients. There are, however, no current efficacious pharmacologic treatments for cocaine use.[20] In contrast, psychosocial counseling strategies have been found to be effective in reducing cocaine use, both in patients abusing cocaine alone[21,22] and in the context of buprenorphine treatment for co-occurring opioid dependence.[7,23] While the data support the efficacy of counseling, these studies have employed intensive manual-guided psychosocial treatments that require significant therapist training and resources. It is unlikely that office-based buprenorphine/naloxone providers would be able to routinely provide this type of treatment in the office setting. However, given the growing use of buprenorphine/naloxone for the treatment of opioid dependence in office-based settings and the considerable prevalence of cocaine use in these patients, physician providers, particularly those providing office-based addiction treatment should be aware of and have plans to address this problem. Providers should provide screening and monitoring for baseline, in-treatment, and new cocaine use and if their practices can not support the provision of intensive psychosocial counseling, should consider referring patients with cocaine use to programs that are able to offer such treatments.

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Table 1

Baseline Patient Characteristics (Overall and by Baseline Cocaine Status)

Characteristic	All patients (n = 162)	Cocaine Negative at Baseline (n = 107)	Cocaine Positive at Baseline (n = 55)	p
Age, mean (SD)	36.0 (9.3)	36.2 (9.7)	35.6 (8.6)	.72
% Male, (n)	78% (126)	79% (85)	74% (41)	.49
Race/Ethnicity				
% White	76% (124)	81% (87)	67% (37)	
% Black	14% (22)	8% (9)	24% (13)	
% Hispanic	9% (14)	9% (10)	7% (4)	.046
% High school education or greater	82% (131)	80% (85)	85% (46)	.44
Monthly income, mean (SD)	$1379 (1490)	$1400 (1531)	$1338 (1418)	.80
% Full-time employed	48% (77)	48% (51)	48% (26)	.99
Years of opioid use, mean (SD)	8.l (8.0)	8.5 (8.7)	7.3 (6.7)	.39
Opioid Use Type				
% Primarily heroin	78% (126)	74% (79)	86% (47)	
% Primarily prescription opioid	22% (36)	26% (28)	14% (8)	.09
% Injection drug use at entry	31% (49)	35% (36)	24% (13)	.17
% Prior methadone maintenance	34% (54)	38% (39)	26% (14)	.12
Days opioid use prior to treatment, mean (SD)	28.3 (4.7)	28.2 (4.7)	28.4 (4.7)	.81
Days cocaine use prior to treatment, mean (SD)	1.6 (3.6)	3.3 (3.9)	0.8 (3.1)	<.001
% positive for benzodiazepines during induction	14% (23)	9% (10)	24% (13)	.01

Table 2

Substance Abuse Outcomes of Patients Receiving Buprenorphine/naloxone, by Baseline Cocaine Status (Controlling for Treatment Group Assignment)

Characteristic	Cocaine Negative at Baseline (n=107)	Cocaine Positive at Baseline (n=55)	P
Substance abuse treatment outcomes			
Weeks of retention, mean (SD)	18.3 (7.7)	15.8 (7.0)	.04*
% completed treatment	50% (53)	33% (18)	.008
% Any positive cocaine test during treatment	37% (40)	87% (48)	.002
Percent opioid negative urines, mean (SD)	46.9 (34.0)	33.7 (30.0)	.02
Weeks of continuous opioid abstinence, mean (SD)	6.7 (6.4)	4.6 (4.5)	.03

* Cox Regression Wald Chi-Square

Table 3

Substance Abuse Outcomes of Patients Receiving Buprenorphine/naloxone, by In-Treatment Cocaine Status (Controlling for Treatment Group Assignment)

Characteristic	Cocaine Negative During Treatment (n=75)	Cocaine Positive During Treatment (n=89)	P
Substance abuse treatment outcomes			
% completed treatment	60% (45)	30% (27)	.004
Percent opioid negative urines, mean (SD)	51.5 (33.8)	34.8 (31.0)	.001
Weeks of continuous opioid abstinence, mean (SD)	7.7 (6.7)	4.7 (4.9)	.001

* Cox Regression Wald Chi-Square