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Patient-Reported Symptoms and Discontinuation of Adjuvant Aromatase Inhibitor Therapy

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Abstract

Background—Aromatase inhibitor (AI) therapy results in substantial survival benefits in hormone receptor-positive breast cancer. Poor adherence and discontinuation rates of AI therapy are high, primarily due to treatment-related toxicities such as musculoskeletal pain. While pain-related symptoms may worsen during AI therapy, we hypothesized that non-persistence with AI therapy was associated with symptoms which were present prior to treatment initiation.

Methods—Postmenopausal women initiating AI therapy who were enrolled in a prospective clinical trial completed questionnaires at baseline to assess sleep, fatigue, mood, and pain. Reasons for treatment discontinuation during the first year of treatment were recorded. Associations

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between baseline patient-reported symptoms and treatment discontinuation due to toxicity were identified using logistic regression.

Results—Four hundred forty-nine patients were evaluable. Odds of treatment discontinuation were higher in patients who reported a greater number of symptoms prior to AI initiation. Baseline poor sleep quality was associated with early treatment discontinuation, with an odds ratio (OR) of 1.91 (95% CI 1.26–2.89; $p=0.002$). Baseline presence of tired feeling and forgetfulness had similar odds ratios for discontinuation (OR 1.76 (95% CI 1.15–2.67, $p=0.009$) and OR 1.66 (95% CI 1.11–2.48, $p=0.015$), respectively). Increasing total number of baseline symptoms was associated with increased likelihood of treatment discontinuation, with an OR 1.89 (95% CI 1.20–2.96; $p=0.006$) for 3–5 symptoms versus 0–2 symptoms.

Conclusions—Symptom clusters in breast cancer survivors present prior to initiation of adjuvant AI therapy may negatively impact persistence with therapy. Interventions to manage these symptoms may improve breast cancer outcomes and quality of life.

Keywords

breast cancer; aromatase inhibitor; patient-reported outcomes; nonpersistence; symptoms

Introduction

Aromatase inhibitors (AI) are routinely used for adjuvant therapy of postmenopausal women with estrogen receptor (ER)-positive early stage breast cancer. Randomized controlled trials have demonstrated improvements in disease free (DFS) and overall survival (OS) with AI therapy compared to tamoxifen.^{1, 2} Early discontinuation of AI therapy however has been observed in more than a quarter of patients, primarily due to toxicity of therapy.^{3, 4} Non-adherence to AI therapy has been associated with increases in mortality.⁵

The most common toxicities reported by AI-treated patients are musculoskeletal symptoms, including arthralgias and myalgias.³ Attempts to identify the cause of these side effects have focused upon clinical and treatment factors such as time since menopause, body mass index, prior tamoxifen therapy, and prior taxane chemotherapy.^{3, 6–8} Despite these studies, the etiology of AI toxicity remains undefined, although it is believed to be due, at least in part, to estrogen depletion.^{9, 10} Vitamin D deficiency may also play a role in the development of toxicity.¹¹

Studies of breast cancer survivors have demonstrated high rates of patient-reported symptoms, including pain, insomnia, fatigue, cognitive dysfunction, and mood disorders, which can be present during all phases of treatment and can persist into the survivorship period.^{12, 13} A similar constellation of symptoms is commonly reported by patients with other chronic pain conditions, including fibromyalgia and temporomandibular joint disorder.¹⁴ In patients with breast cancer, these symptoms may partly arise from the multiple treatment modalities used for disease management, including surgery, chemotherapy, radiation therapy, and/or endocrine therapy. In addition, these symptoms may be related to the stress of the diagnosis itself.¹⁵

Using data from the 503-patient Exemestane and Letrozole Pharmacogenetics (ELPh) Trial, we previously reported associations between clinical and treatment factors and early discontinuation of therapy due to toxicity.³ In that study, more than 75% of patients reported musculoskeletal pain at the time of discontinuation. Based on the literature from other chronic pain disorders, we hypothesized that some breast cancer patients who develop musculoskeletal pain might also have other symptoms seen in response to stressors such as sleep disturbances, fatigue, mood disorders, and cognitive dysfunction.¹⁶ If this were the case, then it is possible that some individuals discontinue AI therapy because of their total symptom burden at baseline, not solely because of emergence of their musculoskeletal pain.^{17, 18} In this manuscript we report associations between the presence of patient-reported symptoms prior to initiation of an AI and treatment discontinuation within 1 year of starting the drug in the ELPh Trial.

Methods

Study participants

Post-menopausal women with stage 0-III hormone receptor positive breast cancer who were initiating treatment with an AI were eligible for enrollment on the ELPh trial (www.clinicaltrials.gov NCT00228956). Details of the ELPh trial have been reported elsewhere.¹⁹ In brief, all indicated surgery, chemotherapy, and radiation therapy were completed prior to enrollment, and patients who previously received tamoxifen therapy were permitted to enroll. The clinical trial was approved by the Institutional Review Boards at all three participating sites, and patients were required to provide written informed consent prior to undergoing study-related procedures.

Study procedures

Patients were randomized 1:1 to treatment with exemestane (Aromasin, Pfizer, New York, USA) 25 milligrams orally daily or letrozole (Femara, Novartis, Basel, Switzerland) 2.5 milligrams orally daily. Prior to AI initiation, enrolled patients completed a battery of questionnaires and underwent phlebotomy. Patients then initiated treatment, and returned to the clinic for follow-up assessments, including phlebotomy and questionnaire completion, after 1, 3, 6, 12, and 24 months of AI therapy.

Questionnaires

At each time point, patients completed the following questionnaires: depression (Center for Epidemiologic Studies – Depression (CESD)),²⁰ anxiety (Hospital Anxiety and Depression Scale-Anxiety (HADS-A)),²¹ sleep quality (Pittsburgh Sleep Quality Index (PSQI)),²² and general symptoms including joint pain, fatigue, difficulty concentrating, forgetfulness, and vaginal dryness (the Breast Cancer Prevention Trial (BCPT) symptom checklist).²³

Laboratory studies

Serum samples obtained at the baseline and 3 month time points were assayed for estradiol (E2), estrone-1-sulfate (E1S), and estrone (E1) using an ultrasensitive gas chromatography tandem mass spectroscopy assay, as previously described.²⁴ The lower limit of quantification for E2 was 0.625 pg/ml, for E1S was 2.88 pg/ml, and for E1 was 1.56 pg/ml.

Statistical plan

The primary objective of the ELPh trial was to determine the genetic predictors of change in breast density after 24 months of either an azole (letrozole) or a steroidal (exemestane) AI medication; these results are being published separately.²⁵ The primary objective of the exploratory analysis reported in this manuscript was to investigate associations between patient-reported symptoms prior to AI initiation and discontinuation of AI therapy due to toxicity during the initial 12 months of therapy.

Validated questionnaires to evaluate fatigue or cognitive dysfunction were not included in this trial. Therefore, to investigate these symptoms, the following individual items on the BCPT questionnaire²³ were analyzed: “joint pain” (pain), “forgetfulness” and “difficulty concentrating” (cognitive dysfunction), and “tired feeling” (fatigue). “Vaginal dryness” was also analyzed as a common AI-related symptom thought to be predominantly peripherally rather than centrally mediated. Presence of each symptom was defined as the patient reporting of any degree of severity of the symptom (i.e., slightly, moderately, quite a bit, or extremely).

Descriptive analyses were conducted for all baseline characteristics for the entire sample and by discontinuation status. Odds ratios and their significance comparing characteristics for those who discontinued AI therapy due to symptoms by the end of one year to those who remained on treatment at one year were calculated using logistic regression. Baseline characteristics that were associated with AI discontinuation due to symptoms by the end of the first year by a p-value <0.20 were included in a multivariable model where a stepwise procedure was utilized to find the variables significantly associated with AI discontinuation due to toxicity. Estrogen measurements were natural log transformed in all models.

Additionally, symptoms were combined to account for the total number of symptoms each patient experienced at baseline. Symptoms included in this variable were sleep quality (poor: PSQI >5 vs. good: PSQI ≤5), concentration (any severity vs. none or no severity), tired feeling (any severity vs. none or no severity), anxiety (no: HADS A ≤7 vs. borderline or definite: HADS A >7), and depression (no: CESD <16 vs. possible or probable: CESD ≥16). If the baseline characteristic score was missing, it was conservatively coded as a 0 and the total number of symptoms was summed for each patient for a final number of symptoms ranging from zero to five. The total number of symptoms was dichotomized as being either 0–2 or 3–5 and association between this variable and AI discontinuation was assessed in the univariate and multivariable setting.

All analyses were performed in SAS v9.3 (SAS Institute, Inc, Cary, NC).

Results

Baseline patient characteristics and treatment discontinuation due to toxicity

The ELPh trial included 503 patients, of whom 500 were randomly assigned to letrozole or exemestane and treated for 24 months (Figure 1). Enrolled patients who discontinued therapy within 1 year of treatment initiation because of toxicity were compared to those who continued study participation beyond the 1 year time point (Table 1). During the 24 month

study, a total of 51 patients discontinued therapy for reasons other than treatment-emergent toxicity, including inability to undergo phlebotomy and recovery of ovarian function, as previously reported.³

Of the 449 patients eligible for the analysis, 140 (31.2%) discontinued AI therapy due to symptoms by the end of the first year of treatment (Table 1). Patients who discontinued therapy were significantly younger than those who continued therapy (median age 56 vs. 60; OR 0.97, 95% CI 0.95–1.00; $p=0.035$). As previously reported,³ no univariate statistically significant association (at the $p=0.05$ level) was identified between treatment discontinuation and BMI ($p=0.76$), baseline serum estrogen concentration ($p=0.50$, 0.18, 0.73 for estradiol, estrone sulfate and estrone, respectively), race ($p=0.33$), previous treatment with chemotherapy ($p=0.51$), taxane-based chemotherapy ($p=0.18$), radiation therapy ($p=0.51$), prior tamoxifen ($p=0.18$), or prior hormone replacement therapy ($p=0.18$). Similarly, there was no statistically significant association between stage of breast cancer at diagnosis and likelihood of treatment discontinuation ($p=0.99$). Treatment with exemestane was significantly associated with an increased risk of treatment discontinuation compared to letrozole (OR 1.67; 95% CI (1.12–2.51); $p=0.012$).

Although half of the analyzed patients started AI therapy within 6 months of undergoing definitive surgery, the time interval ranged from 0 to 109 months. Time from surgery to the initiation of AI therapy was not significantly associated with AI discontinuation due to symptoms. Those who discontinued therapy had a median time since surgery of 8 months (range 1–108), whereas those who remained on AI therapy beyond 12 months had a median time since surgery of 6 months (range 0–109, $p=0.11$).

Patient-reported symptoms prior to AI therapy initiation and treatment discontinuation

In the ELPh trial, 67 (15.0%) patients reported being possibly or probably depressed at the time of AI initiation (using the CESD), and 64 (14.3%) reported being borderline or definitely anxious (using HADS-A, Table 1; Figure 2). Analysis of depressive symptomatology scores as a dichotomous variable (possibly or probably depressed versus not depressed) using the CESD questionnaire did not demonstrate a statistically significant association between depression prior to AI initiation and increased risk of treatment discontinuation within the first year (OR 1.50; 95% CI 0.88–2.58; $p=0.14$). Similarly, no significant association was identified between pre-existing anxiety assessed using the HADS-A questionnaire and discontinuation of AI therapy (OR 1.10; 95% CI 0.62–1.93; $p=0.75$).

In the ELPh trial, 206 patients (47.9%) reported poor sleep quality on the PSQI questionnaire prior to initiation of AI therapy (Table 1; Figure 2). A larger percentage of patients with poor sleep quality prior to AI initiation discontinued therapy because of toxicity by 1 year compared to those with good sleep quality (59.0% vs. 42.9%; OR=1.91, 95% CI 1.26–2.89; $p=0.002$). Of the 206 patients who reported poor sleep quality prior to AI initiation, 139 (67.5%) reported poor sleep quality at 75% or more of their subsequent visits during AI therapy and seven discontinued after reporting sleep problems at the initial assessment. Fifty-seven of these 139 (41.0%) patients discontinued AI treatment by the end of one year.

The other patient-reported symptoms were collected using a general symptom questionnaire (Table 1; Figure 2). No statistically significant association was identified between patient-reported presence of joint pain at baseline and treatment discontinuation due to toxicity (63.8% vs 56.2%, OR 1.37, 95% CI 0.91–2.08; $p=0.14$). Patients who reported forgetfulness or feeling tired prior to AI initiation were more likely to discontinue therapy due to toxicity compared to those who did not report having the symptom (forgetfulness: 55.1% vs. 42.5%; OR 1.66, 95% CI 1.11–2.48; $p=0.015$; tired feeling: 67.4% vs. 54.1%; OR 1.76, 95% CI 1.15–2.67; $p=0.009$). In addition, there was no statistically significant univariate association between presence of difficulty concentrating prior to starting AI therapy and treatment discontinuation (28.1% vs. 21.2%; OR 1.45, 95% CI 0.92–2.13; $p=0.11$) or vaginal dryness and treatment discontinuation (37.0% vs. 29.6%; OR 1.39, 95% CI 0.91–2.13; $p=0.13$).

The following 5 symptoms were combined to assess if having more symptoms at baseline was associated with treatment discontinuation: poor sleep quality (PSQI>5), depression (CESD 16), anxiety (HADS A 7), any degree of tired feeling, and any degree of difficulty concentrating. Patients who reported a greater number of symptoms prior to treatment initiation were more likely to discontinue therapy because of toxicity (Figure 3). There was a statistically significant difference in treatment discontinuation rate among those who reported 0, 1–2, and 3–5 symptoms prior to AI initiation ($p=0.006$). Of the 117 patients who did not report any of these symptoms at baseline, 26 (22%) discontinued AI therapy within 1 year because of side effects. Of the 225 patients who reported one or two symptoms before AI initiation, 69 (31%) discontinued AI therapy. In contrast, of the 107 patients with 3 or more of these symptoms, 45 (42%) discontinued AI therapy. Compared to those patients who reported none of the symptoms at baseline, those patients with 1 or 2 symptoms at baseline had an increased likelihood of AI discontinuation during the first year with an odds ratio of 1.55 (95% CI 0.92–2.60), and those with 3–5 symptoms had an increased likelihood with an odds ratio of 2.54 (95% CI 1.42–4.54; $p=0.007$). Furthermore, we found, on average, that individuals who discontinued AI therapy within 1 year because of toxicity reported having 3 or more symptoms at 37% of their subsequent visits, compared with 22% for who did not discontinue therapy ($p=0.0009$).

Multivariable analysis of predictors of treatment discontinuation due to toxicity

Multivariable logistic regression was used to evaluate predictors of treatment discontinuation due to toxicity. Including all variables univariately related to discontinuation from Table 1 we sought a more parsimonious model using a stepwise approach. Thus we evaluated a model with age, AI medication, sleep quality and concentration (Table 2). EIS at baseline ($p=0.14$) and pain score ($p=0.12$) were the last variables to be removed from the model. With all 5 variables included, the area under the curve (measure of predictive power in logistic regression) was 0.68. In either the full model or the reduced model that excluded EIS and pain score, both poor sleep quality and difficulty concentrating remained statistically significant. In the reduced model shown in Table 2, those with poor sleep quality had 1.79 times the odds of discontinuing AI medication by the end of the first year of treatment, holding age, AI medication, and concentration severity constant ($p=0.01$). Those with moderate to extreme difficulty concentrating had 2.62 times the odds of discontinuing

treatment, holding all other variables constant ($p=0.017$). The area under the curve of this reduced model was 0.65.

A second model was evaluated to specifically analyze the effect of total number of symptoms at baseline (3–5 vs. 0–2; Table 3). In this model, age (OR 0.97; $p=0.03$), AI medication (OR 1.66; $p=0.02$), and 3 or more symptoms (OR 1.68; $p=0.03$) were statistically significantly associated with treatment discontinuation due to toxicity. This model also included pain score (VAS) where each 1 point increase in pain increased the odds of discontinuation by 1.09 ($p=0.07$). This model had an area under the curve of 0.64. When baseline E1S ($p=0.17$) was also included in this base model the area under the curve increased slightly to 0.65.

Discussion

Early discontinuation of AI therapy, which is associated with worse breast cancer outcomes, is frequently due to the development of side effects, especially musculoskeletal toxicity.^{3, 5} Numerous prior studies of AI therapy have reported increased risk of developing musculoskeletal symptoms during AI treatment with factors such as age, body mass index, pre-existing pain or arthritis, prior chemotherapy, and prior tamoxifen.^{3, 6–8} For this analysis, we instead focused on associations between patient-reported non-pain symptoms present before initiation of AI therapy, such as poor sleep quality, fatigue, depression, and anxiety, and increased rates of premature treatment discontinuation because of toxicity. In the relatively large ELPh trial, we found that pre-existing poor sleep quality and difficulty concentrating were strongly associated with early treatment discontinuation due to toxicity. In addition, increased symptom burden prior to AI therapy initiation was associated with both increased symptom burden during AI treatment and increased likelihood of treatment discontinuation within 1 year.

Our findings are consistent with those reported in the MA.27 trial of exemestane versus anastrozole.²⁶ In that study, the hazard ratio of early treatment discontinuation due to bother from side effects from prior treatment that were present at the time of AI initiation was 1.29 (95% CI 1.08–1.55; $p=0.006$). The contributions of specific side effects were not described.

The symptom cluster of mood disorders, fatigue, and difficulty sleeping is frequently identified in patients across diseases, including cancer and chronic pain syndromes.²⁷ Many of the published reports evaluating symptom clusters in breast cancer patients have focused on patients undergoing therapy with short-term treatment modalities, including chemotherapy and/or radiation therapy. For example, in one study patients who reported a greater number of symptoms prior to the start of chemotherapy were more likely to report worse symptoms during the treatment.²⁷ Other studies have identified specific patterns of change in symptoms over time during chemotherapy and radiation. These patterns ultimately impact functional status and quality of life and may influence patient management.^{17, 28} In contrast, few published reports have focused on patterns of specific symptoms that occur during long-term adjuvant endocrine therapy. Analogous to what has previously been seen with chemotherapy, in the ELPh trial we identified an association between greater number of symptoms prior to treatment and decreased persistence with AI therapy due to toxicity.

The symptoms of poor sleep and difficulty concentrating stood out as clinically important contributors to this symptom cluster.

Knowledge of these associations is clinically relevant, since these symptoms are not frequently recognized as problematic and are not typically carefully assessed or aggressively managed by oncologists. Indeed, since difficulty sleeping and complaints of fatigue are common in patients with breast cancer²⁹ and are often thought to be self-limited side effects of prior therapies including chemotherapy and radiation therapy, oncologists may not appreciate that the presence of these symptoms may compromise future treatments. These results raise the possibility that asking patients about these symptoms and addressing them at the time of AI initiation, or even prophylactically, could identify patients at risk, and allow the implementation of measures to improve adherence/persistence with subsequent adjuvant endocrine therapy.

Although management of these symptoms is essential for improving quality of life, these data suggest that it may also impact breast cancer outcomes if improvement in symptoms led to increased adherence to and persistence with therapy. There is a paucity of effective treatment options for poor sleep, cognitive problems, and fatigue in cancer survivors. Numerous clinical trials have been conducted to test various pharmacologic therapies for fatigue, although few studies of pharmacologic treatments have been conducted specifically for sleep disturbance in cancer patients.¹⁸ Meta-analyses have demonstrated a statistically significant benefit from methylphenidate compared to placebo for cancer-related fatigue, although the clinical benefit is modest.³⁰ There are also considerable data to support use of cognitive behavioral therapy (CBT) for treatment of both insomnia and fatigue in cancer patients.^{30–32} Use of CBT is recommended in the National Comprehensive Cancer Network (NCCN) guidelines for management of Cancer-Related Fatigue,³³ although it is unknown how often these behavioral techniques are actually used in clinical practice. Improvements in fatigue have also been noted in cancer patients treated with other non-pharmacologic interventions, including physical activity.³⁰ Although a number of treatment options are listed in the currently available national guidelines, no individual modality is preferred.³³

Our study has multiple strengths. The findings were derived from a large, prospective clinical trial in which reasons for discontinuation were prospectively recorded. Validated questionnaires were used to assess patient-reported sleep, pain, and mood disorders, although fatigue and cognitive function data elements had to be obtained from a more general symptom questionnaire. The study medication was provided to the patients by the study, so cost of the medication was not a factor in persistence with therapy.

In this analysis we identified a numerically greater but not statistically significant increased risk of treatment discontinuation within 1 year in patients treated with a taxane-based chemotherapy regimen, which we and others have previously reported. One important difference between the prior analysis of the ELPh trial and this one is the focus on discontinuation specifically within the first year of AI therapy. This 1 year limitation was intended to restrict analysis to symptoms likely due to the AI medication, and less likely to changes that can occur over time with the natural aging process, such as worsening osteoarthritis. Our findings suggest that pre-existing symptoms are more strongly associated

with AI discontinuation due to toxicity than clinical factors such as prior treatment with chemotherapy. However, it remains possible that prior treatments such as chemotherapy contributed to the symptoms reported by patients at the time of the baseline study visit.

Our findings demonstrate the importance of symptom clusters that include poor sleep and difficulty concentrating in patients with breast cancer, and the potential detrimental effects of these symptoms not just on quality of life but also on AI treatment adherence and breast cancer outcomes. Therapies to improve the constellation of symptoms rather than those that target individual symptoms should be considered to allow optimal patient care. Clinical trials are warranted to evaluate the impact of management of symptom clusters on adherence to potentially life-saving adjuvant endocrine therapies.

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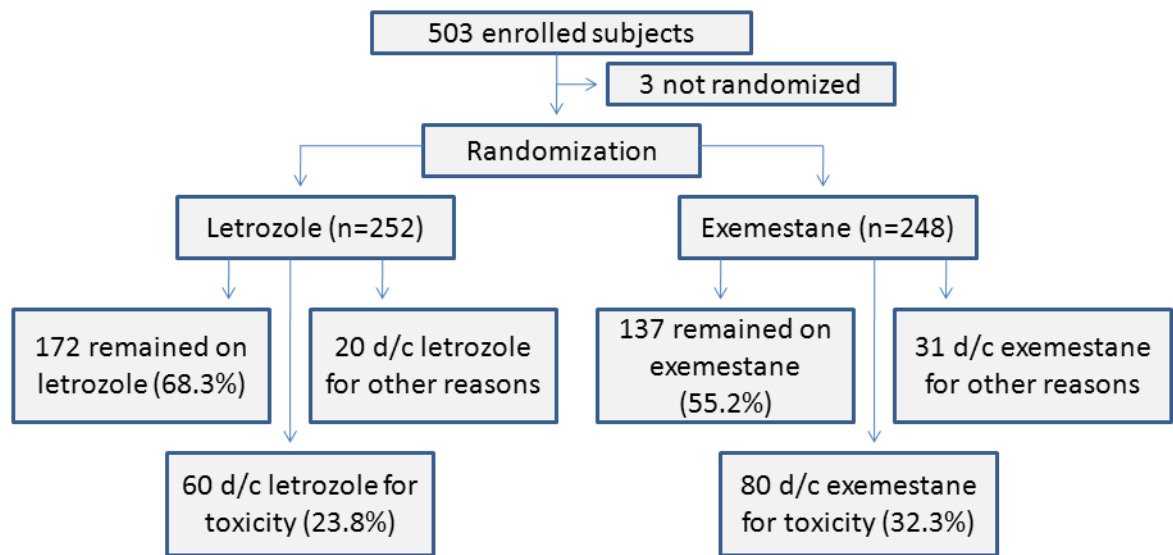


Figure 1. Consort diagram of patient flow in the ELPh trial

D/c = discontinued

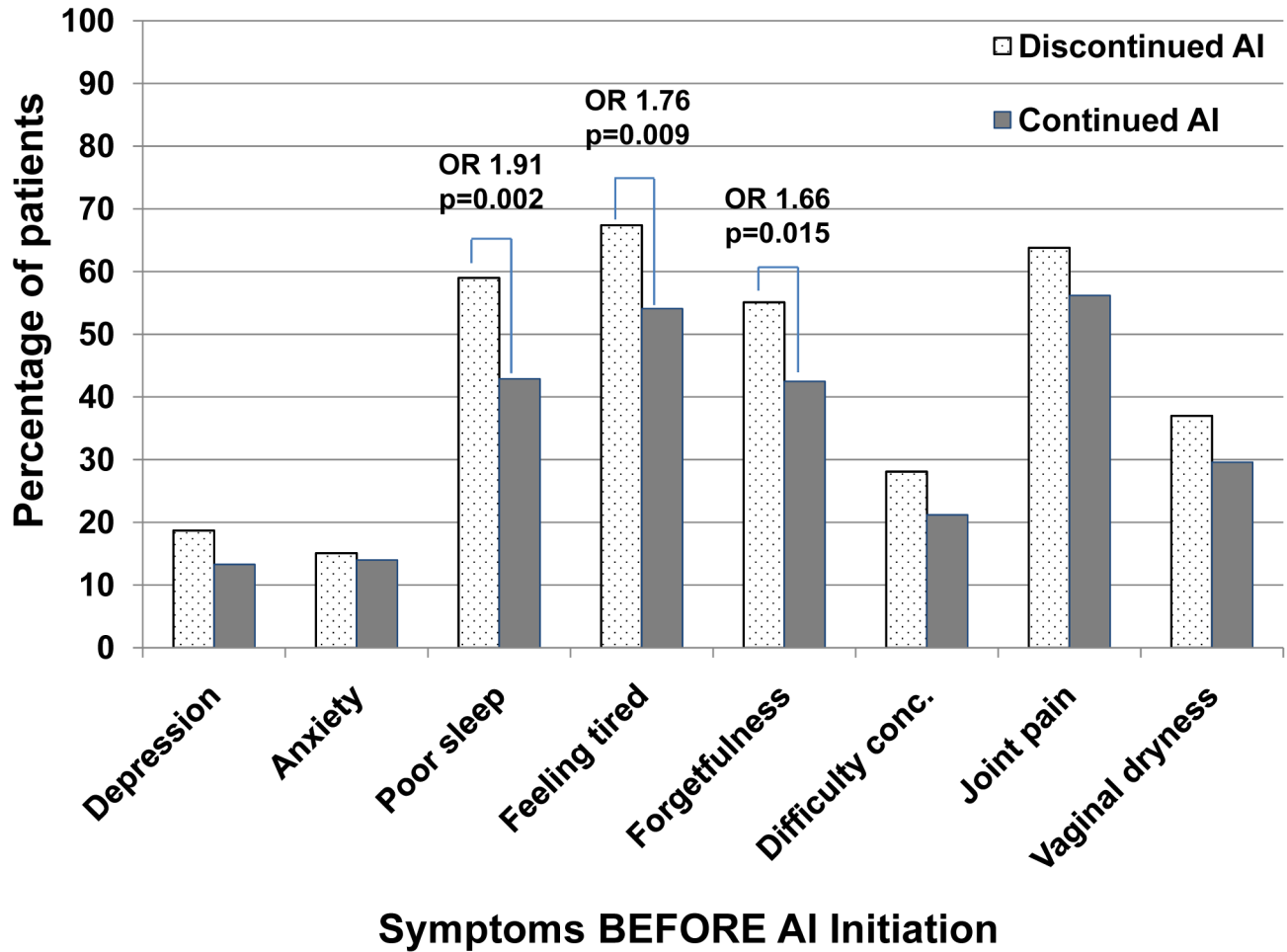


Figure 2. Percentage of evaluable patients who continued or discontinued aromatase inhibitor (AI) therapy within the first year of treatment by baseline symptoms present before AI initiation. Dotted bars represent the percentage of total evaluable patients who discontinued AI therapy within 1 year, and solid bars represent the percentage of total evaluable patients who continued AI therapy beyond 1 year. Odds ratios (OR) and p values are given for those comparisons that were statistically significant. Conc = concentrating.

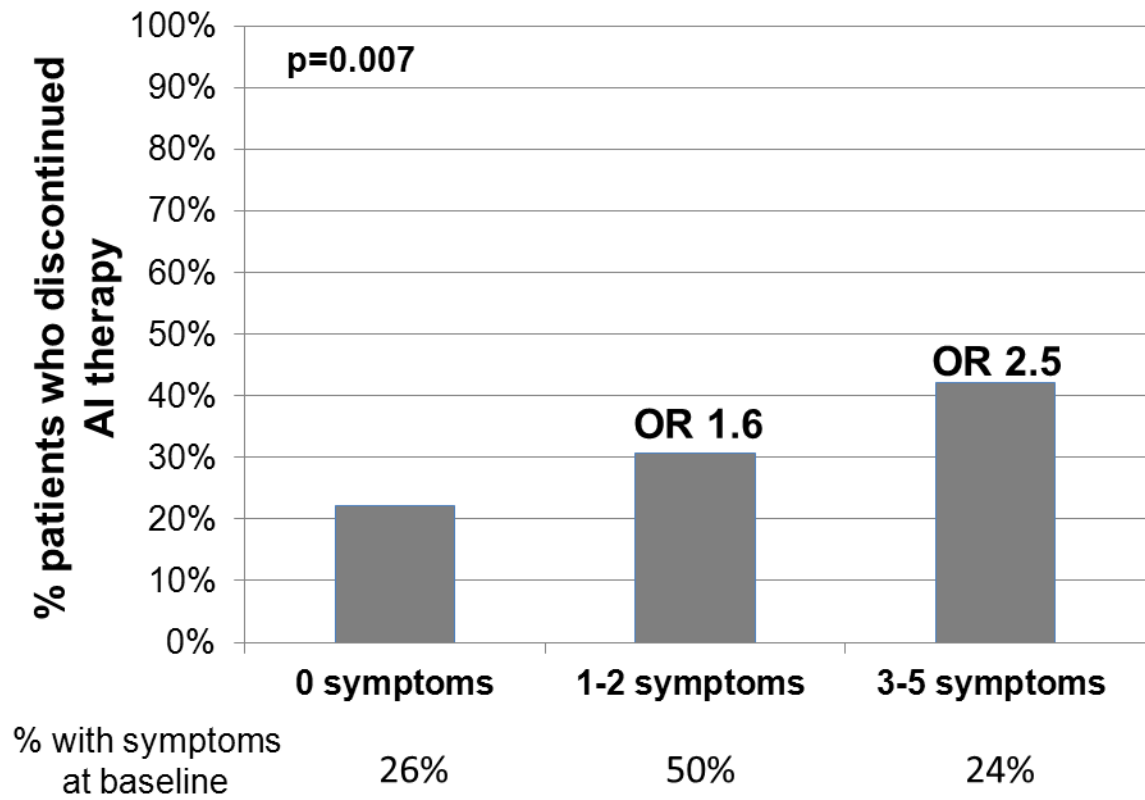


Figure 3. Percentage of patients who discontinued aromatase inhibitor (AI) therapy according to the number of symptoms present prior to AI initiation

The number of patients in each group is given below the x axis. OR: odds ratio.

Table 1

Baseline patient characteristics by AI treatment discontinuation status

Baseline dichotomous characteristics of patients enrolled in the ELPb trial who discontinued AI therapy due to any symptom by or at 12 months versus all others. Comparison of cohort that discontinued versus all others was performed using logistic regression. Mean values are given in parenthesis.

Characteristic	Total (n=449)		Discontinued due to Symptoms (n=140)		All Others (n=309)		Odds Ratio (95% CI)	p value
	N	%	N	%	N	%		
Age	491	(59.0)	140	(56.0)	309	(60.0)	0.97 (0.95–1.00)	
Body Mass Index	490	(29.1)	140	(28.7)	308	(29.3)	1.00 (0.96–1.03)	0.76
Estradiol pg/mL*	463	(4.7)	132	(4.1)	304	(4.9)	0.91 (0.71–1.18)	0.50
Estrone Sulfate pg/mL*	459	(243.5)	128	(275.0)	304	(228.0)	1.20 (0.92–1.56)	0.18
Estrone pg/mL*	464	(23.0)	133	(21.7)	304	(23.8)	0.95 (0.68–1.31)	0.73
Race								
White	401	89.3	128	91.4	273	88.3	1.00 (-)	0.33
Black/Other	48	10.7	12	8.6	36	11.7	0.71 (0.36–1.41)	
Breast cancer stage								
DCIS	27	6.0	8	5.8	19	6.2	1.00 (-)	
I	234	52.3	73	52.5	161	52.3	1.08 (0.45–2.57)	0.99
II	143	32.0	45	32.4	98	31.8	1.09 (0.44–2.68)	
III	43	9.6	13	9.4	30	9.7	1.03 (0.36–2.95)	
Chemo Treatment								
Yes	200	44.5	64	45.7	136	44.0	1.07 (0.72–1.60)	0.51
No	249	55.5	76	54.3	173	56.0	1.00 (-)	
Taxane								
Yes	144	32.1	51	36.4	93	30.1	1.33 (0.87–2.03)	0.18
No	305	67.9	89	63.6	216	69.9	1.00 (-)	
Radiation Therapy								
Yes	355	79.4	113	81.3	242	78.6	1.19 (0.72–1.97)	0.51
No	92	20.6	26	18.7	66	21.4	1.00 (-)	
Tamoxifen								
Yes	163	36.5	57	41.0	106	34.4	1.33 (0.88–2.00)	0.18

Characteristic	Total (n=449)		Discontinued due to Symptoms (n=140)		All Others (n=309)		Odds Ratio (95% CI)	p value
	N	%	N	%	N	%		
No	284	63.5	82	59.0	202	65.6	1.00 (-)	
Hormone Replacement Therapy								
Yes	231	51.8	65	47.1	166	53.9	0.76 (0.51-1.14)	0.18
No	215	48.2	73	52.9	142	46.1	1.00 (-)	
Drug Assignment								
Exemestane	217	48.3	80	57.1	137	44.3	1.67 (1.12-2.51)	0.012
Letrozole	232	51.7	60	42.9	172	55.7	1.00 (-)	
Depression (CESD)								
Normal	381	85.0	113	81.3	268	86.7	1.00 (-)	0.14
Possible/ Probable Depression (>16)	67	15.0	26	18.7	41	13.3	1.50 (0.88-2.58)	
Anxiety (HADS A)								
Non-Case	383	85.7	118	84.9	265	86.0	1.00 (-)	0.75
Borderline or Case	64	14.3	21	15.1	43	14.0	1.10 (0.62-1.93)	
Sleep Quality (PQSI)								
Good Sleep Quality (5)	224	52.1	55	41.0	169	57.1	1.00 (-)	0.002
Poor Sleep Quality	206	47.9	79	59.0	127	42.9	1.91 (1.26-2.89)	
Joint Pain Severity								
None or Not at All	184	41.4	50	36.2	134	43.8	1.00 (-)	0.14
Slight - Extreme	260	58.6	88	63.8	172	56.2	1.37 (0.91-2.08)	
Forgetfulness								
None or Not at All	239	53.6	62	44.9	177	57.5	1.00 (-)	0.015
Slight - Extreme	207	46.4	76	55.1	131	42.5	1.66 (1.11-2.48)	
Tired Feeling								
None or Not at All	186	41.8	45	32.6	141	45.9	1.00 (-)	0.009
Slight - Extreme	259	58.2	93	67.4	166	54.1	1.76 (1.15-2.67)	
Concentration								
None or Not at All	342	76.7	100	71.9	242	78.8	1.00 (-)	0.11
Slight - Extreme	104	23.3	39	28.1	65	21.2	1.45 (0.92-2.30)	
Vaginal Dryness								

Characteristic	Total (n=449)		Discontinued due to Symptoms (n=140)		All Others (n=309)		Odds Ratio (95% CI)	p value
	N	%	N	%	N	%		
None or Not at All	301	68.1	87	63.0	214	70.4	1.00 (-)	0.13
Slight - Extreme	141	31.9	51	37.0	90	29.6	1.39 (0.91-2.13)	

* Logged values were used in logistic regression

CESD: Center for Epidemiologic Studies – Depression. HADS-A: Hospital Anxiety and Depression Scale – Anxiety. PSQI: Pittsburgh Sleep Quality Index.

Table 2
Multivariable logistic regression analysis of predictors of AI treatment discontinuation, including individual symptoms

Multivariable logistic regression resulting from step-down analysis of treatment discontinuation during the first year of AI therapy due to baseline sleep and concentration difficulties before AI initiation and patient characteristics (n=428, area under the curve = 0.65)

Variable	Odds Ratio (95% CI)	p-value
Age	0.97 (0.95–1.00)	0.028
Drug (exemestane vs. letrozole)	1.63 (1.07–2.49)	0.024
Sleep quality (PSQI >5 vs. 5)	1.79 (1.15–2.79)	0.010
Concentration (vs. none)		0.017
Not at all or slight	0.75 (0.42–1.33)	
Moderate-extreme	2.62 (1.22–5.65)	

Table 3
Multivariable logistic regression analysis of predictors of AI treatment discontinuation including symptom clusters

Multivariable logistic regression resulting from step-down analysis of treatment discontinuation during the first year of AI therapy due to number of symptoms present before AI initiation and patient characteristics (n=447, area under the curve = 0.64)

Variable	Odds Ratio (95% CI)	p-value
Age	0.97 (0.95–1.00)	0.025
Drug (exemestane vs. letrozole)	1.66 (1.10–2.50)	0.016
VAS	1.09 (0.99–1.20)	0.067
Total Number of Symptoms (vs. 2 or less)		
3 or more	1.68 (1.05–2.70)	0.031