

## Sexual Problems During the First 2 Years of Adjuvant Treatment with Aromatase Inhibitors

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### ABSTRACT

**Introduction.** Sexual dysfunction has only recently been recognized as a highly prevalent side effect of adjuvant aromatase inhibitor (AI) therapy for breast cancer.

**Aims.** A cross-sectional survey using standardized measures of female sexual function was designed to provide a detailed view of sexual problems during the first 2 years of adjuvant AI therapy and secondarily to examine whether sexual dysfunction leads to nonadherence to this therapy.

**Methods.** Questionnaires were mailed to all 296 women in a breast oncology registry who had been prescribed a first-time AI for localized breast cancer 18–24 months previously.

**Main Outcome Measures.** Items assessed medication adherence, demographic, and medical information. Scales included the Female Sexual Function Index, the Menopausal Sexual Interest Questionnaire, the Female Sexual Distress Scale-Revised, the Breast Cancer Prevention Trial Eight Symptom Scale to assess menopausal symptoms, and the Merck Adherence Estimator<sup>®</sup>.

**Results.** Questionnaires were returned by 129 of 296 eligible women (43.6%). Respondents were 81% non-Hispanic white with a mean age of 63 and 48% had at least a college degree. Only 15.5% were nonadherent. Ninety-three percent of women scored as dysfunctional on the Female Sexual Function Index, and 75% of dysfunctional women were distressed about sexual problems. Although only 52% of women were sexually active when starting their AI, 79% of this group developed a new sexual problem. Fifty-two percent took action to resolve it, including 24% who stopped partner sex, 13% who changed hormone therapies, and 6% who began a vaginal estrogen. Scores on the Adherence Estimator (beliefs about efficacy, value, and cost of medication) were significantly associated with adherence ( $P = 0.0301$ ) but sexual function was not.

**Conclusions.** The great majority of women taking AIs have sexual dysfunction that is distressing and difficult to resolve. Most continue their AI therapy, but a large minority cease sexual activity. **Schover LR, Baum GP, Fuson LA, Brewster A, and Melhem-Bertrandt A. Sexual problems during the first 2 years of adjuvant treatment with aromatase inhibitors. J Sex Med 2014;11:3102–3111.**

**Key Words.** Breast Cancer; Aromatase Inhibitor; Sexual Dysfunction; Medication Adherence

### Introduction

Aromatase inhibitors (AIs) have become the adjuvant endocrine treatment of choice to prevent recurrence and second primary tumors in postmenopausal women with localized, hormone

receptor positive breast cancer [1]. Starting endocrine therapy with an AI, or switching to an AI after initial treatment with tamoxifen, has a significant benefit over tamoxifen alone in preventing recurrence of breast cancer. However, the superiority of AIs in increasing overall survival compared

with endocrine therapy with tamoxifen remains in question [1]. Tamoxifen increases the risk of endometrial cancer or thromboembolic events. AIs, on the other hand, may promote adverse cardiovascular events and definitely lead to osteoporosis [1]. Nevertheless, the American Society of Clinical Oncology's 2014 updated clinical practice guideline on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer suggests that postmenopausal women be offered 5 years of an AI as first-line endocrine therapy, or if they already had been given tamoxifen for 5 years, that they be switched to an AI for an additional 5-year period [1]. Two recent randomized trials have also demonstrated AIs' effectiveness for primary prevention in postmenopausal women at high risk for breast cancer [2,3]. AIs thus are increasingly prescribed rather than tamoxifen in the postmenopausal group.

Women taking tamoxifen or AIs score similarly on quality of life, menopause symptom scales, and self-reported hot flashes and fatigue [4–8]. However, AIs are far more likely than tamoxifen to cause vaginal dryness and dyspareunia [8–11], as well as troublesome arthralgias [12]. Tamoxifen acts like a weak estrogen in the vagina [7], whereas AIs exacerbate vulvovaginal atrophy by preventing estrogen production in peripheral tissues [5,9,13]. The three commonly used third-generation AIs (exemestane, letrozole, and anastrozole) appear to have equivalent sexual side effects [13,14].

Early clinical trials of AIs failed to assess sexual dysfunction, or only surveyed a subset of participants [15,16]. Table 1 summarizes the prevalence and types of sexual problems in women on AIs in publications since 2004. A third to a half of women in most cohorts reported loss of desire, vaginal dryness, and painful sex. However, methodological flaws make it difficult to interpret these data. It is rarely clear whether sexually inactive women were

excluded, yet about half of women over age 50 report a lack of sexual activity with a partner, particularly those who are unmarried or more elderly [20,21]. Women's distress about having a sexual problem decreases sharply with age and lack of a partner [22,23]. Sexually inactive women may not even be aware of a change in sexual function with AI use. Instead of using standardized questionnaires measuring female sexual function, researchers created questions or depended on three items from the Functional Assessment of Cancer Treatment-Endocrine Symptoms (FACT-ES) [24]. The FACT response format is a five-point Likert scale from "not at all" to "very much." Surveys by Cella et al. [6,7] only counted responses in the two most severe categories, reporting lower rates of sexual dysfunction than studies that included reports of mild problems [5,9].

After the first few weeks of AI treatment, sexual problems remain fairly stable across time [7,10]. One recent study reported the "encouraging" finding that sexual function did not decline during the first 6 months of adjuvant endocrine therapy and that only 30% of women with a sexual problem were distressed about it [8]. However, 85% of the women already had sexual problems at baseline and 85% were dysfunctional at follow-up. Furthermore, 62% were taking tamoxifen rather than an AI. Seventy percent had prior chemotherapy, probably accounting for the ubiquity of initial sexual dysfunction [25]. The outcome measure included only 10 of 19 items of the Female Sexual Function Index (FSFI), scored in a nonstandard fashion.

Unfortunately, rates of nonadherence to AIs remain disturbingly high, including failure to fill an initial prescription, discontinuation of medication, and also having a Medication Possession Ratio (MPR) of less than 80% [26,27]. Nonadherence is seen in 12–28% of women in the first year

**Table 1** Sexual function in women on aromatase inhibitors (AIs)

Publication	N	Months on AIs	Assessment questionnaire	Low sexual desire %	Vaginal dryness %	Dyspareunia %
Morales et al. [10]	37	3	Item written for study	68	50	62
Cella et al. [6]	335	60	FACT-ES	34	18	17
Jones et al. [17]	808	12	Item written for study	58	50	—
Antoine et al. [18]	14	Unknown	Women's Health Questionnaire	84	88	—
Oberguggenberger et al. [9]	233	Unknown	FACT-ES	51	32	16
Baumgart et al. [5]	35	Unknown	FACT-ES	—	42	62
Kyvernitakis et al. [4]	181	24	Item written for study	43*	57	—
Aiello Bowles et al. [19]	314	Unknown	Item written for study	36	36	—
Fallowfield et al. [7]	83	24	FACT-ES	32	17	13

\*Item was reported as "sexual problems" so it may reflect more than low desire.

FACT-ES = Functional Assessment of Cancer Treatment-Endocrine Symptoms (FACT-ES) questionnaire

[13–15,27–30] and increases slowly thereafter. At the end of the recommended 5 years of adjuvant endocrine therapy, a third to a half of women discontinue AIs or have a long period of suboptimal MPR [13,15,27–30]. Nonadherent women suffer increased breast cancer mortality by 10 years post diagnosis [15]. Early discontinuation of endocrine therapy reduces survival from an estimated 80.7% to 73.6% ( $P < 0.001$ ). Continuing endocrine therapy for the full 5 years but at suboptimal dosages reduces 10-year survival from 81.7% to 77.8% ( $P < 0.001$ ).

Adherence to endocrine therapy is somewhat higher in women on AIs than in women taking tamoxifen [15,19,30]. Age may be a factor, as adherence is lower in younger women, the group most likely to be prescribed tamoxifen [13,15,26,28]. The risk of nonadherence to adjuvant endocrine therapy is highest in women younger than 50 or older than 65, women who have more health comorbidities, and who pay higher out of pocket costs for the prescriptions [13,15,19,27–30]. Socioeconomic factors such as ethnicity, income, education, and marital status have not been strong or consistent predictors [31].

Patient-reported side effects of hormone therapy have consistently been associated with nonadherence [4,27]. Muscle and joint pain are almost twice as common for women on AIs as in matched postmenopausal controls, worsening over the first year of treatment for up to 60% [12,32]. The prevalence of arthralgia, hot flashes, and sexual dysfunction are correlated across the first year of hormone therapy [33]. This co-occurrence of unpleasant side effects complicates attempts to understand how individual symptoms influence women's adherence to AIs. Reports of moderate to severe symptoms on the FACT-ES questionnaire, particularly joint pain, but also hot flashes and decreased libido, were associated with early discontinuation of adjuvant endocrine therapy in women in the National Cancer Institute of Canada Clinical Trials Group MA-27 trial [14]. In a randomized trial to promote adherence to AIs, sexual symptoms were more severe in women who discontinued AI therapy [4]. However, in multivariate analyses, sexual dysfunction has not been a significant predictor of nonadherence [4,19].

### Aims

The current cross-sectional survey was designed to provide a more detailed picture of sexual problems during the first 2 years on AI therapy to provide a

benchmark for a prospective, intervention trial. Our hypothesis was that sexual problems would be associated with nonadherence in sexually active women.

### Methods

This protocol was approved by the University of Texas MD Anderson Cancer Center's Internal Review Board.

### Subjects

Eligible participants ( $N = 302$ ) were identified from the Breast Cancer Management System, a registry in our Breast Medical Oncology department. The following inclusion criteria were used: female; diagnosed with stage I to IIA, node-negative breast cancer; age over 18 years; and received a prescription for an AI as first-line, adjuvant endocrine therapy 18–24 months prior to the mailing, in October 2012. Respondents were excluded if they had developed metastatic disease or could not read English.

### Survey Methodology

We sent a survey by mail, including a cover letter explaining elements of informed consent, the questionnaire, and a postage-paid return envelope. A reminder postcard was sent 3 weeks later. The questionnaire was anonymous in order to maximize return rates for this sensitive topic. A stamped postcard was included so that independently of returning the survey, women could request a handout presenting detailed information about coping with side effects of AIs.

### Main Outcome Measures

The questionnaire assessed demographic and medical information as shown in Table 2. The FSFI measured sexual function and satisfaction [34]. It is a 19-item multiple-choice questionnaire, with a Cronbach's alpha of 0.93–0.97 for the total score. Subscale scores, calculated using a weighted algorithm, measure desire, arousal, orgasm, pain, and satisfaction. Because sexual dysfunction after breast cancer usually involves multiple phases of the sexual response cycle [11,25,35], the total FSFI score is an appropriate outcome measure. A value of  $\leq 26.55$  indicates sexual dysfunction [34]. The FSFI has been validated for women with cancer [35], but scores are negatively biased for women who are not sexually active. Therefore we also included the 10-item Menopausal Sexual Interest

**Table 2** Medical and demographic factors in adherent (N = 109) and nonadherent women (N = 20)

Factor	Adherent women		Nonadherent women		P value
Age (mean $\pm$ SD)	63.3 $\pm$ 8.7		64.5 $\pm$ 8.9		0.5751
Marital status (N, %)					0.4121
Married	70	67.3	13	65.0	
Separated/divorced	17	16.4	6	30.0	
Widowed	10	9.6	1	5.0	
Never married	7	6.7	0	0.0	
Unknown	0	0.0	0	0.0	
Unmarried but in committed relationship (N, %)	8	23.5	3	42.9	0.3608
Race/ethnicity (N, %)					0.3298
White, not Hispanic	82	80.4	17	85.0	
Hispanic	8	7.8	2	10.0	
African-American	10	9.8	0	0.0	
Asian/Pacific Islander	2	2.0	1	5.0	
Unknown	0	0.0	0	0.0	
Highest level of education (N, %)					0.3034
High school degree or less	14	13.5	3	15.0	
Some college	42	40.4	5	25.0	
4-year college	33	31.7	6	30.0	
Postgraduate degree	15	14.4	6	30.0	
Unknown	0	0.0	0	0.0	
Household income (N, %)					0.6908
<\$25,000	8	8.9	4	21.1	
\$26,000–50,000	18	20.0	3	15.8	
\$51,000–75,000	17	18.9	3	15.8	
\$76,000–100,000	20	22.2	4	21.1	
>\$100,000	27	30.0	5	26.3	
Months since cancer diagnosis (mean $\pm$ SD)	26.8	$\pm$ 5.7	26.2	$\pm$ 3.5	0.5051
Type of breast surgery (N, %)					0.1794
Partial mastectomy	40	42.1	7	38.9	
Mastectomy without reconstruction	17	17.9	8	44.4	
Mastectomy with reconstruction	18	18.9	2	11.18	
Bilateral mastectomy with reconstruction	13	13.7	1	5.6	
Bilateral mastectomy, no reconstruction	7	7.4	0	0	
Chemotherapy (%)	49	47.6	10	50.0	0.8424
Current hormone use (%)					0.8179
Testosterone	1	1.0	0	0.0	
Vaginal estrogen cream, tablet, or ring	3	2.9	0	0.0	
Other	2	1.9	0	0.0	
Drug for mood, anxiety, pain, hot flashes (%)	40	38.5	8	40.0	0.8971
Health comorbidities (%)					0.4680
None	37	34.9	6	33.3	
One	42	41.5	12	55.6	
Two	20	18.9	2	11.1	
More than two	5	4.7	0	0	

Questionnaire (MSIQ) [36], which is less affected by inactivity. Subscales measure desire, responsiveness (orgasm and pleasure), and satisfaction, and a total score is calculated [36]. We also asked if a woman noticed a new sexual problem after starting the AI, if she took action to solve a sexual problem, and if so, what options she tried.

As many women are unconcerned about sexual problems, distress is now included as a diagnostic criterion for a dysfunction. The 13-item Female Sexual Distress Scale-Revised (FSD-R) has excellent discriminant validity between normal and sexually dysfunctional women, a Cronbach's alpha of 0.86, and a 4-week test-retest reliability of 0.93 [37].

To measure menopausal symptoms we included the Breast Cancer Prevention Trial Eight Symptom Scale (BESS) [38]. Its 21 items group into subscales: cognitive symptoms, musculoskeletal pain, vasomotor symptoms, gastrointestinal symptoms, dyspareunia, bladder control, weight concerns, and gynecologic symptoms. The response format ranges from 0 = not at all; 1 = slightly; 2 = moderately; 3 = quite a bit; 4 = extremely.

We also used a three-item Adherence Estimator<sup>®</sup> developed by Merck (Merck, Sharpe, & Dohme, Inc., Whitehouse Station, NJ, USA) [39,40], which classifies women as at low, medium, or high risk for nonadherence to a particular medication. It asks about the importance of the medication, worries

that it will do more harm than good, and the burden of out-of-pocket expenses. These beliefs predicted adherence in previous studies. Adherence was measured by items asking if a woman had (i) ever filled her prescription, or (ii) discontinued taking her prescribed AI. We also asked how many days she took her AI during the previous 2 weeks.

## Results

### Statistical Analyses

All statistical analyses were carried out using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). Demographic and clinical characteristics were summarized with means, standard deviations, ranges, and frequencies, and compared between intervention groups by Fisher's test, *t*-test, or a Wilcoxon test depending on the data distribution. Questionnaires were not scored if more than an allowed number of items were missing. Univariate analyses comparing adherent and nonadherent women were performed with *t*-tests for continuous variables and  $\chi^2$  tests or Fisher's tests for categorical variables.

### Return Rate

Out of 302 patients identified from the registry, six were excluded because they had metastatic disease and two were excluded because they were male. Six patients were deceased or had an invalid address, yielding 296 eligible women invited to participate. Questionnaires were returned by 129 of these women (43.6%). In our original sample from the registry, 73.9% of women were non-Hispanic white, 10.3% were Hispanic surnamed, 9.7% were African American, 5.5% were Asian/Pacific Islanders, and 0.6% were of other ethnicities. Our respondents were 81.1% non-Hispanic white (see Table 2). Although differences between responders and nonresponders were not significant, minorities were slightly less likely to complete the survey, as is common in psychosocial research (Fisher's test,  $P = 0.1081$ ) [41], and the mean age of women in the original sample was  $60.9 \pm 14.6$  years, compared with  $63.4 \pm 8.7$  among respondents (*t*-test,  $P = 0.0711$ ).

### Nonadherence

Eighteen women reported that they were not taking their AI. Three women never filled their initial prescription. Fifteen women discontinued the AI. Four women had been switched to tamoxifen, and 14 women were not on any adjuvant endocrine therapy. Two additional women took

their AI for 7 days or less in the past 2 weeks. Although we do not have information on whether these women had a prolonged period of <80% MPR, we included them in the nonadherent group. Self-reports of inadequate medication dosage appear to be underestimates in other surveys [26,27], and their inclusion did not change the significance of between-group comparisons. Thus, 20 women were classified as nonadherent (15.5%). All others had taken the AI  $\geq 12$  out of 14 days.

Table 2 presents clinical and demographic factors characterizing the adherent vs. nonadherent women. No between-group differences reached significance in univariate analyses. As both younger and older age have been associated with nonadherence, we divided our sample into quartiles by age (no significant relationship; Fisher's test,  $P = 0.4701$ ). Being an ethnic minority (82.8% adherent) vs. non-Hispanic white (87.0% adherent) was not significantly related to adherence (Fisher's test,  $P = 0.7629$ ). Being married or in a committed relationship ( $N = 94$ ) vs. not in a relationship ( $N = 30$ ) also was not associated with adherence (13.3% of single women nonadherent vs. 17.0% of women in a relationship; Fisher's test,  $P = 0.7796$ ).

Table 3 compares scores on self-report questionnaires for adherent vs. nonadherent women. The Adherence Estimator [39,40] correlated with self-reports of adherence ( $P = 0.0301$ ). Mean Adherence Estimator scores for the nonadherent group (mean = 11.6) indicated a high risk for being nonadherent ( $>8$ ), and the mean scores for the adherent group (4.8) suggested low risk for nonadherence. Contrary to our hypothesis, nonadherence was similar among sexually active women (12.5% of 80 women) vs. women who were not engaging in sexual activity with a partner (18.2% of 33 women;  $\chi^2$ ,  $P = 0.4308$ ).

As we assessed sexual dysfunction *after* the nonadherent women had discontinued their AI, it is not surprising that nonadherent women reported less vaginal dryness/pain on the BESS dyspareunia subscale than women taking AIs ( $P = 0.0544$ ). No significant differences were found between adherent and nonadherent women on FSFI or MSIQ subscales or total scores, however (Table 3).

### Sexual Function

As Table 3 illustrates, 93% of women taking AIs scored in the dysfunctional range on the FSFI, as well as 75% of women completing the MSIQ (total score <2 standard deviations [SDs] below the normative mean) [36]. Of 75 women with abnormal

**Table 3** Questionnaire results of women continuing AIs (N = 109) and nonadherent women (N = 20)

Factor	Adherent women Mean $\pm$ SD	Nonadherent women Mean $\pm$ SD	P value
Female Sexual Function Index (FSFI)			
Desire	1.9 $\pm$ 0.9	1.7 $\pm$ 0.9	0.4458
Arousal	1.6 $\pm$ 1.6	1.4 $\pm$ 1.3	0.5706
Lubrication	1.3 $\pm$ 1.7	1.4 $\pm$ 1.9	0.8687
Orgasm	1.7 $\pm$ 2.0	1.3 $\pm$ 1.5	0.2247
Satisfaction	2.7 $\pm$ 1.5	2.5 $\pm$ 1.7	0.7146
Pain	2.2 $\pm$ 1.7	2.2 $\pm$ 1.8	0.9533
Total score	12.7 $\pm$ 8.0	11.4 $\pm$ 8.6	0.6115
FSFI Total score $\leq$ 26.55	92.7%	91.7%	0.4163
Menopausal Sexual Interest Questionnaire (MSIQ)			
Desire	9.4 $\pm$ 5.0	8.3 $\pm$ 4.0	0.4068
Responsiveness	10.0 $\pm$ 5.1	8.3 $\pm$ 5.2	0.2630
Satisfaction	5.8 $\pm$ 3.7	5.3 $\pm$ 4.4	0.6247
Total	22.6 $\pm$ 11.6	23.3 $\pm$ 11.4	0.8418
Female Sexual Distress Scale-Revised (FSDS-R)			
BESS Plus Menopause Symptom Scale	18.8 $\pm$ 16.3	19.4 $\pm$ 17.5	0.8969
Cognitive symptoms			
Musculoskeletal pain	3.7 $\pm$ 3.1	4.0 $\pm$ 3.3	0.7293
Vasomotor symptoms	6.5 $\pm$ 3.2	6.8 $\pm$ 3.7	0.6744
Gastrointestinal symptoms	3.2 $\pm$ 2.9	3.4 $\pm$ 3.3	0.7469
Dyspareunia	0.7 $\pm$ 1.6	1.0 $\pm$ 2.1	0.3998
Weight concerns	3.7 $\pm$ 3.0	2.3 $\pm$ 2.6	0.0544
Gynecologic symptoms	3.3 $\pm$ 2.5	3.4 $\pm$ 2.8	0.9208
Bladder control	0.9 $\pm$ 1.3	1.3 $\pm$ 2.4	0.5443
Merck Adherence Estimator score	1.9 $\pm$ 2.0	2.1 $\pm$ 2.6	0.6882
	4.8 $\pm$ 6.5	11.6 $\pm$ 11.1	0.0301

FSFI total scores, 75% met the criterion of distress about their dysfunction on the FSD-R by scoring 11 or higher [37]. FSD-R scores indicated more distress in women who were married or in a committed relationship (mean  $\pm$  SD: 21.14  $\pm$  16.57) than in women who were single (mean  $\pm$  SD: 6.29  $\pm$  8.07;  $P < 0.001$ ). Similarly, women who met criteria on the FSFI [35] for being sexually active had significantly more distress about sexual dysfunction (20.48  $\pm$  15.64) than women who were not active (13.00  $\pm$  17.36;  $P = 0.034$ ).

Table 4 presents detailed information about sexual problems after beginning an AI. Only 67 women (52% of respondents) were sexually active when prescribed an AI, but 79% of these women developed a new sexual problem. Seventy-one women reported a preexisting or new sexual problem during AI therapy, and 52% took action to try to solve it. The most common strategy was trying a vaginal lubricant. Seventeen (24%) discontinued having sex. Only one woman stopped her AI because of a sexual problem, but four tried a different AI and four switched to tamoxifen, so that 13% made a change in their adjuvant endocrine therapy. Four women (6%) added vaginal estrogen.

## Conclusions

In this sample of women surveyed at 18–24 months after starting on an AI for localized, hormone

receptor-positive breast cancer, sexual dysfunction was very severe. Ninety-three percent had sexual dysfunction, and 75% were distressed about the problem, especially partnered women trying to maintain an active sex life. Although only about half of women were sexually active, almost 80% of that subgroup experienced new sexual problems after starting on an AI. Half of women with sexual problems took some kind of action to try to resolve them, including 24% who stopped having sexual activity with their partner. The fact that 39% of sexually active women with a new problem

**Table 4** Prevalence of sexual problems and options to cope with them

Item	N	%
Noticed new sexual problem after started AI (out of N = 67 sexually active women who began an AI):	53	79
Took action to solve a sexual problem (out of N = 71 women who had a previous or new sexual problem on AI; some checked multiple actions):	37	52
Tried vaginal moisturizer	23	32
Tried vaginal lubricant	40	56
Stopped having sex with partner	17	24
Asked doctor's advice on vaginal dryness	28	39
Asked doctor's advice on loss of desire	13	18
Tried vaginal estrogen	4	6
Switched to different AI	4	6
Switched to tamoxifen	4	6
Stopped taking the AI because of sexual side effects	1	1

AI = aromatase inhibitor

consulted a physician about vaginal dryness, and 18% sought help for low desire also may be indicative of the severity of these problems, as in a previous survey of women with breast or gynecologic cancer, only 7% had recently had professional help for a sexual problem [42].

Thirteen percent of women with sexual problems changed their type of adjuvant endocrine therapy, and 6% added vaginal estrogen despite the potential risk of compromising AI therapy. Although low-dose vaginal estrogen decreases vulvovaginal atrophy, fewer than 10% of menopausal women in the United States use it [43]. Oncologists worry that vaginal estrogen therapy could elevate serum estradiol levels enough to interfere with the benefits of AIs [44]. AI therapy requires very low estradiol levels to be effective and may not be the treatment of choice for newly menopausal women or for women whose ovarian function has been suppressed by recent chemotherapy [45]. Unfortunately, it has been difficult to gather adequate data on absorption of vaginal estrogen in women on AI therapy because many patients will not participate in clinical trials due to anxiety about the risk of promoting cancer recurrence by using an estrogen product. The total and subscale scores on the FSFI were extremely low, even compared with other cohorts of women treated for gynecologic malignancies or posthematopoietic transplantation [35]. On the MSIQ, which is less biased by sexual inactivity, total and subscale scores were similar to those in healthy women complaining of low desire for sex after menopause [36]. Scores on both questionnaires resembled baseline values in our recent trial of an intervention for survivors of breast or gynecologic cancer with sexual dysfunction [46]. Sexual problems affected all aspects of the sexual response, not just vaginal dryness and pain.

The 43.6% return rate, although it is typical for long surveys of oncology patients that focus on sexual function, may limit generalizability of results [47,48]. However, women who participated were not significantly different from the original cohort in age or ethnicity. If sexually inactive women were less interested in participating, our data may actually underestimate the prevalence of sexual dysfunction. Women who had stopped taking their AIs may also have decided not to complete the survey, perhaps accounting for the slightly lower than anticipated rate of nonadherence. We also relied on women's self-reports of adherence, which may underestimate actual rates [15,27]. The cross-sectional design also limits our

ability to ascertain whether treatment with AIs causes sexual dysfunction.

Would better management of sexual problems improve adherence to AIs? The moderate return rate, high rate of sexual inactivity, and low rate of nonadherence limited our power to detect significant associations, but even in this small sample, 7% of women coped with a sexual problem by switching to tamoxifen or stopping their AI completely. Six percent switched to a different AI, and another 6% took the risk of adding a vaginal estrogen. Sexually active women may have characteristics, such as being younger or healthier, that would achieve significance in a larger sample as mediators of an association between sexual activity and adherence. For example, nonadherent women were much more likely to have had mastectomy without breast reconstruction (44% vs. 18% in adherent women), perhaps suggesting a lack of concern about appearance.

Despite the limitations of sample size and return rate, we did identify a significant factor associated with nonadherence: the three-item Adherence Estimator, which asked about belief in the efficacy and importance of taking an AI and concern about medication costs [39,40]. Although it is normally administered when a patient is first prescribed a new medication, we presented it retrospectively, using the past tense and asking about initial perceptions of the AI. Recall could be biased by a subsequent choice to discontinue the endocrine therapy. However, if our data are confirmed in a prospective study, this brief questionnaire could identify women at high risk for nonadherence who may benefit from counseling about their concerns.

We are conducting a randomized, prospective trial in women with localized breast cancer starting on an AI for the first time, intervening early with combined behavioral sex therapy and use of non-hormonal vaginal moisturizers and lubricants [49–52].

Another option would be endocrine therapy for breast cancer prevention using new selective estrogen receptor modulators (SERMs) such as ospemifene or lasofoxifene. These drugs, unlike tamoxifen, can reduce vulvovaginal atrophy and increase bone density, with far less risk of endometrial carcinoma and severe hot flashes [53]. A recent meta-analysis of clinical trials suggests that lasofoxifene is also very promising as an endocrine therapy to prevent breast cancer and should be a high priority target for more research [54]. Ospemifene was recently approved as a treatment

for vulvovaginal atrophy in the United States [55]. Preliminary animal trials and safety studies in humans suggest at worst a neutral effect in the breast and a potential ability to prevent breast cancer [55], although it is not currently recommended for use in women with a history of breast cancer. Even if third-generation SERMs, like second-generation tamoxifen, prove slightly less effective than an AI in preventing breast cancer, positive effects on sexual function and bone health and the absence of arthralgias may increase long-term adherence enough for a favorable net result in terms of mortality over AIs when used as preventive or adjuvant endocrine therapy.

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*Conflict of Interest:* This study has not been presented at a national meeting. All authors declare that they have no conflict of interest.

### Statement of Authorship

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#### Category 2

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#### Category 3

##### (a) Final Approval of the Completed Article

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