Clinical Pharmacology & Biopharmaceutics

Agabio et al., Clin Pharmacol Biopharm 2016, 5.2
DOI: 10.4172/2167-065X.1000155

Research Article Open Access

Oxytocin Nasal Spray in the Treatment of Binge Eating Disorder and Obesity: A Pilot, Randomized, Double-Blind Trial

Roberta Agabio[1,2]*, Anna Maria Giulia Farci[3], Olga Curreli[3], Raffaele Deidda[4], Silvia Mercuro[3], Romina Naitana[3], Angelo Restivo[5], Elisa Tronci[3], Gian Luigi Gessa[1,2] and Maria Rosaria Melis[1,2]

[1]*Department of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Italy*
[2]*Center of Excellence on Neurobiology of Dependence, University of Cagliari, Italy*
[3]*Clinical Nutrition Center, Department of Medical Sciences "M. Aresu", University of Cagliari, Italy*
[4]*Pharmaceutical Service, University of Cagliari, Italy*
[5]*Colorectal Surgery Center, Department of Surgical Sciences, University of Cagliari, Italy*

Abstract

1.1. Background

Preclinical studies suggest that the neuropeptide oxytocin reduces food intake and body weight, but only a few clinical studies have investigated the translatability of these findings in humans. The present study investigated the safety and efficacy of oxytocin nasal spray in patients affected by binge eating disorder and obesity.

1.2. Methods

Seventeen outpatients affected by binge eating disorder and obesity participated in a 8 week double-blind trial and received oxytocin (n=8; 24 IU, four times a day, 20 min before each of three meals and before going to bed) or placebo (n=9) with an energy-restricted diet. Primary outcomes included adverse events and the number of binge eating episodes per week. Secondary measures included body weight, BMI, severity of BED, craving for food, quality of sleep, quality of life, anxiety, and depressive symptoms.

1.3. Results

One patient of oxytocin group discontinued prematurely the trial before the first post-randomization efficacy measure. Among the other 16 participants, 13 (81.2%) completed the trial, and 3 (18.8%) discontinued [3 in the oxytocin group; 0 in the placebo group (p=0.0625, Fisher's exact test)]. No significant difference between groups was found in any outcome evaluated. Patients of the placebo group performed slightly better than patients of the oxytocin group in some secondary outcomes, but these differences were not significant.

1.4. Conclusion

Oxytocin nasal spray resulted to be safe, including in women of childbearing age but did not significantly reduce the number of binge eating episodes per week in outpatients affected by binge eating disorder and obesity. These findings are discussed in light of the human oxytocin literature.

Keywords: Oxytocin nasal spray; Obesity; Binge eating disorder; Body weight; Sex differences

Introduction

Binge eating disorder (BED) is a mental disorder characterized by recurrent consumption of an unusually large amount of food in a discreet period of time, accompanied by a sense of lack of control, without inappropriate compensatory behaviors typical of bulimia [1]. Consequently, BED is often associated with obesity and obese individuals with BED have a higher concern for body weight and body-shape dissatisfaction than obese individuals without BED [2]. BED is also associated with significant psychiatric comorbidities, such as mood and anxiety disorders [1].

Pharmacologic agents (antidepressants, anticonvulsants, and obesity drugs) have shown moderate effectiveness for the treatment of BED and the only medication approved in the US, but not in Europe, is a prodrug of dextroamphetamine, lisdexamfetamina dimesylate [3].

In the last 20 years, knowledge regarding the central and peripheral mechanisms controlling food intake, energy balance, metabolism, and related aspects, such as appetite and satiety, has greatly increased and numerous neurotransmitters, neuropeptides, and hormones involved in these mechanisms have been identified [4]. Interestingly, a large body of findings supports a prominent role for oxytocin in the modulation of food intake and body weight in animal models [5].

Oxytocin is a neuropeptide primarily produced in the supraoptic (SON) and paraventricular (PVN) hypothalamic nuclei and released by the neurohypophysis into the bloodstream for its hormonal effects in lactation and uterine contractions [6]. Hypothalamic oxytocinergic neurons also project to specific central areas involved in the modulation of motivation, sense of well-being, and sexual performance [6,7]. A large number of studies found that administration of oxytocin reduces food intake and body weight in animal models of obesity [5,8].

Only a few studies have investigated the role of oxytocin in human nutrition [9-12]. In the first study, intravenous administration of oxytocin to healthy subjects reduced, instead of increasing, the sensation

***Corresponding author:** Roberta Agabio, Department of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari, Cittadella Universitaria, Monserrato (CA), Italy, Tel: +39 070 6754325; E-mail: agabio@unica.it

Received March 16, 2016; **Accepted** April 06, 2016; **Published** April 12, 2016

Citation: Agabio R, Farci AMG, Curreli O, Deidda R, Mercuro S, et al. (2016) Oxytocin Nasal Spray in the Treatment of Binge Eating Disorder and Obesity: A Pilot, Randomized, Double-Blind Trial. Clin Pharmacol Biopharm 5: 155. doi:10.4172/2167-065X.1000155

of satiety [9]. More recent trials used the new intranasal formulation of oxytocin [13]. This route of administration allows oxytocin to penetrate into the central nervous system, likely through olfactory epithelial intercellular spaces [13]. In one study, the administration of this formulation (24 IU) to individuals of normal weight reduced the consumption of palatable food but not hunger-driven eating [10]. In another study, the administration of oxytocin nasal spray (24 IU) to obese patients, four times a day, approximately 20 min before meals and sleep for 8 weeks effectively reduced body weight [11]. In the last study, the administration of oxytocin nasal spray (24 IU) to fasting healthy subjects, 60 min before meal, reduced caloric intake with a preferential effect on fat intake without affecting appetite [12].

Oxytocin increases the ability to identify emotions and the empathy towards others [14] and may have therapeutic potential for psychiatric illnesses that impact social functioning, such as autism, schizophrenia, anxiety, and depression [15,16].

Some features of BED are similar to those of Substance Use Disorders (SUDs) [1]. For example, the urge to consume food and the sense of lack of control in BED patients are similar to the urge to consume alcohol or other substances of abuse (craving) and the sense of lack of control in SUD patients. BED and SUDs also share similar neural substrates [17]. The consumption of food (particularly foods rich in carbohydrates and fats), as well as the consumption of substances of abuse, induce rewarding effects, at least in part, through activation of the mesolimbic dopaminergic "reward" system that in vulnerable individuals may induce the development of BED and SUDs, respectively [17]. The interactions of central oxytocinergic neurons with the "reward" system are well documented [18]. In animal models, the administration of oxytocin attenuates several behaviors related to different substances of abuse (heroin, alcohol, cocaine, and psychostimulants) [19,20]. Conversely, the role of oxytocin in the treatment of SUDs in humans is unclear as only a few clinical studies [21,22] investigated its effects with contrasting results.

Oxytocin nasal spray may have a role in the treatment of patients affected by BED and obesity (BED+O), but no study has been conducted to date to investigate its safety and efficacy in these patients.

Materials and Methods

Participants

Study participants were recruited at the Clinical Nutrition Unit of the University Hospital of Cagliari. Patients were eligible for the study if they met DSM-5 criteria for BED and had a body mass index (BMI; body weight in kg divided by height in m^2) ≥ 30 kg/m^2. Other inclusion criteria were: (1) 21-65 years of age; (2) residence in a location that allowed the patient to comply with the scheduled visits; (3) the ability to understand the aims of the study, agree to participate in the study, and sign the informed consent form. The exclusion criteria were: (1) current bulimia or anorexia; (2) current physical diseases (cancer, hypertension, heart disease, and cirrhosis) or psychiatric disorders (psychotic and personality disorders) that, in the physician's opinion, may constitute a danger for participation in the study; (3) start of any pharmacologic treatment within the past 2 months; (4) use of psychotherapy and/or pharmacotherapy for BED; (5) abnormal liver and/or kidney function; (6) for women of childbearing age, to be pregnant, lactating, or not practicing a form of medically accepted contraception. The Institutional Review Board at the University of Cagliari approved the study protocol (EudraCT number: 2014-002983-33; authorization no. 12888, 23 July 2014). The study was conducted in compliance with the Declaration of Helsinki. All patients signed approved written informed consent forms. Patients were enrolled from December 2014 through April 2015.

Study Design

The study was a pilot 8 week, outpatient, randomized, double-blind trial. The trial consisted of the following phases: (1) a 2 week screening period; (2) a 8 week double-blind treatment period; and (3) a 1 week treatment discontinuation period. Patients were evaluated twice during the screening period, three times during the pharmacologic treatment (after 1, 4 and 8 weeks), and once one week after medication discontinuation.

During the screening period, patients were interviewed to collect demographic and clinical information and submitted to a physical examination during which vital signs, height, and weight were measured and the BMI was calculated. Then, blood chemical and hematologic tests were requested. Women of childbearing age were given a urine pregnancy test. Only patients with normal blood chemical and hematologic tests and negative pregnancy tests were eligible for the psychiatric visit. One week later, patients were submitted to the psychiatric visit during which the diagnosis of BED and co-morbid mental disorders were investigated using the Structured Clinical Interview for DSM-IV, Axis I Disorders (SCID-I). Patients who satisfied the inclusion and exclusion criteria were asked to take part in the study, and to sign the written informed consent forms. Then, BED+O patients who accepted and signed the consent forms were randomized to receive oxytocin or placebo according to computer-generated coding. Allocation concealment was achieved by having the research pharmacy perform the randomization, package the study medication, and maintain the integrity of the blinded information throughout the trial, including the statistical evaluation of the results. One week after medication discontinuation, patients were submitted to a visit aimed at investigating possible disorders due to discontinuation.

Medications

Medications were supplied by Defiante/Sigma-Tau Industrie Farmaceutiche Riunite S.p.A. in packs containing 40 IU of oxytocin per ml or placebo. The composition of oxytocin and placebo nasal sprays was identical, except for the hormone. Medication kits were marked with progressive numbers by the research pharmacy. Each kit contained a sealed envelope, marked by the same number of the kit, which contained the contents of the packs (oxytocin or placebo). The opening would have allowed the investigators to discover the contents of the medication spray if necessary without affecting the double-blind trial of the other patients. Drugs were kept by the research pharmacy at 4°C until given to patients.

At the end of the first psychiatric visit, patients received medications and recommendations for their nasal administration [13]. Doses of placebo and oxytocin were equal to 6 puffs (24 IU), four times a day, 20 min before each of three meals and before going to bed (96 IU per day). After the first week of treatment, the appearance of possible acute side effects was evaluated.

Diet

Participants received a balanced, energy-restricted (-200 kcal/day of resting energy expenditure) diet (% carbohydrate:fat:protein= ~ 55:25:20) containing a specific list of appropriate foods compatible with their individual preferences.

Outcome measures

The primary outcomes were the appearance of adverse effects and the number of binge eating episodes per week self-registered in diaries by participants and confirmed on clinical interview. The diaries were provided to participants at the screening evaluation. Participants

were instructed to monitor and record into the diary the binge eating episodes, including a detailed description of the type of food consumed, the duration of each episode as well as the possible adverse effects. Binge eating episodes were defined using DSM-5 criteria. At each visit, the diaries were reviewed with participants. Information on menstrual cycles and possible uterine side effects were requested to female participants of childbearing age.

Secondary efficacy measures included body weight (BW), BMI, and scores achieved on scales used to investigate the severity of BED, craving for food, quality of sleep, quality of life, anxiety, and depressive symptoms. The severity of BED was evaluated using the Clinical Global Impression-Severity scale (CGI-S) according to the physician's opinion [23] and the Binge Eating Scale (BES) according to the participant's opinion [24]. The severity of craving for food and quality of life were evaluated using visual analogue scales, asking patients to indicate a score from 0-100 mm. Quality of life was evaluated using the Short-Form Health Survey (SF-12) [25]. Severity of anxiety symptoms was evaluated using the Spielberger State Anxiety Inventory (STAI) and severity of depressive symptoms using the Zung Self Rating Depression Scale (ZUNG) [26]. Compliance was evaluated by counting the returned bottles. At each visit, patients were assessed for adverse events, number of binge episodes per week, BW, BMI, vital signs, medication compliance, and scores on the CGI-S, BES, SF-12, STAI, VAS, and ZUNG.

Statistical analysis

Data were analyzed using IBM SPSS Statistics software (version 21.0).

We performed an efficacy analysis by comparing changes between groups in the outcome variables during the treatment period. The analysis assessed the change of the mean of each variable measured at each visit during the treatment period (number of binge episodes per week, BW, BMI, scores obtained in the CGI-S, BES, SF-12, STAI, VAS, and ZUNG). To explore statistical significance, we performed a longitudinal repeated-measures random regression analysis with a model that included terms for treatment, time, and treatment-by-time interaction [27]. Time was modeled as a continuous variable, with weeks ranging from 0 (baseline) to 8, after beginning treatment with oxytocin or placebo. For the analyses of binge frequency the logarithmic transformation log ([binge days/week] + 1) was used to normalize the data and stabilize the variance. The measure of effect was the estimated change in the outcome at week 8. The data were analyzed by using a mixed effect model with maximum likelihood estimation. Heterogeneous first-order autoregressive covariance structure for repeated and random effect was used, as this resulted the best fitting model with the lowest standard error of the estimates.

The analysis was intent-to-treat (ITT), using available observations on all participants who completed a baseline evaluation. Data of all randomized participants who took at least 1 puff and completed at least 1 safety assessment were included in the safety analysis. Data of all participants who took at least 1 puff of the medications under study and had at least 1 post baseline efficacy assessment were included in the efficacy analysis.

The baseline characteristics of each group were compared by using chi-square or Fisher's exact test for categorical variables and independent-samples t tests for continuous variables. A two sided p value 0.05 was considered significant.

Results

Of the 69 individuals screened, 52 were not enrolled because they did not meet entry criteria (N=17), chose not to participate (N=15), had a physical disease (hypertension) that contraindicated participation in the study (N=16), started a new pharmacotherapy within the past 2 months (N=1), or were lost to follow-up after the screening visit (N=3). Seventeen BED+O patients met the entry criteria and were randomized to oxytocin (N=8) or placebo (N=9). Sixteen participants (94%) were women; 8 were of childbearing age (4 in the oxytocin group and 4 in the placebo group) and 8 were post-menopausal or pre-menopausal (3 in the oxytocin group and 5 in the placebo group). Three patients (17.6%) had mood or anxiety disorders. There were no significant differences between the treatment groups at baseline (Table 1).

	Oxytocin (n=8)	Placebo (n=9)	p value [a]
Women, n (%)	7 (87.5)	9 (100.0)	0.4706
Mean age in years (SD)	47.5 (4.5)	49.8 (10.2)	0.5685
Actual mood disorders, n (%)	1 (12.5)	1 (11.1)	1.0000
Actual anxiety disorders, n (%)	0 (0.00)	1 (11.1)	1.0000
BE mean (SD)	4.9 (3.3)	6.0 (2.7)	0.4535
BW mean (SD)	90.8 (23.4)	95.3 (17.2)	0.6554
BMI mean (SD)	34.1 (3.7)	37.6 (5.2)	0.1408
BES mean (SD)	21.6 (8.4)	23.3 (7.2)	0.6578
CGI–S mean (SD)	4.0 (0.9)	4.9 (1.1)	0.0862
Quality of sleep mean (SD)	75.3 (27.0)	59.7 (36.3)	0.3370
SF-12 mean (SD)	31.5 (6.9)	28.1 (7.2)	0.3399
STAI mean (SD)	48.5 (13.2)	53.0 (14.0)	0.5076
VAS mean (SD)	80.3 (16.6)	81.1 (15.4)	0.9193
ZUNG mean (SD)	41.3 (11.5)	41.3 (12.2)	0.9887
ALT mean (SD)	37.2 (29.6)	24.2 (11.3)	0.2385
AST mean (SD)	21.3 (8.2)	22.8 (9.7)	0.7336
Creatinine mean (SD)	0.8 (0.1)	0.7 (0.2)	0.2531
Urea mean (SD)	33.0 (9.3)	34.8 (11.0)	0.7620
Cholesterol mean (SD)	209.3 (25.4)	209.4 (28.0)	0.9883
HDL Cholesterol mean (SD)	56.4 (9.8)	58.6 (8.1)	0.6242
LDL Cholesterol mean (SD)	124.8 (31.8)	135.7 (17.1)	0.4089
Triglycerides mean (SD)	137.3 (67.7)	107.6 (47.3)	0.3063

Table 1: Baseline characteristics of obese participants with binge eating disorder randomly assigned to 8 weeks of double-blind treatment with oxytocin or placebo.

ALT: Serum Alanine Transaminase Levels
AST: Serum Aspartate Transaminase Levels
BE: Number of episodes of binge eating per week
BES: Binge Eating Scale Score [a 16-itemscale used to assess the severity of binge eating behavior with a total score varying from 0 to 46; (non-binging ≤ 17; moderate binging=18-26; severe binging ≥ 27)]
BMI: Body Mass Index (weight in kilograms divided by height in m^2, normal value<25)
BW: Body Weight (in kilograms)
CGI-S: Clinical Global Impression-S, rating scale for clinical global impression of severity of binge eating disorder (BED) [total score varies from 1 (no BED) to 7 (the most severe BED)]
HDL Cholesterol: High-Density Lipoprotein Cholesterol (recommended ranges >60 mg/dl)
LDL Cholesterol: Low-Density lipoprotein Cholesterol (recommended ranges<100 mg/dl)
Quality of sleep: Score achieved on a visual analog 100 mm scale (0=the worst quality of sleep and 100 mm=the best quality of sleep)
SD: Standard Deviation
SF-12: Score achieved on a 12 item questionnaire used to measure the quality of life [total score varies from 12 to 47 (12=the worst quality of life; 47=the best quality of life)]
STAI: Score achieved on the Spielberger State Anxiety Inventory scale used to measure the severity of anxiety symptoms (total score varies from 40 to 80; scores ≥40 are indicative of significant anxiety)
VAS: Score achieved on a Visual Analogue Scale of food craving (0=no craving and 100 mm=the worst craving)
ZUNG: Score achieved on a 20 item scale used to assess the severity of depressive symptoms (total score varies from 20 to 80; scores ≥ 50 are indicative of significant depression)
[a] Chi-square, Fishers exact test or t-tests were used to determine statistical differences between the oxytocin and placebo groups

The ITT sample for safety analysis included all 17 participants. The adverse events are described in Table 2. There was no difference in their number between the two groups [6 in the oxytocin group (75.0%) and 6 in the placebo group (66.7%), p=1.0000, Fisher's exact test]. One patient of oxytocin group discontinued the trial after 1 week of treatment (before the first post-randomization efficacy measure) due to erythema. Other three patients of the placebo group developed erythema without discontinuing the trial. Two patients of oxytocin groups and one patient of the placebo group reported an episode of palpitations. No women reported uterine cramping. Only one female participant reported an increased sense of uterine pain during a menstrual cycle and she was in the placebo group.

Sixteen participants (7 receiving oxytocin and 9 receiving placebo) had at least one post-randomization efficacy measure and constituted the ITT sample for efficacy analysis. Among these patients, 13 (81.2%) completed the 8 week trial, while the other 3 (18.8%) discontinued prematurely after the first month of treatment. All the participants who discontinued were in the oxytocin group (p=0.0625, Fisher's exact test). The reasons for withdrawal were unknown (N=1), lack of efficacy (N=1), and medical reasons not related to the trial (N=1).

The observed mean outcome measures at week 8 (for the 13 completers) along with the analysis of change in outcome measures are presented in Tables 3 and 4. Both the longitudinal and end point analyses revealed no statistically significant differences between groups in the changes in any of the outcomes evaluated. A tendency to different effects between the two groups was found for some outcomes (BMI, CGI, and STAI scores) with patients of the placebo group showing the better results. However, this difference was not significant. A high degree of compliance was observed in completing the diaries in both the groups, with no difference between them. At study termination, 7 patients (43.8% of the ITT sample for efficacy analysis) reduced the number of binge-eating episodes per week [(4 in the oxytocin group (42.9%) and 3 in the placebo group (33.3%); (p=1.0000, Fisher's exact test)] and 5 participants achieved remission of binge eating (31.2%) [(1 in the oxytocin group (14.3%) and 4 in the placebo group (44.4%); (p=0.3077, Fisher's exact test)] with no differences between the two groups. No participant exhibited significant changes in laboratory test results and no disorders due to discontinuation treatment were observed (data not shown).

Discussion

As far as our best knowledge, this is the first study to evaluate the efficacy and safety of oxytocin nasal spray in BED and obese patients. No difference was found between oxytocin and placebo in the number of episodes of binge eating, body weight, severity of craving for food, anxiety and depressive symptoms. Patients of the placebo group performed slightly better than patients of the oxytocin group in BMI, CGI and STAI scores, although these differences were not significant. No difference was also found in the number and typology of side

Event, n (%)	Oxytocin (n=8)	Placebo (n=9)	Fisher's exact test
Any	6 (75.0)	6 (66.7)	p=1.0000
Sleepness	1 (12.5)	2 (22.2)	p=1.0000
Headache	1 (12.5)	2 (22.2)	p=1.0000
Uterine pain during menstrual cycle	0 (0.0)	1 (11.1)	p=1.0000
Nausea	0 (0.0)	1 (11.1)	p=1.0000
Erythema	1 (12.5)*	3 (33.3)	p=0.5765
Dizzness	0 (0.0)	1 (11.1)	p=1.0000
Dry mouth	1 (12.5)	1 (11.1)	p=1.0000
Palpitations	2 (25.0)	1 (11.1)	p=0.5765

Table 2: Adverse events reported by obese participants with binge eating disorder receiving treatment with oxytocin or placebo.

* This patient discontinued the trial due to erythema

		Placebo	Oxytocin	p
Body weight (kg)	Mean W0	95.3 (17.2)	90.8 (23.4)	0.655
	Difference W8	-2.589 (0.894)	-1.185 (1.188)	
	Difference in variation		1.404 (1.487)	0.345
BMI	Mean W0	37.6 (5.2)	34.1 (3.7)	0.141
	Difference W8	-1.061 (0.226)	-0.363 (0.300)	
	Difference in variation		0.698 (0.376)	0.073
BED/week (Log10)	Mean W0	0.744 (0.080)	0.603 (0.085)	0.454
	Difference W8	-0.308 (0.215)	-0.150 (0.240)	
	Difference in variation		0.158 (0.322)	0.633
VAS	Mean W0	81.111 (4.954)	80.313 (5.254)	0.919
	Difference W8	-46.667 (7.885)	-42.547 (10.606)	
	Difference in variation		4.119 (12.216)	0.758
BES	Mean W0	23.333 (2.313)	21.625 (2.454)	0.658
	Difference W8	-12.222 (3.473)	-6.027 (4.756)	
	Difference in variation		6.195 (5.889)	0.305
CGI	Mean W0	4.889 (0.314)	4.000 (0.333)	0.086
	Difference W8	-2.444 (0.628)	-0.495 (0.881)	
	Difference in variation		1.949 (1.082)	0.088
SF-12	Mean W0	28.111 (2.278)	31.500 (2.416)	0.340
	Difference W8	4.555 (2.104)	0.241 (2.696)	
	Difference in variation		4.796 (1.082)	0.173
STAI	Mean W0	53 (4.535)	48.500 (4.811)	0.508
	Difference W8	-9.444 (4.844)	6.280 (6.512)	
	Difference in variation		-15.724 (8.116)	0.064
ZUNG	Mean W0	41.333 (3.548)	41.250 (3.763)	0.989
	Difference W8	2.222 (5.733)	5.099 (7.992)	
	Difference in variation		-2.877 (9.836)	0.773

Table 3: Analysis of change in outcome measures.

BE: Number of episodes of binge eating per week
BES: Binge Eating Scale score [a 16 item scale used to assess the severity of binge eating behavior with a total score varying from 0 to 46 (non-binging ≤ 17; moderate binging=18-26; severe binging ≥ 27)]
BMI: Body Mass Index (weight in kilograms divided by height in m^2, normal value<25)
BW: Body Weight (in kilograms)
CGI-S: Clinical Global Impression-S, rating scale for clinical global impression of severity of binge eating disorder (BED) [total score varies from 1 (no BED) to 7 (the most severe BED)]
Quality of sleep, score achieved in a visual analog 100 mm scale (0=the worst quality of sleep; 100=the best quality of sleep)
SF-12: Score achieved on a 12-item questionnaire used to measure the quality of life [total score varies from 12 to 47 (12=the worst quality of life; 47=the best quality of life)]
STAI: Score achieved on the Spielberger State Anxiety Inventory scale used to measure the severity of anxiety symptoms (total score varies from 40 to 80; scores ≥40 are indicative of significant anxiety)
VAS: Score achieved on a Visual Analogue Scale of food craving (0=no craving; 100 mm=the worst craving)
W0: Week 0 (baseline)
W8: Week 8 (end of treatment, after 8 weeks of treatment)
ZUNG: Score achieved on a 20-item scale used to assess the severity of depressive symptoms (total score varies from 20 to 80; scores ≥ 50 are indicative of significant depression)

	W0 (n=16)		Last Observation [a] (n=16)		W8 [b] (n=13)	
	Oxytocin (n=7)	Placebo (n=9)	Oxytocin (n=7)	Placebo (n=9)	Oxytocin (n=4)	Placebo (n=9)
BE mean (SD)	5.1 (3.6)	6.0 (2.7)	4.0 (4.6)	2.4 (3.2)	4.3 (4.7)	2.4 (3.2)
BW mean (SD)	92.5(24.7)	95.3(17.2)	91.4 (24.9)	92.7 (16.8)	102.7 (29.0)	92.7 (16.8)
BMI mean (SD)	34.7 (3.5)	37.6 (5.2)	34.4 (3.7)	36.5 (5.2)	36.2 (3.9)	36.5 (5.2)
BES mean (SD)	21.4 (9.1)	23.3 (7.2)	15.4 (7.3)	11.1 (10.1)	14.8 (9.0)	11.1(10.1)
CGI–S mean (SD)	4.0 (1.0)	4.9 (1.1)	3.1 (1.3)	2.4 (1.9)	3.5 (1.3)	2.4 (1.9)
Quality of sleep mean (SD)	74.6 (29.1)	59.7 (36.3)	75.7 (31.0)	86.7 (21.2)	87.5 (25.0)	86.7 (21.2)
SF-12 mean (SD)	31.9 (7.4)	28.1 (7.2)	31.6 (8.9)	32.9 (7.0)	34.8 (8.2)	32.9 (7.0)
STAI mean (SD)	45.9 (11.8)	53.0(14.0)	50.1 (12.5)	43.6 (18.3)	46.3 (12.0)	43.6 (18.3)
VAS mean (SD)	84.6 (12.1)	81.1 (15.4)	40.7 (24.4)	34.4 (20.2)	37.5 (18.9)	34.4 (20.2)
ZUNG mean (SD)	42.3 (12.0)	41.3 (12.2)	43.6 (10.3)	43.6 (20.2)	39.5 (7.9)	43.6 (20.2)

Table 4: Efficacy measures.

BE: Number of episodes of binge eating per week
BES: Binge Eating Scale score [a 16 item scale used to assess the severity of binge eating behavior with a total score varying from 0 to 46 (non-binging ≤ 17; moderate binging=18-26; severe binging ≥ 27)]
BMI: Body Mass Index (weight in kilograms divided by height in m^2, normal value<25);
BW: Body Weight (in kilograms)
CGI-S: Clinical Global Impression-S, rating scale for clinical global impression of severity of binge eating disorder (BED) [total score varies from 1 (no BED) to 7 (the most severe BED)]
Quality of sleep, score achieved on a visual analog 100 mm scale (0=the worst quality of sleep; 100=the best quality of sleep)
SF-12: Score achieved on a 12-item questionnaire used to measure the quality of life [total score varies from 12 to 47 (12=the worst quality of life; 47=the best quality of life)]
STAI: Score achieved in the Spielberger State Anxiety Inventory scale used to measure the severity of anxiety symptoms (total score varies from 40 to 80; scores ≥40 are indicative of significant anxiety)
VAS: Score achieved on a Visual Analogue Scale of food craving (0=no craving; 100 mm=the worst craving)
W0: Week 0 (baseline)
W8: Week 8 (end of treatment, after 8 weeks of treatment)
ZUNG: Score achieved on a 20-item scale used to assess the severity of depressive symptoms (total score varies from 20 to 80; scores ≥ 50 are indicative of significant depression)
[a] Last observation end point was defined using last observation carried forward
[b] Week 8 end point was available for only those participants who completed the study

effects. A higher rate of patients of oxytocin group reported an episode of palpitations. However, this difference did not achieve a statistical significance.

Several factors may have contributed to the lack of efficacy observed in the present study. Preclinical studies indicate that oxytocin administration decreases food consumption and body weight in obese and lean animals [5] but the few clinical studies conducted to date have produced conflicting results [9-12].

Only one of these studies evaluated the efficacy of oxytocin nasal spray in obese subjects finding that it significantly decreased the body weight [11]. Despite we used the same schedule of administration and dose of this study, in our study oxytocin nasal spray failed to reduce body weight. Some methodological differences between the two studies may at least in part explain this discrepancy. First, the presence of a mental disorder (e.g. BED) was an exclusion criterion in the study by Zhang et al. [11] and an inclusion criterion in our study. It has been found that the presence of binge eating behavior predicted worse weight outcomes in overweight/obese veterans enrolled in weight loss treatment [28]. Namely, subjects without binge eating lost almost twice as much weight compared to those with binge eating, and high-frequency binge eating was associated with weight gain. It is possible that in our study, the lack of efficacy of oxytocin may be due to the presence of BED. Accordingly, BED+O patients may require higher doses of oxytocin to reduce body weight than those required by obese subjects without BED.

Another difference between the two studies consists in the energy-restricted diet that participants received in our study, while in the study conducted by Zhang et al. [11], participants did not receive an energy-restricted diet. It has been observed that oxytocin reduced the intake of palatable foods, but was not able to modify food intake in the fasted state [10]. Accordingly, the lack of efficacy in reducing food intake observed in our study may be due to the energy-restricted diet received by participants. It is possible that to reveal possible anorexic effects of oxytocin in BED+O patients, subjects should receive a free diet.

The high response to placebo of BED patients [29] may have also contributed to conceal the response to oxytocin. The effects induced by oxytocin may vary in individuals affected by different eating disorders. For example, a dysregulation of oxytocin secretion has been found in anorexic women but not in bulimic women [30,31]. Another study found that the administration of oxytocin nasal spray (40 IU) reduced food consumption in bulimic women but not in anorexic women [32].

The response to oxytocin may also vary according to the schedule of administration. In our study, a fixed schedule was used (20 min before meals and before going to bed) even if two patients asked to modify it into a flexible schedule, "as needed treatment". Interestingly, in humans, increased salivary oxytocin levels last for less than 2 h after the administration of oxytocin nasal spray (24 IU, the same dose used in our study) [33]. It may be possible that the fixed schedule of oxytocin administration could reduce food craving during this 2 h period but not after. Further clinical trials should be conducted to investigate the potential efficacy of oxytocin for the treatment of BED using flexible schedules, according to the need of patients.

Preclinical studies suggest a possible role of oxytocin in the treatment of SUDs [19,20]. Considering the analogies between SUDs and BED, we hypothesized that the administration of oxytocin nasal spray may be able to reduce the severity of craving for food in BED+O subjects. However, in our study, oxytocin did not reduce the severity of food craving in BED+O subjects. Another study recently failed to demonstrate positive effects of oxytocin nasal spray in SUD patients [21]. In details, a single administration of oxytocin nasal spray (24 IU) increased the severity of craving for cocaine (instead of reducing it) in cocaine-dependent patients.

Another study showed that oxytocin nasal spray did not induce beneficial effects in individuals with Prader-Willi syndrome (PWS) [34]. This genetic syndrome is characterized by complex physical, behavioral, and intellectual abnormalities, and hyperphagia [35]. If food consumption is left unmanaged, individuals with PWS develop obesity. It has been hypothesized that hyperphagia might be due to oxytocin deficiency found in PVN of patients affected by PWS [34]. Accordingly, it has been hypothesized that oxytocin nasal spray may reduce food consumption and body weight in patients affected by PWS. Conversely, its administration (36-80 IU daily, divided into two daily administrations) did not reduce food consumption and body weight in these individuals [34].

Other studies reported unattended results [36-38]. For instance, oxytocin nasal spray resulted to be anxiogenic instead of anxiolytic in depressed patients [36], increased the perception of social stress instead of decreased it [37], and did not reduce anxiety and depressive symptoms in fibromyalgic patients [38]. It has been proposed that the effects induced by oxytocin may also vary according to the social or behavioral context [39].

Another factor that may have contributed to the unattended results found in the present study may be due to the large number of female participants recruited. Recent studies have suggested that the response to oxytocin nasal spray may differ between male and female participants. A recent meta-analysis of imaging studies found that in certain brain regions, oxytocin nasal spray induces almost opposite effects in men and women during the processing of different tasks [40].

The majority of preclinical studies conducted to investigate the efficacy of oxytocin in reducing food intake and body weight used mostly male animals [8]. Also clinical studies conducted to investigate the efficacy of oxytocin nasal spray in nutrition recruited mainly male participants [9-12]. Interestingly, the only male participant (who also received oxytocin) recruited by the current study had a positive response to medical treatment. Another study found that the daily administration of oxytocin nasal spray (40 IU) for four months did not modify BMI of 32 schizophrenic patients, mainly constituted by male participants (27 man and 5 women) [41]. Globally, these data suggest that further studies aimed at investigating the effects of oxytocin nasal spray in reducing food consumption and/or body weight should evaluate possible sex differences to these effects. But only recently, possible sex differences in the response to oxytocin as well as among BED patients are under investigation [42-44].

This study has several limitations, one being the small number of subjects recruited. This number was in part justified by the need to investigate the safety of oxytocin in a population of patients at high risk of possible complications, such as BED+O patients. One patient of oxytocin group discontinued the trial after 1 week of treatment due to erythema, but other three patients of the placebo group developed the same side effect although they did not discontinue the trial. Accordingly, this side effect does not seem to be related to the presence of oxytocin in the nasal spray formulation. In addition, no participant required higher doses of oxytocin during the study, suggesting the lack of craving for this medication. Oxytocin nasal spray resulted to be devoid of uterine side effects in female participants of childbearing age. Furthermore, no side effect was observed at the end of the pharmacological treatment (one week after treatment discontinuation), suggesting that the interruption of an 8 week oxytocin treatment did not induce health problems in the sample of BED+O patients who completed the study.

In conclusion, despite the rationale for evaluating the effects in BED+O patients, the present study showed that a 8 week treatment with oxytocin nasal spray did not reduce craving for food and body weight but resulted to be safe in this sample of patients, the majority of whom were women. Possible reasons for the lack of efficacy of oxytocin nasal spray include the almost exclusively presence of female participants, the energy-restricted diet, the dose, and the fixed schedule of administration. Globally, these results suggest that future studies aimed at investigating the efficacy of oxytocin nasal spray in obese patients with BED should recruit adequate number of female and male participants to investigate possible gender differences, permit a free diet, and administer higher doses of oxytocin, in a flexible schedule.

Acknowledgement

The authors express gratitude to Defiante/Sigma-Tau Industrie Farmaceutiche Riunite S.p.A. for supplying oxytocin and placebo nasal spray.

The authors express also sincere gratitude to Alessandra Chessa, Clinical Nutrition Center, Department of Medical Sciences “M. Aresu”, University of Cagliari, Italy for her contribution and to David Cushley for language editing of the manuscript.

Conflict of Interest

The authors have no financial or non-financial conflict of interest to declare.

References

1. American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders Fifth edition. Arlington, VA, American Psychiatric Association.
2. Amianto F, Ottone L, Abbate Daga G, Fassino S (2015) Binge-eating disorder diagnosis and treatment: A recap in front of DSM-5. BMC Psychiatry 15: 70.
3. McElroy SL, Hudson JI, Mitchell JE, Wilfley D, Ferreira Cornwell MC, et al. (2015) Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. JAMA Psychiatry 72: 235-246.
4. Morton GJ, Meek TH, Schwartz MW (2014) Neurobiology of food intake in health and disease. Nat Rev Neurosci 15: 367-378.
5. Blevins JE, Ho JM (2013) Role of oxytocin signaling in the regulation of body weight. Rev Endocr Metab Disord 14: 311-329.
6. Stevens FL, Weisman O, Feldman R, Hurley RA, Taber KH (2013) Oxytocin and behavior: Evidence for effects in the brain. J Neuropsychiatry Clin Neurosci 25: 96-102.
7. Melis MR, Argiolas A (2011) Central control of penile erection: A re-visitation of the role of oxytocin and its interaction with dopamine and glutamic acid in male rats. Neurosci Biobehav Rev 35: 939-955.
8. Blevins JE, Baskin DG (2015) Translational and therapeutic potential of oxytocin as an anti-obesity strategy: Insights from rodents, nonhuman primates and humans. Physiol Behav 152: 438-449.
9. Borg J, Simrén M, Ohlsson B (2011) Oxytocin reduces satiety scores without affecting the volume of nutrient intake or gastric emptying rate in healthy subjects. Neurogastroenterol Motil 23: 56-61.
10. Ott V, Finlayson G, Lehnert H, Heitmann B, Heinrichs M, et al. (2013) Oxytocin reduces reward-driven food intake in humans. Diabetes 62: 3418-3425.
11. Zhang H, Wu C, Chen Q, Chen X, Xu Z, et al. (2013) Treatment of obesity and diabetes using oxytocin or analogs in patients and mouse models. PLoS One 8: e61477.
12. Lawson EA, Marengi DA, DeSanti RL, Holmes TM, Schoenfeld, et al. (2015) Oxytocin reduces caloric intake in men. Obesity (Silver Spring) 23: 950-956.
13. Guastella AJ, Hickie IB, McGuinness MM, Otis M, Woods EA, et al. (2013) Recommendations for the standardization of oxytocin nasal administration and guidelines for its reporting in human research. Psychoneuroendocrinology 38: 612-625.
14. Bartz J, Simeon D, Hamilton H, Kim S, Crystal S, et al. (2011) Oxytocin can hinder trust and cooperation in borderline personality disorder. Soc Cogn Affect Neurosci 5: 556-563.
15. Hofmann SG, Fang A, Brager DN (2015) Effect of intranasal oxytocin administration on psychiatric symptoms: A meta-analysis of placebo-controlled studies. Psychiatry Res 228: 708-714.

16. Guastella AJ, Hickie IB (2016) Oxytocin Treatment, Circuitry and Autism: A Critical Review of the Literature Placing Oxytocin into the Autism Context. Biol Psychiatry 79: 234-242.

17. Volkow ND, Wang GJ, Baler RD (2011) Reward, dopamine and the control of food intake: Implications for obesity. Trends Cogn Sci 15: 37-46.

18. Love TM (2014) Oxytocin, motivation and the role of dopamine. Pharmacol Biochem Behav 119:49-60.

19. McGregor IS, Bowen MT (2012) Breaking the loop: oxytocin as a potential treatment for drug addiction. Horm Behav 61: 331-339.

20. Carson DS, Guastella AJ, Taylor ER, McGregor IS (2013) A brief history of oxytocin and its role in modulating psychostimulant effects. J Psychopharmacol 27: 231-247.

21. Lee MR, Glassman M, King-Casas B, Kelly DL, Stein EA, et al. (2014) Complexity of oxytocin's effects in a chronic cocaine dependent population. Eur Neuropsychopharmacol 24: 1483-1491.

22. McRae-Clark AL, Baker NL, Maria MM, Brady KT (2013) Effect of oxytocin on craving and stress response in marijuana-dependent individuals: A pilot study. Psychopharmacology (Berl) 228: 623-631.

23. Guy W (1976) ECDEU Assessment Manual for Psychopharmacology, US Department of Health, Education and Welfare publication (ADM). Rockville, MD: National Institute of Mental Health.

24. Gormally J, Black S, Daston S, Rardin D (1982) The assessment of binge eating severity among obese persons. Addict Behav 7: 47-55.

25. Ware J, Kosinski M, Keller SD (1996) A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. Medical Care 34: 220-233.

26. Zung WW (1965) A self-rating depression scale. Arch Gen Psychiatry 12: 63-70.

27. Faul F, Erdfelder E, Buchner A, Lang AG (2009) Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods 41: 1149-1160.

28. Masheb RM, Lutes LD, Kim HM, Holleman RG, Goodrich DE, et al. (2015) High-frequency binge eating predicts weight gain among veterans receiving behavioral weight loss treatments. Obesity (Silver Spring) 23: 54-61.

29. Blom TJ, Mingione CJ, Guerdjikova AI, Keck PE Jr, Welge JA, et al. (2014) Placebo response in binge eating disorder: a pooled analysis of 10 clinical trials from one research group. Eur Eat Disord Rev 22: 140-146.

30. Lawson EA, Holsen LM, Santin M, Meenaghan E, Eddy KT, et al. (2012) Oxytocin secretion is associated with severity of disordered eating psychopathology and insular cortex hypoactivation in anorexia nervosa. J Clin Endocrinol Metab 97: E1898-1908.

31. Monteleone AM, Scognamiglio P, Volpe U, Di Maso V, Monteleone P (2016) Investigation of Oxytocin Secretion in Anorexia Nervosa and Bulimia Nervosa: Relationships to Temperament Personality Dimensions. Eur Eat Disord Rev 24: 52-56.

32. Kim YR, Eom JS, Yang JW, Kang J, Treasure J (2015) The Impact of Oxytocin on Food Intake and Emotion Recognition in Patients with Eating Disorders: A Double Blind Single Dose Within-Subject Cross-Over Design. PLoS One 10: e0137514.

33. Daughters K, Manstead AS, Hubble K, Rees A, Thapar A, et al. (2015) Salivary Oxytocin Concentrations in Males following Intranasal Administration of Oxytocin: A Double-Blind, Cross-Over Study. PLoS One 10: e0145104.

34. Einfeld SL, Smith E, McGregor IS, Steinbeck K, Taffe J, et al. (2014) A double-blind randomized controlled trial of oxytocin nasal spray in Prader Willi syndrome. Am J Med Genet 164A: 2232-2239.

35. Griggs JL, Sinnayah P, Mathai ML (2015) Prader-Willi syndrome: From genetics to behavior, with special focus on appetite treatments. Neurosci Biobehav Rev 59: 155-172.

36. MacDonald K, MacDonald TM, Brüne M, Lamb K, Wilson MP, et al. (2013) Oxytocin and psychotherapy: A pilot study of its physiological, behavioral and subjective effects in males with depression. Psychoneuroendocrinology 38: 2831-2843.

37. Eckstein M, Scheele D, Weber K, Stoffel-Wagner B, Maier W, et al. (2014) Oxytocin facilitates the sensation of social stress. Hum Brain Mapp 35: 4741-4750.

38. Mameli S, Pisanu GM, Sardo S, Marchi A, Pili A, et al. (2014) Oxytocin nasal spray in fibromyalgic patients. Rheumatol Int 34: 1047-1052.

39. Olszewski PK, Klockars A, Levine AS (2016) Oxytocin: a conditional anorexigen whose effects on appetite depend on the physiological, behavioral and social contexts. J Neuroendocrinol.

40. Wigton R, Radua J, Allen P, Averbeck B, Meyer-Lindenberg A, et al. (2015) Neurophysiological effects of acute oxytocin administration: systematic review and meta-analysis of placebo-controlled imaging studies. J Psychiatry Neurosci 40: E1-22.

41. Busnelli M, Dagani J, de Girolamo G, Balestrieri M, Pini S, et al. (2015) Unaltered oxytocin and vasopressin plasma levels in patients with schizophrenia after a 4 month daily treatment with intranasal oxytocin. J Neuroendocrinol.

42. Rilling JK, Demarco AC, Hackett PD, Chen X, Gautam P, et al. (2014) Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. Psychoneuroendocrinology 39: 237-248.

43. Scheele D, Striepens N, Kendrick KM, Schwering C, Noelle J, et al. (2014) Opposing effects of oxytocin on moral judgment in males and females. Hum Brain Mapp 35: 6067-6076.

44. Shingleton RM, Thompson-Brenner H, Thompson DR, Pratt EM, Franko DL (2015) Gender differences in clinical trials of binge eating disorder: An analysis of aggregated data. J Consult Clin Psychol 83: 382-386.