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Does the use of intranasal oxytocin in the treatment of women with anorexia nervosa improve recognition of emotional expression compared to placebo?

Alyssa N. Kearney
Philadelphia College of Osteopathic Medicine

Does the use of intranasal oxytocin in the treatment of women with anorexia nervosa improve recognition of emotional expression compared to placebo?

Alyssa N. Kearney, PA-S

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not “Does the use of intranasal oxytocin in the treatment of women with anorexia nervosa improve recognition of emotional expression compared to placebo?”

STUDY DESIGN: A systematic review of three studies that were published in English between 2014-2018.

DATA SOURCES: Three randomized controlled trials (RCTs), two with a crossover design, that were published in peer-reviewed journals and found via PubMed. Articles were chosen based on pertinence to the clinical question.

OUTCOMES MEASURED: Improvement in the ability to recognize facial expressions were measured through the Reading the Mind in the Eyes Test (RMET) and attentional bias scores from a visual probe test. Images for the visual probe test were gathered from the Korean Facial Expressions of Emotion collection.

RESULTS: Kim et al. conducted a cross-over designed study that found increased vigilance to anger during administration of intranasal oxytocin. The calculated t-score was -2.847 (df = 30). This calculation is statistically significant with a p-value of 0.008. A study performed by Leppanen et al. found a mean change ± standard deviation in accuracy on RMET as 78.83 ± 13.74 for women using a placebo. The change with regards to the intranasal oxytocin spray was 81.77 ± 10.67. This study did not include a calculation for statistical significance. Russell et al. found in an RCT that the mean change in accuracy in performance on the RMET was of 1.6 ± 3.1 in the placebo group as contrasted to 0.1 ±2.0 in the experimental group. This study also failed to provide a statistical significance calculation.

CONCLUSION: Evidence presented in this review was inconclusive at determining whether intranasal oxytocin was effective at improving emotional recognition in women with anorexia nervosa. Statistical significance with a large treatment effect was shown in the study by Kim et al. in regards to increased vigilance of an angry expression. The studies by Leppanen et al. and Russell et al. did not provide a measure of statistical significance. Further research is needed to determine efficacy of intranasal oxytocin.

KEYWORDS: anorexia nervosa, intranasal oxytocin

INTRODUCTION

Anorexia Nervosa (AN) is a psychiatric disorder in which patients have an intense fear of gaining weight leading to a restricted caloric intake, inability to accurately perceive their body shape, and using their weight as a means of self-appraisal. It is estimated that 9% of the American population will develop an eating disorder throughout their lifetime.[1] While this does include other diagnoses such as bulimia nervosa and binge eating disorder, this constellation of disorders is the second most deadly mental illness, following opioid overdose.[1] Due to the grave nature of anorexia nervosa, it is imperative that healthcare providers are able to effectively recognize the warning signs in patients, however, this has been ineffective. It is estimated that currently only 10% of patients with anorexia nervosa are actively seeking treatment.[2] Even with this seemingly low treatment rate, the cost of eating disorders is $64.7 billion per year and the annual loss of well-being attributed to eating disorders is estimated at $326.5 billion.[3]

The cause of AN is not well understood, but many models incorporate the potential factors of genetics, psychological wellness, personality traits, life experiences, and biologic properties. These factors interplay to cause severe distress in a patient's life as seen by symptoms over a vast array of wellness determinants, including those in the physiological, behavioral, and social dimensions. Prominent indicators of anorexia nervosa may include weight loss, obsessive dieting, meal rituals, secondary amenorrhea, constipation, dizziness, cold intolerance, thinning hair, and social withdraw. In a 2018 study by Cardi et al.,[4] it was found that while social difficulties are a feature of eating disorder pathology, they may also be a predisposing factor to the development of anorexia nervosa. Fear of judgement, lack of social competence, and submissive tendences in early childhood can be predictors of a future diagnosis.[4]

Once a patient with anorexia nervosa begins treatment, the standard regimen begins with weight stabilization through either an in-patient or out-patient program. Eating disorder treatment encompasses 23,560 inpatient hospitalizations per year in the United States.[3] During this critical stage of treatment, patients are at risk of refeeding syndrome. This is where the body cannot handle an increased metabolic demand leading to edema, organ failure, muscle weakness, delirium, or death. Due to this potential complication, weight gain should be carefully monitored by a patient's treatment team. Another vital aspect of treatment for AN is psychotherapy. Therapy should be aimed at creating a healthy mindset towards food and body image and can be accomplished through a vast array of techniques including cognitive behavioral therapy (CBT), family therapy, interpersonal therapy, or acceptance and commitment therapy.[5] Adjunctive therapies may include nutritional counseling or pharmacotherapy.

Even with a multifaceted treatment approach, the relapse rate for anorexia nervosa is between 9-52%, the highest risk is within the first year of treatment.[6] These high rates could be due to residual symptoms causing continued distress after completion of a treatment program.[6] It is believed that the social difficulties that are causative and propagated through AN may be present after a seemingly successful treatment attempt.[4] During psychotherapy patients may be able to improve some aspects of their social functioning, such as how to navigate anxiety surrounding eating in front of others. However, not every pathologic thought process can be corrected through psychotherapy and pharmacotherapy. For example, typical methods of treatment are unable to help a patient with anorexia nervosa recognize facial expressions. This social skill is vital in being able to navigate social scenarios. It is theorized that administration of a physiologic hormone may be able to accentuate nuanced social skills that psychotherapy cannot teach.[7-9] Oxytocin is known as the social bonding hormone. Current literature suggests

that levels of oxytocin in cerebrospinal fluid are lowered during the course of anorexia nervosa.[7] Preliminary studies have shown potential benefits in the use of oxytocin in adolescents with autism spectrum disorder.[8] Intranasal administration of this hormone improves emotional recognition and facilitates trusting of strangers in this group.[8] This paper evaluates three randomized controlled trials to investigate the use of intranasal oxytocin in the treatment of AN.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Does the use of intranasal oxytocin in the treatment of women with anorexia nervosa improve recognition of emotional expression compared to placebo?"

METHODS

This study incorporates three randomized controlled trials (RCTs) that were published in peer-reviewed journals. The studies were found through searching the PubMed database with the keywords of "anorexia nervosa" and "intranasal oxytocin". Articles were selected based on relevance to the clinical question and use of patient-oriented outcomes (POEMS). Inclusion criteria consisted of studies published after 2009. Exclusion criteria consisted of studies published before 2009 and those that included patients with bulimia nervosa. Inclusion and exclusion criteria for each individual study can be found in Table 1.

The patient population included was women with anorexia nervosa. Studies focused on comparing an intranasal oxytocin intervention to an intranasal placebo spray. Each study had varying formulations for these intranasal sprays. The outcomes measured in all of the studies was improvement of a patient's ability to recognize emotional expression. Recognition was assessed through the Reading the Mind in the Eyes Test (RMET) or based on attentional bias from a

visual probe test. The statistics reported and used in this systematic review are t-scores, mean change from baseline, and mean ± standard deviation.

OUTCOMES MEASURED

The outcome measured in each of the three studies was ability to recognize facial expressions. The study performed by Kim et al. measured facial recognition based on attentional bias from a visual probe task.[7] This task utilized images of faces modeling happiness, anger, or disgust from the Korean Facial Expressions of Emotions collection. Participants were shown a neutral and an emotionally expressive face side-by-side for 1,000 milliseconds. The pictures were then replaced by two visual dotted probes and participants had to press a button corresponding to which visual probe they saw first.[7] Attentional bias was measured based on which probe the participant chose and how fast they reacted to the probe.[7] Scores were calculated by subtracting mean reaction times for emotional stimuli from mean reaction times for neutral stimuli (Pneutral – Pemotional). This means that positive scores show increased attention to emotional stimuli, while negative scores are interpreted as avoidance of emotional stimuli.[7]

The studies performed by Leppanen et al. and Russell et al. utilized a Reading the Mind in the Eyes Test (RMET).[8,9] In each study, participants were shown 36 pictures of eyes portraying emotions and given the choice of four options to see if they could correctly identify the expression portrayed.[8,9] The participants of these studies were then assessed based on response times and accuracy. It was theorized that a shorter reaction time for accurate guesses meant the patients were more familiar with the facial expression.[8,9] Longer reaction times meant the patients had to think harder about the expression in front of them.

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Kim[7], 2014	Double-blind, placebo-controlled crossover study	31	Median 23.10	Active illness as defined in the DSM-IV and a clinical interview	Weight-recovered, substance use or psychotic disorder, autism or Asperger's syndrome, psychiatric medication influencing attentional bias	0	40 IU oxytocin intranasally given 45 minutes before tasks (35.2 mg oxytocin, sodium chloride, and acetic acid)
Leppanen[8], 2017	Double-blind, placebo-controlled crossover study	30	16-65 years old	DSM-5 diagnosis of anorexia nervosa, female, over 16 years old	Pregnancy, drug/alcohol abuse, hormonal disturbance, impaired cardiovascular functioning, regular medication use	0	5 puffs per nostril of nasal spray with 40 IU oxytocin
Russell[9], 2018	Randomized control trial	41	16-60 years old	Female, DSM-IV diagnosis of anorexia nervosa, over 16 years old	Less than 16 years old, male, BMI ≥19.5 kg/m^2, IQ < 80, pregnancy, psychosis, alcohol/drug dependence, suicidality, medical comorbidity, septal deviation or nasal condition, & involuntary admissions	8	Intranasal spray [with 9 IU oxytocin per spray, glycerol, sorbitol, benzyl alcohol, and distilled water] one puff per nostril given twice daily

RESULTS

Kim et al. utilized a double-blinded, placebo controlled cross-over designed study to determine the effects of intranasal oxytocin on the attentional bias to facial expressions in women with anorexia nervosa.[7] A total of 31 participants with anorexia nervosa, diagnosed by the DSM-IV criteria, were recruited between 2012-2013 from the Eating Disorder Clinic of Seoul Paik Hospital in South Korea.[7] Exclusion criteria involved diagnoses that could further distort a patient's social processing and can be found in Table 1. Patients were randomly assigned to receive either the intranasal oxytocin spray or an intranasal placebo via a Microsoft Excel program.[7] In this study, patients self-administered the nasal spray under guidance of a researcher. The dot probe task was then completed within 45-minutes of administration.[7] Participants then returned within 4-7 days to complete their second trial with the other spray.[7]

In this study by Kim et al.[7], attention was measured based on the speed with which the patient responded to each visual probe trial. The authors postulated that a faster response time would be seen if the patient had already been paying attention to the image that the probe replaced.[7] Mean response times were recorded for each participant and outlying data beyond 2 standard deviations from the average were removed for each patient.[7] Statistical analysis was completed with t-scores and a calculated p-value. The angry expression had a t-score of -2.847 with 30 degrees of freedom and a p-value of 0.008.[7] Due to the p-value being less than 0.01, this shows that the change for the anger stimuli was statistically significant.[7] The interpretation for this value is that patients with anorexia nervosa treated with intranasal oxytocin had increased vigilance for angry facial stimuli as compared to the avoidance of angry faces seen with the intranasal placebo trials.[7] The happy and disgust stimuli did not have clinical significance due to low p-values of 0.868 and 0.120, respectively.[7] The attentional bias for "happy" stimuli had a

resultant t-value of -0.168 with 30 degrees of freedom.[7] The t-score for disgust stimuli was 1/602 with 30 degrees of freedom.[7] Results are listed in Table 2.

Table 2. Attentional Bias Scores based on Emotional Expression (data from Kim et al.[7])

Emotion	T-Score (df = 30)	P-Value
Happy	-0.168	0.868
Angry	-2.847	0.008
Disgust	1.602	0.120

A 2017 study conducted by Leppanen et al.[8] investigated the efficacy of a dose of intranasal oxytocin in the interpretation of emotional expression in women with anorexia nervosa. Thirty women meeting the DSM-V diagnostic criteria for anorexia nervosa were recruited through the South London and Maudsley National Health Service.[8] Exclusion criteria are listed in Table 1. The study design was a double-blinded, placebo-controlled cross-over design with randomization.[8] Patients self-administered either the oxytocin or placebo intranasal spray and completed the Reading the Mind in the Eyes test (RMET) 15 minutes later.[8] Participants returned to complete the crossover after a two-week interval.[8]

The treatment effect for the Leppanen et al.[8] study was considered small. This study utilized mean accuracy ± standard deviation to assess treatment effect. For participants with anorexia nervosa, their accuracy percentage when calculated for the placebo intranasal spray was 78.83 ± 13.74.[8] The values with regards to the oxytocin spray were 81.77 ± 10.67.[8] These results can be found in Table 3. There was no measure of precision calculated in regards to the

desired outcome for the patients with anorexia nervosa. Therefore, statistical significance surrounding interpretation accuracy cannot be determined for this study.[8]

Table 3. Performance on RMET in Patients with Anorexia Nervosa (data from Leppanen et al.[8])

	Drug	Mean ± SD
Accuracy (%)	**Placebo**	78.83 ± 13.74
	Oxytocin	81.77 ± 10.67

In a 2018 randomized controlled trial, Russell et al.[9] sought to investigate the long-term effects of intranasal oxytocin on the identification of emotional expression in women with anorexia nervosa. The study was conducted in two phases. Phase one was a six-week trial that recruited participants from December 2011 until May 2012.[9] Phase two recruited patients from May 2013 to December 2013, but was shortened to four weeks for an unspecified reason.[9] In total, 41 patients were recruited from a hospital-based Eating Disorder Unit at Northside Clinic in Sydney, Australia.[9] All patients were receiving nutritional rehabilitation and met the DSM-IV diagnosis for anorexia nervosa.[9] Pregnant women, suicidal patients, women with septal deviation, and other conditions listed in Table 1 were excluded from this study.[9] The participants were blindly randomized to either the experimental or placebo group with a computer randomization software.[9] Four women from the experimental group and four women from the placebo group were lost to follow-up.[9] Russell et al.[9] continued with a worst-case analysis by replacing the mean of the intervention group or the last case carried forward when able.

Patients in this study were tested with the RMET at baseline and at the conclusion of the trial.[9] Throughout the experiment, women were given 2 doses of intranasal oxytocin or placebo spray per day.[9] The doses were supervised by a nurse and vials were weighed after administration to ensure dose compliance.[9] Statistical analysis was calculated with mean change in accuracy ± standard deviation from baseline on the RMET. The placebo group had a resulting change of 1.6 ±3.1 in contrast to the experimental oxytocin group whose mean change was 0.1 ±2.0.[9] Results can be found in Table 4. Despite these figures, Russell et al. did not calculate a precision value for this outcome measurement so statistical significance is unknown.[9]

Table 4. Outcome Measures for Baseline, Follow-Up, and Change over Time on the Reading Mind in the Eyes Test (data from Russell et al.[9])

Time	Placebo (N = 17)	Oxytocin (N = 16)	Total (N = 33)
Baseline	28.5 ±3.8	30.3 ±2.2	30.3 ±2.5
Follow-Up	30.2 ±2.7	30.4 ±2.2	29.7 ±4.6
Δ Change	1.6 ±3.1	0.1 ±2.0	0.9 ±2.7

DISCUSSION

This systematic review assessed the efficacy of intranasal oxytocin as an adjunctive therapy to target social functioning in the treatment of anorexia nervosa. Kim et al.[7] found that doses of intranasal oxytocin increased patient's vigilance to angry faces as compared to placebo with a p-value of 0.008 and a large treatment effect. The study performed by Leppanen et al.[8] suggests that oxytocin was effective in identification of emotional expression with higher accuracy percentages on the RMET test compared to placebo, 81.77 ± 10.67 compared to 78.

± 13.74. However, this study did not demonstrate statistical significance.[8] The study conducted by Russell et al.[9] suggests that the placebo group (1.6 ±3.1) had a larger change in ability to recognize expressions correctly by the end of the trial as compared to the experimental group (0.1 ±2.0), but statistical significance was again, not demonstrated.

A limitation found in all three studies used in this review was the use of adjunctive medications. There were participants in each of the three studies utilizing either antidepressant or antipsychotic medications. Three patients in the study by Kim et al.[7] were taking a 20 mg fluoxetine prescription daily leading up to and throughout the trial. Half of the participants in the 2017 study by Leppanen et al.[8] were allowed to continue their psychotropic medications. Patients included in the study conducted by Russell et al.[9] were allowed to stay on their medications due to ethical considerations. In this study, 59% of patients were taking an antidepressant and 66% of patients were prescribed an antipsychotic medication.[9]

In the study by Kim et al.,[7] patients were allowed to self-administer the nasal spray under supervision by a study clinician. This may have skewed the medication administration and delivery due to human error. The patients were not trained in how to use an intranasal spray correctly. A limitation found in the study conducted by Leppanen et al.[8] was that some patients had completed the RMET assessment in prior studies. The patients with prior knowledge of the task had higher scores than those who were unfamiliar with the test.[8] This undermines the study because prior experience seemed to have more of an effect on patient accuracy than the oxytocin treatment.

CONCLUSION

The evidence presented in this systematic review was inconclusive in determining if the use of intranasal oxytocin is effective at improving recognition of emotional expression in women with anorexia nervosa. While Kim et al.[7] provided statistically significant evidence that a dose of intranasal oxytocin can increase vigilance to angry stimuli, the studies conducted by Leppanen et al.[8] and Russell et al.[9] did not provide statistical significance for the treatment group compared to placebo. More research is required to form a more precise conclusion.

Larger scale studies with statistical significance calculations are needed to further assess the efficacy of intranasal oxytocin as a treatment in anorexia nervosa. Future studies can begin to investigate the ideal dosing of intranasal oxytocin that will derive benefits for women with anorexia nervosa. These studies provided standardized dosing for all patients and weight-based dosing was not considered. Dosing schedules may also be examined in later studies to assess whether daily, twice daily, or weekly dosing would be more effective in seeing psychosocial benefits and how long therapy should be maintained. Other studies in this field can also examine the effects of utilizing both a psychotropic medication and intranasal oxytocin on psychosocial functioning of women with anorexia nervosa compared to just intranasal oxytocin.

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