HHS Public Access

Author manuscript

J Sex Med. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

J Sex Med. 2014 December ; 11(12): 3102–3111. doi:10.1111/jsm.12684.

Sexual problems during the first two years of adjuvant treatment with aromatase inhibitors

Leslie R. Schover, PHD[1], **George P. Baum, MS**[1], **Lisa A. Fuson, APN**[1], **Abenaa Brewster, MD**[1], and **Amal Melhem-Bertrandt, MD**[2]

[1]University of Texas MD Anderson Cancer Center, US

[2]Astellas Pharma, US

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 two 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 aromatase inhibitor for localized breast cancer 18 to 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®.

Results—Questionnaires were returned by 129 of 296 eligible women (43.6%). Respondents were 81% non-Hispanic Caucasian 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.

Corresponding author: Leslie R. Schover, PhD, UT MD Anderson Cancer Center, Department of Behavioral Science, Unit 1330, P. O. Box 301439, Houston, TX 772301439; lschover@mdanderson.org; Phone: 713-745-2681; Fax: 713-745-4286.

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

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.

Keywords

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 to 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 five years of an AI as first-line endocrine therapy, or if they already had been given tamoxifen for five years, that they be switched to an AI for an additional five-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]. Aromatase inhibitors 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 FACT-ES [24]. The FACT response

format is a 5-point Likert scale from “not at all” to “very much.” Surveys by Cella and colleagues [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, scored in a nonstandard fashion.

Unfortunately, rates of nonadherence to aromatase inhibitors 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% to 28% of women in the first year [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 five 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, since 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 Functional Assessment of Cancer Treatment-Endocrine Symptoms (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 two 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 to 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 three 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 aromatase inhibitors.

Main Outcome Measures

The questionnaire assessed demographic and medical information as shown in Table 2. The Female Sexual Function Index (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. Since 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 ≤ 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 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.

Since 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 (FSDS-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 3-item Adherence Estimator® developed by Merck [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 1) ever filled her prescription or 2) discontinued taking her prescribed AI. We also asked how many days she took her AI during the previous two weeks.

Results

Statistical Analyses

All statistical analyses were carried out using SAS version 9.3. 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-square tests or Fisher's tests for categorical variables.

Return Rate

Out of 302 patients identified from the registry, 6 were excluded because they had metastatic disease and 2 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 ± 14.6 years, compared to 63.4 ± 8.7 among respondents (T-test, P = 0.0711).

Nonadherence

Eighteen women reported that they were not taking their AI. Three never filled their initial prescription. Fifteen discontinued the AI. Four had been switched to tamoxifen and 14 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 ≥ 12 out of 14 days.

Table 2 presents clinical and demographic factors characterizing the adherent versus nonadherent women. No between-group differences reached significance in univariate analyses. Since 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) versus white non-Hispanic (87.0% adherent) was not significantly related to adherence (Fisher's test, P = 0.7629). Being married or in a committed relationship (N = 94) versus not in a relationship (N = 30) also was not associated with adherence (13.3% of single women nonadherent versus 17.0% of women in a relationship, Fisher's test, P = 0.7796).

Table 3 compares scores on self-report questionnaires for adherent versus 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) versus women who were not engaging in sexual activity with a partner (18.2% of 33 women), Chi Square, P = 0.4308.

Since 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 SDs below the normative mean) [36]. Of 75 women with abnormal 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 ± SD: 21.14 ± 16.57), than in women who were single (mean ± SD: 6.29 ± 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 ± 15.64) than women who were not active (13.00 ± 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 pre-existing 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 4 tried a different AI and 4 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 to 24 months after starting on an aromatase inhibitor 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 consulted a physician about vaginal dryness, and 18% sought help for low desire also may be indicative of the severity of these problems, since 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 to other cohorts of women treated for gynecologic malignancies or post-hematopoietic 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% versus 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 3-item Adherence Estimator,® that 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 nonhormonal 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.

Acknowledgements

This work was supported by a grant from The University of Texas MD Anderson Cancer Center Duncan Family Institute for Cancer Prevention and Risk Assessment. Support was provided by the Patient-Reported Outcomes, Survey, and Population Research (PROSPR) Shared Resource, NCI funded #CA 16672. The Adherence Estimator® is subject to copyrights, trademarks and pending patent applications by Merck Sharp & Dohme Corp. and was used with their permission. The authors thank Tamara Machado and Evan Odensky, MPH for assistance in collecting and entering data.

REFERENCES

1. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Towden D, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. American Society of Clinical Oncology Clinical Practice Guideline focused update. J Clin Oncol. 2014; 32 [May 27, 2014, Epublication ahead of print].
2. Goss PE, Ingle JN, Alés-Martínez JE, Chlebowski RT, Wactawski-Wende J, McTiernan A, Robbins J, Johnson KC, Martin LW, Winquist E, Sarto GE, Garber JE, Fabian CJ, Pujol P, Maunsell E, Farmer P, Gelmon KA, Tu D, Richardson H, NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011; 64:2381–2391. [PubMed: 21639806]
3. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, Saunders C, Roche N, Mansel RE, von Minckwitz G, Bonanni B, Palva T, Howell A, the IBIS-II investigators. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014; 383:1041–1048. [PubMed: 24333009]
4. Kyvernitakis I, Ziller V, Hars O, Bauer M, Kalder M, Hadji P. Prevalence of menopausal symptoms and their influence on adherence in women with breast cancer. Climacteric. 2014; 17:252–259. [PubMed: 23805799]
5. Baumgart J, Nilsson K, Evers AS, Kallak TK, Poromaa IS. Sexual dysfunction in women on adjuvant endocrine therapy after breast cancer. Menopause. 2013; 20:162–168. [PubMed: 22990756]
6. Cella D, Fallowfield L, Barker P, Cuzick J, Locker G, Howell A, ATAC Trialists Group. Quality of postmenopausal women in the ATAC (“Arimidex”, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for early breast cancer. Breast Cancer Res Treat. 2006; 100:273–284. [PubMed: 16944295]
7. Fallowfield LJ, Kilburn LS, Langridge C, Snowdon CF, Bliss JM, Coombes RC. Long-term assessment of quality of life in the Intergroup Exemestane Study: 5 years post-randomisation. Br J Cancer. 2012; 106:1062–1067. [PubMed: 22353807]
8. Frechette D, Paquet L, Verma S, Clemons M, Wheatley-Price P, Gertler SZ, Song X, Graham N, Dent S. The impact of endocrine therapy on sexual dysfunction in postmenopausal women with early stage breast cancer: Encouraging results from a prospective study. Breast Cancer Res Treat. 2013; 141:111–117. [PubMed: 23942873]
9. Oberguggenberger A, Hubalek M, Sztankay M, Meraner V, Beer B, Oberacher H, Giesinger J, Kemmler G, Egle D, Gamper EM, Sperner-Unterweger B, Holzner B. Is the toxicity of adjuvant aromatase inhibitor therapy underestimated? Complementary information from patient-reported outcomes (PROs). Breast Cancer Res Treat. 2011; 128:553–561. [PubMed: 21311968]
10. Morales L, Neven P, Timmerman D, Christiaens MR, Vergote I, Van Limbergen E, Carbonez A, Van Huffel S, Ameye L, Paridaens R. Acute effects of tamoxifen and third-generation aromatase inhibitors on menopausal symptoms of breast cancer patients. Anticancer Drugs. 2014; 15:753–760. [PubMed: 15494636]
11. Panjari M, Bell RJ, Davis SR. Sexual function after breast cancer. J Sex Med. 2011; 8:294–302. [PubMed: 21199377]
12. Castel LD, Hartmann KE, Mayer IA, Saville BR, Alvarez J, Boomershine CS, Abramson VG, Chakravarthy AB, Friedman DL, Cella DF. Time course of arthralgia among women initiating

aromatase inhibitor therapy and a postmenopausal comparison group in a prospective cohort. Cancer. 2013; 119:2375–2382. [PubMed: 23575918]

13. Hadji P, Ziller V, Kyvernitakis J, Bauer M, Haas G, Schmidt N, Kostev K. Persistence in patients with breast cancer treated with tamoxifen or aromatase inhibitors: a retrospective database analysis. Breast Cancer Res Treat. 2013; 138:185–191. [PubMed: 23334803]
14. Wagner LI, Zhao F, Chapman J-AW, Cella D, Shepherd LE, Sledge GW, Goss PE. S6-2: Patient-reported predictors of early treatment discontinuation: NCIC JMA.27/E1Z03 Quality of life study of postmenopausal women with primary breast cancer randomized to exemestane or anastrozole. Cancer Res. 2011; 71(24 Supplement):S6–2.
15. Shao T, Buono D, Kershenbaum A, Tsai W, Fehrenbacher L, Gomez SL, Miles S, Neugut AI. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol. 2010; 28:4120–4128. [PubMed: 20585090]
16. Coates AS, Keshaviah A, Thürlimann B, Mouridsen H, Mauriac L, Forbes JF, Paridaens R, Castiglione-Gertsch M, Gelber RD, Colleoni M, Láng I, Del Mastro L, Smith I, Chirgwin J, Nogaret JM, Pienkowski T, Wardley A, Jakobsen EH, Price KN, Goldhirsch A. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol. 2007; 25:486–492. [PubMed: 17200148]
17. Jones SE, Cantrell J, Vukelja S, Pippen J, O'Shaughnessy J, Blum JL, Brooks R, Hartung NL, Negron AG, Richards DA, Rivera R, Holmes FA, Chittoor S, Whittaker TL, Bordelon JH, Ketchel SJ, Davis JC, Ilegbodu D, Kochis J, Asmar L. Comparison of menopausal symptoms during the first year of adjuvant therapy with either exemestane or tamoxifen in early breast cancer: report of a Tamoxifen Exemestane Adjuvant Multicenter trial substudy. J Clin Oncol. 2007; 25:4765–4771. [PubMed: 17947724]
18. Antoine C, Vandromme J, Fastrez M, Carly B, Liebens F, Rozenberg S. A survey among breast cancer survivors: treatment of the climacteric after breast cancer. Climacteric. 2008; 11:322–328. [PubMed: 18645698]
19. Aiello Bowles EJ, Boudreau DM, Chubak J, Yu O, Fujii M, Chestnut J, Buist DS. Patient-reported discontinuation of endocrine therapy and related adverse effects among women with early-stage breast cancer. J Oncol Pract. 2012; 8:e149–157. [PubMed: 23598850]
20. Lutfey KE, Link CL, Rosen RC, Wiegel M, McKinlay JB. Prevalence and correlates of sexual activity and function in women: Results from the Boston Area Community health (BACH) survey. Arch Sex Beh. 2009; 38:514–527.
21. Huang AJ, Subak LL, Thom DH, Van Den Eeden SK, Ragins AI, Kuppermann M, Shen H, Brown JS. Sexual function and aging in racially and ethnically diverse women. J Am Geriatr Soc. 2009; 57:1362–1368. [PubMed: 19558473]
22. Howard JR, O'Neill S, Travers C. Factors affecting sexuality in older Australian women: sexual interest, sexual arousal, relationships and sexual distress in older Australian women. Climacteric. 2006; 9:355–367. [PubMed: 17000584]
23. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: Prevalence and correlates. Obstet Gynecol. 2008; 112:970–978. [PubMed: 18978095]
24. Fallowfield LJ, Leaity SK, Howell A, Benson S, Cella D. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. Breast Cancer Res Treat. 1999; 55:189–199. [PubMed: 10481946]
25. Rosenberg SM, Partridge AH. Premature menopause in young breast cancer: effects on quality of life and treatment interventions. J Thorac Dis. 2013; 5(Suppl 1):S55–S61. [PubMed: 23819028]
26. Ruddy KJ, Mayer E, Partridge AH. Patient adherence and persistence with oral anticancer treatment. CA Cancer J Clin. 2009; 59:56–66. [PubMed: 19147869]
27. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: A systematic review. Breast Cancer Res Treat. 2012; 134:459–478. [PubMed: 22689091]

28. Sedjo RL, Devine S. Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. Breast Cancer Res Treat. 2011; 125:191–200. [PubMed: 20495864]
29. Wigertz A, Ahlgren J, Holmqvist M, Fornander T, Adolfsson J, Lindman H, Bergkvist L, Lambe M. Adherence and discontinuation of adjuvant hormonal therapy in breast cancer patients: a population-based study. Breast Cancer Res Treat. 2012; 133:367–373. [PubMed: 22286315]
30. Nekhlyudov L, Li L, Ross-Degnan D, Wagner AK. Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence among insured women with early-stage breast cancer. Breast Cancer Res Treat. 2012; 130:681–689. [PubMed: 21842245]
31. Livaudais JC, Hershman DL, Habel L, Kushi L, Gomez SL, Li CI, Neugut AI, Fehrenbacher L, Thompson B, Coronado GD. Racial/ethnic differences in initiation of adjuvant hormonal therapy among women with hormone receptor-positive breast cancer. Breast Cancer Res Treat. 2012; 131:607–617. [PubMed: 21922245]
32. Dent SF, Gaspo R, Kissner M, Pritchard KI. Aromatase inhibitor therapy: toxicities and management strategies in the treatment of postmenopausal women with hormone-sensitive early breast cancer. Breast Cancer Res Treat. 2011; 126:295–310. [PubMed: 21249443]
33. Shi Q, Giordano SH, Lu H, Saleeba AK, Malveaux D, Cleeland CS. Anastrozole-associated joint pain and other symptoms in patients with breast cancer. J Pain. 2013; 14:290–296. [PubMed: 23452648]
34. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): Cross-validation and development of clinical cutoff scores. J Sex Marital Ther. 2005; 31:1–20. [PubMed: 15841702]
35. Baser RE, Li Y, Carter J. Psychometric validation of the Female Sexual Function Index (FSFI) in cancer survivors. Cancer. 2012; 118:4606–4618. [PubMed: 22359250]
36. Rosen RC, Lobo RA, Block BA, Yang HM, Zipfel LM. Menopausal Sexual Interest Questionnaire (MSIQ): a unidimensional scale for the assessment of sexual interest in postmenopausal women. J Sex Marital Ther. 2004; 30:235–250. [PubMed: 15205062]
37. Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the Female Sexual Distress Scale-Revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med. 2007; 5:357–364. [PubMed: 18042215]
38. Cella D, Land SR, Chang C-H, Day R, Costantino JP, Wolmark N, Ganz PA. Symptom measurement in the Breast Cancer Prevention Trial (BCPT) (P-1): psychometric properties of a new measure of symptoms for midlife women. Breast Cancer Res Treat. 2008; 109:515–526. [PubMed: 17851765]
39. McHorney CA. The Adherence Estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. Curr Med Res Opin. 2009; 25:215–238. [PubMed: 19210154]
40. McHorney CA, Spain CV, Alexander CM, Simmons J. Validity of the Adherence Estimator in the prediction of 9-month persistence with medications prescribed for chronic diseases: A prospective analysis of data from pharmacy claims. Clin Ther. 2009; 31:2584–2607. [PubMed: 20110004]
41. Schneider KL, Clark MA, Rakowski W, Lapane KL. Evaluating the impact of non-response bias in the Behavioral Risk Factor Surveillance System (BRFSS). J Epidemiol Community Health. 2009; 66:290–295. [PubMed: 20961872]
42. Hill EK, Sandbo S, Abramsohn E, Makelarski J, Wroblewski K, Wenrich ER, McCoy S, Temkin SM, Yamada SD, Lindau ST. Assessing gynecologic and breast cancer survivors' sexual health care needs. Cancer. 2011; 117:2643–2651. [PubMed: 21656742]
43. Nappi RE, Kingsberg S, Maamari R, Simon J. The CLOSER (CLarifying Vaginal Atrophy's Impact On SEx and Relationships) survey: implications of vaginal discomfort in postmenopausal women and in male partners. J Sex Med. 2013; 10:2232–2241. [PubMed: 23809691]
44. Wills S, Ravipati A, Venuturumilli P, Kresge C, Folkerd E, Dowsett M, Hayes DF, Decker DA. Effects of vaginal estrogens on serum estradiol levels in postmenopausal breast cancer survivors and women at risk of breast cancer taking an aromatase inhibitor or a selective estrogen receptor modulator. J Oncol Pract. 2012; 8:144–148. [PubMed: 22942807]

45. Pan K, Chlebowski RT. Adjuvant endocrine therapy of perimenopausal and recently postmenopausal women with hormone receptor-positive breast cancer. Clin Breast Cancer. 2014; 14:147–153. [PubMed: 24503025]

46. Schover LR, Yuan Y, Fellman BM, Odensky E, Lewis PE, Martinetti P. Efficacy trial of an internet-based intervention for cancer-related female sexual dysfunction. J Natl Compr Canc Netw. 2013; 11:1389–1397. [PubMed: 24225972]

47. Carter J, Huang H, Chase DM, Walker JL, Cella D, Wenzel L. Sexual function of patients with endometrial cancer enrolled in the Gynecologic Oncology Group LAP2 Study. Int J Gynecol Cancer. 2012; 22:1624–1633. [PubMed: 23095778]

48. Rowland JH, Desmond KA, Meyerowitz BE, Belin TR, Wyatt GE, Ganz PA. Role of breast reconstructive surgery in physical and emotional outcomes among breast cancer survivors. J Natl Cancer Inst. 2000; 92:1422–1429. [PubMed: 10974078]

49. Carter J, Goldfrank D, Schover LR. Simple strategies for vaginal health promotion in cancer survivors. J Sex Med. 2011; 8:549–559. [PubMed: 20722792]

50. Linhares IM, Summers PR, Larsen B, Giraldo PC, Witkin SS. Contemporary perspectives on vaginal pH and lactobacilli. Amer J Obstet Gynecol. 2011; 204:e1–e5. [PubMed: 20832044]

51. Ekin M, Yasar L, Savan K, Uhri M, Genser I, Kevanç E. The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. Arch Gynecol Obstet. 2011; 283:539–543. [PubMed: 20135132]

52. Markowska J, Madry R, Markowska A. The effect of hyaluronic acid (Cicatridine) on healing and regeneration of the uterine cervix and vagina and vulvar dystrophy therapy. Eur J Gynaecol Oncol. 2011; 32:65–68. [PubMed: 21446328]

53. Soe LH, Wurz GT, Kao C-J, DeGregorio MW. Ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy: potential benefits in bone and breast. Int J Women's Health. 2013; 5:605–611. [PubMed: 24109197]

54. Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, Dowsett M, Forbes JF, Ford L, LaCroix AZ, Mershon J, Mitlak BH, Powles T, Veronesi U, Vogel V, Wickerham DL, the SERM Chemoprevention of Breast Cancer Overview Group. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet. 2013; 381:1827–1834. [PubMed: 23639488]

55. Berga SL. Profile of ospemifene in the breast. Reprod Sciences. 2013; 20:1130–1136.

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., 2004 [10]	37	3	Item written for study	68%	50%	62%
Cella et al., 2006 [6]	335	60	FACT-ES	34%	18%	17%
Jones et al., 2007 [17]	808	12	Item written for study	58%	50%	--
Antoine et al., 2008 [13]	14	Unknown	Women's Health Questionnaire	84%	88%	--
Oberguggenberger et al., 2011 [9]	233	Unknown	FACT-ES	51%	32%	16%
Baumgart et al., 2011 [17]	35	Unknown	FACT-ES	--	42%	62%
Kyvernitakis et al., 2013 [4]	181	24	Item written for study	43%*	57%	--
Aiello Bowles et al., 2012 [19]	314	Unknown	Item written for study	36%	36%	--
Fallowfield et al., 2012 [7]	83	24	FACT-ES	32%	17%	13%

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

* Item was reported as “sexual problems” so it may reflect more than low desire

Table 2

Medical and demographic factors in adherent (n = 109) and nonadherent women (N = 20)

Factor	Adherent Women		Nonadherent Women		P-Value
Age (mean ± SD)	63.3 ± 8.7		64.5 ± 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%	
Post-graduate 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 ± SD)	26.8 ± 5.7		26.2 ± 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

Factor	Adherent Women		Nonadherent Women		P-Value
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%	

Table 3

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

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

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