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CLINICAL TRIAL

A randomized, double-blind, crossover trial comparing a silicone- versus water-based lubricant for sexual discomfort after breast cancer

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Abstract Discomfort during sexual activity is common after breast cancer. Vaginal estrogens are effective but commonly avoided due to systemic absorption. Despite the large commercial market for vaginal lubricants, no randomized studies have compared products. We aimed to compare efficacy and acceptability of two major types of lubricant for discomfort during sexual activity in postmenopausal breast cancer patients. In a single-center, randomized, double-blind, AB/BA crossover design, sexually active postmenopausal breast cancer patients used each lubricant for 4 weeks. The primary patient-reported efficacy outcome was total discomfort related to sexual activity (Fallowfield Sexual Activity Questionnaire Discomfort subscale SAQ-D). Acceptability was measured by patient preference and reported intention to continue using the products. Of 38 women analyzed, over 90 % experienced clinically significant sexually related distress at baseline. Water- and silicone-based lubricants did not differ statistically in efficacy based on total sexual discomfort (difference 0.7, 95 % confidence interval (CI) 0–1.4, $p = 0.06$). In a post hoc analysis, pain/discomfort during penetration improved more during silicone-based lubricant use than during water-based lubricant use (odds ratio 5.4, 95 % CI 1.3–22.1, $p = 0.02$). All aspects of sexual discomfort measured with diaries were reported more commonly with water- than silicone-based lubricant. Almost twice as many women preferred silicone-based to water-based lubricant than the converse ($n = 20$, 65 %, vs. $n = 11$, 35 %). 88 % continued to experience clinically significant sexually related distress despite use of either lubricant. Total sexual discomfort was lower after use of silicone-based lubricant than water-based, but many women continue to experience sexually related distress.

Keywords Dyspareunia · Sexual activity · Lubrication · Quality of life · Survivorship

Background and objectives

Discomfort during sexual activity is common after breast cancer treatment and may be exacerbated by anti-estrogen endocrine therapy (ET) [12, 17]. The prevalence of vaginal dryness causing sexual discomfort in this population is unknown, but figures of 30–60 % are commonly reported [26, 37]. In younger breast cancer patients, vaginal dryness and pain with sexual intercourse significantly reduce quality of life [4, 41]. In clinical practice, menopausal symptoms including vaginal discomfort may contribute to discontinuation of ET [6, 26]. Hence, effective treatment of these symptoms may increase adherence to ET and improve survival from breast cancer.

To optimize clinical management more information is needed about safe, effective treatments for sexual discomfort in breast cancer patients. Systemic or topical

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(vaginal) estrogens are effective [39] but are commonly avoided after breast cancer due to systemic absorption [13, 42]. Topical testosterone [43] and dehydroepiandrosterone (DHEA) [33] may be effective, but safety after breast cancer is not established. Ospemifene, a nonsteroidal selective estrogen receptor modulator, is licensed in the US for vaginal dryness, but not for use after breast cancer.

Little evidence exists to guide practice for oncologists and patients in managing discomfort during sexual activity. Nonhormonal treatment options include moisturizers, applied intravaginally every few days to maintain hydration and pH, and lubricants, applied to contact surfaces during sexual activity to minimize friction. The most common lubricant bases are water and polymerized siloxanes (silicone-based) [31]. Silicone-based lubricants, like water-based, form gas-permeable, high-slip films on skin and mucous membranes [32], but persist longer [2]. There are fewer silicone-based products on the market, and they are more expensive than water-based formulations [44]. Neither has hormonal action.

The aim of this study was to compare the efficacy and acceptability of a widely used silicone-based lubricant versus a widely used water-based lubricant on discomfort during sexual activity in breast cancer patients.

Methods

Participants, setting, and study design

The study was conducted in the Research Precinct of the Royal Women's Hospital (RWH), Melbourne, Australia, a public tertiary women's hospital. Participants were recruited from RWH clinics, the Australian National Breast Cancer Foundation Register4, consumer groups, and referral from specialty providers. Recruitment, interviews, and examinations were conducted by trained nurse-midwives. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria were having a personal history of breast cancer, being sexually active with symptoms of vaginal dryness or pain during sexual activity, willingness to be randomized and try both products, willingness to keep a sexual activity diary, and having a normal Pap smear in the previous 2 years (where uterus was intact). Exclusion criteria were use of systemic or vaginal sex steroids in the previous 6 weeks, current symptoms of vaginal infection, postmenopausal bleeding, allergy to water- or silicone-based lubricant products, and clinically significant anxiety or depression.

We selected one best-selling [1], widely available representative of the two major types of nonhormonal lubricant (silicone-based: pjur®, pjur group, Wasserbillig, Luxembourg; water-based: Astroglide®, BioFilm Inc., Vista, California) to compare in a randomized, double-blind, AB/BA crossover design. Both colorless and odorless clear fluids were repackaged identically and dispensed free of charge by RWH Pharmacy. Participants were randomly allocated 1:1 to sequence A-B or B-A using a fixed block size of four (sequence generated and maintained by Pharmacy using Excel software, Microsoft Corporation, Redmond, USA, 2010). Participants and non-Pharmacy study staff were blinded until individual study completion, when participant and study nurse were informed of treatment sequence. As lubricants do not persist locally and are not absorbed systemically, the study was designed without a wash-out period between products.

The study protocol was approved by the RWH institutional review board (Project 11/57) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611001249943). There were no major changes to the protocol after the trial began. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This manuscript follows Consolidated Standards of Reporting Trials parallel-group trials statements [5, 36, 38], including patient-reported outcomes extension [10], modified for crossover design.

Follow-up

At baseline (Fig. 1), participants were screened and consented. Participants provided medical and reproductive health histories, completed questionnaires, and underwent pelvic examination, then were randomized and dispensed the first study preparation. After 4 weeks (end of crossover period 1), they were examined, completed questionnaires, and exchanged the first for the second preparation. After another 4 weeks (end of crossover period 2), participants were examined, completed questionnaires and were referred for follow-up care if needed. Four weeks later, the study participants were finally contacted through a short semi-structured telephone interview to ascertain continuing symptoms and any current treatments.

At all visits, participants completed patient-reported outcome instruments: the Fallowfield Sexual Activity Questionnaire (SAQ) [40], the Female Sexual Distress Scale-Revised (FSDS-R) [14], the Functional Assessment of Cancer Therapy General scale (version 4) [11] (FACT-G) with Breast Cancer and Endocrine Symptoms Subscale modules (BCS, version 4, and ES) [8, 18]. At the second and third visits, participants completed the Female Intervention Efficacy Index (FIEI) [7], modified to focus on local side effects. For each treatment period, participants

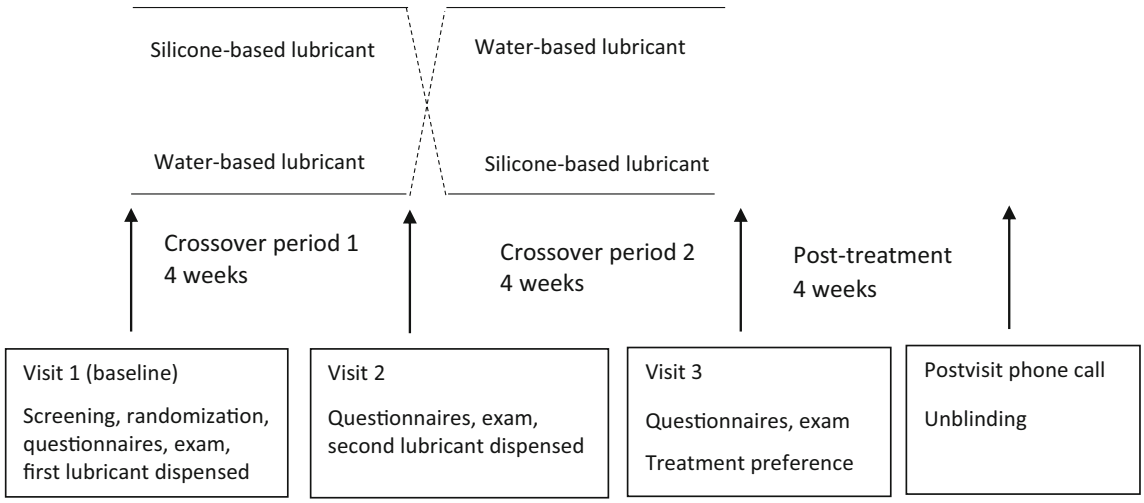

Fig. 1 Study flow schematic, Sexuality after Breast Cancer (SAB) trial

completed investigator-designed sexual activity diaries assessing characteristics of lubricant application and discomfort. At the final visit, before unblinding, patients completed an investigator-designed preference item (Online Appendix 1).

Study variables

The primary efficacy outcome was total discomfort during sexual activity, measured using the Discomfort subscale of the Fallowfield Sexual Activity Questionnaire (SAQ) [3, 40]. The administered section of the SAQ, aimed at sexually active women, consists of 11 Likert-type items (two unscored) regarding sexual feelings and experiences of the previous month, in scales of Discomfort (SAQ-D), Pleasure (SAQ-P), and Habit (SAQ-H). The total sexual discomfort score (SAQ-D; range 0–6) sums responses to two items, dryness ("During sexual relations, how frequently did you notice dryness of your vagina this month?") and dyspareunia ("Did you feel pain or discomfort during penetration this month?"), each of which is answered on a four-point scale (3 = "very much," 2 = "somewhat," 1 = "a little," and 0 = "not at all").

The primary acceptability outcome was an item comparing patient preference (Online Appendix 1). We measured the acceptability of each lubricant independently with an FIEI [7] item asking if and how the preparation changed sexual experience.

Secondary efficacy outcomes included sexual pleasure (SAQ-Pleasure subscale, SAQ-P), sexual habit (SAQ-Habit subscale, SAQ-H), and sexually related personal distress (FSDS-R). The SAQ-P (range 0–18) consists of six items evaluating importance, enjoyment, and satisfaction related to sexual activity. The SAQ-H (range 0–3) is a single item asking how that month's sexual frequency compares to what is usual for the respondent (3 = "much more," 2 = "somewhat more," 1 = "about the same," 0 = "less than usual"). The FSDS-R (range 0–52) is a 13-item scale consisting of Likert-type items scored from 0 "never" to 4 "always," regarding the frequency of symptoms of sexually related personal distress over the past 30 days. Clinical examinations were recorded with modifications of the Vaginal Atrophy Index [34] and Vaginal Health Index [20]. Cancer-related quality of life was assessed using the FACT-G [11], 19-item ES [18], and 9-item BCS [8]. The FACT-G provides global quality of life scores by summing scores in domains of Physical Well-Being, Social/Family Well-Being, Functional Well-Being (all 7-item scores, ranges 0–28), and Emotional Well-Being (6 items, range 0–24). All the FACT instruments consist of Likert-type items concerning past-week function, scored from 0 "not at all" to 4 "very much."

Statistical analysis

At the time of study design, no information was available to inform assumptions regarding change in SAQ-D following water- or silicone-based lubricants. To detect a moderate effect size of 0.5 standardized treatment difference in SAQ-D using a paired t test with 80 % power and two-sided 0.05 level of significance requires 34 participants per treatment sequence, or 40 women after accounting for a 15 % attrition (SSS Sample Size Calculator for Clinical Studies 1.0, National Cancer Centre, Singapore, 2008). Other studies of similar size (e.g., [9, 35]) have detected changes in vaginal dryness and dyspareunia.

The analysis set was defined as all randomized postmenopausal participants who had breast cancer, were not

using systemic or vaginal estrogen, and had at least one post-baseline SAQ-D value. Using a paired *t* test with 80 % power and a two-sided 0.05 level of significance, with analysis set of 38 participants, post hoc calculation shows the minimum detectable standardized treatment difference was 0.7.

Post-baseline efficacy outcomes (SAQ-D, SAQ-P, SAQ-H, and sexually related distress) were evaluated using a linear regression model including treatment sequence, participant nested within treatment sequence, treatment, and period. No tests were performed for carry-over. Components of SAQ-D (dryness and dyspareunia) and sexual habit (SAQ-H) were analyzed post hoc using cumulative proportional odds models, including treatment order, based on the difference in post-baseline scores. Acceptability was measured by comparing the proportion of respondents preferring each lubricant using a binomial test with underlying probability 0.5.

Secondary analyses compared well-being (from FACT instruments), lubrication, genital sensation, orgasmic capacity and overall sexual satisfaction (from FIEI), and characteristics of lubricant use, vulvar pain, and vaginal pain with sexual activity (from diaries) by lubricant type. Continuous variables were summarized using means and standard deviations, and compared using paired *t* tests. Categorical variables were summarized using percentages and compared using exact symmetry tests (which simplify to exact McNemar's tests for binary variables).

To analyze diary data, we calculated the mean proportion of sexual episodes per treatment where participants reported "yes" to binary items (e.g., vulvar burning). Women also reported their highest level of vaginal discomfort during each episode of sexual activity using a visual analogue scale (VAS) anchored at "no pain" and "worst possible pain." VAS scores were averaged per woman per treatment. Means were compared using paired *t* tests.

A two-sided 0.05 level of significance was used. No correction for multiple testing was done. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA, 2015) and Stata 13.1 (StataCorp, College Station, TX, USA, 2013.)

Results

Participants and recruitment

From 3/12 to 5/14, 65 (43 %) of 150 women screened for eligibility were ineligible—almost half (31, 48 %) because they were not sexually active (Fig. 2). Forty-six women were randomized but only 38 were included in the analysis sample; one patient was excluded for not having had breast cancer, one for having resumed menstruation (i.e., not being postmenopausal), one for having started to use vaginal estrogen, and five for having only a baseline SAQ-D. Outcomes of routine monitoring (protocol violations, harms, and adverse events) and of comparison to breast cancer patient norms are detailed in Online Appendix 2.

Baseline data

The average age of participants was 53.1 years, SD 8.4 years (Table 1). All participants were Caucasian, and all but one was partnered. All were postmenopausal, with average age at menopause 45.8 years (SD 5.2 years). Median time since cancer diagnosis was 3.0 years (range 0.3–25.7 years). Most ($n = 32$, 84.2 %) had received and the majority ($n = 24$, 63 %) were still taking ET of whom half ($n = 12$) were taking aromatase inhibitors.

For three women, internal examination was not possible due to discomfort or inability to pass a speculum. For nine others, examination was possible only with a pediatric speculum. Many others could not tolerate more than one finger inserted in the vagina due to discomfort and pain ($n = 27/36$, 75.0 %; two women did not attend the examination). The labia appeared dry and atrophic in most women ($n = 30/36$, 83.3 %). Most had an alkaline vaginal pH (>5.0, $n = 28/32$, 87.5 %; four insufficient secretions). No participants reported postmenopausal bleeding before examination, but a substantial minority ($n = 11/33$, 33.3 %) experienced bleeding after gentle examination.

Baseline patient-reported measures are summarized in Table 2. The mean baseline total sexual discomfort score was 4.8 (SD 1.7). The mean baseline sexually related distress score was 31.1 (SD 12.0), and nearly all participants (33/36, 91.7 %) exceeded the cut-off for clinical significance (>11).

Primary outcomes

There was no statistically significant difference between silicone- and water-based lubricants in total sexual discomfort (difference 0.7, 95 % confidence interval (CI) 0.0–1.4, $p = 0.06$, Table 3). In a post hoc analysis pain/discomfort during penetration improved more during silicone lubricant use compared to the water-based product (odds ratio 5.4, 95 % CI 1.3–22.1, $p = 0.02$). Participants were around five times more likely to report increased pain with vaginal intercourse when changing from silicone- to water-based lubricant compared to those changing from water- to silicone-based. When asked which lubricant they would use again, 11 women (33.3 %) responded silicone-based but not water-based, 9 (27.3 %) would use either but preferred silicone-based, 5 (15.1 %) would use water-based but not silicone-based, 6 (18.2 %) would use either but

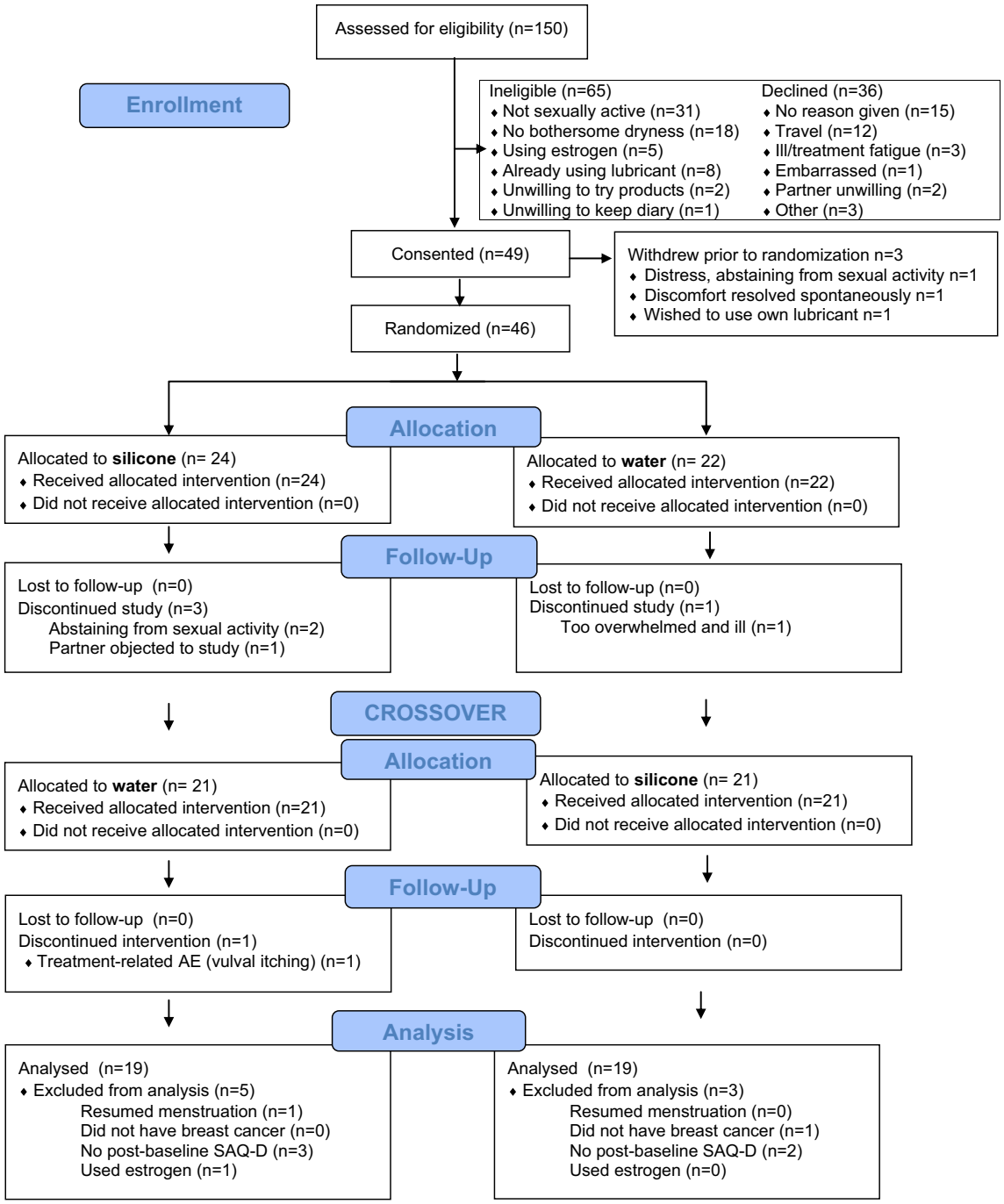

Fig. 2 CONSORT diagram, Sexuality after Breast Cancer (SAB) trial. Subjects were randomized to treatment sequence (silicone-based then water-based or water-based then silicone-based). The analysis set was defined as all randomized postmenopausal participants who had breast cancer, had collected the lubricant, and had at least one post-baseline SAQ-D value. *AE* adverse event, *SAQ-D* Sexual Activity Questionnaire Discomfort subscale

preferred water-based, 1 (3.0 %) would use either without preference, and 1 (3.0 %) would use neither. Five subjects had missing values. Almost twice as many women reported that they preferred silicone- to water-based lubricant than conversely, but this did not reach statistical significance ($p = 0.15$).

The majority of women reported that lubricants improved sexual experience and they would continue to use them (water-based: $N = 23$, 63.9 %; silicone-based: $N = 27$, 73.0 %), a few no change but would continue use (water-based: $N = 3$, 8.3 %; silicone-based: $N = 2$, 5.4 %), some no change and would not continue use

Table 1 Demographic and clinical characteristics of Sexuality after Breast Cancer (SAB) trial participants, $N = 38$

Characteristic	All
Age, years, mean, SD	53.1, 8.4
Height[a], cm, mean, SD	164.0, 6.6
Weight[a], kg, mean, SD	70.1, 12.2
BMI[a], kg/m^2, mean, SD	26.1, 4.5
Marital status, *n* (%)	
Partnered/married	37 (97.4)
Single	1 (2.6)
Highest education, *n* (%)	
High school	13 (34.2)
Tertiary education	25 (65.8)
Employment[a], *n* (%)	
Part-time	10 (27.0)
Full-time	16 (43.2)
Other (e.g., student, home duties)	11 (29.7)
Smoking, *n* (%)	
Never	23 (60.5)
Former	14 (36.8)
Current	1 (2.6)
Alcohol use past 6 months, *n* (%)	
Never	5 (13.2)
Seldom	4 (10.5)
Occasionally	16 (42.1)
Regularly	13 (34.2)
Parity[b], *n* (%)	
0 births	8 (21.6)
1 birth	4 (10.8)
2 births	11 (29.7)
3 + births	14 (37.8)
Age at menopause[a], years, mean, SD	45.8, 5.2
Type of menopause, *n* (%)	
Spontaneous	8 (21.1)
Surgical	12 (31.6)
Chemotherapy	17 (44.7)
Endocrine	1 (2.6)
Years since cancer diagnosis[c], median, range	3.0, 0.3–25.7
Adjuvant therapy[d], *n* (%)	
Radiation	28 (75.7)
Chemotherapy	22 (62.9)
Endocrine therapy	32 (84.2)
Current endocrine therapy, *n* (%)	24 (63.1)
Tamoxifen	10 (41.7)
Aromatase inhibitors	12 (50.0)
Goserelin	1 (4.2)
Tamoxifen and goserelin	1 (4.2)

Not all percentages sum to 100 % due to rounding or not being mutually exclusive

[a] One participant missing data

[b] One participant declined this item

[c] Two participants missing data

[d] Categories are not mutually exclusive

(water-based: $N = 7$, 19.4 %; silicone-based: $N = 6$, 16.2 %), and a few worsened experience and would not continue use (water-based: $N = 3$, 8.3 %; silicone-based: $N = 2$, 5.4 %). Of 31 (67 %) who continued to use a lubricant after the study, more than twice as many used silicone-based as water-based ($n = 18$, 58 % vs. $n = 8$, 25.8 %). Five used other treatments.

Secondary outcomes

There was no statistically significant difference between silicone- and water-based lubricants for SAQ-P and SAQ-H (Table 3). Sexually related distress did not differ between lubricant type, and remained above twice the clinically significant cut-off score for both the preparations (Table 3), with 88 % ($n = 30$) of participants still experiencing clinically significant distress at the end of the study. After the trial, all but one respondent ($n = 33$, 86.9 %) reported continuing symptoms of sexual discomfort. One participant volunteered that she was no longer sexually active due to ongoing discomfort.

From the diaries, all participants reported at least one episode of sexual activity per treatment period. On average, after correction for length of treatment period, women had 6.5 sexual episodes during water-based and 7.4 during silicone-based treatment. For nearly all episodes (water-based 95 %, silicone-based 97 %), participants reported using lubricant and thus provided details of lubricant application and sexual discomfort (Table 4). Participants reported pain during sexual activity using a 100-mm VAS. On treatment, the average pain score was 28.03 (95 % CI 20.34–35.74) per sexual episode using the water-based lubricant, and 18.56 (95 % CI 12.84–24.28; $p = 0.05$) during silicone-based. Most sexual episodes (87–93 %) involved vaginal penetration. For more than 96 % of episodes, lubricant was applied to the vagina (at the introitus or internally), and (>90 %) to the vulva. Nearly all (>97 %) who applied lubricant vaginally applied it before penetration. Many women continued to experience vulvar (25–42 %) or vaginal (47–60 %) discomfort during sexual activity even with a lubricant. All measured aspects of sexual discomfort recorded in the diaries were more common with water- than silicone-based lubricant, but no differences reached statistical significance. Analyses restricted to first episodes per day yielded similar estimates (data not shown).

Responses to the FIEI are summarized in Table 5. Only the lubrication item differed significantly ($p = 0.02$), with more observing increased lubrication after silicone-based than after water-based lubricant (84 vs. 67 %).

Among measures of quality of life, only Functional Well-Being differed significantly between treatments, and was better with silicone- compared to water-based

Table 2 Patient-reported baseline measures of Sexuality after Breast Cancer (SAB) trial participants by treatment sequence, $N = 38$

Baseline characteristic	Overall	Treatment sequence	
	All $N = 38$	Water-based first $n = 19$	Silicone-based first $n = 19$
Sexual discomfort[a] mean, SD	4.81, 1.69[b]	5.06, 1.30[c]	4.56, 2.01[c]
Dyspareunia[a] *n* (%)			
Not at all	3 (7.9)[b]	1 (5.3)[c]	2 (10.5)[c]
A little	4 (10.5)	1 (5.3)	3 (15.8)
Somewhat	9 (23.7)	6 (31.6)	3 (15.8)
Very much	20 (52.6)	10 (52.6)	10 (52.6)
Vaginal dryness[a] *n* (%)			
Not at all	2 (5.2)	0 (0)	2 (10.5)
A little	2 (5.2)	2 (10.5)	0 (0)
Somewhat	7 (18.4)	2 (10.5)	5 (26.3)
Very much	27 (71.1)	15 (79.0)	12 (63.2)
Sexual pleasure[a], mean, SD	7.63, 4.46	8.74, 3.96	6.53, 4.77
Sexual habit[a] *n* (%)			
Much more	11 (28.9)[b]	5 (26.3)[c]	6 (31.6)[c]
Somewhat more	16 (42.1)	8 (42.1)	8 (42.1)
About the same	6 (15.8)	4 (21.1)	2 (10.5)
Less than usual	3 (7.9)	1 (5.3)	2 (10.5)
Sexual distress[d] mean, SD	31.14, 12.01[b]	29.27, 12.77[c]	33.00, 11.24[c]
Quality of life[e], mean, SD			
Global Well-Being	80.70, 14.65	82.92, 14.08	78.48, 15.25
Physical Well-Being	21.20, 5.06	21.92, 4.90	20.47, 5.24
Social/Family Well-Being	20.79, 5.22	21.42, 5.45	20.16, 5.05
Emotional Well-Being	18.13, 3.99	18.53, 4.01	17.73, 4.04
Functional Well-Being	20.58, 4.44	21.05, 4.49	20.11, 4.46
Breast Cancer Subscale	23.49, 5.37[c]	24.74, 5.18	22.17, 5.38[c]
Endocrine Symptoms	46.57, 11.60[c]	49.96, 7.33[c]	43.35, 14.00
Anxiety[f], mean, SD	7.42, 4.12	7.47, 4.80	7.37, 3.44
Depression[f], mean, SD	3.92, 3.38	3.58, 3.31	4.26, 3.51

Not all percentages sum to 100 % due to rounding

SD standard deviation

[a] Measurements derived from Fallowfield's Sexual Activity Questionnaire (SAQ). Sexual discomfort: SAQ-D (range 0–6), higher score corresponding to worse function, past month, sum of two Likert items (dyspareunia and vaginal dryness). Sexual pleasure: SAQ-P (range 0–18), higher score corresponding to better function, past month, sum of six Likert items. Sexual habit: SAQ-H (range 0–3), past month, single Likert item comparing sexual frequency to usual experience

[b] Two participants missing data

[c] One participant missing data

[d] Measurement derived from the Derogatis Female Sexual Distress Scale-Revised (range 0–52), higher score corresponding to worse function, past 30 days, sum of 13 Likert items

[e] Measurements derived from Functional Assessment of Cancer Therapy (FACT) instruments, higher scores corresponding to better function, past week. Global Well-Being measured with FACT-General (FACT-G) (range 0–108), sum of scores of the four Well-Being Likert items. Physical Well-Being, Social/Family Well-Being, and Functional Well-Being, (range 0–28) each, sum of seven Likert items each. Emotional Well-Being (range 0–24), sum of six Likert items. Breast Cancer Subscale (range 0–36), sum of nine Likert items. Endocrine Symptoms subscale (range 0–76), sum of 19 Likert items

[f] Measurements derived from the Hospital Anxiety and Depression Scale. Subscales, Anxiety and Depression (range 0–21) each, sum of seven items each, higher scores corresponding to worse function, past week

Table 3 Efficacy outcomes of Sexuality after Breast Cancer (SAB) trial participants, $N = 38$

	N	Mean after water-based lubricant (SD)	n	Mean after silicone-based lubricant (SD)	Estimated mean difference, water-based minus silicone-based[a] (95 % CI)	p[a]
Total sexual discomfort[b]	37	4.2 (1.9)	35	3.5 (1.8)	0.7 (0.0, 1.4)	0.06
Sexual pleasure[b]	37	10.1 (4.9)	35	11.3 (3.8)	−1.0 (−2.5, 0.4)	0.16
Sexual distress[c]	37	24.9 (13.6)	35	22.7 (14.3)	1.9 (−1.1, 4.9)	0.20

	Score change from water-based to silicone-based, accounting for period[d] n (%)					Estimated OR (95 % CI)[e]	p[e]
	Much better	Better	Same	Worse	Much worse		
Dyspareunia[b]	2 (5.9)	12 (35.3)	16 (47.1)	4 (11.8)	0 (0)	5.4 (1.3, 22.1)	0.02
Vaginal dryness[b]	2 (5.9)	10 (29.4)	14 (41.1)	8 (23.6)	0 (0)	1.9 (0.6, 6.8)	0.30
Sexual habit[b]	0 (0)	16 (47.1)	11 (32.4)	7 (20.6)	0 (0)	1.1 (0.3, 3.9)	0.87

Not all percentages sum to 100 % due to rounding

OR odds ratio, *SD* standard deviation, *CI* confidence interval

[a] Estimated (least-squares) mean differences, 95 % CI, and *p* values obtained from linear regression models

[b] Measurements derived from Fallowfield's Sexual Activity Questionnaire (SAQ). Total sexual discomfort: SAQ-D (range 0–6), higher score corresponding to worse function, past month, sum of two Likert items: pain/discomfort during sexual activity (dyspareunia) and vaginal dryness. Sexual pleasure: SAQ-P (range 0–18), higher score corresponding to better function, past month, sum of six Likert items. Sexual habit: SAQ-H (range 0–3), past month, single Likert item comparing sexual frequency to usual experience

[c] Measurement derived from the Derogatis Female Sexual Distress Scale-Revised (range 0–52), higher score corresponding to worse function, past 30 days, sum of 13 Likert items

[d] (See also footnote b) "Much better": three-point improvement (e.g., change from "very much" on water-based to "not at all" on silicone-based); "better": one- or two-point improvement (e.g., change from "somewhat" on water-based to "a little" or "not at all" on silicone-based); "same": score unchanged; "worse": one- or two-point deterioration (e.g., change from "more than usual" on water-based to "about the same" or "less than usual" on silicone-based); "much worse": three-point deterioration (e.g., change from "not at all" on water-based to "very much" on silicone-based)

[e] Estimated OR, 95 % CI, and *p* value obtained from cumulative proportional logistic regression models

lubricants (water-based mean 21.61, SD 4.96 vs. silicone-based mean 20.49, SD 5.68, $p = 0.04$).

Discussion

The number of breast cancer survivors is growing, with 2.8 million women in the US alone (www.cancer.org). Most are postmenopausal and the prevalence of sexual dysfunction due to vaginal symptoms is substantial [27]. Vaginal dryness contributes to sexual dysfunction, and lubricants may improve this. However, while a wide range of lubricants are available there is very little evidence to inform patient choice. Our aim was to provide high quality evidence for health care providers and consumers regarding the relative efficacy and acceptability of the two main types of vaginal lubricant.

The most striking finding from our study was the high levels of sexually related distress in this relatively young postmenopausal population (mean age 53 years). At baseline, mean sexually related distress score was close to three times greater than the clinically significant cut-off [14] and remained at double the cut-off despite the use of vaginal lubricants. Almost half of those screened were ineligible because they were not sexually active, mostly due to sexual discomfort. Even in those who were sexually active, vaginal examination was too uncomfortable for some and several others could tolerate only a small (pediatric) speculum or a single finger at examination. Most published studies of breast cancer and sexual function have focused on younger women. Our data suggest that sexual dysfunction is associated with distress for older postmenopausal women and that while lubricants might reduce pain and increase sexual pleasure, they do not reduce distress. Lubricants were applied to the vulva and vagina with the aim of reducing friction during vaginal penetration. Most of the published literature addressing sexual function in postmenopausal women has focused on vaginal dryness, but vulvar symptoms may also contribute to discomfort. Recent evidence demonstrates that local anesthetic applied to the vulva effectively reduces pain during sexual activity [24], and a small but growing body of evidence suggests that the mechanism underlying some postmenopausal dyspareunia, including in breast cancer patients, may be a chronic vestibular pain syndrome rather than hypoestrogenic atrophic dryness [21–23, 25, 29, 30]. If so, additional

Table 4 Sexual activity diary of Sexuality after Breast Cancer (SAB) trial participants, $N = 38$

Characteristic	Average proportion of sexual episodes per woman that featured listed characteristic % (95 % CI)[a]	
	Water-based	Silicone-based
Vaginal penetration	87.2 (77.9, 96.4)	92.6 (86.9, 98.3)
Lubricant application pattern		
Applied to vulva	94.6 (89.3, 99.9)	93.9 (88.4, 99.4)
Applied at introitus or internally	98.3 (96.7, 100.0)	96.8 (93.7, 99.9)
Prior to penetration[b]	99.5 (98.5, 100.0)	97.2 (93.7, 100.0)
During penetration[b]	37.4 (21.6, 53.1)	44.2 (28.7, 59.7)
After penetration[b]	6.6 (<0.1, 14.3)	10.5 (<0.1, 22.7)
Vulvar discomfort	42.0 (27.9, 56.1)	24.8 (13.1, 56.2)
Vulvar burning	19.9 (9.1, 30.8)	12.8 (3.2, 22.4)
Vulvar itching	6.3 (<0.1, 13.0)	1.3 (<0.1, 3.1)
Vulvar bleeding	3.8 (<0.1, 9.7)	1.3 (<0.1, 3.1)
Vulvar tearing	7.2 (<0.1, 14.5)	7.1 (0.1, 14.1)
Vaginal discomfort	60.2 (46.5, 73.8)	47.1 (34.8, 59.3)
Vaginal burning	35.0 (20.5, 49.5)	24.2 (13.2, 35.2)
Vaginal itching	4.2 (<0.1, 8.5)	1.8 (<0.1, 4.7)
Vaginal bleeding	8.4 (<.1, 17.0)	0.5 (<.1, 1.4)
Vaginal tearing	11.9 (1.7, 22.1)	5.8 (<0.1, 12.3)
Pain inside vagina at entry[c]	66.1 (53.4, 78.9)	54.2 (39.9, 68.6)
Pain inside vagina during penetration[c]	54.5 (40.3, 68.8)	46.7 (31.9, 61.6)
Pain inside vagina after penetration[c]	32.0 (17.7, 46.3)	24.8 (13.3, 36.4)

[a] $p > 0.05$ for all comparisons

[b] Limited to episodes with penetration where lubricant was applied at introitus or internally

[c] Limited to episodes involving penetration (34 women during water-based treatment, 37 women during silicone-based treatment)

Table 5 Female Intervention Efficacy Index items of Sexuality after Breast Cancer (SAB) trial participants

	Water-based *N*=36	Silicone-based *N*=37
Vaginal lubrication[a]		
More than before use	24 (66.7)	31 (83.8)
Less than before use	2 (5.6)	3 (8.1)
Same as before use	9 (25.0)	2 (5.4)
Could not tell difference	1 (2.8)	0 (0)
Could not tell, partner noticed increase	0 (0)	1 (2.7)
Could not tell, partner noticed decrease	0 (0)	0 (0)
Sensation/feeling in genitals was		
More than before	21 (58.3)	21 (55.3)
Less than before	0 (0)	3 (7.9)
Unchanged	15 (41.7)	13 (34.2)
Change[b] was		
Pleasant/satisfying	16 (76.2)	17 (70.8)
Unpleasant/disturbing	2 (9.5)	2 (8.3)
Neither	2 (9.5)	3 (12.5)
Other[c]	1 (4.8)	2 (8.3)
Intercourse/sexual activity was		
Pleasant/satisfying/better	17 (47.2)	20 (54.1)
Unpleasant/worse	2 (5.6)	3 (8.1)
Unchanged	5 (13.9)	2 (5.4)
Pleasant, different from before cancer treatment	12 (33.3)	12 (32.4)
Ability to orgasm		
Increased	13 (36.1)	17 (45.9)
Decreased	3 (8.3)	1 (2.6)
Unchanged	20 (55.6)	19 (50.0)
Irritation		
No	25 (69.4)	31 (83.8)
Yes	11 (30.6)	6 (16.2)
Other unpleasant sensation		
No	27 (75.0)	29 (78.4)
Yes[d]	9 (25.0)	8 (21.6)

Not all percentages sum to 100% due to rounding

[a] $p = 0.02$; $p > 0.05$ for all other comparisons

[b] Limited to those reporting change in sensation

[c] Water-based: "less painful/uncomfortable but not satisfying for me"; Silicone-based: "comfortable, not painful but not arousing," "felt numbed, smothered, affected orgasm"

[d] Water-based: pain symptoms $n = 4$, tightness/swelling $n = 2$, sticky $n = 2$, dried out too soon $n = 1$. Silicone-based: pain symptoms $n = 5$, too lubricated $n = 1$, oily/greasy $n = 2$

lubrication could not address the fundamental cause of pain in these patients. More information is needed about what causes pain and discomfort in this population in order to effectively target treatments.

Our data suggest that silicone-based lubricant might reduce total sexual discomfort with sexual intercourse more effectively than the water-based product. The difference between the products was 0.7 (95 % CI 0, 1.4). On this scale, a single point change represents moving a single step on a troublesomeness scale of "very much," "somewhat," "a little," and "not at all" for one of the two component symptoms (pain or discomfort during penetration (dyspareunia), and dryness). A single point change in the total sexual discomfort scale is thought to be clinically meaningful and is equivalent to the impact of surgical menopause on this scale [3, 19]. Although the magnitude of the difference we saw in the discomfort score was smaller than the clinically relevant value, and the 95 % CI contained zero, the CI also comfortably includes 1.0, the clinically relevant value. Post hoc analysis suggested that

the silicone-based product showed a statistically significant improvement in the component symptom dyspareunia (pain or discomfort during penetration) but did not improve vaginal dryness, consistent with a lubricant that is not locally absorbed. This difference might also be attributable to qualities of the two types of lubricants: although water-based lubricants generally contain humectants (most commonly, glycerin) to decrease evaporation, silicone-based lubricants still persist longer [2, 15]. As well, most water-based lubricants are substantially hyperosmolar relative to normal vaginal secretions, while silicone-based lubricants, containing no water, have no osmolality [16]. Such hyperosmolality has been shown to increase the risk of mucosal irritation [15]. In recent testing, the water-based lubricant exemplar used here has the highest osmolality of those available over the counter, about 5–6 times higher than the value recommended by recent World Health Organization guidelines (380 mOsm/kg) [16, 44]. Diary measures of sexual discomfort also consistently suggested a slight advantage for silicone-based over water-based products, but did not reach statistical significance.

Almost twice as many women ($n = 20$, 65 %) preferred silicone- to water-based lubricant ($n = 11$, 35 %), but this did not reach statistical significance. Most reported that they would continue to use vaginal lubricants, with more (around one half) preferring the silicone-based lubricant to the water-based product (around one quarter).

Most participants (63 %) were taking ET, reflecting current clinical recommendations for estrogen receptor-positive breast cancer. However, our study was not powered to determine the impact of particular ET on the efficacy of different lubricants.

Strengths of this study include the randomized double-blind design and use of standardized clinical instruments to measure sexual function outcomes. Diary data confirmed that participants were sexually active during the treatment period, particularly with vaginal penetration, and that they used the lubricants consistently. Limitations include low power due to insufficient sample size and that baseline measures were not repeated before crossover between lubricants. Several follow-ups were outside protocol schedule. Our population was drawn from clinic patients at a single center and from the general population, but may have been biased towards those with more severe symptoms.

The vaginal lubricant market is substantial, at around $208 m per annum in the US [28]. Given the prevalence of sexual discomfort after breast cancer and the dearth of effective treatments, more information is needed about which treatments are safe and effective. Our findings suggest that silicone-based lubricants may be more effective than water-based to treat discomfort during sexual activity in postmenopausal women but are unlikely to reduce sexually related distress.

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Author's Contribution M Hickey and JL Marino designed the study. M Hickey recruited the participants and provided supervision and overview of findings. JL Marino constructed the database and contributed to the statistical analysis of the data. S Wong managed the randomization and lubricant allocation. S Braat contributed to the statistical analysis of the data. All authors contributed to the manuscript.

Compliance with ethical standards

Conflict of interest The study was partially supported by an educational grant from pjur, Luxembourg, which included supply of both water- and silicone-based lubricants but not packaging for double blinding. The company had no input into the study design, data collection, analysis of findings, interpretation of results, or writing of this manuscript. The pjur group approved the submitted version of this manuscript.

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