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Augmenting Prolonged Exposure therapy for PTSD with intranasal oxytocin: A randomized, placebo-controlled pilot trial

Julianne C. Flanagan[a,*], Lauren M. Sippel[b,c], Amy Wahlquist[d], Megan M. Moran-Santa Maria[a], Sudie E. Back[a,e]

[a] Department of Psychiatry & Behavioral Sciences, Medical University of South Carolina, 67 President St., Charleston, SC 29425, USA
[b] National Center for Posttraumatic Stress Disorder, Veterans Affairs Medical Center (116D), 215 North Main Street, White River Junction, VT 05009, USA
[c] Geisel School of Medicine at Dartmouth, Department of Psychiatry, 1 Rope Ferry Road, Hanover, NH 03755, USA
[d] Department of Public Health Sciences, Medical University of South Carolina, 135 Cannon St., Charleston, SC 29425, USA
[e] Ralph H. Johnson Veterans Affairs Medical Center, 109 Bee St., Charleston, SC 29401, USA

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a chronic, debilitating condition for which Prolonged Exposure (PE) therapy is highly efficacious. However, for some individuals, premature dropout and residual PTSD symptoms remain obstacles. The neuropeptide oxytocin is a promising candidate to enhance PE due to its ability to enhance 1) prosocial cognition and behavior, which are theorized to promote positive working alliance, and 2) extinction learning, which is the central mechanism of action underlying successful PE treatment. Despite a robust theoretical rationale, no studies to date have combined evidence-based psychotherapy for PTSD with oxytocin. This randomized, placebo-controlled, double-blind pilot trial examined the feasibility, safety, and preliminary efficacy of augmenting PE with oxytocin. Participants were 17 individuals with diverse index traumas. Participants self-administered intranasal oxytocin (40 IU) or matching placebo 45 min prior to each weekly PE therapy session. One adverse event occurred in the placebo group and three individuals dropped out (17.6%; 2 oxytocin group and 1 placebo group). The oxytocin group demonstrated lower PTSD and depression symptoms during PE, and had higher working alliance scores, although these differences did not reach statistical significance. Although preliminary, the findings support the feasibility of oxytocin combined with PE. Adequately powered studies are necessary to determine whether oxytocin enhances PE treatment outcomes and to examine potential mechanisms, such as accelerating extinction learning, enhancing early response, and preventing premature dropout. NCT03238924.

1. Introduction

Posttraumatic stress disorder (PTSD) is a chronic, prevalent, and debilitating disorder (Kessler et al., 2012). If left untreated, individuals with PTSD incur risk for other psychiatric problems (e.g., depression, substance use disorder), neuropsychological impairment, suicidality, physical health problems and increased mortality, reduced resiliency, unemployment, and family/couples impairment (Marx et al., 2009; Monson et al., 2009; Pietrzak et al., 2009, 2011).

Prolonged Exposure (PE; Foa et al., 2007) is a manualized, cognitive-behavioral therapy that is considered a "gold standard" treatment for PTSD (Institute of Medicine, 2008; The Management of Posttraumatic Stress Disorder Work Group, 2017). PE consistently outperforms control and waitlist conditions in randomized controlled trials (Powers et al., 2010; Resick et al., 2002) and typically demonstrates robust improvement of 1–2 standard deviations in symptom severity (Eftekhari et al., 2013; Foa et al., 2005; Powers et al., 2010). However, there is a critical need to improve retention and substantial room to improve outcomes in PE. Dropout rates are approximately 30% across populations and treatment settings (Bradley et al., 2005; Eftekhari et al., 2013; Hembree et al., 2003) and a substantial proportion of patients maintain clinically significant residual symptoms and/or continue to meet diagnostic criteria for PTSD following PE (Bradley et al., 2005; Goodson et al., 2013).

As proposed by Olff et al. (2010), the neuropeptide oxytocin is a promising candidate for improving retention and outcomes in PE for two reasons. First, oxytocin may enhance retention by reducing excessive distress and facilitating therapeutic alliance. Many patients struggle with distress and avoidance during treatment, and fail to receive an adequate dose of PE (Foa et al., 2005; Tuerk, 2014). The

* Corresponding author. Medical University of South Carolina, 67 President St., MSC 861, Charleston, SC 29425, USA.
E-mail address: Hellmuth@musc.edu (J.C. Flanagan).

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capacity to establish and navigate an effective working alliance is essential to maximize the benefits of behavioral intervention (Horvath and Luborsky, 1993), and particularly integral to the success of PE (Cloitre et al., 2004; McLaughlin et al., 2014). Extensive data indicate that oxytocin exerts prosocial properties such as enhancing affiliative behavior, trust, and warmth (Bartz and Hollander, 2006; MacDonald and MacDonald, 2010). Interpersonal challenges and impaired relational functioning are deficits among individuals with PTSD (Beck et al., 2009). One small laboratory study among participants with PTSD found that a single dose of oxytocin had positive effects on anxiety, irritability, mood, intensity of intrusive thoughts, and desire for social interaction (Yatzkar and Klein, 2010).

The development of PTSD is often conceptualized as a function of Pavlovian fear conditioning (Rauch et al., 2006), while effective fear extinction is the foundation of PE treatment (Foa and Kozak, 1986; Rothbaum and Davis, 2003; Smith et al., 2017). Oxytocin has demonstrated the ability to enhance fear extinction in preclinical models (Eskandarian et al., 2013) and among healthy individuals (Acheson et al., 2013; Eckstein et al., 2014). These findings suggest that oxytocin has potential as an adjunctive therapy for extinction-based PTSD treatments such as PE (Koch et al., 2014; Olff et al., 2010).

Some medications have been examined for the specific purpose of enhancing exposure-based treatments (de Kleine et al., 2013; Tuerk, 2014; Zoellner et al., 2017). For example, preliminary studies investigating medications such as yohimbine and d-cycloserine to enhance treatment efficiency have shown some promise (Litz et al., 2012; Wangelin et al., 2013). While these medications are similar to oxytocin in that they also have a short half-life and are administered prior to therapy sessions, both yohimbine and d-cycloserine are stimulating medications designed to increase within-session arousal. No medications to date have demonstrated the ability to improve patient tolerability or retention in psychotherapy for PTSD (Hetrick et al., 2010; Litz et al., 2012; Wangelin et al., 2013; Zoellner et al., 2017). Prevailing hypotheses suggest that oxytocin may uniquely help mitigate barriers to engaging in behavioral treatments that specifically target avoidance (Preckel et al., 2014), which would thereby allow patients who might otherwise be unable to tolerate PE to engage effectively, complete the treatment, obtain an adequate therapeutic dose, and experience long-term remission of PTSD (Frijling et al., 2014; Koch et al., 2014; Olff et al., 2010).

While both preclinical and clinical oxytocin studies have expanded tremendously in recent years, several critical gaps in the literature remain with regard to translating oxytocin into a meaningful therapeutic application for PTSD treatment. First, no previous studies pairing oxytocin with a behavioral intervention have taken place among PTSD populations, and studies in related clinical populations have not utilized more than a single intervention session. For example, two small preliminary studies augmented a single-session exposure therapy for social anxiety (N = 25) and arachnophobia (N = 44) with only one low dose (24 IU) of oxytocin with null findings (Acheson et al., 2015; Guastella et al., 2009). One previous study paired a dose of oxytocin with a single 20-minute therapy session among men with depression with mixed findings (MacDonald et al., 2013). No studies to date have paired oxytocin with a manualized, evidence-supported behavioral therapy to treat PTSD.

Second, only two previous studies have examined oxytocin in the context of PTSD. One study found that a single dose of oxytocin was not effective in reducing physiological reactivity during one-session exposure therapy for PTSD (Pitman et al., 1993). A more recent study by van Zuiden and colleagues (van Zuiden et al., 2016) targeting the prevention of PTSD found that twice daily doses of 40 IU oxytocin for 8 days did not significantly attenuate the onset on PTSD compared to placebo among emergency department patients. However, oxytocin was more effective among individuals who had more severe baseline PTSD severity in this sample.

Finally, while some studies among patients with other psychiatric disorders (e.g., autism, alcohol use disorder) have utilized a repeated dosing strategy in the form of 1–3 daily doses, most of these studies are only 8 days or less (Dadds et al., 2014; Guastella et al., 2015; Pedersen et al., 2011). While the overall safety of single doses of intranasal oxytocin are well established (MacDonald et al., 2011), the feasibility, safety and efficacy of repeated dosing at weekly intervals is less clear.

This pilot study addressed these gaps in the literature by examining the synergistic effects of combining oxytocin with PE using a randomized, placebo-controlled, double-blind design. We hypothesized that individuals randomized to the oxytocin condition would demonstrate significantly greater improvement in PTSD symptom severity during treatment. Because depression commonly co-occurs with PTSD, and is typically identified as an important outcome in clinical trials treating these disorders (see Stander et al., 2014; for review), we also examined depression symptom severity as a treatment outcome. In order to assess feasibility, we compared client satisfaction and working alliance among individuals in the oxytocin versus placebo conditions.

2. Material and methods

2.1. Participants

Of 36 respondents evaluated, 9 were ineligible and 10 declined participation. Reasons for declining participation included being unable to commit to weekly therapy sessions (n = 3), already engaged in another therapy that they did not want to discontinue (n = 4), not wanting to discuss their trauma (n = 1), and being uncomfortable taking a medication (n = 2). Seventeen individuals enrolled in the study and were randomized in a 1:1 manner to receive oxytocin (OT; n = 8) or placebo (n = 9) conditions as well as 10 individual, manualized PE therapy sessions. Three participants dropped out during treatment (at sessions 3, 4, and 6), and one participant was withdrawn after the first PE session and referred to more intensive clinical services. The remaining 13 participants (OT = 6) completed all 10 PE sessions. Participants were 82.4% male (n = 14) and 58.8% (n = 10) were military veterans, among whom 38.5% (n = 5) had served in the Iraq or Afghanistan conflicts. An equal number of participants were White or African American (n = 6; 35.3%, respectively), and Native American or Pacific Islander (5.9%; n = 1, respectively), while 17.6% (n = 3) identified as more than one race. Most participants were single/never married (n = 10; 58.8%) and were either unemployed (n = 6; 35.3%) or part/full-time employed (n = 8; 47.1%). Eight participants reported an index trauma related to combat exposure (47.1%), 23.5% (n = 4) reported sexual assault, and the remaining five participants endorsed transportation accidents, assault, witnessing sudden violent death, and service as a first responder in the World Trade Center attacks on September 11, 2001. All participants had achieved a minimum of 12 years of education. There were no significant differences in demographic or baseline clinical characteristics between groups (see Table 1).

2.2. Measures

Psychiatric diagnoses were assessed for inclusion/exclusion using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). DSM-5 PTSD diagnosis was assessed using the Clinician Administered PTSD Scale for DSM-5 (Weathers et al., 2013). The CAPS-5 was administered at baseline, session 5 and session 10 by trained evaluators blind to treatment condition. Weekly self-reported PTSD and depression symptoms were assessed with the PTSD Checklist for DSM-5 (PCL-5; Weathers, 2013) and Beck Depression Inventory, 2nd edition (BDI-II; Beck et al., 1996). The Helping Alliance Questionnaire (HAQ-II; Luborsky et al., 1996) and Client Satisfaction Questionnaire (CSQ; Nguyen et al., 1983) were administered at sessions 5 and 10 to assess feasibility and acceptability. Safety was assessed by monitoring adverse events (AEs) each week.