ORIGINAL RESEARCH—ENDOCRINOLOGY

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®.

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