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Effect of oxytocin on craving and stress response in marijuana-dependent individuals: a pilot study

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Abstract

Rationale—Stress has been shown to be a significant factor in the maintenance of marijuana use. Oxytocin is a hypothalamic neuropeptide that has been shown to moderate behavioral responding to stress as well as play a role in the neuroadaptations that occur as a consequence of long-term drug use.

Objectives—The current study evaluated the impact of oxytocin pre-treatment on craving, stress, and anxiety responses following a psychosocial stress task in marijuana-dependent individuals.

Methods—In a laboratory setting, baseline measurements of craving (assessed using the Marijuana Craving Questionnaire; MCQ), salivary cortisol and dehydroepiandrosterone (DHEA), stress, and anxiety were collected in 16 participants (age 19–40) meeting DSM-IV criteria for marijuana dependence. Participants were then administered either oxytocin 40IU (n=8) or placebo (n=8) nasal spray 40-minutes prior to completion of the Trier Social Stress Task (TSST). Measurements were repeated pre-TSST, immediately post-TSST, and 5-, 35-, and 60-minutes post-TSST.

Results—Oxytocin reduced both MCQ total score and DHEA levels from before to after the TSST. It also decreased anxiety, but not subjective stress ratings.

Conclusions—Although preliminary, these results suggest that oxytocin may play a role in the amelioration of stress-induced reactivity and craving in marijuana-dependent individuals.

Keywords

marijuana; oxytocin; stress; craving

INTRODUCTION

Marijuana is the most commonly used illicit drug in the United States (SAMSHA, 2010), and there is a tremendous need for the development of effective clinical interventions for marijuana use disorders. Among users of marijuana, stress has been shown to be a significant factor in maintenance of use (see Hyman and Sinha, 2009, for review). For example, negative life events (Wills et al., 2001; Windle and Wiesner, 2004) and traumatic

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experiences (Lipschitz et al., 2003; Bremner et al., 1996; Vlahov et al., 2004; Schiff et al., 2007) have been demonstrated to be associated with marijuana use. Further, marijuana users report expecting relaxation and stress relief from use (Copeland et al., 2001; Galen and Henderson, 1999), and coping motives have been associated with levels of marijuana use (Bonn-Miller et al., 2007) and marijuana-related problems (Simons et al., 2005; Lee et al., 2007).

Oxytocin is a neuropeptide with peripheral endocrine and central neural actions. Peripherally, oxytocin elicits physiologic events necessary for copulation, parturition, and lactation (Ludwig and Leng, 2006). Central release of oxytocin has been implicated in “pro-social” behaviors and may also have anxiolytic effects. For example, several preclinical studies have shown that oxytocin increases approach and pair bonding behavior (Witt et al., 1992; Williams et al., 1994). Neonatal nurturing promotes long-term plasticity within the limbic circuitry, while childhood maltreatment has been associated with low urinary and cerebrospinal fluid oxytocin levels (Francis et al., 2002; Fries et al., 2005; Heim et al., 2009). Intranasal administration of oxytocin attenuates anticipatory anxiety, subjective stress, and hypothalamic-pituitary-adrenal (HPA) axis activation to a psychosocial laboratory stress task and increases trust (de Oliveira et al., 2011; Heinrichs et al., 2003; Kosfeld et al., 2005). Oxytocin also reduces memory retrieval and fear-conditioned responding of Vietnam veterans with post-traumatic stress disorder (Pitman et al., 1993). In agreement, neuroimaging studies demonstrate that intranasal administration of oxytocin attenuates amygdala activation following stressful and fearful stimuli (Baumgartner et al., 2008; Domes et al., 2007; Kirsch et al., 2005; Labuschagne et al., 2010). Taken together, these studies demonstrate that oxytocin may play a potential therapeutic role in ameliorating stress and anxiety.

In rodent models of drug use, it has been suggested that oxytocin reduces reinforcement and drug-seeking behavior (Carson et al., 2010; Kovacs et al., 1998; Sarnyai et al., 1991; Sarnyai et al., 1992); in contrast, limited clinical research has examined the role oxytocin may play in drug-dependent populations. Immunohistochemical analysis of post-mortem brains from alcoholics indicate a significant reduction in oxytocin immunoreactivity in the hypothalamus (Sivukhina et al., 2006). Further, mothers using cocaine during pregnancy exhibit significantly lower plasma oxytocin levels, as well as greater hostility and depression as compared to control mothers (Light et al., 2004). Based on a positive preclinical study in which increasing oxytocin levels were hypothesized to moderate the effects of lithium-attenuated cannabinoid withdrawal in rats (Cui et al., 2001), an open-label trial of lithium on marijuana withdrawal symptoms demonstrated positive outcomes, including decreased anxiety (Winstock et al., 2009). These findings suggest that oxytocin may decrease some symptoms associated with marijuana dependence such as negative affect and craving. The purpose of the current study was to evaluate the impact of oxytocin pre-treatment on subjective craving, stress, and anxiety responses and neuroendocrine measurements of stress (cortisol and dehydroepiandrosterone) following a psychosocial stress task in marijuana-dependent individuals; we hypothesized that individuals receiving oxytocin would have an attenuated stress and craving response compared to individuals receiving placebo.

METHODS

Screening

Participants were recruited primarily through community advertisements between March 2011 and August 2011. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and received approval from the Medical University of South Carolina (MUSC) Institutional Review Board. The trial was registered

with www.clinicaltrials.gov (NCT01335789). All participants gave written, informed consent prior to study procedures.

To be eligible for participation, individuals had to be between 18 and 65 years of age and meet DSM-IV criteria for marijuana dependence. Exclusion criteria included other current substance abuse or dependence (with the exception of nicotine); presence of a current major Axis I disorder; use of any psychoactive medication or medication known to alter HPA axis function; and presence of a medical condition which could alter HPA axis response. All potential participants were evaluated for medical exclusions through routine physical exam. The MINI International Neuropsychiatric Interview (Sheehan and Lecrubier, 2006) was used to assess for psychiatric exclusions, and the substance use module of the Structured Clinical Interview for DSM-IV (First et al., 1994) was used for substance use disorder diagnosis. Following completion of the assessment procedures, eligible individuals were scheduled to complete the laboratory session.

Laboratory Procedures

The test session was conducted in the MUSC Clinical and Translation Research Center (CTRC). Prior to leaving the assessment interview, participants were instructed to arrive at 10:00am on test day, and to avoid caffeine on the day of the test session. Participants were also instructed to abstain from marijuana the day of testing and other drug (including alcohol) use for three days prior to testing. A urine sample was screened for the presence of drugs (marijuana, cut-off 50 ng/ml; cocaine, cut-off 300 ng/ml; opiates, cut-off 300 ng/ml; benzodiazepines, cut-off 300 ng/ml; and amphetamines, cut-off 1,000 ng/ml) on the day of testing (Instant Technologies iCup, Norfolk, VA); if positive for any drug with the exception of marijuana the session was rescheduled. Abstinence from recent marijuana use was assessed via saliva testing (Varian OraLab, Lake Forest, CA; delta-9-tetrahydrocannabinol concentration cut-off 50 ng/ml); if positive, the session was rescheduled. A pregnancy test was performed for female participants, and nicotine patches were provided to participants who smoked cigarettes to avoid nicotine withdrawal.

At 11:30am, baseline marijuana craving was assessed with the Marijuana Craving Questionnaire (MCQ) (Heishman et al., 2009), a 12-item instrument with four subscales (Expectancy, Purposefulness, Emotionality, and Compulsivity). Each item is scored on a scale of 1–7, with a possible scoring range of 3–21 for each subscale, and a total composite scoring range of 12–84. Measurements were also taken of subjective stress and anxiety (rating on a 0–10 Likert scale); salivary cortisol and dehydroepiandrosterone (DHEA) were collected to both confirm validity of the stress intervention and to also provide empirical assessments of stress reactivity. Samples were collected via passive drool, and hormone measurements were analyzed using Salimetrics enzyme immunoassay kits (Salimetrics LLC, State College, PA). The minimal concentration of cortisol that can be distinguished from 0 is < 0.003 µg/dL. The intra-assay precision was determined from the mean of 14 low (coefficient of variation 3.35%) and 18 high (coefficient of variation 3.65%) replicates each. The minimal concentration of DHEA that can be distinguished from 0 is 5 pg/mL. Intra-assay precision was determined from the mean of 12 replicates at high (618.6 pg/mL) and low (44.6 pg/mL) DHEA levels. The average intra-assay coefficient of variation was 5.6%. Inter-assay precision was determined from the mean of averaged duplicates for 12 separate runs. The average inter-assay coefficient of variation was 7.9% for high (579.5 pg/mL) and 8.5% for low (34.8 pg/mL) DHEA levels.

Participants were provided with a light lunch, and allowed sedentary activities. At 1:15pm, oxytocin (40IU) or matching placebo was administered intranasally. This dose was selected based on previous studies that have used similar doses of oxytocin (Ditzen et al., 2009; Heinrichs et al., 2003; Kubzansky et al., 2009). Timing of administration is also based on

previous studies showing central activity of oxytocin approximately 40 minutes after intranasal administration (Heinrichs et al., 2009). Oxytocin and placebo (saline) nasal spray was compounded by a local compounding pharmacy (Pitt Street Pharmacy, Mount Pleasant, SC). Participants received 4IU per spray; as such 5 sprays were alternately administered per nostril by nursing personnel. An Investigational New Drug application (109,726) for the use of oxytocin in this population was filed with the Food and Drug Administration prior to initiation of the study. Participants were randomly assigned to the treatment condition and assignment was double-blinded. Craving, subjective, and hormone measurements were collected again at 1:40pm and 1:55pm. At 2:00 PM, the Trier Social Stress Test (TSST) began. The TSST is a standardized psychological stress challenge which has shown utility for evoking an HPA axis stress response in a laboratory setting (Dickerson & Kemeny, 2004). The participant was told that (s)he would be asked to give a speech and perform a follow-up task. The topic of the speech was why (s)he should be hired for a particular job, and the participant was instructed that the speech would be delivered to a group of hiring managers and that the presentation would be recorded. The participant was allowed five minutes to prepare his/her speech, at which point three individuals unknown to the participant entered the room. The participant was instructed to stand and deliver his/her prepared speech without notes for five minutes; instructions were given by an audience member to continue if the participant paused prior to the end of the five-minute time period. At the end of the speech task, the participant was instructed to serially subtract 13 from 1,022 as quickly and accurately as possible. The mental math recitation continued for five minutes, at the end of which time (2:15pm) the audience left the room. Craving, subjective, and hormone measurements were collected immediately following completion of TSST, and 5-, 35-, and 60-minutes post task. After the final assessment, subjects were debriefed and compensated (\$125). In the event that a participant's craving level was elevated at the time of discharge, he or she was asked to remain in the CTRC until their craving subsided.

Statistical analysis

Standard descriptive statistics were used to summarize the general demographic and clinical data. A Wilcoxon rank sum test statistic assessed baseline treatment group differences in continuous characteristics. Differences in categorical characteristics were assessed using a Fisher's Exact test statistic.

A linear mixed effects model that assessed all serially measured time points following administration of the study drug (including pre-TSST time point) tested the craving, stress, and neuroendocrine responses to oxytocin compared to placebo. Model estimation was constructed in *SAS Proc Mixed* and model based estimates were used to construct group level comparisons at each planned time point (Post-study drug treatment/Pre-TSST; Immediately following TSST; 5 minutes following TSST). Overall statistical significance for the effects of group and time, their interaction, and the baseline measure were assessed. Pair-wise comparisons between the treatment groups were assessed at time points both prior to and immediately following the TSST. Estimated group differences at each time point and their 95% confidence intervals are presented in the tables. Effect sizes calculated are completed at each time point and are presented as Cohen's d values (Small effect~0.2; Moderate effect~0.5; Large effect~0.8+) (Cohen, 1988). Due to highly skewed distributions, both cortisol and DHEA measures were natural log transformed prior to analysis. All stated comparisons and statistical analysis are adjusted for baseline outcome levels as well as the self-reported number of marijuana use sessions per using day for the 90 days prior to study entry.

Since the primary aim of the pilot trial was to estimate treatment effect and variability of oxytocin on marijuana craving and neuroendocrine response for design of a larger trial, a pre-trial power calculation was not performed. Table results are stated as model based group

mean estimates (95% CI) as well as model based mean differences between groups and effect sizes (Cohen's *d*). Figure values are shown as model based group means and associated standard errors. Spaghetti plots of individual response patterns over time were examined to assure that effects stated are not due to the influence of individual outlying observations. Cigarette smoking status was also of interest as a possible moderator of group responses to the TSST. A sensitivity analysis was performed to examine the effects of smoking status on the relationship between oxytocin treatment and response to the TSST. All analyses were performed using standard randomized control trial methodology and results presented are from intent to treat analysis. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). Significance for all planned pair-wise comparisons was set at a 2-sided *p*-value of 0.05 and no correction for multiple testing was applied to reported *p*-values.

RESULTS

Baseline Clinical Characteristics

A total of 23 individuals were evaluated for study participation; 16 met initial eligibility requirements and took part in the pilot study. The reasons for study exclusion were medical or psychiatric issues (*n*=5), inability to provide a negative urine drug screen (*n*=1) or inability to provide a saliva sample (*n*=1) at the laboratory session. Two participants had study session procedures rescheduled due to initial positive drug screens. The mean age of the study participants was 23.3 (SD: 6.5), 75% were male, and 75% were Caucasian. There were no between group differences for any of the demographic or clinical baseline characteristics measured. The two treatment groups were similar in age, cigarette smoking status, and baseline levels of marijuana craving, stress and anxiety. Both groups reported similar frequency of marijuana use; however, the oxytocin treatment group had a trend for higher number of marijuana use episodes per day (*p*=0.06; Table 1). Thus, adjustments were made for the amount of daily marijuana use episodes in all statistical models.

Effects of Oxytocin Administration

Prior to the stressor, administration of oxytocin did not significantly reduce craving, anxiety, stress, or neuroendocrine measures (Table 2). Following the stressor, the study group receiving oxytocin showed an attenuated craving response as measured by the MCQ total score [Table 2; 43.1 (33.2, 53.0) vs. 57.5 (47.6, 67.4); Cohen's *d*=1.20; see Figure 1a], primarily driven by. A blunted response in both the expectancy and emotionality subscales of the MCQ total score (Cohen's *d*=1.22 and *d*=1.15, respectively; figure 2a and 2b). Subjects receiving oxytocin also had significantly lower levels of DHEA [log transformed: -0.2 (-0.4, 0.1) vs. 0.2 (0.0, 0.5); *d*=1.08; Figure 1b] and anxiety [3.3 (1.8, 4.7) vs. 5.5 (4.0, 6.9); *d*=1.02; Figure 1d] following the TSST. The cortisol measure had a similar response pattern, but failed to reach a level of statistical significance (*d*=0.69; Figure 1c). Although subjective measures of stress increased following the TSST, the stress rating between those who received oxytocin and placebo were small and not different [3.0 (0.8, 5.2) vs. 3.7 (1.5, 5.9); *d*=0.34]. In order to aid in the interpretation of the results, unadjusted change from baseline individual level responses to the TSST (Pre and Post) by randomization group are presented in Figure 3, found in the supplementary materials.

Cigarette smoking and response to the TSST

Although there was no difference in the proportion of subjects that reported smoking cigarettes between the two treatment groups (oxytocin 75% vs. placebo 63%; *p*=0.36), cigarette smoking status was significantly associated with reported MCQ scores during the study (MCQ Total Score and subscales: emotionality and expectancy). Results show that cigarette smokers (*n*=11) reported numerically (not statistically) higher craving scores than

non-smokers ($n=5$) at the pre medication measure (mean $\pm$ SD: 48.0 ± 15.8 vs. 40.6 ± 12.9 , respectively, $p=0.63$). Evaluation of inclusion of smoking status with the adjusted model revealed a possible association between those that smoked cigarettes and the number of marijuana smoking sessions per day (smokers 2.5 ± 0.7 vs. non-smokers 1.9 ± 0.3 ; Wilcoxon $p=0.06$); thus, to avoid issues associated with small samples and collinearity (variance inflation and over fitting), a separate model was developed containing smoking status as a model covariate. The resulting estimated treatment group differences were similar to those reported for models adjusting for marijuana use (Table 2) but with slightly lower variance estimates. In a similar fashion, this effect was consistent across all subscales of the MCQ but had little effect on measured anxiety or the physiologic outcome measures (cortisol and DHEA).

Safety and Adverse Events

Adverse events were assessed following medication administration. One participant receiving placebo reported nasal irritation and headache, one participant receiving placebo reported headache, and one participant receiving oxytocin reported irritability and unpleasant taste in the mouth.

DISCUSSION

To our knowledge, this is the first controlled trial of oxytocin administration in a drug-dependent population. Although results should be considered preliminary given the small sample size of this pilot study, oxytocin administered prior to a psychosocial stress task resulted in decreased marijuana craving in response to the stressor. Subjective reports of stress were not reduced; however, there was a significant reduction in DHEA levels in individuals receiving oxytocin compared to placebo. A significantly lower anxiety response to the TSST in oxytocin versus placebo-treated participants was also observed. However, it should be noted that oxytocin administration resulted in a trend for reduced craving and DHEA prior to the TSST, suggesting some effect of oxytocin in the absence of the stressor. The current study was underpowered to explore the interactions of pre and post TSST time points; it would be important for larger studies to further assess the group $\times$ TSST response differential to determine the effect of oxytocin on stress-induced anxiety and craving versus its effects on anxiety and craving in the absence of stress.

Our findings in regards to marijuana craving are not unexpected given previous preclinical findings. Molecular studies have localized oxytocin receptors to the mesolimbic dopamine reward circuit, including the amygdala, nucleus accumbens, and ventral tegmental area (VTA) (Vaccari et al., 1998). Similar to drugs of abuse, oxytocin infusion directly into the VTA promotes dopamine release in the nucleus accumbens (Melis et al., 2007). Behavioral studies utilizing animal models of drug reinforcement demonstrate that oxytocin dose-dependently decreases cocaine-induced hyperactivity and stereotypy (Sarnyai et al., 1991; Sarnyai et al., 1992). Interestingly, chronic administration of oxytocin reduces dopamine release in the nucleus accumbens, indicating that oxytocin may be involved in the plasticity that occurs within the reward circuit as a function of repeated drug use (Kovacs et al., 1998). In addition, oxytocin inhibits the development of tolerance to repeated cocaine administration (Sarnyai et al., 1992) and may also attenuate self-administration of cocaine (Sarnyai & Kovacs, 1994). Oxytocin administration has been shown to block methamphetamine-induced locomotor activity and reduce methamphetamine reinstatement (Carson et al., 2010). Of direct relevance to the current study, chronic delta-9-THC administration has been shown to modulate oxytocin expression in the nucleus accumbens and ventral tegmental area (Butovsky et al., 2006); this oxytocin downregulation may be a factor in the long-term effects of cannabinoids.

Of note, differences in craving scores following completion of the TSST were largely driven by the expectancy and emotionality subscales of the MCQ. These subscales measure anticipation of positive outcomes from smoking marijuana such as a reduction in nervousness and feeling more content, and may therefore be reflective of the anxiolytic properties of oxytocin. Although Cui and colleagues investigated the effects of oxytocin on cannabinoid withdrawal in rats as opposed to stress response, our results are somewhat congruent as in Cui's study oxytocin was shown to block anxiety-associated withdrawal symptoms (Cui et al, 2001).

Unexpectedly, a reduction in subjective stress was not noted in oxytocin-treated individuals nor was there a significant attenuation in cortisol response. However, a reduction in DHEA was observed. DHEA is secreted synchronously with cortisol in response to ACTH, and has been shown to be elevated in response to psychosocial stress (Izawa et al., 2008; Lennartsson et al., 2012; Morgan et al., 2004). As opposed to cortisol, a catabolic hormone, DHEA has anabolic and antiglucocorticoid effects (Kalimi et al., 1994; Maninger et al., 2009). As such, it has been suggested that DHEA may promote an adaptive response to stress by antagonizing the effects of cortisol (Morgan et al., 2004).

The lack of effect on subjective stress observed may be attributable to the method used to assess stress (i.e., reliance on a single question). Of note, de Oliveira and colleagues (2012) recently reported similar findings in a non-dependent population participating in a comparable stress task in which oxytocin was found to decrease anticipatory anxiety but did not affect public speaking fear. Additionally, other researchers have reported reductions in stress hormones following oxytocin administration in stressful situations without reductions in subjective anxiety measures (Cardoso et al., in press; Ditzen et al., 2009; Linnen et al., 2012). These studies, along with the present findings, suggest that oxytocin's role in modulation of the HPA axis may be distinct from its effects on subjective emotional states.

These findings should be interpreted in light of some limitations. As this was a pilot study, the sample size was small and replication of the results is needed. Further, our sample was nontreatment seeking and predominantly male, which may impact the generalizability of the results. More research is needed to determine the role oxytocin may play in the amelioration of stress-induced reactivity and craving in marijuana-dependent individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Outcome response to TSST for primary variables

Reported outcomes in response to the TSST for Oxytocin (n=8) and Placebo (n=8) treated subjects. Data are shown as group level means and associated standard errors adjusted for average marijuana use sessions prior to the study. * $p < 0.05$. BL= Baseline, TSST = Trier Social Stress Task, MCQ TS = Marijuana Craving Questionnaire Total Score, DHEA = Dehydroepiandrosterone. Responses are shown as adjusted means and associated 95% confidence intervals. Overall global group F Statistics for the primary outcome measures were MCQ Total Score ($F_{1, 72} = 3.67$; $p = 0.059$), DHEA ($F_{1, 66} = 2.97$; $p = 0.089$), Cortisol ($F_{1, 66} = 0.69$; $p = 0.408$), and Anxiety ($F_{1, 72} = 0.19$; $p = 0.661$).

Figure 2. MCQ Subscale response to TSST

MCQ subscales in response to the TSST for Oxytocin (n=8) and Placebo (n=8) treated subjects. Data are shown as group level means and associated standard errors adjusted for average marijuana use sessions prior to the study. * $p < 0.05$. BL= Baseline, TSST = Trier Social Stress Task.

Table 1

Demographic and baseline clinical characteristics of treatment groups.

Variable	Treatment Group		P Value
	Oxytocin n=8	Placebo n=8	
<i>Demographics</i>			
Age (yrs)	23.7 ± 6.3	22.9 ± 7.1	0.73
Male n (%)	7 (88%)	5 (63%)	0.36
Caucasian n (%)	6 (75%)	6 (75%)	1.00
Married n (%)	1 (13%)	0 (0%)	0.99
Some College n (%)	6 (75%)	6 (75%)	1.00
Smoke Cigarettes n (%)	6 (75%)	5 (63%)	0.36
<i>Clinical Characteristics</i>			
Cortisol nmol/L	7.3 ± 4.2	6.6 ± 2.8	0.76
DHEA nmol/L	0.95 ± 0.47	0.98 ± 0.46	0.88
Stress	2.3 ± 2.4	1.9 ± 3.4	0.36
Anxiety	2.4 ± 2.7	2.0 ± 2.5	0.83
<i>Marijuana Use Characteristics</i> *			
Times used per using day	2.6 ± 0.8	2.0 ± 0.2	0.06
% of days using	90.8 ± 11.5	87.6 ± 19.2	0.92
<i>Marijuana Craving Questionnaire</i>			
MCQ Total Score (possible range 12–84)	44.5 ± 11.4	46.9 ± 18.6	0.80
Compulsion Subscale (3–21)	5.3 ± 2.6	7.1 ± 6.3	0.87
Emotionality Subscale (3–21)	14.6 ± 3.5	13.8 ± 4.7	0.92
Expectancy Subscale (3–21)	9.0 ± 3.4	9.5 ± 5.7	0.68
Purposefulness Subscale (3–21)	15.6 ± 4.8	16.5 ± 5.8	0.72

Table values are shown as mean ± SD or n (%). Group differences between continuous and ordinal variables are assessed using a 2-sided Wilcoxon Rank Sum test statistic and categorical variables are assessed using a Fisher's Exact test statistic.

* Marijuana use characteristics are compiled over the 90 days prior to study admission.

Table 2

Outcome measure response by treatment group at time points of interest.

Outcome	Treatment Group		Group Difference	Effect Size [†]	P Value [*]
	Oxytocin n=8	Placebo n=8			
Post Study Drug Administration / Pre Stressor					
MCQ Total Score	37.7 (30.0, 45.4)	45.5 (37.8, 53.2)	7.8 (-0.2, 15.8)	0.95	0.061
Emotionality	7.4 (4.9, 9.9)	10.5 (8.0, 13.0)	3.1 (-0.6, 6.8)	0.82	0.105
Purposefulness	13.8 (11.7, 15.9)	16.3 (14.2, 18.4)	2.5 (-0.2, 5.3)	0.89	0.078
Compulsion	5.0 (3.7, 6.3)	6.0 (4.7, 7.3)	1.0 (-0.9, 3.0)	0.34	0.296
Expectancy	11.6 (9.8, 13.3)	12.7 (10.9, 14.5)	1.1 (-1.5, 3.8)	0.43	0.396
Ln DHEA (nmol / L)	-0.3 (-0.6, -0.1)	0.0 (-0.3, 0.2)	0.3 (0.0, 0.7)	0.92	0.072
Ln Cortisol (nmol / L)	1.5 (1.3, 1.7)	1.7 (1.4, 1.9)	0.2 (-0.2, 0.5)	0.54	0.278
Anxiety (Likert)	2.2 (0.8, 3.5)	2.6 (1.2, 3.9)	0.4 (-1.5, 2.4)	0.21	0.676
Stress (Likert)	1.5 (-0.7-3.7)	1.2 (-1.0-3.4)	-0.3 (-2.3-1.6)	0.17	0.737
Immediately Following Stressor					
MCQ Total Score	43.1 (33.2, 53.0)	57.5 (47.6, 67.4)	14.4 (2.6, 26.2)	1.20	0.020
Emotionality	8.9 (5.2, 12.6)	15.2 (11.5, 19.0)	6.3 (1.0, 11.7)	1.15	0.024
Purposefulness	15.7 (13.2, 18.2)	18.2 (15.7, 20.7)	2.5 (-0.9, 5.9)	0.71	0.158
Compulsion	6.2 (4.1, 8.3)	7.9 (5.8, 10.0)	1.7 (-1.4, 4.7)	0.54	0.286
Expectancy	12.3 (10.2, 14.4)	16.2 (14.1, 18.3)	3.9 (0.8, 7.0)	1.22	0.017
Ln DHEA (nmol / L)	-0.2 (-0.4, 0.1)	0.2 (0.0, 0.5)	0.4 (0.0, 0.8)	1.08	0.035
Ln Cortisol (nmol / L)	1.8 (1.5, 2.0)	2.1 (1.8, 2.3)	0.3 (-0.1, 0.7)	0.69	0.172
Anxiety (Likert)	3.3 (1.8, 4.7)	5.5 (4.0, 6.9)	2.2 (0.1, 4.3)	1.02	0.046
Stress (Likert)	3.0 (0.8-5.2)	3.7 (1.5-5.9)	0.7 (-1.3-2.6)	0.34	0.506
5 Minutes Following Stressor					
MCQ Total Score	41.1 (32.4, 49.8)	53.4 (44.7, 62.1)	12.3 (2.5, 22.1)	1.23	0.017
Emotionality	7.4 (3.7, 11.1)	12.4 (8.7, 16.0)	5.0 (-0.3, 10.3)	0.92	0.071
Purposefulness	15.4 (12.9, 17.9)	17.7 (15.2, 20.2)	2.3 (-1.2, 5.7)	0.65	0.199

Outcome	Treatment Group			Group Difference	Effect Size [†]	P Value [*]
	Oxytocin n=8	Placebo n=8				
Compulsion	6.0 (4.0, 7.9)	7.6 (5.7, 9.6)		1.7 (-1.1, 4.5)	0.58	0.248
Expectancy	12.3 (10.6, 14.0)	15.7 (14.0, 17.4)		3.4 (0.9, 5.9)	1.53	0.009
Ln DHEA (nmol / L)	-0.3 (-0.5, 0.0)	0.1 (-0.2, 0.3)		0.3 (0.0, 0.7)	0.95	0.063
Ln Cortisol (nmol / L)	1.8 (1.5, 2.2)	2.1 (1.7, 2.4)		0.2 (-0.3, 0.7)	0.40	0.428
Anxiety (Likert)	3.0 (1.7, 4.4)	3.7 (2.4, 5.0)		0.7 (-1.3, 2.6)	0.34	0.500
Stress (Likert)	2.4 (0.2-4.6)	3.0 (0.8-5.2)		0.54 (-1.4-2.5)	0.28	0.589

Results are shown adjusted for both baseline outcome measures as well as daily marijuana use frequency with associated 95% confidence intervals.

[†] Effect size listed is defined as Cohen's d (|group difference| / Pooled SD of group difference).

^{*} P value listed is testing H₀: |group difference| = 0 vs. H_a: |group difference| > 0 at α=0.05.