Original Contribution

Patient-Reported Discontinuation of Endocrine Therapy and Related Adverse Effects Among Women With Early-Stage Breast Cancer

By Erin J. Aiello Bowles, MPH, Denise M. Boudreau, PhD, Jessica Chubak, PhD, Onchee Yu, MS, Monica Fujii, MPH, Janet Chestnut, MD, and Diana S.M. Buist, PhD

Group Health Research Institute; and Group Health Physicians, Seattle, WA

Abstract

Background: Approximately 20% to 50% of women diagnosed with hormone receptor–positive breast cancer discontinue endocrine therapy early; most reports come from automated pharmacy data or small self-report evaluations. We conducted a larger self-report evaluation of endocrine therapy discontinuation associated with patient characteristics and therapy-related adverse effects.

Methods: We surveyed 538 women from a single health plan who were diagnosed with early-stage breast cancer from 2002 to 2008 and received endocrine therapy. Women reported adverse effects and reasons for discontinuation via mailed survey; tumor characteristics were obtained via registry linkage. We classified women as discontinuers if they self-reported stopping therapy and their self-reported duration of tamoxifen plus aromatase inhibitor (AI) use was < 5 years, and nondiscontinuers if they self-reported ≥ 5 years use or current use. We estimated odds ratios (ORs) with 95% CIs for discontinuation versus continuation by using logistic regression adjusted for age and year of diagnosis.

Results: Among 538 women, 98 (18.2%) discontinued endocrine therapy early. Women with positive lymph nodes (*v* negative) were significantly less likely to discontinue therapy (odds ratio [OR] = 0.54; 95% CI, 0.31 to 0.93). Almost all women (94%) experienced adverse effects. Experiencing headaches was associated with discontinuation of AIs (OR = 4.16; 95% CI, 2.16 to 8.01) and tamoxifen (OR = 2.34; 95% CI, 1.24 to 4.41); few other individual adverse effects were related to discontinuation despite most discontinuers reporting they "did not like adverse effects" (AIs: 66.7%, tamoxifen: 59.1%).

Conclusion: Few individual adverse effects or patient characteristics were significantly associated with endocrine therapy discontinuation, yet adverse effects were prevalent and were the most common reason women reported for discontinuing therapy.

Introduction

Approximately 80% of women diagnosed with invasive breast cancer have hormone receptor–positive disease, making them potential candidates for adjuvant endocrine therapy.[1,2] Clinical trials have consistently demonstrated that endocrine therapy (ie, tamoxifen and aromatase inhibitor [AI] use) significantly improves disease-free survival and overall breast cancer mortality.[3,4] Despite these benefits, studies have shown 20% to 50% of women discontinue endocrine therapy before completing the recommended 5 years of treatment.[5-18] Discontinuation of endocrine therapy is concerning and has been linked to increased mortality rates.[12,18]

Most studies of endocrine therapy discontinuation have only evaluated tamoxifen discontinuation. Tamoxifen discontinuation is related to younger and older age,[5-9,11-14,16,17] earlier stage of disease,[12] additional prescription medication use,[9,15,16] and comorbidities.[5,6,8,10,12,16] Many prior discontinuation studies relied on automated pharmacy data; although pharmacy data are useful for studying discontinuation rates, they are of limited use in studying reasons for discontinuation, including adverse effects.[14,15,19-21] Some studies have used self-reported measures,[14,15] but most were limited by small sample sizes (n = 100-300 women).[19,20,22,23] We are aware of only one small study (n = 100) that examined AI discontinuation using self-reported data.[22] Because of these gaps in evidence, several researchers have called for additional work on predictors and reasons for endocrine therapy discontinuation.[17,23,24]

We used self-reported data to study endocrine therapy discontinuation (including associations with patient characteristics, adverse effects, and reasons for discontinuation) among 538 women with early stage breast cancer.

Methods

Study Setting and Population

All participants were part of the COMBO (Commonly Used Medications and Breast Cancer Outcomes) study. Briefly, COMBO is a retrospective cohort study of women 18 years or older who were diagnosed with early-stage invasive breast cancer (American Joint Committee on Cancer version 5 stages I, IIa, or IIb) from 1990 through 2008. Women in the COMBO study (n = 4,426) were enrolled continuously in Group Health for at least 12 months before their breast cancer diagnosis. We included women who received care within facilities owned and operated by Group Health and resided in areas covered by the western Washington Surveillance, Epidemiology, and End Results (SEER) registry. We identified breast cancer cases by linking Group Health enrollees with the SEER registry. We

obtained a waiver of consent to review electronic data and abstract medical records; all study procedures were approved by the Group Health Human Subjects Review Committee.

We conducted a survey from September to December 2010 to collect data on endocrine therapy use (including self-reported adverse effects, adherence, and reasons for discontinuation) that are not typically available from administrative data (Data Supplement, Appendix A). We mailed surveys to women in the COMBO study who were diagnosed with breast cancer between 2002 and 2008, received at least one prescription for tamoxifen or AIs within 12 months after diagnosis according to automated pharmacy data, and were postmenopausal (based on age 52 years or older) at the time of the first endocrine therapy dispensing (N = 693). Women were mailed a $2 preincentive followed by a reminder postcard within 5 days. Once the survey was returned, women received an additional $10. Nonresponders were sent another copy of the survey within 19 days, and then a phone call (to conduct the survey over the phone) 14 days later. A total of 591 women (85.3%) returned the survey (including 50 via phone), and 538 (77.6%) provided complete data on endocrine therapy discontinuation.

Discontinuation and Duration of Endocrine Therapy

We combined self-reported duration of AI and tamoxifen use because women were advised to complete 5 years of therapy whether they used one or both drugs. Women were considered discontinuers of endocrine therapy if they reported they were no longer using tamoxifen or AIs and their self-reported duration of use was < 5 years after breast cancer diagnosis. For example, a woman who reported only 3 years of tamoxifen use was classified as a discontinuer, as was a woman who reported 2.5 years of tamoxifen use followed by 1 year of AI use. Women who reported 5 or more years of tamoxifen and/or AI use (ie, completers), or who reported current tamoxifen or AI use (ie, continuers) at the time of the survey (even if they reported < 5 years of use) were classified as women who did not discontinue. We could not evaluate discontinuation of AIs and tamoxifen separately because some women switched treatments, and we did not ask women why they switched. For example, a woman with 2.5 years of tamoxifen use followed by AI use may have planned to switch after 2.5 years of tamoxifen (thus completing her tamoxifen treatment) or switched at 2.5 years because of intolerable adverse effects (thus discontinuing her tamoxifen treatment). Therefore we could not determine whether the individual treatments were discontinued. We used pharmacy data to validate our self-reported measures. Our validation results showed $> 80\%$ overall agreement (kappa = 0.59) for ≥ 5 versus < 5 years duration of endocrine therapy use, and $> 95\%$ overall agreement (kappa = 0.92) for current versus former endocrine therapy use.

Adverse Effects

We asked all women, regardless of whether they had discontinued therapy, about adverse effects they experienced at any point while taking each type of treatment (ie, tamoxifen and AIs). Adverse effects included shortness of breath; headaches; cataracts or changes in eyesight; dizziness; aches or pains in joints or muscles; osteoporosis or brittle bones; bone fracture; incontinence; water retention; depression or other changes in mood; insomnia or other sleep problems; feeling tired; loss of appetite, upset stomach, or vomiting; weight gain; breast sensitivity or tenderness; hot flashes; vaginal bleeding, spotting, or discharge; vaginal dryness; sexual symptoms or loss of sex drive; hair thinning or loss; blood clot or thrombosis; stroke; and endometrial, ovarian, or uterine cancer. We asked women whether they ever had each adverse effect, and if yes, whether they thought the adverse effect was related to tamoxifen or AIs. We evaluated all adverse effects individually and combinations of related adverse effects; these included bone-related adverse effects (osteoporosis or brittle bones, and fracture), sleep-related adverse effects (insomnia or other sleep problems, and feeling tired), and hormone- or menopause-related adverse effects (hot flashes; vaginal bleeding, spotting, or discharge; vaginal dryness; and sexual symptoms or loss of sex drive).

Reasons for Discontinuation

We asked women who reported they were no longer using tamoxifen or AIs why they stopped. Women could check multiple reasons for early discontinuation, including adverse effects, safety, cost, breast cancer recurrence or other cancer diagnosis, switching treatments, and decreased quality of life.

Patient and Tumor Characteristics

Demographic and tumor characteristics were collected from electronic administrative databases including enrollment files (age, comorbidities or Charlson score,[25]), Group Health's Breast Cancer Surveillance project data[26] (education and body mass index [BMI]), and SEER data (date of breast cancer diagnosis, race, ethnicity, stage at diagnosis, tumor size, lymph node status, hormone receptor status). Household income was collected from the mailed survey.

Statistical Analyses

We described the distribution of patient and tumor characteristics by discontinuation status. We used logistic regression to calculate the odds of discontinuation with 95% CIs by each patient and tumor characteristic, adjusted for age and year of diagnosis. We did not adjust for stage of disease because it was highly correlated with tumor size and number of positive lymph nodes and did not alter the estimates for the other characteristics. Women diagnosed more recently (from 2005 to 2008) had less of an opportunity to discontinue therapy because they did not have a full 5 years of follow-up after diagnosis (although they still could be considered discontinuers if they self-reported stopping therapy between their diagnosis date and the survey date). In addition, the type of endocrine therapy prescribed changed over time, and women were more likely to be prescribed tamoxifen through 2004.[27] However, a sensitivity analysis stratified by year of diagnosis (2002 to 2004 *v* 2005-2008)

did not change our results, and we present only the combined analysis.

We further described the distribution of self-reported adverse effects, and the proportion of women who believed their adverse effects were related to AI or tamoxifen use, by discontinuation status. Using logistic regression, we calculated the odds of discontinuation associated with each adverse effect, adjusting for age and year of diagnosis. These associations were modeled by type of endocrine therapy because women reported adverse effects separately for tamoxifen and AIs. Only women who used AIs were included in the AI models, and only women who used tamoxifen were included in the tamoxifen models. We also described the reasons women stopped endocrine therapy and how they stopped, among discontinuers only. All analyses were conducted in Stata 11. P values of $< .05$ were considered statistically significant, and all tests were two-sided.

Results

Among 538 postmenopausal women who used endocrine therapy, 98 (18.2%) discontinued use before completing 5 years of therapy; 25% of discontinuers reported $<$ 1 year duration. In addition, 5% of discontinuers reported from 1 to $<$ 2 years duration, 22% from 2 to $<$ 3 years, 12% from 3 to $<$ 4 years, and 35% from 4 to $<$ 5 years total duration of endocrine therapy. Among the 98 discontinuers, 55 women used AIs, and 76 women used tamoxifen (33 used both). When we limited the analysis to women diagnosed from 2002 to 2004, the discontinuation rate increased to 29.3%. Among women who did not discontinue (n = 440), 187 completed therapy (ie, reported $\geq$ 5 years duration), and 253 reported they were current users at the time of the survey.

Women who discontinued endocrine therapy were more likely to have used tamoxifen only (43.9%) and less likely to have used AIs only (22.4%) compared with women who did not discontinue (28.6% and 38.2%, respectively); approximately one third of discontinuers and nondiscontinuers switched between tamoxifen and AIs (Table 1). After adjustment for age and year of diagnosis, women who used AIs only had a significantly reduced odds of discontinuing compared with women who used tamoxifen only (odds ratio [OR] = 0.45; 95% CI, 0.25 to 0.83).

Discontinuers were slightly older than women who did not discontinue (8.2% *v* 4.5% $>$ 80 years), were diagnosed at earlier stages (63.3% *v* 55.0% stage I), and had earlier years of diagnosis (64.3% *v* 34.5% 2002-2004; Table 1). After adjustment for age and year of diagnosis, only positive lymph nodes were significantly associated with a lower odds of early endocrine therapy discontinuation (OR = 0.54; 95% CI, 0.31 to 0.93).

Women reported a high frequency of adverse effects (Table 2). Commonly reported adverse effects were hot flashes (57.2% of AI users and 55.5% of tamoxifen users), feeling tired (53.1% of AI users and 50.3% of tamoxifen users), and insomnia or other sleep problems (44.2% of AI users and 39.1% of tamoxifen users). Discontinuers were more likely to believe their adverse effects were related to tamoxifen or AI therapy compared with women who did not discontinue. When we calculated the odds of discontinuing endocrine therapy early according to the occurrence of each adverse effect (regardless of whether respondents believed the adverse effect was a result of endocrine therapy), headaches were associated with increased odds of early discontinuation of AIs (OR = 3.20; 95% CI, 1.59 to 6.45) and tamoxifen (OR = 2.58; 95% CI, 1.29 to 5.14). Loss of appetite, upset stomach, or vomiting was associated with an increased risk of discontinuing tamoxifen (OR = 2.45; 95% CI, 1.14 to 5.28). Among adverse effect combinations, hormone- or menopause-related adverse effects were associated with decreased odds of discontinuation (AIs: OR = 0.35; 95% CI, 0.18 to 0.70; tamoxifen: OR = 0.45, 95% CI, 0.24 to 0.83).

The most common self-reported reasons for discontinuing AIs or tamoxifen (Table 3) were adverse effects (66.7% of AI discontinuers and 59.1% of tamoxifen discontinuers) and decreased quality of life (43.8% of AI discontinuers and 33.8% of tamoxifen discontinuers). Most women reported that their decision to discontinue endocrine therapy was based on a collective decision with their health care provider. However, more than one fourth of AI and tamoxifen discontinuers (n = 35) reported stopping on their own. When we examined reasons for discontinuation among these 35 women, slightly higher proportions reported discontinuing because of adverse effects, decreased quality of life, or a belief that the therapy was not helping, compared with the overall study population (data not shown).

Discussion

Discontinuing recommended therapies—especially oral anticancer drugs—is not uncommon for oncology patients,[28,29] and there are many valid reasons for early discontinuation. For example, the adverse effects may be unbearable, life threatening, or decrease quality of life. Although discontinuation as a result of adverse effects is understandable, the benefits of therapy (longer disease-free survival) among early discontinuers may be diminished.[30] This analysis included 538 women, making it one of the largest studies of self-reported endocrine therapy use including AIs. Our results showed nearly 20% of women with early stage breast cancer discontinued endocrine therapy before completing the recommended 5 years of treatment, and more than one fourth of these women discontinued without first consulting their health care provider. Adverse effects were extremely prevalent among all women and were the most common reason for discontinuation of tamoxifen and AIs.

Our discontinuation rate of 18% is lower than that of most previous reports, which estimated discontinuation rates from 20% to 50%.[5-18] Only women with positive lymph nodes were significantly less likely to discontinue endocrine therapy. Our study population was from an integrated health care delivery system, where all women had access to prescription drugs and continuous medical care; these factors may help explain our low discontinuation rate. However, a study from Kaiser Permanente Northern California (KPNC), also an integrated delivery system, found a discontinuation rate of 32%.[8]

Table 1. Characteristics of Women With Early-Stage Breast Cancer Who Self-Reported Discontinuing Endocrine Therapy (stopping treatment before 5 years) Compared With Those Who Did Not

	Did Not Discontinue		Discontinued			
Characteristic	**No.**	**%**	**No.**	**%**	**OR***	**95% CI†**
No. of patients	440		98			
Endocrine therapy use						
Tamoxifen only	126	28.6	43	43.9	1	Reference
AIs only	168	38.2	22	22.4	0.45	0.25 to 0.83†
Both	146	33.2	33	33.7	0.63	0.36 to 1.10
Age at diagnosis, years						
Mean	64		65			
SD	8.4		9.7			
52-59	158	35.9	34	34.7	1	Reference
60-69	174	39.5	36	36.7	1.04	0.61 to 1.78
70-79	88	20.0	20	20.4	1.27	0.67 to 2.41
≥ 80	20	4.5	8	8.2	2.25	0.86 to 5.86
Race						
White	394	90.2	89	90.8	1	Reference
Other	43	9.8	9	9.2	1.14	0.52 to 2.52
Missing	3		0			
Education						
High school or less	73	19.2	13	14.9	1	Reference
Some college	143	37.5	33	37.9	1.49	0.71 to 3.14
College graduate	76	19.9	17	19.5	1.41	0.61 to 3.28
Post-college	89	23.4	24	27.6	1.72	0.78 to 3.79
Missing	59		11			
Household income, $						
≤ 25,000	53	14.4	14	16.5	1	Reference
25,001-50,000	135	36.8	36	42.4	1.37	0.64 to 2.94
50,001-100,000	129	35.1	26	30.6	0.99	0.43 to 2.23
> 100,000	50	13.6	9	10.6	1.02	0.35 to 2.92
Missing	73		13			
BMI, kg/m^2						
Mean	31		29			
SD	9.8		5.9			
< 25.0	92	29.4	19	26.8	1	Reference
25.0-29.9	102	32.6	27	38.0	1.23	0.61 to 2.49
≥ 30.0	119	38.0	25	35.2	1.29	0.63 to 2.62
Missing	127		27			
Stage at diagnosis						
I	242	55.0	62	63.3	1	Reference
IIA	139	31.6	25	25.5	0.67	0.39 to 1.14
IIB	59	13.4	11	11.2	0.63	0.30 to 1.18
Tumor size, mm						
< 10	72	16.4	20	20.4	1	Reference
10-19	240	54.5	49	50.0	0.59	0.32 to 1.10
≥ 20	128	29.1	29	29.6	0.6	0.30 to 1.18
Lymph node status						
Negative	296	67.3	77	78.6	1	Reference
Positive	144	32.7	21	21.4	0.54	0.31 to 0.93†

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Table 1. (Continued)

Characteristic	Did Not Discontinue		Discontinued		OR*	95% CI†
	No.	%	No.	%		
Charlson score						
0	344	78.2	83	84.7	1	Reference
1	63	14.3	11	11.2	0.73	0.35 to 1.49
≥ 2	33	7.5	4	4.1	0.58	0.19 to 1.80
Year of diagnosis						
2002-2004	152	34.5	63	64.3	1	Reference
2005-2008	288	65.5	35	35.7	0.29	0.18 to 0.45†

Abbreviations: BMI, body mass index; OR, odds ratio; SD, standard deviation.
* Adjusted for age and year of diagnosis.
† $P < .05$.

Several differences in study design may explain different discontinuation rates between studies. KPNC included earlier study years (1996-2007), in which tamoxifen was more likely to be prescribed; we showed that tamoxifen use was associated with an increased odds of discontinuation compared with aromatase inhibitors. KPNC had a longer follow-up period (4.5 years for most women); our discontinuation rate among women with at least 5 years of follow-up was 29.3%, closer to KPNC's estimate. Finally, our discontinuation definition was based on self-report of current endocrine therapy use and total duration of use. Self-report may be affected by recall bias and considered unreliable for assessing medication adherence, further contributing to our low discontinuation rate. Women diagnosed more recently may have recalled their duration of endocrine therapy use more accurately than women diagnosed earlier, which could have resulted in misclassification of discontinuers. In addition, our self-reported data did not include information on providers' recommendations for endocrine therapy duration, which could have further misclassified discontinuers. Other studies have defined discontinuation on the basis of women's self-report of stopping treatment (without duration of use) or, as in the KPNC study, pharmacy-based medication possession ratio (the percentage of time that a patient has access to medication).[31] However, we were able to validate our self-reported data, which suggests that our results are accurate for our study population.

Adverse effects were reported by all but 6% of women in our study. Although most previous studies have reported that AIs generally have better adverse effect profiles than tamoxifen,[32,33] the prevalence of each adverse effect was similar among AI and tamoxifen users in our study, with few exceptions. Despite the high prevalence of adverse effects in our study, few individual adverse effects were significantly associated with early discontinuation. In addition, hormone- or menopause-related adverse effects, including hot flashes, were associated with decreased odds of discontinuation. Knowledge of data suggesting that hot flashes and other vasomotor symptoms are associated with a greater response to endocrine therapy (ie, reduced recurrence) may help explain this finding.[34] However, other studies have shown that adverse effects, specifically hot flashes, are associated with increased odds of endocrine therapy discontinuation.[14,15,19-21]

Our adverse effect data are not immune to the limitations of self-report, particularly recall bias. Women who discontinued therapy may recall adverse effects differently than women who did not discontinue. This may have occurred differentially over time, as women diagnosed more recently had less of an opportunity to discontinue therapy than women diagnosed earlier. In addition, our study collected adverse effect information at one point in time; some women were still taking endocrine therapy, and others had quit several years earlier. Other studies collected adverse effect information at systematic points in time (eg, 12 months) after therapy initiation. We also did not examine adverse effect severity, which may be a better predictor of discontinuation than adverse effect occurrence[14,15] and may explain why women reported "not liking adverse effects" as the most common reason for discontinuation. We had no data on baseline symptoms that women may have experienced before starting therapy, or change in symptoms since therapy initiation. Finally, we examined the association between adverse effects and discontinuation regardless of whether women attributed the adverse effect to the medication. Because of these limitations, readers should use caution when interpreting the association between adverse effects and discontinuation in this study.

The fact that 25% of women in our study discontinued therapy on their own, without consulting a medical provider, is not trivial. This finding is particularly concerning within an integrated health plan, where these women should have had multiple opportunities to address their treatment concerns with their oncology or primary care providers. Although there are many studies on improving shared medical decision making, most are targeted toward providers, rather than patients, with regard to improving conversations and using decision aids.[35,36] In addition, we are unaware of any study that has focused specifically on endocrine therapy adherence. This topic deserves additional research to understand why these women did not involve their providers in their decision.

In addition to the limitations mentioned above, we were not able to completely separate discontinuation of tamoxifen and AIs. Because some women switched treatments (including 33

Table 2. Self-Reported Prevalence of Adverse Effects From AIs or Tamoxifen and Associations With Discontinuing Endocrine Therapy

Adverse Effect	Total (N = 538; AIs, 369; Tam, 348)		Did Not Discontinue (n = 440*; AIs, n = 314; Tam, n = 272)			Discontinued (n = 98*; AIs, n = 55; Tam, n = 76)			Odds of Discontinuation†	
	No.	%	No.	% of AI or Tam	% Related to Drug Use	No.	% of AI or Tam	% Related to Drug Use	OR	95% CI
None										
AIs	22	6.0	17	5.4	N/A	5	9.1	N/A	N/A	
Tam	21	6.0	15	5.5	N/A	6	7.9	N/A	N/A	
Individual adverse effects										
Feeling short of breath										
AIs	72	19.5	64	20.4	21.9	8	14.5	50.0	0.65	0.27 to 1.58
Tam	43	12.4	33	12.1	27.3	10	13.2	60.0	1.39	0.61 to 3.14
Headaches										
AIs	62	16.8	41	13.1	36.6	21	38.2	61.9	3.20	1.59 to 6.45‡
Tam	55	15.8	36	13.2	47.2	19	25.0	68.4	2.58	1.29 to 5.14‡
Cataracts or changes in eyesight										
AIs	99	26.8	87	27.7	29.9	12	21.8	41.7	0.68	0.32 to 1.45
Tam	81	23.3	65	23.9	33.9	16	21.1	37.5	0.93	0.48 to 1.81
Feeling dizzy										
AIs	70	19.0	59	18.8	61.0	11	20.0	68.8	1.24	0.56 to 2.78
Tam	62	17.8	46	16.9	50.0	16	21.1	63.6	1.74	0.87 to 3.50
Aches or pains in joints or muscles										
AIs	229	62.1	196	62.4	61.2	33	60.0	81.8	0.90	0.46 to 1.78
Tam	159	45.7	127	46.7	48.0	32	42.1	62.5	0.98	0.56 to 1.71
Osteoporosis or brittle bones										
AIs	92	24.9	79	25.2	60.8	13	23.6	53.9	0.97	0.47 to 2.01
Tam	50	14.4	41	15.1	29.3	9	11.8	22.2	0.80	0.36 to 1.80
Fracture or broken bone										
AIs	34	9.2	30	9.6	20.0	4	7.3	75.0	0.71	0.22 to 2.28
Tam	22	6.3	17	6.3	17.7	5	6.6	100.0	0.92	0.31 to 2.68
Incontinence										
AIs	88	23.8	72	22.9	15.3	16	29.1	25.0	1.19	0.59 to 2.41
Tam	100	28.7	81	29.8	23.5	19	25.0	10.5	0.88	0.47 to 1.65
Retaining water										
AIs	72	19.5	64	20.4	48.4	8	14.5	62.5	0.65	0.27 to 1.54
Tam	253	72.7	198	72.8	42.9	55	72.4	73.3	1.34	0.68 to 2.67
Depression or changes in mood										
AIs	64	17.3	49	15.6	40.5	15	27.3	73.3	1.14	0.57 to 2.29
Tam	96	27.6	75	27.6	38.7	21	27.6	61.9	1.24	0.67 to 2.28
Insomnia or other sleep problem										
AIs	163	44.2	135	43.0	37.8	28	50.9	60.7	1.52	0.81 to 2.85
Tam	136	39.1	106	39.0	40.6	30	39.5	56.7	1.11	0.63 to 1.94
Feeling tired										
AIs	196	53.1	167	53.2	47.3	29	52.7	72.4	1.05	0.56 to 1.99
Tam	175	50.3	133	48.9	46.6	42	55.3	61.9	1.77	0.99 to 3.18
Loss of appetite, upset stomach or vomiting										
AIs	39	10.6	29	9.2	55.2	10	18.2	70.0	2.05	0.84 to 4.97
Tam	42	12.1	28	10.3	53.6	14	18.4	78.6	2.45	1.14 to 5.28‡

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Table 2. (Continued)

Adverse Effect	Total (N = 538; AIs, 369; Tam, 348)		Did Not Discontinue (n = 440*; AIs, n = 314; Tam, n = 272)			Discontinued (n = 95*; AIs, n = 55; Tam, n = 76)			Odds of Discontinuation†	
	No.	%	No.	% of AI or Tam	% Related to Drug Use	No.	% of AI or Tam	% Related to Drug Use	OR	95% CI
Weight gain										
AIs	121	32.8	105	33.4	67.6	16	29.1	75.0	0.89	0.45 to 1.78
Tam	109	31.3	86	31.6	33.7	23	30.3	21.7	1.12	0.61 to 2.04
Breast sensitivity or tenderness										
AIs	80	21.7	67	21.3	41.8	13	23.6	53.9	0.95	0.44 to 2.05
Tam	83	23.9	66	24.3	50.0	17	22.4	64.7	0.85	0.45 to 1.63
Hot flashes										
AIs	211	57.2	185	58.9	74.6	26	47.3	73.1	0.64	0.33 to 1.24
Tam	193	55.5	157	57.7	77.1	36	47.4	83.3	0.78	0.44 to 1.39
Vaginal bleeding, spotting, or discharge										
AIs	20	5.4	17	5.4	64.7	3	5.5	66.7	0.54	0.11 to 2.55
Tam	44	12.6	38	14.0	73.7	6	7.9	83.3	0.58	0.23 to 1.50
Vaginal dryness										
AIs	133	36.0	119	37.9	49.6	14	25.5	71.4	0.42	0.20 to 0.86‡
Tam	106	30.5	89	32.7	49.4	17	22.4	52.9	0.53	0.28 to 0.99‡
Sexual symptoms or loss of sex drive										
AIs	133	36.0	119	37.9	53.8	14	25.5	57.1	0.54	0.26 to 1.09
Tam	106	30.5	88	32.4	55.7	18	23.7	55.6	0.64	0.34 to 1.22
Hair thinning or loss										
AIs	128	34.7	115	36.6	66.1	13	23.6	69.2	0.45	0.21 to 0.93‡
Tam	99	28.4	82	30.1	54.9	17	22.4	58.8	0.66	0.35 to 1.25
Blood clot or thrombosis§										
AIs	10	2.7	8	2.6	12.5	2	3.8	50.0		
Tam	9	2.6	5	1.9	100.0	4	5.3	75.0		
Stroke§										
AIs	2	0.5	2	0.7	100.0	0	0	0		
Tam	1	0.3	0	0	0	1	1.4	100.0		
Endometrial, ovarian, or uterine cancer§										
AIs	4	1.1	4	1.3	25.0	0	0	0		
Tam	6	1.7	5	1.9	20.0	1	1.4	100.0		
Adverse effect combinations										
Bone related										
AIs	114	16.5	94	21.4	N/A	14	14.3	N/A	0.80	0.39 to 1.62
Tam	68	9.8	51	11.6	N/A	13	13.3	N/A	0.92	0.46 to 1.86
Sleep related										
AIs	251	36.2	205	46.6	N/A	37	37.8	N/A	1.27	0.63 to 2.55
Tam	216	31.2	161	36.6	N/A	47	48.0	N/A	1.43	0.79 to 2.56
Hormone/menopause related										
AIs	270	39.0	230	52.3	N/A	29	29.6	N/A	0.35	0.18 to 0.70‡
Tam	249	35.9	202	45.9	N/A	41	41.8	N/A	0.45	0.24 to 0.83‡

Abbreviations: AI, aromatase inhibitor; N/A, not applicable; Tam, tamoxifen.
* AI and tamoxifen users are not mutually exclusive.
† Odds of discontinuation are associated with self-reported occurrence of adverse effects, not whether the adverse effect was related to drug use. Adjusted for age and year of diagnosis.
‡ $P < .05$.
§ Odds ratios were not calculated because of the very low prevalence of women with each adverse effect.

Table 3. Self-Reported Reasons for and Decision Making About AI or Tamoxifen Discontinuation

Self-Report	AI Discontinuers (n = 55)*		Tamoxifen Discontinuers (n = 76)*	
	No.	%	No.	%
Reason for discontinuation†				
Did not like adverse effects	32	66.7	39	59.1
Decreased quality of life	21	43.8	23	33.8
Switched from AI to tamoxifen (or vice versa)	14	29.8	23	35.4
Did not think AIs or tamoxifen were helping	9	20.9	17	27.9
Developed a medical condition and not safe to stay on AIs or tamoxifen	5	10.6	11	17.2
Medication cost too much	7	14.3	1	1.5
Had too many medications to take	3	6.4	2	3.1
Began a treatment that made it unsafe to stay on AIs or tamoxifen	2	4.2	4	6.1
Diagnosed with another case of breast cancer	2	4.3	2	3.1
Diagnosed with a different kind of cancer	0	0.0	2	3.1
Decision making				
Decided by myself to stop	15	27.3	20	26.3
Health care provider decided I should stop	15	27.3	21	27.3
Health care provider and I decided together I should stop	21	38.2	35	46.1
None of the above	4	7.2	0	0.0

Abbreviation: AI, aromatase inhibitor.
* AI and tamoxifen discontinuers are not mutually exclusive.
† Reasons are not mutually exclusive.

discontinuers), we had no way of knowing whether individual durations of tamoxifen and AIs represented planned changes in therapy or incomplete treatment. Therefore, we could only evaluate discontinuation as < 5 years of AIs and tamoxifen combined. However, women who switched treatments were not more likely to discontinue than those who did not. We may have lacked statistical power to examine differences by some patient characteristics. We did not ask women who stopped endocrine therapy how they felt after they stopped. Lifestyle and behavioral factors have also been shown to influence medication adherence,[37] but we did not measure these in our study.

Overall, our results showed a low discontinuation rate (< 20%) that was not related to most patient characteristics or specific adverse effects. Despite these results, the prevalence of adverse effects in our study was quite high and was cited as the major reason for discontinuing endocrine therapy. These results should be interpreted with caution, but they may suggest that other aspects of adverse effects, such as severity, may be better predictors of discontinuation. These estimates may also be useful for future studies aimed at understanding adverse effects and improving endocrine therapy adherence and persistence. Finally, our study should be used to raise awareness that a nontrivial number of women may be discontinuing endocrine therapy without first consulting their health care providers.

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Author Contributions

Conception and design: Erin J. Aiello Bowles, Denise M. Boudreau, Diana S.M. Buist

Financial support: Denise M. Boudreau, Diana S.M. Buist

Administrative support: Monica Fujii

Provision of study materials or patients: Erin J. Aiello Bowles, Denise M. Boudreau, Jessica Chubak, Monica Fujii, Diana S.M. Buist

Collection and assembly of data: Erin J. Aiello Bowles, Denise M. Boudreau, Monica Fujii, Diana S.M. Buist

Data analysis and interpretation: Erin J. Aiello Bowles, Denise M. Boudreau, Jessica Chubak, Onchee Yu, Janet Chestnut, Diana S.M. Buist

Manuscript writing: All authors

Final approval of manuscript: All authors

Corresponding author: Erin J. Aiello Bowles, MPH, Group Health Research Institute, 1730 Minor Ave, Suite 1600, Seattle, WA 98101; e-mail: Bowles.e@ghc.org.

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