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Effect of oxytocin pretreatment on cannabis outcomes in a brief motivational intervention

Brian J. Sherman^{a,*}, Nathaniel L. Baker^b, and Aimee L. McRae-Clark^a

^aDepartment of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, 29425, USA

^bDepartment of Public Health Sciences, Medical University of South Carolina, Charleston, SC 29425, USA

Abstract

Motivational enhancement therapy (MET) is efficacious in reducing cannabis use, yet benefits are generally short-lived. Oxytocin is a hypothalamic neuropeptide that promotes prosocial behaviors and plays a role in drug-related neuroadaptations; as such, oxytocin may enhance the effect of MET on cannabis outcomes. Cannabis dependent adults were randomized to receive MET plus oxytocin (n = 8) or placebo (n = 8). Participants receiving oxytocin showed reductions in amount of cannabis used daily and number of sessions per day. Participants receiving placebo did not evidence significant reductions. Powered clinical trials of oxytocin-enhanced MET for cannabis use disorder are warranted.

Keywords

oxytocin; cannabis; treatment

1. Introduction

According to the most recent national treatment data, almost one million people received treatment for cannabis use disorder (CUD) in 2013 (SAMHSA, 2014). Despite the high demand for treatment, abstinence rates remain modest and durability is limited (Sherman and McRae-Clark, 2016). There is a clear need for novel interventions to improve treatment outcomes.

*Corresponding author: Brian J. Sherman, 125 Doughty Street, Suite 190, Charleston, SC 29403, shermanb@musc.edu.

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Contributors

Author ALM designed the study, wrote the protocol, interpreted results, and assisted in manuscript preparation. Author BJS interpreted results and wrote the first draft of the manuscript. Author NLB conducted statistical analysis. All authors have approved the final manuscript.

Conflict of Interest

All authors declare they have no conflict of interest.

Oxytocin is a hypothalamic neuropeptide that plays a critical role in complex social cognition and behavior. Oxytocin promotes various prosocial behaviors including approach, pair bonding, empathy, and trust (Meyer-Lindenberg et al., 2011). Oxytocin also plays a role in neuroadaptations resulting from chronic drug abuse (Lee et al., 2016), and has been shown to attenuate the development of opioid tolerance, and inhibit cocaine- and methamphetamine-induced drug-seeking behaviors, reward, and reinstatement in rodents (see Sarnyai and Kovacs, 2014, for review). With respect to cannabis, oxytocin is associated with reduced craving in humans (McRae-Clark et al., 2013) and endocannabinoid signaling appears to mediate oxytocin social reward (Wei et al., 2015). As such, oxytocin is an ideal candidate to enhance psychosocial treatments for CUD, particularly those grounded in empathy and collaboration.

Motivational Enhancement Therapy (MET) is a client-centered therapeutic style that involves expressing empathy, developing discrepancy, rolling with resistance, and supporting self-efficacy (Miller and Rollnick, 2013). MET has shown efficacy in reducing cannabis use (MTPRG, 2004), yet there is considerable room for improvement (Sherman and McRae-Clark, 2016). The current pilot study investigated whether oxytocin would enhance the efficacy of MET for cannabis dependence.

2. Methods and Materials

2.1 Participants

Sixteen cannabis-dependent adults participated in this pilot study. All study procedures were approved by the Medical University of South Carolina Institutional Review Board. Individuals were excluded due to past or current major psychiatric or medical conditions, other substance dependence (except nicotine) in the past 60 days, and psychiatric medication (except stimulants for ADHD, which were allowed to account for comorbidity of ADHD and cannabis). Women who were pregnant, nursing, or of child-bearing potential and not practicing effective means of birth control were also excluded.

2.2 Procedures

Participants were randomized to receive either MET plus oxytocin ($n = 8$) or MET plus placebo ($n = 8$). Oxytocin (40 IUs) or placebo was administered intranasally 30 minutes prior to the first 2 of 3 MET sessions over the 4 week study period. The MET intervention consisted of three 45–60 minute sessions at study weeks 1, 2, and 4 and included an initial personalized feedback report followed by discussion of problems related to use, reasons for quitting, challenges to behavior change, and goal setting. Subjects who presented for a study visit intoxicated or with recent substance use within past 24 hours were rescheduled.

2.2.1 Assessments—Psychiatric and substance use diagnoses were assessed using the Mini-International Psychiatric Interview (M.I.N.I., Sheehan et al., 1998) and Structured Clinical Interview for DSM-IV (SCID; First et al., 1996), respectively. Past 90 days substance use and cannabis use during the study period were assessed using the Timeline Follow-Back (TLFB; Sobell and Sobell, 1992). Cannabis use was assessed with the TLFB at

baseline and again at each study visit. Urine and saliva drug screens, and alcohol breathalyzer were used to confirm recent abstinence from all substances at each study visit.

2.2.2 Data Analytic Plan—Standard descriptive statistics were used to summarize baseline demographic and clinical data. A Wilcoxon Rank sum test was used to evaluate continuous measures between treatment groups while the Fisher's exact test was used to assess the relationship for categorical and ordinal variables. A multilevel model for repeated measures was used to examine the hypothesis that oxytocin would attenuate cannabis use compared to placebo. This methodology allows for an estimation of variance associated with a random intercept for each subject and can accommodate partially missing data (Brown and Prescott, 1999). Initial models were developed using the main effects of randomized treatment assignment and session, the interaction between the two, and screening levels of use. Results are reported as model based means and associated standard errors, and global standardized effect sizes are noted as Cohen's d values (Nakagawa and Cuthill, 2007) for the main treatment effects. All analysis was conducted using SAS v. 9.4 (SAS Institute, Cary NC, USA).

3. Results

Participants were $M[SD]/25.5 [7.6]$ years of age, 62.5% male, 56.3% Caucasian, and 62.5% had at least some college education. Experimental groups did not differ on these demographic variables or any baseline cannabis use characteristics. Although stimulant use was allowed, no study participants were using them. One participant was excluded from outcome analysis due to concerns regarding data integrity.

There was no significant overall treatment effect of oxytocin on mean daily cannabis use amounts between sessions as reported on the TLFB ($M = 0.55$, $SEM = 0.65$, $p = 0.412$, $d = 0.49$); however, there was a significant decrease in use during the active treatment study period (Session 1 to Session 3: $M = -1.24$, $SEM = 0.40$, $p = 0.006$). Participants who received oxytocin showed a statistically significant reduction in the amount of cannabis used daily ($M = -1.45$, $SEM = 0.58$, $p = 0.022$) while participants in the placebo condition did not evidence significant reductions ($M = -1.03$, $SEM = 0.54$, $p = 0.075$), though the differential group effect was insignificant (Group $\times$ Time interaction: $p = 0.785$). In addition to daily cannabis use amounts, distinct daily cannabis use sessions were reported on the TLFB. Similar to the amount of daily use, there was no significant main effect of treatment assignment ($M = 0.61$, $SEM = 0.39$, $p = 0.139$, $d = 0.92$) and the number of daily use sessions declined over time during the study (Session 1 to Session 3: $M = -0.84$, $SEM = 0.25$, $p = 0.003$). Interestingly, there was some indication that this decline may be differential between the oxytocin ($M = -1.43$, $SEM = 0.34$, $p < 0.001$) and placebo ($M = -0.26$, $SEM = 0.37$, $p = 0.482$) treated groups (Group $\times$ Time interaction: $p = 0.091$). At MET session 1, participants in the oxytocin group reported a greater number of use sessions per day as compared to those in the placebo group (Figure 1; $M = 1.21$, $SEM = 0.45$, $p = 0.015$).

4. Discussion

Though preliminary, oxytocin appears to enhance the effect of MET on cannabis outcomes. One possible explanation involves the role of oxytocin in promoting pro-social behavior. Given that oxytocin promotes trust (Kosfeld, et al., 2005), personal information sharing (Mikolajczak, et al., 2010), and openness (Cardoso et al., 2012) it may help deepen the therapeutic relationship and promote dialogue. Second, oxytocin has been localized in reward-related brain regions implicated in addiction suggesting a shared neurobiology between prosocial behavior and addictive processes. Chronic drug use results in blunted oxytocin expression, specifically in the nucleus accumbens (NAc) and ventral tegmental area (VTA) among rodents exposed to delta-9-THC (Butovsky et al., 2006), theoretically short-circuiting rewarding prosocial behaviors associated with healthy oxytocin expression. Exogenous oxytocin administration may provide an “exit strategy” from compulsive drug taking and allow refocus towards naturally rewarding social interaction (McGregor and Bowen, 2012). Lastly, oxytocin demonstrates anxiolytic properties including attenuation of hypothalamic-pituitary-adrenal (HPA) axis activation, subjective stress, and anticipatory anxiety in laboratory stress tasks (de Oliveira et al., 2012; Heinrichs et al., 2003). Given the significant comorbidity of anxiety disorders and CUD (Hasin et al., 2016), oxytocin-induced anxiety reduction may also facilitate reductions in cannabis use.

Despite its strengths (study design, innovation), study limitations are worth noting. Specifically, as a pilot study the sample size is small and results should be interpreted with caution. As the overall model time×treatment interaction effects were non-significant, independent models showing reductions in daily use and sessions do not necessarily suggest the two groups responded differently. Replication is needed. Second, individuals with other substance dependence were excluded so generalizability is limited to cannabis-dependent adults. Third, cannabis use was assessed using self-report, which introduces the possibility of recall bias. In addition, since oxytocin plays a critical role in social bonding, under-reporting of cannabis use in the service of maintaining rapport, is possible. However, a recent study demonstrated improved accuracy among methadone-maintained cocaine-dependent subjects receiving oxytocin (Stauffer et al., 2016). Finally, we only tested the effect of administering oxytocin at two time points. In this initial pilot study we chose this design as we were interested in reduction in use from week 1 to week 4. Future studies should consider dosing schedules and frequency of oxytocin administration. Given the study findings, powered clinical trials of MET plus oxytocin for cannabis use disorder are warranted.

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Highlights

- Novel and effective treatments for cannabis use disorder (CUD) are needed
- Oxytocin promotes prosocial behavior and may attenuate cannabis craving
- A pilot study examined the effect of oxytocin on cannabis outcomes
- Oxytocin enhanced cannabis outcomes compared to placebo in an MET intervention

Figure 1. Amount of cannabis used per day (grams) and number of sessions per day over three MET sessions between placebo (n = 7) and oxytocin (n = 8) conditions. Data are shown as model based means and associated standard errors. * p<0.05.