

THE EFFECT OF ANTIDEPRESSANT USAGE ON THE EFFICACY OF ZESTRA™ FOR WOMEN IN WOMEN WITH, AND WITHOUT, FEMALE SEXUAL AROUSAL DISORDER.

D. Ferguson, C. Steidle, G. Singh, S. Alexander, K. Weihmiller, and M. Crosby, 2001. Test articles provided by QualiLife Pharmaceuticals, Inc.

Introduction: Zestra™ for Women is a topically applied, botanical feminine massage oil formulated to enhance female sexual pleasure, increase warmth, sensitivity, & sensation, & facilitate arousal when applied to the clitoris, labia, and vaginal opening. Zestra™ for Women is not a drug. This product is not intended to diagnose, treat, cure, or prevent any disease and has not been evaluated by the FDA. Antidepressants of the serotonin selective reuptake inhibitor class (SSRIs) are well known to decrease sexual desire, arousal, orgasms, and sexual pleasure. This study was conducted to evaluate the effect of SSRI usage on the efficacy of Zestra™ for Women compared to a placebo oil in women with, and without, Female Sexual Arousal Disorder (FSAD) in conditions of home use in conjunction with sexual activities.

Methods:

Design: Zestra™ for Women was studied in 10 women with Female Sexual Arousal Disorder (FSAD) and 10 normal women in a double-blinded, placebo-controlled, 2-way crossover design. The placebo was matched to the active test article based on viscosity, fragrance, color, absorbency, and lubricity. At the screening visit, each subject was interviewed by a sex therapist, underwent a physical examination, and completed the Female Sexual Function Index (FSFI)© and the Female Sexual Distress Scale (FSDS)©. Women with FSDS scores greater than 60 were excluded from participation. Subjects were randomized to treatment paths, given five 1 ml doses of test article, and instructed in the use of the diary, the Female Sexual Encounter Profile (FSEP)©. Subjects were to return to the clinic for Visit 2 after completing 5 usages of the test article at home. At Visit 2, they completed the FSFI, the FSDS, two global assessment questions (GAQ)©, and the QualiLife Consumer Testing Survey (QCTS)©. They were then given five 1 ml doses of the cross-over test article and provided 5 more diaries. At the final visit, Visit 3, subjects again completed the FSFI, the FSDS, the GAQ, and the QCTS.

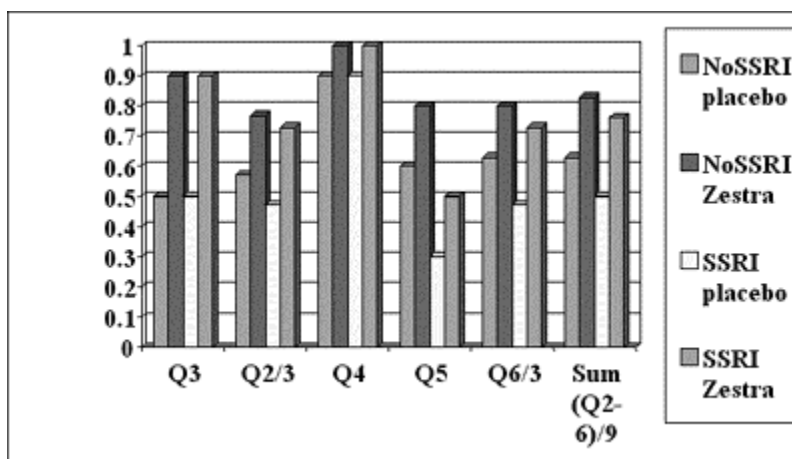
Inclusion/exclusion criteria: Subjects were diagnosed as "normal" or FSAD based on interview by the sex therapist. Subjects were postmenopausal, or using hormonal contraception for at least 3 months prior to study entry, or had a documented tubal ligation at least 3 months prior to study entry, or their partner was vasectomized. FSAD subjects were required to have previously been fully functional, now have a score between 40 and 60 on the FSDS, and be willing to attempt sexual activities at least 3 times weekly. Normal subjects were required to have a FSDS score less than 40. Exclusion criteria included unresolved sexual trauma or abuse; primary anorgasmia, vaginismus, sexual pain disorder, or sexual aversion disorder; pregnancy or nursing; currently active moderate to severe vaginitis; use of neuroleptics or lithium, or bupropion within previous 3 months; and any condition which in the Investigator's opinion would endanger the subject, would interfere with the subject's ability to provide informed consent or to comply with study instructions, or which might confound the interpretation of the study results. Subjects were not excluded due to use of antidepressants, nutritional supplements, or hormonal replacement therapy. Specific effort was made to enroll up to 5 women using SSRIs into each group.

Endpoints: The primary efficacy variable was the number of successes (satisfaction with sexual arousal as indicated by YES responses to diary question 3) divided by the number of attempts (FSEP Q3). The secondary efficacy parameters were the responses to the global assessment questions, the remaining diary questions, the Female Sexual Function Index, the QCTS, and the Female Sexual Distress Scale. Paired-t analyses were employed to assess treatment effects for each subject compared to placebo effects. Group means were compared to assess any differences in response between subjects using SSRIs and those not using SSRIs.

Results: Enrollment, Completion, and analysis Plan: Twenty subjects were enrolled, and all completed the study. Three SSRI users were recruited in the normal group; four SSRI users were recruited in the FSAD group. Since Normal and FSAD women showed positive responses to Zestra™*, the two groups were pooled, then separated by SSRI use. Thus, there were 7 subjects using SSRIs and 13 subjects not using SSRIs. All comparisons were SSRI vs. No SSRI.

Efficacy: At baseline, the SSRI subjects had significantly ($P < 0.05$) lower FSFI domain scores for lubrication and orgasm. No other baseline variables were significantly different between the groups. The primary efficacy variable, FSEP Q3, which assesses satisfaction with level of arousal, has a range of 0 to 1. Secondary efficacy variables included the FSEP questions 2, 4, 5, and 6, as well as a FSEP total score (sum of Q2-Q6). FSEP Q2 assesses level of desire and has a range of 0 to 3. FSEP Q4 asks if the subject had lubrication sufficient to allow comfortable intercourse (even if intercourse did not actually occur). FSEP Q5 asks if orgasm occurred. FSEP question 6 assesses level of arousal and has a range of 0 to 3. Figure 1 shows FSEP responses for both groups and both treatments.

FIGURE 1



The Female Sexual Function Index (FSFI)© provides six factored domain scores with a maximum score of 6 for each domain. Additionally, a total score (maximum = 36) is calculated. Higher scores indicate a more "healthful" condition. The domains are desire, arousal, lubrication, orgasm, satisfaction, and pain. The Female Sexual Distress Scale (FSDS)© is a 20 question instrument with a range of 0 to 80. A lower score indicates a less distressed situation. The Global Assessment Questions (GAQ)© were these: GAQ 1: While using the study medication, did you feel that your level of sexual arousal (excitement) improved? [0=Not at all; 1=A little, but barely noticeable; 2=Somewhat; 3=Quite; 4=Greatly]. GAQ 2: While using the study medication, did you feel that your sexual pleasure was enhanced? [0=Not at all; 1=A little, but barely noticeable; 2=Somewhat; 3=Quite; 4=Greatly]. Table 1 shows the mean changes (Zestra™ minus placebo) for the primary and all secondary efficacy variables except the QCTS. No between groups, within treatment comparisons of any of the efficacy parameters were significantly different. Table 1 indicates that both the SSRI subjects and the No SSRI subjects showed significant improvements by paired-t analyses in satisfaction with level of arousal (FSEP Q3), level of desire (FSEP Q2), frequency of orgasms (FSEP Q5), level of arousal (FSEP Q6), total FSEP scores, FSFI arousal domain, FSFI orgasm domain, FSFI total score, global level of arousal (GAQ 1), and enhancement of sexual pleasure (GAQ 2). No deleterious changes were seen in any efficacy parameter.

The QualiLife Consumer Testing Survey (QCTS)© consists of twelve questions intended to assess users' responses and attitudes regarding the product. Questions 1, 6, 7, 8, 9, 10, and 12 are quantitative and amenable to paired-t analyses, but means of the changes are problematic. Question 1 assesses genital sensation. Question 6 assesses pleasure associated with sexual activities. Question 7 assesses lubrication. Question 8 addresses enhancement of ability to have orgasms. Question 9 addresses enhancement of sexual experiences. Question 10 addresses willingness to purchase the product. Question 12 asks subjects how much they would pay for the product. Table 2 shows the group mean results of these questions for both subject groups with asterisks indicating significance from paired-t analyses. Both SSRI and No SSRI subjects showed significant improvements in sensation, pleasure, enhancement of sexual experiences, and willingness to purchase the product. SSRI subjects also showed a significant improvement in ability to have orgasms, while the NoSSRI group showed a significant improvement in what they would pay for the product.

Discussion: This study is a landmark in demonstrating the elimination of the undesirable sexual side effects of SSRIs in women. It should also be noted that Zestra™ produced beneficial effects in women not using SSRIs. The primary efficacy variable FSEP Q3 directly addresses the critical question established in FDA guidelines for drug products pursuing an indication in Female Sexual Arousal Disorder. This nondrug product produced significant improvements in this parameter in both SSRI and No SSRI women. This result was supported by 14 significant improvements out of 21 secondary efficacy variables in both groups of women. No efficacy variable showed a deleterious change in either subject group.

TABLE 1: Mean Change (Zestra™ - Placebo)		
Endpoint	No SSRI	SSRI
FSEP Q3/Q7	0.4 ± 0.4**	0.4 ± 0.3*
FSEP Q2/Q7	0.6 ± 0.4***	0.8 ± 0.3***
FSEP Q4/Q7	0.06 ± 0.15	0.11 ± 0.30
FSEP Q5/Q7	0.2 ± 0.3*	0.3 ± 0.2*
FSEP Q6/Q7	0.6 ± 0.6**	0.8 ± 0.5***
FSEP TOTAL	1.8 ± 1.4***	2.4 ± 1.2**
FSFI Desire	0.14 ± 1.4	0.6 ± 1.4
FSFI Arousal	1.08 ± 1.3*	1.5 ± 1.5**
FSFI Lubrication	0.62 ± 1.3	0.7 ± 1.5
FSFI Orgasm	1.02 ± 1.4*	1.4 ± 1.4*
FSFI Satisfaction	.52 ± 1.7	1.2 ± 1.3
FSFI Pain	.09 ± 0.5	.2 ± 0.4
FSFI Total	3.48 ± 5.5*	5.69 ± 5.1**
FSDS (20)	-6.2 ± 14.9	-1.5 ± 14.3
GAQ 1	1.7 ± 1.5**	2.0 ± 1.6**
GAQ 2	1.8 ± 1.2***	2.0 ± 1.6**
Paired-t Analyses: *P < .05 **P < .01 ***P < .001 No Between Group Comparisons were significant		

TABLE 2: QualiLife Consumer Testing Survey Results				
QCTS Question	No SSRI Placebo	No SSRI Zestra™	SSRI Placebo	SSRI Zestra™
Q1: sensation	-.1 ± .3	.8 ± .4***	-.3 ± .5	1.0 ± .0***
Q6: pleasure	.1 ± .3	.8 ± .4***	.1 ± .4	.9 ± .4**
Q7: lubrication	.2 ± .4	.4 ± .6	.7 ± .5	1.0 ± .0
Q8: orgasm	.1 ± .3	.4 ± .5	.0 ± .6	.6 ± .5*
Q9: enhanced	.2 ± .6	1.4 ± 1.0**	.0 ± .6	1.7 ± .8**
Q10: purchase	.8 ± 1.7	4.3 ± 1.9**	0.0 ± 0.0	5.8 ± .8***
Q12: price	.2 ± .3	2.3 ± 3.1*	.1 ± .4	3.2 ± 3.2
Paired-t Analyses: *P < .05 **P < .01 ***P < .001				

No Between Group Comparisons within treatment were significant

Conclusions: The use of SSRIs in normal or FSAD women has no effect on the responses to Zestra™ for Women. Zestra™ for Women improves level of desire, satisfaction with level of sexual arousal, frequency of orgasm, level of sexual arousal, genital sensation, sexual pleasure, ability to have orgasms, and enhancement of sexual experiences in normal and FSAD women regardless of SSRI usage. Zestra™ for Women eliminates the undesirable sexual side effects of SSRIs.

Reference: *Ferguson, D., Steidle, C., Singh, G., Alexander, S., Wehmiller, K., and Crosby, M. Randomized, placebo-controlled, double blind, crossover design pilot trial of the efficacy and safety of Zestra™ for Women in women with, and without, Female Sexual Arousal Disorder. Presented at the Female Sexual Function Forum, Boston, 2001.