Effect of long-term intranasal oxytocin on sexual dysfunction in premenopausal and postmenopausal women: a randomized trial

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Objective: To assess the effect of on-demand intranasal oxytocin administration on female sexual function and activity.
Design: Randomized, prospective, double-blind, placebo-controlled, crossover trial with duration of 22 weeks.
Setting: Academic medical center.
Patient(s): Thirty pre-and postmenopausal women with sexual dysfunction.
Intervention(s): Over 8 weeks, intranasal oxytocin (32 IU) or placebo self-administered by women within 50 minutes before sexual intercourse; after a washout period of 2 weeks, crossover with patients switched to the alternate group for another 8 weeks.
Main Outcome Measure(s): Primary outcome parameter: Female Sexual Function Index (FSFI); secondary outcome parameters: Female Sexual Distress Scale (FSDS), Sexual Quality of Life–Female (SQOL-F), Sexual Interest and Desire Inventory–Female (SIDI-F), and Hamilton depression scale (HDS).
Result(s): After oxytocin and placebo, the FSFI score increased by 26% and 31%, SQOL-F score by 144% and 125%, and SIDI-F score by 29% and 23%, respectively (repeated measures analysis of variance between groups). After oxytocin and placebo, the FSDS score decreased by 36% and 45%, respectively (repeated measures analysis of variance between groups). There was no statistically significant treatment, sequence (placebo first/second), or interaction effect.
Conclusion(s): Long-term intranasal oxytocin and placebo administration both improved sexual function and symptoms of depression in women over time with no treatment, sequence (placebo first/second), or interaction effect.
Clinical Trial Registration Number: NCT02229721. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Depression, female sexual dysfunction, orgasm, oxytocin, placebo

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According to the Diagnostic and Statistical Manual of Mental Diseases (DSM-5), female sexual dysfunction (FSD) falls into three categories: genitopelvic pain/penetration disorder, female orgasmic disorder, and sexual interest/arousal disorder. The latter comprises female arousal dysfunction and hypoactive sexual desire dysfunction (HSDD), which is the most prevalent form of FSD, affecting approximately 21% to 36% of European women (1). Hypoactive sexual desire dysfunction is defined as persistently or recurrently deficient sexual fantasies and desire for sexual activity causing significant distress, all of which must be present for at least 6 months with a frequency of 75% to 100% (3). Pharmacologic treatment

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for female HSDD such as intranasal testosterone, sublingual testosterone with sildenafil, topical alprostadil, or intravaginal dehydroepiandrosterone are still under investigation in early phase clinical trials but have shown some promising effects (4).

Oxytocin, a nanopeptide produced in the hypothalamus, acts both centrally and peripherally, where it is most commonly known for its actions during parturition and lactation. Oxytocin release seems to play a further role in social interactions and intimate bonding. In studies of sexual function, oxytocin was shown to increase the sympathetic outflow in men during sexual events with a subjective perception of increased arousability (5), to improve male sexual function including ejaculation (6, 7), and to promote sexual arousal in lactating women, as reported in few cases (8). Recently, the acute effects of intranasal oxytocin administered to heterosexual couples were investigated and resulted in increased intensity of orgasm, contentment, and sexual satiety in men (9). This suggests that oxytocin may be promising to augment sexual function when given exogenously.

In an effort to identify whether long-term intranasal administration of oxytocin improves the Female Sexual Function Index in pre- and postmenopausal women with diagnosed sexual dysfunction, we studied its effect compared with placebo over a treatment period of 22 weeks. Our secondary outcome parameters were scores on the Female Sexual Distress Scale, Sexual Quality of Life, Hamilton Depression Scale, and Sexual Interest and Desire Inventory.

MATERIAL AND METHODS

Study Design

The study was designed as a prospective double-blind, placebo-controlled, crossover trial at the Department of Clinical Pharmacology at the Medical University of Vienna. We randomized patients into group 1 or 2 using computer software (Supplemental Fig. 1, available online). In group 1, the women received placebo first for 8 weeks then were switched to oxytocin nasal spray for an equivalent treatment duration after a washout phase. In group 2, the women received oxytocin nasal spray first then were given placebo in the second study period after the washout phase.

The study participants were seen at baseline and every 4 weeks. In the first visit (visit 1), we gathered the women's demographic data, sexual, medical, and surgical history, and a current list of medication. The physical examination entailed measurement of height and weight, calculation of the body mass index, measurement of systolic and diastolic blood pressure, and tracing of an electrocardiogram to exclude any severe comorbidities. Before enrollment, hematologic and biochemical blood tests, urine analysis, and plasma hormone levels—thyroid-stimulating hormone (TSH), prolactin, progesterone, estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), early morning cortisol, vasopressin, free and total testosterone, sex hormone-binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS)—were assessed. The oxytocin plasma levels were assessed at baseline and after 15 and 30 minutes of oxytocin or placebo intranasal administration.

For prospective home documentation, all participants were provided with the Sexual Activity Record (SAR) questionnaire, which had to be completed, dated, and timed by the participants after each sexual event. During follow-up periods 1 and 2, the participants were seen at visits 3 and 4, each 4 weeks apart, and visits 6 and 7, respectively. During those visits, the participants were asked to complete questionnaires, including the Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS), Sexual Quality of Life–Female (SQOL-F), Sexual Interest and Desire Inventory-Female (SIDI-F), and Hamilton Depression Scale (HDS). The latter questionnaire was applied to exclude the patients with moderate to severe depression and to help us follow up with the baseline severity of depressive symptoms over the study period and evaluate its effect on sexual function. There is a bidirectional association between depression and sexual dysfunction; it has been shown that depression increases the risk for sexual dysfunction by 50% to 70%, and vice versa: patients with sexual dysfunction are at a risk by 130% to 210% to become depressed (2, 10).

The investigation conformed with the principles outlined in the Declaration of Helsinki and was performed according to the good clinical practice guidelines of the European Union. Formal approval to conduct this study was granted by the local institutional review board and ethics committee of the Medical University of Vienna (EK-Number 230/2011; EudraCT Number 2011-001310-34; AGES Number PHMS-717505/0002; Clinical Trial Registration Number NCT02229721). The nature of this study was explained to all participants and written consent obtained before enrollment.

Patient Population

Women between 41 and 65 years of age with diagnosed hypoactive sexual desire, arousal, or orgasmic disorder as assessed by FSFI <27 and who had been in a heterosexual relationship for at least 3 months were eligible to participate. Recruitment followed after media campaigns and from medical referral from general practitioners and sexual therapists. Exclusion criteria were primary sexual dysfunction, dyspareunia, sexual abuse, severe psychiatric diseases, untreated conditions, and medication intake with associated reduction of sexual function. The diagnosis of sexual dysfunction was determined on the basis of FSFI and FSDS scores and was confirmed by clinical physical and psychological assessment during visit 1 (for details see there). Q2

Patients with primary sexual dysfunction who had never experienced one of the phases of the sexual response cycle before were excluded. Severe psychiatric diseases, as per psychiatric conditions that had required hospitalization in the past and/or previous or current use of antipsychotic medication, was determined on basis of patient's history and clinical assessment at visit 1. Sexual abuse history was determined based on DSM-5 definitions and criteria for partner sexual and physical abuse (14). The relationship context was specifically evaluated during visit 1 to exclude participants with sexual problems attributable to relationship conflicts. In