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Laboratory-induced stress and craving predict opioid use during follow-up among individuals with prescription opioid use disorder

Tanya C. Saraiya, Ph.D.¹, Amber Jarnecke, Ph.D.¹, Jennifer Jones, M.D.¹, Delisa G. Brown, Ph.D.¹, Kathleen T. Brady, M.D., Ph.D.¹, Sudie E. Back, Ph.D.^{1,2}

¹ Department of Psychiatry, Addiction Sciences Division, Medical University of South Carolina, Charleston, SC

² Ralph H. Johnson VA Medical Center, Charleston, SC

Abstract

Background: Opioid use disorder (OUD) remains a public health crisis in the USA. Although stress and craving are common precipitants of substance use, no research to date has investigated the impact of laboratory-induced stress and craving on subsequent opioid use.

Method: Participants (N=31) were individuals with prescription OUD who completed a human laboratory study followed by a one-month follow-up visit. Participants were randomly assigned to either a stress task (i.e., Trier Social Stress Task; TSST) or a no-stress condition, and then all participants completed an opioid cue paradigm. Measures of subjective (e.g., stress, craving), and neuroendocrine (e.g., cortisol, dehydroepiandrosterone) reactivity were assessed before and after each task. Survival and regression models tested the association between reactivity to the laboratory tasks and a) time to first opioid use and b) amount of opioid use during follow-up.

Results: On average, participants first used opioids 3.65 (SD=2.08) days following the study. Craving after the opioid cue paradigm (B=0.44, Exp(B)=1.55, 95% CI [1.06, 2.28], $p=.02$) and after the TSST/no-stress condition plus opioid cue paradigm (B=1.06, Exp(B)=2.88, 95% CI [1.70, 4.85], $p < .001$) predicted time to first use. Additionally, there was a significant interaction between randomization to the TSST, stress reactivity, and amount of opioids used.

Correspondence of this article should be made to: Tanya C. Saraiya, Ph.D., Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 125 Doughty Street, Suite 300, Charleston, SC, 29403. saraiya@musc.edu.

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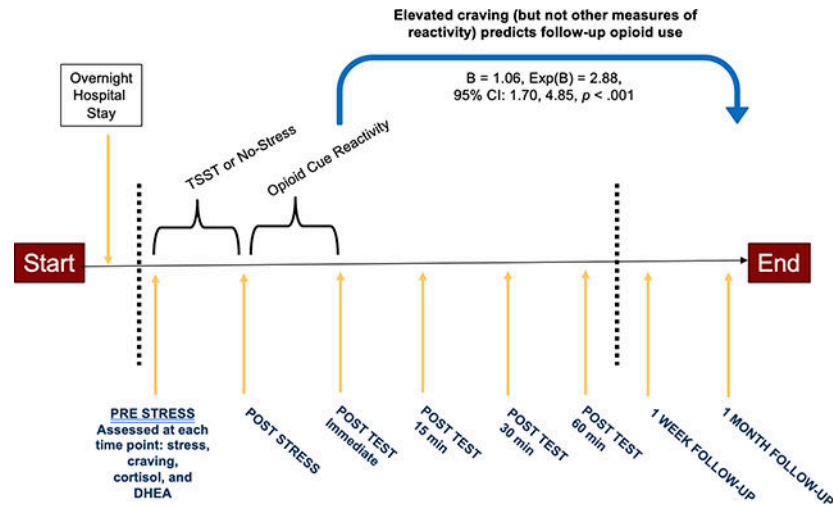
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Conclusions: Findings demonstrate that elevated cue-induced craving, either in the context of a stressor or not, is associated with shortened time to opioid use, whereas stress reactivity impacts the amount of opioids consumed. Preliminary findings add to the literature on stress, craving and opioid use and implicate treatment.

Graphical Abstract



Keywords

prescription opioids; stress; Trier; cues; opiates

1. Introduction

Prescription opioid use disorder (OUD) is an ongoing public health crisis in the United States. In 2017, the National Survey on Drug Use and Health showed that ~2 million individuals started misusing prescription pain relievers for the first time that year and approximately 18 million misused prescription opioids at least once in the past year (SAMHSA, 2018). Increased misuse parallels increasing rates of prescription opioid overdose. From 1999—2018, there was a four-fold increase in the number of prescription opioid overdose deaths (CDC, 2020).

Previous literature demonstrates that stress is a risk factor for substance use. Stress can be defined as an individual's emotional, perceptual, and cognitive reaction to difficult acute events (e.g., interpersonal arguments) and chronic conditions (e.g., racism, poverty) (Sinha, 2008). Impaired stress regulation, though, can lead an individual to seek out substances to reduce negative affect and attain physiological homeostasis (Cleck and Blendy, 2008; Koob and Volkow, 2016; Sinha, 2008). Pre-clinical studies (Bossert et al., 2013; Cleck and Blendy, 2008), human laboratory experiments (Back et al., 2015; Back et al., 2010; Daughters et al., 2009; Moran-Santa Maria et al., 2014; Sinha et al., 2006), and ecological momentary assessment (EMA) studies (Preston et al., 2017, 2018b; Preston et al., 2018c) demonstrate that psychological and physiological reactions to stressors impact substance use. However, to our knowledge, no study to date has examined the relationship between laboratory-

induced stress response and subsequent prescription opioid use among individuals with prescription OUD.

Stress is often investigated by measuring “reactivity” to a laboratory stress task or drug-related cue. For example, participants are exposed to an acute stress task in the laboratory and the change from baseline in emotions and physiology is measured to assess the impact of the task. The utility of these designs is their high control over extraneous factors, and thus efficiency in detecting the role of stress in substance use (Foley and Kirschbaum, 2010). Subjective responses to a stress task may include changes in self-reported stress or anxiety, whereas neuroendocrine responses may involve changes in cortisol and dehydroepiandrosterone (DHEA). Some studies have shown cortisol and DHEA levels/changes to be associated with craving or substance use (Lovallo, 2006; McRae et al., 2006; Sinha et al., 2006; Wemm and Sinha, 2019) while others have not (Chao et al., 2018).

Subjective craving is also associated with substance use. Cue reactivity studies demonstrate that formerly neutral stimuli (e.g., pill bottle) can be paired with drug cues (e.g., opioid pills) through classical conditioning and increase craving, use, or relapse (Brady et al., 2006; Carter and Tiffany, 1999; McRae-Clark et al., 2011). Given their dual influence on substance use, a handful of research studies have examined the synergistic effects of stress and craving on substance use. Among individuals with OUD, two studies using EMA show that craving is associated with relapse (Marhe et al., 2013) and may have a stronger influence as compared to stress alone (Preston et al., 2018a).

The current study adds to the literature by examining whether reactivity (subjective and neuroendocrine) to a laboratory stress task, the Trier Social Stress Task (TSST; Allen et al., 2016; Kirschbaum et al., 1993), and opioid cue paradigm is associated with subsequent opioid use during follow-up. We hypothesized that higher subjective (i.e., craving and stress) and neuroendocrine reactivity would be associated with a shorter time to use and a greater amount of opioid use at follow-up (Back et al., 2010; Sinha et al., 2006).

2. Methods

2.1 Participants

The parent study enrolled 39 individuals with prescription OUD and 36 healthy controls (Back et al., 2015). In order to examine the associations between reactivity and opioid use, this secondary analysis only examined participants with OUD who completed the laboratory study and the one-week and/or the one-month follow-up visits ($N = 31$). Information on healthy controls can be found in the parent study (Back et al., 2015). For this study, participants included those who completed all study time points ($n = 27$), the 1-week follow-up but not the 1-month follow-up ($n = 2$), and the 1-month follow-up but not the 1-week follow-up ($n = 2$). Participants met DSM-IV criteria (American Psychiatric Association, 2000) for current opioid dependence (past 6 months) using the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002). The Mini International Neuropsychiatric Interview for DSM-IV was used to assess other Axis I disorders (MINI; Sheehan et al., 1998). Exclusion criteria included: pregnancy or nursing; BMI ≥ 39 ; methadone use in the prior 3 months; use of medications (e.g., beta-blockers) in the past month or psychiatric conditions

(e.g., PTSD) that could influence HPA axis functioning; and major medical problems (e.g., HIV). Participants were compensated \$150 after completing the study.

2.2 Laboratory Procedures

A detailed description of the parent study procedures has been previously reported (Back et al., 2015). Eligible participants were scheduled for a one-night hospital stay followed by testing the next morning. Procedures were conducted at the same time of day to control for diurnal variation in cortisol. Participants were randomly assigned to the TSST or a no-stress condition stratified by sex and using urn randomization (Wei and Lachin, 1988) to control for OUD severity. In the TSST condition, participants completed a standardized 15-min stress provocation where they were asked to prepare (5 min) and deliver (5 min) a speech and then verbally complete serial subtractions (5 min) in front of an audience of three peers (Allen et al., 2016; Kirschbaum et al., 1993). The audience would only comment on the participant's performance when they miscalculated a subtraction, informing the participant that their subtraction was incorrect and then ask them to start again. In the no-stress condition, participants were allowed to sit and relax for 15 minutes. Participants in both the TSST and no-stress groups then completed a 15-min opioid cue paradigm (Back et al., 2014). During the opioid cue paradigm, participants listened to an audio induction script (5 min), handled and viewed drug paraphernalia (5 min), and watched a video depicting people using prescription opioids (5 min). Participants were assessed at 15-, 30-, and 60-min following the task (Figure 1). They were then debriefed, compensated, and discharged. All participants were given referrals for treatment at the baseline visit and after the laboratory visit. Participants returned to the laboratory 1-week and 1-month following the laboratory visit to complete assessments. All procedures were approved by the Medical University of South Carolina's Institutional Review Board.

2.2 Measures

2.2.1 Substance Use.—The Timeline Follow Back (TLFB; Sobell and Sobell, 2000) was used to assess opioid use (frequency and amount) for the past 30 days at baseline, past 7 days at 1-week follow-up, and past 30 days at 1-month follow-up.

2.2.2 Subjective Reactivity.—Subjective stress and craving were assessed using a visual analogue scale (VAS; 0 = *not at all* to 10 = *extremely*) adapted from the Within Session Rating Scale (Childress et al., 1994). Stress and craving reactivity were selected as the two predictors of interest based on prior research and to increase model convergence and power (Back et al., 2015; Back et al., 2010; Sinha et al., 2006). Subjective reactivity was assessed prior to and immediately after the stress condition (TSST or No-stress), and at 15-, 30-, and 60-minutes after the opioid cue paradigm.

2.2.3 Neuroendocrine Biomarker Reactivity.—Salivary samples of cortisol and DHEA were collected at the same time points as the subjective reactivity measures. Cortisol and DHEA samples were each assayed in duplicate using enzyme immunoassay systems (precision of 5.6% with a sensitivity of 5 pg/mL for DHEA; precision of 3.35% to 3.65% with a sensitivity of <0.003 µg/dL for cortisol). A PowerWave HT Microplate

Spectrophotometer in combination with a Precision Series Automate Liquid Handling System was used to analyze levels of cortisol and DHEA.

2.3 Statistical Analyses.

Three sets of predictor variables were calculated for this study (Figure 1). Changes in subjective and neuroendocrine reactivity were calculated following (a) the TSST/no-stress condition, (b) the TSST/no-stress condition plus the opioid cue paradigm, and (c) the opioid cue paradigm. Change scores were computed, respectively, by (a) subtracting the baseline value from the reactivity value immediately after the TSST/no-stress condition; (b) subtracting the baseline value from the peak reactivity value measured 15-, 30-, and 60-min following the opioid cue paradigm; and (c) subtracting the post-TSST/no-stress condition value from the peak post cue-reactivity levels. The computation of change scores aligns with procedures in prior literature on reactivity (Back et al., 2015; Daughters et al., 2009; McRae-Clark et al., 2011). Randomization to the TSST/no-stress condition was included as a factor in all analyses.

Opioid use during follow-up was measured in two ways: 1) time to first opioid use in days following the laboratory visit, and 2) average amount of opioid pills used per using day during the 1-month follow-up. Cox proportional hazards regression analysis was completed on models predicting time to use in days. Subjective and neuroendocrine reactivity variables did not show statistical multicollinearity with squared multiple correlations greater than 0.90 (Tabachnick and Fidell, 2007). Craving reactivity violated the proportionality assumption in models assessing changes in reactivity following the opioid cue paradigm and the TSST/No-Stress condition plus the opioid cue paradigm. Thus, a time variable (craving reactivity*log(days to use)) was included to adjust for the interaction between the covariate and time (Tabachnick and Fidell, 2007). Participants who did not endorse using within the 1-month follow-up were considered right-censored cases meaning opioid use did not occur during follow-up and it is unknown if it will occur in the future. To include these cases in the analysis a value of 30 was inputted to demonstrate lack of known use within the 30-day measurement period while use status was defined as 0 which equates to no use during follow-up (Tabachnick and Fidell, 2007).

Multiple linear regressions were completed on the average amount of opioids used at 1-month follow-up. For all predictors, tolerance and variance inflation factor values were within guidelines (Field, 2009). Residuals violated a Gaussian distribution and multiple linear regression was used because this approach is robust to non-normality. Models with significant predictors were re-run as hierarchical multiple linear regressions where all predictors were entered in the first step, followed by interaction terms in the second step. Interaction terms were centered for interpretability. Gender was included in initial models due to prior significant findings (Gilmore et al., 2019), but removed due to nonsignificant effects and to increase model parsimony and power. For participants who were lost to 1-month follow-up ($n = 2$), average amount of opioid use on using days at 1-month follow-up was replaced with the amount participants reported using at 1-week follow-up. Four missing values for DHEA were also mean-replaced. Data are presented as mean \pm SD, and all analyses were completed in IBM SPSS v25.

2. Results

3.1 Demographic Sample

Characteristics of the sample by stress condition are reported in Table 1. Across all OUD participants, the most commonly used opioids included: Lortab (87.1%), Hydrocodone (58.1%), Percocet (58.1%), oxycodone/OxyContin (53.25%), and Vicodin (54.8%). Participants had last used opioids $M = 5.70$ ($SD = 3.23$) days prior to the laboratory visit. At 1-month follow up, 64.5% participants self-reported using opioid pills since the laboratory visit. Of the ten participants who did not use during the 1-month follow-up period, three had been randomized to the TSST and seven had been randomized to the No-Stress condition. There was no significant difference on follow-up use and randomization to the TSST or No-Stress condition ($p = .22$). Mean time to first use of opioids was $M = 3.65$ ($SD = 2.08$) days with an average of 2.91 opioid pills consumed per using day. All participants who reported using during the follow-up period, used within the 7 days following the laboratory visit. Mean change scores in response to the stress condition, the opioid cue paradigm, and the stress condition plus opioid cue paradigm by group assignment (TSST/No-Stress) are reported in Table 2.

3.2 Reactivity to the TSST/No-Stress Condition

The Cox proportional hazards regression model that assessed whether changes in response to the TSST or no-stress condition were associated with time to first use was not significant ($X^2(5) = 3.97, p = .55$) and none of the predictors were significantly associated with time to use. When the average amount of opioid pills used in the past month was regressed on reactivity to the TSST/no-stress condition, the model approached significance ($R^2 = 0.31, p = .08$). Randomization to the TSST was the only significant predictor ($B = 3.83, SE = 1.31, \beta = 0.77, p = .007$). Participants in the TSST showed a 3.83 increase in the average amount of opioid pills used in comparison to participants in the no-stress condition.

3.3 Reactivity to the TSST/No-stress Condition and the Opioid Cue Paradigm

The Cox proportional hazards regression model assessing changes in reactivity to the TSST/No-stress condition plus the opioid cue paradigm was significant ($X^2(6) = 43.9, p < .001$). Change in subjective craving was significantly associated with a greater likelihood of follow-up use ($B = 1.06, \text{Exp}(B) = 2.88, 95\% \text{ Confidence Interval [CI]: } 1.70, 4.85, p < .001$). While holding all other predictor variables in the model constant (randomization to TSST/no-stress condition, subjective stress reactivity, cortisol, and DHEA), there was a 1.06 increase in the expected log of the relative hazard for follow-up opioid use for each one-point increase in subjective craving reactivity; that is, there is an expected hazard of follow-up opioid use that is 188 times higher in a person who is one point higher in craving reactivity following the TSST/No-stress condition plus opioid cue paradigm. The survival rate to follow-up use decreased one week after the laboratory study, suggesting greater risk for follow-up use in the week after the study.

A hierarchical multiple regression model examining the relationship between changes in reactivity following the TSST/no-stress condition plus the opioid cue paradigm with the average amount of opioids use at follow-up was completed (Table 3). Step 1 included all

main effects and showed a significant model ($R^2 = .35, p = .04$), where predictors accounted for 35.4% of the variance in average amount of opioid pills used on using days at follow-up. In Step 2, inclusion of an interaction variable of subjective stress reactivity multiplied by group (TSST/no-stress) significantly improved the model ($R^2 = .13, p = .02$) and was significant ($B = -0.78, SE = 0.32, \beta = -.85, p = .02$). Inspection of the simple slopes (Figure 2) by splitting stress reactivity into three groups based on the mean and standard deviation showed that average amount of opioids used at follow-up varied by subjective stress response to the TSST. Among participants randomized to the TSST, those with one standard deviation of *greater* subjective stress following the TSST plus opioid cue paradigm showed *lower* average opioid use at follow-up. In comparison, those with one standard deviation of *lesser* subjective stress reactivity after the TSST plus opioid cue paradigm showed *higher* average opioid use at follow-up.

3.4 Reactivity to the Opioid Cue Paradigm

When examining changes in response to the opioid cue paradigm, the Cox proportional hazards regression model was significant ($X^2(6) = 28.37, p < .01$). Increases in subjective craving following the opioid cue paradigm were associated with fewer days to first use after the laboratory visit ($B = 0.44, \text{Exp}(B) = 1.55, 95\% \text{ CI } [1.06, 2.28], p = .02$). Specifically, there was a 0.44 increase in the expected log of the relative hazard for each one-point increase in subjective craving while holding all other predictor variables in the model constant; thus, there was an expected hazard 55 times higher in a person who was one-point higher in subjective craving reactivity following the opioid cue paradigm when holding randomization to the TSST/No-stress condition, subjective stress reactivity, cortisol, and DHEA constant. The final multiple regression model assessing changes in reactivity following the opioid cue paradigm approached significance ($R^2 = .31, p = .08$). None of the predictors in this model were significant.

4. Discussion

This study examined associations between laboratory-induced stress and craving and subsequent prescription opioid use among individuals with current OUD. Two main findings emerged. First, greater increase in craving following the opioid cue paradigm was associated with fewer days to first opioid use during follow-up; this was true regardless of whether the opioid cue was preceded by the TSST/no-stress condition or not. Secondly, changes in subjective stress reactivity following the TSST and opioid cue paradigm were associated with the amount of opioid pills consumed during follow-up. Exposure to the TSST plus opioid cue paradigm increased the amount of use during follow-up but in an unexpected direction: those with higher subjective stress in response to both the TSST and the opioid cue paradigm consumed *fewer* opioid pills during follow-up, whereas those with lower subjective stress reactivity to the TSST and opioid cue paradigm consumed *more* opioid pills during follow-up.

In survival models, subjective craving was the only significant predictor of time to first use of opioid pills at 1-month follow-up, and all participants used within a week after the laboratory visit. This corresponds with research demonstrating that craving is a better

disorders and may inhibit individuals with OUD from detecting and acknowledging craving or subjective stress within themselves. Another interpretation of these findings could be that some individuals with OUD may be avoidant of experiencing stress. Avoiding stressful experiences has been shown to have long-term consequences in other disorders, such as anxiety disorders (Foa et al., 2006). If following a similar pattern, the avoidance of state stress could have a deleterious consequence in which individuals with OUD use greater amounts of opioids during follow-up.

Contrary to our hypotheses, cortisol and DHEA were not associated with time to first use. This finding is in contrast to prior research showing cortisol is associated with heroin relapse (Fatseas et al., 2011). There are several ways to interpret the absence of this finding. Chronic opioid use is associated with complex changes in the stress response system, including cortisol and DHEA (Brennan, 2013; Daniell, 2006; de Vries et al., 2019). Exposure to a short-term stressor typically results in activation of the HPA axis and increased cortisol. However, in response to long-term stressors, the body allostatically adapts with a higher basal level of cortisol and cortisol responses to additional acute stressors are blunted (See Figure 2 in Lee et al., 2015). Although participants in this study did not have a higher basal cortisol levels than healthy controls in post-hoc tests, they appear to have shown a blunted response to the laboratory paradigm. Table 2 shows the change scores in cortisol following each part of the laboratory task. For the TSST group, cortisol levels decreased following the TSST and opioid cue paradigm, which may suggest a blunted response. However, another consideration is the difficulty in measuring neuroendocrine variables which are indicators of biological changes and may fluctuate widely within a day and across individuals (Heck and Handa, 2019; Lee et al., 2015).

Although this was not a treatment-seeking sample, results lend support to the use of clinical interventions that reduce craving. Previous research has shown that both laboratory-induced and personally-relevant drug cues increase craving, but personally-relevant cues have a stronger effect on craving (Childress et al., 1994; Childress et al., 1986). This may account for why all participants in the current study used within the first week of follow-up. Medications for OUD (MOUD) are well-known to address opioid withdrawal and target craving (Sofuoglu et al., 2019), but other pharmacological (e.g., clonidine, Kowalczyk et al., 2015) and psychotherapeutic interventions may also enhance MOUD despite some mixed findings (Carroll and Weiss, 2017; Dugosh et al., 2016; Schacht et al., 2017; Schiff et al., 2015; Sofuoglu et al., 2019). Many psychotherapies bring greater awareness to situations that trigger cravings and teach skills that are useful in managing craving. In addition, the results from this study also suggest lower subjective stress in response to a stressor is associated with greater opioid use at follow-up. Although more research is needed to examine the mechanisms underlying this finding, if blunted stress responses or cognitive avoidance helps explain these results, adjunctive psychotherapy treatments focused on decreasing stress, mindfulness, and approaching (versus avoiding) situations may be beneficial for this subpopulation. For example, previous research has shown that an adjunctive mindfulness-based treatment in individuals with OUD and chronic pain is associated with reductions in craving, pain, stress, and self-control (Garland et al., 2019). Likewise, in individuals with OUD and posttraumatic stress disorder, a disorder

characterized in part by a blunted stress response, exposure-based treatments have shown efficacy in preventing opioid relapse (Schacht et al., 2017; Schiff et al., 2015).

Several limitations of the current study warrant consideration. The sample size was small, and thus, the findings need to be replicated in a larger sample. The parent study's focus on prescription OUD, rather than heroin use disorder, led us to have a less racially and ethnically diverse sample due to health disparities between individuals with prescription OUD who tend to self-identify as white/Caucasian as compared to heroin users, who tend to self-identify as Black/African American or of another non-white race and ethnicity (Alexander et al., 2018). Similarly, prior work on this data has shown gender differences in stress reactivity and OUD when examining participants who completed the laboratory study but were lost follow-up (i.e., a larger sample, Gilmore et al., 2019). No differences were observed in this secondary analysis most likely due to low power. An additional limitation to this study was the parent study's exclusion criteria (e.g., psychiatric and medical comorbidities, BMI > 39) which limited generalizability of these findings to a more diverse patient population, although prevented possible confounds on study results. Furthermore, research on stress induction within the laboratory does not perfectly translate to stress in real-life experiences (Sinha, 2008). It may be useful for future work to assess ongoing stressors to examine the potential impact with laboratory induced-stress or use EMA to compare the impact of real-life stressors with laboratory stressors on opioid use.

4.1 Conclusions

This study is the first to our knowledge to examine the relationship between laboratory-induced stress and craving, and subsequent prescription opioid use. Results suggest that for individuals with OUD, craving predicts the time to first use, and all users will use within one week following the study. This points to the strong influence of craving, rather than stress, on future opioid use. Subjective stress also seems to play a role in the amount of opioids used during follow-up. However, the mechanisms of this relationship are unclear and require additional work. It will be important for future work to consider unique responses to stress among individuals with OUD, how those responses may be related to craving and use, and means to mitigate craving to assist in long-term recovery.

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Highlights

- Participants with opioid use disorder used opioids, on average, 3.65 days after the study.
- Subjective craving predicted time to follow-up opioid use.
- The stress task and subjective stress levels predicted the amount of opioids used.

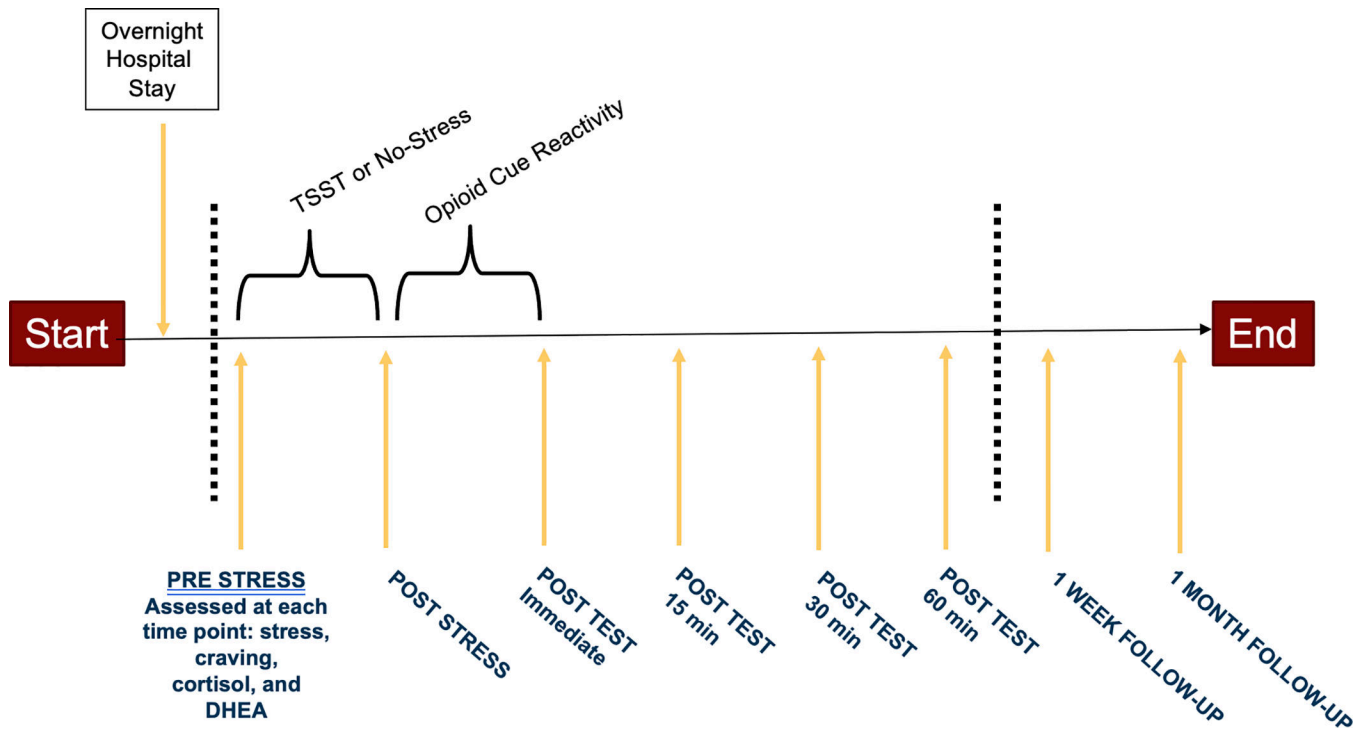


Figure 1. Laboratory Study Design

Note: Participants in this study were randomized to the Trier Social Stress Task (TSST) or a No-Stress condition followed by all participants completing an opioid cue paradigm. Stress, craving, cortisol, heart rate, and dehydroepiandrosterone (DHEA) reactivity were measured at baseline, immediately following each task, and 15-, 30-, and 60- minutes after the opioid cue paradigm. Participants were also asked to come back into the laboratory to complete 1-week and 1-month follow-up visits. For analyses, three change scores in reactivity were calculated: (a) reactivity to the stress condition was calculated by subtracting pre-stress scores from immediate post-stress scores after the TSST/No-Stress condition (i.e., post-stress—pre-stress); (b) reactivity to the TSST/No-Stress condition and the opioid cue paradigm was calculated by subtracting pre-stress scores from peak post-test scores following the opioid cue paradigm (i.e., peak post-test—pre-stress); (c) reactivity to the opioid cue paradigm was calculated by subtracting post-stress scores from peak post-test scores following the opioid cue paradigm (i.e., peak post-test—post-stress).

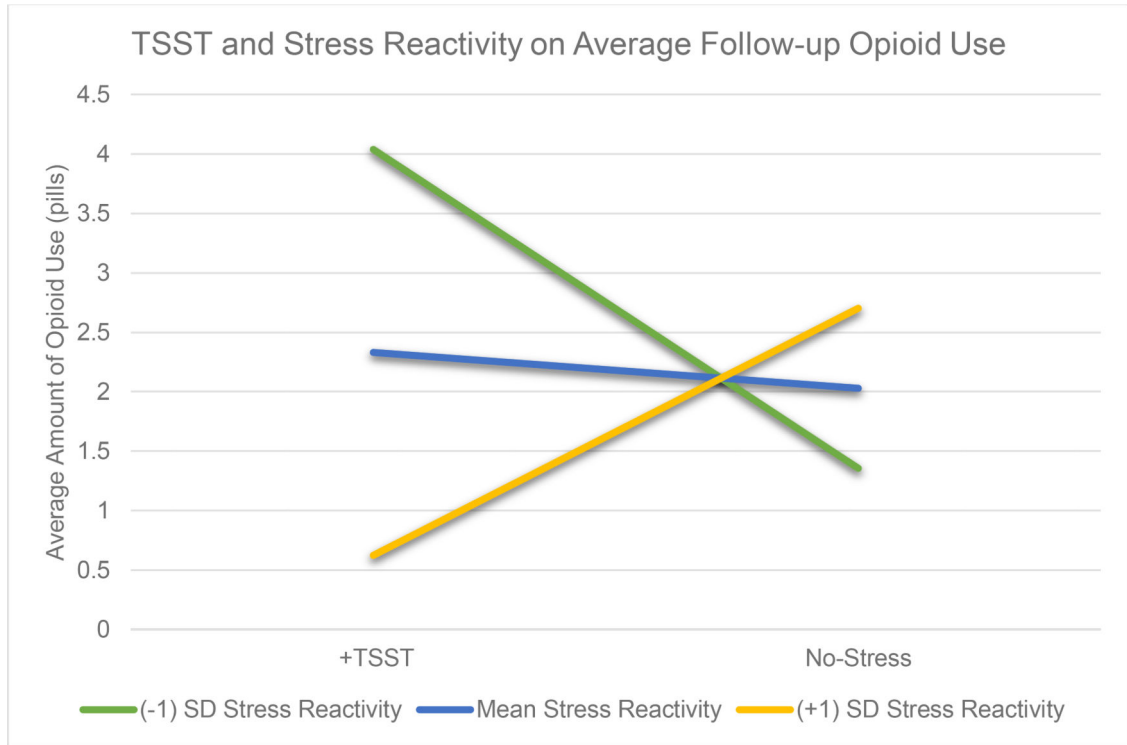


Figure 2. Predicted Values from the Interaction between Stress Reactivity to the Trier Social Stress Task (TSST) or No-Stress Task and Average Amount of Prescription Opioids Used during Follow-Up

Note: This figure demonstrates the predicted values from the multiple regression model for the interaction between stress reactivity and randomization to the Trier Social Stress Task (TSST) or to the No-Stress condition with follow-up opioid use. The model outcomes show that individuals randomized to the TSST showed variation in the number of opioid pills they used at 1-month follow-up depending on their changes in stress reactivity. Following the TSST, those with a greater change in stress reactivity (+1 SD Stress Reactivity; yellow line) consumed fewer opioid pills at one month follow up whereas those with less change in stress reactivity (-1 SD Stress Reactivity, green line) used more pills at 1-month follow-up.

Table 1.

Demographics and Clinical Characteristics of Individuals with Opioid Use Disorder (N = 31)

Variable	TSST (n = 16)	No Stress (n = 15)
	Mean (SD) or n (%)	
Age	36.19 (12.69)	32.60 (12.31)
Gender (% Male)	9 (56.3%)	9 (53.3%)
Education (% some college or more)	8 (50%)	12 (80%)
Employment		
Employed (part/full time)	5 (31.3%)	2 (13.3%)
Student	2 (12.5%)	3 (20%)
Unemployed	9 (56.3%)	10 (66.7%)
Race & Ethnicity		
Caucasian	13 (81.3%)	11 (73.3%)
Black/African American	2 (12.5%)	0 (0%)
Hispanic/Latino	2 (6.3%)	1 (6.7%)
Native American	0 (0%)	3 (20%)
Relationship Status (% single, never married)	10 (62.5%)	8 (53.3%)
Smokes Nicotine (% yes)	13 (81.3%)	13 (86.7%)
Prescription Opioid Use		
Age first used prescription opioids	22.13 (10.04)	24.13 (10.97)
Age of onset of opioid dependence	27.48 (10.31)	27.87 (11.42)
Total days using opiates at baseline ^a	18.69 (8.70)	19.40 (8.27)
Average number of opioid pills used per using day at baseline ^a	4.09 (2.37)	3.93 (2.44)
Days since last opioid use before laboratory visit	5.42 (4.08)	6.00 (2.41)
Days to first use of opioids during follow-up ^b	4.08 (2.19)	3.00 (1.85)
Average number of opioid pills used per using day during follow-up	3.80 (2.77)	1.96 (1.87)
Comorbid Psychiatric Conditions		
Alcohol use disorder	3 (18.8%)	1 (6.7%)
Cannabis use disorder	0 (0%)	3 (20%)
Sedative use disorder	0 (0%)	2 (13.3%)
Cocaine use disorder	0 (0%)	0 (0%)
Major Depression	0 (0%)	1 (6.7%)

Variable	TSST (<i>n</i> = 16)	No Stress (<i>n</i> = 15)
	Mean (SD) or <i>n</i> (%)	
Panic disorder [*]	3 (18.8%)	6 (40.0%)
Posttraumatic Stress disorder (PTSD)	0 (0%)	0 (0%)
Social Anxiety disorder	3 (18.8%)	1 (6.7%)
Generalized anxiety disorder	3 (18.8%)	2 (13.3%)
Bipolar I and II disorder	0 (0%)	0 (0%)
Pain disorder	1 (6.3%)	1 (6.7%)
Obsessive compulsive disorder	0 (0%)	2 (13.3%)
Attention-deficit/hyperactivity disorder	1 (6.3%)	1 (6.7%)
History of Treatment (% yes)		
History of chronic pain treatment	6 (37.5%)	4 (26.7%)
History of addiction treatment	8 (50%)	5 (33.3%)
History of mental health treatment	5 (31.3%)	5 (33.3%)

^aBaseline measures assessed use for past 30 days. All participants reported using in the past 30 days.

^bSubsample of participants who reported using opioids at follow-up, *n* = 20

* *p* < .05 between-group differences

Table 2

Average Reactivity Change Scores by Stress Condition (N = 31)

	TSST (<i>n</i> = 16)	No-Stress (<i>n</i> = 15)
Laboratory Task	Mean (SD)	
Stress condition (TSST/No-Stress)		
Stress *	4.31 (3.14)	-0.60 (1.68)
Craving *	2.13 (3.01)	-0.27 (1.03)
DHEA *	109.30 (102.94)	23.81 (67.84)
Cortisol *	0.15 (0.25)	-0.03 (0.08)
TSST/No-stress condition plus Opioid Cue Paradigm		
Stress	2.44 (3.90)	1.93 (1.94)
Craving	3.38 (2.28)	3.33 (1.88)
DHEA	119.88 (150.21)	96.45 (99.28)
Cortisol	0.07 (0.13)	0.06 (0.15)
Opioid Cue Paradigm		
Stress *	-1.88 (2.78)	2.53 (2.20)
Craving *	1.25 (1.98)	3.60 (1.76)
DHEA	10.39 (133.80)	72.64 (100.43)
Cortisol *	-0.08 (0.22)	0.09 (0.14)

Note: Mean changes scores included in the survival analysis by group assignment to the Trier Social Stress Task (TSST) or the No-Stress condition. For example, the first row shows the average change score for individuals following the stress condition (either randomization to the TSST or No-Stress task). Participants who were randomized to the TSST showed an average change score of $M=4.31$ ($SD = 3.14$), suggesting increases in stress following the TSST. Oneway ANOVAs tested for group differences.

* $p < .05$; DHEA = dehydroepiandrosterone

Table 3

Average Amount of Opioid Use during Follow-up Regressed on Change in Reactivity to the TSST/No-stress condition and Opioid Cue Paradigm

	B	Standard Error	β
Step 1			
Constant	2.64 *	1.00	
TSST/No-Stress Group	2.09 *	0.81	-.42
Stress	-0.39 *	0.14	-.47
Craving	0.09	0.21	.07
Cortisol	0.36	3.27	.02
DHEA	-0.002	0.003	-.12
Step 2			
Constant	1.52	1.03	
TSST/No-Stress Group	2.00 *	0.74	.40
Stress	0.22	0.28	.27
Craving	0.12	0.20	.10
Cortisol	-0.66	3.02	-.04
DHEA	-0.003	0.003	-0.18
Stress x TSST/No-Stress Group	-0.78 *	0.32	-.85

Note: Results from multiple regression examining how change in reactivity to the stress condition (TSST/No-Stress Task) and the opioid cue paradigm predicted follow-up opioid use. In Step 1, predictors include changes in reactivity for stress, craving, cortisol, and DHEA in addition to randomization to either the TSST or No-Stress task. In Step 2, the interaction of the randomization to the TSST or No-Stress task multiplied by stress reactivity is included in the model.

* = $p < .05$; $R^2 = .35$ for Step 1 ($p = .04$), $R^2 = .13$ for Step 2 ($p = .02$).