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Sexual frequency and pain in a randomized clinical trial of vaginal estradiol tablets, moisturizer and placebo in postmenopausal women

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Abstract

Objective: To evaluate the efficacy of two common interventions for bothersome postmenopausal vaginal symptoms on improving sexual frequency and pain.

Methods: This is a post-hoc analysis of data from a 12-week double-blind placebo-controlled trial that randomized postmenopausal women (ages 45–70 years) with moderate-severe genitourinary discomfort to vaginal 10mcg estradiol tablet plus placebo gel (n=102), placebo tablet plus vaginal moisturizer (n=100), or dual placebo (n=100). Outcomes were proportion of sexually active women at 12 weeks, frequency of sexual activity, and pain severity with sexual

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activity (0–3 scale). Consistent with the original study design, comparisons were made between each active arm and the dual placebo arm.

Results: Most women enrolled in the trial, 294/302 (97%), had sufficient data to be included in this analysis. Mean age of participants was 61 years, most were white (88%), college educated (66%), and most reported sexual activity in the month prior to enrollment (81%). After 12 weeks of treatment, a similar proportion of women in the vaginal estrogen and dual placebo groups reported sexual activity in the past week (50% and 40%; p=0.10) and the past month (78% and 84%, p=0.52). Mean (SD) pain with sexual activity scores at 12 weeks were similar between vaginal estrogen [1.0 (1.0)] and placebo [0.9 (0.9), p=0.52] groups. The proportion sexually active at 12 weeks (35%) and mean (SD) pain severity in the vaginal moisturizer group [1.1 (0.9)] did not differ from placebo (p=0.36).

Conclusions: Compared to placebo, neither low dose vaginal estradiol nor vaginal moisturizer treatment over 12 weeks resulted in significantly greater increases in the proportions of women reporting sexual activity or improvement in pain scores with sexual activity.

Keywords

clinical trials network; postmenopausal sexual activity; dyspareunia; vaginal estrogen; vaginal moisturizer

INTRODUCTION

Dissatisfaction and pain with sexual activity among postmenopausal women are well recognized and reports of diminished sexual function are prevalent. In a probability-selected Internet panel survey of 3,046 US women with vulvar and vaginal atrophy (VVA) symptoms, 44% reported dyspareunia, and 48% reported that dyspareunia negatively impacted their relationship with their partner. [1] The North American Menopause Society recommends the following treatments for painful sexual activity in postmenopausal women: vaginal lubricants and moisturizers, regular sexual stimulation, expanding views of sexual pleasure to include “outercourse,” vaginal dilators, pelvic floor physical therapy, vaginal or systemic estrogen, vaginal DHEA or systemic ospemifene.[2,3] However evidence is limited to support the relative benefit of any of these treatments for frequency of sexual activity and pain severity with vaginal penetration.

The MsFLASH Network evaluated the efficacy of two commonly recommended treatments for genitourinary syndrome of menopause (GSM): low-dose vaginal estrogen tablets and a vaginal moisturizer (Replens), in a population of women with moderate to severe bothersome vaginal symptoms. In the primary analysis, we found minimal difference in the change in severity of the most bothersome symptom (MBS) over 12 weeks between vaginal estrogen and placebo or Replens and placebo.[4] Likewise, we observed minimal differences between treatment arms in changes in the Female Sexual Function Index (FSFI) or the Female Sexual Distress Scale - Revised (FSDS-R) over 12 weeks. More women in the estradiol tablet group reported “meaningful benefit” from treatment than in the placebo group (80% vs. 65%, P=0.02), but “meaningful benefit” was similar among moisturizer (Replens) and placebo groups, (59% vs. 65%, P=0.39).[4] Notably, in additional analyses,

vaginal estrogen treatment showed modest benefit compared to placebo in postmenopausal quality of life as measured by the MENQOL, primarily due to improvements in the sexual function domain.[5] The clinical relevance of this modest benefit is not known, but the magnitude of change in total MENQOL is comparable to differences seen after treatment for hot flashes.[6]

We wondered if the small differences in quality of life and report of "meaningful benefit" between treatment arms, which were not seen in analysis of overall discomfort, might be related to differences in the frequency of or discomfort with sexual activity between treatment arms. We aimed to better understand treatment effects on frequency of sexual activity and associated pain by conducting a detailed evaluation of participants' report of sexual activity and sexual pain using daily diary data collected in weeks 1 and 11 of the study and questionnaire report of sexual activity over the past month at baseline and 12 weeks. Based on best available evidence, we hypothesized that treatment with estradiol, but not Replens or placebo, would be associated with decreased pain with sexual activity and increased frequency of sexual activity.

METHODS

Study Design:

A randomized, double-blind, placebo-controlled 12-week trial was conducted at two centers: Kaiser Permanente Washington Health Research Institute in Seattle, WA and University of Minnesota in Minneapolis, MN. For this post-hoc analysis, we compared quantitative measures of sexual activity (proportion of women sexually active, proportion having penetrative sex, average number of sexual acts per week, and severity of pain with penetration) among three groups: Vagifem 10 mcg tablet + placebo vaginal gel ("estrogen group"); placebo vaginal tablet + Replens vaginal moisturizer ("moisturizer group"); or placebo tablet + placebo gel ("placebo group"). The study was approved by Institutional Review Boards at participating institutions. Detailed methods were previously described.[4]

Participant Selection and Randomization:

Women were recruited through direct mailings and Facebook ads. Inclusion criteria were: 45–70 years old, ≥2 years since last menses, report of ≥1 moderate-severe symptom of vulvovaginal itching, pain, dryness, or irritation experienced at least weekly within the past 30 days; or pain with penetration at least once monthly. Exclusion criteria included: current vaginal infection, use of hormonal medication in past 2 months, use of antibiotics, vaginal moisturizer, probiotic, prebiotic or douche in past month, and chronic premenopausal vulvovaginal symptoms (including pain). Participants and study site personnel were blinded to treatment assignments.

Interventions:

Women were randomly assigned 1:1:1 to the three intervention groups. The placebo was a hydroxyethylcellulose gel, shown to have minimal effect on vaginal microbiota and inflammation in vaginal microbicide studies.[7,8] Women were instructed to insert the vaginal

tablet daily for two weeks, and then twice weekly for the remaining 10 weeks, and the vaginal gel every three days throughout the trial.

Data Collection:

Telephone contact at 1, 3 and 11 weeks post-randomization assessed protocol adherence and adverse events. Follow-up clinic visits occurred at 4 and 12 weeks post-randomization. At each visit, women completed questionnaires. In the week after the first visit, and immediately before the week 4 and 12 visits women completed structured daily diaries, which included report of any sexual activity, types of sexual activity, number of sexual acts per week, and pain with sexual activity. Women using over-the-counter lubricants were allowed to continue use while on study and use was recorded in diaries.

Baseline and follow-up visit questionnaires included items asking whether the participant was sexually active in the last month, and if so, whether with a male partner, female partner, and/or with self-stimulation. Participants who reported any sexual activity in the month prior to enrollment were defined as "sexually active." Additional questionnaire items included Menopausal Quality of Life (MENQOL),[9] Generalized Anxiety Disorder (GAD7),[10] Patient Health Questionnaire (PHQ-8),[11] Female Sexual Function Index (FSFI)[12] and Female Sexual Distress Scale – R (FSDS-R).[13] At visit 12 participants were asked if they experienced "meaningful benefit" from the study intervention. At enrollment, we collected descriptive information using a list of descriptive statements about attitudes and views about sexuality, relationships, and intimacy. Participants circled statements that were applicable (Table 2).

Outcomes:

The primary outcomes for this analysis were evaluated at 12 weeks: 1) report of any sexual activity in the past week (diary), or the past month (questionnaire), 2) report of penetrative sexual activity in the past week (diary), 3) mean number of days with sexual activity during week 12 (diary), and 4) mean severity score for pain with sexual activity during week 12 (diary), selected from a 0–3 scale of "None", "Mild", "Moderate" or "Severe." Prior analyses reported pain severity response from the visit questionnaires,[4] which asked about pain with vaginal penetration in the past month, while the current analysis used pain with sexual activity scores recorded in diaries on the day of the sexual act, which may limit reporting bias.

Statistical analysis:

This post-hoc analysis included all randomized participants with available data, regardless of adherence to treatment assignment. Consistent with the original study design, comparisons were made between each active arm and the dual placebo arm. Distributions of baseline characteristics were compared between each active intervention arm and placebo using t-tests for continuous characteristics and chi-square or Fisher exact tests (as appropriate) for categorical characteristics. Home diaries with no more than 1 day of missing data were included in analysis of sexual activity incidence and frequency in the past week. Analysis of mean level of pain with sexual activity severity score per week included diaries reporting at least one day of sexual activity during that week. Because women who were sexually active

at trial entry might be more likely to be sexually active at trial end, we adjusted analyses for baseline report of sexual activity. Statistical differences in the proportions of women with sexual activity and penetrative sex between each active intervention arm versus placebo were estimated from logistic regression models as a function of arm, clinical site, and baseline report of sexual activity, and were reported as odds ratios. Statistical differences in mean number of days with sexual activity per week and mean pain with sexual activity severity score were assessed with linear regression models as a function of intervention group, clinical site, and baseline report of sexual activity in the past month. To facilitate comparisons with prior studies, outcomes were re-analyzed among participants meeting eligibility criteria for previously published trials: baseline pH > 5 and VMI with ≤ 5% superficial cells.[14–16] We compared report of "meaningful benefit" from study treatment, as well as MBS severity, FSFI, and MENQOL overall and sexual domain scores between women who were sexually active at week 12 and those who were not using chi square or t-tests, as appropriate. Analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC) with 2-sided P value ≤0.05 considered statistically significant for these secondary outcomes. Since missingness was uncommon for the outcomes presented, no attempt was made to impute unknown values. A post-hoc power calculation for the comparison between each active arm and the placebo arm calculated that we have 80% power to detect a 22% difference in prevalence of sexual activity between arms, based on the 40% prevalence of sexual activity in the placebo arm.

RESULTS

Three hundred two women were randomized to receive vaginal estradiol tablet plus placebo gel (N= 102), placebo tablet plus vaginal moisturizer (n=100), or dual placebo (N=100). The majority, 294 of 302 (97%) women had either diary or questionnaire data about sexual activity at week 12, similar to the number of women for whom data were available in the primary planned analysis.[4] Most women were between 55–64 years old (235, 78%), white (267, 88%), non-Hispanic (296, 98%), heterosexual (289, 96%), married or partnered (257, 85%). Mean total FSFI score was 15.5 (range 2–36); values below 26 are considered indicative of a high risk for sexual dysfunction.[17] More than 50% of women reported being "frequently" or "always" distressed about their sex life in the single question of the FSDS-R. Baseline characteristics were comparable between intervention groups (Table 1).

Although sixty percent of women (182/302) chose pain with vaginal penetration as their most bothersome symptom, most women reported moderate-severe pain with vaginal penetration (246, 81%) and most reported being sexually active in the past month (245, 81%). At baseline, 134 (44%) reported self-stimulation in the past month. Of the 56 women who did not report any sexual activity in the past month at enrollment, 10 (18%) were not married or not in a marriage-like relationship. More than half of women indicated that vaginal symptoms were causing problems in their sexual relationship (198/296; 67%) (Table 2). A majority of women reported that "I wish that I wanted to have more sex" (245, 81%) and that "my partner wants to have sex more often than I do" (219, 74%). There were no differences in these proportions between treatment groups.

Using the diary data from the first week of treatment, 37 women in the estradiol group reported any sexual activity (36%), 37 (37%) in the moisturizer group, and 43 (43%) in the dual placebo group. Most women reporting any sexual activity in that week also reported penetrative intercourse: 34 in the estradiol group (92% of sexually active women), 29 (78%) moisturizer group, 37 (86%) dual placebo group. Diary mean pain scores in the first week of treatment were similar between groups: estradiol 1.6 (SD 0.9), moisturizer 1.3 (0.9), dual placebo 1.3 (0.8) (estradiol vs. placebo, $p>0.05$; moisturizer vs. placebo, $p>0.05$). Measures of mood, quality of life and sexual function did not differ between treatment groups (Table 1). Women who were sexually active in the first week of the trial had a higher baseline FSFI score than women who were not sexually active in the first week (18.0 vs. 13.5, $p<0.001$). Use of lubricant, reported in week 1 diaries, was infrequent (14%) and did not vary between intervention groups.

At week 12, the overall number of women reporting sexual activity in the past week reported in daily diaries was similar to the rate reported in the first week of the trial: 115 (week 12) vs. 117 (week 1). Report of self-stimulation in the past month was comparable to enrollment (130/277, 43%). Report of sexual activity in the past week was similar between women receiving vaginal estrogen (50%) and those receiving placebo (40%), $p=0.10$. The proportion of women reporting penetrative sex in daily diaries from the last week of the trial, and report of sex in the last month on questionnaires was also similar in the estrogen group compared to the placebo group (Table 3). Among the women who filled out a diary during the last week of the intervention (n=277), 58% had no days with sexual activity, 31% had 1 day, 7% had 2 days, and 3% had 3 or more days with sexual activity. These frequencies were similar to baseline. The mean number of days of sexual activity and mean pain severity scores with sexual activity at 12 weeks was similar among treatment groups (Table 4). None of the sexual activity or pain outcomes in the vaginal moisturizer group differed significantly from those in the placebo group (Tables 3 and 4). These results were similar in participants with baseline pH > 5 and VMI with ≤ 5% superficial cells. Reported use of lubricant in the weekly diaries at week 12 was infrequent (9%) and did not differ between groups.

Of the women who were not sexually active at baseline, a similar proportion in each group had resumed sexual activity by week 12 (9/20 estradiol vs. 8/16 dual placebo, $p=0.77$; 12/20 moisturizer vs. 8/16 dual placebo, $p=0.55$). Sexual activity at week 12 was not associated with week 12 ratings of “meaningful benefit” of the treatment, MBS severity, MENQOL sex, or overall MENQOL scores (data not shown). Irrespective of intervention group and similar to enrollment, participants who reported any sexual activity during the last week of the intervention also reported significantly better week 12 sexual function (FSFI score) than those who were not sexually active (22.2 vs 18.0, $p<0.001$).

DISCUSSION

In this post-hoc analysis of data from a 12-week randomized trial, we observed that treatment of moderate-severe genitourinary syndrome of menopause (GSM) with vaginal estradiol and placebo gel did not result in a statistically greater increase in the proportion of sexually active women, proportion having penetrative intercourse or mean frequency of sexual acts compared to dual placebo, nor was there improvement in reported severity of

pain with sexual activity. This is similar to the primary outcome of the trial, where we did not observe significant benefit from estradiol over placebo in improving vaginal symptom severity nor sexual function scores (FSFI). However, it contrasts with analyses showing greater improvement in quality of life by MENQOL in the estrogen group compared to placebo (p=0.01)[5] and greater report of "meaningful benefit" with estradiol treatment (80%) than placebo (65%).[4] We initially hypothesized that our contrasting findings might be due to differences in frequency of sex, or of ability to have penetrative sex. At enrollment, many women reported that their partners wanted more sex, or that they wished they wanted more sex. The sexual function domain of the MENQOL, which accounted for most of the improvement in quality of life, includes three questions about avoidance of intimacy, change in sexual desire and the presence and bother of vaginal dryness.[5] We hypothesized that there might be unmeasured improvements for women in the estradiol arm leading to less avoidance of intimacy, more sexual activity, improved MENQOL and greater "meaningful benefit." However, the results of this analysis suggest that our contrasting findings cannot be explained by quantitative differences in the frequency of sexual activity or reported pain with sexual activity. In addition, results from the primary trial analysis showed similar improvements across all three treatment arms in the FSFI domains of desire, arousal, and orgasm, suggesting there are few overall differences between the treatment arms in other components of sexual function.

Sex does not stop after menopause. A majority (60–75%) of women reporting that "sexuality" is important to their well-being and overall quality of life.[18,19] Over 60% of women between 57–64 years of age reported being sexually active in the past year, and of those 63% reported sexual activity at least 2–3 times per month.[19] In a survey of women over 40, half reported sexual activity within the past month[20] and in a separate population-based study survey of partnered, older women (mean age 72), 35% reported sexual activity in the prior week.[21] Among 2,394 women participating in the Irish Longitudinal Study on Ageing who were married or co-habitating, average age 60.8, 21.6% reported they were not sexually active, 6.5% were sexually active once or twice a year, 15.4% were sexually active every few months, 30.5% were sexually active once or twice a month, and 26.0% were sexually active once a week or more. [22] Over 80% of women enrolled in our trial were sexually active in the month prior to enrollment, and 39% reported sexual activity during the first week of the trial, thus our study population was slightly more active or comparable to the reports outlined above.

Interventions to treat GSM have been shown to change some measures of sexual behavior, but not all. In an RCT of ospemifene for pain with intercourse in postmenopausal women, participants randomized to active drug were less likely to use lubricant with sex after 12 weeks than those in the placebo group, but report of frequency of sexual activity was not different between groups.[23] In a study of systemic ultra-low dose transdermal estrogen (0.014mg/day) in 417 women, 226 (54%) of whom were sexually active, self-reported prevalence and frequency of sexual activity did not differ between intervention groups at baseline or at 4, 12, or 24-month follow-up (p=0.20 for each comparison), although ultralow-dose estradiol resulted in modest improvement in vaginal pain and dryness with sexual activity.[24] Although we found similar symptom improvement in all three treatment groups in the primary analysis, we hypothesized that local effects of estrogen might facilitate

more frequent sexual activity, or penetrative sex, which might be the mechanism explaining the significantly greater report of “meaningful benefit” or improved MENQOL in the estrogen group. However, this was not the case – there was no difference in sexual frequency, use of lubricant, or penetrative sex between the study arms.

This study has several limitations. Women enrolled in this study do not reflect the general US population – they were primarily white and college-educated, the majority were sexually active, and all consented to be randomized to an intervention for moderate to severe postmenopausal vulvovaginal symptoms. The majority reported moderate to severe pain with vaginal penetration at baseline (81%) and over 50% were frequently or always distressed about their sex life. Women were anticipating benefit from the intervention, thus increased sexual activity with diminished pain was expected in all groups. This is a post-hoc analysis that was not originally specified in the trial design, and would only have power to detect large differences in outcomes between the treatment groups. We were not powered to make a direct comparison between the two active intervention groups (estradiol and vaginal moisturizer), thus can only draw indirect conclusions based on their relative effectiveness vs. placebo. The intervention was only 12 weeks. It is unknown if further treatment would have resulted in differences in outcomes, however two studies of the low dose vaginal estradiol tablet over 52 weeks did not show additional improvement in severity of MBS beyond 12 weeks; frequency of sexual activity and pain with penetration were not reported.[14,16] We did not ask about a history of sexual assault or abuse, but did exclude women with a history of premenopausal vaginal or pelvic pain to try and limit enrollment to women with primarily menopause-related vaginal discomfort.

Conclusion:

In the primary analysis of the MsFLASH study, we found no statistically significant differences in in sexual function as measured by the FSFI, comparing the two treatment arms to placebo.[4] In the current analysis we found that compared to placebo, neither low dose vaginal estradiol nor vaginal moisturizer treatment over 12 weeks resulted in significantly greater increases in the proportions of women reporting sexual activity or improvement in pain scores with sexual activity. This analysis suggests that findings in the primary analysis of greater “meaningful benefit” and slightly greater improvement in quality of life among women in the estradiol arm do not seem to be attributable to differences between intervention groups in diminished pain with sexual activity, or change in sexual frequency. Overall, these results suggest that providers and women should choose treatments for postmenopausal vaginal discomfort based on individual preference regarding cost and formulation.

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Table 1.

Characteristics of study population at enrollment

	Vaginal Estradiol (n=102)		Vaginal Moisturizer (n=100)		Dual Placebo[a] (n=100)	
Baseline Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age at screening (years), mean (SD)	61 (4)		61 (4)		61 (4)	
Race						
White	87	85	90	90	90	90
African American	7	7	3	3	2	2
Other / unknown	8	8	7	7	8	8
Body mass index (kg/m^2), mean (SD)	27 (5)		26 (4)		26 (6)	
Education						
≤ High school diploma / GED	2	2	3	3	6	6
School after high school	31	30	27	27	31	31
College graduate	67	66	70	70	63	63
Marital status						
Never married	8	8	2	2	4	4
Divorced/widowed	10	10	8	8	12	12
Married or like relationship	83	81	90	90	84	84
Partner duration[b] (years), mean (SD)	30 (12)		27 (24)		28 (26)	
Children in the house <18						
Yes	13	13	4	4	7	7
No	88	86	96	96	93	93
Pregnancy ≥ 5 months ever						
Yes	60	60	62	62	68	68
No	41	40	37	37	32	32
Smoking						
Never	66	65	67	67	66	66
Past	31	30	33	33	32	32
Current	4	4	0	0	2	2
Alcohol use (drinks/week)						
0	30	29	31	31	28	28
1 – <7	50	49	46	46	53	53
7+	21	21	23	23	19	19
MENQOL total, mean (SD)	3.3 (1.2)		3.2 (1.1)		3.3 (1.0)	
PHQ-8 depression						
None (0–4)	69	68	75	75	69	69

	Vaginal Estradiol (n=102)		Vaginal Moisturizer (n=100)		Dual Placebo[a] (n=100)	
Baseline Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Mild (5–9)	25	25	22	22	23	23
Moderate/severe (10+)	7	7	3	3	8	8
GAD-7 anxiety						
None (0–4)	64	63	75	75	64	64
Mild (5–9)	25	25	21	21	24	24
Moderate/severe (10+)	12	12	4	4	12	12
Sexually active in past 4 weeks[c]	81	79	80	80	84	84
Male partner	62	61	69	69	72	72
Female partner	0	0	1	1	1	1
Self-stimulation	42	41	44	44	48	48
FSFI total, mean (SD)	15.2 (5.9)		15.2 (6.5)		16.1 (6.6)	
FSDS-R, Distressed about sex life						
Never/rarely	15	15	12	12	18	18
Occasionally	33	32	33	33	33	33
Frequently/always	53	52	54	54	49	49
pH						
≤ 5	18	18	12	12	9	9
> 5	81	79	87	87	90	90
Vaginal Maturation Index						
≤ 5% superficial cells	86	84	78	78	81	81
> 5% superficial cells	6	6	11	11	7	7
Missing	10	10	11	11	12	12
Most Bothersome Symptom						
Vulvar and/or vaginal itching	10	10	4	4	6	6
Vulvar and/or vaginal soreness	5	5	7	7	2	2
Vulvar and/or vaginal irritation	7	7	4	4	8	8
Vaginal dryness	23	23	17	17	23	23
Pain with vaginal penetration	54	53	68	68	60	60
Self-reported health						
Excellent	26	26	27	27	20	20
Very good	41	40	55	55	47	47
Good	33	32	15	15	30	30
Fair	1	1	3	3	3	3
Poor	0	0	0	0	0	0

[a] p>0.05 for all comparisons between each active arm vs. placebo as tested by t-test or chi-square test.

[b] Among participants reporting that they are married or in an intimate relationship

[c]Participants could select more than one answer about their type of sexual activity

Abbreviations: MENQOL - Menopausal Quality of Life, PHQ-8 - Patient Health Questionnaire, GAD-7 - Generalized Anxiety Disorder, FSFI - Female Sexual Function Index, FSDS-R - Female Sexual Distress Scale – Reduced

Table 2.

Views regarding sexual activity, symptoms, and sexuality at enrollment (% reporting affirmative)

Question	Total n	Affirmative	%
I wish that I wanted to have more sex	301	245	81
I am happy with the amount of sex I have	301	60	20
My partner wants to have sex more often than I do	294	219	74
My symptoms are causing significant problems in my sexual relationship	296	198	67
I want to have sex more often than my partner	295	41	14
Sex has never been enjoyable for me	301	18	6
I just don’t want to have sex	300	77	26
My partner can’t have sex because of health reasons	295	10	3
My partner and I are sexually active without intercourse	293	136	46
I have had more than one sexual partner in the last year	300	3	1
I do not have a sexual partner and am not looking for one	299	9	3
I do not currently have a sexual partner, but wish that I did	301	22	7

p>0.05 for all comparisons between each active arm vs. placebo as tested by Fisher exact test, except for “sex has never been enjoyable” question: 8% affirmative in Vaginal Estradiol, 9% in Vaginal Moisturizer, 1% in Dual Placebo. Given 24 hypothesis tests, we would expect at least one to be “statistically significant.”

Table 3.

Proportion of women reporting sexual activity at week 12 by intervention arm. Report of sexual activity in the past month was obtained from week 12 visit questionnaires, while report of sexual activity or penetrative sex in the past week was from participant diaries for the week prior to the final study visit.

	Vaginal estradiol + placebo gel		Vaginal moisturizer + placebo tablet		Dual placebo		Difference			
							Estradiol vs. Placebo		Moisturizer vs. placebo	
Outcome	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**	**OR** [a]	**p value**	**OR** [a]	**p value**
Sexual activity in the past month	99	77.8 (69.4, 86.1)	99	86.9 (80.1, 93.6)	94	84.0 (76.5, 91.6)	0.8 (0.4, 1.7)	0.52	1.5 (0.6, 3.7)	0.34
Sexual activity in the past week	93	49.5 (39.1, 59.8)	91	35.2 (25.2, 45.2)	93	39.8 (29.7, 49.9)	1.7 (0.9, 3.1)	0.10	0.8 (0.5, 1.6)	0.59
Penetrative sex in the past week	92	43.5 (33.2, 53.8)	91	33.0 (23.1, 42.8)	92	34.8 (24.9, 44.7)	1.6 (0.9, 3.0)	0.12	1.0 (0.5, 1.8)	0.91

[a] Odds ratio and p-value from a logistic regression model with week 12 outcome as a function of intervention arm, clinical site, and reported sexual activity in the past month at baseline (yes/no)

Table 4.

Days per week with sexual activity and average pain with sexual activity at week 12 by intervention arm, obtained from participant diaries for the week prior to the final study visit.

	Vaginal estradiol + placebo gel		Vaginal moisturizer + placebo tablet		Dual placebo		Difference			
							Estradiol vs. Placebo		Moisturizer vs. placebo	
Outcome	**N**	**Mean (95% CI)**	**N**	**Mean (95% CI)**	**N**	**Mean (95% CI)**	**Estimate[a] (95% CI)**	**P value[a]**	**Estimate[a] (95% CI)**	**p value[a]**
Days with sexual activity	93	0.7 (0.5, 0.9)	91	0.5 (0.3, 0.6)	93	0.6 (0.4, 0.7)	0.2 (−0.1, 0.5)	0.20	−0.1 (−0.3, 0.1)	0.48
Average pain with sexual activity[b]	46	1.0 (0.7, 1.3)	32	1.1 (0.7, 1.4)	37	0.9 (0.6, 1.2)	0.1 (−0.3, 0.5)	0.52	0.2 (−0.2, 0.6)	0.36

[a] Estimate and p-value from a linear regression model with week 12 outcome as a function of intervention arm, clinical site, and reported sexual activity in the past month at baseline (yes/no)

[b] Among participants who reported at least one day of sexual activity the previous week