Review Article

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

INTRANASAL OXYTOCIN: A THERAPEUTIC OPTION FOR TREATMENT OF POST-TRAUMATIC STRESS DISORDER (PTSD).

Medical Science

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ABSTRACT

Most of the people face trauma, in one or the other form, in their lives. In 10 % of such a people the trauma is followed by post-traumatic stress disorder (PTSD) which has been classified in the category "Trauma and Stressor related disorders" in DSM-5. Psychotherapy is the principal therapy for PTSD, but it is effective only in 30 % patients. Different therapeutic targets are being explored for the treatment of PTSD. Most of the research has focussed on adrenergic and hypothalamic-pituitary-adrenocortical systems. Also, there are studies on serotonergic, dopaminergic, opioid, GABA-ergic, glutamatergic and cannabinoid receptor mechanisms. Only two serotonin reuptake inhibitors (SSRIs), sertraline & paroxetine, have been approved for treatment of PTSD by the US FDA, which show only 30 % remission rate after 12 weeks of treatment. Neuropeptide oxytocin (OT) shows widespread behavioral effects and numerous potential therapeutic benefits. Functional magnetic resonance imaging (fMRI) studies concurrently with OT administration show brain regions that are strongest targets for OT to influence human behavior. Intranasal oxytocin has been found to be a promising pharmacological therapy to boost the treatment response to PTSD.

KEYWORDS

Post-traumatic stress disorder, PTSD, Psychotherapy, Intranasal-oxytocin, oxytocin, antidepressants.

Introduction:

More than 5 million people die each year because of injuries resulting from acts of violence against self or others, road traffic accidents, burns, falls and poisons. Worldwide, injuries account for 9% of deaths, additionally tens of millions of people suffer non-fatal injuries which require treatment (WHO). Trauma exposure is higher in lower income countries compared to higher income countries. Post-traumatic stress disorder (PTSD) prevalence rates are mostly similar across countries with high rates being found in postconflict settings. Trauma exposure is also associated with several chronic physical conditions (Atwoli L. et al, 2015). Lifetime prevalence of PTSD in the US is about 8-9%, and it is twice as common in women than in men (Christopher HW. et al, 2013)

PTSD is a debilitating anxiety disorder that may cause significant distress and increased use of health resources. The emotional and physical symptoms of PTSD occur in 3 clusters, i.e. re-experience of the trauma, marked avoidance of the usual activities and increased symptom arousal. Patient symptoms must significantly disrupt normal activities of the patient and last for more than one month before a diagnosis of PTSD can be made. About 80% of the patients with PTSD have at least one co-morbid psychiatric disorder, i.e. depression, alcohol and drug abuse and other anxiety disorders (Kesseler RC. et al, 1995). In the 5th edition of Diagnostic and statistical manual of mental disorders (DSM-5), PTSD is included in a new category "trauma and stressor related disorders", and all these conditions under PTSD require traumatic or stressful event as a diagnostic criterion (APA-2013).

Pathophysiology of PTSD:

For the diagnosis of PTSD, a stressor, an in intrusion, an avoidance of trauma related thoughts, negative alternation in cognition and mood, the alternation in arousal and reactivity for more than one month, with social and occupational distress are required. Persons with symptoms due to other illness, medication or substance use are to be excluded; and full diagnostic criteria are not met for at least 6 months after trauma (APA- 2013).

Fear expression is associated with activity in the dorsal anterior cingulated cortex (dACC) and the amygdala (Milad MR. et al, 2009). Key features of PTSD, increased fear expression and aberrant emotion regulation, are neurobiologically associated with amygdala and dACC hyperreactivity to negative emotional stimuli, and decreased amygdala-prefrontal cortex (PFC) functional connectivity (FC) (Patel R. et al, 2012; Rabinak CA. et al, 2014). Higher amygdala reactivity in PTSD patients, before treatment, predicted worst outcome possibly due to impaired extinction learning and fear regulation (Byrant RA. et al, 2008). Ventromedial prefrontal cortex (vmPFC)-amygdala connectivity is important in fear extinction learning (Milad MR. et al, 2007), which is assumed to the mechanism of exposure therapy in PTSD (Rothbaum & Davis 2003). Decrease in excessive fear processing of amygdala and increasing vmPFC to amygdala connectivity may enhance oxytocin (OT) treatment response in PTSD (Koch SBJ. et al, 2016, b). Inadequate PFC engagement early post-trauma may lead to inadequate inhibition of amygdala and dACC reactivity (Admon R. et al, 2013). This neural pattern ultimately results into prolonged fear responsivity to trauma related stimuli and generalization of these responses to neutral stimuli as observed in PTSD. (Mahan and Ressler, 2012)

Patients with PTSD show a dysregulation in a number of psychological systems, including adrenergic, serotonergic, dopaminergic, glutamineergic, opioid, cannabinoid, hypothalamic-pituitary-adrenocortical (HPA); and other mechanisms. (Shiromani PKTL eds, 2009).

Treatment approaches for PTSD:

Treatment of PTSD relies on multifactorial approaches, i.e. patient education, cognitive behavioral therapy (CBT) and psychopharmacology. Psychotherapy is the primary treatment for PTSD attaining a positive end-state function (50% reduction in symptoms of PTSD) over 6 weeks in 21-46% patients after 9 sessions therapy (Christopher HW et al, 2013). A similar study showed 32-53% of patients achieved positive end-state function of getting 10 sessions of CBT over16 weeks (Bisson JI, 2015) Trauma focused psychotherapies are highly recommended therapies for PTSD, which include prolonged exposure (PE), cognitive processing therapy (CPT) and eye movement desensitization and reprocessing (EMDR); and others, i.e. brief eclectic psychotherapy (BEP), narrative exposure therapy (NET) and specific cognitive behavior therapy (CBT) (National Center for PTSD).

Pharmacotherapy for PTSD:

By now there are only few effective and preventive medicines for PTSD; thus improvements in preventive interventions are required to target neurological processes involved in PTSD at an early post-traumatic period (Fletcher S. et al, 2010). A standard approach to manage PTSD symptoms is by using drugs to inhibit sleep disturbance, pain or hyperarousal.

Drugs useful in the treatment of PTSD are antidepressants (SSRIs and SNRIs) and antianxiety drugs. SSRIs and SNRIs affect levels of neurotransmitters serotonin and epinephrine in the brain. These neurotransmitters play a role in brain cell communication. Among the SSRIs sertraline, paroxetine, fluxoxetine and venlafaxine are most effective in the treatment of PTSD (National Center for PTSD); but only sertraline and paroxetine have been approved by the US FDA for the treatment of PTSD with a remission rate about 30% after 12 weeks of treatment (Friedman MJ. 2013). Other drugs that may be helpful in the treatment of PTSD are nefazodone, imipramine and phenelzine, but there is no strong evidence as for SSRIs and SNRIs (National Center for PTSD). Moderate success is achieved with SSRIs and

SNRIs, and few evidence based pharmacological alternatives are available acting through a different mechanism.

Drugs mentioned in 2010 VA/DoD guideline, to prevent PTSD, are opioids, benzodiazepines and propranolol. But there is limited support of evidence for use of medications in early post-trauma to prevent PTSD, and cannot be recommended. Benzodiazepines have been used as an effective treatment for anxiety and insomnia, but their use cannot be recommended as a preventive measure due to lack of evidence of effectiveness and risks that may outweigh potential benefits (VA/DoD, 2010).

Action of SSRIs and SNRIs is non-specific, hence variable efficacy in a variety of mood, anxiety, OCD, trauma and stress related disorders. SSRIs show lower remission rates than CBT e.g. PE and CPT (Cahill SP. et al, 2009). Clinical trials with antiepileptic drugs (glutamatergic or GABA-ergic) have been more disappointing except topiramate (Briedman MJ. 2013). In a randomized trial α-1 adrenergic antagonist, prazosin, was predicted to reduce traumatic nightmares and other PTSD symptoms (Germain A. 2013).

Complementary and alternative medicine (CAM) i.e. yoga, meditation or acupuncture, biological treatments (hyperbaric oxygen or transcranial magnetic stimulation) may be an option for PTSD, but such treatment do not have strong research behind (National Cencer for PTSD).

Oxytocin and behavioral studies:

Oxytocin (OT), a neuropeptide, is best known for its peripheral effects. It is a social bonding hormone and has been implicated in several neuropsychiatric disorders (Striepens N et al. 2011). OT is synthesized in supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus. Neurons in SON and PVN project to posterior pituitary gland where OT is released into the blood stream in response to physiological events such as sexual stimulation, nursing and stress; and exerts multiple peripheral effects. OT neurons send projections to and had OT receptors in other species-specific CNS regions (Gimpl G. et al 2001; and Insel TR. 1992). A high level of OT binding was found in human basal forebrain e.g. basal nucleus of Maynert, vertical limb of the diagonal band of Broca, and in the substantia nigra (Friedman MJ, 2013). Also, it binds to the lateral septal nucleus, ventral striatum and multiple areas of the brainstem and spinal cord. Like other neuropeptides OT is stored in large dense-core vesicles found in nerve endings, dendrites, soma and axonal varicosities (Stoop R. 2012). CSF and plasma levels of OT are different and are regulated independently. The CSF half life of OT is much longer (28 minutes) compared to than in blood (1-2 minutes), which suggests a variable time scale for CNS effects of OT (Veening JG. et al, 2010). Circulating OT does not easily cross the blood-brain barrier (BBB), and OT in CSF reaches multiple brain areas and thus alters physiology and behavior (Veening JG. et al, 2010). Various studies in humans have co-related peripheral levels of OT (in blood, saliva, urine) to socially relevant behaviors (Stevens FL. et al, 2013). Peripheral OT release is related to childbirth, breastfeeding and copulation. A large, healthy-cohort study negatively correlated anxiety and attachment anxiety with plasma OT levels in men, consistent with its anxiollytic effects (Weisman O. et al, 2013). Altered peripheral OT levels have been correlated with various neurosychiatric disorders. Low OT levels have been reported in some studies of depression, autism-spectrum disorders (ASD) and schizophrenia (Stevens FL. et al, 2013). A positive co-relation has been found between levels of OT and symptom severity in patients with social anxiety disorder (SAD) (Striepens N. et al, 2011). Correlating peripheral OT levels and human behaviors is a complex process. Intranasaly administered neuropeptides (insulin, melanocortin, vasopressin) demonstrate impact of exogenous OT on social behaviours and cognitions in humans (Born J. et al, 2002).

Intranasal oxytocin:

Prolonged increase in peripheral OT has been observed after its intranasal administration (Weisman O. et al, 2012 and van Ijzendoorn MH. et al, 2012), but the only intranasal administration altered event-related potentials evoked by an auditory attention task (Pietrowsky R. et al. 1996). Many reviews strongly support the ability of exogenous OT to modulate social-emotional behavior. OT can improve multiple measures related to social perception suggesting that OT enhances a later stage in processing. There is evidence that OT increases empathy but not cognitive empathy indicating improved recognition of feelings but not greater understanding of problems. There are multiple theories for effects of OT, e.g. anxiety-reduction hypothesis, affiliative-motivation hypothesis and the social salience hypothesis thus variable implications for use OT as a therapeutic agent (Bartz JA. et al, 2011). Functional neuroimaging (fMRI) sheds light on the brain areas affected by intranasal administration of OT. Altered amygdala reactivity to emotional stimuli is the most common finding. These findings are consistent with proposed anxiolytic effects of OT, some modulatory effects of OT appear to be gender specific, amygdala activation was increased in women with negative emotional stimuli. Intranasal OT has been considered as a potential treatment for several neuropsychiatric disorders, although few RTCs have been reported. Two studies have reported symptom reduction in patients with PTSD after a single dose and one reported improved mood (Striepens N. et al. 2011). Two recent RCTs reported the addition of 3,4-methylenedioxymethamphetamine (MDMA) to psychotherapy with better outcomes, and MDMA induced OT release has been implicated as a mechanism of action (Mithoefer MC. et al. 2011, Mithoefer M. et al. 2013, Oehen P. et al. 2013) Administration of OT before psychotherapy may enable the patient to enable trust in the therapist and facilitate the therapeutic process (Macdonald K. et al. 2010 and Olff M. et al. 2010). OT is in early stages of development as a treatment with considerable potential in neuropsychiatry, as an add-on to other medications or psychotherapy. More studies are required to be conducted to clearly define behavioral effects of OT and individual variations.

Intranasal oxytocin clinical studies:

Many clinical studies/trials have been conducted in men and women with PTSD or with trauma exposure but with small sample sizes (Table; 1). Drug intervention was intranasal oxytocin (OT) or placebo (PL) as a single dose or twice daily in different strengths. Functional MRI studies show decreased amygdala activity with inhaled OT.

Table: 1

Sr. No.	Study,Year	Drug Intervention	Study/Trial Design	Sample (N)	Remarks
1.	Acheson DT. et al, 2013	OT 24 IU/PL nasal spray	DB, PC	44 healthy participants	OT may facilitate fear extinction recall in humans, a potential adjunctive treatment for extinction based therapies for fear disorders.
2	Flanagan JC. et al, 2018 (a)	OT 24 IU/PL, IN	DB, PC	34 (16-PTSD;18-trauma-exposed controls)	PTSD patients on OT performed better in 2-back condition compared to PTSD patients on PL. Connectivity between DLPFC and dACC ↑ in 2-back condition in PTSD patients on OT as compared with PL.
3.	Flanagan JC. et al, 2018 (b)	Self administered OT 40 IU/PL, IN 45 before weekly PE therapy session.	R, DB, PC, Pilot trial	17 persons with diverse index traumas.	OT group – ↓ PTSD and depression symptoms during PE; ↑ working alliance scores, but not statistically significant.
4.	Friling JL. et al, 2014	OT 40 IU/PL, IN, BD×7.5 d	R,DB, PC	220 ED patients with ↑ risk of PTSD	Early IN, OT is safe & effective strategy to prevent PTSD in patients with ↑ risk.
5.	Frijling JL. et al, 2016 (a)	OT 40 IU/PL 5 puffs per nostril	DB, R,PC, BS	37	OT ↓ LA-vlPFC FC after trauma script driven imagery c/f ↑ LA-vlPFC FC in PL group. ↓ levels of sleepiness and ↑ flashback intensity in OT group after trauma.

6.	Frijling JL. et al, 2016 (b)	OT 40 IU/PL, Single IN	R, DB, PL,fMRI	41 recently traumatized M & W with moderate to high distress.	OT ↑ RA reactivity to fearful faces compared to PL. Single OT administration may ↑ fearful faces processing.
7.	Frijling JL. Et al, 2017	OT, IN Single dose	fMRI, acute effects of single OT dose on functional fear neurocircuitary.	Recently trauma-exposed ED patients (range n=37=41)	After single dose OT acute ↑ in amygdala reactivity to fearful faces; and ↓ vmPFC and vlPFC FC. Repeated OT administration in recent trauma-exposed ED patients early posttrauma→ ↓ development of PTSD symptoms.
8.	Koch SBJ. et al, 2016 (a)	OT 40 IU in PTSD patients, Single IN	R, PC, CO, fMRI	77 M & W police officers (37-PTSD; 40-without PTSD)	OT administration ↓ amygdala reactivity towards emotional faces in PTSD patients, but ↑ amygdala reactivity in healthy trauma- exposed controls indicating beneficial neurobiological effects of OT in PTSD patients.
10.	Koch SBJ. et al, 2016 (b)	OT 40 IU	DB, PC, CO, resting-state fMRI	77 (37-with PTSD; 40-matching trauma exposed controls)	In PTSD patients OT administration ↓ subjective anxiety and nervousness. OT effect on FC of BLA & CeM sub-regions with prefrontal and salience processing areas was investigated.
11.	Koch SBJ. et al, 2018	OT 40 IU/PL	R, PC, CO, fMRI	76 M & F police officers with or without PTSD	OT administration ↑ L Tha activity during distraction in all patients; also OT ↑ FC between L Tha and amygdala PTSD M & trauma- exposed controls.
12.	Nawijn L. et al, 2016	OT 40 IU/PL, IN	R,PC,BS,CO, fMRI	72 (35-PTSD; 37-trauma-exposed without PTSD)	OT ↑ neural responses during reward and loss anticipation in PTSD patients and controls in striatum, dACC and INS.
13.	Nawijn L. et al, 2017	OT 40 IU/PL, IN	R,DB, PC, CO, fMRI	72 M & F police officers (35-with PTSD; 37 without PTSD).	Under PL, PTSD patients showed ↓ left AI responses to social rewards compared to controls. OT administration ↑ left AI responses during social reward in PTSD patients. OT increased responses to social reward in right putamen.
14.	Otalora GM. et al, 2018	3,4-MDMA (100 & 125 mg with a low dose of MDMA during Psychotherapy	R, DB, dose response comparison during 8 hour psychotherapy sessions.	28 patients with chronic PTSD	↓ in CAPS score for dose 125 mg/100 mg/40 mg. PTSD symptoms remained lower than baseline at 12 month follow up. MDMA assisted psychotherapy is an innovative efficacious treatment for PTSD. No significant drug related ADRs were reported.
15.	Olff M. et al, 2014	OT, IN single dose	fMRI	Acutely traumatized persons admitted to ED.(Frijling et al 2014)	Single dose OT has boosting effect on Amy reactivity in response to emotional faces in PTSD vs traumatized controls.
16.	Palgi S. et al, 2016	OT 24 IU/PL, IN, Single dose	R, DB, PC, CO	62 (32-PTSD; 30-matched controls)	Single IN dose of OT ↑ compassion towards W but not M, both in PTSD patients and controls. OT (IN) may be an effective intervention in patients with PTSD. OT does not improve empathic abilities, it ↑ ability of PTSD men to recognise body motions of anger.
17.	Palgi S. et al, 2017	OT, 24 IU/PL, IN at 1 week interval	R, DB, PC, CO	62 (32-PTSD patients and 30 matching controls)	Patients with PTSD have deficits in emotional and cognitive empathic abilities, that may impair their social an interpersonal skills.
18.	Pierrehumbert B. et al, 2010	OT	Participants were subjected to labortary session involving experimental stress challenge.	80 (26 women + 25 M &W healthy survivors of cancer in childhood oradolescence+ 29 controls)	There was a moderate negative relationship between OT and salivary cortisol. Acute stress stimulates OT secretion.
19.	Sack M. et al, 2017	OT/PL, IN×2 weeks	RCT	35 females with PTSD	OT decreased intensity of provoked PTSD symptoms in female patients.
20..	van Zuiden M. et al, 2017	OT 40 IU, IN, twice daily ×8 days or PL 10 puffs twice daily× 8 days.	R, DB, PC	120 (ED patients with moderate to severe acute distress)	OT administration early after trauma does not ↓ PTSD symptoms in all trauma exposed patients with acute distress, but in high PTSD symptoms severity.

Table 1: Various Clinical trials and studies on intranasal oxytocin (OT) in patients with PTSD.

OT=Oxytocin; IN=Intranasal; IU=International Units; PL= Placebo; DB=Double-blind; R=Randomized; PC=Placebo-controlled; BS=Between-subjects; ED=Emergency door; CO=Cross-over; ; vlPFC= Ventrolateral prefrontal cortex; vmPFC=Ventromedial prefrontal cortex; dACC= dorsal anterior cingulate cortex; Tha= Thalamus; Amy=Amygdala; LA= Left amygdala; RA= Right Amygdala; DLPFC=Dorsolareral prefrontal cortex; fMRI=Functional Magnetic Resonance Imaging; FC= Functional connectivity; BLA= Baso lateral amygdala; CeM=Centromedial; AI= Anterior Insula; MDMA= 3,4-Methylenedioxymethamphetamine; CAPS= Clinician-administered PTSD scale, ADRs=Adverse drug reactions.

Conclusions:

There are a few approved medications, antidepressants, available for the treatment of PTSD. Psychotherapy which is presently the primary treatment for PTSD and shows remission rates only in 1/3rd of PTSD patients; and oxytocin may augment psychotherapy. Many studies have been conducted with intranasal oxytocin administration, in men and women with PTSD or trauma-exposure, with different study designs showing promising results for use in patients with PTSD. Thus intranasal oxytocin is one of the promising therapies, with a different mechanism of action, for patients with PTSDs.

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