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Breast Cancer Survivors And Medication Adherence: The Role Of Health Beliefs, Perceptions Of Aging, And Partner Support

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Abstract
Aromatase inhibitors (AIs) are a daily endocrine therapy for post-menopausal breast cancer survivors and often cause difficult side effects. Women who do not adhere to AI treatment are at higher risk of cancer recurrence and mortality, yet poor adherence is a prevalent problem. This dissertation explores potentially modifiable, psychosocial predictors of AI adherence. In Chapter 1, to determine how to measure adherence in subsequent studies, we examined the psychometric properties of two self-report adherence measures. Using estrogen assays to assess convergent validity, we found that neither measure performed well; however, in exploratory analyses, a "yes/no" item about use of an AI in the past month was found to be associated with estrogen metabolite levels. In Chapter 2, we examined whether survivors' health beliefs about AI treatment predicted their adherence behaviors. Higher perceived barriers to AI treatment, but not perceived susceptibility to cancer recurrence or perceived benefits of AI treatment, predicted non-adherence. In Chapter 3, we examined the role of arthralgia-associated aging perceptions. After controlling for the severity of arthralgia (a common side effect of AIs), we found that the risk of non-adherence was higher among women who perceived that they had aged rapidly while on the treatment. We used a mixed-methods approach in Chapter 4 to examine the role of partner support. Our qualitative findings suggest that integration of partners into follow-up care and partner support around body changes and sexual dysfunction associated with AIs may contribute to women's ability to persist with their treatment. Our quantitative results demonstrated that satisfaction with partner support around AI treatment was determined by affection and emotional support, whereas informational and tangible support had no bearings on their satisfaction levels. Support preferences did not differ between women with lower and higher levels of pain from AI side effects; however, women with higher levels of pain tended to receive more informational support. Together, these findings can inform intervention content for women who are at risk of not adhering to AI treatment.

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A modified version of Chapter 1 has been published as:

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ABSTRACT

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Aromatase inhibitors (AIs) are a daily endocrine therapy for post-menopausal breast cancer survivors and often cause difficult side effects. Women who do not adhere to AI treatment are at higher risk of cancer recurrence and mortality, yet poor adherence is a prevalent problem. This dissertation explores potentially modifiable, psychosocial predictors of AI adherence. In Chapter 1, to determine how to measure adherence in subsequent studies, we examined the psychometric properties of two self-report adherence measures. Using estrogen assays to assess convergent validity, we found that neither measure performed well; however, in exploratory analyses, a "yes/no" item about use of an AI in the past month was found to be associated with estrogen metabolite levels. In Chapter 2, we examined whether survivors' health beliefs about AI treatment predicted their adherence behaviors. Higher perceived barriers to AI treatment, but not perceived susceptibility to cancer recurrence or perceived benefits of AI treatment, predicted non-adherence. In Chapter 3, we examined the role of arthralgia-associated aging perceptions. After controlling for the severity of arthralgia (a common side effect of AIs), we found that the risk of non-adherence was higher among women who perceived that they had aged rapidly while on the treatment. We used a mixed-methods approach in Chapter 4 to examine the role of partner support. Our qualitative findings

suggest that integration of partners into follow-up care and partner support around body changes and sexual dysfunction associated with AIs may contribute to women's ability to persist with their treatment. Our quantitative results demonstrated that satisfaction with partner support around AI treatment was determined by affection and emotional support, whereas informational and tangible support had no bearings on their satisfaction levels. Support preferences did not differ between women with lower and higher levels of pain from AI side effects; however, women with higher levels of pain tended to receive more informational support. Together, these findings can inform intervention content for women who are at risk of not adhering to AI treatment.

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CHAPTER 1:

Self-Reported Measures of Adherence to Aromatase Inhibitors: Are They Valid?

Abstract

Purpose: Two self-report measures of medication adherence were assessed for their validity among breast cancer survivors on aromatase inhibitors (AIs). **Materials and Methods:** Participants (n = 235) who had been prescribed AIs completed a modified version of the Morisky Medication Adherence Scale (MMAS-8) and the Visual Analog Scale (VAS). The internal consistency and factor structure of the modified MMAS-8 were assessed. Convergent and divergent validity of both measures were evaluated using serum estrogen levels and an anxiety measure, respectively. **Results:** Two MMAS-8 items were removed due to poor factor loadings. The resulting scale had a one-factor structure and an internal consistency of 0.69. On the MMAS-8 and VAS, the majority of participants indicated they were fully adherent in the past month. Neither scale demonstrated convergent validity; and contrary to hypothesis, the MMAS-8 was significantly correlated with anxiety (r = 0.16, p = 0.02). Post-hoc analyses revealed that participants' responses to a question asking whether they had taken an AI in the last month was a stronger correlate of estrogen suppression (r = -0.36, p < 0.001) than either the modified MMAS-8 or VAS. **Conclusions:** These analyses suggest that the modified MMAS-8 and VAS may not be valid or clinically useful for measuring AI adherence. Clinicians and researchers whose resources only permit use of self-report measures are advised to ask patients whether they have taken an AI in the last month as a rough estimate of current AI adherence.

Self-reported measures of adherence to aromatase inhibitors: Are they valid?

Over the past 15 years, anticancer treatment has experienced a growth in self-administered oral therapies.[1] Compared to injections or intravenous treatments that must be administered in a medical setting, oral regimens offer advantages such as reduced pain, fewer medical appointments, and more personal control over treatment.[2,3]

As oral regimens have given patients more control, non-adherence has emerged as a barrier to achieving maximal drug effectiveness. Non-adherence to aromatase inhibitors (AIs), an oral therapy that reduces the recurrence of estrogen-positive breast cancer, is of particular concern in light of the cancer's high incidence rate.[4] Early discontinuation of adjuvant hormonal therapy (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.09 to 1.46), as well as frequent missed doses among those who have continued therapy (HR, 1.49; 95% CI, 1.23 to 1.81), have each been shown to be independently associated with increased mortality even after age and disease factors are accounted for.[5]

Measuring adherence to AIs has been recognized as an important element of patient care, from both research and clinical perspectives.[6] By administering valid adherence questionnaires to patients and identifying poor adherers, researchers can study factors that are associated with non-adherence, and clinicians can intervene to help improve adherence behavior and medical outcomes. A quick, accurate, and cost-effective adherence measure is needed to facilitate frequent and meaningful assessment. Daouphars and colleagues developed a self-report measure to assess adherence to imatinib among chronic myeloid leukemia patients, and though it correlated with

prescription refills, it demonstrated poor internal consistency (Cronbach's alpha = 0.55) and its factor structure was not assessed.[7] No research to date has attempted to validate a self-report measure among AI users.

We sought to address the need for a reliable and valid self-report adherence measure for AIs by examining two scales: the modified version of the Morisky Medication Adherence Scale-8 (MMAS-8) and the Visual Analog Scale (VAS). The MMAS-8 is a commonly used adherence measure and has been applied across a variety of illness groups.[8,9] It has been found to be internally consistent,[10] concordant with pharmacy fill rates,[9,11] and predictive of blood pressure control among hypertensive patients.[10] These psychometric properties suggest it may be a useful tool for measuring adherence to AIs. The Visual Analog Scale (VAS) asks patients to indicate on a continuous line the proportion of doses they have taken in the last month (0-100%). Visual analog scales place minimal burden on the patient and are more sensitive than Likert-type scales.[12] The VAS has been found to correlate significantly with unannounced pill counts among HIV populations,[13] suggesting that it too may be a promising tool for breast cancer patients. We evaluated the reliability and validity of these two tools simultaneously against estrogen metabolite levels to examine whether one scale is superior to the other, or if greater accuracy is achieved by using both concurrently.

Method

Participants

Participants were drawn from the Wellness after Breast Cancer (WABC), a large ongoing study examining genetic determinants of symptom distress and disease outcomes among postmenopausal women with hormone receptor positive breast cancer on AIs. This study was conducted with the approval of the Institutional Review Board of the University of Pennsylvania and all participants provided written informed consent. Research assistants recruited participants in two breast cancer clinics, one situated in an academic tertiary care teaching hospital and the other in a community hospital. Eligibility criteria were (1) female sex; (2) age 18 or older; (3) history of stage I, II, or III breast cancer; (4) current use of a third-generation AI or discontinuation of an AI but currently still in the period in which an AI was indicated; (5) postmenopausal; (6) completed primary cancer treatments (surgery, chemotherapy, radiotherapy); and (7) able to understand written English and participate in an informed consent process.

Measures

Participants completed the measures of AI adherence in addition to measures of pain, AI side effects, emotional wellbeing, sleep and fatigue, physical functioning, and physical activity. Participants also provided information about their breast cancer disease and treatment history, as well as demographic information. For the estrogen analysis, participants underwent venipuncture, from which serum was extracted and frozen in aliquots at -80 degree Celsius.

Adherence scales. Participants were first asked, "Have you taken an Aromatase Inhibitor in the last month?" If they responded "yes," they were asked to complete two adherence scales: the MMAS-8 and the VAS. The MMAS-8 is a self-report adherence

scale that was originally developed for hypertension patients.[10] With permission from Dr. Morisky, Item 6 was modified to make it appropriate for breast cancer patients (see Table 1). Interviews were conducted with twelve AI-users (who were not part of the current sample) to ensure the items were clear and relevant. The first seven items are dichotomous, whereas the last item is a 4-point ordinal scale that must be later dichotomized. Higher scores indicate worse adherence over the past month.

Instructions for the VAS asked participants to indicate the percentage of their prescribed AI dosage they took over the past month by marking an "X" on a continuous line with 0% and 100% as anchors on either end-point.

Convergent Validity. Convergent validity is achieved when a measure is shown to be associated with a related construct.[14] As clinical trials have shown that AIs substantially reduce estrone and estradiol levels,[15,16] estrogen suppression was examined to assess the validity of the adherence measures. To quantify total estrone and estradiol levels, serum samples underwent organic solvent extraction and Celite column partition chromatography, followed by radioimmunoassay (University of Southern California Reproductive Endocrine Research Laboratory). The limit of detection was 2 pg/mL for estradiol and 4 pg/mL for estrone. The intra- and interassay coefficients of variation were < 5%. Samples were assayed in duplicate with mean levels used for analyses.[17]

Divergent validity. Divergent validity is achieved when a measure is shown to be unassociated to constructs that it is not theoretically related to.[14] Because meta-analytic work has shown there to be no relationship between anxiety and adherence,[18] the anxiety

subscale of the Hospital Anxiety and Depression Scale (HADS[19]) was used to determine divergent validity.

Statistical Analyses

Confirmatory factor analysis of the MMAS-8 was conducted in MPlus[20] using all participants who reported being on AIs and who completed the measure. A weighted least squares mean and variance (WLSMV) adjusted estimator was used because traditional maximum likelihood estimators can yield biased estimates when used with dichotomous scales, such as the MMAS-8.[21] In accordance with recommendations of Hu and Bentler[22] three fit indices were examined: the chi-square, the comparative fit index (CFI), and the root mean square error of approximation (RMSEA).

To assess convergent and divergent validity, only participants who had reported taking an AI in the last month were included in analyses. For convergent validity, hierarchical linear regressions were conducted with estrone and estradiol as the outcome variables and the self-report adherence scales as predictors. Treatment and demographic variables that have been found in the literature to be associated with estrogen serum levels, including body mass index (BMI[23,24]), years since last menstruation,[17] race,[25] and drug type,[16] were tested to determine if they were associated with estrogen in this sample (see Tables 2 and 3). AI drug (letrozole, anastrozole, or exemestane) and race were found to be associated with estrone and estradiol and were entered as covariates in the final regression models. Race was dichotomized into "Whites" and "Other races" (the large majority of non-White participants were African American [91%]). Correlations

between the adherence scales and anxiety were used to assess divergent validity. These analyses were completed in SPSS version 21.[26]

Results

Our analysis focused on 235 participants in the WABC cohort study for whom estrogen serum levels were available. These women were not selected for any characteristics, but were rather a subset of women recruited during the study period when funds were available to conduct the estrogen assays. No differences were found in baseline characteristics (age, race, BMI, marital status, or education) between the subset represented in this study and the rest of the cohort. Five (2%) participants were removed from the analysis because they completed the adherence scales erroneously. An additional 5 participants were removed due to missing data on the MMAS-8 and one of the covariates. Of the remaining participants, 91% (n = 205) indicated that they had taken an AI in the last month. Participants ranged in aged from 35 to 84 years. The majority was white (86.2%), married or cohabitating (62.2%), and college-educated (56.9%). About half of the sample initiated AI treatment in the last year and a half, with the majority (82.2%) on anastrazole. Tables 2 and 3 show the relationship between participant demographics and serum estrogen levels.

Power Analysis

A power analysis using G*Power[27] was conducted for the linear regressions that assessed convergent and divergent validity. Results indicated that there was 88.9% power to detect a small effect size (f^2 = 0.05) with a sample of 205 participants.

Distributions of MMAS-8 Items

Distributions of each item of the modified MMAS-8 were examined. The cut-off for dichotomizing the ordinal-scale item (Item 8) caused it to have a distribution which suggested that the majority of the sample was non-adherent, whereas the other 5 items suggested that the majority of the sample was adherent. The rule for dichotomizing item 8, which asks patients how often they have difficulty remembering to take their AI, was therefore modified by moving the dichotomization cut-off by 1 point on the ordinal scale. (As a result "Never/Rarely" and "Once in a while" were grouped into the same category, rather than having "Never/Rarely" as one category and all other responses in the second). After this modification was made, the distribution of item 8 mirrored the distribution of the other items (Table 1). This result was cross-validated by randomly splitting the sample in two; the distribution of Item 8 was almost identical in both halves of the dataset.

Confirmatory factor analysis (CFA).

A confirmatory factor analysis (CFA) testing the one-factor structure of the MMAS-8 yielded poor model fit: $\chi 2(20) = 35.326$, $p < .05$; RMSEA = .059; CFI = 0.942. Item 5 had a poor factor loading, and there was insufficient variance in Item 6. Items 5 and 6 were removed and the CFA was repeated. The second analysis yielded strong model fit: $\chi^2(9) = 11.357$, $p > 0.25$; RMSEA = .035; CFI = 0.989. Cronbach's alpha for this modified version was 0.69. Factor loadings and distributions for each item, including the revised version of item 8, are displayed in Table 1.

Convergent validity.

Estradiol and estrone were log-transformed for their distributions to approximate normality. Two hierarchical regressions were conducted for estradiol, with covariates entered in Step 1, and the VAS or modified MMAS-8 entered in Step 2 (see Table 4). Adding either the modified MMAS-8 or the VAS to the model did not significantly improve prediction of estradiol ($\Delta R^2 = .01$, $F(1,200) = 1.24$, $p = .27$; $\Delta R^2 = .02$, $F(1,200) = 3.34$, $p = .07$, respectively). The regressions were repeated for estrone; However, examination of the residuals revealed they were non-normally distributed, indicating that the assumptions for multiple linear regression had not been met. Therefore, estrone was residualized on the covariates, and the residuals were entered into non-parametric correlations (Spearman *r [r_s]*) with both the modified MMAS-8 and the VAS. The correlations between residualized estrone and the modified MMAS-8 and VAS were not statistically significant ($r_s = .02$, $p = .74$; $r_s = -.07$, $p = .32$, respectively). Zero-order correlations between the adherence measures and estrogen (see Table 3) were also small and not statistically significant, suggesting that the failure to find evidence for convergent validity cannot be explained by collinearity between the self-report adherence scales and the covariates.

In post-hoc analysis, the sample was expanded to also include those who reported being off AIs (total $n = 225$), and the same analyses were repeated replacing the self-adherence measures with participants' response to the "yes/no" question whether they had taken an AI in the last month. "No" on this item was coded as 0. "Yes" was coded as 1. Adding this item to the model substantially improved the prediction of estradiol ($\Delta R^2 = .15$, $F(1,220) = 44.67$, $p < .001$). See Table 4. Additionally, residualized estrone

scores were significantly correlated with this item (r_{pb} = -0.45, p < 0.001). Please see Figures 1 and 2 for plots showing the relationship between the "yes/no" item and the distributions of estrone and estrodial.

Further exploratory analyses were done to determine if the VAS could enhance the information provided by the "yes/no" item by inputting 0 on the VAS for all participants who reported not taking an AI in the last month and repeating the convergent validity analyses with the full sample. The modified VAS performed similarly to the "yes/no" item for predicting estradiol: (ΔR^2 = .16, F(1,220) = 48.68, p < .001). See Table 4. Residualized estrone scores were significantly correlated with the modified VAS (r_s = -0.25, p < 0.001), however the association was not as strong as the correlation between estrone and the "yes/no" item. Additional analyses were completed to formally test whether the VAS adds incremental validity to the "yes/no" item. For estradiol, a hierarchical regression was conducted with covariates entered in Step 1, the "yes/no" item entered in Step 2, and the VAS entered in step 3. Adding the VAS to the model did not substantially improve the prediction of estradiol (ΔR^2 = .01, F(1,219) = 3.39, p = .07). For estrone, a hierarachical regression was conducted with residualized estrone scores as the outcome variable, the "yes/no" item entered in Step 1, and the VAS entered in Step 2. The VAS did not substantially improve the prediction of estrone either (ΔR^2 = .003, F(1,222) = 0.85, p = .07).

Divergent validity.

In this sample, internal consistency of the anxiety subscale of the HADS was 0.85. The correlation between anxiety and the modified MMAS-8 was low, but

statistically significant (r_s = .16, p = .02). Higher levels of anxiety were associated with worse adherence scores on the MMAS-8, suggesting that the modified MMAS-8 does not have good divergent validity. The relationship between the VAS and anxiety was not significant (r_s = -.07, p =.31). Further examination of the relationship between the modified MMAS-8 and anxiety revealed that Item 3 ("Have you ever cut back or stopped taking your AI without telling your doctor because you felt worse when you took it?") and Item 4 (When you travel or leave home do you sometimes forget to take your AI?) were the only two items from the modified MMAS-8 that were significantly associated with anxiety (r_s = 0.18, p = .009; r_s = .15, p = .03, respectively). Conversely, anxiety, and responses to the "yes/no" adherence item, were not associated (r_s = -0.10, p = .14).

Discussion

This study evaluated the validity of two self-report instruments of AI adherence using serum estrogen levels. The modified MMAS-8 and VAS demonstrated poor convergent and divergent validity, indicating they may not be valid self-report instruments for measuring adherence among breast cancer patients on AIs. Even though these instruments have been validated among other medical populations, medication adherence in the context of AIs may be sufficiently distinct to warrant measures tailored to the AI experience. For example, some women on AIs take intentional drug holidays to get relief from side effects, which the modified MMAS-8 and VAS likely do not capture but are an important aspect of non-adherence in this population.

In this sample, asking patients whether they had taken an AI in the last month ("yes/no") was significantly associated with estradiol and estrone levels, and was not

associated with anxiety, suggesting that clinicians can glean important information from this straightforward question. Though this type of dichotomous question limits the amount of fine-grained information that one can ideally gather about adherence from patient reports, it is still a useful, even if limited estimation of the patient's estrogen suppression.

Though the MMAS-8 did not provide an accurate picture of estrogen suppression, it may be capturing a meaningful aspect of the AI experience. On the modified MMAS-8, 18% of women reported that they sometimes forget to take their AI, confirming other study findings that missed doses are a prevalent problem,[28] while 10% reported feeling hassled by their AI treatment plan. Additionally, the significant association between anxiety and Item 3 on the MMAS-8 reveals that women who are anxious may not be comfortable initiating discussions with their doctors about their non-adherence and AI side effects.[29] As side effects have been found to be associated with discontinuation of AIs,[30] doctors may be able to improve care for anxious patients by prioritizing AI regimen discussions, and making clear that there are options for relieving side effects even if patients themselves do not mention experiencing any difficulties.

Some limitations should be acknowledged. Adherence in this sample was high. Of the patients in this sample on AIs, less than 2% indicated adherence rates below 80% on the VAS, suggesting that the range of self-reported adherence may be too high and narrow to find a relationship between estrogen serum levels and responses on self-report adherence measures. Reporting or recall bias may explain the high levels of adherence found in this sample.[31] Alternatively, the recall period (one month) for the adherence

measures may have been too short to reveal the total number of non-adherers. Prior studies that have found a higher proportion of non-adherers have looked at AI adherence over much longer time intervals (1 - 4.5 years[5,32]).

It is also unclear what level of adherence is required to achieve the desired degree of estrogen suppression. For instance, an adherence rate of greater than 90% is required to achieve maximal drug efficacy of imatinib for treating chronic myeloid leukemia,[33] but this rate is not known for AIs. It may be that only a persistent level of non-adherence decreases the efficacy of AIs, and that periodic forgetfulness, which the MMAS and VAS may be capturing in this sample, may not actually impact the degree of estrogen suppression. This interpretation is further supported by the finding that the VAS did not enhance information provided by the "Yes/No" adherence item. If this is the case, the measures may in fact be valid but not clinically useful.

In conclusion, we did not find evidence to warrant use of the modified MMAS-8 or VAS in clinical care or research to assess adherence to AI adjuvant therapy for breast cancer. Our research highlights that adherence issues in oncology settings are unique and measures that have been validated among other illness groups may not be appropriate for oncology patients. For the time being, based on our results, patients should be routinely asked whether or not they have taken their AI in the last month. This question places a minimal burden on both patients and clinical staff, and can provide clinicians with a rough estimate of a patient's current level of estrogen suppression.

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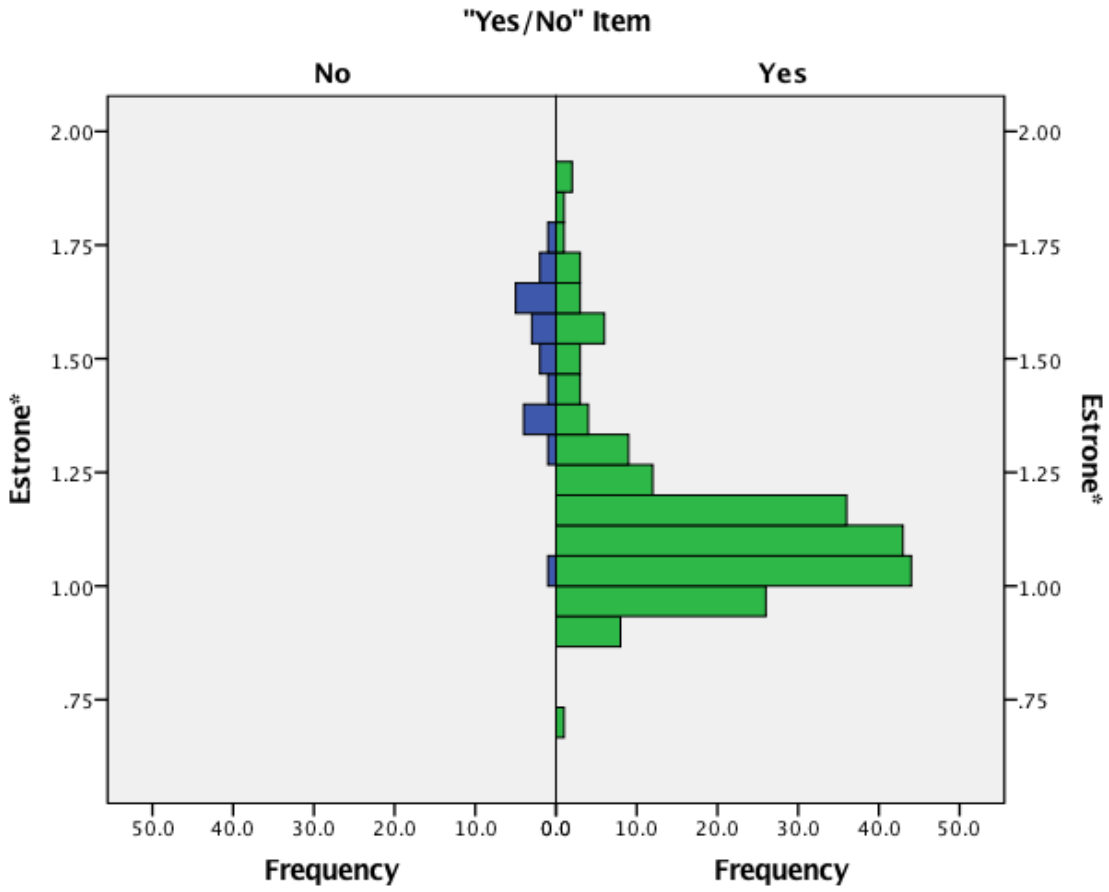

Figure 1. Relationship between distribution of estrone levels and responses to the "yes/no" item.

* pg/ml; log-transformed

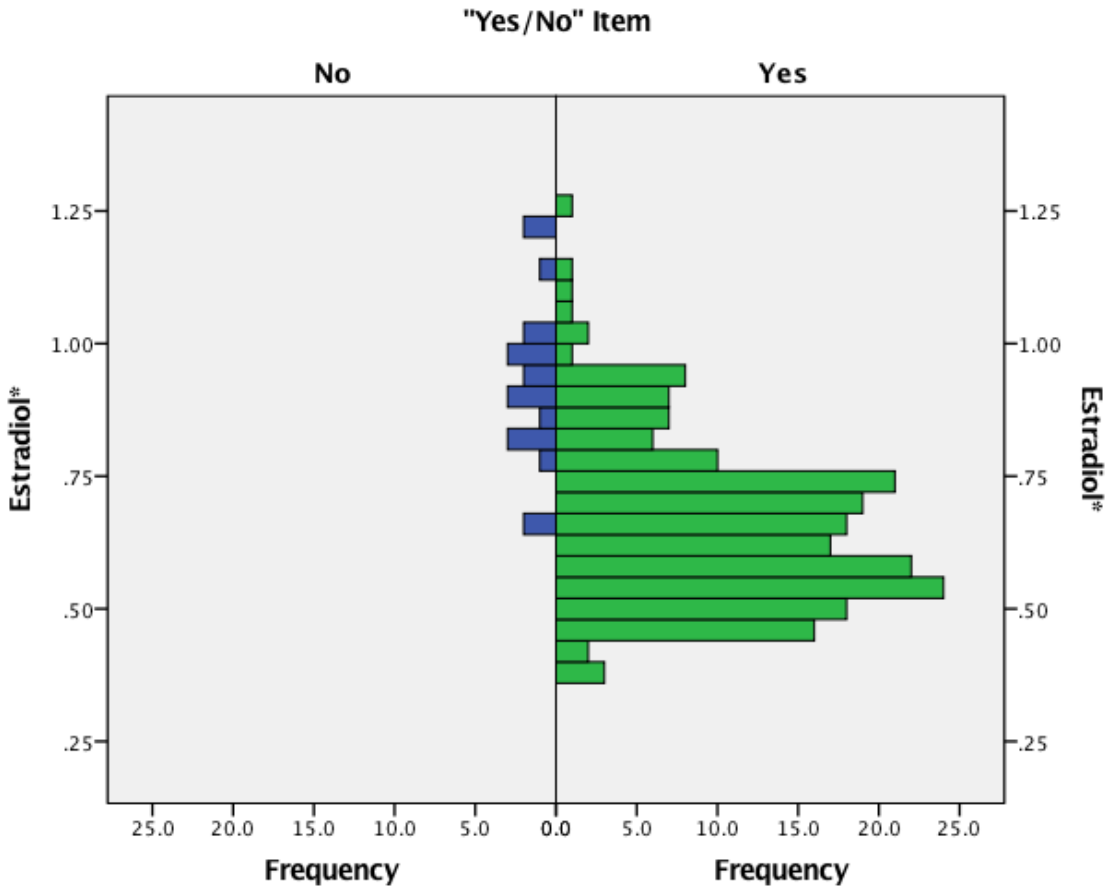

Figure 2. Relationship between distribution of estradiol levels and responses to the "yes/no" item.

* pg/ml; log-transformed

Table 1

Factor Loadings and Distribution of Item Responses for the Modified MMAS-8 (n = 205)

MMAS-8 Item[a]	Factor Loading	No	Yes
1. Do you sometimes forget to take your AI?	0.93	81.8%	18.2%
2. Over the last two weeks, were there any days when you did not take your AI?	0.79	90.0%	10.0%
3. Have you ever cut back or stopped taking your AI without telling your doctor because you felt worse when you took it?	0.59	95.7%	4.3%
4. When you travel or leave home do you sometimes forget to bring along your AI?	0.70	95.2%	4.8%
5. Did you take your AI yesterday? [reverse scored]	Removed from analyses	23.6%	76.4%
6. When you feel your breast cancer is under control do you sometimes stop taking your AI medication?	Removed from analyses	99.0%	1.0%
7. Taking an AI everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your AI treatment plan?	0.51	90.4%	9.6%
8. [original scoring] How often do you have difficulty remembering to take your AI?[b]	Not included in analysis	1.0%	99.0%
8. [revised scoring] How often do you have difficulty remembering to take your AI? [b,c]	0.87	85.7%	14.3%

Note. AI = aromatase inhibitor; MMAS-8 = Morisky Medication Adherence Scale.

[a] Items in bold were included in the final version of the scale for this study.

[b] This item has an ordinal scale. The developers of the scale instruct users to dichotomize the item after participants complete it. "Yes" means that participants' responses fell into the poor adherence category, and "No" means they fell into the good adherence category.

[c] The revised version of item 8 has the same wording as the original version; however the authors dichotomized it differently than was instructed by the scale developers such that "Never/Rarely" and "Once in a while" were grouped into the same category, rather than having "Never/Rarely" as one category and all other responses in the second.

Table 2

Patient Characteristics and Differences in Estrogen Levels (median [interquartile range])

	Expanded Sample (N = 225)			Participants on AIs (N = 205)		
Characteristic	%	E1 (pg/mL)	E2 (pg/mL)	%	E1 (pg/mL)	E2 (pg/mL)
Race[a]						
White	86.2	12.4 [8.6]	3.7 [2.9]	84.9	11.7 [5.4]	3.5 [2.3]
Non-White	13.8	10.9 [14.4][a]	2.9 [1.7][b]	15.1	10.9 [3.7]	2.9 [1.7][a]
Marital status						
Single	12.0	12.6 [5.5]	3.4 [2.3]	12.2	11.9 [5.5]	3.4 [2.4]
Married or cohabitating	62.2	12.1 [6.0]	3.6 [2.4]	61.5	11.5 [4.4]	3.4 [2.1]
Divorced or separated	13.8	12.5 [8.2]	3.3 [2.4]	14.1	12.3 [6.5]	3.2 [2.4]
Widowed	12.0	12.7 [16.1]	4.1 [3.1]	12.2	11.7 [12.4]	3.7 [2.9]
Education level						
High school or less	21.3	11.6 [5.6]	3.4 [3.1]	22.0	10.9 [4.8]	3.3 [2.6]
Some college or trade school	21.8	11.4 [5.7]	3.6 [2.0]	22.4	11.4 [4.9]	3.5 [1.9]
College or more	56.9	12.5 [8.7]	3.6 [2.9]	55.6	12.0 [5.2]	3.4 [2.1]
Prescribed AI						
Letrozole (Femara)	15.1	10.1 [3.8]	2.8 [1.5]	15.6	10.1 [3.3]	2.7 [1.4]
Anastrozole (Arimidex)	82.2	12.4 [6.5]	3.6 [2.5]	82.4	11.9 [4.7]	3.4 [2.2]
Exemestane (Aromasin)[c]	2.7	32.7 [20.1]	7.0 [3.6]	2.0	32.6 [21.8]	7.0 [2.5]

Note. AI = aromatase inhibitor; E1 = Estrone; E2 = Estradiol.

[a] $p < 0.05$ compared to white participants .

[b] $p < 0.01$ compared to white participants.

[c] $p < 0.01$ compared to letrozole and anastrozole.

Table 3

Spearman Rho Correlations of Study Variables[a]

Measure	Mdn [IQR]	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Estrone	11.5 [4.92]	1.00								
2. Estradiol	3.4 [2.1]	0.44**	1.00							
3. MMAS-8	0.0 [1.0]	-0.06	0.00	1.00						
4. VAS (%)	100 [3.0]	-0.03	0.03	-0.48**	1.00					
5. HADS Anxiety	6.0 [6.0]	0.05	0.01	0.16*	-0.07	1.00				
6. Age (yrs)	62.0 [12.0]	-0.02	0.06	-0.10	-0.00	-0.11	1.00			
7. BMI	26.6 [7.2]	0.01	-0.10	0.03	-0.04	0.02	0.03	1.00		
8. Years on AI	1.6 [1.5]	-0.06	0.04	-0.05	0.05	0.07	0.03	-0.03	1.00	
9. Years since LM	12.2 [16.2]	-0.07	0.03	-0.07	0.02	-0.07	0.85**	0.12	0.10	1.00

Note. BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; IQR = Interquartile Range; LM = last menstruation; Mdn = Median; MMAS-8 = Modified Morisky Medication Aderence Scale-8; VAS = Visual Analog Scale; yrs = years.

[a] These correlations represent associations for participants who are currently on an AI (n = 205).

* $p < 0.05$

** $p < 0.01$

Table 4

Summary of Hierarchical Regressions of Estradiol[a] on Adherence Measures

	Independent variables	Beta[b]	R^2	R^2 change	F change	p
Adherence Measure: MMAS-8 (n = 205)						
Step 1	Race[c]	-0.13	0.07	0.07	5.39	<0.01
	Letrozole[d]	-0.60				
	Anastrazole[d]	-0.49				
Step 2	MMAS-8	0.08	0.08	0.01	1.24	0.27
Adherence Measure: VAS (n = 205)						
Step 1	Race[c]	-0.13	0.07	0.07	5.39	<0.01
	Letrozole[d]	-0.60				
	Anastrazole[d]	-0.49				
Step 2	VAS	-0.12	0.09	0.02	3.34	.07
Adherence Measure: "Yes/No" Item (n = 225)						
Step 1	Race[c]	-0.16	0.10	0.10	8.34	<.001
	Letrozole[d]	-0.62				
	Anastrazole[d]	-0.52				
Step 2	"Yes/No" Item	-0.40	0.25	0.15	44.67	<.001
Adherence Measures: Modified VAS (n = 225)						
Step 1	Race[c]	-0.16	0.10	0.10	8.34	<.001
	Letrozole[d]	-0.62				
	Anastrazole[d]	-0.52				
Step 2	Modified VAS	-0.41	0.26	0.16	48.68	<.001

Note. MMAS-8 = modified Morisky Medication Adherence Scale-8; VAS = Visual Analog Scale.

[a] Estradiol scores were log transformed.

[b] Betas reported are those from the step at which the variable was entered.

[c] Race was dummy-coded as 0 for White, and 1 for Other.

[d] Letrozole and anastrazole were dummy-coded with exemestane as the referent group.

CHAPTER 2:

Perceived Barriers to Treatment Predict Breast Cancer Survivors' Adherence to Aromatase Inhibitors

Abstract

Background: While poor adherence to hormonal therapies such as aromatase inhibitors (AIs) are widely documented, less is known about whether health beliefs predict treatment non-adherence. This study aimed to evaluate the relationship between health beliefs (perceived susceptibility to breast cancer, perceived benefits of AI treatment, perceived barriers to AI treatment) and adherence to AIs. **Methods:** Postmenopausal women with early stage hormone receptor-positive breast cancer who were currently on an AI completed the three-factor Health Beliefs and Medication Adherence in Breast Cancer (HBMABC) scale and questionnaires about their demographics and symptoms. Adherence data (treatment gaps and premature discontinuation) were abstracted from participants' medical charts. Logistic regression analyses were conducted to evaluate the relationship between health beliefs and adherence. **Results:** Among 437 participants, 93 (21.3%) were non-adherent. Those who perceived greater barriers to their AI treatment were more likely to display AI non-adherence behaviors by the end of their treatment period than those who reported fewer barriers to AI therapy (adjusted odds ratio, 1.71; 95% confidence interval, 1.03 – 2.86; $p = 0.04$). Conversely, perceived susceptibility to cancer recurrence and perceived benefits of AIs did not predict AI adherence. Minorities had lower perceived susceptibility to breast cancer recurrence and higher perceived barriers to AI treatment ($p < 0.05$ for both). **Conclusions:** Greater perceived barriers predicted non-adherence to AIs. Interventions addressing women's negative beliefs about the challenges of AI treatment are needed to help optimize adherence in breast cancer survivors.

Perceived Barriers to Treatment Predict Breast Cancer Survivors' Adherence to Aromatase Inhibitors

For many women with breast cancer, treatment does not end with chemotherapy, radiation, or surgery. After completing their primary treatments, survivors of hormone dependent breast cancer are often prescribed oral adjuvant hormonal therapy, which include tamoxifen and aromatase inhibitors (AIs). For post-menopausal women, AIs are considered the front-line medication for preventing breast cancer recurrence.[1,2]

Despite the efficacy of AIs, many women do not fully adhere to their medication regimen and even discontinue prematurely. Studies have shown that 19-28% of women on AIs achieve less than 80% adherence one year into treatment, and the proportion of non-adherers grows as treatment time progresses, increasing to 32-50% during the third year of treatment.[3,4] In clinical trials, which tend to have higher adherence rates than in unmonitored settings, early discontinuation of AIs has been found to be as high as 24.1% by the fourth year of treatment.[5]

Risk factors for non-adherence that have been investigated include demographic, cancer, and symptom variables, such as race, age, education level, income, cancer stage, joint pain, etc.[6–8] Findings from this research enhance our understanding of what types of patients may be most likely to non-adhere to AIs, but since many of these factors are not modifiable (such as age), or at least cannot be changed by the health care system (such as income), it is important to identify factors on which clinicians can intervene.

One potentially modifiable factor that may play a role in predicting adherence to AIs is health beliefs. Three major components of the health belief model include perceived

susceptibility, perceived benefits, and perceived barriers.[9] Each of these reflects key elements of the mental calculations an individual makes before taking action to avoid a negative health outcome. Some or all of these constructs have been shown to be associated with adherence behaviors among breast cancer survivors, including adherence to tamoxifen, another form of adjuvant hormonal therapy that is often prescribed to both pre and post-menopausal survivors[10,11]; Breast cancer survivors who perceived their tamoxifen medication to have greater benefits than risks were more likely to adhere to their treatment than those who perceived the opposite.[11] The relationship between health beliefs and AI adherence, however, is currently unknown, and given that tamoxifen has different side effects and health risks than AIs, it is reasonable to speculate that survivors may hold different beliefs about AIs.[12] Additionally, in neither the tamoxifen nor AI adherence literature has the role of perceived barriers and perceived susceptibility to breast cancer been examined.

In this study, we hypothesized that breast cancer survivors with greater perceived benefits of AIs, greater perceived susceptibility to breast cancer recurrence, and lower perceived barriers to taking AIs would be more likely to adhere to AIs. As a secondary aim, we also evaluated whether health beliefs differed by key demographic and medical variables.

Participants and Methods

Participants were drawn from the Wellness after Breast Cancer (WABC), an ongoing cohort study of postmenopausal breast cancer survivors who had been prescribed AIs and were consented between March 2008 and July 2009.[13] We chose this time frame to

ensure all participants in this study had an opportunity to complete the five years of prescribed AI therapy. Inclusion criteria for WABC were as follows: (1) female sex, (2) age 18 or older, (3) postmenopausal status, (4) stage I-III hormone receptor positive breast cancer, (5) use of a third-generation AI, (6) completion of all chemotherapy and/or radiotherapy at least one month prior to survey date, and (7) ability to provide informed consent in English. Recruitment took place at an academic teaching hospital. The study was approved by the Institutional Review Board of the University of Pennsylvania.

Analysis focused on participants who were on an AI at the time of the survey (n = 437). Adherence outcome data and most clinical variables were gathered from participants' medical charts. Other variables came from the WABC baseline survey that participants completed.

Measures

Adherence. Oncology progress notes and telephone calls that dated from the day the participant completed the WABC survey to the end-date of their prescribed AI treatment (typically five years) were searched for medication-related events. Treatment interruptions (defined as any time off an AI during the prescribed treatment) and premature discontinuation (defined as stopping the AI entirely before the prescribed treatment end-date) were both considered forms of non-adherence. Due to power considerations, they were grouped together into one binary outcome variable ("adherent" versus "non-adherent"). Discontinuations after breast cancer recurrence or metastasis were not considered non-adherence events.

Premature discontinuation and treatment interruptions were abstracted from medical records by one of two raters. (Before conducting abstractions for this study, raters were trained by an experienced abstractor on a different dataset and were required to reach interrater reliability of $\kappa \geq 0.70$ for each category). Adherent behavior was coded as 0 and non-adherence was coded as 1. Subsequently, 12.5% of cases were independently re-abstracted by one of two additional raters; interrater reliability was good to excellent (0.78 – 1.00) for both categories of non-adherence.

Health Beliefs. At study entry, all participants completed the Health Beliefs and Medication Adherence in Breast Cancer (HBMABC) scale, a measure adapted from the Champion Health Belief Model Scales (CHBMS) for Mammography Screening (with permission from the author). Each item consists of a Likert-type scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). To determine the factor structure of the scale, we randomly split the sample into two and conducted an exploratory factor analysis (promax rotation) using the first subsample. We followed this with a confirmatory factor analysis to determine whether the solution from the exploratory analysis fit the data for the second subsample.

For the exploratory factor analysis, the pattern of factor loadings as well as the scree plot of eigen values indicated a three-factor solution. Three items were deleted due to lack of salience (factor loading below 0.4) or because when they were removed, the internal consistency of the subscales improved. Factor loadings and communalities are displayed in Table 1. The three factors identified mapped onto the theoretical constructs that informed the development of the HBMABC: perceived susceptibility, perceived

benefits, and perceived barriers. In the context of AIs, susceptibility reflects a survivor's sense of vulnerability to breast cancer recurrence, perceived benefits represent survivors' beliefs about the efficacy of AIs, and perceived barriers captures the difficulties survivors feel they face in adhering to their AI treatment.

For the confirmatory factor analysis, we examined multiple indices to determine the goodness of fit of the three-factor solution for the second subsample: the X^2/df ratio, the Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), and the root mean square error of approximation (RMSEA). The results indicated that the factor structure had a reasonable fit to the data (X^2/df = 2.13; CFI = 0.98; TLI = .98; RMSEA = .07 [90% confidence interval 0.06 – 0.9]).[14] Cronbach's alphas for the three subscales (using the entire sample) were 0.87 (Perceived Susceptibility), 0.77 (Perceived Benefits), and 0.83 (Perceived Barriers). The range of scores on both the Perceived Susceptibility and Perceived Benefits subscales was 3 to 15, and the range on the Perceived Barriers subscale was 8 to 40. Two of the three subscales were highly skewed, therefore all subscales were dichotomized into low and high categories using a median split. A score of eight or below on the Perceived Susceptibility subscale indicated low perceived susceptibility to cancer recurrence; a score of 11 or below on the Perceived Benefits subscale indicated low perceived benefits to AIs; and a score of 12 or below on the Perceived Barriers subscale indicated low perceived barriers to AI treatment.

Covariates. Race, age, education, marital status, joint pain, depression, clinical comorbidities, and date of last menstrual period were collected via self-report. Joint pain was measured with the worst pain item of the pain intensity subscale of the Brief Pain

Inventory. This single item has been found to predict premature discontinuation among breast cancer survivors on AIs [8]. Given that meta-analytic work has shown depression and adherence are related,[15] the Hospital Anxiety and Depression Scale (HADS) was used to measure depressive symptoms. A validated cut-off score was used to categorize participants into depressed and not depressed ($\geq$ 8 = depressed).[16] Clinical variables, including cancer stage and prior use of tamoxifen, were abstracted from medical charts.

Statistical Analyses

Univariate analyses using logistic regression were conducted to assess the association between each variable and non-adherence. Significant variables ($p < 0.10$) were assessed in multivariable logistic regression analyses. Chi-square tests were conducted to determine the relationship between health beliefs and demographic, medical, and psychosocial variables. All tests were two sided with $p < 0.05$ indicating statistical significance. Twenty-four participants were lost to follow-up and we were therefore unable to obtain information about their adherence behaviors. Data for these individuals were imputed using multiple imputation. SPSS version 21[17] was used for all analyses.

Power analysis. A power analysis using G*Power[18] demonstrated that with a sample of 437 participants, we had 80% power to detect an odds ratio of 1.91, assuming that 30% of the sample was non-adherent and that each health beliefs subscale was moderately associated with covariates in the model. The non-adherence rate of 30% was selected based on rates seen in the literature.[3,4]

Results

Participant Characteristics

Of the 437 participants, 82.6% were White, 14.9% were African American, 1.6% were Asian, and 0.9% reported "Other" race-ethnicity. The sample was highly educated: Among participants, 35.1% had a graduate or professional degree, 43.6% attended at least some college, and 21.3% had a high school diploma or less. Most of the participants were married or living with a partner (62.6%) and more than half of the sample had been in a postmenopausal state for over 10 years. See Table 2.

Predictors of Non-Adherence

Using multiple imputation, we estimated that a total of 93 (21.3%) participants exhibited some form of non-adherence after completing the survey. Perceived barriers was significantly associated with non-adherence. Those who reported having more barriers to AI treatment were more likely to later non-adhere to AIs (25.7% vs. 16.3%; odds ratio [OR], 1.78; 95% confidence interval [CI], 1.10 – 2.88; $p = .02$; see Figure 1). Perceived benefits of AI treatment (OR, .90; 95% CI, 0.53 – 1.53; $p = 0.70$) and perceived susceptibility to breast cancer (OR, 1.14; 95% CI, 0.70 – 1.84; $p = 0.60$) did not predict adherence.

The following covariates were also associated with non-adherence in univariate analyses: joint pain and years on an AI at the time of the survey (see Table 2). After we included joint pain and time on an AI in the model, perceived barriers remained a statistically significant predictor of non-adherence (adjusted OR, 1.71; 95% CI, 1.03 – 2.86; $p = 0.04$; see Table 3).

Exploratory analyses were conducted to examine if any particular items on the Perceived Barriers subscale drove the relationship between perceived barriers and adherence. When each item was examined independently, with joint pain severity and length of time on AI included in the model, Item 4, "I have to take my AI for too many years" (OR, 1.25; 95% CI, 1.03 – 1.52, $p = 0.03$) significantly predicted non-adherence, as did Item 5,"Taking my AI is difficult because it causes pain" (OR, 1.30; 95% CI, 1.07 – 1.57; $p = 0.009$). Survivors who perceived that their pain made taking AIs difficult, or that AI treatment lasted too long, were more likely to show some form of non-adherence. To determine the degree to which Item 5 and the joint pain item were measuring overlapping constructs, we calculated their correlation (r *[Spearman]* $= 0.32$, $p < 0.001$).

Correlates of Health Beliefs

Women who had lower perceived susceptibility to cancer recurrence were more likely to be non-White ($p = .01$). Survivors who perceived lower benefits of AI therapy were more likely to be above 55 years old ($p = .02$) and have had more years in menopause ($p = .009$). Participants with higher perceived barriers to AI treatment were more likely to be non-White ($p = .004$), have higher joint pain levels ($p = .004$), and be depressed ($p < .001$). See Table 4.

Discussion

To achieve optimal clinical outcomes for breast cancer survivors, adherence to AI therapy is essential.[19] In this prospective cohort study, we found that participants who perceived greater barriers to AI treatment, as measured by the HBMABC, were more likely to later take breaks from their AI or stop taking it altogether. Conversely,

perceived susceptibility to breast cancer and perceived benefits of AIs were not predictive of adherence. Importantly, health beliefs were found to differ by socio-demographic characteristics with minority women perceiving less risk of breast cancer recurrence as well as greater perceived barriers to AI treatment.

Our findings are particularly important for several reasons. This study is one of the first to identify a potentially modifiable, psychological predictor of AI non-adherence; addressing women's perceptions of perceived barriers may help improve their adherence to AIs. These findings also corroborate earlier work that shows that perceived benefits may not be worth targeting to improve AI adherence. An intervention aimed at increasing patients' knowledge around the importance and benefits of AIs had no significant impact on adherence rates[20]; it appears that survivors who are no longer willing to take AIs are not basing their decision on whether they think AIs are effective. This is in contrast to tamoxifen adherence, for which beliefs about their benefits do seem to matter,[11] underscoring the importance of studying adherence to tamoxifen and to aromatase inhibitors as separate outcomes.

The role of pain perception emerged as an important element in our findings. Prior literature has shown that joint pain is a predictor of adherence to AIs,[8] however in our analysis, joint pain was no longer predictive of adherence when pain beliefs were included in the model. Additionally, pain beliefs and pain intensity were only moderately correlated, suggesting beliefs participants held about pain as a barrier to AI treatment were not completely tied to the degree of pain the participant experienced. These findings imply that cognitions about the experience of pain, as opposed to pain itself,

drives adherence behavior. Prior work among other patient populations has shown that fear of pain, for example, is a powerful predictor of behavior[21–23]; women who experience greater distress due to pain anticipation may consider AIs more difficult to take.

To our knowledge, the HBMABC is the first instrument to evaluate health beliefs related to AI therapy. Our psychometric analyses support the original factor structure of the health belief model. In addition, we found that health beliefs are associated with a number of demographic, medical, and psychological variables. Minorities and those with higher levels of joint pain tended to perceive greater barriers to their AI treatment. Although we found that non-Whites are no more likely to discontinue AI treatment than Whites, previous work has shown that non-Whites are less likely to initiate AI treatment.[24,25] A number of factors have been examined to explain these differences, including lower rates of insurance coverage and a higher presence of comorbidities among minorities, but none have been found to fully explain racial disparities in AI initiation.[25] Health beliefs may help shed light on what is driving poorer rates of AI initiation among minorities as compared to Whites and should be explored in future research.

There are several limitations in this study. First, our measurement of adherence is based on abstracting information from notes in participants' medical records. This process relies on the reports of both participants and their physicians, which may not always be accurate due to recall and response biases. Second, all women in the current sample had been on an AI for at least one month and we were therefore unable to study

whether health beliefs predict AI initiation and non-adherence within the first month of AI usage. Third, health beliefs may change over the course of treatment and different health beliefs may be more salient at one point in time than another. A longitudinal study examining health beliefs at the beginning of treatment and at multiple time points over the course of treatment is needed to assess this. Lastly, our study was conducted in an academic cancer center limiting its generalizability.

Conclusion

We found that breast cancer survivors' beliefs about barriers to treatment predicted their AI adherence. Beliefs about AI-related pain and treatment length appeared to be the most salient barriers. Incorporating health beliefs into research and clinical practice may help to elucidate the challenges patients face in both initiation and continued use of AIs, and to optimize clinical outcomes.

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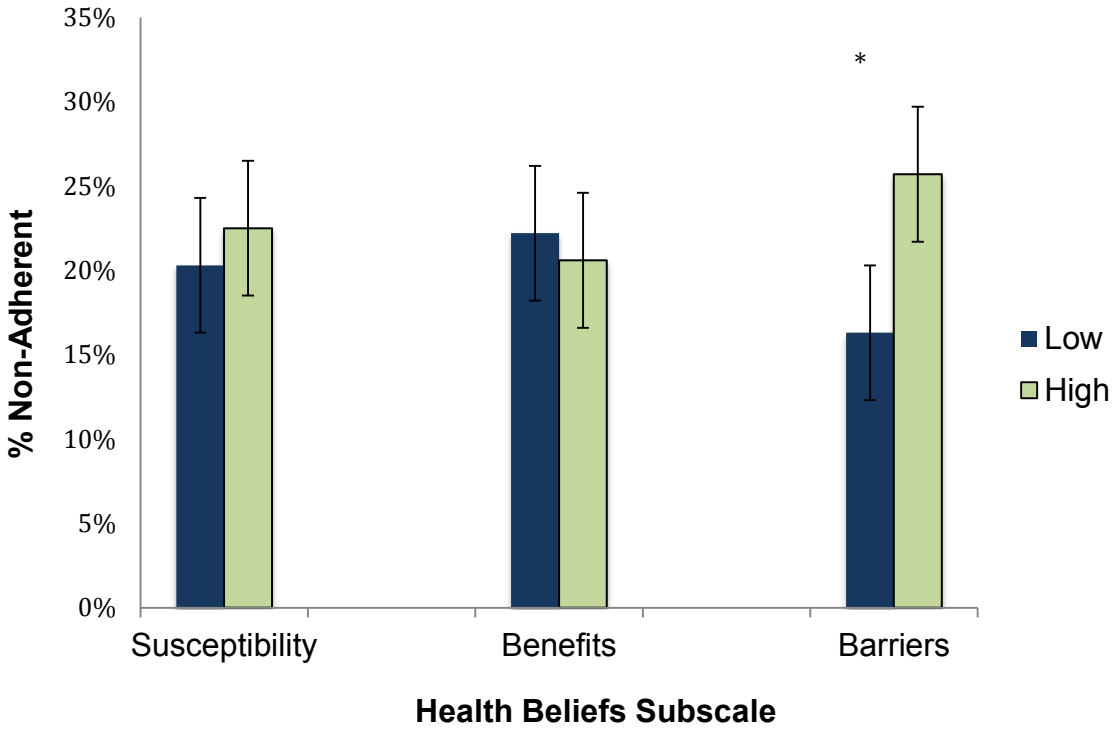

Figure 1. Relationship between non-adherence and health beliefs. Error bars represent 95% confidence intervals.* $p < 0.05$

Table 1

Health Beliefs Scale Items and Scale Properties

Item	Factor Loading[a]	Communality	Internal Consistency[b]
Perceived Susceptibility			0.87
1. It is likely that my breast cancer will come back	0.93	0.89	
2. The chances of my breast cancer coming back in the next few years are great	0.89	0.82	
3. I feel that my breast cancer will come back sometime during my life	0.79	0.61	
Perceived Benefits			0.77
1. Taking my AI exactly as prescribed will decrease the chance of my breast cancer coming back.	0.56	0.37	
2. Taking my AI is the best way to avoid my breast cancer coming	0.87	0.75	
3. Taking my AI will decrease my chances of dying from breast cancer.	0.95	0.89	
Perceived Barriers			0.83
1. I am afraid to take my AI because I don't understand how it works.	0.71	0.62	
2. I don't know how to go about getting my AI prescription filled on a regular basis.	0.80	0.66	
3. Taking my AI causes side effects that are embarrassing	0.75	0.53	
4. I have to take my AI for too many years	0.74	0.56	
5. Taking my AI is difficult because it causes pain.	0.81	0.62	
6. Taking my AI is difficult because it costs too much money.	0.65	0.45	
7. I have difficulty remembering to take my AI.	0.80	0.64	
8. I am too old to need to take an AI.	0.74	0.58	

[a] These loadings are based on the exploratory factor analysis.

[b] The internal consistency was calculated using the entire sample.

Table 2
Logistic Regression Analysis of Baseline Characteristics and Non-Adherence

Characteristic	N (%)	% Non-Adherent[a]	*P*
Total	437 (100%)	21.3%	
Age			0.34
> 70	79 (18.0%)	22.5%	
56-70	247 (56.6%)	19.7%	
≤ 55	111 (25.4%)	24.0%	
Race			0.88
White	360 (82.6%)	21.3%	
Non-White	76 (17.4%)	20.5%	
Living Status			0.61
Living with partner	266 (62.6%)	21.6%	
Living alone	159 (37.4%)	19.5%	
Education			0.10
Graduate school	153 (35.1%)	18.3%	
Four year college	105 (24.1%)	29.1%	
Some college	85 (19.5%)	16.0%	
HS or less	93 (21.3%)	21.7%	
Prior use of tamoxifen			0.22
No	290 (66.4%)	23.1%	
Yes	147 (33.6%)	17.7%	
Years since last menstruation			0.89
> 10	242 (56.1%)	20.7%	
5-10	108 (26.1%)	20.7%	
< 5	81 (18.8%)	23.0%	
Number of comorbidities			0.50
None	68 (15.6%)	20.0%	
One	133 (30.4%)	25.9%	
Two or more	236 (54.0%)	19.1%	
Years since start of AI			<0.001
<1	141 (32.3%)	37.8%	
1-3	152 (34.8%)	19.4%	
>3	144 (33.0%)	6.9%	
Brief Pain Inventory – Worst Joint Pain			0.04
0-3	277 (64.0%)	18.1%	
≥ 4	156 (36.0%)	26.8%	
HADS – Depression Subscale			0.70
Not Depressed	400 (91.5%)	21.0%	
Depressed	37 (8.5%)	24.3%	

Note. HADS = Hospital Anxiety and Depression Subscale.
[a] Based on imputed values for missing adherence data.

Table 3

Analyses of Health Beliefs and Non-Adherence

Characteristic	Univariate Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Perceived Barriers						
Low	1.00	-	-	1.00	-	-
High	1.78	1.10 – 2.88	0.02	1.71	1.03 – 2.86	0.04
Years since start of AI						
<1	1.00	-	-	1.00	-	-
1-3	0.40	0.23 – 0.68	<0.01	0.39	0.22 – 0.68	0.001
> 3	0.12	0.06 – 0.26	<0.001	0.13	0.06 – 0.26	<0.001
BPI – Worst Joint Pain						
0-3	1.00	-	-	1.00	-	-
≥ 4	1.65	1.03 – 2.67	0.04	1.48	0.89 – 2.46	0.14

Table 4

Relationship Between Health Belief Subscales and Demographic and Medical Variables

	Health Beliefs Subscales								
	Susceptibility Subscale			Benefits Subscale			Barriers Subscale		
Characteristic	% L	% H	*p*	% L	% H	*p*	% L	% H	*p*
Age			.54			.02			.57
> 70	54.1	45.9		46.7	53.3		51.3	48.7	
55-70	52.8	47.2		44.6	55.4		45.2	54.8	
≤ 55	59.3	40.7		29.7	70.3		49.5	50.5	
Race			.01			.24			.004
White	52.2	47.8		39.8	60.2		50.7	49.3	
Non-White	68.1	31.9		47.9	52.1		31.9	68.1	
Education			.45			.17			.77
HS or less	49.4	50.6		37.1	62.9		44.3	55.7	
Some college	58.8	41.3		51.8	48.2		45.2	54.8	
Four-year college	59.4	40.6		40.2	59.8		47.6	52.4	
Graduate school	52.8	47.2		38.4	61.6		50.7	49.3	
No of comorbidities			.05			.89			.94
None	41.5	58.5		39.7	60.3		47.8	52.2	
One	54.4	45.6		42.7	57.3		46.2	53.8	
Two or more	58.7	41.3		40.5	59.5		48.1	51.9	
Prior use of tamoxifen			.24			.26			.06
No	56.8	43.2		43.0	57.0		44.2	55.8	
Yes	50.7	49.3		37.4	62.6		53.7	46.3	
Years since LMP			.71			.009			.89
> 10	52.9	47.1		47.2	52.8		46.2	53.8	
5-10	54.9	45.1		32.4	67.6		49.1	50.9	
< 5	58.2	41.8		32.5	67.5		47.5	52.5	
Brief Pain Inventory – Worst Joint Pain			.31			.42			.004
0-3	56.6	43.4		39.3	60.7		53.1	46.9	
≥ 4	51.4	48.6		43.3	56.7		38.4	61.6	
HADS - Depression			.20			.72			.001
Not Depressed	55.6	44.4		41.4	58.6		49.7	50.3	
Depressed	43.8	56.3		37.1	62.9		20.6	79.4	

Note. HADS = Hospital Anxiety and Depression Scale.

%L = percent of participants scoring above the median on a particular health beliefs subscale.

%H = percent of participants scoring below the median on a particular health beliefs subscale.

CHAPTER 3:

Aging Perceptions and Risk of Medication Non-Adherence among Breast Cancer Survivors

Abstract

Background: Aromatase inhibitors (AIs) are a potentially life saving treatment for breast cancer survivors, yet poor adherence to treatment is a prevalent problem. A common adverse effect of AI treatment is arthralgia, which is commonly identified by survivors as a reason for treatment discontinuation. Women who experience arthralgia on AIs often report feeling they have aged rapidly while on the treatment. In the present study, we examined whether arthralgia-associated aging perceptions predicted women's risk of non-adherence. **Participants and Methods:** Five-hundred and nine post-menopausal breast cancer survivors who were on an aromatase inhibitor completed the Penn Arthralgia Aging Scale within two years of AI initiation. Adherence data were abstracted from medical charts by trained raters. Survival analysis was used to determine the relationship between aging perceptions and time to non-adherence. All analyses included adjustments for joint pain severity. **Results:** One-hundred and forty-four participants (28.3%) were non-adherent. As hypothesized, aging perceptions predicted non-adherence risk (adjusted HR, 1.71; 95% CI, 1.10-2.67; p = .02): Women with high levels of aging perceptions were at greater risk of non-adherence than women with low levels of aging perceptions. High levels of depressive symptoms were also uniquely associated with increased risk of non-adherence (adjusted HR, 1.63; 95% CI, 1.03 – 2.59; p = .04). **Conclusions:** These findings suggest that interventions that address negative beliefs about aging due to AI-related arthralgia can potentially improve rates of adherence to aromatase inhibitors.

Aging Perceptions and Risk of Medication Non-Adherence among Breast Cancer Survivors

Breast cancer is the second deadliest cancer among women.[1] Though treatments for early-stage breast cancer are effective, cancer recurrence remains a looming concern for many patients. Aromatase inhibitors (AIs), a form of adjuvant hormonal therapy for post-menopausal patients, help to decrease the risk of cancer recurrence and thereby decrease mortality rates.[2,3] Unfortunately, non-adherence to AIs is a prevalent problem[4–8] and leads to poor disease outcomes.[9] Many women identify joint pain, a common side effect of AIs,[10] as the reason they prematurely discontinue their treatment.[6,11] In a cohort study, joint pain severity was found to be a significant predictor of non-adherence risk such that women who scored above a predefined threshold of pain severity were more than twice as likely to prematurely discontinue their AI.[12]

Despite the strong relationship between joint pain and adherence, not all women with high levels of arthralgia stop taking their AI. Understanding psychological responses to arthralgia may shed light on who is most at risk of non-adherence. Pain often triggers complex cognitive responses that independently contribute to physical and psychological impairment. For example, anticipation of pain and pain catastrophizing explain variance in individuals' activity levels, even after pain severity is accounted for.[13–15]

For women on AIs, joint pain has been found to trigger negative thoughts about aging. Qualitative investigations and case studies have shown that women on AIs who experience joint pain tend to feel they are aging faster than they should be and that time is passing them by.[16–18] In prior cross-sectional work we have found that among AI

patients, arthralgia-associated aging perceptions explain variance in depression, anxiety, and the degree to which pain interferes with daily functioning, over and above pain severity.[19] In longitudinal analyses of non-cancer populations, negative aging perceptions have been associated with lower life satisfaction, worse objective physical functioning, and higher mortality risk, even after adjustments are made for health status.[20–25] Aging perceptions have also been linked to self-reported preventative health behaviors, such as diet and exercise.[22] In sum, negative aging perceptions have been shown to have considerable impact on a person's psychological and physical wellbeing, as well as on self-care behaviors.

We hypothesized that breast cancer survivors who had heightened perceptions of arthralgia-associated aging would be at greater risk of non-adherence to their AIs. Understanding the role of aging perceptions may help clinicians address the psychological component of pain that influences adherence to AI treatment.

Method

Participants were a cohort of postmenopausal breast cancer survivors from the Wellness After Breast Cancer (WABC) study. Inclusion criteria were the following: (1) female sex, (2) age 18 or older, (3) postmenopausal status, (4) diagnosed with stage I-III hormone receptor positive breast cancer, (5) prescribed a third-generation AI, (6) completed all primary cancer treatments (radiotherapy, chemotherapy, and/or surgery) at least one month prior to the survey date, and (7) fluent in English. Research assistants recruited cancer survivors at various stages in their AI treatment. Participants completed

a survey in the breast cancer clinic after providing informed consent. The study was approved by the Institutional Review Board of the University of Pennsylvania.

To provide a clearer picture of the relationship between our variables of interest, we created a more homogenous sample by focusing our analysis on participants who had completed the baseline survey not more than 2 years after AI initiation. Given that arthralgia symptoms tend to emerge early in AI treatment,[26] cognitive appraisals of aging due to arthralgia would also likely develop near the beginning of the treatment course. A total of 862 breast cancer survivors were enrolled in the cohort study. Of these, one withdrew from the study, 11 did not complete the survey, and seven did not have enough information in their charts to discern any adherence behaviors. To create a more homogenous sample, we excluded another 10 participants from the analysis because they were prescribed less than five years of AI treatment (five years is the treatment length recommended by the American Society of Clinical Oncology[27]). Of the remaining 833 participants, 509 were currently on an AI at the time of the survey, and had initiated their AI treatment less than two years prior, thus meeting inclusion criteria.

Measures

Non-Adherence. Adherence outcome data were abstracted from participants' medical charts with the most recent abstractions occurring in January of 2016. Non-adherence was defined as a treatment interruption (any time off an AI during the prescribed treatment period) and/or premature discontinuation (stopping the AI entirely before the prescribed treatment end-date). These two types of non-adherence were combined to achieve greater statistical power.

Trained coders abstracted adherence information from appointment and telephone-call notes in participants' medical charts. On average, participants were observed for 18 months post-survey. Prior to abstracting data for the current study, five research assistants were trained to interrater reliability using a different data set ($\kappa \geq 0.88$ for the occurrence of a treatment interruption; $\kappa = 1.00$ for the occurrence of premature discontinuation; ICC [1,1] ≥ 0.92 for time to first treatment interruption; ICC [1,1] $\geq .86$ for time to premature discontinuation). After data were abstracted from participants' charts, the first author re-abstracted a portion of cases (12.5%) to determine interrater reliability for the data used in the current analyses. The inter-rater reliability coefficients for the occurrence of treatment interruptions and for premature discontinuations were good to very good (treatment interruption: $\kappa = .75$; premature discontinuation: $\kappa = 0.87$). Inter-rater reliability was excellent for months to first treatment interruption (ICC [1,1]: .91) and for months to drug discontinuation or last known date of usage (ICC [1,1]: .94). (The former ICC was only calculated for participants for whom both raters agreed that a treatment interruption had occurred).

Aging Perceptions. As part of the baseline survey, all participants completed the Penn Arthralgia Aging Scale (PAAS), a measure that we previously developed and validated in a subset of the current sample.[19] The scale consists of eight items with a Likert-type scale ranging from 0 (*not at all*) to 4 (*completely*). Instructions ask participants to reflect on how their joint pain over the preceding week has impacted how they currently feel about their "bodies and states of mind." Items are summed, with a maximum possible total score of 32. The distribution of scores in this sample was not

normally distributed so we binned the variable into five categories. After the initial descriptive analyses, we combined the lowest four bins (participants with scores of 17 or below) into a "low aging perceptions" category, and the remaining bin was categorized as "high aging perceptions."

Covariates. Race, age, education, partner status, joint pain, and depression symptoms were collected via self-report. The length of time a participant was on an AI at baseline, the type of AI she was prescribed at AI initiation (anastrozole, letrozole, or exemestane), and the total number of medications the participant had been prescribed at baseline were abstracted from medical charts. We used the first item of the Brief Pain Inventory [28] to assess joint pain severity. This item asks participants to "rate your joint pain by filling in the oval beside the number that best describes your pain at its worst in the past 7 days." Anchors of the Likert-scale are 0 (*No pain*) and 10 (*Pain as bad as you can imagine*). This single item, when dichotomized at four or above, has predicted premature discontinuation in a sample of breast cancer survivors on AIs.[12] Depression, which has been found to be associated with non-adherence in a meta-analysis looking at a variety of illness groups,[29] was measured using the depression subscale of the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). We categorized scores into depressed or non-depressed using a validated cut-off score of eight (≥ 8 = depressed).[31] Age was split into three groups (less than or equal to 55, between 56 and 70, and greater than 70) given that prior research has shown that young and old age are associated with non-adherence.[32]

Statistical Analyses

Survival analyses, using Cox proportional hazards regressions, were used to model the time from participants' completion of the survey to non-adherence. We first conducted univariate analyses to determine which predictor variables should be included in the final model. All variables associated with time to non-adherence with $p < .10$ were selected. Participants were censored if they had not yet completed their AI treatment when their adherence data were abstracted from their charts or if they had experienced any of the following events prior to their completion of five years of AI therapy: breast cancer recurrence, metastasis, death, or lost to follow-up. Since some women in the cohort study discontinued their AI before they completed the baseline survey, and were therefore not included in this study, the current sample was left truncated. To account for the bias thereby imposed, time from AI initiation to study entry was used as the left-truncation (delayed entry) point.[33,34] All analyses were run in STATA version 14.1[35] and were two-sided, with *p*-values less than 0.05 indicating statistical significance.

Power analysis. A power analysis in STATA demonstrated that with a sample of 509 participants, we had 80% power to detect a hazard ratio of = 1.87, assuming 21% of the sample was not adherent, and that arthralgia-associated aging perceptions were moderately associated with covariates in the final model. The non-adherence rate of 21% was selected based on rates of non-adherence found in a similar cohort from the same cancer clinic.

Results

Participants

The majority of participants were White (80.4%), living with a partner (61.1%), and

had at least some college education (77.9%). The high majority of women were prescribed anastrozole and fell in the 56-70 age range. Overall, depression levels were low in this group with only a small portion (12.0%) meeting the clinical cut-off. The average length of time a participant had been on AI when she completed the baseline survey was approximately 12 months. See Table 1.

Non-adherence

Prevalence of non-adherence. Of the 509 participants, 144 (28.3%) did not adhere to their AI during the course of our observation. For 84 women (16.5%), their first non-adherence event was a treatment interruption (some of whom later prematurely discontinued), and for 60 participants (11.8%), their first (and only) non-adherence event was premature discontinuation.

Predictors of non-adherence

In univariate analysis, with the lowest category of aging perceptions as the referent group, only those in the highest of the five categories of aging perceptions had increased risk of non-adherence (HR, 2.30; 95% CI, 1.47 – 3.60, $p < .001$). See Figure 1. Consequently, aging perceptions was transformed into a dichotomous variable with the lowest four categories collapsed into one category (a score of 17 or below on the PAAS; coded as 0; $n = 426$), and the highest category of aging perceptions remained its own category (a score of 18 or above on the PAAS; coded as 1; $n = 83$). In univariate analyses, joint pain, depression, and AI type also predicted time to non-adherence ($p < 0.10$) and were included in the final model. See Table 2. Age, partner status, education

level, and medication count were not significantly associated with adherence (p was equal to or greater than 0.46) and were not included in further analyses.

The results of the Cox proportional hazard regression, which included all the variables selected from the univariate analyses, supported our hypothesis: arthralgia-associated aging perceptions predicted risk of non-adherence (HR, 1.71; 95% CI, 1.10 – 2.67; $p = 0.02$). Participants with high levels of aging perceptions were at 70% increased risk of non-adherence compared to participants with low aging perceptions, even after we adjusted for depression, drug type, and joint pain severity. Depression remained a significant predictor of adherence risk (HR, 1.63; 95% CI, 1.03 – 2.59), whereas joint pain did not (HR, 1.21; 95% CI, 0.84 – 1.75, $p = .30$).

To gain a better understanding of how aging perceptions may have impacted the relationship between the covariates and risk of non-adherence, we built a model without aging perceptions and subsequently added aging perceptions to see how the hazard ratios changed. Adding aging perceptions to the model reduced the hazard ratio for joint pain (from HR, 1.41; 95% CI, 1.01 – 1.98, $p = .047$ to HR, 1.21; 95% CI, 0.88 – 1.75, $p = .30$). Post-hoc examination of the relationship between joint pain and aging perceptions demonstrated that most participants with high aging perceptions also had high levels of joint pain, yet a substantial subset of women with high joint pain levels did not endorse high aging perceptions. See Figure 2.

With aging perceptions in the model, the hazard ratio of depression was reduced but remained a significant predictor of non-adherence (from HR, 1.94; 95% CI, 1.26 – 2.98, $p = .002$ to HR, 1.60; 95% CI, 1.01 – 2.55, $p = .04$). This suggests that although aging

perceptions and depression have overlap in explaining non-adherence risk, each variable also has unique effects. We then examined the relationship between aging perceptions and depression, given the likelihood that one could lead to the other. See Figure 3. They were found to be associated such that high aging perceptions was more common among women with depression than among women with no depression. Given the frequent finding in the literature that pain is associated with depression,[36] and may therefore be a third variable which explains the relationship between depression and aging perceptions, we conducted a logistic regression with depression as the dependent variable and aging perceptions as the predictor, followed by a second regression in which we controlled for joint pain. The odds ratio of aging perceptions was reduced but remained significant when joint pain was included (from OR, 8.59; 95% CI, 4.80 – 15.36, $p < .001$ to OR, 6.94; 95% CI, 3.63 – 13.24, $p < .001$).

Discussion

Our results suggest that breast cancer survivors on AIs who experience a heightened sense of aging in response to their joint pain are approximately 1.7 times more likely to non-adhere to AI treatment. Examination of the relationship between joint pain and aging perceptions revealed that higher levels of joint pain are likely necessary for developing high arthralgia-associated aging perceptions, but not everyone is susceptible to these cognitions: A substantial portion of women with high levels of joint pain did not have heightened levels of aging perceptions. This underscores the importance of considering survivors' psychological reaction to pain, and not just pain severity, in understanding their decisions related to treatment continuation.

Depression was also found to be a significant predictor of AI non-adherence. Prior literature on this topic has been mixed and has had many limitations[32,37–40]; this is the first study to investigate this relationship with a validated measure of depression in a demographically diverse sample of AI patients across multiple years of treatment. Interestingly, depression and aging perceptions were found to be significantly associated and their relationship was only partially explained by joint pain. Depression may be a risk factor for developing heightened aging perceptions. Alternatively, aging perceptions may, in part, lead to depression. Further research is needed to determine the nature of these relationships. Understanding their temporal order is important for knowing how and when to intervene.

Our findings can be used to inform the development of adherence interventions. To address heightened perceptions of aging, clinicians can employ both behavioral and cognitive approaches. Behavioral approaches can be used to increase physical activity (which some women mistakenly believe they need to avoid as a way to prevent further aggravation of their joints); physical activity can simultaneously reduce arthralgia pain[41] and potentially weaken individuals' negative beliefs about their agility. Cognitive interventions can be used to explore alternative interpretations of joint pain. For example, evidence from retrospective analyses of two different clinical trials suggests that AI-associated arthralgia is a positive sign that the treatment is working: Those who developed joint pain had a significantly lower risk of breast cancer recurrence and higher chance of overall survival compared to those who did not develop joint pain.[42,43] The authors of the study recommended that these findings be shared with patients to help

decrease non-adherence behaviors. Making patients aware of the positive associations of joint pain may help them re-conceptualize their side effects as a sign of increased longevity, as opposed to a sign of aging.

Limitations of this study include the method used to measure and summarize adherence. We collapsed treatment interruptions and premature discontinuation into one non-adherence variable even though it is possible that each type of non-adherence may be explained by a different process. Secondly, adherence was abstracted from patients' charts, which are subject to reporting bias on the part of patients, and recall bias on the part of both patients and clinical staff. Third, participants' were not recruited at AI initiation, and patients who discontinued their AI prior to enrolling into the WABC cohort study were not included in these analyses. Though we used statistical tools which greatly reduce this bias,[33] it may not have been completely eliminated.

Conclusions

Given the high prevalence of non-adherence among AI users, and the paucity of effective interventions to address this issue, our findings provide helpful information on what types of pain-related cognitions could be addressed in adherence interventions for women on AIs who experience arthralgia.

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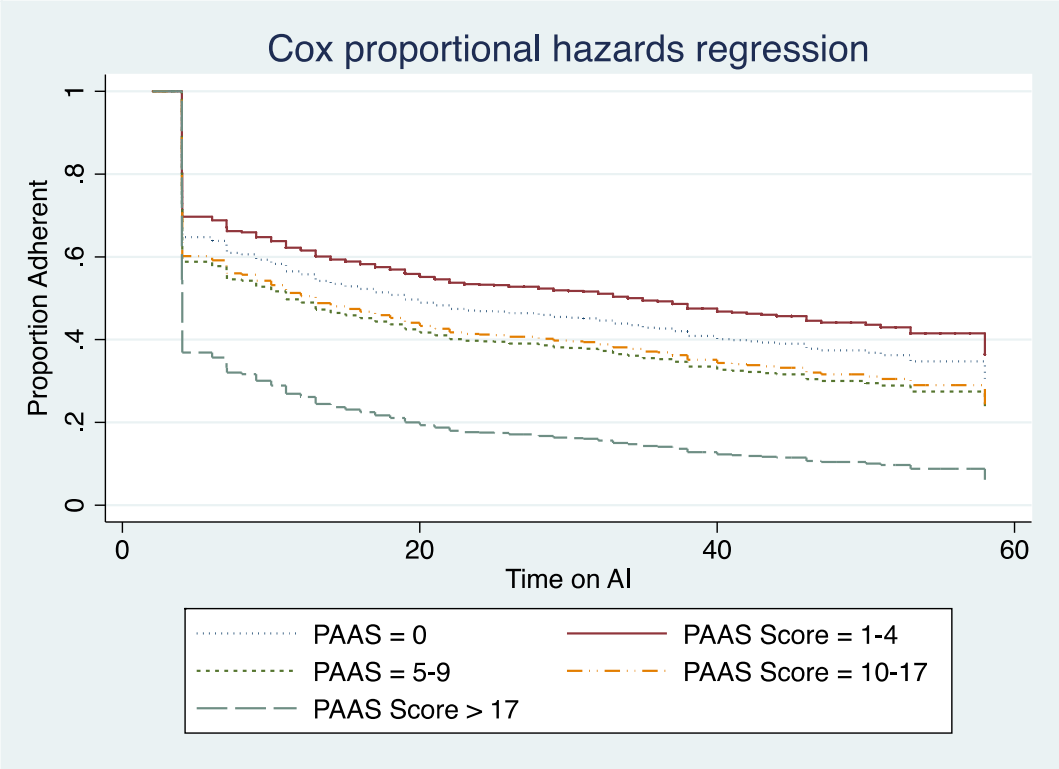

Figure 1. Survival curves of non-adherence by scores on the Penn Arthralgia Aging Scale (curves account for left truncation). PAAS = Penn Arthralgia Aging Scale.

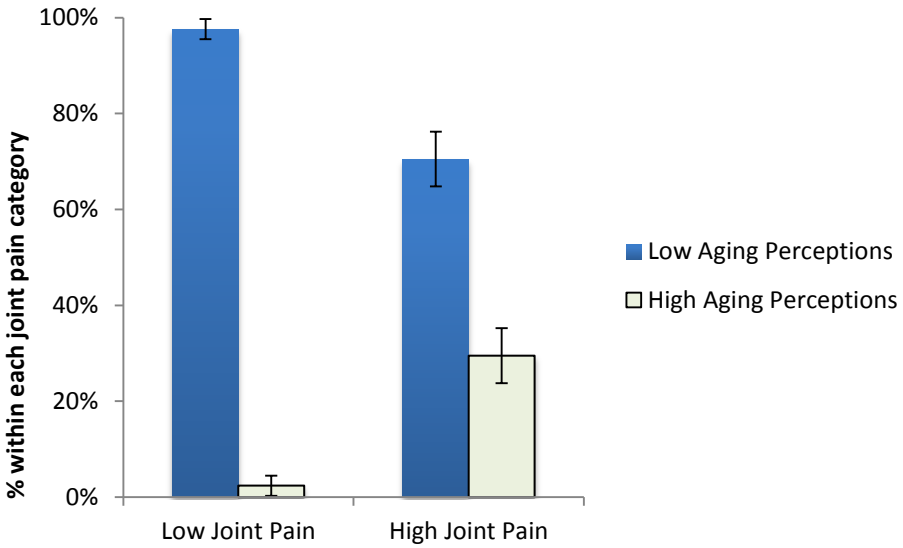

Figure 2. Relationship between arthralgia-associated aging perceptions and joint pain. Bars represent 95% confidence intervals. X^2 (1, N = 509) = 68.34, p < .001.

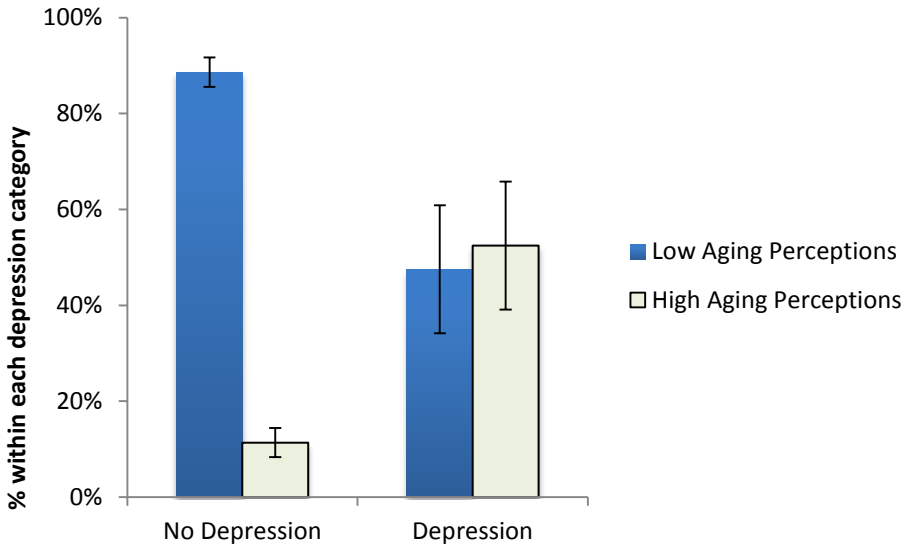

Figure 3. Relationship between arthralgia-associated aging perceptions and depression. Bars represent 95% confidence intervals. X^2 (1, N = 509) = 66.37, p < .001.

Table 1

Participant Characteristics (N = 509)

	N	%
Age		
≤ 55	105	20.6%
56 - 70	299	58.7%
> 70	105	20.6%
Race		
White	409	80.4%
Non-White	100	19.7%
Partner Status		
Living with partner	311	61.1%
Living alone	198	38.9%
Education		
Some college or more	395	77.9%
HS or less	112	22.1%
AI type		
anastrozole	448	88.0%
letrozole	15	9.0%
exemestane	46	3.0%
HADS – Depression Subscale		
Not Depressed (< 8)	448	88.0%
Depressed (≥ 8)	61	12.0%
	Mean	SD
Time since AI initiation (months)	11.9	5.1
Total Medications	9.0	4.8

Note. AI = aromatase inhibitor; HADS = Hospital Anxiety and Depression Scale; HS = high school.

Table 2

Univariate and Adjusted Analyses of Predictors of Time to Non-Adherence (N = 509)

	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Perceptions of aging						
Low	1.00	-	-	1.00	-	-
High	2.20	1.50 – 3.21	<.001	1.71	1.10 – 2.67	.02
Joint pain						
Low	1.00	-	-	1.00	-	-
High	1.51	1.08 – 2.11	.02	1.21	0.84 – 1.75	.30
Depression						
No depression	1.00			1.00		
Mild to severe	2.05	1.34 – 3.12	.001	1.63	1.03 – 2.59	.04
AI type						
anastrozole	1.00			1.00		
letrozole	1.20	0.69 – 2.09	.52	1.18	.68 – 2.06	.56
exemestane	2.36	1.10 – 5.07	.03	2.53	1.17 – 5.47	.02

Note. AI = aromatase inhibitor.

CHAPTER 4:

A Mixed-Methods Exploration of the Role of Partners in Breast Cancer Survivors' Adherence to Aromatase Inhibitors

Abstract

The relationship between marital status and cancer-specific mortality is particularly strong among breast cancer patients. It has been suggested that partner support provided in marriages may improve adherence rates to treatment, thereby increasing survival rates. The purpose of this study was to explore whether partner specific support for aromatase inhibitors (AIs), an adjuvant hormonal therapy for breast cancer survivors, was associated with increased AI adherence. We used both qualitative and quantitative methods to explore this topic. In the qualitative study, we interviewed 25 breast cancer survivors and 15 partners about the role of partner support in decision-making around AI initiation and continuation, and management of AI side effects. The sample represented both survivors who were still on treatment and survivors who had prematurely discontinued. In the quantitative study (n = 240), we examined cross-sectional associations between different types of received support and satisfaction with support, and whether these relationships differed among women with greater levels of pain from AI-related side effects. We also examined whether survivors with side effects received more support. In both studies, we found that breast cancer survivors placed greater value on emotionally nurturing support than on solution-focused support. Results of the qualitative study suggest that compared to partners of non-adherent survivors, partners of adherent survivors were more frequently aware of the impact of AI treatment on survivors' self-concept and provided more support around sexual dysfunction caused by AIs. The results of these studies suggest that couple interventions that focus on emotionally expressive communication

may help improve survivors' abilities to adhere to and manage the challenges of AI treatment.

A Mixed-Methods Exploration of the Role of Partners in Breast Cancer Survivors' Adherence to Aromatase Inhibitors

Marital status is a robust predictor of cancer-specific mortality. Aizer and colleagues found that in a sample of approximately a million patients, those who were married were less likely to die of cancer than unmarried patients, more likely be diagnosed at an earlier stage of disease, and also more likely to receive the most effective treatment available.[1] These relationships were true for both men and women. Surprisingly, for five of the ten cancers examined, including breast cancer, the survival benefits of being married outweighed those of chemotherapy. What explains this relationship is not entirely understood, but the existing evidence suggests that it is likely due to the social features, as opposed to the economic benefits of marriage. In a subsequent study of a similar sample size, Gomez and colleagues controlled for neighborhood SES and insurance status (public versus private), which were superior among married patients compared to unmarried ones, and found that the relationship between marital status and risk of mortality was only marginally reduced by including these covariates.[2] Among female patients, the relationship between marital status and survival was particularly strong for breast cancer. In both studies, widowed status was examined separately from divorced, separated, and never married, and the results held, suggesting that it is not a personality trait of those who are able to become or stay married that explains this association.

Improved adherence to anti-cancer treatments has been suggested as a likely explanation for the benefits of marriage.[1] A meta-analysis found that across a variety of disease groups, married individuals are more likely to be adherent to their treatments.[3] Furthermore, many studies have shown that partner support is a predictor of whether a patient will persist with his or her treatment regimen.[4–8] Among cancer patients, however, the role of partner support in adherence has not been extensively studied. Partner support may directly help women in the daily struggles of managing side effects and the bigger decisions about whether to continue or discontinue their treatment regimens; partner support may also impact adherence by relieving or preventing depression (a robust predictor of adherence outcomes).[1,9] Understanding which elements of a partner's support actually bolster adherence behaviors may improve our ability to help married couples maximize the benefits of support that they can provide one another, as well as help clinicians distill the helpful elements of spousal support into support groups for cancer patients who are not married.[1,10]

Adherence is an especially pressing issue for breast cancer survivors who are on endocrine therapy (ET). Post-menopausal breast cancer patients with hormone-receptor positive cancer are prescribed aromatase inhibitors (AIs), the newest and most effective class of ET.[11] AIs have been shown to decrease the risk of recurrence, but rates of non-adherence are high. In a study of 2,313 breast cancer survivors, 29% prematurely discontinued their AI, and 28% of the remaining participants did not fully adhere to their treatment regimen.[12] Other studies have shown even higher rates of non-adherence.[13] The prescribed length of treatment recommended by the American Society of Clinical

Oncology is five years,[14] but new research suggests 10 years is more effective.[15] If the standard length of treatment increases, non-adherence will likely become an even more prevalent problem.

Partner supportiveness may be especially important for this population given the negative impacts AIs can have on both patients' and partners' quality of life. Vaginal dryness and arthralgia, two commonly experienced adverse effects of AI treatment,[16,17] can be detrimental to couples' sexual intimacy and their general levels of co-activity. A partner who can remain supportive in spite of these potentially adverse effects may make the difference in whether a woman is able to persist with her treatment. Additionally, patients must grapple with the uncertainty of the drug's personal benefit to their health outcomes: Given that the drug's efficacy is measured by the absence of recurrence, it may be difficult for patients to see the immediate benefits of their daily persistence with taking the medication, unlike other diseases such as diabetes or HIV, in which medication adherence has direct and immediate effects on biological outcomes (glucose levels and viral load, respectively) which are easily and frequently measured and given to patients as feedback during routine care. Partner support may be crucial under the strain of such uncertainty.

Despite general findings in the literature that support has beneficial effects on psychological and health outcomes,[18,19] there is also literature to suggest that support can be unhelpful or even detrimental if delivered in certain ways.[20] A number of studies have shown that support that is visible to its recipient can undermine self-efficacy and cause increases in negative mood, whereas support that is provided but the recipient is unaware

of, is most beneficial.[21,22] Building on this literature, one study further examined this phenomenon and found that both visible and invisible support produce either positive or neutral effects if either the recipient, provider, (or both) perceive the support to be responsive to the recipient's need to feel understood, cared for, and valued.[23] In sum, these findings highlight the need for a nuanced investigation of the role that partner support may play in adherence to AIs.

This study will use both qualitative and quantitative methods to explore how partners may impact breast cancer survivors' adherence to AIs. Three studies have examined the role of general support on ET adherence (with no significant findings),[24–26] but to our knowledge no study has specifically looked at the role of either AI-specific support, or partner-specific support. We focused our analyses on the presence of social support behaviors as well as patients' interpretation of how responsive these support behaviors were to their needs.

Both the qualitative and quantitative studies use a multidimensional model of support that comprises four different support dimensions: emotional/esteem support, tangible support, informational support, and physical comfort. These dimensions of support were factor analytically derived and cross validated using three different samples of married and dating partners.[27] These support types provided the framework for the qualitative interviews as well as the self-report support measures for the quantitative study.

The primary purpose of the qualitative study was to provide an in-depth understanding of how partners support survivors who are experiencing side effects on AIs, survivors' internal responses to this support, and how involved their partners are in

decision making around AI treatment. Women who adhered to their AI as well as women who did not were interviewed to ascertain whether their experiences of support differed. Discrepancies between patient and partner reports of social support are common;[28–30] therefore the perspective of spouses was also included in the qualitative analysis.

In the quantitative study, we focused on answering the following questions about women on AIs: 1a) Which type of AI support has the greatest association with satisfaction with support?; 1b) Are different types of support preferred among those who suffer from adverse side effects of AIs? 2) What type of support is most frequently received? 3) Did women with greater side effect severity receive more support?
Both the quantitative and qualitative studies were conducted with samples of women recruited from the same breast cancer clinic at an academic teaching hospital. Therefore, there is some overlap between the samples.

Qualitative Study

Method

Participants. Inclusion criteria for survivors were (1) female sex, (2) age 18 or older, (3) postmenopausal status, (4) diagnosed with stage I-III hormone receptor-positive breast cancer, (5) prescribed a third-generation AI, (6) completed all primary cancer treatments (radiotherapy, chemotherapy, and/or surgery) at least one month prior, (7) fluent in English, (8) currently living with a romantic partner, and (9) currently experiencing or had experienced significant joint pain from the AI treatment. The last inclusion criteria was determined by administering the first item of the Brief Pain Inventory[31], which asks participants to rate their pain at its worst in the past 24 hours. A

score of 4 or higher out of 10 (with 0 indicating *no pain*, and 10 indicating *pain as bad as you can imagine*) was used as the cut-off for inclusion because it has been shown to predict premature discontinuation of AIs.[32] Partners were not contacted until the survivor granted permission to the recruiter to do so. There were no exclusion criteria for partners. Purposive sampling was used to ensure that an approximately equal number of adherent and non-adherent women were included in the study. All participants provided written informed consent. Adherence status was gathered from women's self-report at the time of recruitment. Discontinuation of the drug prior to completion of the prescribed treatment length, or taking a treatment break, were both considered non-adherence. Participation of partners was not a requirement for survivors' participation.

The sample comprised 13 adherent survivors and 9 of their partners, and 12 non-adherent survivors and 6 of their partners. Ten of the non-adherent survivors had completely discontinued treatment prior to being recruited to the study; the remaining two had taken treatment breaks but were currently on the AI at the time of the study. Survivors ranged in age from 36 to 73 years old (M = 59.52, SD = 8.36). All couples were concordant on race. The majority of the sample was White (87.5%), 7.5% were African American, and 5% were Asian. One couple was same-sex; the other couples were heterosexual. Non-adherent survivors had been on an AI an average of nine months (SD = 5.31) before prematurely discontinuing or taking a treatment break. Adherent survivors were on an AI for an average of 27 months (SD = 15.00) at the time they were interviewed. On average, joint pain severity was significantly higher among survivors in

the non-adherent group (M = 7.58, SD = 1.81) than in the adherent group (M = 5.85, SD = 1.77), $t(23) = -2.58$, $p = .02$.

Data collection. The interviews were conducted by the first author who was a doctoral candidate in clinical psychology in her early 30s without any personal experience of breast cancer. Interviews took place in participants' homes ($n = 35$) or at the University of Pennsylvania ($n = 5$). All participants were compensated $25 for their participation. The semi-structured interviews lasted between 12 and 62 minutes and were audio-recorded. Questions at the beginning of the interview were broad and asked participants to reflect on the overall experience of being on an AI (or being the partner of someone on an AI). This was intended to minimize the impact of the authors' assumptions and preconceived notions on the types of responses that were gathered.[33] Questions became more focused on particular aspects of partner involvement as the interview progressed. Undergraduate research assistants and a transcription company (Rev.com) transcribed the interviews. All transcripts underwent a quality check in which the first author listened to a randomly selected portion (10%) of the original audio of each interview and compared it to the transcript. Transcripts that had errors were re-transcribed.

Data analysis.

Coding. As soon as the first five survivor and five partner interviews had been completed, the first and second authors independently coded them using NVivo 11 Software.[34] Each code was intended to capture a recurring idea or topic. Codes were assigned to meaning units, which could be any length of text – a word, full sentences, a

string of paragraphs, etc. The coders met on multiple occasions to come to an agreement on which codes to include in the codebook. Only codes relevant to the topic of partner support are discussed in this study.

The remaining interviews were split between the two coders, and 20% of survivor and partner interviews were randomly selected to be coded by both coders. Inter-rater reliability was assessed on multiple occasions, and the coders met periodically to discuss disagreements and refine and augment the codebook as necessary.

Analysis. Data were analyzed using a grounded theory approach. Codes were placed into higher-order categories to further organize the data. As more interviews were coded, category titles were changed and codes were reorganized. To identify themes, we engaged in a method of constant comparison between cases,[35] with a focus on comparing adherent survivors to non-adherent survivors, and partners of adherent survivors to partners of non-adherent survivors. To identify differences in how survivors and partners interpreted the same events, we also compared survivor and partner interviews. In the last four interviews, no new themes emerged and it was determined that theoretical saturation had been reached.[35] Themes that emerged from this method were then integrated into a theory about the role of partners in AI adherence.

Results and Discussion

Codes fell into the following categories: Partner Engagement in Treatment, Partner Awareness of AI Impact, Partner Support of Symptom Management, Impact of AIs on Partner and Relationship, Partners' Characterization of Survivors' Coping Style, Partner Involvement in Daily Adherence, Survivor Responses to Support, and Integration of

Partner into AI Decisions. A kappa statistic was calculated summarizing the inter-rater reliability of the codes within each category. Inter-rater reliability fell in the good to very good range (K = .71 - .91) for all except two categories: Partner Awareness of AI Impact (K = .60; moderate) and Partner Characterization of Survivor's Coping Style (K = .38; poor). Due to poor reliability, interview content labeled with the latter code was not analyzed. See Table 1.

Partner Engagement in Treatment – Aware But Not Necessarily Present.

Among adherent patients, all partners attended at least some of their wives' follow-up appointments, while others attended every single one. Some even described their partners being actively involved in discussions with the oncologists, by either providing a perspective on the patient's symptoms or asking about treatment options: "Yeah, and he's like filling in and saying no, no, that's not what you said to me. Or, that's not what happened, and so that felt really good." Among patients who were non-adherent, a subset of partners also regularly attended follow-up appointments; however, about half had partners who had not been to any. One patient who had discontinued her AI one month into treatment commented, "If I asked him who my doctor was, he has no idea. No idea what his name is. I think he met him once and that was the day of the surgery. That was it." One partner of a non-adherent patient, who offered to accompany his wife but was turned down, explained that his presence at appointments is only useful when his wife has a physical barrier getting to and from her appointments, but that she is the one with the "steel trap mind" in terms of interpreting and remembering medical information when interacting with the oncologist.

Despite varying levels of involvement in follow-up appointments, the high majority of partners were aware that their partners were on AIs and what the purpose of the medication was. A few did not, but this did not appear to be a more frequent trend among non-adherent patients than adherent ones. Knowledge of AIs ranged from a very in-depth understanding of the mechanism of the drug, to a general understanding that it "kept the cancer at bay."

Received Support.

Physical Affection. Physical affection was infrequently discussed by participants. Occasionally a survivor would mention getting a hug or cuddle from their partner, but there were no apparent differences between adherent and non-adherent patients.

Tangible support. In both groups, some partners took over numerous household responsibilities and/or picked up AI refills for their spouses, while others did nothing in the form of tangible support. One difference that did emerge was that unlike partners of non-adherent survivors, some partners of adherent survivors accompanied their wives to exercise classes.

Informational support. Common suggestions partners would make when survivors were feeling side effects were to call their doctors to discuss their symptoms or to get out of the house to exercise or socialize. In the non-adherent group, many patients reported that their partners suggested they discontinue their AI treatment: "He didn't want me to go back on anything no matter what…he goes, 'because it's not worth it.'"

Emotional support. Among adherent survivors, all participants described ways in which their partners supported them emotionally. Common ways that partners expressed

emotional support were by providing sympathy and comfort, and listening to them. Many adherent survivors also discussed how their partners were very patient and understanding around sexual issues related to vaginal dryness caused by the AI treatment, and supported survivors in their efforts to resolve the issue, whether it be pelvic floor physical therapy, using a vaginal dilator, or "spending more time trying to get me stimulated." In the non-adherent group, sympathy and listening were also provided but supportive behaviors around sexual intimacy specifically were only mentioned by one individual. In addition, a substantial number of non-adherent survivors noted that their partners did not offer any emotional support. One survivor recalled how when she told her husband she was not feeling well, "I just remember him saying it was probably the medicine. That's all. Then he probably got in front of the TV or the couch or whatever." Some non-adherent survivors described how their partners lacked emotional sensitivity; one said hurtful things regarding her symptom management: "…my husband said last night I have been useless for three years pretty much." Another non-adherent survivor, who suffered from cognitive dysfunction (which may have been due to the AI treatment), described how she felt that her symptoms "annoyed" her husband.

Emotional Responses to Partners' Support – Mixed Messages. Though all participants who received support expressed appreciation in the interviews, many acknowledged that they did not always like how it made them feel. Among both groups, mixed emotional reactions to support were common. For example, informational and tangible support sometimes had the unintended effect of making survivors feel misunderstood; suggestions made by partners could feel like superficial solutions to

greater problems. Per one survivor, “My husband's wonderful, and he's very supportive, but I don't think men read things the way we always intend them to. You know what I'm saying? If I say I'm tired, he'll say lay down, I'll rub your back till you fall asleep. That's not what I'm talking about. I'm exhausted from everything.” Another participant explained how suggestions from her partner would often aggravate her:

> *I think it’s a combination of kind of self-pity. It’s like, uh, nothing is going to work; I’m not even going to bother trying, you know, sort of that weariness of please stop suggesting things because my life just sucks, and I just want to wallow in self-pity. And part of it is I’ve you know I’ve tried some of the quick solutions, and it’s, it’s not working, um, and the resentment that I, I don’t want to have to take, I don’t want to do another thing to deal with the side effect of something that is, uh, there’s just like this cascade.*

One partner of an adherent survivor was sensitive to this issue and noted: “It's frustrating too because not having gone through exactly the same kind of experience, it's hard for me to try to come up with ideas. Where I can help her without lecturing.”

Most survivors were appreciative of the day-to day-help their partners provided but partners’ offering too much tangible support could have the negative consequence of making survivors feel “incompetent,” as if their partners did not believe they were capable of managing things anymore. Or it was simply irritating that partners were doing household chores, such as laundry, differently than the survivors would have.

Some survivors also had negative reactions to their partners’ compliments about their physical appearance. They expressed feeling self-conscious about how AIs had impacted

their weight, or the appearance of their hair, and that compliments felt disingenuous. "He'd say your hair is beautiful. You look beautiful. Then I would like inside get really annoyed because I know what I'm supposed to look like, and I look like I'm 90 years old." One individual, who described how her symptoms of vaginal dryness had severely affected her and her partner's sexual lives, explained her emotional response to his compliments on her appearance: "Like it's just something that needs to be, like he's just saying it because he feels he has to, if only, because I just deeply don't see it." The combination of sexual dysfunction and appearance changes caused by AIs may have a compounding effect that may make women feel particularly undesirable, and therefore highly sensitive to any comments related to physical intimacy or appearance:

> *I feel so unattractive on, I mean that's just part of who I am anyway, but this whole experience I just feel so unattractive so that I'm more uncomfortable when he says, you know, oh, you're beautiful, I want to be intimate. And I'm like ugh, but I feel like, you know, I have this big S for survivor hanging over my head and that's all I am. So, ironically it's, it's when he tries to be at his most supportive, it's hardest. Does that make sense?*

Yet for another participant who felt self-conscious about her appearance, not getting any compliments from her partner was also detrimental: "It would be nice for him to say, I still find you attractive…it might be just in that when I was younger, you know, I was sure of my attractiveness, so I would be like, ah, you don't have to say that kind of stuff, I don't need that kind of stuff, and and when you get older, you definitely do." These results suggest that it is challenging for partners to strike the right note in how they offer

emotional support around their wives' appearance, and that the best of intentions may backfire.

Partner Awareness of AI Impact.

Superficial Communication with Partners About Impact of AIs. Communication with partners about symptoms varied. Some survivors and partners reported a lot of communication about symptoms (mostly in the form of "complaining"), while others reported that the survivor conveyed very little to her spouse about the symptoms she was going through. These patterns could be found in both the adherent and non-adherent groups. What was notably absent from either group was mention of any communication with partners about how survivors' symptoms impacted their self-esteem and self-concept, a relevant issue for many women.

Partner Awareness of Survivors' Symptoms and Their Impact – Some Partners Get It. In both the adherent and non-adherent groups, a small minority of partners were not aware of the survivors' AI symptoms. Interestingly, there was a pronounced trend among partners in the adherent group versus the non-adherent group in demonstrating a sensitivity to the ways in which symptoms were affecting their wives' self-concepts. For example, one partner discussed how the AI treatment was negatively impacting her identity as a woman: "Well, it affects how she feels about herself, what she thinks of herself. It makes her ... I think it makes her ... some of the effects make her feel older. That, somehow, she's losing a lot of her, I guess in my case I'd say manhood, in her case it's her feeling of being a woman. I think that bothers her." Another partner of an adherent survivor also picked up on how the drug impacted her sense of age: "She

certainly hasn't enjoyed taking the medicine because she, she feels there are some side effects that you know make her feel decrepit and old." A partner who was not aware of the specific symptoms his wife was dealing with was nevertheless able to articulate her emotional response to her current physical condition: "She doesn't… she feels distance from herself. She doesn't feel like she's in her you know, in, in her proper skin."

Interestingly, the survivors of these partners indicated that though their partners were supportive in one way or another, they were not clued in to their emotional experiences and needs (e.g. "I have to say, comfort is not my husband's strong suit. He's a good guy, but like many men, when you talk about a problem, he wants to solve the problem, instead of just listening to you process the problem"). Therefore, it is unclear how these partners were able to come to these insights about their wives' experiences. Given that there was no mention in the interviews of survivors conveying these feelings to their partners, it is unclear if survivors told their partners about their insecurities but did not think to mention this during the interviews, or partners intuited them without being directly told. If the latter is true, it is possible that some partners may be sensitive to survivors' emotional states and may be supportive in ways that survivors are not fully aware of (invisible support).

Impact of AIs on Relationship.

Impact of AIs on Relationship in Daily Living and Activities – From No Change to Utter Turmoil. About half of the couples in each group reported that the AI did not impact their daily existence or activities with their partner. The other half, on the other hand, did describe how the AI impacted their time together, whether it be that they stayed

home more because the survivor was often fatigued, or cognitive issues caused by the AI caused challenges in daily interactions, or time spent together was not as high in quality as it had once been. In the adherent group, these changes could be substantial but were not described as drastic (e.g. "we used to be physical, we used to hike and…you know, take vacations that were high energy type vacations and stuff"). In the non-adherent group, on the other hand, there were many examples of how the AI had a significant impact on couples' interactions and/or functioning. One spouse explained, "A lot of it has changed. I think it's just the increased responsibilities that are placed on the spouse that's just crazy…It's like, 'Can you do this', but it's because of the side effect or ... There's just no normal…And it's just insane." A survivor who discontinued her AI explained how the side effects of the drug dramatically changed the roles in her relationship: "I feel now like he's more my caretaker than my husband. After a while I started to feel like he was my nurse almost. I think that changes the way things are. I mean we're together 45 years, but it's like you lose your pride." Another survivor explained: "When we talked, we didn't, I mean, we talked, but there was no communication. It was terrible. I mean, we're married 35 years. It was probably the worst time in our marriage. We'd been through some pretty big things." Notably, the survivors for whom the AI seemed to have the most negative impact on their relationship also described symptoms consistent with moderate to severe depression (not getting out of bed for days at a time, losing all interest in spending time with friends, etc.).

Impact of AIs on Sexual Intimacy. Responses to questions about how AIs impacted sexual intimacy fell into one of three categories: 1) AIs have decreased sexual intimacy

or made it more difficult; 2) AIs have had no impact; or 3) AIs have had no impact because there was no sexual intimacy to begin with. The frequency of these different responses did not seem to vary by group. Participants who experienced a decline in sexual intimacy most often cited vaginal dryness as the cause; however, other causes that were mentioned included hot flashes and mood.

Integration of Partner into AI Decisions.

AI Initiation – Not a Joint Decision. Partners tended not to take a decisive role in their partners' initiating AI treatment. A small subset of couples viewed the AI as part of the treatment package, and not necessarily something that was its own decision point. "I think it was just considered part of my treatment…I think it's considered a package deal." For other survivors, initiating the AI was a decision they made with their oncologists with their partners present; in this regard it felt as if their partners were involved in the decision even if they did not necessarily weigh in with an opinion about the treatment. Others explicitly mentioned that they did not consult with their partners about it, and that it was "not a joint decision." No differences emerged between adherent and non-adherent participants.

AI Discontinuation – Unimaginable or Do What you Need to Do. With one exception, partners of adherent survivors never suggested that their wives discontinue the drug. One partner even broached the topic of staying on the AI beyond the prescribed five-year period. Most women did say that if they were to consider discontinuing the AI, they would probably discuss it with their husbands before taking any action. Most partners, when asked how they would respond if their wives broached the topic of

discontinuation, responded by saying that they cannot imagine that scenario ever happening given their wives' commitment to the treatment, or that they would push back.

Among non-adherent patients, per both patient and partner report, there were more instances of partners' advising survivors to explore the options of discontinuation. One survivor described how her frequent complaining about her side effects may have pushed her husband over the edge: "Actually I think at one point he probably in frustration said, just email the doctor and stop." This advice was not always welcomed. One survivor initially pushed back: "He – well no – he didn't want me to go back on anything no matter what. He goes, because it's not worth it…So I said, well, these are the points. He says, that's ridiculous. Why are you even thinking about it?" Another survivor was offended by the suggestion, and thought to herself, "but don't you care if I have a recurrence?" All three of these women, however, eventually discontinued their treatment and expressed an understanding of where their partners were coming from. For other non-adherent survivors, partners felt it was their role to be supportive of their wives' decisions, whatever those decisions were. Before discontinuing, the majority of women did mention to their spouses that they would be going off the treatment; however it was more in the vein of informing them, than asking for input. "Oh yeah, I have this very clear memory of saying, being kind of distressed by it, and thinking, and I was telling him that the neuropathy, I was noticing it again, and it seemed to be getting worse, and I told him I think I am going to go off it." Given their suffering on the drug, most partners responded with encouragement to go forward with their decision to discontinue (even if internally they were nervous about the fallout of that decision: "Of course I would want

her to be on the thing that's most likely to prevent the cancer from coming back, but I also had to be sensitive to the quality of her life and sort of take her cues… It made me slightly anxious, but I trusted her opinion about it.") Only one partner openly objected and expressed concern to his wife: "He said 'well, you have to take it,' he thought it was just too dangerous, that the cancer would come back or something like that." This had no impact, however, on her final decision to discontinue.

Theory of Partner Support and Adherence. The findings of this study suggest that the most crucial aspects of partner support in influencing AI adherence are being tuned into the experience of breast cancer survivorship, through a combination of integrating oneself into follow-up care and being sensitive to the emotional and sexual challenges of being a breast cancer survivor on AIs. These findings lend validity to the importance of looking at AI-specific support for understanding how partners may facilitate survivors' adherence to treatment, and offer ideas for further research in understanding how partners may help survivors adhere to AIs.

Quantitative Study

Method

Participants and setting. Data for this study came from a larger cohort study (WABC) of post-menopausal breast cancer survivors who had been prescribed AIs. Inclusion criteria were the same for this study as the qualitative study, but with two differences: Participants in this study were required to be on an AI at the time they completed the survey, and they were not required to have joint pain (n = 240). All participants provided written informed consent.

Measures.

Social support. To measure received social support, we created a reliable short form of the Support in Intimate Relationships Rating Scale (SIRRS) which asks participants to indicate on a Likert-type scale ranging from 0 (*never*) to 4 (*always*) how often their partners engage in different supportive behaviors. The original measure comprised four different domains of partner support: emotional/esteem support, tangible support, physical comfort support, and informational support.[27] We tailored the items of the SIRRS to the context of AI management and added an item about partners' reminding women to take their AIs. Breast cancer survivors provided feedback on our modifications. Feedback was incorporated into the final version of the 17-item measure. We conducted an exploratory factor analysis on the modified version of this scale (see Results).

Satisfaction with support. An item relating to participants' satisfaction with the support they received was included in the survey: "How satisfied are you with the level of support your partner provides for taking your AI and managing its side effects?" (Likert-type scale ranging from 0 [*not at all*] to 4 [*very much*]).

Depression. Given that depression may impact perceptions of received support, and has been linked to relationship satisfaction in prior literature,[36] we controlled for depressive symptoms in our analyses with the depression subscale of the Hospital Anxiety and Depression Scale. This scale has been validated among cancer patients.[37]

Symptoms. Joint pain, one of the most commonly endorsed side effects of AIs, was measured with the first item of the pain severity subscale of the Brief Pain Inventory.

This 11 point Likert-scale item asks participants to recall the worst join pain they experienced in the past week. This item (when dichotomized at four or above) has been found to predict AI adherence.[32]

Results and Discussion

Power analysis. A power analysis[38] indicated that there was greater than 80% power to detect a medium effect size of $f^2 = .15$ in a hierarchical regression with one independent variable in step 1, and nine independent variables in step 2 (this was the highest number of predictors in any of the models).

Description of the sample. The mean age of participants ($n = 240$) was 61 years old (standard deviation = 8.5 years). Survivors were, on average, 5 years past their diagnosis at the time they completed the survey. The majority of participants were White (89.5%) and highly educated (64% of the sample had at least a college degree). A small subset of participants (8.3%) met the clinical cut-off for depression on the HADS (≥ 8) and 43.6% endorsed joint pain at 4 or above (out of an 11-point scale). Correlations of study measures are presented in Table 2. Given the non-normal distribution of some of the study variables, Spearman correlations were used.

Factor structure of the modified SIRRS. Exploratory factor analysis using mean and variance adjusted weighted least squares (WLSMV) estimation and geomin (oblique) rotation was applied to the modified version of the social support scale to determine its factor structure. An exploratory, rather than confirmatory approach was used given that the wording of most of the items were altered from their original version. The same factors were found as in the original scale: Physical Comfort, Emotional/esteem Support,

Informational Support, and Tangible Support; however, a few items loaded onto different factors. Item 4 ("Said good things to me") loaded onto the Physical Comfort subscale in this sample as opposed to the emotional/esteem support subscale. We therefore renamed it the "Affection" subscale. Item 15 ("Restated what I had told him/her about taking my AI as prescribed or managing its side effects"), which loaded onto Informational Support in the original scale, loaded onto the Emotional/esteem Support subscale; and Item 13 ("Offered to help me indirectly with taking my AI as prescribed or managing its side effects") had salient loadings on both the Tangible Support and Emotional/esteem Support subscales. Given that the loadings were similar in size, we chose to include it in the Tangible Support subscale, since it belonged to this subscale in the original version of the measure. All subscales had good to excellent internal consistencies (α = .93 for Affection; α = .86 for Emotional / Esteem Support; α = .84 for Tangible Support; α = .89 for Informational Support). The correlation between factors ranged from .22 to .71. See Table 3 for factor loadings. Median values for total scores on the Affection subscale were high (11 out of a possible score of 16), whereas median scores on the other subscales were generally low (4/20 for Emotional/esteem Support; 1/12 for Tangible Support; and 0/20 for Informational Support).

Question 1a) Which type of AI support has the greatest association with satisfaction with support? A hierarchical regression with depressive symptoms entered in the first step, and the four support subscales entered into the second step was conducted to determine which type of support had the greatest association with support satisfaction. Cook's D and conditioned indexes were examined to ensure that the

assumptions of linear regression were not violated. One case was removed for exerting too much influence on the analysis. After accounting for depression, which was significantly associated with support satisfaction (semi-partial correlation *[sr]* = -.22, $p <$ .001), received affection had the strongest association with support satisfaction (*sr* = .30, $p <$ .001), followed by emotional/esteem support (*sr* = .11, p = .052). Neither tangible support (*sr* = .02, p = .73) nor informational support (*sr* = .00, p = .98) were significantly associated with support satisfaction. A second regression was repeated with just affection and emotional/esteem support entered into the second step without the other two support subscales. These two support subscales explained an additional 24.4% of the variance in support satisfaction.

Question 1b) Are different types of support preferred among those who suffer from adverse side effects of AIs? A hierarchical regression was conducted with depression entered in the first step, and joint pain, each of the four support subscales, and the interactions between joint pain and each support subscale (four interactions in total) entered in the second step. All predictor variables were mean-centered to reduce multicollinearity. The effect for joint pain was marginally significant (*sr* = -.10, p = .09) such that women with higher joint pain levels were less satisfied with the support they received. None of the interaction terms were statistically significant ($p >$ .13) indicating that women with higher levels of joint pain did not prefer different types of support than women with lower levels of pain.

Question 2) What type of support is most frequently received? Due to the substantial positive skew of the informational and tangible support subscales, the

Friedman non-parametric test for repeated measures was used to test for differences between social support factors. The overall test was significant ($p < .001$). Post-hoc Wilcoxin tests were conducted using the Benjamini-Hochberg procedure to correct for multiple comparisons. Results indicated that affection support was more frequently received ($p < .001$ for all comparisons) than any other type of support. Emotional support was more frequently received than tangible or informational support ($p < .001$ for both comparisons). There were no significant differences in the frequency of tangible or informational support ($p = .19$).

Question 3) Did women with greater side effect severity receive more support?

Four hierarchical regressions were conducted with each subscale of the social support measure as the dependent variable, and depressive symptoms entered in the first step, followed by joint pain severity in the second step. Depression in all models was significantly associated with the outcome. There was no association found between higher levels of joint pain and higher frequency of received affection ($sr = -.02$, $p = .74$). A small, marginally significant association was found between joint pain and higher frequency of received emotional support ($sr = .13$, $p = .05$). The residual plots for the informational and tangible support regressions were both non-normally distributed, indicating the assumptions of linear regression had been violated. Therefore, we obtained the residuals of each type of support after regressing them on depression, and entered the residuals in a Spearman correlation (r_s) with joint pain severity. We found that tangible support was not associated with joint pain severity ($r_s = .05$, $p = .42$) and informational

support had a significant and small relationship with joint pain severity ($r_s = .23$, $p < .001$).

These results suggest that breast cancer survivors on AIs are most satisfied by support that is in the form of affection, regardless of their pain levels. Women with higher levels of pain tended to receive more emotional and informational support than women with lower levels of pain; notably, they did not receive more tangible support or more affection, the most preferred type of support. In general, however, levels of affection were high, suggesting that women may be receiving sufficient amounts at both lower and higher levels of pain. In sum, women who are experiencing greater difficulties on AIs are receiving more emotional support, which is in line with their preferences and more informational support, which they do not seem to find particularly satisfying.

General Discussion

Results of both studies converge to a similar conclusion: for AI-related challenges, regardless of the severity of side effects, breast cancer survivors tend to place greater value on supportive behaviors from their partners that are emotionally nurturing as opposed to solution focused. Findings from the qualitative study also suggest that this type of support may also be associated with greater adherence to AI treatment. These findings are consistent with the broader literature on the superiority of emotional support for facilitating adjustment to cancer, but enhances this research by underscoring its relevance not only for psychological adjustment, but also for medication adherence.[39]

The quantitative findings demonstrated that tangible support made no contributions to support satisfaction, even among women with higher levels of joint pain. Interviews

with survivors provided a sense of why this may be: tangible support was appreciated, but also had the unintended effect of making some survivors feel incompetent. Interestingly, past research on osteoarthritic women, who suffer from similar types of pain and disability as survivors who experience AI-associated arthralgia, found that tangible spousal support prompted negative reactions among women who placed a high value on being independent; and powerlessness associated with receiving tangible support predicted increases in depressive symptomology over time,[40] which is in and of itself undesirable, and may also lead to non-adherence.[9] Sensitivity to how survivors' independence and self-efficacy is threatened by tangible support may be key to preventing negative outcomes.

Informational support from partners was also not associated with support satisfaction. In the qualitative interviews, some survivors discussed how informational support could feel tiresome, and missed the mark in terms of their needs in that moment. This is potentially illustrative of the optimal matching model of support: it is likely that informational support is helpful in some contexts (it has been shown to be positively related to cancer adjustment when received from physicians[39]), but when it does not match the needs of the support seeker, it can feel insensitive.[41] Partners may need guidance on when and how to provide both tangible and informational support so that they do not inadvertently undercut or alienate survivors.

Affection, which included verbal and physical demonstrations of warmth, emerged as the most desired form of support in the quantitative study but was rarely mentioned in the qualitative study. In the interviews, survivors may not have connected affection that

they received to AI-specific challenges, but when they were specifically asked about affection in the survey, they may have been able to identify it as a behavior that has helped them with management of their symptoms. The impact of affection may have been especially strong for women who felt self-conscious about their changes in physical appearance due to breast cancer treatment. Prior research has found that affection from partners of breast cancer survivors is associated with less emotional distress, greater marital satisfaction, and greater psychosexual adjustment.[42] Therefore, affection may not be directly involved in the day-to-day adherence of AIs, but may indirectly help survivors better cope with sexual dysfunction and/or changes in physical appearance associated with AIs, making the treatment more manageable. Those with greater side effect severity did not receive more affection, suggesting partners are not necessarily seeing AI-related struggles as a cue to provide more attention of this kind to their partners; although given that receipt of affection was generally high in this sample, it may be that for many couples additional affection was not desired.

The importance of emotional support emerged in both studies. Emotional support was the second most important type of support to determine support satisfaction in the quantitative study. This mirrors findings in the general support literature (outside the context of cancer), which shows that compared to informational and tangible support, emotional support is the strongest predictor of marital satisfaction.[43] In the qualitative study, all partners of adherent survivors provided some degree of emotional support, however among non-adherent survivors, there were some partners who were emotionally insensitive and potentially destructive. Additionally, among the non-adherent subset, it

was less common for survivors to mention supportive behaviors around sexual dysfunction. Overall, it was unclear how well survivors were communicating to their partners what their emotional needs were. Some partners in the adherent group were able to describe how the AI treatment impacted their wives' self-concepts; it is unclear if these partners were directly told about these impacts, or if they were especially perceptive and deduced them on their own. More research is needed to understand how well survivors are communicating with their partners about their support needs. Prior research has shown that patients' confidence in their ability to effectively communicate with their partner about cancer positively predicts perceptions of their ability to manage the cancer[44]; some of the onus, therefore, may lie on survivors to provide more guidance to their significant others on the types of support that would be helpful.

According to the quantitative results, there was a trend for women with more severe joint pain to feel less satisfied with the support they received, even though they were receiving more informational and emotional support than survivors with lower levels of pain. Based on the qualitative findings, it is likely that survivors with joint pain do not find informational support to be particularly responsive to their needs. Though they are receiving more emotional support, it may still not be sufficient.

In both studies, depression was a personal factor that was associated with satisfaction with support, the amount of support received, the degree to which AIs impacted marital functioning, and non-adherence. Given that AI usage has been shown be associated with depression among some women,[16] its causal role in the constellation of interpersonal factors and AI adherence is unclear. Depression may be a consequence or cause of not

receiving sufficient support. Or, the relationship between depression and support satisfaction may be explained by a third variable, such as poor marital quality. Regardless of the origin of the depression, depressive symptoms may put significant strain on the marital system and disrupt communication, such that providing support for medication adherence is a very challenging endeavor.

Limitations and Future Directions

This study was the first to explore the role of partner support in AI adherence. Its strength lies in its use of both qualitative and quantitative methods; however, the studies did have limitations. In the qualitative study, we asked survivors who had discontinued their AIs to provide retrospective reports on what their partners did while they were still on treatment. These reports may be less reliable than accounts provided by adherent survivors who were able to talk about current supportive behaviors that they were receiving. In addition, some of the women who were categorized as adherent may have ultimately discontinued later on in their treatment after they were interviewed. But since premature discontinuation appears to happen early on in treatment (average time on treatment for the adherent group [27 months] was much greater than for the non-adherent group [nine months]), it is reasonable to assume that if they had not already discontinued the treatment, they were more likely than not to remain adherent. Another limitation of the qualitative study is that not all partners of survivors were able to participate. It is possible that unwillingness to participate on the part of the survivors (survivors had to provide permission for their partners' participation) or on the part of partners reflects something about the relationship that is relevant to the research question but was not

possible to capture in our analyses. Lastly, survivors in the adherent group had significantly less joint pain than in the non-adherent group. It is possible that differences in support between the two groups led to differences in joint pain severity, or that survivors with more pain are more difficult to support in ways that are helpful. The design of our study did not permit us to clarify this relationship.

A limitation of the quantitative study is its cross-sectional design, which prevents us from drawing conclusions about the direction of the relationship between support types, support satisfaction, depression, and pain. Additionally, given that our measure of support is subjective and only measured from the perspective of survivors, we are not able to determine whether the reported levels of support accurately reflected what was provided. Also, our finding that those with greater levels of joint pain received more informational support was not apparent in univariate analysis and only emerged in multiple regression analysis due to a suppressor effect: Such effects often do not replicate.[45] Finally, the generalizability of our findings is limited given the unrepresentatively high level of education in on our sample. It may be that women with less education may have different needs and may therefore value different types of support.

Conclusions

The findings of these studies suggest that spousal support, especially in the form of emotional support and affection, is relevant to the experience of AIs and persistence with treatment. Survivors with adverse effects, who are vulnerable to premature discontinuation of treatment, may benefit from interventions that not only target personal

coping, but also their romantic relationships, to enhance couples' abilities to be emotionally expressive and partners' abilities to provide support that is responsive to survivors' needs.

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Table 1

Codes, Categories, and Inter-rater Reliability

Category	Kappa Statistic	Individual Codes
Partner Engagement in Treatment	.74	Partner attendance at medical appointments
		Partner understanding of AI treatment
		Partner is unaware that survivor is on AI
Partner Support of Symptom Management	.71	Characterization of spouse's personality
		Emotional support
		General supportiveness
		Impact of partner interactions on survivor's aging self-perceptions
		Impossible for partner to eliminate pain
		Informational support
		Partner interference in symptom management
		Partner self-perceived efficacy
		Partner's medical problems
		Survivor request for support
		Physical affection
		Tangible support
Partner Involvement in Daily Adherence	.91	Medication routine – in relation to partner
		Partner involvement in medication adherence
Survivors' Responses to Support	.81	Survivors' emotional response to support
		Survivor's interpretation of partner's motivation for providing support
Integration of Partner into AI Decisions	.80	Partner influence on AI decisions
		Survivor commnication with partner about continuation or discontinuation
		Partner attitude towards survivor's adherence behaviors
Partner Awareness of AI Impact	.60	Partner awareness of symptoms and their impact
		Impossibility of partner to fully understand survivor symptom experience
		Survivor communication about symptoms
Impact of AIs on Partner and Relationship	.74	Impact of AIs on partner
		Impact of AIs on partner relationship – roles, routines, daily interactions
		Impact of AIs on partner relationship – non-routine activities
		Impact of AIs on partner relationship – sexual
		Impact of AIs on partner relationship – general
		Impact of AIs on partner relationship – conflict

Note. AI = aromatase inhibitor.

Table 2

Spearman Correlations Between Study Measures

Variable	*Mdn*	1	2	3	4	5	6	7	8	9
1. Satisfaction with support	4.0	1.00								
2. Affection	11.0	.51**	1.00							
3. Emotional /Esteem Support	4.0	.38*	.54**	1.00						
4. Inform. Support	0.0	.24*	.28*	.68**	1.00					
5. Tangible Support	1.0	.21*	.32**	.69*	.68**	1.00				
6. HADS Depression	2.0	-.31**	-.27**	-.08	.00	.08	1.00			
7. Joint pain severity	3.0	-.14*	-.10	.11	.07	.16*	.37**	1.00		
8. Age	61	.00	-.06	-.14*	-.08	-.10	-.08	-.05	1.00	
9. Time since Breast Cancer Diagnosis	4.1[a]	-.05	.00	-.08	.01	-.06	-.05	-.09	.02	1.00

Note. Mdn = Median.
[a] Time is in years
* $p < .01$
** $p < .05$

Table 3

Factor Loadings for Exploratory Factor Analysis of Modified SIRRS Items

SIRRS Item (Modified for AI context)	Tangible Support	Affection	Informat-ional Support	Emotional / Esteem Support
My partner…				
…did something to help me directly with taking my AI as prescribed or managing its side effects (e.g. ordered refills of my AI prescription)	**0.89**	0.00	-0.01	0.11
...offered to do something to help me directly with taking my AI as prescribed or managing its side effects (e.g. offered to fill my pill box)	**0.83**	0.04	0.11	0.02
…offered to help me indirectly with taking my AI as prescribed or managing its side effects (e.g. offered to cook dinner so that I could rest)	**0.35**	-0.05	0.12	0.48
…hugged me or cuddled with me	0.21	**0.92**	0.00	-0.09
…kissed me	-0.07	**0.88**	0.13	0.07
…patted or stroked me affectionately	-0.04	**0.87**	0.22	0.00
…said good things to me	0.09	**0.79**	-0.19	0.24
…taught me or showed me how to do something related to taking my AI as prescribed or managing its side effects	0.32	0.11	**0.60**	0.03
…helped me think about taking my AI as prescribed or managing its side effects in a new way	0.04	0.11	**0.74**	0.10
…told me what to do to solve a problem or deal with taking my AI as prescribed or managing its side effects	0.37	-0.05	**0.68**	-0.02
…shared facts or information with me about taking my AI as prescribed or managing its side effects	0.01	-0.12	**0.67**	0.39
…reminded me to take my AI[a]	0.33	0.03	**0.55**	0.05
…expressed confidence in my ability to take my AI as prescribed or manage its side effects	-0.01	0.15	0.25	**0.60**
…told me everything would be ok	-0.03	0.30	-0.05	**0.73**
…said he/she thought I handled taking my	0.09	0.02	0.16	**0.66**

AI as prescribed or managing its side effects well				
…said he/she would feel the same way in my situation	0.02	0.01	0.30	**0.55**
…restated what I had told him/her about taking my AI as prescribed or managing its side effects	0.05	0.02	0.31	**0.62**

Note. AI = aromatase inhibitor; SIRRS = Support in Intimate Relationships Rating Scale.

[a]This item was not in the original SIRRS and was added to the measure for this study.

GENERAL DISCUSSION

The results of these studies expand our previously limited knowledge of the psychosocial variables associated with adherence to aromatase inhibitors (AIs) among breast cancer survivors. Prior literature has identified mostly demographic and disease predictors, whereas the variables identified in this dissertation are potentially modifiable and can inform health care providers and researchers on what targets to pursue in adherence interventions.

In Chapter 1, we explored the topic of adherence measurement, which is not only integral to our ability to study what predicts adherence, but is also important for clinicians who want to track their patients' adherence and for researchers who need to measure the efficacy of adherence interventions. Financial and other practical constraints make the use of self-report measures a necessity, even if they are not the ideal format for adherence assessment (given their vulnerability to recall and responses biases). To date, no study has examined the construct validity of a self-report measure for AIs. We found that two self-report measures for AI adherence, a modified version of the Morisky Medication Adherence Scale and the Visual Analog Scale, were not associated with estrogen suppression, suggesting they were not reliable indicators of adherence behaviors. However, in exploratory analyses, a one-item question asking participants whether they had taken an AI in the last month did correlate with estrogen levels. Given that this simple item about adherence outperformed more fine-grained assessments, we deemed it appropriate to measure adherence in subsequent studies with notes from medical records which contained information about what participants told their oncologists about their general adherence behaviors. Medical records provided the added

benefit of multiple assessment points (one from each follow-up visit which occurred approximately every 4-6 months) compared to surveys, which would not have been feasible to distribute as frequently. Indeed, we ultimately found that adherence rates measured through medical record abstractions were similar to adherence rates in the AI literature. A limitation of this study was that adherence rates in this particular sample may have been unrepresentatively high, limiting the amount of variability that the self-report measures could explain. Replication of these findings in another sample from a different setting is essential to building on this work.

Chapters 2 and 3 examined intrapersonal factors that we hypothesized would predict treatment adherence. Chapter 2 focused on health beliefs and Chapter 3 looked at arthralgia-associated aging perceptions. The findings of both studies suggest that how breast cancer survivors assign meaning to pain is more useful information for predicting AI adherence than knowing the intensity of their pain. Chapter 2 suggested that those who perceive pain as a barrier to taking their medication were more likely to non-adhere. The relationship between barrier perceptions and pain intensity was only moderate in size, suggesting that pain intensity and barrier perceptions are distinct constructs. Chapter 3 shed light on which aspect of AI-associated pain may make it particularly challenging for some women to take their AIs: a sense of having aged while on the AI. These findings suggest that cognitive interventions for pain which focus on fears about aging and long-term mobility may help women better cope with their AI-related pain, and therefore better adhere to treatment.

In Chapter 4, we examined the relationship between interpersonal factors and adherence. In the qualitative study, we found that survivors were most satisfied with affection and emotional support, and that tangible and informational support did not contribute to support satisfaction. These preferences were similar among those with both high and low levels of pain. Results of the qualitative study also provided evidence that survivors with emotionally unsupportive partners were more likely to be non-adherent. Other themes that emerged included the importance of partners' integration into follow-up care. Partners of adherent survivors did not seem to be involved in the decision to initiate or persist with AI treatment, but some partners of non-adherent survivors did encourage the option of discontinuation. The results of Chapter 4 support the idea that health behaviors operate within a family system, especially when considering significant others who are often the most influential member of one's network. Many women are grappling with how cancer and its treatment have affected their bodies, their self-esteem, and their sexual relationships. Romantic partners can be intertwined in these emotional reactions. Effective couple interventions have already been developed that improve psychological adjustment to cancer for breast cancer patients.[1,2] Augmenting these existing interventions with AI-specific material may be an efficient and practical approach to achieve improved AI adherence.

Limitations of the studies in Chapter 4 include cross-sectional, as opposed to longitudinal analyses, as well as the possibility of third variables that were not assessed. It is unclear, for example, whether qualities of survivors that may lead them to be non-adherent also make them more difficult to provide support to. Therefore, incorporating

intrapersonal variables identified in Chapters 2 and 3 into social support analyses will clarify both the unique contribution of support, as well as whether personal factors moderate the impact of support. Additionally, this will help to clarify the relative importance of intrapersonal versus interpersonal variables.

Further research is also needed to disentangle the role of depression in AI adherence. In Chapter 2, women with high perceived barriers to AI treatment were more likely to be depressed. In Chapter 3, depression uniquely predicted AI adherence and was also associated with aging perceptions. In the quantitative study of Chapter 4, depression was associated with the receipt of support and satisfaction with support; and in the qualitative study, relationship quality appeared to be particularly low among survivors who had experienced depression while on the AI. To what degree depression is a contributor versus a result of the various constructs explored in this dissertation is unknown. Understanding the temporal relationship of depression to other predictors of adherence will be important for determining when and how to intervene.

Overall, there are limitations that apply to all of these studies that impact their interpretability. First, the samples used to generate these results are unrepresentatively educated and mostly White or African American, with very little presence of other races. Second, in Chapters 2-4, biases in the data were incurred because participants were not recruited at AI initiation. Third, we did not substantiate the medical chart abstractions of adherence behaviors with pill counts or hormonal assays.

Conclusion. Breast cancer is one of the most commonly diagnosed cancers in the United States and has the second highest death rate.[3] Interventions that can help increase

adherence rates for life-saving medications are critical for this population. The findings of this dissertation bring us closer to understanding some of the intra- and interpersonal mechanisms that contribute to non-adherence among breast cancer survivors on AIs and can inform intervention content.

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