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Severity of childhood trauma is predictive of cocaine relapse outcomes in women but not men☆

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Abstract

We prospectively examined the gender-specific effects of childhood trauma on cocaine relapse outcomes in an inpatient sample of treatment engaged cocaine dependent adults. Cocaine dependent men ($n = 70$) and women ($n = 54$) participating in inpatient treatment for cocaine dependence were assessed on severity of childhood trauma and followed for 90 days after discharge from treatment. Greater severity of childhood emotional abuse was associated with an increased risk of relapse in women. Severity of emotional abuse, sexual abuse, and overall childhood trauma was associated with the number of days cocaine was used during follow-up in women, as was the association of severity of physical abuse and overall childhood trauma with the average amount of cocaine used per occasion. No associations between childhood trauma and cocaine relapse outcomes were found in men. These findings demonstrate that childhood trauma increases the likelihood of cocaine relapse and drug use escalation after initial relapse in women but not in men. Comprehensive assessments of childhood trauma and specialized treatments that address trauma-related pathophysiology could be of benefit in improving cocaine treatment outcomes in women.

Keywords: Childhood trauma; Cocaine dependence; Relapse; Treatment outcome; Gender

1. Introduction

Childhood trauma places individuals at risk for disturbances in biological and psychological development (Cicchetti and Toth, 2005) and can lead to the manifestation of psychiatric and substance use disorders (Kendler et al., 2000; MacMillan et al., 2001; Wexler et al., 1997). However, men and women may differ with respect to the nature and consequences of childhood trauma with gender playing a role in determining the types of trauma to which children are exposed and their pathological reactions to specific traumatic events. For instance, while both boys and girls are exposed to various types of childhood trauma, girls are more likely to experience childhood sexual abuse (Ullman and Filipas, 2005; Walker et al., 2004), whereas rates of childhood physical abuse have been reported higher in boys (Thompson et al., 2004). Furthermore, although men and women are both adversely affected by specific types of childhood trauma, the association between childhood trauma and the risk of developing psychiatric and substance use disorders is generally stronger in women (MacMillan et al., 2001; Simpson and Miller, 2002; Sinha and Rounsaville, 2002; Thompson et al., 2004; Widom and Hiller-Sturmhofel, 2001; Widom and White, 1997). For example, childhood trauma is a risk factor in the development of anxiety and mood disorders, both of which are more likely to occur in women (Breslau, 2002; MacMillan et al., 2001; Sinha and Rounsaville, 2002; Thompson et al., 2004; Weiss et al., 1999). Post-traumatic Stress Disorder (PTSD), which is frequently diagnosed in childhood trauma survivors (Rodriguez et al., 1996; Widom, 1999), is more likely to develop following childhood sexual abuse in females as compared to males (Walker

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et al., 2004). Moreover, while substance use disorders are more prevalent in men, the association between childhood trauma and the development of substance use disorders is generally stronger in women (Hyman et al., 2006; MacMillan et al., 2001; Simpson and Miller, 2002; Sinha and Rounsaville, 2002).

These findings indicate that there are gender-specific interactions between childhood trauma and the development of psychiatric and substance use disorders. In contrast, the effects of childhood trauma on substance use relapse and the subsequent clinical course of substance use disorders has received less attention. If research indicates that childhood trauma has enduring gender-specific effects on the clinical course of these disorders, it could have significant implications for the treatment of substance use problems.

There is growing evidence of gender differences in the development and course of substance use disorders including cocaine dependence. Although men are twice as likely to be cocaine dependent than women, women exhibit a more rapid progression of the illness with greater negative consequences compared to men (McCance-Katz et al., 1999; Sinha and Rounsaville, 2002). Cocaine dependent women also report fewer years of regular cocaine use, spend less money on cocaine, have less extensive treatment histories, and are more likely to test positive for cocaine at treatment intake than men (Wong et al., 2002).

Furthermore, preclinical evidence indicates that female rats are more sensitive to the behavioral effects of psychostimulants and self-administer cocaine more rapidly than male rats (Lynch et al., 2002). Recent evidence has also shown that female rats self-administer more cocaine, binge for longer time periods, and display a loss of circadian control over intake as compared to male rats, effects that appear to be estrogen dependent (Lynch and Taylor, 2004; Lynch and Taylor, 2005). Indeed, animal models appear to demonstrate a greater vulnerability to the compulsive aspects of cocaine abuse in females, findings that when extrapolated to humans would suggest a gender-specific vulnerability to a more severe course of the disorder in women as compared to men.

Cocaine dependence is a chronic relapsing disorder despite the availability of efficacious treatments (Carroll et al., 2004; Higgins et al., 1994; Kang et al., 1991; O'Brien et al., 1998). Stress-related factors contribute to the chronic, relapsing nature of the disorder (O'Brien et al., 1998; Sinha, 2001; Sinha et al., 2006), and clinical surveys indicate that women may be more likely to relapse in the context of stress and negative affect whereas men are more susceptible to drug cue-related relapse precipitants (McKay et al., 1996). Cocaine dependent men and women also differ in the biological markers of stress that could be affected by the extent and severity of childhood traumatic experiences (Fox et al., 2006; Heim et al., 2000).

Although some previous research supports a positive association between childhood trauma and treatment outcome following inpatient alcohol treatment, no gender differences were found and the association was no longer significant when current disorders and specific demographic variables (e.g., education level and marital status) were included in multivariate analyses (Greenfield et al., 2002). Thus, a comprehensive examination of the various forms of childhood trauma and the influence of gender on relapse to cocaine in individuals with primary cocaine dependence has not been conducted thus far. On the basis of the aforementioned preclinical and human data on gender differences in the effects of childhood trauma on risk of developing substance use disorders, in the clinical course of cocaine dependence, and in stress responses, we hypothesized that the effects of childhood trauma on relapse susceptibility and the course of cocaine dependence will be gender-specific and observed more strongly in women than men. This hypothesis was tested in a sample of cocaine dependent men and women engaged in inpatient treatment for cocaine dependence. All participants were administered a childhood trauma measure upon admission and prospectively followed for 90 days after discharge from inpatient treatment. The primary outcomes were time to cocaine relapse and escalation of cocaine use as measured by number of days of cocaine use and amount of cocaine used per occasion during the follow-up period.

2. Method

2.1. Participants and procedures

Men and women, between the ages of 19–50 (mean age: 37.1, S.D. = 6.4), seeking inpatient treatment for primary cocaine dependence were evaluated for participation in a comprehensive research program evaluating the effects of childhood and recent life stressors, laboratory-induced stress responses, and their effects on cocaine relapse outcomes (see Sinha et al., 2003, 2006 for additional information on study procedures). One hundred and thirty two individuals (75 men and 57 women) who met DSM-IV criteria for current cocaine dependence and agreed to participate in the stress study and in inpatient treatment for cocaine dependence were admitted to the Clinical Neuroscience Research Unit (CNRU) of the Connecticut Mental Health Center (CMHC) for 2–4 weeks of inpatient treatment and research participation. Treatment seekers who were not interested in research participation were referred to another treatment facility that did not include a research component.

Recent cocaine use was verified by positive urine toxicology screens upon study enrollment. Individuals who met current DSM-IV criteria for dependence on psychoactive substances other than cocaine, alcohol, cannabis, and nicotine were excluded. Those requiring an immediate alcohol detoxification were excluded. Individuals taking medications for medical conditions and those on medications for co-morbid psychiatric disorders were also excluded. This final exclusion was initiated in order to ensure a primary substance dependent sample and not a dual diagnosis sample with co-morbid psychiatric and substance use problems.

All participants underwent a complete medical evaluation, including electrocardiography and laboratory tests of renal, hepatic, pancreatic, hematopoietic, and thyroid functions, to ensure good physical health. Participants were administered a large assessment battery upon admission and were interviewed using the structured clinical interview for the DSM-IV axis I mental disorders (SCID-I) (First et al., 1995) to assess substance use and psychiatric diagnoses. The study procedures were approved by the Human Investigation Committee of the Yale University School of Medicine. All participants signed a written informed consent and were paid for their participation.

The CNRU is a locked inpatient treatment and research facility with no access to alcohol or drugs and limited access to visitors. Drug testing is conducted regularly to ensure continued abstinence. All participants admitted into the study participated in specialized substance abuse treatment that included weekly individual therapy provided by psychiatry residents and twice weekly standardized group drug counseling (Mercer et al., 1994) provided by an addiction specialist. Specialized trauma-focused treatment was not provided. The drug treatment was part of the inpatient treatment program that was initiated upon admission and included additional group programming from 9:00 a.m. to 3:30 p.m. that covered daily life skills and other structured activities.

All participants were invited for a face-to-face follow-up interview to complete assessments and provide a urine toxicology screen to prospectively assess relapse for the 90 days after inpatient treatment and discharge. One hundred and twenty four of the 132 patients (93.9%) who completed inpatient treatment were successfully followed for 90 days. Thus, the data analysis for the current study is based on the follow-up sample of 124 cocaine dependent individuals (70 men and 54 women).

2.2. Measures

2.2.1. The childhood trauma questionnaire-short form (CTQ-SF). The CTQ-SF (Bernstein and Fink, 1998; Bernstein et al., 2003) was used to assess the severity of childhood trauma in all participants. The CTQ-SF is a retrospective self-report questionnaire with 25 clinical items that measure the extent to which respondents experienced five types of negative childhood experiences. *Physical abuse* is defined as bodily assaults on a child by an older person that poses a risk of or results in injury. *Sexual abuse* is defined as sexual contact or conduct between a child and an older person. *Emotional abuse* is defined as verbal assaults on a child's sense of worth or well-being, or any humiliating, demeaning, or threatening behavior directed toward a child by an older person. *Physical neglect* is defined as failure of caregivers to provide a child's basic physical needs including food, shelter, safety, supervision, and health. *Emotional neglect* is defined as the failure of caretakers to provide basic psychological and emotional needs, such as love, encouragement, belonging, and support. Respondents are presented with a number of statements about certain childhood experiences (e.g., "Someone tried to make me do sexual things or try sexual things; People in my family hit me so hard that it left me with bruises or marks; People in my family said hurtful or insulting things to me.") and asked to choose responses on a five-point scale that ranges from "never true" to "very often true" according to the frequency with which each event occurred. Scores from each item are then summed to produce subscale scores that quantify the severity of childhood trauma in each domain. Each trauma subscale is made up of five items, and severity scores for each subscale can range from 5 to 25. A summary score can also be calculated by summing scores from all five clinical subscales as an indicator of overall childhood trauma (Scher et al., 2001). The psychometric properties of the CTQ-SF have been widely studied in clinical, community, and student samples (Bernstein et al., 1997, 2003; Bernstein and Fink, 1998; Paivio and Cramer, 2004; Scher et al., 2001; Wright et al., 2001), and good reliability (internal consistency; test-retest) and validity (content, construct, convergent, discriminant, and concurrent) have been established in a large sample of adult substance abusers (Bernstein and Fink, 1998).

2.2.2. Assessment of cocaine use at 90 days post-inpatient treatment. All participants were given an appointment for a follow-up interview 90 days after discharge from the inpatient unit. Written reminders were sent in the month of the appointment. Cocaine use during baseline (90 days prior to inpatient treatment) and during follow-up (90 days after discharge from inpatient treatment) was assessed using the Form 90 substance use calendar (SUC; Miller and DelBoca, 1994) which is based on the time-line follow-back method (Sobell and Sobell, 1996). The SUC uses a calendar prompt and a number of other memory aids (e.g., holiday, payday, and other personally relevant dates) to facilitate accurate recall of daily drug use during the targeted period. The instrument has been validated in drug abusing samples (Hersh et al., 1999; Fals-Stewart et al., 2000) and has been used to assess cocaine use outcomes in previous treatment studies (Higgins et al., 1994; Carroll et al., 2004). Urine and breathalyzer samples were also obtained at the 90-day follow-up appointment.

In order to capture both initial lapse (any use) and relapse or return to regular patterns of drug use (Rohsenow and Monti, 2001), "relapse" in this study was examined both as a dichotomous variable (no use/success versus any use/failure) and as continuous measures of drug use (e.g., number of days of use and amounts of use per occasion) in the 90-day follow-up period. The following outcomes were computed from the follow-up SUC and urine screen and used for the relapse analysis: (a) *time to relapse* was defined as a dichotomous variable that documented the first day when any cocaine use occurred during the 90-day follow-up period, (b) *frequency of use* was defined as the total number of days of cocaine use during the follow-up period, and (c) *quantity of use* was defined as the average amount of cocaine used per occasion (in grams) during the follow-up period.

3. Data analysis

Men and women were compared on demographic variables (age, ethnicity, employment status, educational background), age of first alcohol and cocaine use, lifetime and current prevalence of mood disorders, anxiety disorders including PTSD, substance abuse disorders, and baseline cocaine use (frequency and amount) using chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. These variables were also examined for their association with cocaine relapse measures. If any variable was significantly associated with a particular relapse outcome, it was included as a control variable while examining the association between childhood trauma and the specific cocaine relapse measure. Because the prevalence and severity of childhood sexual abuse differs significantly between cocaine dependent men and women (Hyman et al., 2005, 2007), and past studies indicate that the relationship between childhood trauma and substance use problems also differs by gender (MacMillan et al., 2001; Simpson and Miller, 2002), we examined the association between childhood trauma and cocaine relapse outcomes separately in men and women.

Cox proportional hazard (PH) regressions (Cox, 1972) were conducted to examine the association between childhood trauma severity and time to relapse. We did not use an intent-to-treat analysis because unlike treatment outcome studies where a specific treatment is an independent variable and its effects on outcome are assessed, the current study focused on prospective predictor analysis and no treatment was varied. Linear regression analyses were used to examine the association of childhood trauma with frequency and amount of cocaine used in the follow-up period. In the Cox proportional hazards regression and the linear regression models, the "stepwise" procedure ($F_{\text{enter}} = 0.15$ and $F_{\text{stay}} = 0.15$) was used with all five CTQ-SF subscales with relevant control variables included to identify the specific types of childhood trauma that predict relapse outcomes after accounting for the control variables. Separate regression models with the CTQ-SF summary score and relevant control variables were used to study the relationship between overall childhood trauma severity and cocaine relapse outcomes.

4. Results

4.1. Relapse rates

On the basis of urine toxicology screens and self-report data, 90 (72.6%) participants [49 (70.0%) men and 41 (75.9%) women] of the 124 individuals that were successfully followed had returned to cocaine use during the 90-day follow-up period.

4.2. Demographics and sample characteristics

Demographic variables, baseline drug use measures, and lifetime and current prevalence rates of psychiatric and substance use disorders are presented by gender in Table 1. Please

Table 1
Demographics and sample characteristics by gender

	Followed-up sample ($N=124$)		Initial sample ($N=132$)	
	Men ($n=70$)	Women ($n=54$)	Men ($n=75$)	Women ($n=57$)
Age (M, S.D.)	36.6 (6.33)	37.7 (6.4)	36.6 (6.4)	37.5 (6.4)
Race (n, %)				
Caucasian	25 (35.7%)	16 (29.6%)	27 (36%)	17 (29.8%)
African American	39 (55.7%)	33 (61.1%)	40 (53.3%)	35 (61.4%)
Other	6 (8.6%)	5 (9.3%)	8 (10.7%)	5 (8.8%)
Employment (n, %)*				
Full time	13 (18.6%)	2 (3.7%)	15 (20%)	2 (3.5%)
Part time	10 (14.3%)	6 (11.1%)	11 (14.7%)	7 (12.3%)
Unemployed	47 (67.1%)	46 (85.2%)	49 (65.3%)	48 (84.2%)
Years of education (M, S.D.)	12.3 (1.8)	12.3 (1.6)	12.3 (1.7)	12.3 (1.5)
Years of cocaine use (M, S.D.)	8.9 (6.7)	9.5 (5.8)	8.9 (6.7)	9.3 (5.8)
Route of cocaine use (n, %)				
Smoked	64 (91.4%)	48 (88.9%)	64 (85.3%)	48 (84.2%)
Lifetime DSM-IV disorders (n, %)				
PTSD	19 (27.1%)	20 (37.0%)	21 (28.0%)	20 (35.1%)
Other anxiety disorder	9 (12.7%)	8 (14.8%)	10 (13.3%)	8 (14%)
Major depression	21 (30.0%)	11 (20.4%)	23 (30.7%)	12 (21.1%)
Cannabis dependence	30 (42.7%)	19 (35.2%)	33 (44%)	20 (35.1%)
Opioid dependence*	5 (7.1%)	0 (0.0%)	5 (6.7%)	0 (0.0%)
ETOH dependence*	44 (62.9%)	24 (44.4%)	48 (64%)	24 (42.1%)
Current DSM-IV disorders (n, %)				
PTSD	8 (11.4%)	9 (16.7%)	10 (13.3%)	9 (15.8%)
Other anxiety disorder	7 (10.0%)	7 (13.0%)	8 (10.7%)	7 (12.3%)
Major depression	8 (11.4%)	2 (3.7%)	10 (13.3%)	3 (5.3%)
Cannabis dependence	16 (22.9%)	6 (11.1%)	17 (22.7%)	7 (12.3%)
Opioid dependence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ETOH dependence	29 (41.4%)	17 (31.5%)	31 (41.3%)	17 (29.8%)

* Indicates a significant difference between men and women.

note that as individuals who were on psychiatric medications were excluded, the prevalence of current mood and anxiety disorders is low in this sample. Men reported higher rates of lifetime opioid [$\chi^2(1)=4.02$, $p<0.05$] and alcohol dependence [$\chi^2(1)=4.17$, $p<0.05$] and women reported higher unemployment rates [$\chi^2(2)=7.13$, $p<0.03$]. Severity scores for each form of childhood trauma indicated that women scored higher than men on severity of childhood sexual abuse [$t(85.7)=3.27$, $p<0.002$ (S*atterthwaite adjustment for unequal variance*)], but there were no gender differences in severity scores for childhood physical abuse, emotional abuse, physical neglect, emotional neglect, or overall childhood trauma (see Table 2).

4.3. Gender-specific childhood trauma effects on time to cocaine relapse

None of the demographic variables or sample characteristics was associated with time to relapse in either men or women. Results from proportional hazards stepwise regression indicated that severity of emotional abuse was associated with time to relapse in women ($\chi^2=4.16$, HR: 1.05, CI: 1.00–1.11, $p<0.05$), but not in men. These findings indicate that for each additional unit increase in the emotional abuse subscale score in women, the risk of using cocaine increased by 5%. As a follow-up to these analyses, a median split of the emotional abuse scores was conducted to divide the sample into high and low abuse groups in order to examine the difference in survival probabilities for the two groups. The high emotional abuse group had lower probabilities of survival compared to the low emotional abuse

Table 2
Means and standard deviations for childhood trauma and relapse outcomes in men and women

	Men ($n=70$)	Women ($n=54$)
Childhood trauma measures (M, S.D.)		
Sexual abuse*	7.3 (4.7)	11.0 (7.2)
Physical abuse	9.7 (5.2)	9.2 (4.8)
Emotional abuse	10.7 (5.6)	11.8 (5.9)
Physical neglect	7.8 (3.0)	7.5 (2.6)
Emotional neglect	11.4 (5.4)	11.7 (5.0)
Overall maltreatment	46.9 (17.8)	51.1 (20.1)
Relapse measures (M, S.D.)		
Number of days of cocaine use	12.2 (19.2)	14.9 (20.1)
Average amount of cocaine used per occasion (in g)	0.3 (0.6)	0.3 (0.5)
Time to first cocaine use after discharge (day)	47.0 (44.7)	46.6 (44.5)

* Indicates a significant difference between women and men on this subscale ($p<0.05$).

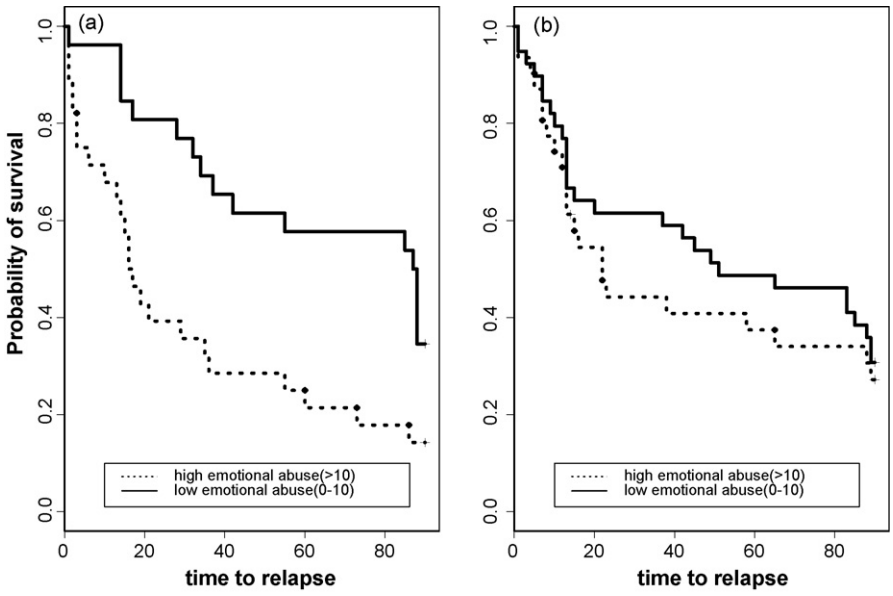

Fig. 1. High and low emotional abuse groups and relapse survival probability. (a) Women: survival curves for low (0–10; $n = 28$) and high (>10, $n = 26$) emotional abuse groups. Log-rank test indicates survival curves for the two groups are significantly different ($\chi^2 = 8.1$; $p < 0.005$). (b) Men: survival Curves for low (0–10; $n = 31$) and high (>10; $n = 39$) emotional abuse groups. Log-rank test indicates survival curves for the two groups are not significantly different ($\chi^2 = 0.4$; $p = 0.54$). *Note*. In women, high and low emotional abuse groups separate immediately upon treatment discharge. A similar, but non-significant, pattern becomes evident in men around day 15.

group for women ($\chi^2 = 8.1$; $p < 0.005$) whereas the two survival curves were not significantly different for men (see Fig. 1). Furthermore, the overall childhood trauma severity score (CTQ-SF summary score) was not associated with time to relapse in either men or women.

4.4. Gender-specific trauma effects on cocaine use escalation during follow-up

None of the demographic variables was associated with frequency or amount of cocaine used during the follow-up period. However, baseline frequency of cocaine use was significantly associated with follow-up frequency of cocaine use for both men ($r = 0.27$, $p < 0.03$) and women ($r = 0.29$, $p < 0.04$). For women, but not men, baseline amount of cocaine used per occasion ($r = 0.40$, $p < 0.003$) and lifetime occurrence of PTSD ($t = -2.14$, $p < 0.04$) was also associated with follow-up amount of cocaine used per occasion.

For frequency of days of cocaine use during follow-up, in women, the stepwise regression model including emotional, sexual, and physical abuse and baseline frequency of cocaine use as the control variable indicated that severity of emotional abuse ($t = 2.96$, $p < 0.005$, partial $R^2 = 0.14$) and sexual abuse ($t = 2.00$, $p = 0.05$, partial $R^2 = 0.03$) was associated with the number of days cocaine was used. Physical abuse was not associated with this outcome. Severity of overall childhood trauma was also associated with the number of days cocaine was used in women ($t = 3.23$, $p < 0.003$, adj. $R^2 = 0.21$). For men, neither of the individual childhood trauma types nor overall childhood trauma severity was associated with frequency of cocaine use.

For average amounts of cocaine used per occasion, a stepwise regression model that included each trauma subscale and the control variables of baseline amount of cocaine use and lifetime diagnosis of PTSD yielded a significant association between severity of physical abuse and average amount of cocaine used per occasion in women ($t = 2.25$, $p < 0.03$, partial $R^2 = 0.07$) Even after adjusting for baseline amount of cocaine use and PTSD, overall childhood trauma severity remained significantly associated with the average amount of cocaine used per occasion in women ($t = 2.27$, $p < 0.03$, adj. $R^2 = 0.26$). For men, none of the childhood trauma subscales nor the overall childhood trauma severity score was associated with the amount of cocaine used per occasion. The number of days of cocaine use and average amount of cocaine used per day are plotted against the CTQ-SF summary score (overall childhood trauma severity) for men and women in Fig. 2a–d.

5. Discussion

The present findings indicate that childhood trauma increases the likelihood of cocaine relapse and cocaine use escalation after initial relapse in women but not in men. This association remained significant even after accounting for the contribution of baseline cocaine use and PTSD on the escalation of cocaine use. Interestingly, associations differed depending upon the form of childhood trauma experienced. Only greater severity of emotional abuse was associated with increased risk of cocaine relapse. Severity of emotional abuse, sexual abuse, and overall childhood trauma was associated with the average number of days of cocaine use, and severity of physical abuse and overall childhood trauma was associated with the average amount of cocaine used per occasion.

Childhood trauma in humans and early life stress in animal models is known to significantly affect psychobiological devel-

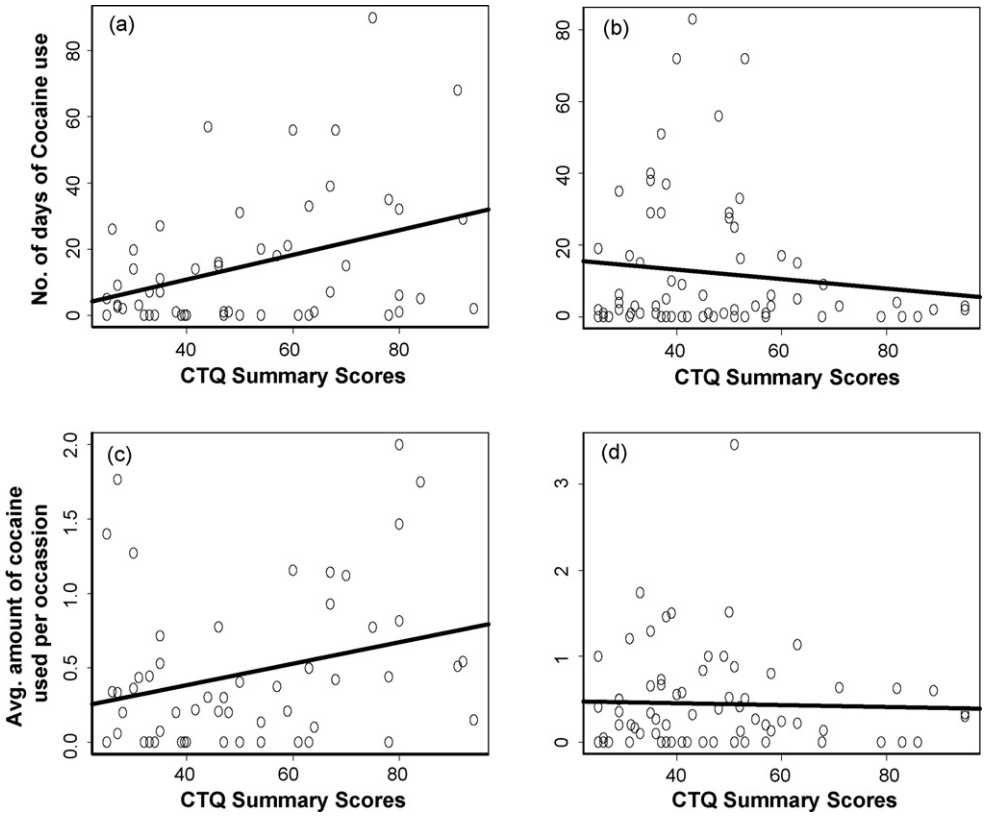

Fig. 2. Scatter plot for CTQ-SF summary score and amount and frequency of cocaine use during follow-up by gender. (a) Women: CTQ-SF summary score vs. number of days of cocaine use ($r = 0.37$, $p < 0.005$); (b) men: CTQ-SF summary score vs. number of days of cocaine use ($r = -0.12$, $p = 0.31$); (c) women: CTQ-SF summary score vs. amount of cocaine used per occasion ($r = 0.28$, $p < 0.04$); (d) men: CTQ-SF summary score vs. amount of cocaine used per occasion ($r = -0.03$, $p = 0.77$).

opment in ways that may partially explain their association with relapse susceptibility and the clinical course of cocaine addiction (Cicchetti and Toth, 2005; De Bellis, 2002; Kosten et al., 2004; Sinha, 2005). Childhood trauma compromises the optimal development of affect regulation and social information processing abilities and places children at risk for insecure attachment relationships, negative self-development, and problems with peer relations (Cicchetti and Toth, 2005). Early trauma in laboratory animals and in humans produces long-lasting changes in the corticotrophin releasing factor (CRF)-hypothalamic-pituitary-adrenal (HPA) axis systems, with increased HPA and behavioral responses to environmental manipulations noted throughout development and in adulthood (Meaney et al., 2002; Plotsky and Meaney, 1993; Heim et al., 2000). Chronic elevations in anxious arousal and HPA-axis hormones can lead to difficulties coping in the face of stress, and can potentially lead to increased susceptibility to relapse (Sinha et al., 2006).

Gender differences in the subjective and physiological responses to stress (Kudielka and Kirschbaum, 2005; Sinha and Rounsaville, 2002) and in treatment response for stress-related psychiatric disorders (Kornstein et al., 2000) are well documented. Women are more likely than men to develop depression in response to stressful life events (Maciejewski et al., 2001) and to report negative emotions in response to stressful situations such as marital conflict (e.g., Levenson et al., 1994). Men show a greater HPA-axis drive compared with females in response to a range of academic-type laboratory challenges (Sinha and Rounsaville, 2002), whereas females show greater responses to interpersonal challenges (Stroud et al., 2002). Among cocaine dependent individuals, men have higher ACTH and cortisol levels at baseline and in response to stress, but women show higher levels of prolactin and more rapid heart rates (Fox et al., 2006). Gender differences in reactions to childhood trauma could well influence these gender differences in stress-related HPA arousal, responses that have been found to explain some of the variance in the amount of cocaine used per occasion upon relapse (Sinha et al., 2006).

We caution that these findings do not suggest that childhood trauma is unimportant in cocaine dependent males. Indeed, rates of childhood trauma are high in cocaine dependent men (Hyman et al., 2007). However, the pathway from childhood trauma to cocaine relapse may be more indirect than it is in women. Intervening variables such as greater externalizing behavior, impulse control difficulties, or greater affiliation with substance using peers may play a more prominent role in mediating the association between childhood trauma and the course of drug addiction in cocaine dependent men. It is also known that men are more likely to relapse in the context of drug cues whereas women are more likely to relapse in the context of stress and negative affect (McKay et al., 1996). Thus, childhood trauma may directly influence relapse more so in women whereas, for men, trauma effects

may be moderated by other factors such as the presence of drug cues.

It is important to note that the association between childhood trauma and relapse was present after accounting for the contribution of baseline levels of cocaine use and lifetime PTSD, both of which were associated with relapse outcomes. We also found that a lifetime PTSD diagnosis was negatively associated with amount of cocaine used per occasion. While somewhat paradoxical, one explanation for the latter finding could be that using too much cocaine on one occasion may be aversive for women with PTSD as it may potentially exacerbate hyperarousal symptoms. Therefore, women with PTSD may temper the amount they use per occasion.

Our findings have significant clinical implications. The data underscore the need to assess childhood trauma in cocaine dependent women entering treatment to inform relapse susceptibility and treatment planning. For example, there is evidence that trauma-focused treatments may be of benefit in women with PTSD and substance use disorders including cocaine dependence (Brady et al., 2001; Hien et al., 2004; Najavits et al., 1998). Current findings support the use of such treatments in cocaine dependent women with severe childhood trauma histories whether or not they meet diagnostic criteria for adult PTSD. In light of the findings that women show significant associations between childhood trauma, cocaine relapse, and drug use escalation following initial relapse, it is possible that pharmacological and psychosocial treatments that target trauma-related pathophysiology could be of benefit in reducing the risk of relapse and subsequent drug use in cocaine dependent women.

It is important to note the limitations of the study. First, reports of childhood trauma relied on retrospective self-report data, and although the CTQ-SF is a reliable and valid instrument for use in those who abuse substances, retrospective self-report data may not represent true histories. However, confidentiality was assured, and participants had no study-related reason to misrepresent their childhood trauma histories. Alternate methods of trauma assessment could have yielded different results. Second, the study design precludes speculation on causality. Other factors in addition to childhood trauma, such as genetics, biological responses to stress, adult trauma, and psychological/cognitive responses may have contributed to the findings. Finally, the study focused on individuals with primary cocaine dependence without additional psychiatric co-morbidity, and therefore, the findings may not be generalizable to patients with co-morbid psychiatric disorders. For instance, Greenfield et al. (2002) found that the association between sexual abuse and relapse to alcohol was no longer significant after accounting for current disorders and specific demographic variables.

Despite these caveats, the current study represents the first comprehensive examination of the gender-specific effects of various types of childhood trauma on cocaine relapse outcomes in a sample of individuals with primary cocaine dependence. Findings underscore the importance of childhood trauma as a direct correlate of cocaine relapse outcomes in women but not men. Although the associations found in women were modest, it is important to note that childhood trauma is a rather distal factor. There may be more proximal factors that also contribute to, or account for, a proportion of the variance in cocaine relapse outcomes. Clearly, future research is needed to further elucidate the mechanisms by which childhood trauma may affect psychological and biological aspects of development and substance abuse vulnerability that continue to impact course of illness and relapse susceptibility in a gender specific manner. Overall, comprehensive assessments of childhood trauma and treatment of trauma-related pathophysiology could potentially enhance treatment outcomes in cocaine dependent women.

Conflict of interest

All authors declare that they have no conflicts of interest.

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