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Review

Oxytocin in the Treatment of Psychiatric Disorders

Psikiyatrik Bozukluklarda Oksitosin Tedavisi

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ABSTRACT

Oxytocin is a peptide hormone that is most known for its role in reproduction. However, many effects other than reproduction have been defined. The lifetime prevalence of mental disorders is approximately 20%, and they have a significant ratio among the diseases that lead to disability. Treatment resistance may cause the mental disorder to become chronic and increase disability. With the examination of the oxytocinergic system, both the elucidation of the etiology of the diseases and their evaluation as a new treatment option have come to the fore. In various studies, it has been desired to create a more effective treatment model by measuring the level of oxytocin in psychiatric disorders, examining its receptor, and applying exogenous oxytocin in the treatment. In this review, an overview of oxytocin's efficacy in treatment is presented by considering the relationship between psychiatric disorders and the oxytocinergic system.

Keywords: Psychiatric disorders, oxytocin, schizophrenia, resistance to treatment, autism

ÖZ

Oksitosin peptid yapısında bir hormondur ve en fazla üremedeki rolü ile bilinir. Ancak üreme dışında da pek çok etkisi tanımlanmıştır. Ruhsal bozuklukların yaşam boyu yaygınlığı yaklaşık yüzde 20 oranlardadır ve yeti yitimine neden olan hastalıklar içerisinde azımsanmayacak düzeydedirler. Tedavilerde karşılaşılan direnç ruhsal bozukluğun kronikleşmesini sağlayıp yeti yitimini artırabilmektedir. Oksitosinerjik sistemin incelenmesi ile hastalıkların hem etiyolojisinin aydınlatılması hem de yeni bir tedavi seçeneği olarak değerlendirilmesi gündeme gelmiştir. Çeşitli çalışmalarda psikiyatrik bozukluklarda oksitosin düzeyinin ölçülmesi, reseptörünün incelenmesi ve tedavide eksojen oksitosin uygulanması ile daha etkin bir tedavi modeli oluşturulmak istenmiştir. Bu derlemede psikiyatrik bozukluklar ve oksitosinerjik sistem arasındaki ilişkiye yer verilerek oksitosinin tedavideki etkililiği hakkında genel bir bakış açısı sunulmaktadır.

Anahtar kelimeler: Psikiyatrik bozukluklar, oksitosin, şizofreni, tedaviye direnç, otizm

Introduction

Recently, neuropeptide hormones have become the focus of attention in investigating the relationships between the physiological and mental systems. One of the most studied of these peptides is the hormone oxytocin. Oxytocin functions as a hormone in the peripheral circulation and as a neurotransmitter in the central nervous system. The sensory and social effects of oxytocin on human behavior have been of interest for psychiatric disorders since its discovery. Because of these features, it has been investigated in terms of the pathophysiology and role in the treatment of various psychiatric diseases such as autism, anxiety disorders, depression, and eating disorders. Although it was found that oxytocin levels were different from those of healthy controls in many diseases such as autism, depression and schizophrenia. However, the results are not yet consistent because of method differences or insufficient sample sizes. The therapeutic use of oxytocin in many psychiatric disorders continues to be investigated. In this article, the relationship between oxytocin and psychiatric disorders will be examined and the treatment aspect will be evaluated. At the same time, it aimed to explain the inconsistent results in the literature and gain a holistic perspective.

Oxytocin Definition

Oxytocin is a peptide hormone. It is synthesized in the paraventricular and supraoptic nuclei of the magnocellular neurons of the hypothalamus. It exerts its effects through a uniform g protein-coupled oxytocin receptor. It is secreted from the posterior pituitary by

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childbirth, breastfeeding, and stress. Oxytocin receptors are found in many parts of the central nervous system, such as the prefrontal cortex, nucleus accumbens, lateral septum, hippocampus, amygdala, and stria terminalis. The hypothalamic-pituitary-adrenal (HPA) axis, acetylcholine, GABA, glutamate, opioid, cannabinoid, catecholamine, indoleamine, and steroid systems are related to the oxytocinergic system[1].

Importance of Oxytocin

Oxytocin is mostly known for its role in reproduction. It is secreted by the contraction of the cervix during childbirth and stimulates contraction of the uterus. Thus, childbirth is facilitated. Oxytocin increases milk secretion with nipple stimulation after childbirth and supports breastfeeding. However, many effects other than reproduction have been described. Some studies affirm that oxytocin has effects in various areas such as social behaviors, attachment, empathy, psychological resilience, response to acute and chronic stress, fear response, processing of emotions and behavior, eating behavior, immunological and anti-inflammatory effects, and wound healing[2]. With the definition of various effects of oxytocin, its use for treating different diseases has come to the fore.

Prevalence of Psychiatric Disorders

The lifetime prevalence of psychiatric disorders varies by society, culture, and country. The lifetime prevalence of psychiatric disorders that meet the diagnostic criteria in adults worldwide was found to be 17.6 percent[3].

Five of the first 20 diseases that may cause disability are psychiatric disorders. These include major depressive disorder (MDD), alcohol use disorder, schizophrenia, bipolar disorder, Alzheimer's disease, and other dementia diseases[4]. Both the loss of labor and treatment resistance may lead to a serious financial burden for countries. Hence, the aim is to increase the rate of reaching remission and reduce disability with the search for new treatment options.

Difficulties in Treatments and New Treatment Search

Medical treatments for psychiatric disorders date back to the 1950s. With the discovery and use of chlorpromazine in the early 1950s, significant progress has been made in the fields of pharmacology, psychotherapy, neuromodulation, and psychosurgery. These treatment options are also effective in psychiatric disorders. However, 20%-60% of mental disorders can be unresponsive to treatments[5]. Despite the development of medical treatment options, treatment resistance is observed in approximately 30% of psychotic conditions such as schizophrenia[6]. Similarly, treatment resistance in depression can be seen at a rate of 30 percent[7]. The resistance encountered in the treatments can lead the psychiatric disorder to become chronic and increase disability. Therefore, the search for new treatment options is gaining importance. To increase the response to treatment, methods such as individual evaluation of the patient, choosing the appropriate treatment according to biomarkers, and determining the response to treatment are applied, apart from applying algorithmic diagnosis and treatment[8]. With the examination of the oxytocinergic system, both the elucidation of the etiology of the diseases and their evaluation as a treatment option have come to the fore. The social and behavioral effects of oxytocin have been defined as the increase in sociability, anxiolytic effect, reduction of fear, and anti-stress effects with intranasal oxytocin applications. Therefore, it was thought that mental disorders and the oxytocinergic system may be closely related. Thus, the etiology and treatment of psychiatric disorders have been investigated by measuring the plasma level of oxytocin, defining the oxytocin receptor, and administering exogenous oxytocin[9].

Relationship Between Oxytocin and Psychiatric Diseases

Recently, biomarker studies have increased to clarify the biological basis of mental disorders. It is thought that oxytocin can also be evaluated as a biomarker of diseases[10]. In the oxytocin system, however, the oxytocin level and oxytocin receptor are mostly considered. Various studies have measured oxytocin levels in psychiatric disorders. At the same time, the relationship between oxytocin and the clinical manifestations of the disease is examined. Studies have shown that oxytocin levels in schizophrenic patients were lower than those in healthy controls and were inversely correlated with negative symptoms of the disease. Oxytocin levels were also found to be lower in patients with autism spectrum disorders (ASD) than in healthy controls. In addition, facial recognition and social communication skills were positively correlated with oxytocin levels. It was found that oxytocin levels were lower in patients with eating disorders than in healthy controls[11]. Lower oxytocin levels were found in patients with post-traumatic stress disorder (PTSD) than in healthy controls. This decrease in the oxytocin level was thought to be a biomarker of chronic stress[12]. Similarly, oxytocin levels were found to be lower in patients with MDD, anxiety disorder, bipolar

disorder, and borderline personality disorder than in the healthy control group. A negative correlation was found between childhood trauma and oxytocin levels in patients with bipolar disorder. However, the higher level of oxytocin measured in patients with treatment-resistant depression compared with healthy controls has led to inconsistent results in the literature[13]. The oxytocin receptor has also been examined in terms of its relationship with psychiatric disorders. Genetic variations, epigenetic modifications, and methylation and polymorphisms in the oxytocin receptor gene may be related to the etiology of psychiatric disorders[14]. It has been reported that the quality of parental care, especially in childhood, is associated with rs53576 and rs2254298 oxytocin receptor gene polymorphisms, which are risk factors for depression, anxiety disorder, borderline personality disorder, and behavioral disorder[15]. Thus, it has been emphasized that the quality of parental care in the early period is a crucial factor in the development of mental disorders through the oxytocinergic system.

Use of Oxytocin for Treating Psychiatric Disorders

The first uses of oxytocin were for labor induction and bleeding control in the 1960s. After the modulatory effects of oxytocin in emotional, behavioral, and cognitive areas were defined, its use in mental disorders came to the fore[16]. The intranasal administration of oxytocin has been increased because of its higher bioavailability and blood-brain barrier crossing rates. At the same time, olfactory and trigeminal transport in the nasal region may contribute to the administration of oxytocin. The fact that intranasal administration is noninvasive and well tolerated and its side effects in children and adults are the same as those of placebo has led to the widespread use of oxytocin in practice. Studies have shown that there is no linear dose-response curve in oxytocin treatment, and this is due to the increased affinity of vasopressin to the receptors as the dose increases. It has been reported that the production of endogenous oxytocin increases with the administration of exogenous oxytocin[17].

Oxytocin for Treating Schizophrenia

Schizophrenia is a mental disorder whose etiology has not yet been completely clarified. It includes positive symptoms such as delusions and hallucinations as well as negative symptoms such as affective bluntness, lack of pleasure and interest, difficulty in establishing interpersonal relationships, avoidance of social environments, and impaired social functioning. Although positive symptoms can be improved with antipsychotic treatment, negative symptoms show more complications. Resistance to treatment is a challenge in achieving remission. In some studies, oxytocin levels were found to be lower in schizophrenia patients; however, there are also some studies in which oxytocin levels are the same as those in healthy controls[18]. In a study conducted with clinical scales and cranial magnetic resonance imaging, follow-up was performed on 16 chronic schizophrenia patients with regular intranasal oxytocin administration for 3 months. Because of the follow-up, a decrease was found in the scores of positive and negative symptoms, especially in terms of negative scores. This reduction was inversely correlated with the gray volume of the right insula and the left cingulate cortex. In addition, an increase in verbal fluency was detected with oxytocin treatment. Clinical symptoms and cognitive functions improve with oxytocin administration in chronic schizophrenia, and this improvement may be related to the volume of the right insula and left cingulate cortex[19]. After 24 international unit (IU) intranasal oxytocin administration twice a day for 12 weeks with 68 patients diagnosed with schizophrenia and schizoaffective disorder, it was found that according to the positive and negative syndrome scale, the negative symptoms improved significantly in patients with schizophrenia, and better social functionality performing in the role play task was observed[20]. However, there are also studies reporting that clinical improvement is not achieved with oxytocin administration. In a meta-analysis of 10 randomized controlled trials investigating the clinical effects of oxytocin therapy in 344 schizophrenic patients, 40-80 IU oxytocin was administered to patients for 2-16 weeks on average, and it was reported that there was no significant improvement in symptomatology compared with the placebo group[21]. In the meta-analysis of variance of 10 randomized controlled studies conducted by considering the diversity of study groups, the difference in dosing, and the duration of administration, it was stated that oxytocin administration to schizophrenia patients does not provide clinically significant improvement[22].

Oxytocin for Treating Mood Disorders

Oxytocin was thought to be closely related to MDD because of the lower oxytocin level in patients with MDD and those with the oxytocin receptor gene polymorphism. Simultaneously, its use for treatment in patients with MDD has come to the fore because oxytocin modulates the HPA axis and is associated with neurotransmitters such as serotonin[23]. However, there are conflicting

results for oxytocin treatment in MDD. There are studies showing that the administration of 8 IU oxytocin in addition to escitalopram for a week reduces depressive symptoms and that the administration of 40 IU oxytocin in a single session increases neural activity in the limbic region of patients with MDD during rest. However, it was found that 24 IU of oxytocin, administered for one week in postpartum depression patients, increased the depressive symptoms[24]. It has been suggested that the effect of the oxytocin administered to postpartum depression patients on depressive symptoms is not significant, but it may improve their cognitions[25]. Lastly, there are no sufficient studies that investigate oxytocin use in bipolar disorder patients.

Oxytocin for Treating Autism Spectrum Disorders

ASD; is a heterogeneous group of neurodevelopmental syndromes with multiple genetic inheritances, characterized by limited and repetitive behavior patterns, interests, and activities, and chronic disability in social communication and interaction. After oxytocin's effects were examined, its use for autism treatment came to the fore. ASD is the most studied field for the use of oxytocin in psychiatric disorders. The first trials of oxytocin for autism treatment were intravenous in the early 2000s. Some studies have shown that using oxytocin for the treatment of people with autism is widespread, but the results are inconsistent. In a randomized controlled study, a decrease in repetitive behaviors and an increase in eye contact fixation time were reported with 48 IU oxytocin treatment for 6 weeks in 106 adult individuals with ASD[26]. Again, after 4 weeks of 24 IU oxytocin administered in 40 adult patients with ASD, a decrease in repetitive behaviors and social avoidance and an increase in feeling more energetic and alive were observed compared with the placebo group. It has also been reported that this effect continued for one year after treatment[27]. However, in a comprehensive meta-analysis, it was stated that oxytocin administration provides a clinically insignificant improvement in repetitive behaviors, and therefore, its clinical effect may be limited[28]. In some studies conducted with pediatric patients with autism, it was stated that a significant social and cognitive well-being could not be achieved with oxytocin administration[29]. In another meta-analysis examining oxytocin levels, it was reported that oxytocin levels were lower in children with autism than in healthy controls, this difference was not observed in adolescence and adulthood, and there was no significant difference according to gender[30]. Thus, the first studies on oxytocin are more promising because oxytocin may be used for treating autism. However, current studies have shown that clinical improvement is not at a significant level.

Oxytocin for Treating Anxiety Disorders

After the anxiolytic effect of oxytocin was defined, its use in anxiety disorders came to the fore. In a study conducted with 40 patients with a diagnosis of social anxiety disorder, 24 IU of oxytocin was administered, and after 40 min, patients were able to perform the meeting task more easily when they entered the social environment, but the effect was limited[31]. In another study, it was determined that anxiety symptoms decreased after 5 days of low-dose oxytocin administration in 147 patients with anxiety disorder. In addition, a decrease in increased amygdala, insula, and prefrontal cortex activity has been observed during threats[32]. Based on these studies, it can be thought that a single dose of oxytocin administration has temporary effects on anxiety disorders, whereas chronic applications are more successful.

Oxytocin for Treating Post-traumatic Stress Disorder

Oxytocin therapy for PTSD was first applied to soldiers who participated in the Vietnam War, and it was suggested that it subjectively reduces re-experiencing and recalling traumatic memories. It has been suggested that it is particularly effective in extinguishing conditioned behavior. However, there are inconsistent results in these studies. Although oxytocin has relieving effect on PTSD symptoms, it has been reported that it is not clinically significant. However, it has been claimed that it can improve arousal and memory impairment when applied together with psychotherapy used in PTSD[33,34].

Oxytocin for Treating Alcohol and Substance Use Disorders

When the relationship between the oxytocin system and alcohol and substance use disorders was examined, a bidirectional effect was suggested. Low oxytocin levels or oxytocin receptor gene polymorphisms increase susceptibility to alcohol and substance use disorders. In postmortem studies, oxytocin levels are lower in patients with alcohol and substance use disorders. Oxytocin has regulatory effects on the reward system, tolerance, memory, and stress responses. Oxytocin may have effects on impulsivity, reward seeking, negative affect, anxiety, and compulsive substance use, which are seen in alcohol and substance use disorders. However, there are conflicting results in clinical studies. Some studies have shown that intranasal oxytocin administration reduces the dose of lorazepam needed

for detoxification, withdrawal, and craving symptoms in alcohol use disorder[35]. However, in a study, it was stated that the dose of oxazepam needed for detoxification with intranasal oxytocin administration of 24 IU twice a day for 3 days did not decrease compared with the placebo group[36]. In another study, it was found that alcohol craving and aggression were not decreased with a single dose of 40 IU oxytocin[37]. In oxytocin studies conducted with patients with alcohol use disorder, it can be stated that the clinical response may change with factors such as the patient's compliance to the treatment, duration of treatment, and dose. Significant results cannot be obtained due to the shorter duration of the studies. In 42 patients with methamphetamine dependance it was reported that with 40 IU oxytocin administration for 4 weeks, the rate of craving for methamphetamine and depressive symptoms were decreased, while the level of anxiety was not different[38]. In another study, it was stated that a single dose of 40 IU oxytocin administration to heroin addicts reduced craving and withdrawal symptoms. Thus, oxytocin may be a promising treatment for heroin addiction[39]. There are more considerable results on the efficacy of oxytocin in substance use disorders, which gives hope for its use in substance use disorders.

Oxytocin for Treating Eating Disorders

The use of oxytocin in eating disorders has come to the fore because of its effects on diet choice and food intake, emotional regulation, and social cognition. The low oxytocin levels and oxytocin gene receptor polymorphism in patients with anorexia nervosa; indicate that the oxytocin system has a role in the development of eating disorders. However, this relationship could not be observed in patients with bulimia nervosa and binge eating disorder. At the same time, it has been suggested that oxytocin has an anorexigenic effect and that weight loss may occur with its use in obesity[40].

There are limited studies examining the relationship between eating disorders and oxytocin. In a study conducted with patients with bulimia nervosa and binge eating disorder, it was observed that oxytocin did not have a significant effect in terms of eating behavior and stress[41]. In a different study conducted with patients with anorexia nervosa, it was found that eating anxiety and salivary cortisol levels, and cognitive rigidity decreased with 36 IU oxytocin treatment for 4-6 weeks[42]. In a meta-analysis study, it was stated that the clinical effects of oxytocin on eating disorders were not significant, but oxytocin may reduce food intake in healthy individuals[43].

Oxytocin for Treating Personality Disorders

The role of oxytocin in personality disorders has been investigated. It has been noted that patients with borderline and antisocial personality disorders have low oxytocin levels and decreased oxytocin receptor gene expression. This alteration in the oxytocin system is thought to be related to childhood maltreatment, genetic-environment interaction, and plasticity[44]. Several studies have investigated the relationship between personality disorders and oxytocin, especially for borderline personality disorder. There are conflicting results in studies in which oxytocin treatment was used to reduce the clinical symptoms of borderline personality disorder. In one study, an increase in emotional empathy and social approach motivation was found with a single dose of 24 IU oxytocin administered to 51 patients with borderline personality disorder. In this study, a similar result was found by finding an increase in emotional empathy and social approach motivation in the healthy control group[45]. Thus, it can be stated that oxytocin is promising for correcting social behaviors. In another study, it was found that in oxytocin, individuals with borderline personality disorder noticed social threat cues more quickly, strengthened their avoidance behavior, and reduced impulsivity[46]. Although there are studies indicating the prosocial effects of oxytocin, the opposite effects have also been reported. It has been stated that confidence in patients with borderline personality disorder decreases with oxytocin administration[47].

Oxytocin for Treating Chronic Pain Disorder

Chronic pain: is a symptom that is difficult to treat and manage clinically. Based on the view that oxytocin may have analgesic activity, its use for the treatment of chronic pain disorder has come to the fore and promising results have been obtained. The analgesic efficacy of oxytocin has been tested in conditions such as migraine, chronic low back pain, chronic pelvic pain, and wound pain. In one study, a reduction in pain was reported in approximately 30% of the participants with oxytocin administered to women with chronic pelvic pain, and no side effects were described[48]. In another study, it was reported that thermal pain decreased with oxytocin administration to patients with chronic low back pain, and this may be due to the caudate nucleus[49]. In a study conducted with migraine patients, it was stated that activation in the trigeminocervical region was decreased with the administration of in oxytocin. Thus, oxytocin could be used in the acute and prophylactic treatment of migraine[50].

General Characteristics of the Studies

When open-label and placebo-controlled double-blind studies on the use of oxytocin for treating psychiatric disorders are examined, there are important limitations. The results obtained using different methods and measurement tools used in sample selection are inconsistent. Most studies on the use of oxytocin in treatment were conducted with patients diagnosed with PTSD, schizophrenia, and ASD. There are few studies on other psychiatric disorders. It is noteworthy that the studies have intensified, especially in recent years (2018-2021). In addition, to draw firm conclusions about the use of oxytocin for treating mental disorders, the results of short-term studies with small sample groups should be re-evaluated in randomized, placebo-controlled, long-term studies in larger study populations. The general characteristics of the open-label and double-blind, randomized, placebo-controlled studies performed so far are presented in Table 1.

Conclusion

After the effects of oxytocin, apart from its effects on reproduction, were defined, its use in psychiatric disorders came to the fore. In many disorders such as schizophrenia, ASD, mood disorders, eating disorders, and personality disorders, oxytocin levels were measured and its receptor was examined. Its use as a treatment has been tried and different results have been obtained. Although some studies have reported that the clinical response is better with treatment, there are also studies stating that it has no effect. Many factors are responsible for these inconsistent results in oxytocin studies. Age and gender differences are the most important factors. It has been stated that women in the menstrual cycle may show different oxytocin levels and responses to treatment. In addition, it was stated that childhood trauma can also determine the level of oxytocin, and this factor should be considered. The lack of standardization in the dose and duration of oxytocin therapy may also affect the response to treatment. The presence of additional medical and psychiatric disorders may also affect the oxytocin system. The explanation of many heterogeneities and factors affecting oxytocin level and response to treatment shows the limited aspects of studies. Thus, inconsistent results are obtained, and the evaluation of oxytocin's efficacy is weakened. However, because studies with a larger sample group are conducted in autism and schizophrenia diseases in the literature, the relationship between oxytocin and diseases has been discussed in a broader framework and has given more explanatory information about its use for therapeutic purposes. Demonstration of the effect of oxytocin on stress response and social behaviors in psychiatric diseases and evidence that it can be used for therapeutic purposes show the strengths of oxytocin studies. In particular, in autism and other psychiatric diseases where medical treatment options are limited, there is a need for studies in which the oxytocin level, its relationship with clinical symptoms, and response to oxytocin treatment are evaluated and oxytocin is examined holistically. To reduce heterogeneity and evaluate the efficacy of oxytocin treatment more objectively, the holistic approach stands out in the fact that studies should be conducted with a larger number of patients, with appropriate dosage and duration. Thus, more answers can be obtained regarding oxytocin's relationship with psychiatric diseases.

Table 1. General characteristics of the studies.

Study	Study type	Study subtype	Disorder	Sample	Form of treatment/ method	Outcomes
Carmassi et al.[12] (2021)	Case-control study	Oxytocin-level measurement	PTSD	n: 26 (13 male, 13 female, mean age: 40.3)	The oxytocin plasma levels of PTSD and healthy controls were compared.	In this study, decreased oxytocin levels were determined in PTSD patients when compared with healthy controls. There was no dissimilarity in the patient groups, both male and female.
Jobst et al.[13] (2018)	A pilot study	Oxytocin-level measurement	Chronic depression	n: 16	The CBASP inpatient program was examined in terms of serum oxytocin levels and clinical scales.	After CBASP, it was observed that depressive symptoms decreased considerably. In this study, lower oxytocin plasma levels at baseline correlated with lesser alterations in BDI-II scores. However, there was no difference in HAMD-24 scores.
Ota et al.[19] (2018)	Clinical trial	Oxytocin treatment	Schizophrenia	n: 16 chronic schizophrenia patients	3 months of IN oxytocin treatment	After oxytocin treatment it was found that positive and negative symptoms decreased and verbal fluency increased.
Jarskog et al.[20] (2017)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Schizophrenia and schizoaffective disorder	n: 62 (47 male, 25 female, mean age: 39.1)	12 weeks of twice daily 24 IU IN oxytocin	No statistically significant difference was found between the two groups regarding social cognition. The authors reported that oxytocin contributed less to social functioning than placebo. However, it is noteworthy that a significant improvement in negative symptoms was observed in the group of patients diagnosed with schizophrenia administered oxytocin.
Modabbernia et al.[51] (2013)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Schizophrenia	n: 40 (aged 18-50 years)	IN oxytocin treatment was administered with 5-6 mg risperidone. (First week =40 IU/day, following 7 weeks =80 IU/day)	A statistically significant decrease was found in the PANSS negative and positive sub-scores compared with the placebo group.
Korann et al.[52] (2022)	Controlled clinical trial	Oxytocin treatment	Schizophrenia	n: 31 (all male), HC: 21 (all male)	Resting fMRI scans with IN oxytocin (24 IU)	In this study, it was reported that there was a significant increase in connections extending from the left caudate to the left supplemental motor area, to the left precentral gyrus, and to the left frontal lower triangular gyrus because of oxytocin administration.
Donadon et al.[53] (2021)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Postpartum depression	n: 20, HC: 35	Single IN dose of oxytocin (24 IU)	It was found that the happiness rate of postpartum mothers increased and negative cognitions decreased in the oxytocin-administered group.

Table 1. Continued

Study	Study type	Study subtype	Disorder	Sample	Form of treatment/ method	Outcomes
Ozsoy et al.[54] (2009)	Clinical trial	Oxytocin level measurement	Depression	n: 40 (30 female, 10 male, 29 major depressive disorder, 11 bipolar disorder depressive episode. HC: 32 (20 female, 12 male)	The relationship between serum oxytocin levels and treatment (antidepressants and ECT) was examined.	In this study, it was found that there was a decrease in the patients' serum oxytocin levels both before and after treatment compared with the control group. It has also been reported that serum oxytocin levels do not change with antidepressant drug treatment and ECT application. It was noted that the oxytocin levels of the female patients participating in the study were significantly lower than those of the women in the control group.
Scantamburlo et al.[55] (2015)	An open-label trial	Oxytocin treatment	Resistant depression	n: 14, patients included in the study who did not respond to 8 weeks of 40 mg/ day escitalopram treatment and were diagnosed with treatment-resistant depression lasting at least 2 years.	The daily dosage of 16 IU IN oxytocin during 4 weeks in addition to escitalopram 40 mg	HDRS-17 scores were significantly reduced by the administration of oxytocin.
Andari et al.[56] (2021)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Schizophrenia	n: 20 (all male)	Single IN dose of 24 IU oxytocin	It has been reported that a single dose of IN oxytocin, which has a limited effect on emotion recognition, has a significant effect on social cue processing.
Yamasue et al.[26] (2020)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	ASD	n: 106 (18 to 48 years of age)	6-week of IN oxytocin (48 IU/day)	A decrease in repetitive behaviors and an increase in eye contact fixation time were detected in the oxytocin-administered group.
Bernaerts et al.[27] (2020)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	ASD	n: 40 (adult men)	4 weeks of IN oxytocin treatment (24 IU once daily in the morning)	Compared with the placebo group, the group administered oxytocin showed a decrease in repetitive behaviors and social avoidance and an increase in feeling more energetic and lively. The authors stated that this effect continued in the first year after treatment.
Sikich et al.[29] (2021)	Placebo-controlled trial	Oxytocin treatment	ASD	n: 146 and 144 placebo groups (3-17 years of age)	24-week IN oxytocin (48 IU/day)	It was reported that there was no statistically significant increase in social and cognitive functioning compared with the placebo group.

Table 1. Continued

Study	Study type	Study subtype	Disorder	Sample	Form of treatment/ method	Outcomes
Kanat et al.[57] (2017)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	ASD	n: 29 (mean years: 38.2. All patient was male)	Single IN dose of 24 IU of oxytocin	It has been reported that because of oxytocin administration to patients diagnosed with ASD, attention to faces increased compared with the control group. Additionally, it was also stated that a significant level of social anxiety was represented by careful avoidance of faces in the placebo-administered group.
Kosaka et al.[58] (2016)	Double-blind (12 weeks), open-label (12 weeks), and follow-up (8 weeks) phases inplacebo-controlled trial	Oxytocin treatment and oxytocin receptor investigation	ASD	n: 60 (47 male and 13 female adults over 15 years of age)	32 IU IN oxytocin per day or 16 IU per day IN oxytocin administration or placebo groups, it was measured SNPs in the OXTR	It was determined that there was a significant improvement in the CGI-I score with high-dose oxytocin administration and that people with a T allele in rs6791619 showed a higher rate of improvement with low-dose oxytocin dosage. It has been reported that the administration of high doses of oxytocin over a long time tends to significantly increase gaze fixation to areas of the face that attract social attention, such as the eyes and biomotion.
Guastella et al.[59] (2010)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	ASD	n: 16 (male youth aged 12 to 19)	Single IN dose of 18 or 24 IU oxytocin	In the study, it was stated that oxytocin application improved mind reading through the eyes compared with the placebo group. However, the authors pointed out that this result was limited to participants aged 12-15 years.
Watanabe et al.[60] (2015)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	ASD	n: 20 (high-functional adult males)	6-week IN oxytocin (48 IU/ day)	In the oxytocin-administered group, an improvement in the ADOS scale and an increase in the connection between ACC and DMPFC were found.
Voncken et al.[31] (2021)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	SAD	n: 40	Single IN dose of 24 IU of oxytocin	Compared with the placebo group, an improvement in social behavior, especially the acquaintance task, was observed as a result of oxytocin administration in patients diagnosed with SAD.
Fang et al.[61] (2017)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	SAD	n: 52 (all male)	Single IN dose of 24 IU of oxytocin	Oxytocin increases social performance in patients diagnosed with SAD with lower social anxiety levels.
Labuschagne et al.[62] (2010)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	GSAD	n: 18 (all male, aged between 18 and 55 years)	Single IN dose of 24 IU of oxytocin	In the study, it was reported that oxytocin application in the GSAD group decreased the increased amygdala reactivity to fearful faces. The authors stated that in the healthy control group, oxytocin had no effect on amygdala activity in terms of emotional faces.

Table 1. Continued

Study	Study type	Study subtype	Disorder	Sample	Form of treatment/ method	Outcomes
Fang et al.[63] (2019)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	BDD	n: 18, HC: 16	Single IN dose of 24 IU of oxytocin	No significant change was observed in the oxytocin group compared to placebo. It was found that oxytocin led to greater internal attributions in other-referent contexts for those with BDD compared with HCs.
Flanagan et al.[64] (2018)	Double-blind, placebo-controlled trial	Oxytocin treatment	PTSD	n: 16 (7 female, 9 male) and 18 (11 female, 7 male) control groups	Single IN dose of 24 IU of oxytocin	It was determined that individuals with a diagnosis of PTSD administered oxytocin performed better than the placebo group. In addition, they reported that the connection between the dorsolateral prefrontal cortex and anterior cingulate increased in individuals with PTSD treated with oxytocin.
Flanagan et al.[65] (2018)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment with PE therapy	PTSD	n: 17 (14 male, 3 female)	40 IU of oxytocin was administered 45 min before PE. Total 10 individual, 90-minute PE therapy sessions per week.	In the study, it was determined that the group administered oxytocin showed lower PTSD and depression symptoms during PE. It was also reported that working alliance scores were higher, but these differences were not statistically significant.
Sippel et al.[66] (2021)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	PTSD	n: 34 (13 male, 21 female)	Single IN dose of 24 IU of oxytocin	Oxytocin in response to fearful faces was found to reduce left amygdala-left and right anterior insula connections in women. It was also found to increase the left amygdala-right anterior insula connection in men.
Melby et al.[36] (2019)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment with oxazepam	Alcohol withdrawal syndrome	n: 40 (29 male, 11 female)	IN oxytocin (24 IU twice daily) during 3 days with mean: 56.8 mg oxazepam in the oxytocin group, mean: 79 mg oxazepam in the placebo group	It was found that compared with placebo, IN oxytocin did not considerably lessen the oxazepam dose required for the entire 3-day trial of alcohol detoxification and withdrawal therapy.
Flanagan et al.[37] (2022)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Alcohol craving and subjective aggression	n: 200 (100 couples)	Single IN dose of 40 IU of oxytocin	In the study, it was reported that the administration of a dose of IN oxytocin was not effective in alleviating alcohol cravings or aggression.
Azadbakht et al.[38] (2022)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Methamphetamine dependent	n: 42 Methamphetamine-dependent patients	4-week IN oxytocin (40 IU/day)	This study demonstrated that oxytocin administration is linked with a considerable development in craving and depression scores. However, there was no meaningful change in anxiety scores compared with the placebo group. Furthermore, it was observed that oxytocin administration substantially reduced cortisol and ACTH levels.

Table 1. Continued

Study	Study type	Study subtype	Disorder	Sample	Form of treatment/ method	Outcomes
Moeini et al.[39] (2019)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Heroin dependent	n: 58 (all male)	Single IN dose of 40 IU of oxytocin	In this study, it was reported that acute oxytocin administration reduced craving and withdrawal scores but did not change anxiety at a statistically significant level. The authors reported that a single dose of oxytocin in people using heroin reduced cortisol levels during withdrawal and improved the cortisol/ DHEAS ratio.
Leslie et al.[41] (2019)	Double-blind, placebo-controlled trial	Oxytocin treatment	Bulimia nervosa and binge eating disorder	n: 25 (all female), HC: 27	Divided dose of 64 IU IN oxytocin	In this study, it was reported that oxytocin did not have any significant effect on eating behavior, subjective stress, or salivary cortisol levels.
Russel et al.[42] (2018)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Anorexia nervosa	n: 41	4-6 weeks IN oxytocin (36 IU/day)	In this study, it was reported that after IN oxytocin administration, EDE eating anxiety subscale scores decreased statistically and cognitive rigidity. The authors stated that after oxytocin administration, salivary cortisol levels decreased significantly compared with the placebo group.
Domes et al.[45] (2019)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	BPD	n: 51, HC: 51	Single IN dose of 24 IU of oxytocin	In the study, it was found that the placebo group exhibited a decrease in cognitive and emotional empathy and a decrease in motivation for social approach behavior compared with patients diagnosed with BPD and healthy controls. The authors pointed out that IN oxytocin significantly increased emotional empathy and approach motivation in both patients diagnosed with BPD and the healthy control group compared with placebo.
Bertsch et al.[67] (2013)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	BPD	n: 40 (adult female) HC: 41	Single IN dose of 26 IU of oxytocin	The study found that, compared with the control group, patients with borderline personality disorder experienced increased amygdala activation in response to angry faces, as well as more and faster baseline fixation changes to the eyes of angry faces. It has been reported that this condition improves after oxytocin administration.
Simeon et al.[68] (2011)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	BPD	n: 14, HC: 13	Single IN dose of 40 IU of oxytocin	A significant reduction in stress-related dysphoria was observed in borderline patients administered oxytocin. Cortisol, which increased in response to stress, tended to decrease in borderline patients administered oxytocin.

Table 1. Continued

Study	Study type	Study subtype	Disorder	Sample	Form of treatment/ method	Outcomes
Flynn et al.[48] (2021)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Chronic pelvic pain	n: 12 (adult female)	24 IU IN oxytocin twice daily during 2 week	In the study, it was reported that oxytocin administration for two weeks decreased pain intensity and a significant improvement compared with placebo. The authors drew attention to the results of 4 female patients suffering from chronic pain who were administered IN oxytocin.
Boll et al.[49] (2020)	Randomized double-blind, placebo-controlled trial	Oxytocin treatment	Chronic low back pain	n: 22, HC: 22	Single IN dose of 24 IU of oxytocin	In this study, it was reported that oxytocin reduced pain intensity compared with placebo and increased BOLD reactions in the caudate nucleus of the striatum in patients suffering from chronic low back pain according to HC.

PTSD: Post-traumatic stress disorder, CBASP: The Cognitive Behavioral Analysis System of Psychotherapy, BDI-II: Beck Depression Inventory-II, HAMD-24: The 24-item Hamilton Depression Rating scale, IN: Intra-nasal, IU: International units, PANSS: Positive and Negative Syndrome scale, fMRI: Functional magnetic resonance imaging, HC: Healthy controls, ECT: Electroconvulsive therapy, HDRS-17: The 17-item Hamilton Depression Rating scale, ASD: Autism spectrum disorder, OXT: Oxytocin, OXTR: Oxytocin receptor gene, SNPs: Single-nucleotide polymorphisms, ADOS: Autism Diagnostic Observation scale, ACC: Anterior cingulate cortex, DMPFC: Dorsomedial prefrontal cortex, BDD: Body dysmorphic disorder, SAD: Social anxiety disorder, GSAD: Generalized social anxiety disorder, PE: Prolonged exposure, ACTH: Adrenocorticotropic hormone, EDE: Eating disorders examination, BPD: Borderline personality disorder, BOLD: Blood oxygen level dependent

Ethics

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: S.C.K., C.H., Design: S.C.K., C.H., Data Collection and/or Processing: S.C.K., C.H., Analysis and/or Interpretation: S.C.K., C.H., Literature Search: S.C.K., C.H., Writing: S.C.K., C.H.

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