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ORIGINAL REPORT

A Practical Solution for Dyspareunia in Breast Cancer Survivors: A Randomized Controlled Trial

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See accompanying editorial on page 3370

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ABSTRACT

Purpose
Dyspareunia is common in breast cancer survivors because of low estrogen. This study explored whether dyspareunia is introital pain, preventable with analgesic liquid.

Patients and Methods
In a randomized, controlled, double-blind trial, estrogen-deficient breast cancer survivors with severe penetrative dyspareunia applied either saline or 4% aqueous lidocaine to the vulvar vestibule for 3 minutes before vaginal penetration. After a 1-month blinded trial of patient-assessed twice-per-week tampon insertion or intercourse, all patients received lidocaine for 2 months in an open-label trial. The primary outcome was patient-related assessment of penetration pain on a scale of zero to 10. Secondary outcomes were sexual distress (Female Sexual Distress Scale), sexual function (Sexual Function Questionnaire), and resumption of intercourse. Comparisons were made with the Mann-Whitney *U* and Wilcoxon signed rank test with significance set at $P < .05$.

Results
In all, 46 patients, screened to exclude those with pelvic muscle and organ pain, uniformly had clinical evidence of severe vulvovaginal atrophy, dyspareunia (median pain score, 8 of 10; interquartile range [IQR], 7 to 9), increased sexual distress scores (median, 30.5; IQR, 23 to 37; abnormal, > 11), and abnormal sexual function. Users of lidocaine reported less pain during intercourse in the blinded phase (median score of 1.0 compared with saline score of 5.3; $P = .007$). After open-label lidocaine use, 37 (90%) of 41 reported comfortable penetration. Sexual distress decreased (median score, 14; IQR, 3 to 20; $P < .001$), and sexual function improved in all but one domain. Of 20 prior abstainers from intercourse who completed the study, 17 (85%) had resumed comfortable penetrative intimacy. No partners reported penile numbness.

Conclusion
Breast cancer survivors with menopausal dyspareunia can have comfortable intercourse after applying liquid lidocaine compresses to the vulvar vestibule before penetration.

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INTRODUCTION

Dyspareunia is an extremely difficult symptom of the postmenopausal state, and women with breast cancer are especially vulnerable because therapy is anchored in establishing and maintaining a low-estrogen state.[1] Problems related to menopause are known to affect quality of life in breast cancer survivors[2,3] who numbered 2.89 million as of 2011 in the United States.[4] Our study aimed to explore the menopause symptom of genital pain and its role in sexual dysfunction and sexual distress in this population.

From experience with patients who have vulvar pain, we hypothesized that postmenopausal dyspareunia could be successfully treated as a pain condition localized to the vulvar vestibule, a small zone of entryway mucosa outside the vagina but deep to the labia. A phenomenon of proliferation of nerves in the vulvar vestibule is present in the condition of vestibulodynia,[5-7] which results in dyspareunia that is localized to the vulvar vestibule. Our group has found vestibular neural proliferation to be present in tissue samples from patients with postmenopausal dyspareunia.[8]

We hypothesized that painful intercourse in breast cancer survivors could not be fully addressed unless increased nerves in the vulvar vestibule were targeted for use of a numbing agent in addition to using an effective artificial lubricant to reduce friction across this mucosa. In this proof-of-concept study, our specific aim was to determine whether a

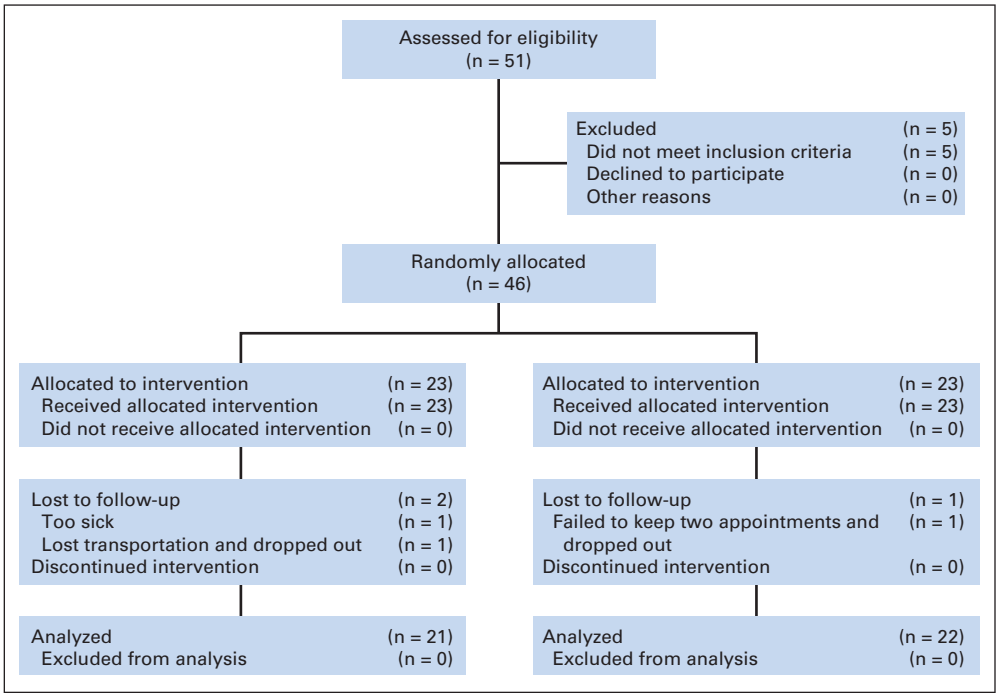

Fig 1. CONSORT diagram for part 2 of study. See Data Supplement for full CONSORT diagram.

self-administered topical anesthetic applied to the vulvar vestibule just before penetration is effective in preventing entry dyspareunia in postmenopausal breast cancer survivors.

PATIENTS AND METHODS

The full Methods section is provided in the Appendix (online only).

Design Overview

A randomized, double blind, placebo-controlled study targeted dyspareunia in survivors of breast cancer. Eligible women had undergone a screening gynecologic examination (part 1, reported separately)[9] to assess locations of genital pain. Part 2 compared patient-reported outcomes during home use of a study drug or placebo (Fig 1). Part 3 assessed patient-reported outcomes during open-label use of the active study drug (see Data Supplement for full CONSORT diagram). Two institutional review boards approved the study protocol and materials.

Setting and Participants

Our study took place in the Department of Obstetrics and Gynecology in Portland, Oregon, at Oregon Health & Science University (OHSU). Candidate women were postmenopausal with a history of 1 or more years of invasive breast cancer and a complaint of moderate or severe dyspareunia for at least 6 months. Inclusion criteria were being in a long-term stable heterosexual relationship for at least 5 years, not using estrogen products for at least 4 months, speaking English, and being age 18 to 70 years. Patients were excluded if their dyspareunia was a result of pelvic pain, pelvic floor myalgia, or vulvar dermatoses. Genital tenderness had to be localized in the vulvar vestibule and extinguishable by application of topical 4% lidocaine solution for several minutes. Dyspareunia was defined as penetrative pain severe enough with every act of intercourse to result in reduced frequency of intercourse or abstinence. Postmenopausal status was defined as more than 1 year without menses with accompanying climacteric symptoms, prior bilateral oophorectomy, or use of a gonadotropin-releasing hormone agonist to suppress ovaries to allow antiestrogen medications.

Randomization and Interventions

Patients were randomly assigned to 1 month of at-home use of either 4% aqueous lidocaine or placebo applied as a compress to the vulvar vestibule just before vaginal penetration with either their partner or a tampon. They agreed to attempt penetration twice per week and record pain scores in a study diary. Both the placebo (physiologic saline) and aqueous 4% lidocaine are clear odorless liquids. The OHSU Research Pharmacy randomly assigned patients and dispensed their study liquid. All patients were given a silicone lubricant. After 1 month, patients returned for a second gynecologic examination, administration of questionnaires, and discussion of any difficulties. Patients then entered part 3 of the study and received open-label aqueous 4% lidocaine for 2 months during which they tried penetration twice per week and documented pain scores in diaries. Part 3 concluded with a final gynecologic examination and administration of questionnaires. Final study contact was at 6 months by using a telephone questionnaire.

Outcomes and Follow-Up

Our primary patient-related outcome was pain with intercourse, scored by using the Numeric Rating Scale.[10] Values were between zero (no pain) and 10 ("the worst pain you have ever experienced"). Secondary outcomes were resumption of intercourse and quality of sexual life as measured by two validated instruments. The Sexual Function Questionnaire tabulates scores in six domains of sexual function.[11] The Female Sexual Distress Score-Revised[12] tabulates emotional distress regarding sex.

Patient Instructions

Patients were shown the vulvar vestibule by using a mirror to point out where they were to apply the study liquid. They were instructed to use cotton balls or large cotton swabs fully saturated with study liquid held against the vestibule mucosa for 3 minutes; they were then to immediately apply silicone lubricant liberally and attempt vaginal penetration twice per week. The same study nurse who performed consent and administered the questionnaires then gave each patient a supply of cotton balls, large swabs, regular tampons, silicone lubricant, and 30-day diary forms.

Table 1. Demographic and Clinical Characteristics by Randomization Group at Baseline

Characteristic	Saline (n = 23)			4% Lidocaine (n = 23)		
	No. (%)	Mean ± SD	Median (IQR)	No. (%)	Mean ± SD	Median (IQR)
Age, years		54.0 ± 9.2			56.6 ± 8.2	
Race/ethnicity						
White	21 (91.3)			20 (87)		
Asian	0 (0)			2 (8.7)		
Native Hawaiian	1 (4.4)			0 (0)		
More than one race	1 (4.4)			1 (4.4)		
Highest education level						
> 12th grade	20 (86.9)			20 (86.9)		
9th through 12th grade	3 (13.0)			3 (13.0)		
Years with present partner		23.9 ± 12.8			25.9 ± 11.8	
Years since diagnosis of breast cancer			3 (2-6)			5 (3-14)
Specifics of menopause						
Breast cancer before menopause	11 (47.8)			11 (47.8)		
Prior oophorectomy	7 (30.4)			9 (39.1)		
Currently taking a SERM	4 (17.4)			2 (8.7)		
Currently taking an aromatase inhibitor	9 (39.1)			9 (39.1)		
No. of years without ovarian or exogenous estrogen			3 (2-7)			4 (2-12)
Baseline score for pain with sex (NRS)			8 (7-10)			8 (6-9)
Duration of dyspareunia, years			2 (1-4)			3 (2-10)
Stopped having penetrative intimacy	12 (48)			13 (54.2)		
Follicle-stimulating hormone (mIU/mL)		59.6 ± 30.6			63.5 ± 24.5	
Serum estradiol-17β (pg/mL)			5 (5-8.5)			5.7 (5-10.9)

NOTE. Randomization groups were similar in all characteristics.
Abbreviations: IQR, interquartile range; NRS, Numerical Rating Scale (scores of 0 to 10); SD, standard deviation: SERM, selective estrogen receptor modulator.

Statistical Analysis

Referencing a previously reported vestibule mean pain score of 8.0 ± 1.4,[13] we estimated that a sample size of 44 would achieve 94% power to detect at least 1.5 points mean difference in pain scores between treatment and placebo. This sample size also achieved more than 90% power with adjustment for a two-sided Mann-Whitney *U* test, assuming the actual distribution was not normal. Allowing for a dropout rate of 5%, 46 participants were needed for random assignment.

Characteristics of the randomly assigned groups were analyzed by using a *t* test or Mann-Whitney *U* test, depending on the distribution for continuous variables. Categorical variables were analyzed by χ^2 or Fisher's exact test. Comparisons of reported numeric rating scale or Female Sexual Distress Scale values used the two-tailed Mann-Whitney *U* test, and patients' changes in those scales were tested by using two-tailed Wilcoxon signed rank test, each with significance set at $P < .05$. Missing data were handled per the validated tool scoring instructions. Study data were managed by using REDCap electronic data capture tools hosted at OHSU.[14] Statistical analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC) and R version 2.14.1.

RESULTS

Between January 27, 2012, and February 7, 2013, we enrolled 46 breast cancer survivors who had entry dyspareunia and tenderness in the vulvar vestibule that could be extinguished with lidocaine. Findings from screening 51 candidates have been reported.[9]

The demographic characteristics for all patients are provided in Table 1. All participants had previously used artificial lubricants, and 13 (28%) had tried vaginal moisturizers, noting modest or no reduction in dyspareunia. The median intercourse pain score for participants was 8 of 10, (interquartile range, 7 to 9). Fifty percent had become abstainers from intercourse. Forty-three (93%) completed the blinded intervention phase and 41 (89%) completed the full study. In the blinded phase, users of saline and silicone lubricant who tried intercourse (71%) noted a 38% reduction in pain (median score, 5.3; $P = .007$). In comparison, users of lidocaine and silicone lubricant who attempted intercourse (73%) had 87.5% less pain (median pain score, 1.0; $P < .001$; Fig 2). Two patients tried intercourse with their

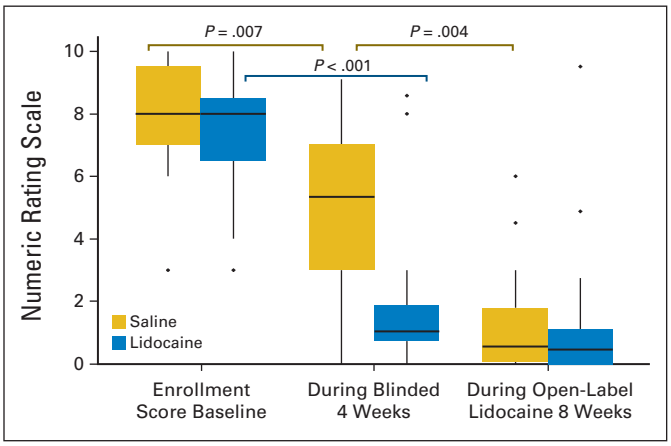

Fig 2. Median pain scores during or after intercourse as recorded in weekly diaries using the Numeric Rating Scale. Black horizontal lines indicate medians; colored boxes indicate the values of the interquartile range (IQR) between Q1 (the 25th) and Q3 (the 75th) percentiles. Vertical black lines indicate the ranges between Q3 + 1.5 IQR and Q1 − 1.5 IQR. Black diamonds are outliers. At enrollment, patients assigned to saline versus lidocaine did not differ significantly from each other ($P = .61$). During the blinded weeks, the two groups differed significantly ($P = .01$), and later during the open-label weeks, the two groups again did not differ ($P = .41$). During the open-label lidocaine period, each group had a median score that was significantly lower than baseline ($P < .001$).

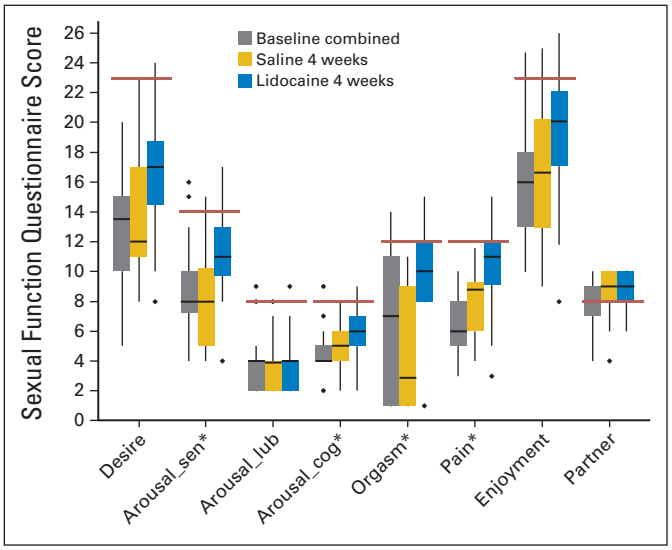

Fig 3. Sexual Function Questionnaire domain scores after 4 weeks of blinded interventions. Black horizontal lines indicate medians; colored boxes indicate the values of the interquartile range (IQR) between Q1 (the 25th) and Q3 (the 75th) percentiles. Vertical black lines indicate the ranges between Q3 + 1.5 IQR and Q1 − 1.5 IQR. Black diamonds are outliers. Red lines represent the minimum scores considered to represent normal function. All patients were instructed to use lubricant, so the "Arousal_lub" domain score does not accurately reflect spontaneous arousal. Asterisks show domains in which the scores for placebo and lidocaine were significantly different. cog, cognitive; lub, lubrication; sen, sensation.

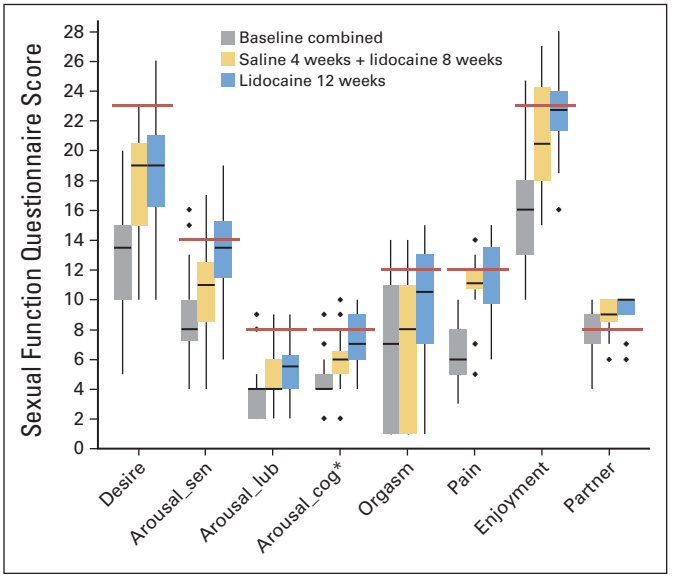

Fig 4. Sexual Function Questionnaire scores after 12 weeks. Black horizontal lines indicate medians; colored boxes indicate the values of the interquartile range (IQR) between Q1 (the 25th) and Q3 (the 75th) percentiles. Vertical black lines indicate the ranges between Q3 + 1.5 IQR and Q1 − 1.5 IQR. Black diamonds are outliers. Red lines represent the minimum scores considered to represent normal function. After completion of blinded and then open-label interventions, scores were not significantly different for any domain except Arousal-cognitive (Arousal_cog), indicated by an asterisk (P = .049), which measured two questions: how much and how often the patient felt "excited, 'turned on,' and wanting sexual activity to continue." Improvement was statistically significant by 12 weeks compared with baseline in all domains except Orgasm. All patients were instructed to use lubricant, so the "Arousal_lub" domain score does not accurately reflect spontaneous arousal. cog, cognitive; lub, lubrication; sen, sensation.

husbands only after testing their liquids using tampons 17 times, beginning in the randomized weeks and extending into the open-label weeks (one had saline/lidocaine, and one had lidocaine/lidocaine).

After 2 months of open-label lidocaine use, 37 (90%) of 41 patients reported comfortable penile penetration. On use of lidocaine, 73% of users achieved low pain scores by their third intercourse event. Of 20 abstainers who completed the study, 17 (85%) had resumed comfortable penetrative intimacy. Dyspareunia did not resolve in two patients who were found to have concurrent muscle pain that was not evident on the initial screening examination. Each could identify an entry pain that resolved with lidocaine use, but their coital pain scores were still high and prohibited intercourse. The third patient declined to resume intimacy with her husband, although she did not experience tenderness in her trials with tampons.

At baseline, the majority of patients had abnormal scores in all domains of sexual function except Partner, a category that summarizes worry about their partner's satisfaction and fidelity. At 4 weeks, placebo and lidocaine users were significantly different in three domains in addition to the Pain domain (Fig 3). With lidocaine use, all domains improved significantly by 12 weeks except for Orgasm, a domain already normal in 19% (Fig 4). The percentage of patients scoring in the normal range of each domain after 12 weeks is provided in Table 2.

Sexual Function Questionnaire scores at baseline and after the interventions were not different for women using aromatase inhibitors or selective estrogen receptor modulators compared with nonusers. In addition, women with more than 5 years of dyspareunia improved their sexual function to the same degree as patients with a shorter duration of dyspareunia.

At baseline, sexual distress scores were abnormally high (median, 30.5; interquartile range, 23 to 37). Distress scores diminished significantly for both interventions after 4 weeks and again significantly after 12 study weeks (Fig 5).

At the 6-month phone interview, all patients reported that they still had introital tenderness with penetration if they did not use lidocaine. None were using the silicone lubricant alone for intercourse, although all patients except one preferred it to water-based lubricants. Ninety-five percent of patients were using lidocaine as

Table 2. No. and % of Patients Whose Scores Per Domain Suggest Normal Function

Domain	Visit 1 (n = 46) No. (%)	Visit 2		Visit 3 (n = 41) No. (%)
		Saline (n = 21) No. (%)	4% Lidocaine (n = 22) No. (%)	
Desire	0	1 (4.76)	1 (4.55)	5 (12.20)
Arousal_sen	3 (6.52)	1 (4.76)	5 (22.73)	14 (34.15)
Arousal_lub	2 (4.35)	1 (4.76)	1 (4.55)	5 (12.20)
Arousal_cog	1 (2.17)	1 (4.76)	5 (22.73)	12 (29.27)
Orgasm	9 (19.57)	0	10 (45.45)	12 (29.27)
Pain	0	0	7 (31.82)	21 (51.22)
Enjoyment	1 (2.17)	2 (9.52)	5 (22.73)	18 (43.90)
Partner*	30 (65.22)	18 (85.71)	17 (77.27)	35 (85.37)

NOTE. All patients were instructed to use lubricant, so the domain Arousal_lub does not accurately reflect spontaneous arousal.
*Partner summarizes two questions about worries regarding partners' fidelity and possible negative feelings like anger or rejection.

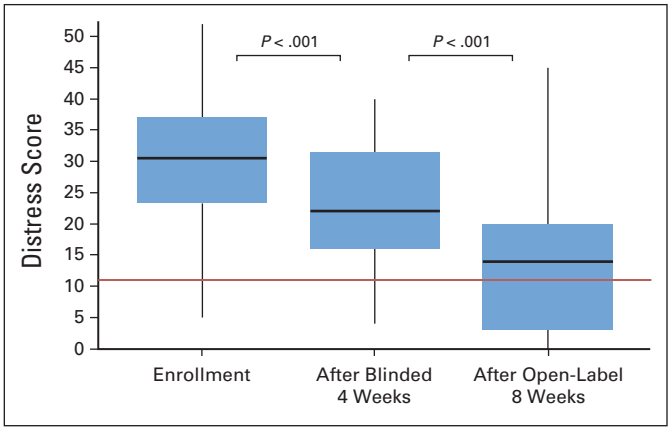

Fig 5. Female Sexual Distress Score values. Scores at each interval combined randomization groups because there was not a significant difference between them at any time interval. Scores of more than 11 are considered abnormal (indicated by the red line). Black horizontal lines indicate medians; colored boxes indicate the values of the interquartile range (IQR) between Q1 (the 25th) and Q3 (the 75th) percentiles. Vertical black lines indicate the ranges between Q3 + 1.5 IQR and Q1 − 1.5 IQR.

often as they wished with no pain or negligible pain during and after intercourse. Eighty-three percent reported having more sexual enjoyment; 49% said the quality of orgasms had improved, and 51% reported improved libido.

Visual gynecologic examinations after 1 and 3 months showed no change in the extreme introital and vaginal atrophy. Median vaginal pH values remained ≥ 5. The vaginal maturation indices showed no mature cells in any microscopic fields in 98% of patients at visit 2 and in 92% at visit 3.

A mild rash associated with silicone lubricant caused one patient to substitute a water-based lubricant. One patient receiving oral steroids for arthritis and chemotherapy for metastatic disease experienced a 1-cm mucosal tear in the introitus in month 3. It healed, but she had recurrences over time. No male partners reported phallic numbness. No couples reported lack of genital capacity.

DISCUSSION

This proof-of-concept study suggests that dyspareunia associated with a low-estrogen postmenopause state is caused by a pain condition in the vulvar vestibule rather than the vagina. Timely applications of self-applied aqueous lidocaine compresses to the mucosa of the vulvar vestibule followed by silicone lubricant allowed 95% of breast cancer survivors with distressing dyspareunia to prevent penetrative pain. When only the tender vestibule zone was treated, there was no intercourse pain except in the few patients who had tender pelvic floor muscles as a cofactor in their dyspareunia. Vaginal pH, vaginal cell maturation indices, and visual parameters of atrophy did not change with the study interventions of lidocaine for the vulvar vestibule, silicone lubricant, and frequent intercourse.

Our success when focusing on pain rather than on atrophy raises questions about current assumptions regarding postmenopausal dyspareunia. Postmenopausal intercourse pain has been attributed to lack of moisture, thinning of vaginal tissues, and diminished vascular supply that accompanies atrophy.[15] The US Food and Drug Administration has stipulated that any new product for treatment of vulvovaginal atrophy must demonstrate efficacy in changing vaginal pH and vaginal epithelial cell maturation in addition to addressing "the most bothersome symptom."[16] Our study results suggest that this policy is misguided. Our study focused only on the most bothersome symptom and achieved relief without modifying severe atrophy.

In the field of vulvar pain, it is recognized that a relatively common cause of severe dyspareunia is vestibulodynia (painful vulvar vestibule),[17,18] associated with proliferation of mucosal pain nerves in the introitus.[5,19] It has been more thoroughly studied in premenopausal women, but our group has demonstrated neural hyperplasia in the vestibule tissues of postmenopausal patients with acquired dyspareunia.[8] To explain the findings in this study, two separate but coincident conditions may coexist. Lack of estrogen causes vulvovaginal atrophy but is also associated with localized neural proliferation in menopause. The vulvar vestibule is embryologically derived from endoderm whereas the vagina is mesodermal in origin.[20] In this trial, pain was prevented by pretreatment of the tender vulvar vestibule rather than the atrophic vagina. Although in our patients each derivative zone developed significant atrophy from lack of estrogen, the vestibule was the location of exquisite postmenopausal tenderness that caused dyspareunia.

A link between genital nerve hyperplasia and estrogen levels has been noted in both humans and animals. In our previous study of postmenopausal vestibular neural hypertrophy,[8] 70% of patients had noted the onset of dyspareunia with lowering of estrogen levels either with menopause or some years before when they were postpartum. There is evidence that a low estrogen state can provide a stimulatory effect on peripheral genital pain nerves in rat and mouse models, and there is a plasticity of nerve growth and retreat depending on lower or higher estrogen levels.[21,22]

The development of a painful, chronic introital condition as a result of declining estrogen levels would seem to confer no benefit for postmenopausal women, and in fact it reduces quality of life.[2] However, intermittent neural hyperplasia in the vulvar vestibule may have provided an evolutionary species benefit by occurring in the breastfeeding phases of reproductive life. There are limited data on this phenomenon,[23] but if verified with larger studies, it could be considered to be contraception by means of pain. This would promote longer interpregnancy intervals with a resultant positive effect on survival of the offspring.[24] The menopausal transition with falling estrogen levels repeats this hormonal signal and may similarly provoke introital dyspareunia. However, in postmenopause, it will be chronic if not treated with estrogen and can progressively worsen, sometimes to a state of unprovoked burning pain.[15,25] The success of an anesthetic that prevented dyspareunia in this survivor group will hopefully encourage research about the vestibule with clarification of pain physiology in postmenopausal dyspareunia.

Validated study tools for sexual dysfunction divide healthy function into several domains, of which the presence of pain is only one. At baseline, our group of estrogen-deficient women had abnormal scores in most domains, leaving unanswered the question of how much dysfunction was due to severe pain and how much might be due to lack of estrogen or another cause. Successful targeting of pain alone allowed improvement in other aspects of sexual function in these patients without estrogen. Having more intercourse when it continued to provoke pain was not beneficial for those using placebo. This contradicts the common advice that having more intercourse will improve vaginal health and reduce atrophy and pain.[26] "Use it or lose

it" is an aphorism that is not supported by our data. Those who had been abstaining succeeded as well as those who had not, and women with many years of dyspareunia and presumably a longer duration of sexual dysfunction, achieved the same degree of normalization as women affected for a shorter time.

Patients in this study had significant levels of sexual distress. The distress scale measures qualities such as worry, sexual inadequacy, and frustration. Sexual Distress Scores improved significantly, even in the group that was randomly assigned to placebo/lubricant. We hypothesize that patients felt hopeful about the prospect of improving their sexual relationships, and scores represented their optimism as a participation effect of being studied.[27]

Pain scores with intercourse diminished significantly for the saline/lubricant users, but the median value was 5 of 10, a level still representing significant pain. Effective lubricant is helpful, but no patients found use of the lubricant alone to be sufficient for comfortable sex. All stated that without the lidocaine they would have pain.

Use of vaginal moisturizers has been widely encouraged,[4] although clinical studies are few and have been small. In two randomized controlled trials in breast cancer survivors, long-term success was not measured, and 16% and 39% reported annoying effects from a moisturizer or pH balancer.[28,29] A 2013 survey of 3,000 postmenopausal women reported that in 176 users of moisturizers, 42% felt they got inadequate or no relief.[30] Lubricants and moisturizers alone do not seem to sufficiently correct moderate to severe dyspareunia.

Use of tampons as surrogates for penetration benefited patients, considering that the dread of intercourse pain had led 50% to give up penetrative intimacy. Tampons were familiar objects[31] that allowed patients to practice and gain some accuracy in lidocaine application before trying more emotionally laden intercourse.

The results of this study answered several potential questions about use of lidocaine, because application of a numbing agent to facilitate a pleasurable activity strikes some as counterintuitive and others as risky. The numbing effect is localized to the mucosa of the introitus and does not numb subsurface proprioceptive or pain nerves. In addition, it is not applied to the clitoris. Patients could feel touch but not insertional pain. In the setting of severe atrophy, the resumption of intercourse for those who have been abstaining can be associated with minor tissue injury as shown by one patient. Her tissue integrity was likely especially compromised because of systemic steroids. In such patients, assessment with serial dilators might be a helpful initial measure to ensure the capacity of atrophic tissues to stretch adequately with intercourse. This 44-year-old patient was very determined to continue penetrative intimacy because she so valued this in her marriage in the face of shortened life expectancy.

Despite the success in reducing coital pain and sexual distress, this study had limitations. It was small. In addition, it is difficult when studying pain to choose a placebo that blinds all participants throughout the trial. Enrollment of primarily white and well-educated women may reduce generalizability. Success in clinical settings may depend on the quality of instructions given to patients. Simple provision of a prescription without a demonstration using a mirror likely will not be sufficient. Confirmatory studies will be important to show that our success can be reproduced.

In conclusion, this proof-of-concept study gives credence to the concept that postmenopausal dyspareunia is a pain condition located in the vulvar vestibule in addition to being a condition of dryness from atrophy. In our cohort, 95% of postmenopausal breast cancer survivors with disturbing dyspareunia mastered the application of prepenetration liquid lidocaine to the vulvar vestibule and thus prevented dyspareunia. Their success was associated with a reduction in sexual distress and improvement in all aspects of their sexual function and therefore quality of life. These findings have ramifications for public health, cancer survivorship, and research regarding postmenopausal dyspareunia.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Martha F. Goetsch, Aaron B. Caughey
Collection and assembly of data: Martha F. Goetsch
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

A Practical Solution for Dyspareunia in Breast Cancer Survivors: A Randomized Controlled Trial

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Appendix

Methods

Design overview. A randomized, double blind, placebo-controlled study targeted dyspareunia in survivors of breast cancer. Eligible women had undergone a screening gynecologic examination (part 1, reported separately[9]) to specially assess locations of genital pain. Part 2 compared patient-reported outcomes during home use of a study drug or placebo. Part 3 assessed patient-reported outcomes during open-label use of active study drug. The institutional review boards of the Knight Cancer Institute and Oregon Health & Science University (OHSU) approved the study protocol and materials.

Setting and participants. Our study took place at the Women's Health Research Unit of the Department of Obstetrics and Gynecology in Portland, Oregon, at OHSU. Candidate women were in postmenopause with a history of 1 year or more of invasive breast cancer and a complaint of moderate or severe dyspareunia for at least 6 months. They were recruited for enrollment by means of fliers in community and academic cancer centers in our metropolitan area. Inclusion criteria included being in a long-term stable heterosexual relationship for at least 5 years, not using estrogen products for at least 4 months, speaking English, and being age 18 to 70 years. Patients were excluded if their dyspareunia was due to pelvic pain, pelvic floor myalgia, or vulvar dermatoses. Genital tenderness had to be localized in the vulvar vestibule and had to be extinguishable by application of topical 4% lidocaine solution (part 1).[9] Use of medication for erectile dysfunction by partners was permissible. Dyspareunia was defined as penetrative pain severe enough with every act of intercourse to result in reduced frequency of intercourse or abstinence. Postmenopausal status was defined as more than 1 year without menses with accompanying climacteric symptoms, prior bilateral oophorectomy, or use of a gonadotropin-releasing hormone agonist to suppress ovaries to allow use of anti-estrogen medications.

Randomization and interventions. Patients were randomly assigned 1:1 without restriction to 1 month of at-home use of either 4% aqueous lidocaine or placebo applied as a compress to the vulvar vestibule just before vaginal penetration with either their partner or a tampon (Original Regular Tampax Tampons, Procter & Gamble, Cincinnati, OH). They agreed to attempt penetration twice per week and record pain scores in a study diary. Both the placebo (physiologic saline) and aqueous 4% lidocaine (Roxane; National Drug Code 00054-3505-47) are clear odorless liquids. The OHSU Research Pharmacy randomly assigned patients by using randomization software (www.randomization.com) and dispensed their study liquid, thus concealing allocation from the research team until all patients had completed the study. All patients were given a 100-gm dispenser of silicone lubricant (Pjur; Pjur Group, Wasserbillig, Luxembourg). After 1 month, patients returned for a second full gynecologic examination, administration of questionnaires, and discussion of any application difficulties. Patients then entered part 3 of the study and received open-label aqueous 4% lidocaine; for 2 months, they tried penetration twice per week and documented pain scores in diaries. Part 3 concluded with a final gynecologic examination, administration of questionnaires, and discussion of practical issues. Final study contact was at 6 months at which time the research nurse administered a telephone questionnaire.

Outcomes and follow-up. Our primary patient-related outcome was pain with intercourse, scored by using the Numeric Rating Scale (NRS) with values between zero (no pain) and 10 ("the worst pain you have ever experienced").[10] Secondary outcomes were resumption of intercourse and quality of sexual life as measured by two validated instruments. The Sexual Function Questionnaire (SFQ; Pfizer, Sandwich, United Kingdom) tabulates scores in six domains of sexual function.[11] The Female Sexual Distress Score-Revised (American Foundation for Urological Disease, 2000)[12] tabulates emotional distress regarding sex.

Patient instructions. The principal investigator used a mirror to show patients the vulvar vestibule and to point out where the patients were to apply the study liquid. They were instructed to use cotton balls or large cotton swabs fully saturated with study liquid held against the vestibule mucosa for a duration of 3 minutes; they were then to immediately apply silicone lubricant liberally before attempting vaginal penetration twice per week. The study nurse who obtained patients' consent also administered the questionnaires and gave each patient a supply of cotton balls, large swabs, regular tampons, silicone lubricant, and 30-day diary forms.

Statistical analysis. Referencing a previously reported vestibule mean pain score of 8.0 ± 1.4,[13] we estimated by using a two-sample t test that a sample size of 44 would achieve 94% power to detect at least 1.5 points mean difference in pain scores between treatment and placebo. We made adjustments on the basis of the asymptotic relative efficiency (ARE) of the Mann-Whitney U test relative to the t test, assuming a nonnormal underlying distribution, and confirmed that the given sample size of 44 still achieved more than 90% power. Allowing for a dropout rate of 5%, 46 participants were needed for randomization.

Characteristics of randomized groups were analyzed by using a t test or Mann-Whitney U test, depending on the distribution for continuous variables. Categorical variables were analyzed by χ^2 or Fisher's exact test. Comparisons of reported numeric rating scale or Female Sexual Distress Scale values used the two-tailed Mann-Whitney U test, and patients' changes in those scales were tested by using two-tailed Wilcoxon signed rank test, each with significance set at $P < .05$. Missing data were handled per the validated tool scoring instructions. Study data were managed by using REDCap electronic data capture tools hosted at OHSU.[14] Statistical analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC) and R version 2.14.1.