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ORIGINAL INVESTIGATION

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Relationship of serum prolactin with severity of drug use and treatment outcome in cocaine dependence

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Abstract *Rationale:* Alteration in serum prolactin (PRL) levels may reflect changes in central dopamine activity, which modulates the behavioral effects of cocaine. Therefore, serum PRL may have a potential role as a biological marker of drug severity and treatment outcome in cocaine dependence. *Objective:* We investigated whether serum PRL levels differed between cocaine-dependent (CD) subjects and controls, and whether PRL levels were associated with severity of drug use and treatment outcome in CD subjects. *Methods:* Basal PRL concentrations were assayed in 141 African–American (AA) CD patients attending an outpatient treatment program and 60 AA controls. Severity of drug use was assessed using the Addiction Severity Index (ASI). Measures of abstinence and retention during 12 weeks of treatment and at 6-month follow-up were employed as outcome variables. *Results:* The basal PRL (ng/ml) in CD patients (9.28±4.13) was significantly higher than controls (7.33±2.94) (t=3.77, P<0.01). At baseline, PRL was positively correlated with ASI-drug (r=0.38, P<0.01), ASI-alcohol (r=0.19, P<0.05), and ASI-psychological (r=0.25, P<0.01) composite scores, and with the quantity of cocaine use (r=0.18, P<0.05). However, PRL levels were not significantly associated with number of negative urine screens, days in treatment, number of sessions attended, dropout rate or changes in ASI scores during treatment and at follow-up. Also, basal PRL did not significantly contribute toward the variance in predicting any of the outcome measures. *Conclusion:* Although cocaine use seems to influence PRL levels, it does not appear that PRL is a predictor of treatment outcome in cocaine dependence.

Keywords Cocaine · Prolactin · Dopamine · Treatment · Outcome

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Introduction

A wealth of evidence shows that cocaine binds to the dopamine transporter and blocks the neuronal reuptake of dopamine, resulting in increased synaptic dopamine concentrations (Kuhar et al. 1991; Carroll et al. 1992). These dopaminergic effects appear to be critical in mediating the rewarding effects of cocaine (Dackis and Gold 1985; Koob et al. 1994). In contrast, repeated cocaine exposure is reported to decrease levels of extracellular dopamine in the brain (Weiss et al. 1992). While investigators have postulated that this depletion in dopamine after chronic cocaine use may be associated with craving (Dackis and Gold 1985; Gawin and Kleber 1985), other data have not been consistent with this hypothesis. For example, clinical trials have generally failed to establish the effectiveness of dopamine agonists in promoting cocaine abstinence (Kosten et al. 1992). It seems that in addition to dopamine, other neurotransmitter and second messenger systems are also affected by cocaine and that the addictive properties of cocaine may be related to the complex interactions between these multiple neuronal systems (Nestler and Aghajanian 1997; Nestler 2001).

Due to its interactions with dopamine and other neuromodulatory systems, cocaine has important effects on anterior pituitary, gonadal, and adrenal hormones, particularly prolactin (PRL) (Mello and Mendelson 1997). The secretion of PRL is mediated, in part, by the inhibitory influence of the tuberoinfundibular dopaminergic neurons (Neill et al. 1981) and therefore changes in basal PRL have been considered to reflect changes in central dopamine

activity (Tuomisto and Mannisto 1985). However, the specificity of basal PRL as a biological measure of dopamine remains a matter of debate, since it is reported to be affected by a wide range of factors such as diet (Chakravarty et al. 1982), smoking (Martin et al. 1987), and stress (Martin et al. 1987). PRL secretion may also be influenced by serotonergic neurotransmission (Fishbein et al. 1989), and it remains unclear to what extent it is an accurate measure of dopamine in the reward pathways. Nevertheless measurement of peripheral PRL levels in the basal state or as a response to a challenge to dopamine agonists has been widely employed as an estimate of central dopamine activity in psychopharmacological studies (Joyce et al. 1995; Appleberg et al. 2000; Basturk et al. 2001).

Animal experiments have shown decreased PRL levels following acute administration and elevation in PRL after chronic administration of cocaine (Baumann and Rothman 1993; Levy et al. 1994). Among humans, however, the findings have not been consistent. PRL levels have been found to be increased (Mendelson et al. 1988; Teoh et al. 1990; Kranzler and Wallington 1992), decreased (Gawin and Kleber 1985), or unchanged (Swartz et al. 1990; McDougle et al. 1992; Baumann et al. 1995) among cocaine abusers. The conflicting results may be due to differences in assay techniques, timing or extent of recent cocaine use, or sample characteristics.

Research examining the relationship between biological markers such as PRL and treatment outcome among cocaine abusers has been sparse. Weiss et al. (1994) found that cocaine patients with hyperprolactinemia during inpatient treatment were less likely to remain abstinent at 6 months compared with patients with normal PRL levels. Similarly, in a study of hospitalized cocaine abusers, Kranzler and Wallington (1992) reported that patients with hyperprolactinemia were more likely to drop out of treatment and receive premature discharges. These findings were also replicated in an outpatient study, which found that hyperprolactinemia may be associated with an increased risk of relapse to cocaine abuse (Baumann et al. 1995). Supporting these findings, in a study on a smaller sample of cocaine abusers, we found that higher PRL levels were related to poor treatment response (Patkar et al. 2002). Taken together, this evidence suggests that elevated PRL may indicate adverse prognosis for cocaine patients. However negative results have also been reported. For example, in controlled and uncontrolled clinical trials with bromocriptine, plasma PRL was not correlated with intensity of withdrawal, symptom improvement or drop-out rate in cocaine patients (Eiler et al. 1995; Teller and Deveny 1988). Along the same lines, Satel et al. (1991) found that PRL levels after cessation of cocaine use are not a good predictor of withdrawal severity and need for treatment in hospitalized cocaine patients.

This study had two objectives. First to determine whether basal PRL levels in cocaine-dependent (CD) patients differed from those in controls, and second, to examine the relationship of basal PRL levels with measures of drug severity and with treatment outcome in CD patients. The present study differed from our previous study (Patkar et al. 2002) in three respects. The sample was nearly twice as large, the drug severity and outcome measures were more comprehensive and follow-up data was included.

Materials and methods

Subjects

One hundred and forty-one subjects with a DSM-IV (American Psychiatric Association 1994) diagnosis of cocaine dependence were recruited from a publicly funded, university-affiliated, intensive outpatient cocaine treatment program in Philadelphia. The sample was restricted to African–American (AA) subjects only because over 90% of the patient population in the program were of AA background. The study was approved by the Institutional Review Board of the University. Following a description of the study, written informed consent was obtained from individuals who volunteered for the study. The structured clinical interview (SCID) for DSM-IV Axis I Disorders (First et al. 1997) was then administered to study participants. Individuals with a diagnosis of schizophrenia, major depression, bipolar disorder, schizoaffective disorder, an unstable medical illness, those who were pregnant or received psychotropic medications in the previous 12 weeks were excluded. If patients used more than one substance, they were included only if their primary drug of abuse was cocaine. The subjects were recruited between October 1997 and February 2002.

Sixty AA controls were recruited from those responding to local advertisements. Consenting and screening procedures were similar to those followed for cocaine subjects. Control subjects were excluded if they had a history of substance abuse (tobacco use was not an exclusion criterion), a major psychiatric disorder (schizophrenia, major depression or bipolar disorder), a positive urine drug screen or were taking psychotropic medications in the previous 12 weeks.

Assessments

Eligible subjects and controls were assessed using the Beck depression inventory (BDI) (Beck and Steer 1987). The BDI is a widely used, self-report questionnaire that requires about 10 min to complete. Smoking status was rated on the Fagerstrom test for nicotine dependence (FTND), a widely used and validated six-item questionnaire to assess severity of smoking (Fagerstrom and Schneider 1989; Heatherton et al. 1991). Severity of drug use in cocaine subjects was assessed using the Addiction Severity Index (ASI) (McLellan et al. 1985, 1992). The ASI is a 30–40 min structured interview assessing seven problem areas in substance dependent persons. For each domain, a composite score that ranges from 0 (minimum) to 1 (maximum) is provided to assess the adequacy of functioning in these areas during the previous 30 days. All the assessments were performed at admission to the treatment program at least 2 weeks prior to the blood draw for PRL determination.

PRL determination

To minimize any effects of recent cocaine use on PRL, subjects had blood samples withdrawn after at least 2 weeks of abstinence from cocaine. The 2-week abstinence period was documented by monitoring urines twice a week. On the test day, subjects were asked to come in the morning after an overnight fast and instructed not to smoke. Aliquots of 20 ml venous blood were collected in EDTA-treated tubes, and the sera were separated and frozen at

−20°C. Samples were identified by code numbers for blinding purposes. PRL was assayed using the Active PRL DSL-4500 Immunoradiometric Assay Kit (Diagnostic Systems Laboratories, Tex., USA). This assay employs a standardized two-site immunoradiometric assay technique (Miles et al. 1974) to provide quantitative estimates of PRL in the serum. The assay sensitivity was 0.1 ng/ml and specificity tests carried out by the manufacturer indicate that other hormones were unlikely to cross-react with the PRL-antibody. The interassay and intraassay coefficients of variation were 11.2 and 4.0%, respectively.

Treatment approach

The study participants received the same treatment that was offered to the non-research patients in the program. Treatment consisted of outpatient group counseling sessions 3 times a week, each session lasting for 3 h for a total of 12 weeks. In addition, patients participated in one 45-min individual counseling session per week over the 12-week period. Patients completing the intensive program were offered other treatment options, including an aftercare program which included one individual counseling session per week for up to 6 months. The treatment approach was problem oriented and focused on attaining well-defined goals. Pharmacotherapy was not routinely used, but was available when needed and attendance at self-help meetings was encouraged. Such a multimodal approach seems to be fairly typical of many outpatient addiction treatment programs. The research data were not made available to the treatment providers while the study was active.

Follow-up

Follow-up interviews for CD subjects were performed at 6 months after the end of 12-week treatment by research assistants and included administration of an abbreviated form of the ASI and urine drug screens. The follow-up personnel were blind to the treatment condition or PRL measurements. Ninety (64%) of the subjects were followed up.

Outcome measures

In-treatment, end-of-treatment and follow-up assessments were performed to provide objective estimates of abstinence, retention and attrition from treatment. These were as follows: (a) *Number of negative urines*: urine drug screens (UDS) were obtained for all subjects at admission to the treatment program and following each group counseling session. The UDS was a one-step immunoassay for the detection of cocaine, opiates, cannabinoids, barbiturates, and amphetamines. A urine sample was considered positive if it was positive for any substance. The number of UDS negative for all tested substances was used as a measure of substance use during treatment. (b) *Days in treatment*: this reflects treatment retention and was recorded as the number of days between the first and last counseling session. (c) *Number of group and individual counseling sessions attended*: the total number of group and individual sessions attended by each patient offers another estimate of treatment retention and participation. (d) *Dropouts*: these were defined as individuals who attended no more than two treatment sessions during the 12-week program. (e) *Symptom reduction during treatment and at follow-up*: the baseline (admission) composite score in each of the seven problem areas of the ASI minus the last composite score obtained during the 12-week counseling period was employed as a measure of problem reduction during treatment. Similarly, the follow-up composite scores on the ASI were subtracted from the baseline ASI to compute problem reduction at follow-up.

Statistical analyses

PRL levels and demographic characteristics were compared between cases and controls using two-tailed *t*-tests for continuous variables and chi-square tests for categorical variables. Pearson product moment correlation was employed to correlate PRL levels with measures of drug severity. Pearson or biserial correlations, as appropriate were used to examine the relationship of PRL with continuous and dichotomous outcome variables. Tests of partial correlation were used to control for effects of potential confounders on the relationship between primary and dependent variables. Subsequently, the distribution of basal PRL scores among cocaine patients was examined and a split was performed at PRL values that were 1 standard deviation (SD) above the mean values to capture a more severe subgroup. This "higher PRL" subgroup was compared with rest of the patients using two-tailed *t*-tests and chi-square analyses to examine for differences in severity and outcome variables. Hierarchical regression models were used to predict outcome measures from combinations of independent variables, and to examine whether basal PRL contributed towards predicting outcome.

Results

Subjects

Out of 262 AA CD patients screened, a total of 141 subjects were enrolled in the study. Excluded subjects were: 31 patients with current major psychiatric disorder or receiving psychotropic medications, 78 patients who did not meet the criteria for 2-week abstinence from cocaine before PRL determination, three patients with serious medical disorders, three patients who withdrew consent, and six subjects whose blood samples could not be analyzed for technical reasons. Sixty AA controls were recruited after screening 119 volunteers and excluding 35 persons who either had a positive urine drug screen or were unable to provide a urine sample, 19 individuals who had a diagnosis of major psychiatric disorder or were taking psychotropic medications, two patients with unstable medical illnesses, and three persons whose blood samples could not be analyzed. Table 1 summarizes the demographic and clinical characteristics of the sample. The CD patients and controls did not differ significantly in gender. However, significantly more patients were older, single and unemployed compared to controls. The admission UDS for 35% of the patients was positive for cocaine. Patients whose UDS were cocaine-negative at admission reported on average 14.4 days of abstinence from cocaine prior to admission. A significant proportion of the CD subjects had additional substance abuse and dependence diagnoses. About 53% had abused or were dependent on alcohol, approximately 82% were nicotine dependent, nearly 31% were abusing or dependent on marijuana, and about 14% had opioid abuse or dependence during their lifetime or at the present time. About 35% of controls smoked and none abused alcohol during the study period. The mean FTND scores were significantly higher among cocaine subjects (4.92±2.28) compared with controls (2.32±2.70) (t=6.77, df=198, P<0.01), indicating that cocaine patients were more severely nicotine depen-

dent compared to controls. Cocaine patients smoked 15.8 ±4.6 cigarettes per day compared to controls (7.4±3.6 cigarettes per day) (t=8.16, df=198, P<0.001). Because tobacco smoking has been found to influence PRL levels, we examined whether it could have confounded the results. PRL levels were not significantly correlated with FTND scores in cocaine patients (r=0.09) or controls (r=0.12). Similarly, no significant correlation was observed between FTND scores or any of the outcome measures—number of negative urine screens (r=−0.12), days in treatment (r=0.03), number of treatment sessions (r=−0.09) and dropout (χ^2=1.68). No significant correlation was found between PRL levels and number of cigarettes smoked per day among cocaine patients (r=0.07) or controls (r=0.10). Also, cigarettes per day were not correlated with any of the outcome measures (all r<0.12, P>0.05). Because there were between-subject variations in time from admission to blood draw for PRL determination, we examined and found no association between this factor and PRL levels (r=−0.09). Body mass index (BMI) has been found to be positively associated with PRL levels in some studies (Komorowski et al. 2000). We found no significant difference in BMI between cocaine patients and controls (Table 1) and no significant association between BMI and PRL in patients or controls (r ranged from 0.07 to 0.09).

PRL levels among cocaine-dependent patients and controls

The assay range for normals was 2.9–17.1 ng/ml for men and 3.2–25.3 ng/ml for women. Figure 1 summarizes the overlap of cocaine patients and controls across the range of basal PRL. Figure 2 summarizes the distribution of individual PRL values among patients and controls. The basal PRL levels (ng/ml) in CD patients (9.28±4.13) were significantly higher than controls (7.33±2.94) (t=3.77, df=199, P<0.01). There were no significant differences in PRL levels between men (9.01±4.03) and women (9.92 ±4.35) in CD patients (t=1.19, df=139, P=0.24) or controls (men=7.20±2.67; women=7.55±3.37, t=0.45, df=58, P=0.65). Hyperprolactinemia was detected in five CD men (PRL >17.1 ng/ml) but not in any CD women (PRL >25.3 ng/ml). None of the controls had hyperprolactinemia. The difference in basal PRL between cocaine patients and controls continued to remain significant after excluding the five patients with hyperprolactinemia (t=3.11, df=194, P<0.01). Since cocaine patients were significantly older than controls, we examined and found no correlation between age and PRL (P=0.11).

Table 1 Characteristics of cocaine-dependent patients and controls

Characteristics	Cocaine patients (n=141) mean (SD)	Controls (n=60) mean (SD)	t/χ^2
Age (years)	36.29 (6.35)	32.60 (5.74)	t=3.89***
Male	72%	61%	χ^2=2.31
Single	73%	46%	χ^2=6.23**
Unemployed	85%	29%	χ^2=40.61***
Education	11.60 (1.77)	14.31 (3.13)	t=3.62***
Beck depression	11.84 (7.79)	6.24 (3.43)	t=5.26***
Body mass index (kg/m^2)	25.1 (6.2)	26.4 (4.9)	t=1.89
Time from admission to blood draw (days)	17.7 (8.2)		
Cocaine use[a]			
Age at first use	20.42 (4.13)		
Quantity (g/day)	1.23 (0.54)		
Frequency (days/week)	5.5 (1.6)		
Duration (years)	14.62 (7.78)		
Addiction severity (ASI)[b]			
Drug	0.24 (0.23)		
Alcohol	0.23 (0.26)		
Employment	0.85 (0.27)		
Family	0.13 (0.21)		
Legal	0.04 (0.15)		
Medical	0.07 (0.16)		
Psychological	0.17 (0.21)		

*P<0.05, **P<0.01, ***P<0.001, all t-tests two-tailed, df=193–199 for t-tests, df=1 for χ^2
[a]Measures of drug use only obtained for cocaine-dependent patients
[b]Measures of drug use only obtained for cocaine-dependent patients. Represent composite scores on the ASI

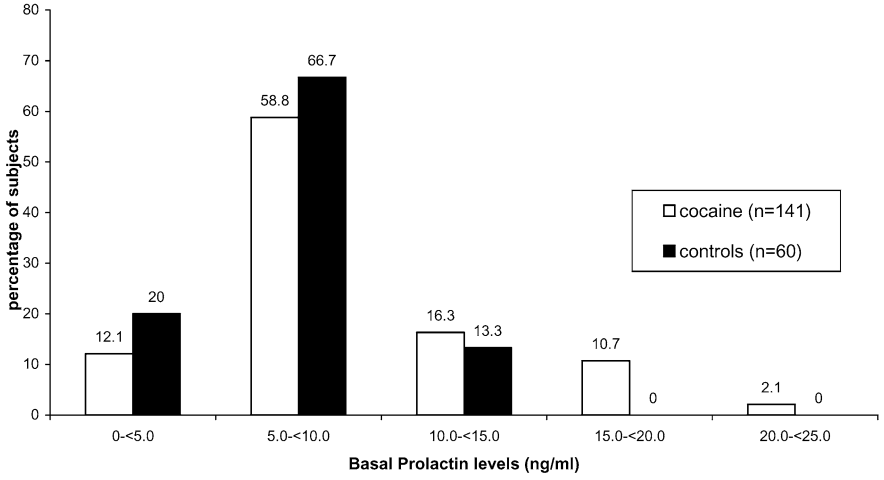

Fig. 1 Bar graph showing distribution of cocaine-dependent patients and controls across the range of basal prolactin levels controls (normal assay range: 2.9–17.1 ng/ml for men and 3.2–25.3 ng/ml for women)

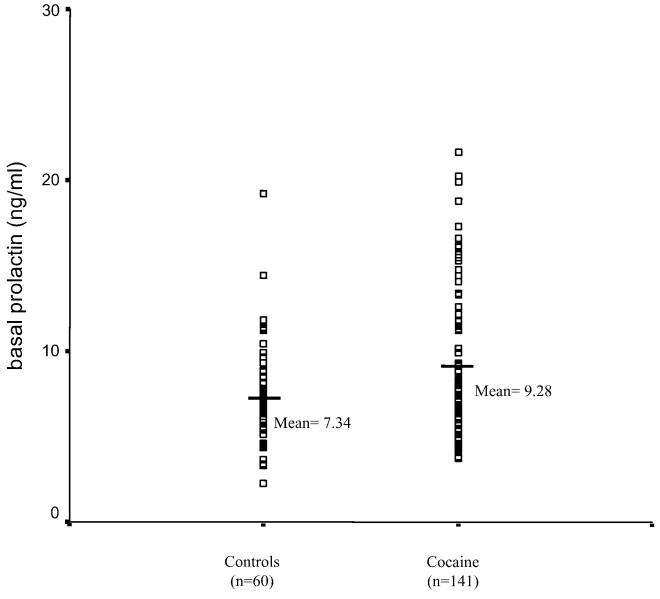

Fig. 2 Scatterplot showing distribution of basal prolactin values among cocaine-dependent subjects and controls

PRL levels and severity of addiction in cocaine-dependent patients

We explored the relationship between measures of cocaine use and PRL levels. As summarized in Table 2, PRL showed a significant positive correlation with quantity of cocaine use and composite scores on the drug, alcohol and psychological scales of the ASI. The correlation of PRL with amount of cocaine use is summarized in Fig. 3. A trend towards a negative correlation of PRL with length of abstinence was also observed (r=−0.17, P=0.07, two tailed). Correlations of PRL with other measures of ASI and cocaine use were not significant (Table 2). The correlations of PRL with the severity measures continued to remain significant after controlling for BDI scores (partial correlation coefficient r ranged from 0.19 to 0.40, P ranged from <0.05 to <0.001). We also reanalyzed the data by comparing the higher PRL group (PRL >13.42) (mean PRL >1 SD above the mean) (n=26) with the rest of the patients (mean PRL ≤13.42) (n=115) across the severity measures. The strength and direction of the between-group differences in severity measures were consistent with the correlations shown in Table 2 (t ranged from 0.09 to 2.86, df=130–139, P ranged from <0.01 to <0.05).

PRL levels and outcome measures during treatment and at follow-up

We found that cocaine patients had remained in treatment for 62.8±47.1 days, and attended 15.1±9.7 group and 4.4 ±7.4 treatment sessions. They provided 5.4±4.8 urine samples that were negative for all drugs and 7.6±3.9 urine samples that were negative only for cocaine. The proportion of 2-week dropouts was 30%. We first examined whether change in symptoms occurred in the sample during treatment and at follow-up by comparing the mean pretreatment and end of treatment ASI composite scores

Table 2 Correlation between PRL levels and measures of cocaine use (n=138)

Cocaine use	Correlation coefficient r
Quantity (g/day)	0.18*
Frequency (days/week)	0.09
Duration (years)	0.11
Length of abstinence (days)	−0.17
Addiction severity (ASI)[a]	
Drug	0.38**
Alcohol	0.19*
Employment	0.11
Family	0.15
Legal	0.09
Medical	0.07
Psychological	0.25**
Positive admission urine[b]	0.15

*P<0.05; **P<0.01
[a]Composite scores on the ASI
[b]Biserial correlation for dichotomous variable

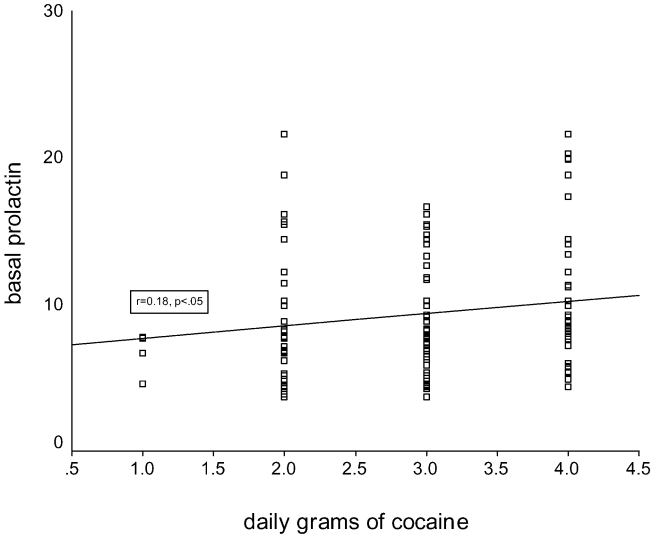

Fig. 3 Correlations between basal prolactin levels and amount of cocaine use

and the mean pretreatment and follow-up ASI scores. At the end of the treatment program, statistically significant reduction in ASI composite scores had occurred in five of the seven areas functioning during treatment: drug (t=3.08, P<0.01), alcohol (t=2.92, P<0.01), medical (t=2.68, P<0.05), family (t=2.73, P<0.05) and psychiatric (t=3.61, P<0.01). No differences were observed in ASI composite scores for employment (t=0.06) and legal (t=0.11) domains. At 6-month follow-up, the symptom reduction on ASI was maintained in four domains: drug (t=2.81, P<0.01), alcohol (t=2.82, P<0.01), medical (t=2.44, P<0.05), and psychiatric (t=2.97, P<0.01).

We then determined whether basal PRL was associated with any of the outcome measures among cocaine patients. PRL was not significantly correlated with number of urines negative for all drugs (r=−0.08), number of cocaine-negative urines (r=−0.10), days in treatment (r=0.02), number of group (r=0.11) or individual (r=0.10) sessions or dropout rate (χ^2=2.31). Because PRL was related to severity measures, we re-examined the relationship between PRL and outcome measures adjusting for baseline ASI scores. The correlations of PRL with outcome measures continued to be non-significant (all partial correlation coefficients r<0.11). We then compared the higher PRL group (PRL >13.42) (n=26) with the rest of the patients (mean PRL ≤13.42) (n=115) across the outcome measures during treatment and at follow-up. The two groups did not differ across measures treatment retention, abstinence, treatment participation and symptom reduction during treatment or at follow-up (t-values ranged from 0.28 to 1.12, χ^2 ranged from 0.61 to 1.22, P>0.05 in each case).

Since patients who were mandated to attend our program by the courts were likely to stay longer in treatment, we evaluated and found no significant differences in their PRL levels (9.32±4.18) compared to patients who were voluntary referrals (9.22±4.11) (t=0.41, df=139, P=0.73).

Basal PRL as a predictor of outcome among cocaine patients

Hierarchical regressions were used to determine whether basal PRL was associated with outcome measures after covarying for demographics (age and educational level), severity of drug use (ASI-drug and alcohol scores) and behavioral measures (Beck depression measures). These variables have been associated with poor treatment outcome for cocaine patients. Step 1 entered educational level, step 2 added ASI-drug and alcohol composite scores and step 3 examined whether basal prolactin levels added any significant variance. The results are summarized in Table 3.

The results indicated that although the variables entered in the model predicted certain outcome measures (days in treatment and follow-up measures of drug severity), basal PRL did not contribute to any significant increase in variance in predicting any of the outcome measures. Five male cocaine patients were noted to have absolute hyperprolactinemia (PRL >17.1). These patients did not fare differently than the rest of the male cocaine patients on outcome measures. None of the controls had hyperprolactinemia.

Because the results were negative, i.e. PRL did not predict any of the outcome measures, we conducted a post hoc power analysis to determine the magnitude of

Table 3 Regression analysis for predictors of outcome among cocaine patients

Outcome variables	β	R^2	F/χ^2
Days in treatment[a]			
Step 1. Age and education level	0.27	0.08**	
Step 2. ASI-drug, ASI-alcohol and BDI	−0.18	0.12	
Step 3. Basal prolactin	−0.01	0.12	2.28
Negative urines during treatment[b]			
Step 1. Age and education level	0.22	0.05*	
Step 2. ASI-drug, ASI-alcohol and BDI	−0.13	0.09	
Step 3. Basal prolactin	−0.07	0.09	1.71
Treatment sessions attended[c]			
Step 1. Age and education level	0.23	0.08*	
Step 2. ASI-drug, ASI-alcohol and BDI	−0.12	0.12	
Step 3. Basal prolactin	−0.01	0.12	1.77
Follow-up ASI drug scores[d]			
Step 1. Age and education level	−0.15	0.01*	
Step 2. ASI-drug, ASI-alcohol and BDI	0.45	0.22**	
Step 3. Basal prolactin	−0.01	0.22**	3.13
Follow-up urine drug screen[e]			
Step 1. Age and education level	−0.09	0.01	
Step 2. ASI-drug, ASI-alcohol and BDI	−0.13	0.26*	
Step 3. Basal prolactin	−0.10	0.28*	0.285

*P<0.05, **P<0.01
[a]F(6,107)=2.28, P<0.05
[b]F(6,107)=1.71, P=0.12
[c]F(6,107)=1.77, P=0.15
[d]F(6,107)=3.13, P<0.01
[e]χ^2=39.68, P=0.39

relationship between PRL and outcome that could be detected in the present study. For this purpose, we selected positive or negative urine drug screens as an outcome measure of abstinence. The analysis estimated that a sample of 141 subjects could detect a 11% relationship between PRL and urine drug screens at end of treatment (α=0.05, power=80). A weak and statistically non-significant relationship of 2% was observed between PRL and urine drug screens in the study. For this relationship to reach a 0.05 level of significance, a sample size of nearly 600 cocaine patients is required, indicating that for all practical purposes, PRL did not have a meaningful association with treatment outcome.

Discussion

Our study has three main findings of interest. First, the results suggest that basal PRL levels are significantly higher in CD patients compared to controls. Second, we found a positive association between measures of drug severity and PRL. Finally, PRL was not associated with outcome measures during treatment or at follow-up.

The higher basal PRL levels found among cocaine patients relative to controls in our study replicate our previous findings (Patkar et al. 2002) and are consistent with several reports of increased PRL levels among chronic cocaine abusers (Cocores et al. 1986; Mendelson et al. 1988; Teoh et al. 1990; Kranzler and Wallington 1992; Miller et al. 1993). Because secretion of PRL is mediated by the inhibitory influence of the tuberoinfundibular dopaminergic neurons (Neill et al. 1981), the increased PRL levels may reflect decreased central dopamine activity in CD individuals. However, PRL is an indirect measure of dopamine in the brain and may not accurately reflect mesolimbic dopaminergic activity.

Our results are in contrast to other investigators who reported no changes in PRL (Swartz et al. 1990; Baumann et al. 1995; Eiler et al. 1995) or found lower PRL levels (Gawin and Kleber 1985) among cocaine abusers. Differences in sample characteristics and assay techniques may account for the inconsistencies in findings in the literature. For example mean duration of cocaine use was 14.6 years among our patients as opposed to 3.6 years in Gavin and Kleber's sample (1985) and we studied both men and women in contrast to only men in studies conducted by Swartz et al. (1990) and Eiler et al. (1995).

We also found a modest positive correlation of PRL levels with quantity of cocaine use and the certain ASI domains. Although other severity measures were not significantly correlated with PRL, the relationships were in the expected direction. Therefore, it is unlikely that the results could be chance errors occurring due to multiple testing. The failure to find a significant relationship between cocaine positive urine drug screen at admission and PRL could be explained by the timing of PRL determination. We measured PRL levels after at least 2 weeks of abstinence to minimize alterations in PRL from acute effects of cocaine. Therefore, the admission urine screens and PRL determinations were performed at different time points and it was not surprising that the two measures were not related. Nevertheless, the relationship of drug severity with PRL levels suggests that the elevated PRL may be a consequence of cocaine use. Considering the modest strength of the correlations, further research that involves serial measurements of PRL and quantitative estimates of cocaine may help to clarify the relationship of cocaine use with PRL.

Unlike our previous findings (Patkar et al. 2002), we did not observe a relationship of baseline PRL with outcome measures. In our earlier study, although cocaine patients with higher PRL performed poorly on outcome measures of negative urines and counselor ratings of improvement, the differences were not statistically significant on the other outcome measures. We had cautioned that the findings should be considered preliminary and needed replication. In the present study, we expanded our sample pool, included follow-up data and used more comprehensive outcome measures. Therefore the data from this study are stronger than our earlier study. In this context, it is worth noting that the studies supporting a relationship of PRL with outcome in cocaine dependence were either performed in hospitalized patients, with small sample sizes or were short-term treatment (Kranzler and Wallington 1992; Weiss et al. 1994; Baumann et al. 1995). The negative findings from the present study indicate that at least in an outpatient, primarily psychotherapeutic treatment program for cocaine dependence, serum PRL seems to have a limited role as a biological marker to predict 12-week and 6-month outcome. Whether serum PRL has the potential to be a marker of treatment outcome in pharmacological studies of cocaine patients remains to be clarified.

The strengths of our study include a large sample size, recruitment of controls, 6-month follow-up data and controlling for potential confounders such as depression and tobacco smoking. The research was conducted with patients from an ongoing, publicly funded treatment program and therefore the results may be representative of other public sector outpatient programs. However, interpretations of our findings are subject to certain limitations. First the sample only included individuals of AA background. Second, we restricted the sample to patients who had a minimum of 2 weeks abstinence to minimize the acute effects of cocaine. The exclusion of subjects who had recently used cocaine could have led to a lack of representation of the full range of addiction severity in the sample. This in turn could have confounded any possible relationship between PRL and treatment outcome. Third, reflecting the high prevalence of poly-substance abuse in inner city treatment settings, a substantial proportion of our patients used other substances in addition to cocaine. Fourth, a single peripheral measurement of PRL can be influenced by various external factors, and may not fully reflect dopamine activity in the mesolimbic pathways. Finally, the follow-up rate (64%) was modest, limiting the data captured after 6 months.

In conclusion, although cocaine use seems to influence PRL levels, it does not appear that PRL is associated with treatment outcome in cocaine dependence. Further studies in this area may clarify the role of biological markers as predictors of treatment outcome in cocaine dependence.

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