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Original research paper

Beliefs about medicines' association with endocrine therapy adherence in early breast cancer survivors in Croatia

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ABSTRACT

This observational, cross-sectional study conducted at the University Hospital Centre Zagreb (UHC Zagreb) aimed to explore patients' beliefs about adjuvant endocrine therapy (AET) as well as their association with non-adherence and sociodemographic and clinical factors. Out of 420 early breast cancer (BC) patients included in the study, 79.5 % perceived AET necessary and important for their health, as measured by the Belief About Medicines Questionnaire (BMQ), with the mean necessity score (20.4 ± 3.68) significantly higher than the mean concerns score (13 ± 4.81) ($p < 0.001$). Based on the Medication Adherence Report Scale (MARS-5), 44.4 % ($n = 182$) of the participants were non-adherers, out of which 63.2 % ($n = 115$) were unintentional and 36.8 % ($n = 67$) intentional non-adherers. Significantly higher concern beliefs were found among patients that were younger ($p < 0.001$), employed ($p < 0.001$), intentionally non-adherent to AET ($p = 0.006$), had a lower body-mass index ($p = 0.005$) and a higher level of education ($p < 0.001$), were premenopausal at the time of diagnosis ($p < 0.001$), taking tamoxifen treatment ($p = 0.05$) and receiving ovarian suppression ($p < 0.001$). Younger patients should be recognized as being at risk of non-adherence as they hold greater concern beliefs about medicines.

Keywords: breast cancer, adjuvant endocrine therapy, beliefs about medicines, medication adherence, sociodemographic factors, clinical factors, hormone-positive breast cancer survivors

INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed type of cancer and the leading cause of cancer mortality among women worldwide (1). In Europe, BC accounts for 28.7 % of all new cancers diagnosed in women, with Croatia being slightly below the European Union average in both, incidence and mortality (2). The steady increase in the availability

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and the use of oral anticancer drugs has led to a paradigm shift in treatment approach raising issues such as prolonged treatment period, treatment adherence, management of side effects, reimbursement conditions, and patient and family education (3). Adjuvant endocrine therapy (AET), recommended for early-stage hormone receptor-positive (HR+) breast cancer (BC) patients, significantly reduces the risk of disease recurrence and death (4, 5) and is recommended for 5 to 10 years following the initial treatment (4, 6). Nevertheless, literature reports suboptimal adherence and persistence to AET (7–12), thus consequently lowering its beneficial and protective effects. According to the published literature, adherence to AET ranges between 40–95 % (12–19) depending on the definition of adherence and the method used to measure it. Moreover, adherence rates on average decrease by 25.5 % between the first and the fifth year of treatment (19), with treatment discontinuation ranging from 31–73 %, measured at the end of the 5-year treatment period (13, 14, 18–20).

Due to the seriousness of malignant conditions with their potentially life-threatening outcomes, it has been mistakenly assumed that cancer patients are inherently highly motivated to comply with their treatment regimens (21). Although non-adherence to treatment is a complex phenomenon, evidence shows that adherence to AET is influenced by various factors including patient-provider relationships (22), adverse drug events (19, 23–26), comorbidity burden (27), attitude toward AET, and certain cultural and sociodemographic factors such as age, employment, education and cultural background (23, 25, 27–29).

Even more, studies have shown that patients' beliefs about medicines tend to be more powerful predictors of adherence than clinical and sociodemographic factors (22, 30–33). Namely, the conceptual model developed by Horne and Weinman groups beliefs about the prescribed medicines into two categories: a) perceptions of the necessity of treatment and b) concerns about the potential adverse effects (31, 33). The "Necessity-Concerns Framework" has been proven to be adequate for addressing key beliefs driving patients' attitudes and decisions about the AET (24, 28, 29, 32), and a recent meta-analysis suggests that necessity and concern beliefs about medicines are one important factor to consider when understanding reasons for non-adherence (30).

Prior studies identified sociodemographic and clinical factors linked to women's beliefs regarding the necessity and concerns associated with AET, however, to the best of our knowledge, there have been no previous studies that have specifically investigated these factors in relation to intentional and unintentional non-adherence to AET.

Thus, to improve adherence and persistence to AET, it is of paramount importance to focus on patients' beliefs about their endocrine therapy, as the latter represents a powerful modifiable factor influencing adherence (34).

The study aimed to explore patients' beliefs about their AET and investigate its association with both intentional and unintentional non-adherence, as well as sociodemographic and clinical factors.

EXPERIMENTAL

Design

This observational, cross-sectional study was conducted at the University Hospital Centre (UHC) Zagreb from September 2019 until January 2023. The study is a part of a larger multi-center observational, cross-sectional research and it represents a secondary subset analysis of trial data evaluating the level of adherence to AET in HR+ early BC patients in Croatia as a primary outcome measure (unpublished to date).

Patient recruitment

A total of 421 women diagnosed with early BC, prescribed AET for at least three months and over the age of 18 were eligible for inclusion in the study. Participants suffering from mental or behavioural disorders, having metastatic BC, and those with impaired decision-making capacity at the time of the recruitment were considered ineligible. Patients were invited to participate in the study at the routine follow-up appointments conducted at the Department of Oncology, UHC Zagreb where they were handed a self-administered survey after signing informed consent.

University Hospital Centre Zagreb is the largest health institution in the Republic of Croatia, and is the base for 70 referral centres of the Republic of Croatia Ministry of Health. The study was approved by the UHC Zagreb Ethical Committee and Ethics Committee of the University of Zagreb Faculty of Pharmacy and Biochemistry. This study conformed to the principles outlined in the Declaration of Helsinki and Tokyo.

Data collection

Each consenting patient completed a written anonymous questionnaire thus providing self-reported information regarding sociodemographic characteristics, anthropometric data, current and previous medical conditions and medication history. Additionally, data on patients' personal views about medicines and adherence were collected through two validated questionnaires: the Beliefs About Medicines Questionnaire (BMQ) and the Medication Adherence Report Scale (MARS-5). When needed, the study researcher assisted the patients in administering the survey via face-to-face interview. The final questionnaire took approximately 25 minutes to complete.

The BMQ was employed to assess patients' personal beliefs about medicines (31, 33), both beliefs about medicines prescribed specifically to them (BMQ-Specific) and beliefs about medicines in general (BMQ-General). The BMQ-Specific consists of two subscales, *necessity* and *concern*, where the former explores the beliefs about the necessity of taking a specific medication (in this case AET) and the latter explores concerns about the negative influence of medication. The BMQ-General comprises three subscales (*harm, overuse* and *benefit*) with four questions each. *Harm* addresses the perceived harmful nature of medicines in general, *overuse* perceived notion that doctors overuse or put too much trust in medicines, while *benefit* examines the perceived potential benefits of medicines in general.

For this study, the wording of the items in the BMQ-Specific section was adopted from the study that evaluated BMQ-AET psychometric properties in order to be more specific to women taking AET following breast cancer diagnosis (28, 29). The responses were recorded on a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = uncertain, 4 = agree, 5 = strongly agree) where higher scores imply stronger beliefs in the concepts represented by the subscales. Total scores per BMQ scale were calculated in a manner that *necessity* and *concerns* subscales range from 5 to 25, while *harm, benefit,* and *overuse* subscales range from 4 to 20. The two sections of the BMQ can be used in combination or separately.

Self-rated non-adherence to AET was assessed using the 5-item version of the MARS-5 questionnaire (35). The measure includes five statements about non-adherent behaviour (*I forget to take my medicine, I alter the dose of my medicine, I stop taking my medicine for a while, I decide to miss out a dose, I take less than instructed*), both intentional and unintentional, and is scored on a 5-point Likert scale where 1 represents always and 5 represents never. Since the scale was positively skewed towards higher adherence, it was dichotomised into adherers (total score of 25) and non-adherers (total score of 24 or below), as recommended by previous researchers (16, 36, 37). Non-adherers were further divided into intentional (total MARS-5 score < 25, score ≤ 5 on item 1, and score < 5 on items 2–5) and unintentional non-adherers (total MARS-5 score < 25, score < 5 on item 1; *"I forget to take my medicine (AET)"*, score $= 5$ on items 2–5).

Both BMQ and MARS-5 questionnaires were translated into Croatian language with back-translation approved by the author of the original questionnaires.

Statistical analysis

The primary hypothesis of the study posited that individuals with early BC generally hold favourable beliefs about medicines. This implies that they perceive the AET as necessary and medicines beneficial, outweighing any concerns or potential harm associated with their use. Furthermore, it is also hypothesized that patients do not find that medicines are overused.

Data analysis was performed with the program STATISTICA 6.1 StatSoft inc., Tulsa, Oklahoma, USA. The relationship between BMQ subscales scores; *necessity, concern, harm, overuse*, and *benefit* (dependent variables) and continuous variables such as age, BMI, time from diagnosis, and length of endocrine treatment (independent variables) was explored by multiple linear regression analyses (MLRA). Furthermore, the association between non-adherence (dependent variable) and numerical factors such as BMQ summary scores, age, BMI, time from diagnosis, and length of endocrine treatment (independent variables) were explored by multiple logistic regression analysis (MLGRA). The Spearman correlation coefficient was utilized to assess the association between the BMQ subscale score and continuous variables. To compare the differences between adherers and non-adherers, and intentional and unintentional non-adherers, as well as between all three groups, independent *t*-test analysis and ANOVA were employed, respectively. Statistical testing was performed at a significance level of 95 % ($\alpha = 0.05$).

The sample size was calculated based on the estimated proportion of women expected to be adherent to AET (38). In accordance with the results from the studies on adherence to AET conducted in the United States and Europe (10, 12, 14, 17, 36, 38) we assumed that that 80 % of women who have suffered from HR+ early BC in Croatia adhere to the prescribed AET (38).

RESULTS AND DISCUSSION

Response rate

Overall, 420 women with HR+ BC participated in the study. The questionnaire was handed in to 421 women out of which only one woman refused to participate. Out of these

Table I. Sociodemographic and clinical data of all participating patients

	Total number of patients (n = 420)
Age	
Range (years)	21 – 95
Median (years)	55
≤ 50 (%)	166 (40)
51–64 (%)	133 (31)
≥ 65 (%)	121 (29)
BMI	
Range	17–40
Median	25
Marital status	
Married (%)	303 (72)
Divorced (%)	36 (9)
Widowed (%)	51 (12)
Single (%)	26 (6)
Employment status	
Employed (%)	205 (49)
Unemployed (%)	34 (8)
Retired (%)	154 (37)
Sick leave/unable to work (%)	27 (6)
Education	
Primary school (%)	27 (6)
Secondary school (%)	195 (47)
Higher education (college degree) (%)	197 (47)
Menopause (at the time of the diagnosis)	
Yes (%)	177 (43)
No (%)	231 (57)
AET therapy	
Tamoxifen (%)	164 (41)
AI (%)	242 (59)
Letrozole (%)	122 (29)
Anastrozole (%)	97 (24)
Exemestane (%)	23 (6)
Length of endocrine therapy	
Range	6 months – 21 years
Median	2 years
Comorbidities and comedication	
GnRH agonist (%)	107 (26)
Oophorectomy (%)	30 (7)
Comorbidities (one or more)(%)	235 (56)
Comedication (Rx medicine)(%)	282 (67)
Surgery type	
Lumpectomy (%)	192 (46)
Mastectomy (%)	221 (53)
No surgery (%)	2 (1)
Chemotherapy	
Yes (%)	252 (60)
No (%)	168 (40)
Radiation therapy	
Yes (%)	290 (69)
No (%)	130 (31)

AET – adjuvant endocrine therapy; AI – aromatase inhibitor; BMI – body mass index; GnRH – gonadotropin-releasing hormone; Rx – medical prescription; SD – standard deviation

420 participating women, 410 women answered all the survey questions pertaining to MARS-5, and 414 women fully completed BMQ survey questions, rendering the response rates of 97 % and 98 %, respectively. The demographical and clinical characteristics of the study sample are summarised in Table I.

Internal consistency

The internal consistency of the item scales was evaluated using Cronbach's alpha (α). The BMQ subscales; *necessity*, *concern,* and *overuse* demonstrated acceptable internal consistency with Cronbach's alpha values of 0.83, 0.77, and 0.71, respectively. Cronbach's alpha values for the general BMQ subscales *harm* and *benefit* were slightly lower, measuring 0.69

and 0.65, respectively. Overall, these values align with those commonly reported in previous research studies (28, 31).

In this sample, Cronbach's alpha for MARS-5 was 0.52 and thus below the generally accepted threshold of 0.7. Potential reasons for this finding could be attributed to the brevity of the scale, consisting of only 4 to 5 items, and deviation from a normal distribution (40). However, a decrease in Cronbach's alpha due to these factors does not necessarily indicate a lack of reliability in the scale, as previously reported in the literature (16).

Beliefs about medicines scores

The majority of the study participants (79.5 %) had the *necessity* score greater than the scale midpoint, agreeing or strongly agreeing with necessity statements, thus implying

Table II. The BMQ necessity and concerns item mean scores and summary scores compared between adherers and non-adherers

	All patients agreeing/ strongly agreeing (%)	Adherers ($n = 228$) M (SD)	Non-adherers ($n = 182$) M (SD)	p-value (adherers *vs*. non-adherers)
BMQ concern				
Having to take hormone treatment worries me. (C1)	29.3	2.34 (1.35)	2.50 (1.26)	0.223
I sometimes worry about the long-term effects of taking hormone treatment. (C2)	47.4	2.85 (1.46)	3.24 (1.27)	0.006*
Endocrine treatment is a mystery to me. (C3)	25.9	2.63 (1.28)	2.56 (1.17)	0.539
Taking endocrine treatment disrupts my life. (C4)	20.6	2.01(1.23)	2.37 (1.23)	0.004*
I sometimes worry about having hormone treatment over a long period. (C5)	42.7	2.66 (1.49)	3.17 (1.26)	0.000*
Concern summary score	33.2	12.33 (5.02)	13.74 (4.37)	0.003*
BMQ necessity				
My health at present depends on my taking endocrine treatment. (N1)	78.2	4.13 (0.81)	3.94 (0.93)	0.029*
Taking endocrine treatment makes me feel I am taking positive steps to remain well. (N2)	91.5	4.52 (0.65)	4.30 (0.77)	0.002*
Without taking endocrine treatment, I would be more likely to develop breast cancer again. (N3)	82.0	4.23 (0.93)	4.16 (0.87)	0.433
My health in the future will depend on my taking endocrine treatment. (N4)	67.8	3.99 (1.01)	3.73 (0.99)	0.010*
Endocrine treatment protects me from becoming ill. (N5)	77.8	4.09 (0.97)	3.98 (0.83)	0.206
Necessity summary score	79.5	20.84 (3.55)	19.95 (3.59)	0.013*

Agree/strongly agree: The percentage of patients who responded with "agree" or "strongly agree" on the BMQ item. The percentage of patients indicating agreement or strong agreement (on a Likert scale) with items in the concern or necessity subscales was computed as the mean of the percentages from all individual items within the respective subscales; M – mean item score; SD – standard deviation; *t-test, $p < 0.05$.

they perceived the medication as necessary and important for their health (Table II). Adjuvant endocrine therapy was deemed important for both current and future health as over 60 % of the patients had item scores over the scale midpoint (Table II, items N1 and N4). Nevertheless, about 33 % of women had *concern* scores above the scale midpoint suggesting worries about their AET (Table II). The mean *necessity* score (20.4 ± 3.68) was significantly higher than the mean *concern* score (13 ± 4.81) with the mean *necessity-concern* differential of 7.45 ± 6.63 (*t*-test, $p < 0.001$), indicating a significant difference between the perceived necessity and concerns regarding AET. Around 50 % of the patients were concerned about potential long-term adverse effects of their AET, and approximately 40 % about taking AET over a long period (Table II, items C2 and C5). There was much less concern about the endocrine treatment disrupting their life and worrying over having to take the treatment (Table II, items C1 and C4).

In the BMQ-General scale, 83 % of patients had *benefit* scores greater than the scale midpoint again suggesting positive views about medicines in general. Furthermore, around 14 % of patients scored over the scale midpoint in the *overuse* subscale and 18 % in the *harm* subscale, implying that a minor subset of patients has concerns related to the overuse of medications and the potential harms associated with them. On average, participants displayed high beliefs regarding the benefits of medicines, as indicated by a mean score of 16.3 ± 2.5 on the *benefit* subscale. Their beliefs regarding the *harm* and *overuse* of medicines were somewhat moderate, as evidenced by mean scores of 9.3 ± 3 and 10.2 ± 3.1, respectively, on the corresponding subscales.

Beliefs about medicines and their association with adherence

Based on the MARS-5 scores, 44.4 % ($n = 182$) of the participants were non-adherers (not taking all indicated doses), out of which 63.2 % ($n = 115$) were unintentional and 36.8 % ($n = 67$) intentional non-adherers (Table III). In addition, women that were both intentional and unintentional non-adherers were categorised as intentional non-adherers.

Compared to adherent patients, non-adherent patients had significantly higher *concerns* and significantly lower *necessity* summary scores (Tables II and IV). Furthermore, significant differences were found between adherers and intentional non-adherers in both *concerns* (Fisher LSD test post-hoc to ANOVA, *p*-value = 0.006) and *necessity* summary

Table III. MARS-5 results

MARS-5 ($n = 410$)	Median = 25 Interquartile range 24–25 Range 15–25 Cronbach's alpha = 0.52	

Adherence category	MARS-5 score	*n*
Adherers	= 25	228
Intentional nonadherers	< 25, score ≤ 5 on item 1, and score < 5 on items 2–5	67
Unintentional nonadherers	< 25, score < 5 on item 1, score = 5 on items 2–5	115

n – number of patients

Table IV. The BMQ subscales summary scores for adherers and non-adherers

BMQ subscale	Adherers ($n = 228$) M (SD)	Non-adherers ($n = 182$) M (SD)	Intentional non-adherers ($n = 67$) M (SD)	Unintentional non-adherers ($n = 115$) M (SD)	p-value* adherers *vs.* non-adherers	p-value** adherers *vs.* intentional non-adherers	p-value** adherers *vs.* unintentional non-adherers
Concerns	12.33 (5.02)	13.74 (4.37)	14.37 (4.29)	13.36 (4,39)	0.003*	0.006**	0.055
Necessity	20.84 (3.55)	19.95 (3.59)	19.2 (3.79)	20.4 (3.41)	0.013*	0.005**	0.142
Benefit	16.47 (2.53)	16.07 (2.44)	15.70 (2.53)	16.39 (2.21)	0.102	0.074	0.419
Harm	9.18 (3.32)	9.31 (2.57)	10 (2.38)	8.9 (2.62)	0.656	0.190	0.607
Overuse	10.03 (3.20)	10.29 (3.04)	10.78 (3.08)	10.06 (2.97)	0.40	0.019**	0.491

* t-test, $p < 0.05$; **Fisher LSD test post-hoc to ANOVA , $p < 0.05$; M – mean summary score; SD – standard deviation

scores (Fisher LSD test post-hoc to ANOVA, p-value = 0.005) with higher *concerns* and lower *necessity* scores exhibited among intentional non-adherers (Table IV). Conversely, no significant differences were found in *concern* or *necessity* scores between adherers and unintentional non-adherers. In addition, intentional non-adherers, as opposed to unintentional non-adherers, exhibited lower scores in beliefs regarding the *necessity* of taking AET medication (t-test, $p = 0.04$).

In the General BMQ subscales (*harm, benefit,* and *overuse*), no significant differences between adherers and non-adherers were found in the mean summary scores (Table IV). However, intentional non-adherers had higher *overuse* summary score (Fisher LSD test post-hoc to ANOVA, p-value = 0.019) when compared to adherers. Additionally, intentional non-adherers exhibited a higher *harm* summary score (t-test, $p = 0.009$) when compared to unintentional non-adherers.

Beliefs about medicines and their association with demographical factors

Our study results revealed a significant association between the BMQ *concerns* subscale and age, as determined by a multiple linear regression analysis (MLRA) ($p < 0.001$). Additionally, a negative correlation ($r = –0.216$, $p < 0.001$) indicating an inverse relationship between age and concerns related to AET, was observed (Table V). Namely, younger patients (< 50 years) tended to have significantly greater *concerns* about their AET than their older counterparts (≥ 65 years) (Fisher LSD test post-hoc to ANOVA, $p < 0.001$). Although the BMQ *necessity* subscale did not show any significant correlation with age, a trend towards older women (≥ 65 years) scoring higher on the subscale was observed. Moreover, a significant association between the BMI and the *necessity* subscale (MLRA, $p = 0.001$) was found. Notably, a positive correlation was detected between the BMI and the *necessity* subscale, while the *concerns* and the *overuse* subscales correlated negatively with the BMI (Table V), implying that individuals with higher BMI tend to hold stronger beliefs regarding the necessity of their medication while at the same time have lower levels of concerns about medication or its potential overuse.

Table V. The correlation between BMQ subscales and age and BMI

BMQ subscale	Age	BMI
	r (p-value)	
necessity	0.016 (p = 0.759)	**0.191 (p = 0.000)***
concerns	**−0.215 (p = 0.000)***	**−0.151 (p = 0.005)***
benefit	0.018 (p = 0.736)	0.038 (p = 0.469)
harm	0.032 (p = 0.551)	0.001 (p = 0.993)
overuse	−0.028 (p = 0.603)	**−0.106 (p = 0.046)***

r – correlation coefficient; * $p < 0.05$

The length of the endocrine treatment was found to be associated with the *overuse* subscale (MLRA, p = 0.015), however without correlation with any of the BMQ subscale summary scores. Marital status did not emerge as a significant factor for any of the BMQ subscales, except for the *harm* subscale. In this particular subscale, women without a partner (single, divorced, or widowed) exhibited higher mean scores compared to those in a relationship (t-test, p = 0.05). Women in menopause at the time of the diagnosis were less concerned than premenopausal women (t-test, $p < 0.001$). All of these findings align with the negative correlation observed between the age and the *concerns* subscale, suggesting that with older age, concerns regarding the AET use tend to decrease. Women prescribed tamoxifen exhibited a significantly higher *concerns* score than those prescribed an aromatase inhibitor (t-test, p = 0.05), and women receiving ovarian suppression treatment with gonadotropin-releasing hormone analogues (GnRH) had higher *concerns* score than women with oophorectomy or not receiving GnRH (ANOVA, $p < 0.001$). Furthermore, women without comorbidities and comedication scored higher on the *concerns* subscale compared to women with comorbidities (t-test, p = 0.007) and comedication (t-test, p = 0.0156), all of which could again be attributed to age as a factor.

Education was found to be significantly associated with three BMQ subscales: *necessity, concerns*, and *harm* (ANOVA, p = 0.023, $p < 0.001$, and p = 0.004, respectively). Participants with a higher level of education (college degree or above) had lower scores on the *necessity* (ANOVA, p = 0.014) and *harm* (ANOVA, p = 0.012) subscales, while scoring higher on the *concern* subscale (ANOVA, $p < 0.001$) compared to those with secondary education. Retired women scored lower on the *concern* subscale compared to employed (ANOVA, $p < 0.001$) or unemployed (ANOVA, p = 0.049) participants.

Other sociodemographic and clinical factors such as lymph node involvement, use of food supplements, and surgery type were not significantly associated with any of the BMQ subscales.

To the best of our knowledge, this is the first study conducted among the early HR+ BC patients in both Croatia and South-Eastern Europe that assessed medication beliefs and adherence to AET. Moreover, it is one of the first studies that looked into differences in women's beliefs about AET in relation to their adherence as well as sociodemographic and clinical characteristics. Namely, intentional non-adherence to AET among younger, employed women with a lower BMI and a higher level of education, premenopausal at the time of diagnosis thus taking tamoxifen and receiving ovarian suppression treatment, was associated with a higher *concern* level. Previous research identified both sociodemographic and clinical characteristics associated with women's *necessity* and *concern* beliefs about AET, as well as healthcare factors, such as patient-provider communication, healthcare satisfaction, and trust in healthcare providers (41, 42). Nevertheless, this study was the first one to have characterized intentional and unintentional non-adherers with regard to their beliefs about medicines and AET. Similar to the existing evidence base (29, 43–46), high *necessity* beliefs found in our patient sample were associated with better adherence, whereas greater *concern* beliefs have been linked to lower adherence. However, unlike in previous studies (29), intentional as opposed to unintentional non-adherers exhibited higher *harm* beliefs regarding medicines in general and lower *necessity* beliefs regarding their AET. Given that medication beliefs have been widely acknowledged as a modifiable factor associated with medication adherence (29, 34), the former represents a promising target for interventions aimed at adherence improvement. Additionally, gaining a comprehensive understanding of the types of patients pertaining to one of the two non-adherence subgroups (intentional or unintentional) is vital for it serves as a crucial step in tailoring specific interventions that could effectively support adherence behaviours.

Compared to similar studies (39, 41, 42, 47), the *necessity-concern* differential was quite high in our study, suggesting a rather high perceived necessity for the treatment, outweighing the concerns about the therapy (37).

In our cohort, older women reported having fewer medication *concerns* which are often associated with increased adherence. Similarly, although insignificant, in a study conducted by Salgado *et al.* in postmenopausal women, participants older than 70 years of age reported having fewer medication concerns (41). On the other hand, in a study among pre- and postmenopausal women, age was not a predictor of women's *concern* score (42). Nevertheless, results from the analysis conducted by Wenzel *et al*. suggest that women below the age of 50 experience more pronounced disruptions in the quality of life (QoL) compared to their older counterparts diagnosed with breast carcinoma (> 50 years), and should thus be candidates for targeted interventions (48).

Our study findings could partially be interpreted by the fact that AET is an oestrogen-depleting treatment with more pronounced adverse effects in premenopausal as opposed to postmenopausal patients, rendering this age group more concerned (23, 49). Namely, in premenopausal BC survivors, the use of AET can cause even more prominent side effects due to the abrupt suppression of oestrogen associated with the most intense endocrine therapies, having major consequences in terms of treatment adherence and patients' QoL (23). Moreover, another proposed explanation concerns age differences in terms of competing demands and future expectations with respect to the QoL (48). As noted by Wenzel *et al.*, "*because a disease such as cancer is non-normative for younger people, this becomes an unexpected psychologic and physical shock*" (48). By inducing temporary or permanent ovarian suppression, AET has a significant impact on fertility which can be emotionally challenging for women who have not yet completed their family planning (50, 51). The combination of adverse effects, fertility concerns, and emotional effects significantly impacts their QoL (52) as well as their ability to work, engage in social activities, and maintain relationships. Older women (≥ 65 years), on the other hand, had significantly lower *concern* scores which can be attributed to the fact that older patients may have a higher burden of comorbidities and other health concerns, thus shifting their focus from the potential side effects of AET. Moreover, they may be more accustomed to managing multiple medications and dealing with treatment-related issues, making them less concerned about the specific AET side effects, which also tend to be less severe in postmenopausal women.

As previously noted, although our findings revealed that *concerns* scores were associated with factors such as higher level of education, employment, lower BMI, premenopausal status at the time of diagnosis, being prescribed tamoxifen and GnRH, and having no other comorbidities and comedication, it is important to consider age as a moderator in this context as age correlates with all of the abovementioned factors. Namely, older patients often have a higher BMI or are typically prescribed aromatase inhibitors (as opposed to tamoxifen and GnRH prescribed to premenopausal women). Therefore, although age may directly influence their *concerns* beliefs, it can also indirectly influence it through its association with the identified mediating factors. Understanding the relationship between age, these mediating factors, and concerns about medication could provide insights into specific areas where intervention or support may be beneficial.

Somewhat conversely expected, but in line with previously published results (42), a lower degree of education was associated with a higher *necessity* score. Interestingly, Salgado *et al.* (41) did not find any association between education and *necessity* score in postmenopausal women taking AIs. Additionally, in our patient sample higher education level was also associated with higher *harm* scores, a finding that can be partially explained by literature reports notifying the association between higher education and non-adherence to AET (29). It can be hypothesised that women with a lower level of education are possibly inclined to follow their healthcare providers' advice without much scepticism, whereas more educated women are prone to questioning assertions made by their physicians.

In accordance with heretofore literature (16, 29, 37, 53), a significant proportion of study participants (44.4 %) did not adhere to their prescribed medication regimen among which approximately two-thirds were pertaining to unintentional and one-third to intentional non-adherers. Moreover, our study revealed that non-adherers, specifically intentional non-adherers, had lower beliefs in the necessity of AET and exhibited higher levels of concern towards it, a finding corroborated by previous research (28, 29, 32). However, no difference in *necessity* nor *concerns* scores was found between unintentional non-adherers and adherent patients, similar to those formerly reported (29). To the best of our understanding, this until now unpublished finding, holds significance as it provides insights into differences in non-adherent behaviours, specifically highlighting that intentional non-adherence is associated with perceived harm and concern. Therefore, this information suggests that modifying these beliefs could potentially have a positive impact on supporting medication adherence.

Until now, interventions aiming at increasing adherence to AET did not show relevant improvement in patients' behaviour (54–59). Nevertheless, they were not created to explicitly modify factors associated with non-adherence but were rather focused on education alone. Tailoring interventions based on the type of non-adherence and taking into account the age-related differences in beliefs, received social support and adverse effects management, may enhance adherence rates across different age groups. Further research and analysis are needed to determine the precise nature of these relationships.

Several limitations this study has should be acknowledged. Firstly, design employed is cross-sectional, meaning that causal relationships between associated factors could not be established. Hence, further investigations should use a pre- and post-interventional design examining the causal nature of the identified associations, aiming to pinpoint areas of intervention that could effectively enhance adherence.

Additionally, adherence and beliefs about medicines were assessed through self--reporting measures which tend to introduce biases such as recall or social desirability bias, meaning that respondents struggle to accurately recall their behaviours, or they provide socially acceptable answers instead of their true behaviours or beliefs. Literature reports that self-reporting tends to overestimate adherence (60, 61). Moreover, response bias should also be taken into consideration since participants may exhibit a tendency to answer questions in a particular manner, such as selecting the middle option or providing extreme responses. To address biases associated with self-reporting and improve the overall quality of the collected data, several strategies were implemented; patients were provided with clear instructions on how to fill in the survey or, when needed, the survey was administered in the form of a face-to-face interview aimed at enhancing the accuracy of their responses. Furthermore, patients were informed that the collected data would remain anonymous and confidential, particularly with respect to their healthcare providers, so as to reduce social desirability bias. Additionally, validated scales were utilized to ensure the reliability and accuracy of the responses provided.

Moreover, our study included a convenience sample comprising patients compliant with their follow-up appointments, accessible at UHC Zagreb and willing to participate in the study which may in turn not fully represent the entire population of HR+ BC patients in Croatia. However, it should be acknowledged that UHC Zagreb is the largest healthcare institution in the country, attracting women from various regions of Croatia and as such is representative. Additionally, our study achieved a high response rate, enabling us to include nearly all women attending routine follow-up appointments and thus yielding an ample sample size for conducting various analyses.

CONCLUSIONS

Concerns regarding AET vary depending on the age at which a woman is diagnosed with an HR+ BC. In order to tailor targeted interventions focused on adherence enhancement, it is pivotal to recognize that younger HR+ BC survivors exhibited higher concern beliefs regarding their AET. Nevertheless, intentionally non-adherent patients also exhibited higher concern and additionally lower necessity beliefs compared to the adherers. Further research should focus on investigating the impact of targeted interventions aimed at changing beliefs about AET, consequently addressing non-adherence in younger HR+ BC patients.

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