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## Comparison of distress in breast cancer survivors treated with different adjuvant endocrine therapies: a single-centre cross-sectional study

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### ABSTRACT

**AIM:** To compare the depression and anxiety scores among breast cancer (BC) survivors who received different adjuvant endocrine therapies.

**PATIENTS AND METHOD:** A total of 154 patients (with 6 months to 10 years follow-up) were recruited in this cross-sectional study. The patients were divided into three groups according to the type of endocrine therapy: selective oestrogen receptor modulator (tamoxifen), third-generation aromatase inhibitors (AIs; e.g. anastrozole and letrozole), and luteinizing hormone releasing hormone (LHRH) analogue with tamoxifen. Patients' age, menopausal status at diagnosis, educational level, marital status, and disease characteristics including stage, treatment, and follow-up period since diagnosis were noted. Beck Depression Inventory, Beck Anxiety Inventory, and Duke-University of North Carolina Functional Social Support Questionnaire were used to assess the depression, anxiety, and functional social support, respectively. Statistical significance of the associations was analysed using Spearman correlation, Student's *t*, Mann-Whitney *u*, and ANOVA tests.

**RESULTS:** Patients' mean age was 49.8 (28–77) years. Age and perceived social support which are patient-related factors affected anxiety and depression scores, while disease-related factors did not affect. Patients who received LHRH analogue with tamoxifen presented more anxiety scores. Patients who received tamoxifen had more depression scores than those who received AIs. This may have been due to the fact that the tamoxifen group is composed of young and pre-menopausal patients.

**CONCLUSION:** Young age and lower social support are important determinants of higher anxiety and depression scores. The use of LHRH analogue is one of the risk factors for the development of anxiety in BC survivors.

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### KEYWORDS

Breast cancer; endocrine therapy; anxiety; depression; social support

## Introduction

Breast cancer (BC) is the most common malignancy among women worldwide. However, it has a decreasing mortality rate, thanks to early detection and new treatment modalities [1,2]. The extended life span of BC patients can increase the likelihood of encountering distress. Previous studies reported that the prevalence of distress is higher in BC survivors than in general female population [3,4]. Non-metastatic BC patients are more exposed to distress, especially during the diagnostic process and early treatment periods such as surgery, chemotherapy, and radiotherapy. On the other hand, patients continue to suffer from distress even after one year of the diagnosis and after completion of these treatments [5,6]. We know that longer term distress was associated with previous psychological conditions, lack of social support, younger age, and severely stressful non-cancer life experiences, whereas disease characteristics including tumour stage,

histology, or type of adjuvant treatment such as chemotherapy, radiotherapy, or hormonotherapy were not associated with depression and anxiety any time [4,7–9]. The latest recommendations suggest that endocrine therapy should be used for at least 5–10 years for patients with hormone expressing tumours [10]. In this instance, treatment of BC with endocrine therapy continues for years and this generates further adverse effects and also develops distress.

Oestrogen affects the growth and survival of BC cells by activating oestrogen receptors (ER) and this leads to cell division, inhibition of cell death, and new blood vessel formation from the earliest stages of BC [11]. Therefore, blocking oestrogen has been at the centre of BC treatment for patients with hormone expressing tumor in both metastatic setting and adjuvant therapy to prevent the recurrence. Tamoxifen, a selective ER modulator, used in both pre-menopausal and post-menopausal women acts with competitive antagonism

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of oestrogen at the receptor site and thus provides improving effects on lipid profiles and bone mineral density, thanks to its partial tissue-specific agonist effects. Tamoxifen is combined with an LHRH analogue in patients with pre-menopausal gonadotropin levels for approximately 3–5 years [12]. On the other hand, the most direct mechanisms which reduce the level of oestrogen by interfering with its production are ovarian ablation with surgery or medical therapy with an LHRH analogue for pre-menopausal woman or AIs for post-menopausal woman. Anastrozole and letrozole are third-generation non-steroidal AIs binding to aromatase enzyme reversibly. Different anti-oestrogenic mechanisms of tamoxifen, AIs, and LHRH analogues may cause different distress scores in patients who use these drugs for a long time. Moreover, sudden hypo-oestrogenic condition with the added LHRH analogue might cause the development of anxiety or depression. In this context, we aimed to investigate the effect of different endocrine therapies on depression and anxiety scores with other disease- and patient-related factors in patients who received endocrine therapy for 6 months to 10 years.

## Study design features and methods

### Hypothesis

We hypothesized that the sudden decrease in the oestrogen level is an important parameter of distress in BC patients using endocrine therapy.

### Ethics

This study was conducted at a single centre – Gaziantep University, Oncology Hospital in Turkey. The protocol and informed consent documentation were reviewed and approved by the Independent Ethics Committee of the University and agreed with the ethical principles of the Declaration of Helsinki.

### Patient selection

BC patients who were treated in Gaziantep Oncology Hospital between January 2005 and January 2015 were recruited for this cross-sectional study. Patients were eligible if participants were diagnosed with stages I–III hormone receptor-positive and operated BC. After the completion of intravenous (IV) chemotherapy, and/or radiotherapy, patients currently taking adjuvant endocrine therapy (tamoxifen or AIs) for at least 6 months were included. We assessed the effects of the potential risk factors on depression and anxiety for three periods following the completion of their IV chemotherapy treatment: 6 months to 2 years, 2–5 years, and over 5 years. These periods were chosen according to the frequency of follow-up at the centre

(every 3 months for 2 years, every 6 months in 2–5 years, and annually after 5 years). The following informations were recorded: age, menopausal status at diagnosis, educational level, marital status, disease stage, follow-up period since diagnosis, and rate of “functional social support” (FSS). Patients were divided into three groups according to the use of tamoxifen with an LHRH analogue, tamoxifen, or AIs. After completion of chemotherapy, luteinizing and follicle-stimulating hormone and oestradiol levels were assessed. An LHRH analogue was added to tamoxifen in patients who had pre-menopausal gonadotropin levels, whereas patients who had post-menopausal gonadotropin levels did not receive an LHRH analogue. LHRH analogue was administered only for 3–5 years, even if patients had the pre-menopausal gonadotropin levels. While patients were categorized according to the use of hormone therapy, especially the use of LHRH analogue was considered at the time of participation in this study due to cross-sectional design.

The “inclusion criteria” were as follows: (1) aged 18 years old or older when diagnosed with BC; (2) received IV chemotherapy ± radiotherapy and completed the treatment; (3) having modified radical mastectomy or breast conserving surgery (BCS); (4) having no obvious mental abnormalities, psychological disorder, and cognitive impairment.

The “exclusion criteria” were as follows: (1) recurrence of BC or metastatic disease; (2) suspicious of recurrence; (3) combination with another tumour or major morbidity, such as chronic obstructive pulmonary disease, coronary heart disease, and cerebrovascular disease; and (4) psychotherapy or medical treatment for psychological disorders before the primary diagnosis.

### Study measures

Participants completed a standardized questionnaire assessing the demographic factors and medical data, FSS, anxiety, and depression. Thus, the following measures were used:

- (1) Beck Depression Inventory (BDI). This was used to measure the severity of depression. The scale composed 21 items and a range from 0 to 63. The classification of the BDI score of depression was as follows: <10, none or minimal; 10–18, mild to moderate; 19–29, moderate to severe; and 30–63, severe.
- (2) Beck Anxiety Inventory (BAI). This was used to measure the severity of anxiety. The classification of the BAI score was as follows: <8, none; 8–15, mild; 16–25, moderate; and >25, severe.
- (3) FSS. This was determined using the Duke-University of North Carolina’s Functional Social Support (DUFSS) Questionnaire. The DUFSS

questionnaire includes eight items assessing the self-perceived affective support and the support from a confidant. It consists of five-category items to assess the social support network. A high average score would reflect a better perceived FSS. The DUFSS Questionnaire has been validated in a primary care setting and regarded as a suitable measure for studying social support of patients with cancer.

### Statistics

First, univariate analyses were performed. Two independent groups were compared with Student's *t*-tests (for normally distributed continuous variables) or Mann-Whitney *u* test (for non-normally distributed continuous variables). To compare more than two independent groups, ANOVA test was used. To determine any relationship between variables, Chi-squared tests (for categorical variables), Spearman's rank correlation (for two numerical or ordered variables), and Pearson's correlation test (for continuous variables) were used. Multiple linear regression models were used for making specific predictions. Clinically related variables were included in the model if significance at the 10% level was obtained from the univariate analysis. Multicollinearity was checked by calculating variance inflation factors. All univariate analyses were performed in SPSS for windows version 20.0. A two-sided *p* value  $\leq .05$  was accepted as statistically significant.

### Results

A total of 154 female BC survivors with stages I–III were recruited in this study. The demographic and disease characteristics of the participants are listed in Table 1. The mean age was 49.8 years (range: 28–77 years). All patients were treated with IV chemotherapy following surgery and 64% of the patients also received radiotherapy. Their educational level was low (84.4% were illiterate or primary school level). All of the patients received tamoxifen or AIs. Approximately half of the women (48.7%) were peri- or post-menopausal before disease diagnosis. An LHRH analogue was added to hormone therapy for 3–5 years or until post-menopausal gonadotropin levels were reached for pre-menopausal patients who had low gonadotropin levels after the chemotherapy.

Table 1 shows the relationship between patients' disease-related factors and mean anxiety and depression scores.

### Disease-related factors

It was found that the prevalence of the moderate and severe anxiety and depression rates were 12.3% and 12.9% after 5 years in all stages, respectively. The rates of moderate and severe anxiety were 47.9%, 41.2%, and 41.1% after follow-up durations of 6 months to 2 years, 2–5 years, and over 5 years, respectively. For the same periods, the rates of moderate and

**Table 1.** Association between the demographic/clinical characteristics of patients and Beck Anxiety and Depression scores.

Characteristics	N (%)	BAI		BDI	
		Mean score $\pm$ SD	<i>p</i> -Value	Mean score $\pm$ SD	<i>p</i> -Value
Age (years)					
18–40	26 (16.8)	18.5 $\pm$ 11.1	.050	17.6 $\pm$ 11.0	.123
41–50	66 (42.8)	13.9 $\pm$ 9.3		15.1 $\pm$ 9.5	
>50	62 (40.2)	13.0 $\pm$ 9.7		13.6 $\pm$ 10.8	
Menopausal status					
Pre-menopausal	79 (51.3)	16.0 $\pm$ 10.0	.025	16.4 $\pm$ 10.2	.066
Peri-post-menopausal	75 (48.7)	12.5 $\pm$ 9.4		13.4 $\pm$ 10.2	
Marital status					
Married	121 (78.5)	14.6 $\pm$ 10.3	.448	15.3 $\pm$ 10.5	.436
Single, divorced, or widowed	33 (21.5)	13.1 $\pm$ 7.9		13.7 $\pm$ 9.9	
Educational level					
Illiterate	43 (27.9)	12.8 $\pm$ 8.6	.053	11.8 $\pm$ 9.3	.027
Primary school (1–12)	87 (56.5)	13.9 $\pm$ 9.2		15.4 $\pm$ 10.4	
Secondary school and high school	24 (15.5)	18.6 $\pm$ 12.5		18.7 $\pm$ 9.0	
Type of surgery					
Radical surgery	146 (94)	14.6 $\pm$ 9.8	.09	14.9 $\pm$ 10.4	.109
BCS	8 (6)	17.7 $\pm$ 5.9		17.8 $\pm$ 9.4	
Radiotherapy					
Received	100 (64)	13.9 $\pm$ 9.8	.408	14.3 $\pm$ 10.1	.116
Not received	54 (36)	15.1 $\pm$ 9.7		16.1 $\pm$ 10.1	
Stage					
I	19 (12.3)	16.5 $\pm$ 8.2	.313	18.3 $\pm$ 10.4	.215
II	93 (60.3)	14.02 $\pm$ 9.3		15.0 $\pm$ 9.0	
III	42 (27.2)	14.3 $\pm$ 10.2		14.1 $\pm$ 9.1	
Follow-up period					
6 months to 2 years	48 (31.2)	15.1 $\pm$ 11.2	.726	13.4 $\pm$ 10.5	.259
2–5 years	63 (40.9)	13.6 $\pm$ 8.5		14.6 $\pm$ 10.0	
>5 years	43 (27.9)	14.5 $\pm$ 9.9		14.0 $\pm$ 9.6	
Endocrine therapy					
Tamoxifen with LHRH	37 (24.0)	17.9 $\pm$ 10.3	.019	16.7 $\pm$ 10.3	.041
Tamoxifen	39 (25.3)	15.3 $\pm$ 11.0		17.5 $\pm$ 11.3	
AIs	78 (50.6)	12.1 $\pm$ 8.3		12.8 $\pm$ 9.6	

Note: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory.

severe depression were 45.1%, 43.2%, and 41.1%, respectively. Type of surgery and added radiotherapy had no effect on anxiety and depression scores, as shown in Table 1 ( $p > .005$ ).

### Patient-related factors

Patients who were secondary and high school graduates had higher anxiety and depression scores compared to others. Pre-menopausal women had statistically higher anxiety scores compared to post-menopausal women ( $p = .025$ ), while it was not statistically significant for depression scores. Statistically significant associations were not observed between anxiety and depression and marital status (Table 1).

Anxiety and depression were negatively correlated with perceived social support ( $r = -.323$ ,  $p < .01$ ;  $r = -.306$ ,  $p < .01$ , respectively). This means that having greater perceived social support was related to lower anxiety and depression scores. The age of patients was related to depression scores ( $r = -.159$ ,  $p = .048$ ) and anxiety scores with statistical significance ( $r = -.168$ ,  $p = .037$ ). Young age was related to higher anxiety and depression scores. When social support and age were evaluated with multiple linear regression analysis, it was shown that these parameters had a more powerful effect on anxiety and depression scores, as shown in Table 2.

Patients were divided into three groups for the evaluation of endocrine therapy: tamoxifen with LHRH analogue, only tamoxifen, and only AIs groups. The mean age of the three groups was 39.5, 50.5, and 54.4 years ( $p < .001$ ), respectively. The mean anxiety and depression scores are indicated in Table 1. When age and endocrine therapy were evaluated with a multiple linear regression analysis, significant results were lost for anxiety and depression scores ( $p = .818$ ,  $p = .206$ ). When we compared tamoxifen with LHRH analogue and the other groups, we obtained statistically significant results on anxiety scores, but not on depression scores ( $p = .011$ ,  $p = .239$ ). When we compared only tamoxifen and AIs groups, higher depression scores were observed with only tamoxifen group ( $p = .019$ ). When age and endocrine therapy (tamoxifen vs. AIs) were evaluated with a multiple linear regression analysis, the  $p$  value was .034.

**Table 2.** Multiple linear regression analyses (including FSS and age) for Beck Anxiety and Depression scores.

Dependent variables	Independent variables	Unstandardized coefficients		
		<i>B</i>	Std. error	<i>p</i> -Value
BAI score	Constant	36.702	4.897	<.001
	FSS	-2.911	0.659	<.001
	Age	-0.205	0.077	.009
BDI score	Constant	36.168	5.257	<.001
	FSS	-2.917	0.708	<.001
	Age	-0.182	0.083	.030

Note: FSS: functional social support; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory.

### Discussion

A large proportion of BC patients have been treated with adjuvant anti-oestrogenic hormonal therapy for years after the completion of chemotherapy and/or radiotherapy and this might affect the psychological conditions of these patients. Several studies have evaluated the effect of patient- and disease-related factors on distress until now [4,7–9]. In our study, while we assess the effect of different endocrine therapies on anxiety and depression scores, we also included the assessment of the patient- and disease-related factors in this study. And we observed that patient-related factors are more significant determinants than disease-related factors of distress. Although patients experienced more distress in the disease diagnosis and treatment period, it was not different statistically among follow-up periods, such as 6 months to 2 years, 2–5 years, and after 5 years, in our study. As in other studies, anxiety and depression scores did not vary according to the follow-up period, disease stage, and treatment modalities such as radiotherapy and surgery [4,9,13].

Patient-related factors such as age, menopausal status at diagnosis, educational level, marital status, and rate of social support were assessed in our study. In line with Gómez-Campelo et al., we found that higher educational level was associated with more psychological distress [14]. There are contradictory consequences for this issue, because different outcomes may emerge depending on the sociocultural property of the community [15]. Our findings suggest that patients with higher education levels may have greater awareness of the disease and this may lead to stressful conditions; on the other hand, patients with lower education levels may be more easily convinced by their physicians. Distress of married women was similar to that of unmarried women in our study. Although married women may have advantages in terms of transportation, and social and financial support as found in some studies [13], this did not reflect the FSS scores of the patients participating in our study. Consistent with many studies, we showed the powerful association of anxiety and depression scores and social support [16,17]. This means that having greater perceived social support was related to lower anxiety and depression scores. And also young age was related to higher anxiety and depression scores. When social support and age were evaluated with a multiple linear regression analysis, it was found that these parameters had a more powerful effect on anxiety and depression scores.

Oestradiol is a potent neuroactive steroid that acts on both nuclear and membrane ER which is commonly found in the different brain regions. We know that oestrogen has a neuroprotective effect on the brain and cognitive functions [18,19]. Previous animal studies indicated that oestradiol acts by altering the expression

of genes that suppress apoptotic cell death pathways, enhances the survival of cells, protects against ischaemic damage, and has anti-inflammatory actions on brain cells [20,21]. More studies demonstrated that oestradiol affects not only learning and memory, but also anxiety and depressive symptoms [22]. In this regard, we found that pre-menopausal patients whose oestradiol levels were suddenly changed with an LHRH analogue had more anxiety scores than post-menopausal patients who had used tamoxifen or AIs.

AIs interfere with the production of oestrogen from androgens by the aromatase enzyme which highly exists in oestrogen-sensitive tissues, such as the breast, uterus, vagina, bone, brain, heart, and blood vessels. Common adverse events of AIs are hot flushes, vaginal dryness, loss of libido, fatigue, arthralgias, joint stiffness, and loss of bone mineral density, which are related to its direct effect on oestrogen production [23,24]. Tamoxifen has anti-oestrogenic effects on BC cells by blocking ER, and also exhibits oestrogenic activities on other tissues, for example bone and endometrium, which causes more gynaecological problems, vasomotor symptoms, leg cramps, and bladder control problems compared to AIs. On the other hand, it is not known whether tamoxifen has oestrogenic or anti-oestrogenic effects on brain tissues. There are evidences of detrimental effects on memory [25]. Nevertheless, a study showed that there were lower concentrations of myo-inositol, a brain marker that is associated with brain damage, in both tamoxifen and oestrogen users than in controls, suggesting that tamoxifen and oestrogen have possibly protective effects on brain functioning [26]. Despite different mechanisms of tamoxifen and AIs, previous studies showed that both have detrimental effects on cognitive function in post-menopausal BC survivors [27–29], and a difference was not observed between the effects of tamoxifen and AIs on the level of cognitive function [30,31].

A phase III randomized trial comparing tamoxifen and AIs one year after the completion of chemotherapy in post-menopausal patients who had already experienced a progressive hypo-oestrogenic condition showed that anxiety and depression scores were not significantly different between the two arms [32]. The median age of the patients in that study was 62 years for the tamoxifen arm and 61 years for the AIs arm, and all patients were post-menopausal. Studies performed by Takei H. et al. and Ohsumi S et al. also evaluated depression scores in post-menopausal patients whose mean age was also about 60–63 years in a longer follow-up term. According to these studies, the tamoxifen and AIs arms did not differ in the depression scores for a long follow-up period too [33,34]. In our study, we found that patients who received only tamoxifen had more depression scores compared with AIs users. Since age is a known significant determinant of

anxiety and depression scores, including patients with younger age and also pre-menopausal status in the tamoxifen group in our study, different from the other studies, may lead to different results. At the same time, depression has also been reported to be associated with a lack of oestrogen or failure of oestrogen to bind to its receptors [35,36]. Therefore, exposure to more decreasing levels of oestrogen in younger age populations may lead to their higher depression scores. However, this result showed that the partial oestrogenic effect of tamoxifen did not protect against depression in BC survivors.

In our study, we found more anxiety scores in patients treated with the LHRH analogue. As pre-menopausal patients receiving tamoxifen and LHRH agonists initially have a hyper-oestrogenic environment due to younger age, sudden decreased levels of oestrogen may account for more anxiety scoring compared to that in tamoxifen and AIs patients. In addition, in assessing all included groups, pre-menopausal onset is a risk factor for more anxiety points in the direction of these findings. Since patients taking AIs already had a progressively developing hypo-oestrogenic environment, they presented the lowest anxiety and depression scores. Unlike other studies, we separately evaluated the anxiety and depression scores and also included pre-menopausal and younger patients in our study. This assessment has informed us that we should be more careful of anxiety in any treatment period in BC patients in whom LHRH analogues will be administered.

The major limitation of this study was that it was not designed as a cohort. BAI and BDI scores prior to cancer diagnosis and after hormone therapy should be assessed for more reliable results; although we designed as cross-sectional study, we observed that the anxiety scores of patients using LHRH analogues were significantly higher. Another limitation of the study is that the number of women in the group using LHRH analogues was low, that is, 26 patients. On the other hand, despite the low number of patients, there was a statistically significant difference in the BAI scores in the group receiving LHRH analogues, and this result may be the basis for future studies.

## Conclusion

Patient-related factors are more significant determinants of distress than disease-related factors including follow-up period, stage, and treatment modalities. Younger age and lower social support, which are patient-related factors, are important determinants of higher anxiety and depression scores. The type of endocrine therapy also has an effect on distress, and the use of LHRH analogues is one of the risk factors for the development of high BAI scores in BC survivors.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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