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Review

Oxytocin in the prevention and the treatment of post-traumatic stress disorder: a systematic review of randomized controlled trials

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SUMMARY

Recent evidences are revealing the role of oxytocin in the pathophysiology of post-traumatic stress disorder (PTSD) and its possible application in prevention and the treatment of PTSD. Aim of the present article is to provide a systematic review of randomized controlled trials (RCT) of clinical effects of oxytocin in PTSD and trauma-related disorders was conducted. Only six articles were selected after applying the inclusion and exclusion criteria. We compared acute and long clinical effects of oxytocin administration on acute trauma symptomatology and PTSD. The acute clinical effects of oxytocin remain unclear, despite some studies show a reduction of global or single cluster of PTSD and of others clinical symptomatology. The long clinical effects of oxytocin administration show a non-statistically reduction of PTSD, although effect of oxytocin seem to be correlated to the severity on acute PTSD symptom. In fact, the presence of high acute PTSD symptoms showed significantly lower PTSD symptom severity across follow-up, indicating a long-term protective effect of oxytocin administration. Future clinical studies, with accurate psychopathological assessments and a structured clinical follow-up, are mandatory to understand the clinical efficacy of oxytocin administration in patients with PTSD or in patients with acute distress and an increasing risk in developing PTSD.

Key words: oxytocin, post-traumatic stress disorder, trauma-related disorder, psychopharmacology, treatment

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Conflict of interest
The Authors declare no conflict of interest

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Introduction

Post-traumatic stress disorder (PTSD) is an invalidating psychiatric illness caused by psychological trauma, with aberrantly consolidated and persistent traumatic memories, and failing in fear extinction [1]. Despite psychological traumatic experiences are common in the general population, the prevalence of trauma-related disorders, including PTSD, is relatively low, around to 2 to 6%, expect for veteran population where the percentage reaches 30% [2]. The clinical picture in PTSD is heterogeneous, mainly characterized by re-experiencing phenomena of traumatic experience, avoidance thoughts and behaviours, hyperarousal symptoms, emotional mumbling, cognitive impairment and, sometimes, severe dissociative symptoms, self-harm and suicidality [3-7]. The psychotherapeutic approaches are relevant in alleviating of psychopathology of trauma-related disorders and PTSD [2,8]. However, psychopharmacological treatment has a relevant role in managing the PTSD symptoms [9]. Several neurobiological mechanisms are implicated in the PTSD pharmacological strategies [10].

Recent evidences are revealing the role of oxytocin (OXT) in the pathophysiology of PTSD and its possible application in prevention and

the treatment of PTSD. Aim of the present article is to provide a brief description of OXT effects on biological systems implicated in the pathophysiology of trauma-related disorders and to conduct a systematic review of randomized controlled trials (RCT) of clinical effects of oxytocin in PTSD and trauma-related disorders.

Pathophysiology of oxytocin in stress-related disorders

The stress response features many physiological processes, such as cognitive and behavioral ones, that are able to ensure survival and restore homeostasis. Perceived unexpected threats or aversive situations can elicit cardiovascular, immune and neuroendocrine processes, leading to adaptive or maladaptive responses [11,12].

Trauma exposure can have enduring and overwhelming psycho-physiological consequences. On one hand, the risk of psychiatric conditions such as anxiety disorders, depression, alcohol abuse and, most of all, PTSD is highly enhanced [13]. On a physiological level instead trauma exposure can lead to disruptions of the neuroendocrine system, most frequently with regard to the hypothalamic-pituitary-adrenal (HPA) axis. Being able to respond either to internal and external stimuli, e.g. many life stressors, is one of the HPA axis' fundamental role [14-16]. Many stressful events, mostly during early life, could impact on HPA axis' homeostasis, resulting to be either hyperactivated or hypoactivated. This may lead to multiple pathophysiological effects, ranging from the vulnerability to many physical and mental disorders to the weakening of the immune system [17 19]. Many factors are well known to affect the function of the HPA axis and among them the neurotransmitter OXT plays a significant role. OXT is a neurohormone produced in the central nervous system (CNS), specifically by the hypothalamus in the supraoptic (SON) and paraventricular (PVN) nuclei, and is deeply involved in affecting social behaviors [20]. Through axons projections, hypothalamic neurons send OXT to the posterior hypophysis, or neurohypophysis, and, from there, to the bloodstream. When stressful experiences occur, the central OXT secretion exerts the function of maintaining and modulating cortisol levels, minimizing the response of the HPA axis and therefore allowing the body to uphold its prestress homeostasis [21-23].

Other than modulating the HPA pathway, OXT is an important regulator of anxiety for further reasons. Existing evidence suggests that this neuropeptide wields anxiolytic effects acting on the main stress-related and salience network in the brain. In humans, in fact, many regions express the oxytocin receptor (OR). These include the brainstem, olfactory nucleus, anterior cingulate cortex and both central and basolateral amygdala [24]. The OR-mediated anxiolytic effect features a intracellular activation of mitogen-activated protein kinase signaling pathways, which leads to long

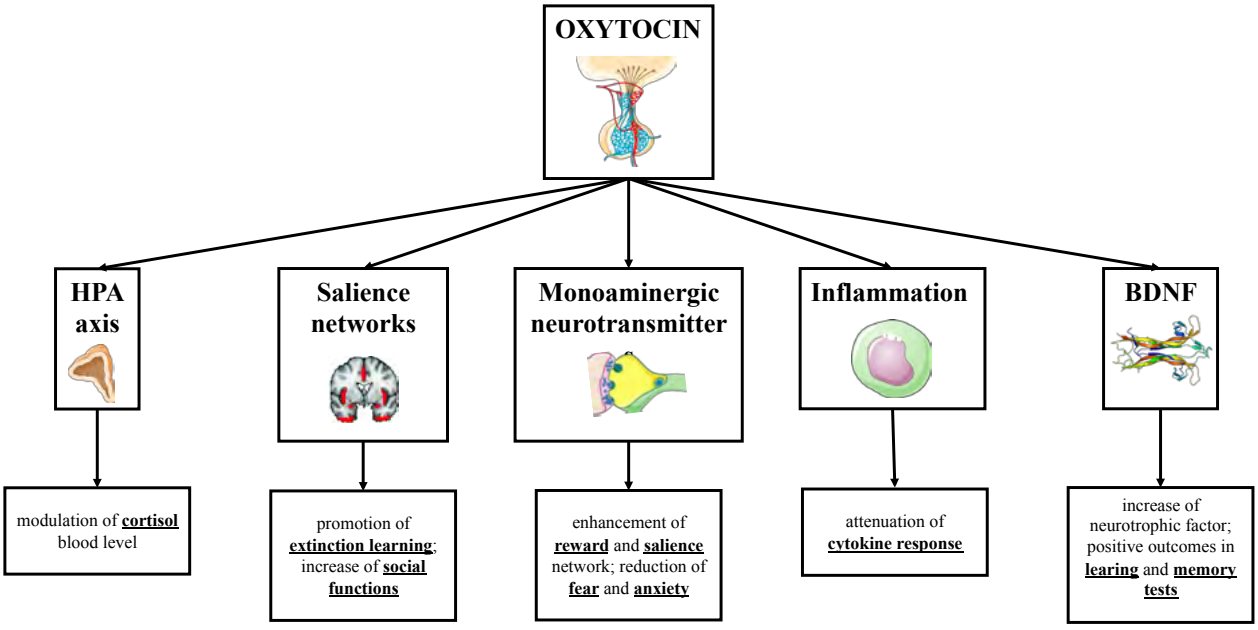

FIGURE 1. *Schematic representation of oxytocin effects on biological systems implicated in the pathophysiology of trauma-related disorders.*

term behavioral adaptations through differential gene expression [25,26]. In addition, oxytocin-related neural activity is deeply connected to other neurotransmitters of the salience and reward regions, with evidence of its effects on norepinephrine, serotonin and dopamine systems [27-29].

A growing research suggests that OXT has anti-inflammatory effects, which encourages future studies, given the evidence of high pro-inflammatory cytokine levels in patients with stress-related disorders. Intravenous administration of OXT in humans demonstrated to dampen cytokine effects in healthy individuals and, on the other hand, in hamsters enhanced wound healing [30,31].

Although preliminary, promising data show that OXT enhances BDNF levels in chronic stress rat models [32,33]. BDNF is a key factor that participate in neural development, growth and plasticity whereas its

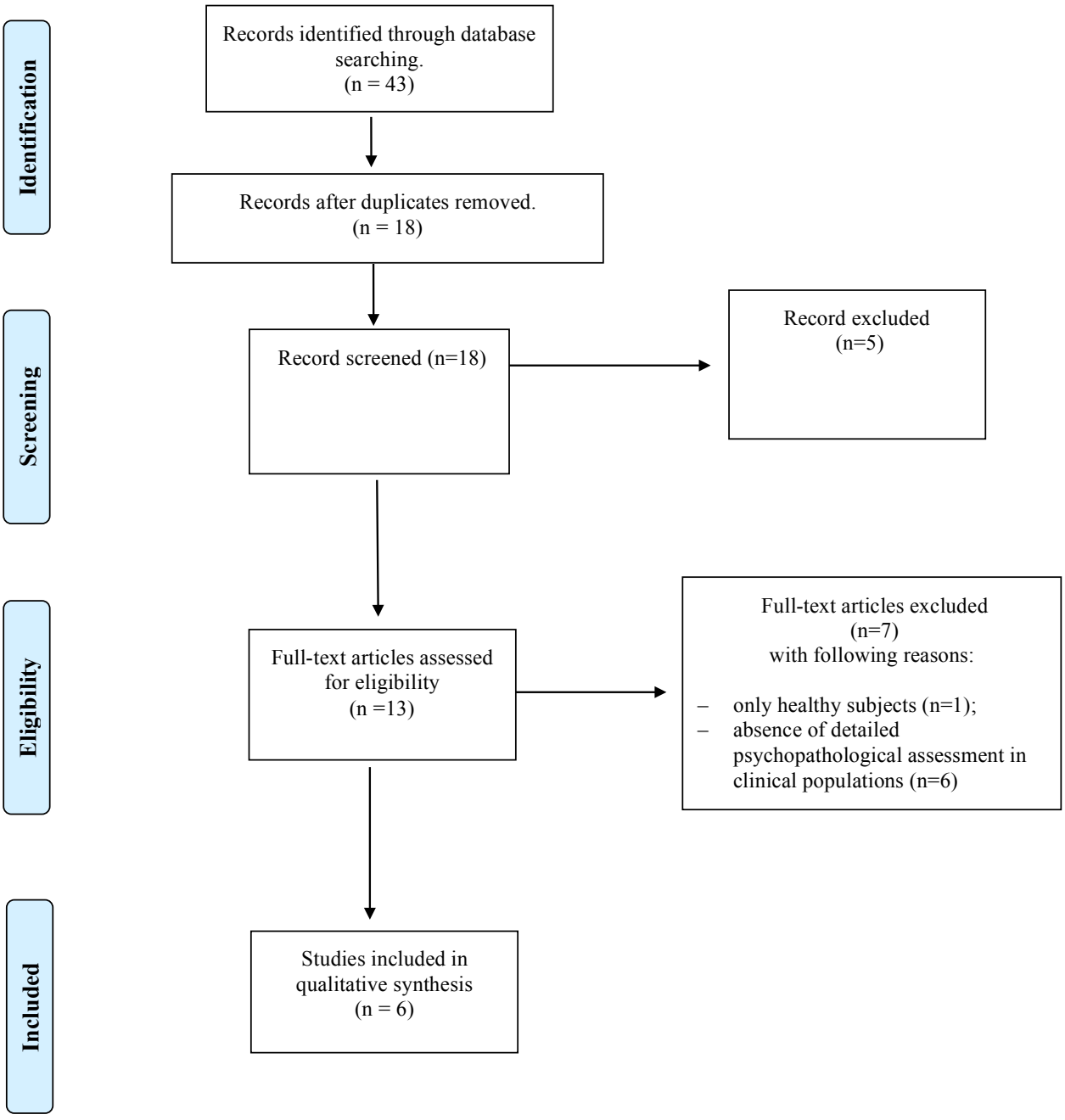

FIGURE 2. *Stages of the screening process applied in the selection of studies.*

TABLE I. *Acute clinical effect of intranasal oxytocin administration.*

Author/ Year	N/sex	Sample	Trauma characteristics	PTSD assessment scale
Koch et al., 2019	Interest sample (P/O)	CAPS ETI IES-R	MINI-plus SCID AUDIT HADS fMRI, WMT	40IU
	15F 21M 36T	PP with PTSD	W-RTE and CTE	
	Interest sample (P/O)			
	20F 20M 40T	PP trauma-exposed	W-RTE and CTE	
Sack et al., 2017	Interest sample (O+P)	SKID IES	SCID-D DES RSDI Second study (TSST challenge experiment) : M-CIDI	24 IU
	35 F	PTSD outpatients Psychosomatic Clinic	17 SV by a family member, 6 non-SV by a family member, 4 accident, 3 organized SV, 2 SV by a stranger 1 natural disaster	
	Comparison sample (O+P) (second study)			
	10 F	HS	No traumatic history	
Frijling et al., 2016 B	Interest sample (O)	TSQ PDI CAPS ETI	MINI RSDI Script driven imagery and resting state fMRI	40IU
	15F 9M 24T	ED, patients with AD and increasing risk of PTSD	12 traffic accident, 5 accident at work/ home, 6 interpersonal trauma, 1 other	
	Comparison sample (P)			
	9F 9M 18T	ED, patients with AD and increasing risk of PTSD	14 traffic accident, 3 accident at work/ home, 3 interpersonal trauma	
Koch et al., 2016	Interest sample (O/P or P/O)	CAPS	MINI-plus SCID VAS fMRI	40 IU

Other variables/ Instrument	Dose	Other drugs/ placebo	Adverse events	Clinical findings
Placebo (0.9% saline)	N.E.	Severity of PTSD, anxiety and depression symptoms did not differ between scanning sessions.		
Placebo	N.E.	Intranasal oxytocin treatment significantly attenuated PTSD symptoms triggered by trauma-script exposure. Oxytocin-mediated reduction in dissociative and re -experiencing symptoms was not significant. Oxytocin treatment attenuated avoidance with a trend for statistical significance.		
Placebo (0.8% NaCl)	N.E.	Treatment effects on RSDI scores after the trauma script were considered statistically significant. O-treated participants specifically reported higher flashback intensity during RS-trauma than P-treated participants.		
Placebo (NaCl 0.9%)	N.E.	Compared with placebo, O administration in PTSD patients was associated with lower ratings of subjective anxiety and nominally lower ratings of nervousness but not happiness and sadness.		

follows **TABLE I.** *Acute clinical effect of intranasal oxytocin administration.*

Author/ year	N/sex	Sample	Trauma characteristics	PTSD assessment scale
	16F 21M 37T	PP with PTSD	Early trauma and W-RTE, non-specified	
	Comparison sample (P/O or O/P)			
	20F 20M 40T	PP trauma-exposed without PTSD	Early trauma and W-RTE, non-specified	

Legend of sample: Acute Distress (AD), Childhood traumatic events (CTE), Emergency Department (ED), Healthy Subjects (HS), Police Personnel (PP), Sexual Violence (SV), Work-related traumatic event (W-RTE).
Legend of PTSD assessment scale: Clinician Administered PTSD Scale for DSM-5 (CAPS), Early Trauma Inventory, short version (ETI), German translation of the Structured Clinical Interview for DSM-IV (SKID-PTSD), Impact of Event Scale (IES), Impact of Event Scale-Revised (IES-R), Peritraumatic Distress Inventory (PDI), Posttraumatic diagnostic Scale (PDS), Trauma Screening Questionnaire (TSQ).

deficiency can cause aggressive behavior and anxiety disorders [34,35], including PTSD [36].
Having these evidences in mind, it is easily comprehensible why this hormone has an important role in social behaviors. This in fact has a powerful evolutionary significance, since interactions like mating, nursing, sex and lactation are situations where stress must be dramatically avoided.
Figure 1 summarizes schematically main actions of OXT on biological systems that are involved in the pathophysiology of trauma-related disorders and PTSD.

Methods

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA - Moher et al., 2009) were adopted as the methodological framework of this study.
The electronic database PsycINFO, PubMed, Scopus, Web of Science were searched with limitation in terms of type of articles (randomized controlled trials). The following keywords were used followed by "AND" or "OR" oxytocin; PTSD; post-traumatic stress disorder; traumatic events; trauma-related disorder, acute trauma. Textbooks on psychiatry were also consulted.
The selection of papers suitable for this review was restricted to articles published in English peer-reviewed journals and those that added an original contribution to the literature. Studies on healthy samples were excluded from our research. At the same way, studies of neural responses or specific task with no clinical correlates were excluded (see Fig. 2 for search results as well the reasons for article exclusion).
Two reviewers (L.L., T.B.J.) independently inspected all citations of studies identified by the search and grouped them according to the topic of the papers. Reviewers acquired the full-text article for all papers located. Where disagreement occurred, this was resolved by discussion with the senior author (G.D.L.) who also independently inspected all articles located and grouped them following the major areas of interest identified by the reviewers.

Results

A total of 43 articles were found, but only 6 articles were selected after applying the inclusion and exclusion criteria (Fig. 2).
The studies were divided into two groups, based on the number of intranasal oxytocin administrations: four studies with less than 2 OXT administrations were included in the "acute clinical effects of oxytocin administration" group (Tab. I); studies with more than 2 OXT administrations were included in the "long clinical effects of oxytocin administration" group (Tab. II).
The major results of each study group are presented below.

Acute clinical effects of oxytocin administration

In a recent study [37] of 36 PTSD police officers and 40 police officers trauma-exposed controls Koch *and colleagues* showed that after oxytocin administration (40 IU) or placebo (0.9% saline) on average 83.48 (± 4.21) minutes before task performance; severity of PTSD, anxiety and depression symptoms did not differ between scanning session (all $p > 0.05$).
In contrast, Sack *and colleagues* [38], in a study of 35 PTSD women (outpatients of Psychosomatic Clinic) and

Other variables/ Instrument	Dose	Other drugs/ placebo	Adverse events	Clinical Findings

Legend of other variables/ Instrument: Alcohol use disorder identification test (AUDIT), Dissociative Experiences Scale (DES), Hospital Anxiety and Depression Scale (HADS), Mini International Neuropsychiatric Interview (MINI), Munich Composite International Diagnostic Interview (M-CIDI), neutral script condition (RS-neutral), Profile of Mood States (POMS), Responses to Script-Driven Imagery Scale (RSDI), Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D), trauma script condition (RS-trauma), Trier Social Stress Test (TSST),Visual analog scale (VAS), Working memory task (WMT).

10 healthy women, showed that after 1 dose (24 IU) of oxytocin or placebo administered, Responses to Script-Driven Imagery Scale (RSDI) was significantly reduced in oxytocin-treated patients (p = 0.012). Consequently, intranasal oxytocin treatment significantly attenuated PTSD symptoms triggered by trauma-script exposure. Furthermore, oxytocin treatment attenuated avoidance, at least with a trend for statistical significance (p = 0.093). Contrarily oxytocin-mediated reduction in dissociative and re-experiencing symptoms was not significant (respectively p = 0.26 and p = 0.15).

Also Frijling *and colleagues* [39], in a study of 42 subjects with acute distress and increasing risk of PTSD (TSQ ≥ 5, PDI ≥ 17), showed that, after 40 IU of oxytocin (24 patients) or placebo (0.8% NaCl, 18 patients) administered forty-five minutes before script driven imagery and resting state fMRI, treatment effects on Responses to Script-Driven Imagery Scale (RSDI) were considered statistically significant. In particular, the study showed that Sleepiness attenuation from RS-neutral to RS-trauma was significantly higher in oxytocin-treated participants than in placebo-treated participants (p = 0.03). Sleepiness during RS-trauma was significantly lower in oxytocin-treated participants (p = 0.04). Furthermore, the study showed no group differences on RSDI subscale scores after the trauma script (i.e., PTSD symptoms during RS trauma) (p = 0.45), but oxytocin-treated participants specifically reported higher flashback intensity during RS-trauma than placebo-treated participants (p = 0.046). CAPS re-experiencing scores were associated with RSDI flashback intensity scores (p = 0.018), but did not explain the observed group difference. Adjusting for duration between intranasal administration and scanning, the oxytocin effect on lowering sleepiness during RS-trauma became marginally significant (p = 0.053), and adjusting for lifetime PTSD, oxytocin-treated participants had marginally higher flashback intensity scores during RS-trauma than placebo-treated participants (p = 0.07). Moreover, the study concluded that all other results were unaltered.

Also Koch *and colleagues* [40], in a study on 37 police personnel with PTSD and 40 police personnel trauma exposed without PTSD, with randomized administration of oxytocin (40 IU) during one fMRI session and placebo (NaCl 0.9%) during another fMRI session (or the contrary), showed lower ratings of subjective anxiety (p = 0.044) and nominally lower ratings of nervousness (p = 0.055) but not happiness and sadness (all p > 0.05) in patients with oxytocin administration in PTSD sample.

Long clinical effects of oxytocin administration group

Only two studies of long clinical effects of oxytocin were found.

In a recent study, Flanagan *and colleagues* [41] has evaluated the effects of 8 doses of oxytocin (40 IU for dose, 8 subjects) or placebo (8 doses, 9 subjects) administered 45 minutes prior to each weekly of Prolonged Exposure (PE) therapy session in 17 patients with PTSD. The study concluded that the oxytocin group show lower PTSD and depression symptoms during PE, and had higher working alliance scores, although these differences did not reach statistical significance. Furthermore, the oxytocin group had a marginally lower estimated mean PCL-5 score at end of treatment as compared to the placebo group (31.0 *vs* 40.9, p = 0.09). Between-group differences in the trajectory

TABLE II. *Long clinical effect of intranasal oxytocin administration.*

Author/ year	N/sex	Sample	Trauma characteristics	PTSD assessment scale
Flanagan et al., 2018	Interest sample (O)	Global sample: 8 trauma related to combat exposure 4 sexual assault 5 other trauma	CAPS PCL-5	MINI HAQ-II CSQ BDI-II
	1 F 7 M 8T	PTSD sample (5 veterans)		
	Comparison sample (P)			
	2 W 7 M 9 T	PTSD sample (5 veterans)		
Van Zuiden et al., 2017	Interest sample (O)	TSQ PDI CAPS PDEQ IES-R ETI	MINI HADS PSS	40 UI twice daily for 8 days
	27F 26M 53T	Adult ED patients with current trauma	43 accidents 10 assault	
	Comparison sample (P)			
	26F 28M 54T	Adult ED patients with current trauma	48 accidents 6 assault	

Legend of sample: Emergency Department (ED),
Legend of PTSD assessment scale: Clinician Administered PTSD Scale for DSM-5 (CAPS), Early Trauma Inventory, short version (ETI), Impact of Event Scale (IES), I mpact of Event Scale-Revised (IES-R), Peritraumatic Dissociation Experience Questionnaire (PDEQ), Peritraumatic Distress Inventory (PDI), PTSD Checklist for DSM-5 (PCL-5), Trauma Screening Questionnaire (TSQ).
Legend of other variables/ Instrument: Beck Depression Inventory, second edition (BDI-II), Client Satisfaction Questionnaire (CSQ), Hospital Anxiety and Depression Scale (HADS) Helping Alliance Questionnaire (HAQ-II), Mini International Neuropsychiatric Interview (MINI), Perceived Stress Scale (PSS).

Other variables/ Instrument	Dose	Other drugs/ placebo	Adverse events	Clinical findings
40 IU (8 doses)	Placebo (8 doses)	NO	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. Between-group differences in the trajectory of symptom improvement, session 3 PCL-5 scores showed a statistically significant group difference.	
Placebo (0.9% NaCl)	Yes (see results section for details)	An effect of oxytocin dependent on acute PTSD symptom severity was found, as assessed at baseline within 10 days post trauma. Oxytocin- treated participants with high acute PTSD symptoms had significantly lower PTSD symptom severity across the complete follow-up period up to 6 months post trauma. IES, HAD-anxiety and HAD-depression scores at follow-up significantly decreased over time, without significant group differences in overall symptom severity or symptom decrease over time.		

of symptom improvement, PCL-5 scores showed a statistically significant group difference (O = 30.3 *vs* P = 45.4, p = 0.03).

Van Zuiden *and colleagues* [42] in a study of adult emergency department patients with current trauma (with TSQ ≥ 5 and PDI ≥ 17), 12 days after trauma, administered 40 IU of oxytocin twice daily for 8 days (53 subjects) or placebo (0.9%) with the same scheme (54 subjects). Participants recorded their self-reported administration time and potential adverse effects in a diary. Patients treated with oxytocin showed the following adverse events: ear, nose, and/or throat symptoms (12), headache (4), gastrointestinal symptoms (4), neurological symptoms (3), sleep problems (4), positive sensation/feeling (1), light-headedness and/or dizziness (1), planned surgery (10), fatigue (1), pulmonary symptoms (1), neck and back pain (1), dermatological symptoms (1), traffic accident without hospital admission (1), deep venous thrombosis (1), suicidal ideation (1), other (8), gynaecological women symptoms (3) [42]. In all participants, oxytocin administration did not result in significantly lower clinician rated PTSD symptom severity compared to placebo at 1.5 months post-trauma or across follow-up compared to placebo-controls. Nevertheless, the study showed that effect of oxytocin dependent on acute PTSD symptom severity, as assessed at baseline within 10 days post-trauma. Relative to placebo-treated individuals with high acute PTSD symptoms, oxytocin- treated participants with high acute PTSD symptoms had significantly lower PTSD symptom severity across the complete follow-up period up to 6 months post trauma, indicating a long-term protective effect. In contrast, oxytocin administration had no effect on follow-up PTSD symptoms for individuals with relatively low acute PTSD symptom severity. Furthermore, IES, HAD-anxiety and HAD-depression scores at follow-up significantly decreased over time, without significant group differences in overall symptom severity or symptom decrease over time.

Discussion

Very few RCT were found for this review. The results of our review are exiguous and presents different limitations.

The group "Acute clinical effects of oxytocin administration" consists of four studies. For two studies, the sample consists in police officers with PTSD or trauma-exposed controls [37,40]. One study's sample it's composed only by women with PTSD or healthy subjects [38], and the last study analyzed not PTSD patients, but patients with acute distress and increasing risk of PTSD [39]. Furthermore, also the characteristics of trauma are different: work-related traumatic event and childhood traumatic events [37,40], different traumas with a prevalence of violence [38] and different traumas with a prevalence of traffic accidents [39]. The PTSD assessment and the other instruments utilized are also different (Tab. I). Different doses of oxytocin were administered: three studies administered 40 IU [37,39,40], one study 24 IU [38]. No psychological treatment was implemented in the analyzed studies and no adverse events are reported in the full-text papers.

The results of acute clinical effects of oxytocin administration were in contrast. After administration of oxytocin, it was reported a reduction of levels of PTSD global symptomatology [38,39], anxiety [40], sleepiness [39] and nervousness [40]. For specific cluster of PTSD symptomatology, Sack *and colleagues* showed that only avoidance was attenuated with a trend for statistical significance, while reduction of dissociative and re-experiencing symptoms was not statistically significant [38]. In contrast, a recent study [37] did not show differences in PTSD symptomatology, anxiety and depression. Furthermore, Frinjling *and colleagues* [39] showed that after oxytocin administration, patients specifically reported higher flashback intensity at trauma script condition (RS-trauma) respect to the placebo controls.

The "long clinical effects of intranasal oxytocin administration" group consists of only two articles. Also in this group, the samples of the studies were different for clinical features. In particular, one study [41] consists of PTSD patients (10 of 17 patients were veterans), the other study consists of patients with acute distress and increasing risk of PTSD [42]. Moreover, the trauma characteristics were different: different traumas with a relative prevalence of trauma related to combat exposure in one study [38] and different traumas with a prevalence of traffic accidents in the other study [39]. The PTSD assessment and the other instruments utilized are also different (Tab. II) but both the studies utilized the CAPS for PTSD assessment scale. The dose of oxytocin administered were different: 40 IU for 8 doses [41] and 40 IU twice daily for 8 days [42] 12 days after trauma exposure. Furthermore, in one study the single dose was administered before each weekly of Prolonged Exposure therapy [41] while in the other study, no psychological treatment was provided. One study, report reports several side effects (see results section for details). During Prolonged Exposure, patients treated with oxytocin show a non-statistically significant reduction of PTSD global and depression symptomatology, only in session-3 the authors found a significant group difference [41]. In contrast, Van Zuiden *and colleagues* [42] showed that oxytocin administration did not result in significantly lower clinician rated PTSD symptom severity compared to placebo at 1.5 months post-trauma or across follow-up compared to placebo-

controls. But the same study [42] showed that the effect of oxytocin depends on acute PTSD symptom severity, as assessed at baseline within 10 days post trauma. In particular, participant with high acute PTSD symptoms had significantly lower PTSD symptom severity across the complete follow-up period up to 6 months post trauma, indicating a long-term protective effect, while oxytocin administration had no effect on follow-up PTSD symptoms for individuals with relatively low acute PTSD symptom severity. Furthermore, at follow-up, scores of Impact of Event Scale (IES), Hamilton Rating Scale for Anxiety (HAM-A) and Hamilton Rating Scale for Depression (HAM-D) decreased significantly over time, without significant group differences in overall symptom severity or symptom decrease over time.

Conclusions

The studies analyzed for this systematic review present a small number of patients included and are highly heterogeneous for clinical features, presenting differences in the samples for types of traumas and clinical assessment, as well as for dosages of oxytocin. Furthermore, in one study the use of oxytocin was analyzed in add-on other specific treatment (psychotherapy). Future clinical studies, with accurate psychopathological assessments and a structured clinical follow-up, are mandatory to understand the clinical efficacy of oxytocin administration in patients with PTSD or in patients with acute distress and an increasing risk in developing PTSD.

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