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Augmenting Treatment for Posttraumatic Stress Disorder and Co-Occurring Conditions with Oxytocin

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Abstract

Purpose of review: The goal of this manuscript is to review the extant literature examining the neurobiological and behavioral mechanisms underlying the potential utility of intranasal oxytocin as a novel pharmacologic intervention for the treatment of posttraumatic stress disorder (PTSD), and for the treatment of co-morbid PTSD and alcohol and substance use disorders.

Recent findings: Research indicates that intranasal oxytocin is a low-cost and easily accessible medication with an excellent safety profile. Oxytocin holds promise for facilitating more effective PTSD treatment, particularly when used in combination with evidence-supported psychotherapy interventions. There is still a significant need to identify the mechanisms of action underlying oxytocin treatment of PTSD, and to maximize methods of nasal spray delivery, examine dose-response outcomes, and clarify the characteristics of individuals and populations that are most likely to benefit from adjunctive oxytocin treatment.

Summary: Collectively, preclinical and human laboratory research suggest that oxytocin may be an effective mechanism by which treatment outcomes for PTSD and common comorbidities can be enhanced. Adequately powered randomized controlled trials are needed to address efficacy, identify predictors of treatment outcome, and to assess the use of intranasal oxytocin within appropriate PTSD populations.

Keywords

oxytocin; posttraumatic stress; comorbidity; treatment; medication-enhanced psychotherapy

Introduction

Posttraumatic Stress Disorder (PTSD) is a widespread, chronic, and debilitating psychiatric condition. Approximately 8% of individuals in the general population will experience PTSD

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during their lifetime, although the prevalence is nearly four times greater among high-risk populations such as military veterans (1, 2). If left untreated, individuals with PTSD are at risk for developing other psychiatric problems (e.g., depression, substance use disorders), neuropsychological impairment, suicidality, physical health problems, and family/occupational impairment. Substance use disorders (SUD) are among the most common and deleterious of PTSD comorbidities, with nearly 40% of individuals meeting diagnostic criteria for both disorders concurrently (3, 4). The high rates of disability, healthcare utilization, and co-occurring medical and mental health problems associated with PTSD and its negative sequelae result in a tremendous economic burden for our nation (5).

Novel behavioral, pharmacological, and combined strategies to more effectively treat PTSD are currently being investigated. Although several promising psychosocial interventions have been developed, there is still substantial room for improvement. For example, approximately one third of patients drop out of behavioral PTSD treatment prematurely (6–8). Furthermore, a significant proportion of patients experience unresolved PTSD symptoms following treatment completion (8–11). Data also suggest that useful pharmacologic treatments are markedly lacking (12). Consequently, there is a critical need to develop effective pharmacologic strategies to enhance treatment outcomes for individuals with PTSD.

One promising candidate in the myriad of potential therapeutics is the neuropeptide oxytocin (13). Preliminary data indicate that central and systemic oxytocin administration exerts anxiolytic and anti-stress properties in animal models (14, 15), and oxytocin has anxiolytic and prosocial effects in humans, including increased trust and improved social cue recognition (16). In addition, oxytocin enhances fear extinction memory in healthy individuals (17), suggesting that oxytocin has potential as an adjunct therapy for behavioral PTSD treatments (18). The goal of the current review is to describe the existing research examining the translational potential of oxytocin in the treatment of PTSD and commonly co-occurring conditions such as SUD. Since previous reviews have focused on the neurobiological and behavioral mechanisms linking oxytocin with PTSD onset and maintenance (13, 18), here we will 1) provide a brief overview of the current state of the science regarding existing pharmacologic and behavioral treatment approaches, 2) describe the pharmacologic properties of oxytocin, 3) outline the growing literature supporting the translation of oxytocin as a treatment for PTSD, and 4) examine the current limitations of the science in this area in order to inform future directions.

Existing Treatments for PTSD

Several articles have comprehensively reviewed behavioral treatment approaches for PTSD and have identified four evidence-based psychotherapies with sufficient empirical evidence to be deemed effective (19, 20). These treatments include Prolonged Exposure Therapy, Cognitive Processing Therapy (21), and Eye Movement Desensitization Reprocessing (22). Prolonged Exposure and Cognitive Processing Therapies have the greatest number of randomized controlled trials supporting their efficacy (19).

While many pharmacologic treatment approaches have been investigated, only selective serotonin reuptake inhibitors (SSRIs) have received FDA approval for treatment of PTSD. However, only 20–30% of patients experience PTSD remission with SSRI treatment (23–

25). SSRIs have also not demonstrated improved patient tolerability or retention in psychotherapy, and results are mixed regarding whether augmenting behavioral treatments with SSRIs is superior to behavioral intervention alone (26, 27). Another potential medication for the treatment of PTSD is the alpha-1 adrenergic antagonist prazosin. Despite null findings in the largest RCT to date examining prazosin (N = 304)(28), several smaller randomized controlled trials demonstrate safety, tolerability and efficacy of prazosin to reduce PTSD nightmares, associated sleep impairment, and overall symptom severity (29–32).

The existing literature indicates that behavioral and pharmacologic treatment approaches have differing strengths and limitations. While behavioral treatment incurs greater risk for early dropout, treatment gains are more likely to be sustained following behavioral intervention compared to pharmacologic treatment (19). Therefore, it is possible that a combined behavioral and pharmacologic treatment approach would maximize therapeutic outcome and that medication-enhanced psychotherapy could address some of the challenges to stand alone behavioral treatments, such as retention, tolerance, and engagement (12, 13, 33). Current clinical practice guidelines regarding best practices for treatment of PTSD disseminated by both the Department of Veterans Affairs and the Department of Defense suggest that more information is required to examine the utility of augmenting behavioral treatment with pharmacological approaches (20).

Recent efforts to combine behavioral and pharmacologic treatment approaches have met with mixed results. One large multi-site randomized controlled trial (N=207) compared the efficacy of the SSRI sertraline against either PE therapy alone or in combination with sertraline and found comparable efficacy between the three groups when evaluating both clinician assessments and self-report measures of symptom severity (27). One small randomized controlled trial among veterans (N=27) found that combining virtual reality exposure sessions with dexamethasone did not afford additional treatment benefit. Instead, drug treatment was associated with a higher rate of dropout compared to the placebo group (34). In contrast, some studies have found success in combining glucocorticoids with exposure therapy for PTSD (35, 36). For example, one pilot project among veterans (N= 24) showed that combined hydrocortisone with Prolonged Exposure Therapy resulted in greater treatment completion rates and PTSD symptom reduction in the experimental drug condition (37). Preliminary investigations of oxytocin, 4-methylenedioxymethamphetamine (MDMA), yohimbine, and d-cycloserine to enhance PTSD treatment have all also shown some promise when using both self-report and clinician-administered measures (38–43).

Pharmacologic Properties of Oxytocin

Oxytocin is a hypothalamic nonanuropeptide that initiates physiologic events necessary for parturition and lactation. Intravenous administration is FDA-approved for initiation and facilitation of uterine contractions during childbirth, emptying of the uterus, and management of postpartum bleeding or hemorrhage. In the field of psychiatry, oxytocin is most commonly self-administered intranasally. Intranasal oxytocin has a half-life of approximately 2–4 hours and takes between 30–45 minutes to reach peak concentration levels. Dysregulation of the oxytocin system, which includes functional impairments in the

hypothalamic-pituitary-adrenal (HPA) axis and corticolimbic brain regions such as the prefrontal cortex (PFC) and amygdala (AMY), are well-established biomarkers of PTSD pathophysiology and maintenance. Individuals with PTSD exhibit lower basal oxytocin levels as compared to healthy controls (44), although one recent study found that endogenous oxytocin levels did not predict PTSD development over combat exposure (45). Moreover, variants in the oxytocin receptor gene have been linked to the brain's responsiveness to stress. For example, recent findings from the National Health and Resilience in Veterans Study found that one polymorphism in the oxytocin receptor gene (rs53576), in combination with attachment style, contributed to risk for PTSD among veterans (46). Outstanding questions regarding dose-response still remain and significant effort is necessary to establish standardized dose and timing strategies that presently differ across clinical settings and populations (47). Related research seeking to improve the method by which intranasal oxytocin is delivered is currently also a topic of increasing inquiry (48, 49).

Modifiers of Oxytocin Response

A growing literature suggests that individual and contextual factors such as sex, social circumstances, and psychiatric history influence the behavioral and neurobiological effects of oxytocin (50–53). The social salience hypothesis posits that, rather than universally enhancing prosocial cognition and behavior, oxytocin might enhance an individual's preexisting social tendencies, which, depending on widely varying psychosocial and psychiatric predispositions, may or may not be adaptive (54). Further studies are necessary to parse apart the circumstances under which oxytocin administration is more or less psychologically or behaviorally beneficial.

Contraindications

Intranasal oxytocin has an excellent safety profile, having been used clinically for over 50 years (55). Due to its established effects on the reproductive system and lactation, oxytocin is currently contraindicated for psychiatric indications among women who are pregnant or breastfeeding. A separate literature has found that oxytocin might play a role in the proliferation of cancer cells (56, 57), suggesting that it should not be used among individuals with a history of, or current, cancer diagnosis.

Human Laboratory Studies

The majority of clinical oxytocin research supporting its translation to treatment has focused on human laboratory and neuroimaging research. Current perspectives on the effects of oxytocin support its role in enhancing adaptive social behavior and cognition (16). Individuals with some psychiatric diagnoses (such as anxiety or PTSD) have lower basal oxytocin levels than healthy controls (44, 58) and variants in the oxytocin receptor gene have been linked to stress responsivity (59). Some studies have found preliminary support for the ability of oxytocin to mitigate fear reactivity (14, 60), startle, and threat response (61, 62). One study also found that oxytocin enhanced fear extinction recall in healthy individuals (17), in keeping with the mechanism of action underlying behavioral PTSD treatments such as PE. Notably, the prosocial behaviors associated with oxytocin treatment are also known to facilitate successful psychosocial treatment outcomes (63, 64).

Randomized Controlled Treatment Studies

Despite the robust theoretical support for enhancing behavioral PTSD treatment with oxytocin (13, 18), only two randomized placebo-controlled trials have directly examined the effects of oxytocin in the prevention or treatment of PTSD (65) (43). Previous research has hypothesized that prosocial and anxiolytic medications such as oxytocin might potentiate sensitivity to adaptive social cues and attenuate threat detection. Additionally, it has been suggested that oxytocin might facilitate the therapeutic alliance and mitigate fear reactivity, thereby enhancing efficacy of other evidence-based treatments for PTSD (13, 18, 66–68). One study by van Zuiden and colleagues (65) found that in a sample of trauma-exposed emergency room patients, oxytocin treatment (40 IU twice daily for 8 consecutive days) was no more effective than placebo in preventing PTSD (as measured by the Clinician Administered PTSD Scale for DSM-5; CAPS). However, intriguingly, participants that already exhibited PTSD symptoms at baseline (again as measured by the CAPS) reported lower symptom severity throughout the study compared to those in the placebo condition, suggesting that there was some efficacy of oxytocin treatment on existing PTSD but not on development of new PTSD. In a randomized, double blind, placebo controlled pilot study, Flanagan and colleagues (43) found that when 40 IU oxytocin versus placebo was administered prior to 10 Prolonged Exposure therapy sessions, no differences emerged between groups at end of treatment on either self-reported or clinician-administered scales. However, modest differences emerged in self-reported PTSD symptoms at PE session 3, when imaginal exposures begin and dropout is most likely to occur (55, 56, 57)

Oxytocin Treatment of Co-Occurring PTSD and Substance Use Disorders

PTSD is highly co-morbid with SUD across multiple populations (3, 69, 70). Effective treatments for this complex dual diagnosis are scant and, as a result, individuals with co-occurring PTSD and SUD experience less favorable treatment outcomes than individuals with either disorder alone (71–75). Evidence demonstrating efficacy of several integrated psychosocial interventions to treat PTSD and co-occurring SUD has grown in recent years (76–78). However, while PTSD and SUD share common behavioral and neurobiological underpinnings, such as exacerbated negative emotional reactivity, dysregulation of the HPA-axis, and disrupted functioning in corticolimbic brain regions (79), effective pharmacological treatments to specifically address this dual diagnosis remain rare.

Several therapeutic agents have been investigated for comorbid PTSD and SUD with mixed results. For example, trials examining noradrenergic reuptake inhibitors (NRIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) have typically shown mixed or modest effects (80, 81). However, one study that compared Seeking Safety Therapy (SS) with sertraline versus placebo within a predominately female population showed a significantly greater decrease in PTSD symptoms following sertraline (82), perhaps underscoring the need to consider sex differences in assessing potential treatment effects. The α_1 adrenergic agonist prazosin, which is currently FDA approved for use as a hypertensive agent, has also demonstrated limited benefit in comorbid populations (30, 83), and a similar longer-acting medication (doxazosin), is currently being examined (84). Additional medications that have shown

promise include the supplement N-acetylcysteine (NAC) and the anticonvulsant topiramate (85–89).

In addition to the aforementioned literature on oxytocin for treatment of PTSD, there is an extensive literature that shows oxytocin reduces withdrawal symptoms, craving, and self-administration among individuals with dependence on drugs such as marijuana and stimulants (90, 91), as well as literature suggesting oxytocin significantly reduces alcohol withdrawal symptoms among treatment-seeking patients (92). Related research suggests that oxytocin may reduce the effects of social stress on alcohol craving and consumption (52, 93) and reduces alcohol self-administration and reinstatement of alcohol seeking (94, 95). (84)Because oxytocin is one of few medications that show promise in addressing the shared neurobiological and psychosocial underpinnings of co-occurring PTSD and SUD, additional studies into the therapeutic value of oxytocin for this deleterious dual diagnosis are imperative.

Discussion

Preclinical and human laboratory models demonstrate that intranasal oxytocin has the ability to simultaneously target the neurobiological and psychosocial underpinnings of PTSD (13, 18, 65, 96, 97). These findings suggest that oxytocin holds promise in the treatment of PTSD, particularly when used to augment evidence-based behavioral interventions.

Despite growing inquiry into PTSD, several critical methodological limitations remain. Perhaps the most significant of these is the growth of clinical research studies employing small sample sizes and exploratory data analyses. The literature is also limited by the extensive use of single-dose cross-sectional designs, and could be improved by increased use of within-subjects crossover designs and longitudinal treatment approaches (98). These limitations, in conjunction with heterogeneous assessment and outcome measures, have led to extensive challenges with replicability. As a result, adequately powered randomized controlled trials are essential, along with coordinated research efforts across multiple study sites to adequately evaluate both efficacy and potential moderating factors that influence treatment outcomes (99, 100).

Another critical step in the translational process is to establish standardized dosing strategies for oxytocin. While safe and feasible, the current dosing range is widely variable. It therefore remains possible that inconsistent findings between studies might be attributed, in part, to inconsistent dosing strategies. It is also possible that optimal dose and timing strategies might differ for protocols focused on PTSD prevention versus medication-enhanced therapy efforts toward tertiary intervention.

Similar questions remain regarding the mechanism of action by which intranasal oxytocin produces behavioral changes. Few viable biomarker candidates of oxytocin psychiatric efficacy (i.e., heart rate variability, hypothalamic-pituitary-adrenal axis response, and amygdala activity) have been proposed, and none have been validated (101). Even fewer studies have examined interactions between intranasal oxytocin administration and endogenous oxytocin levels in humans, and the literature is inconsistent with respect to the

proportion of intranasal oxytocin that crosses the blood brain barrier to reach plasma or cerebrospinal fluid (102–104). It is therefore essential to examine neurobiological and behavioral mechanisms of action within randomized, controlled treatment trials and to simultaneously explore improvements to intranasal delivery systems.

Conclusions

A number of important questions must still be addressed in order to determine if oxytocin is a useful therapeutic in the treatment or prevention of PTSD, whether alone or in combination with SUD. However, when taken together, the current literature suggests that oxytocin holds promise as a safe, effective, inexpensive, and easily dispensed medication to treat this all too common comorbidity.

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