



Facilitators and barriers to medication adherence with adjuvant endocrine therapy in women with breast cancer: a structural equation modelling approach

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Abstract

Purpose To identify a structure to explain the relationship between socio-clinico factors, necessity-concerns beliefs, and perceived barriers to adherence with adjuvant endocrine therapy (AET) amongst women with breast cancer.

Methods Participants were 244 patients with early-stage breast cancer recruited from two tertiary hospitals from May 2015 to December 2018 who completed questionnaires on medication adherence (Simplified Medication Adherence Questionnaire), necessity-concerns beliefs (Beliefs about Medicine Questionnaire), and barriers to adherence (Adherence Starts with Knowledge Questionnaire). Socio-clinico variables were collected via interview and medical records review. Structural equation modelling was applied to examine the relationships between these variables and possible mediating effects of necessity-concerns beliefs on adherence to AET.

Results The median age of the study participants was 61 (range 32–80) years and the median duration on AET was 1.6 (IQR 1.2–2.6) years. Adherence was positively associated with age ($\beta=0.145$, 95% CI: 0.011 to 0.279, $p=0.034$) and negatively associated with barriers ($\beta=-0.381$, 95% CI: -0.511 to -0.251 , $p<0.001$). There was no effect of Necessity ($\beta=0.006$, 95% CI: -0.145 to 0.158 , $p=0.933$) or Concerns ($\beta=0.041$, 95% CI: -0.117 to 0.199 , $p=0.614$) on adherence. Necessity-concerns beliefs were also not significant mediators in the relationship between socio-clinico factors and medication adherence.

Conclusions Older age and lower barriers to adherence were associated with higher adherence scores. Necessity-concerns beliefs did not have a significant effect on adherence as majority of the patients identified forgetfulness as a reason for non-adherence.

Keywords Adjuvant endocrine therapy · Adherence · Breast cancer · Necessity-concerns framework · Structural equation modelling

Abbreviations

AET	Adjuvant Endocrine Therapy
AI	Aromatase Inhibitors
ASK	Adherence Starts with Knowledge
BMQ	Beliefs about Medicines Questionnaire
CFI	Confirmatory Factor Index
EFA	Exploratory Factor Analysis
NCF	Necessity-Concerns Framework
RMSEA	Root Mean Square Error of Approximation
SEM	Structural Equation Modelling

SMAQ	Simplified Medication Adherence Questionnaire
SRMR	Standardised Root Mean Squared Residual

Introduction

In Singapore, breast cancer is the leading cause of cancer mortality among women [1]. Deprivation of estrogen signalling via adjuvant endocrine therapy (AET), including tamoxifen or aromatase inhibitors (AI) such as anastrozole, exemestane, or letrozole, is the mainstay treatment for patients with hormone receptor positive breast cancer. Medication adherence is defined by the World Health Organization as the extent to which a person's medication-taking

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behaviour corresponds with agreed recommendations from a health care provider [2]. A systematic review revealed suboptimal adherence to AET, which ranged from 41 to 72% in studies of breast cancer survivors with at least 4 years of follow up [3]. Non-adherence to AET is associated with increased mortality and higher recurrence risk [4–6]. Therefore, it is imperative to understand the facilitators and barriers underlying medication adherence. Socio-clinico and demographic characteristics may be important for identifying subgroups at risk for non-adherence but are not modifiable via targeted interventions. It has been suggested that younger age and increased frequency of hospitalization were associated with non-adherence to AET [7]. On the other hand, psychosocial factors such as perceptions about medication and illness have been successfully modified to improve adherence in patients with coronary heart disease [8] and asthma [9]. In an integrative review of patient-reported factors of adherence to AET, necessity beliefs (judgement about the personal need for medication), self-efficacy (belief in managing medications and their side effects) were positively associated with adherence whereas perceived barriers to treatment (concerns about side effects, treatment period is too long) were related with non-adherence [10].

Psychosocial factors, namely the necessity-concerns framework (NCF), are postulated to be mediators in the relationship between socio-clinico factors and medication adherence [11, 12]. The NCF offers a model for clinicians to elicit key beliefs reinforcing patients' attitudes and judgments about treatment [13]. This study aims to identify a structure to explain the relationship between socio-clinico factors, necessity-concerns beliefs, and perceived barriers to adherence to AET among patients with breast cancer.

Methods

Study design

Women on AET for early-stage breast cancer were recruited from the National University Cancer Institute and Ng Teng Fong General Hospital in Singapore between May 2015 and December 2018. The participants were part of a randomised controlled trial previously described and reported [14, 15].

Measures

Socio-clinico and treatment-related factors

Ethnicity, education level, use of medication reminder, and presence of AET-related adverse effects were collected via interview by the research co-ordinator. Age, comorbidities, breast cancer stage, duration of diagnosis, duration of AET,

and use of other medications were extracted from the hospitals' electronic medical records by the same interviewer. Information on barriers and facilitators were elicited using validated instruments, namely Adherence Starts with Knowledge (ASK-12) [16] and Beliefs about Medicine Questionnaire (BMQ) [17].

Adherence starts with knowledge (ASK-12)

The ASK-12 is a 12-item questionnaire measuring a patient's barriers towards medication adherence, and includes items related to inconvenience/forgetfulness, confidence, motivation, support, patient-physician relationship, side effects, perceived inefficacy, and cost. Scores within each item measured on a five-point Likert scale are summed to provide a total score, ranging from 12 to 60. The item and scoring details are described in "Appendix A" section. Higher scores represent more barriers towards medication adherence.

Beliefs about medicine questionnaire (BMQ)

The NCF was measured by the BMQ-Specific, a 10-item questionnaire which consists of two scales (five items each) measuring patient's perceptions towards medications. Each item is measured based on a five-point Likert scale. Scores within each item are summed to provide a scale score, thus possible scores range from 5 to 25 for each scale. The item and scoring details are described in "Appendix B" section. Higher scores indicate stronger beliefs in the concepts represented by the scales. The two scales of BMQ-Specific assess beliefs about AET, corresponding to the themes Necessity and Concerns. The former examines the beliefs of necessity towards taking AET, while the latter examines concerns about the negative effects of AET.

Simplified medication adherence questionnaire (SMAQ)

Medication adherence was assessed via self-report using the validated six-item Simplified Medication Adherence Questionnaire (SMAQ) [18]. Medication non-adherence was defined if a patient provided a non-adherence response to any of items 1 to 4 in the SMAQ (which included timeliness, forgetfulness, and omission of dose when not feeling well), had skipped more than two doses during the last week (item 5), or had not taken medication for more than 2 days in the past 3 months (item 6). Adopting the standard scoring instruction such as that of the 36 item short-form survey (SF-36) [19], items 1 to 5 were recoded and item 6 linearly transformed to a scale from 0 to 100 as shown in "Appendix C" section. The six items were averaged to form the SMAQ score, with a high score indicating higher adherence.

Statistical analysis

The data were analysed using Structural Equation Modelling (SEM). SEM allows the inclusion of latent variables such as beliefs regarding Necessity and Concerns that are not directly observed and accounts for measurement errors in the items forming the latent construct [20]. The theoretical model is presented in Fig. 1. Adherence is hypothesized to be associated with stronger beliefs in the necessity of treatment and fewer concerns about treatment.

Firstly, predictors of adherence in the univariate SEM with p -values ≤ 0.1 were selected to be inputs in the multi-variable SEM. The outcome variable of the SEM was medication adherence measured by the SMAQ score. The SEM was specified using maximum likelihood estimation, with backward elimination procedure implemented to derive a parsimonious model. The direct, indirect, and total effects of each variable associated with medication adherence were estimated by the path coefficients. The goodness of fit indices for the SEM were examined via model chi-square statistics, confirmatory factor index (CFI), root mean square error of approximation (RMSEA), and standardised root mean squared residual (SRMR). The following cut-offs are recommended [20]: CFI > 0.95 , RMSEA < 0.08 (reasonably close fit) or < 0.05 (good fit), and SRMR < 0.08 . To

improve goodness of fit, modification indices were considered. All statistical analyses were performed using STATA version 14.2, assuming a two-sided test at the 5% level of significance.

Results

The median age of the study population ($n = 244$) was 61 years (range 32–80). Majority of the patients were Chinese (74.6%) and had at least secondary education (75.0%). The median duration since breast cancer diagnosis until study recruitment was 2.2 years (interquartile range 1.8–3.2) and the median duration on AET was 1.6 years (interquartile range 1.2–2.6 years). The most common comorbidities were hyperlipidaemia (57.8%), hypertension (43.0%), and diabetes (24.6%). The median number of concomitant medications was three (range 0–13). There were 82 patients (33.6%) who reported having an AET-related adverse effect, the most common being arthralgia (24.6%). The distribution of the key variables is presented in Table 1.

The mean SMAQ score was 86.3 (standard deviation [SD] 17.2). The mean ASK-12 total score was 22.0 (SD 4.5); with forgetfulness being the item with the highest proportion of patients reporting it as a barrier to adherence (38.1%) and

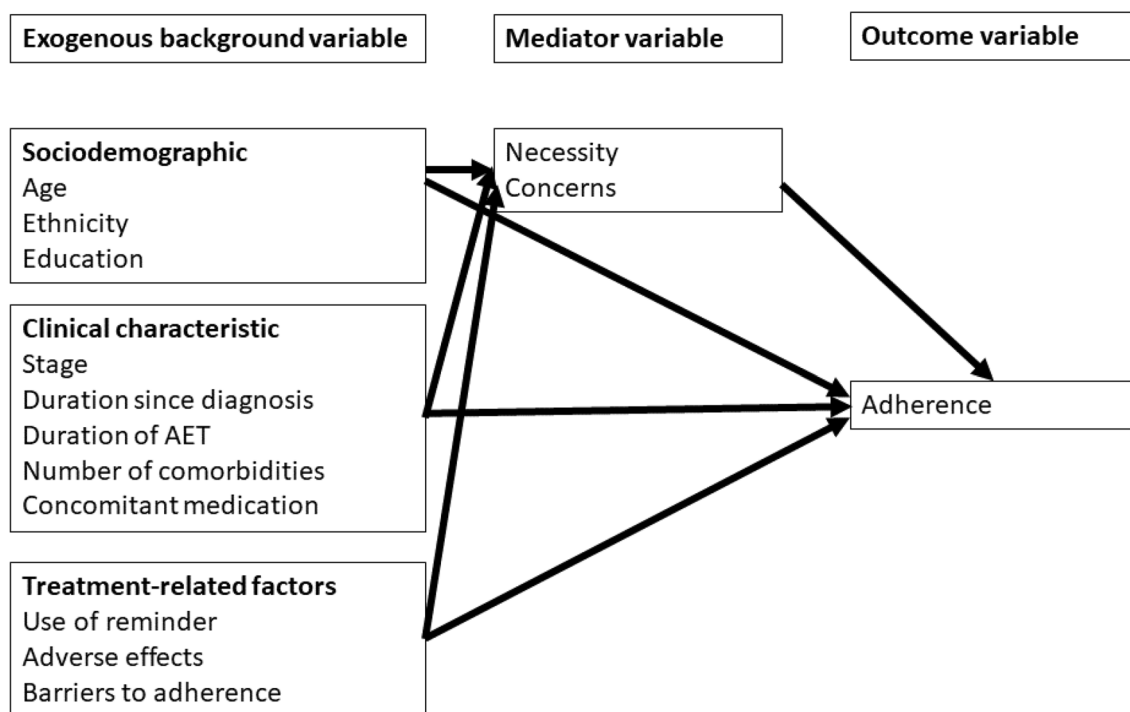


Fig. 1 Theoretical model of influencing and mediating factors of adherence. AET Adjuvant endocrine therapy. This model outlines the hypothesised direct and indirect relationships between the background variables (sociodemographic, clinical characteristic, and

treatment-related factors), the mediating variables (Necessity and Concerns), and medication adherence. Unidirectional straight arrows indicate the predicted direction of the theoretical relationship

Table 1 Summary characteristics of the study participants

	Total (n=244)
<i>Socio-clinico variables</i>	
Median age (range), years	61 (32–80)
Ethnicity (%)	
Chinese	182 (74.6)
Malay	34 (13.9)
Indian	19 (7.8)
Others	9 (3.7)
Education level (%)	
Primary and below	59 (24.2)
Secondary	124 (50.8)
Pre-university	33 (13.5)
University	28 (11.5)
Breast cancer stage (%)	
0	1 (0.4)
I	95 (39.8)
II	93 (38.9)
III	50 (20.9)
Median duration since diagnosis, years (IQR)	2.2 (1.8–3.2)
Median duration on AET, years (IQR)	1.6 (1.2–2.6)
Use of medication reminder (%)	51 (20.9)
Presence of adverse effect* (%)	
Arthralgia	60 (24.6)
Myalgia	13 (5.3)
Hot flush	8 (3.3)
Generalised body aches	6 (2.5)
Other adverse effects	35 (14.3)
Comorbidities (%) ^a	
Hypertension	105 (43.0)
Hyperlipidaemia	141 (57.8)
Diabetes	60 (24.6)
Coronary heart disease	33 (13.5)
Pulmonary disease	12 (4.9)
Other cancer	13 (5.3)
Other comorbidities	109 (44.7)
Median number of concomitant medications (range)	3 (0–13)
<i>Psychometric variables</i> [@]	
ASK-12 total score	22.0 (4.5)
BMQ	
Necessity	15.0 (3.3)
Concerns	12.9 (3.9)
SMAQ	86.3 (17.2)

AET adjuvant endocrine therapy, ASK-12 Adherence Starts with Knowledge questionnaire, BMQ Beliefs about Medicine Questionnaire, IQR interquartile range, SD standard deviation, SMAQ Simplified Medication Adherence Questionnaire

*Patients can report more than one adverse effect/comorbidity

[@]Mean and standard deviation are presented for psychometric variables

not having medicine when it was time to take it was the most frequent reason for missing their dose (21.7%) (“Appendix A” section). The mean BMQ Necessity score was 15.0 (SD 3.3); with the highest proportion of patients (60.2%) agreeing with the item “My medicine protects me from becoming worse”. The mean BMQ Concern score was 12.9 (SD 3.9); with the highest proportion of patients (58.6%) agreeing with the item “I sometimes worry about long-term effects of my medicine”. (“Appendix B” section).

Structural equation modelling

In the univariate SEM, age was the only significant sociodemographic variable; duration of AET and number of comorbidities were significant clinical variables; barriers to adherence as measured by ASK-12 score was the only significant treatment-related factor, associated with adherence. Concerns were significantly associated with adherence, but not Necessity. Figure 2 presents the multivariable model involving age, duration of AET, number of comorbidities, and ASK-12 score, with Necessity and Concerns as latent mediator variables for predicting adherence as measured by SMAQ. Duration on AET ($\beta = -0.148$, 95% CI: -0.295 to -0.002 , $p = 0.047$) and ASK-12 score ($\beta = -0.241$, 95% CI: -0.388 to -0.094 , $p = 0.001$) were negatively associated with Necessity. Age ($\beta = -0.219$, 95% CI: -0.366 to -0.072 , $p = 0.003$), and ASK-12 score ($\beta = 0.429$, 95% CI: 0.312 to 0.546 , $p < 0.001$) had a significant effect on Concerns. However, only age ($\beta = 0.145$, 95% CI: 0.011 to 0.279 , $p = 0.034$) and ASK-12 score ($\beta = -0.381$, 95% CI: -0.511 to -0.251 , $p < 0.001$) were found to have a significant effect on adherence. There was no evidence of indirect effects of the explanatory variables via the mediating effects of either Necessity or Concerns. The fit statistics for the full model were: $\chi^2 = 146.92$, $df = 74$, $p < 0.001$; CFI = 0.888; RMSEA = 0.064; SRMR = 0.075. Although the CFI was less than the recommended cut-off, the RMSEA and SRMR were low.

We further refined the model to exclude number of comorbidities which was not associated with the mediating variables nor the outcome. The Necessity and Concerns latent variables were fit separately (Fig. 3A and B) to explore a more parsimonious relationship. For the model with Necessity as a possible mediator, age ($\beta = 0.153$, 95% CI: 0.040 to 0.266 , $p = 0.008$) and ASK-12 score ($\beta = -0.361$, 95% CI: -0.471 to -0.251 , $p \leq 0.001$) had a significant effect on adherence. Duration on AET ($\beta = -0.152$, 95% CI: -0.298 to -0.005 , $p = 0.043$), and ASK-12 score ($\beta = -0.239$, 95% CI: -0.386 to -0.092 , $p = 0.001$) had a significant effect on Necessity (Fig. 3A). For the model with Concerns as a mediating variable, age ($\beta = 0.161$, 95% CI: 0.045 to 0.278 , $p = 0.007$) and ASK-12 score ($\beta = -0.383$, 95% CI: -0.506 to -0.259 , $p \leq 0.001$) had a significant

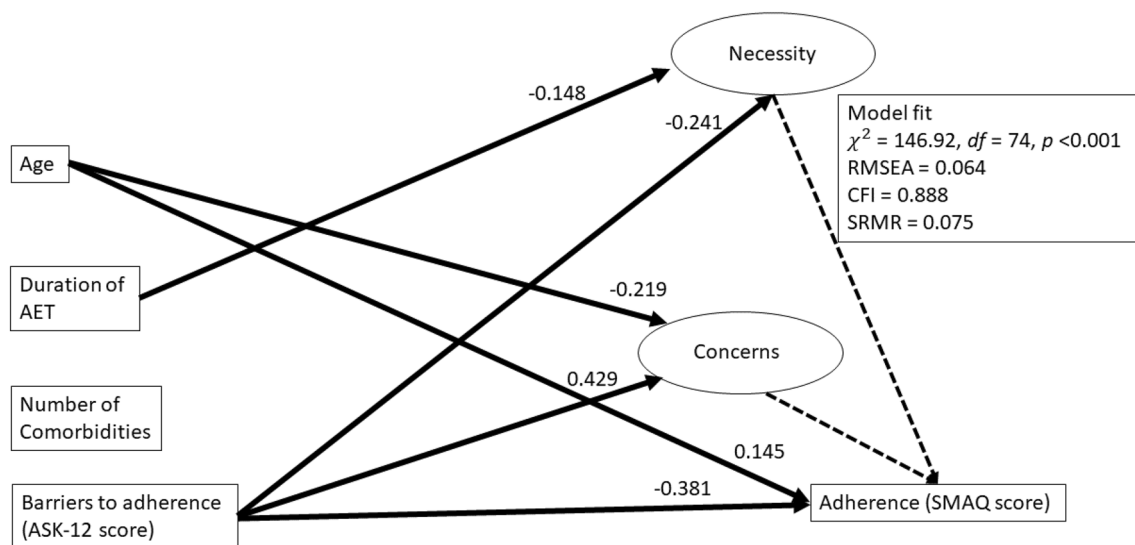


Fig. 2 SEM for treatment adherence assuming the theoretical Necessity-Concerns Framework. *AET* Adjuvant endocrine therapy. Latent variables (Necessity and Concerns) are represented in oval. Observed variables are represented in rectangle. Significant standardized path

coefficients ($p < 0.05$) are presented at the end of the unidirectional paths. Non-significant paths of observed variables are not shown. Non-significant paths of mediators are shown by dashed lines

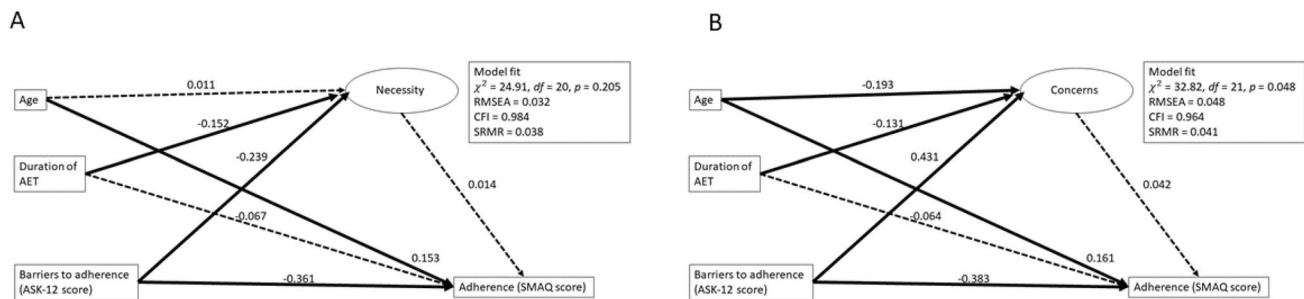


Fig. 3 SEM for treatment adherence with **A** Necessity, and **B** Concerns as mediator. *AET* Adjuvant endocrine therapy. Latent variables (Necessity and Concerns) are represented in oval. Observed variables

are represented in rectangle. Significant standardized path coefficients ($p < 0.05$) are presented at the end of the unidirectional paths. Non-significant paths are shown by dashed lines

effect on adherence. Age ($\beta = -0.193$, 95% CI: -0.322 to -0.065 , $p = 0.003$), duration on AET ($\beta = -0.131$, 95% CI: -0.260 to -0.001 , $p = 0.048$), and ASK-12 score ($\beta = 0.431$, 95% CI: 0.314 to 0.548 , $p < 0.001$) had a significant effect on Concerns (Fig. 3B). Both models suggest no mediating effect of either Necessity or Concerns. Both models showed good fit (Necessity model $\chi^2 = 24.91$, $df = 20$, $p = 0.205$; CFI = 0.984; RMSEA = 0.032; SRMR = 0.038, Concerns model $\chi^2 = 32.82$, $df = 21$, $p = 0.048$; CFI = 0.964; RMSEA = 0.048; SRMR = 0.041).

Discussion

Medication adherence to AET has been shown to decrease over time. Apart from clinical risk factors such as age and length of hospitalisation, psychosocial factors—for example, concerns about side effects of AET outweighing its necessity, have been shown to be associated with non-adherence [21, 22]. This study aimed to construct a model to identify the facilitators and barriers to adherence of AET in women with early-stage breast cancer who have been on AET for at least 1 year. We found age and barriers to adherence to have a significant effect on adherence but there was little association between beliefs about AET and its adherence.

In terms of socio-clinico factors, we found that older age was associated with higher adherence scores, which was

consistent with studies cited in systematic reviews [3, 7]. In our patient population, those who reported forgetting to take their medication, especially during the weekend were younger. Reasons for missing their doses included being busy at work or social activities during the weekend which differed from their usual weekday schedule. Age was also positively associated with the number of concomitant medications. Calip et al [23] found that increased polypharmacy was associated with greater adherence to AET, although the effects differed by medication class. A systematic review by Moon et al [7] reported two studies [24, 25] which showed increased adherence with more prescribed medications, while eight studies demonstrated no effects.

In our study, presence of adverse effects was not associated with non-adherence, which was consistent with the report from a systematic review [7]. Qualitative research has revealed that patients will persist on AET despite experiencing side effects [7, 26]. Prescribers may also switch patients to an alternative AET if the side effects from a prescribed AET became intolerable. However, our study comprised patients who were on AET for at least a year, as such those who had experienced severe side effects could have discontinued the medication and would not have been selected to participate in this study.

Higher ASK-12 score was associated with higher concerns about AET and lower adherence score. Evidence has shown that good patient–healthcare provider relationship and social support were positively associated with adherence with AET [7, 10]. However, the component ASK-12 items that were most significantly associated with adherence in our study were item 1 (I just forget to take my medicines some of the time) and item 12 (Have you not had medicine with you when it was time to take it?). There was a high prevalence of forgetfulness (89.5%) as a reason for non-adherence to AET in our study. Thus, our study population may be more prone to unintentional non-adherence which is less affected by treatment beliefs.

In a meta-analysis, necessity was associated with a higher odds of adherence but there was no significant effect of concerns on adherence among cancer patients [13]. Focus groups conducted by Wouters et al [26] revealed that women on AET judged their own perceptions and experiences about AET as more relevant to adherence than beliefs measured in the BMQ. Specifically, the concept of tenacity, that is to deliberately do everything possible to prevent the recurrence of cancer, was not captured in the BMQ. Identification of specific barriers to adherence could tailor interventions to improve adherence such as the use of pillboxes or reminder systems for forgetfulness and education to target behaviour change [27]. In our study, age and forgetfulness were identified as the main barriers to adherence. The use of SMS reminders has demonstrated short-term effect for improvement of medication adherence [15, 28]. A tailored reminder

program according to a patient's daily schedule may better improve its sustainability [29].

The strengths of this study were the comprehensive framework utilising socio-clinical and psychosocial factors to elicit facilitators and barriers to adherence, the use of validated instruments [30], and the application of SEM to account for latent constructs and measurement errors. Studies on adherence to AET frequently used prescription records to define adherence [3]. However, this may not be applicable in the local context due to prescription habits. In a pilot study, we found that the median baseline medication possession ratio was 101% (IQR: 95–115) amongst breast cancer patients who were dispensed AET in a tertiary hospital. This suggests that it is common to prescribe oversupply of medication to prevent patients from running out of medication in case of changes in appointment times. A gold standard for measuring medication adherence has not been identified as each method has its strengths and disadvantages [31]. While self-reporting of medication adherence may be a limitation in this study, of note, the SMAQ was assessed to be a valid and reliable instrument [18, 32, 33]. and measurement invariant across different time periods [33]. Thus, self-reported adherence measured by the SMAQ, albeit subject to social desirability bias, was used to define adherence to AET in this study.

Another limitation was the cross-sectional nature of the data, which restricts the possibility of causal conclusions. Future studies may consider a longitudinal design to assess the changes in facilitators and barriers and their effects on adherence over time. Lastly, the magnitude of the indirect effect in our mediation models was small, hence our study may have been underpowered [34] to detect significant mediating effects of Necessity and Concerns.

Conclusion

In conclusion, older age and lower barriers to adherence were associated with higher adherence scores. Necessity-concerns beliefs did not have a significant effect on adherence as majority of the patients identified forgetfulness as a reason for non-adherence.

Appendix A

See Table 2

Table 2 Distribution of scores of the ASK-12 scale

Item description	Percentage response				
	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
1. I just forget to take my medicines some of the time.	2.0	36.1	2.9	18.4	40.6
2. I run out of my medicine because I don't get refills on time.	0	7.0	0	19.3	73.8
3. Taking medicines more than once a day is inconvenient.	10.3	27.0	13.1	33.6	16.0
4. I feel confident that each one of my medicines will help me.	20.1	54.5	18.9	6.1	0.4
5. I know if I am reaching my health goals.	11.5	57.4	18.4	12.7	0
6. I have someone who I can call with questions about my medicines.	7.0	41.8	22.5	25.8	2.9
7. My doctor/nurse and I work together to make decisions.	16.0	65.6	4.9	13.1	0.4
	In the last week	In the last month	In the last 3 months	More than 3 months ago	Never
8. Taken a medicine more or less often than prescribed?	4.9	2.1	1.2	1.6	90.2
9. Skipped or stopped taking a medicine because you didn't think it was working?	0.4	0.8	0	3.3	95.5
10. Skipped or stopped taking medicine because it made you feel bad?	1.6	0.8	0.8	2.9	93.9
11. Skipped, stopped, not refilled, or taken less medicine because of the cost?	0.4	0.4	0	1.6	97.5
12. Not had medicine with you when it was time to take it?	2.9	4.5	6.2	8.2	78.3

For items 1 to 3: Strongly agree = 5, Agree = 4, Neutral = 3, Disagree = 2, Strongly disagree = 1

For items 4 to 7: Strongly agree = 1, Agree = 2, Neutral = 3, Disagree = 4, Strongly disagree = 5

For items 8 to 12: In the last week = 5, In the last month = 4, In the last 3 months = 3, More than 3 months ago = 2, Never = 1

Appendix B

See Table 3

Table 3 Distribution of scores of the BMQ Necessity and Concerns items and scales

Scale	Item description	Percentage response				
		Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
Necessity	S1. My health, at present, depends on my medicine	2.9	16.8	28.3	43.0	9.0
	S3. My life would be impossible without my medicine	11.5	41.4	29.1	13.9	4.1
	S4. Without my medicine I would be very ill	13.5	40.6	32.0	11.1	2.9
	S7. My health in the future will depend on my medicine	4.1	34.4	27.9	28.7	4.9
	S10. My medicine protects me from becoming worse	1.6	13.9	24.2	47.1	13.1
Concerns	S2. Having to take medicine worries me	19.3	47.5	3.7	26.2	3.3
	S5. I sometimes worry about long-term effects of my medicine	11.9	25.4	4.1	41.8	16.8
	S6. My medicine is a mystery to me	9.4	48.4	14.3	25.0	2.9
	S8. My medicine disrupts my life	20.9	60.7	3.7	13.1	1.6
	S9. I sometimes worry about becoming too dependent on my medicine	16.0	52.5	7.4	21.7	2.5

Strongly disagree = 1, Disagree = 2, Uncertain = 3, Agree = 4, Strongly agree = 5

Appendix C

See Table 4

Table 4 Scoring of the SMAQ

Item description	Original response	Recoded value	Percentage response
1. Do you always take your medication at the appropriate time?	Yes	100	88.9
	No	0	11.1
2. When you feel bad, have you ever discontinued taking your medication?	Yes	0	8.2
	No	100	91.8
3. Have you ever forgotten to take your medication?	Yes	0	41.8
	No	100	58.2
4. Have you ever forgotten to take your medications during the weekend?	Yes	0	15.2
	No	100	84.8
5. In the LAST WEEK, HOW MANY TIMES did you fail to take your prescribed dose?	Never	100	86.9
	1–2 times	75	11.5
	3–5 times	50	1.2
	6–10 times	25	0.4
	> 10 times	0	0.0
6. OVER THE PAST 3 MONTHS, how many whole days have you gone by in which you did not take your medication?	<i>N</i>	$(1 - N/91) * 100$	97.9 (9.0) [#]

For item 6, the number of days which patient did not take medicine, *N* was divided by the maximum response (91 days). It was then reverse scored as a higher value should indicate higher adherence, and multiplied by 100

[#]Figure presented as mean (standard deviation)

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Author contributions AW, CCT, PW, SCL and BCT participated in the design of the study and research protocol. AW, CCT, SHT, LEYA, SEL, WQC, JH, SCL significantly contributed to patient recruitment. EHT collected the data. EHT and BCT conducted the statistical analysis. All authors were involved in the writing, editing, and approval of the final manuscript.

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Data availability The datasets generated and/or analysed during the current study are not publicly available due to patient confidentiality and institutional guidelines.

Declarations

Conflict of interests SCL received speaker invitations to conferences and is on the advisory board for Novartis, Pfizer, and Astra Zeneca. SCL also received research grants from Pfizer. BCT received honoraria for speaking at symposia from Boehringer Ingelheim and royalty from

Wiley-Blackwell. All other authors declare that they have no conflict of interest.

Ethical approval The study was approved by the National Healthcare Group Domain-Specific Review Board (Reference number 2014/01316). All procedures performed were in accordance with the ethical standards of the institution.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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