The Breast 75 (2024) 103731

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

The impact of symptom clusters on endocrine therapy adherence in patients with breast cancer

Sommer Agnew [a,*], Megan Crawford [a], Iain MacPherson [b], Victor Shiramizu [a], Leanne Fleming [a]

[a] University of Strathclyde, 16 Richmond St, Glasgow, G1 1XQ, Scotland, UK
[b] University of Glasgow, Glasgow, G12 8QQ, Scotland, UK

ARTICLE INFO

Keywords:
Breast cancer
Endocrine therapy
Adherence
Symptom clusters

ABSTRACT

Background: When taken as prescribed, endocrine therapy is effective in reducing risk of recurrence and mortality in the treatment of patients with breast cancer. However, treatment side effects can act as a barrier to medication adherence. Existing research has not identified any specific side effects as consistent predictors of nonadherence. Our aim was to explore the influence of symptom clusters on self-reported adherence in patients with breast cancer.

Methods: A cross-sectional online survey was conducted, including patients with breast cancer currently or previously prescribed endocrine therapy ($N = 1051$). This included measures of self-reported endocrine therapy adherence and common symptoms among this population (insomnia, depression, anxiety, fatigue, musculoskeletal, and vasomotor symptoms).

Results: Unintentional nonadherence was higher than intentional nonadherence (50.8 % vs 31.01 %). The most troublesome symptom was insomnia (73.83 % displayed probable insomnia disorder). K-means cluster analysis identified 2 symptom clusters: overall High symptoms, and overall Low symptoms. Participants in the Low symptoms cluster were significantly more likely to be classed as adherent based on unintentional and intentional items.

Conclusions: Nonadherence was high in the current sample, and significantly more likely in participants reporting overall severe symptoms. Clinicians should be aware of the scale of common side effects and facilitate open conversation about potential barriers to adherence. Follow-up care should include assessment of common symptoms and signpost patients to appropriate support or treatment when required. Future research should explore potential for a central symptom to act as a target for intervention, to relieve overall side effect burden and facilitate better medication adherence.

1. Introduction

Breast cancer is the most prevalent form of cancer worldwide, and the leading cause of cancer-related death in women [1]. Around 70 % of cases are hormone-receptor positive, therefore treatable with endocrine therapy (ET) in the form of a Selective Oestrogen Receptor Moderator (SERM, such as Tamoxifen), or Aromatase Inhibitor (AI, including Letrozole, Exemestane, and Anastrozole). Adjuvant ET is typically prescribed for up to 10 years and can be used alone, or in combination with ovarian function suppression or ablation [2]. Five years of Tamoxifen can half the risk of breast cancer recurrence during the treatment term and reduce mortality risk by one third for up to 15 years after initiation [3]. AIs can reduce breast cancer recurrence by a further 30 % and mortality by 15 % relative to tamoxifen [4].

Despite these clinical advantages, ET is associated with a range of treatment side effects [5–8] [5–8] [5–8]. Common side effects include sleep difficulties, musculoskeletal pain, vasomotor symptoms (hot flashes, cold sweats, and night sweats), fatigue, headaches, depression, anxiety, and cognitive dysfunction (memory deficits and difficulty concentrating) [9–11]. These symptoms can impact patients' ability or motivation to take their medication as prescribed [11], and there are reports of poor adherence rates in this population. Adherence is defined as the extent to which a patient takes medication as directed, specifically regarding timing, frequency, and dosage. The extent to which a patient's

* Corresponding author.
E-mail addresses: sommer.agnew.2019@uni.strath.ac.uk (S. Agnew), megan.crawford@strath.ac.uk (M. Crawford), iain.macpherson@glasgow.ac.uk (I. MacPherson), victor.shiramizu@strath.ac.uk (V. Shiramizu), l.fleming@strath.ac.uk (L. Fleming).

https://doi.org/10.1016/j.breast.2024.103731
Received 21 November 2023; Received in revised form 2 April 2024; Accepted 5 April 2024
Available online 6 April 2024

acted in accordance with instruction may also be referred to as 'compliance'. However, the term 'adherence' has commonly replaced 'compliance' in the literature to reflect a more cooperative process where the patient and clinician work together [6]. Nonadherence may be intentional (deliberately not following prescription instructions) or unintentional (forgetting a dose or misunderstanding instructions) [12].

In a review of 12 community-based, real-world studies, Inotai et al. [13] reported ET adherence rates of 52.4–84.8%. This is concerning because suboptimal ET adherence may undermine treatment efficacy.: nonadherence is associated with shorter distant disease-free survival, distant metastasis [13], and a 49 % increased risk of all-cause mortality [14].

Fleming et al. [15] state that the existing literature does not consistently point to any specific treatment side effect as a predictor of ET nonadherence. Fleming's review reported that many studies report the general presence of individual symptoms, or an overall side effect profile. This may not capture the complex interrelationships among symptoms, as they often present as 'symptom clusters' rather than individually. Patients typically experience at least 10, co-occurring symptoms which may share common aetiology, and influence the presence and severity of one another [16]. Exploration of symptom clusters may therefore allow greater insight into ET side effect burden than capturing symptoms in isolation. This could lead to identification of potential targets for intervention to improve quality of life and promote medication adherence. In order to identify symptom clusters that may offer the most promise as intervention targets, we aim to: 1) reliably estimate the rate of ET self-reported nonadherence in a large sample of patients with breast cancer 2) measure and quantify the scale of ET side-effect burden, and 3) explore the relationship between these side effects and ET nonadherence.

2. Methods

2.1. Study design

A large, international, cross-sectional online survey was conducted. Following an exploratory cluster analysis, cluster membership was used as the predictor variable, and self-reported ET nonadherence was the dependent variable in the subsequent regression analysis.

2.2. Participants

Recruitment took place from September 2021 to July 2022. Participants were aged 18 or over, had previously received a breast cancer diagnosis, and had internet access. No other inclusion/exclusion criteria were set.

2.3. Measures

Demographic information on gender, age, ethnicity, nationality, marital status, employment, and education level was collected. Clinical information was collected on time since breast cancer diagnosis, breast cancer stage and grade at diagnosis, menopausal status, presence of comorbidities, cancer treatment duration, treatments received (chemotherapy, radiotherapy, surgery, and ET), and where applicable, type of ET received. The survey also included six standardized and validated questionnaires to measure adherence[1] (MARS-5 [17], sleep [18] (Sleep Condition Indicator (SCI)), depression (Patient Health Questionnaire [19] (PHQ-9)), anxiety (General Anxiety Disorder Assessment [20] (GAD-7), fatigue (Flinders Fatigue Scale (FFS) [21], and menopausal symptoms (Breast Cancer Eight Symptom Scale (BESS) [22].

The MARS-5 comprises 5 statements intended to measure self-reported medication adherence. Item 1 measures unintentional non-adherence, whereas 2–5 represent intentionally not taking medication as prescribed, with higher scores meaning better adherence. Scores of $\leq$4 (unintentional nonadherence subscale) and $\leq$19 (intentional non-adherence subscale) were used to classify participants as nonadherent [23,24]. Internal consistency for MARS intentional items was good (α = 0.87).

The SCI includes 8 items which measure symptoms of insomnia disorder. Higher scores indicate better sleep, with a total score $\leq$16 representing probable insomnia disorder [18]. High internal consistency was found for this measure (α = 0.87).

The PHQ-9 includes 9 items, with higher scores indicating more severe depressive symptoms. A score of $\geq$10 is recommended as a threshold for caseness [19]. The PHQ-9 had high internal consistency (α = 0.86).

The GAD-7 measures symptoms of General Anxiety Disorder using 7 ordinal items with higher scores indicating worse symptoms. Cut-off scores of 5 (mild), 10 (moderate), and 15 (severe) are recommended [20]. Excellent internal consistency was found for this measure (α = 0.91).

Fatigue was measured using the FFS [25]. This scale includes 7 items with higher scores indicating more fatigue. A score of $\geq$16 indicates moderate to severe ($\geq$21 = severe) fatigue [21]. Internal consistency in the current sample was good (α = 0.88).

Cognitive, musculoskeletal and vasomotor subscales of the BESS(22) were used to measure menopausal symptoms. Each subscale includes 3 items, with higher scores representing worse symptoms. In the current sample, internal consistency was good or excellent for each subscale. Cronbach's Alpha values for cognitive, musculoskeletal, and vasomotor subscales were 0.87, 0.94, and 0.80, respectively.

2.4. Procedures

The study was approved by the Strathclyde University Ethics Committee (UEC21/29). The study was advertised through websites, social media pages and mailing lists of breast cancer support organisations. Data was collected online using the Qualtrics survey platform. Participants followed a link provided in the study advertisement to access the digital patient information sheet and consent form prior to accessing the survey, which took approximately 15 min to complete. Following survey completion, a written debrief was provided online.

2.5. Statistical analysis

2.5.1. Cluster analysis

All analyses were carried out using R (R Core Team, 2021). All data, full outputs, packages, and code are publicly available at OSF.

A *k*-means clustering analysis was conducted to classify participants into groups based on their self-reported symptoms. This is an unsupervised machine learning approach, which organises data points into meaningful groups based on their similarity to others in their cluster, and dissimilarity to those in other clusters. This strategy allows groups to be identified where the researcher makes no a-priori assumptions about the data [26].

Total scores for all symptom measures (SCI, PHQ-9, GAD-7, FFS, and BESS musculoskeletal, vasomotor, and cognitive subscales) were standardized by converting to z-scores. To determine the optimal number of clusters, 30 indices were simultaneously computed via the NbClust package, and the majority rule was applied [27].

2.5.2. Logistic regression

The potential relationships between membership of the clusters that emerged and self-reported nonadherence were investigated using

[1] Adherence is defined as the extent to which a patient takes medication as directed, specifically regarding timing, frequency, and dosage [6]. Non-adherence may be intentional (deliberately not following prescription instructions) or unintentional (forgetting a dose or misunderstanding instructions) [12].

logistic regression. In both intentional and unintentional adherence, variables were coded as (adherent = 1; non-adherent = 0). Cluster membership was coded so that 0.5 corresponded to the cluster scoring lower in the target variables (indicating less severe side effects), and −0.5 corresponded to the cluster scoring higher (indicating worse side effects).

3. Results

3.1. Participants

In total, 1624 individuals consented to participate. Of those who reported that they were currently ($N = 1067$) or previously ($N = 232$) prescribed ET, only complete cases for each symptom variable were included in the analysis for current study ($N = 1051$). The sample was predominantly female (99.7%F, 0.2%*M*, 0.1 % Non-binary), aged between 45 and 54 years (39.7 %) and 55–64 years (27.4 %), and white (94 %). The most frequent nationalities were UK/Irish ($N = 194$), USA ($N = 236$), and Australian ($N = 86$).[2] Over 40 % had been diagnosed with a stage I tumour, 33.4 % with a stage II tumour. The most frequently reported tumour grade was grade 2 (37.7 %). Full sample characteristics are reported in Table 1.

Table 1 presents demographic and clinical characteristics of the sample ($N = 1051$).

3.2. Self-reported adherence

MARS-5 scores were summed to create an overall total ($M(SD)$ = 23.04(3.07)). Separate scores were calculated for intentional (18.68 (2.69)) and unintentional (4.35(0.76)) items, with higher scores indicating better adherence. The rate of nonadherence was 50.8 % (unintentional) and 31.02 % (intentional).

Table 2 presents the proportion of participants prescribed each ET type who were considered unintentionally (scoring ≤4 for item 1) and intentionally (scoring ≤19 on items 2–5) nonadherent.

3.3. Endocrine therapy side effects

Table 3 presents the mean scores for side effect measures, self-reported ET adherence, the proportion of the sample meeting cut-off scores for 'caseness' on measures of sleep (SCI), depression (PHQ-9), anxiety (GAD-7), and fatigue (FFS), and intentional and unintentional ET nonadherence.

3.4. Relationship between cluster membership and nonadherence

3.4.1. Cluster analysis

According to the majority rule, 10 among 30 indices selected 2 as the optimal number of clusters (Fig. 1). Therefore, 2 clusters were deemed optimal in the *k*-means cluster analysis.

Cluster 1 (Low overall side effects cluster) is comprised of 560 participants, whose scores in all symptom measures indicate less severe symptoms. Cluster 2 (High overall symptoms cluster) includes 491 participants, whose scores indicate more troublesome symptoms in all symptom variables. Cluster information is summarised in Table 4; Fig. 2 shows the heatmap for both clusters, and their features.

3.4.2. Logistic regression

Both unintentional and intentional nonadherence (MARS scores ≤4 and ≤ 19, respectively) were significantly predicted by cluster membership. Participants in the Low symptoms cluster were significantly

[2] This study was originally restricted to UK participants. However, following the decision to expand recruitment beyond the UK, a question was added to collect data regarding participant nationality.

Table 1
Demographic and clinical sample characteristics.

Characteristic	Frequency (%)
Gender	
Male	2 (0.2 %)
Female	1047 (99.7 %)
Non-binary/3rd gender	1 (0.1 %)
Missing	1 (0.1 %)
Age	
18–24	1 (0.1 %)
25–34	22 (2.1 %)
35–44	194 (18.5 %)
45–54	417 (39.7)
55–64	288 (27.4 %)
65–74	111 (10.6 %)
75–84	17 (1.6 %)
85+	1 (0.1 %)
Missing	(0 %)
Race/ethnicity	
White British	356 (33.9 %)
White Other	631 (60.1 %)
Black Other	7 (0.7 %)
Asian British	3 (0.3 %)
Asian Other	8 (0.8 %)
Mixed British	2 (0.2 %)
Mixed Other	10 (1.0 %)
Other	33 (3.1 %)
Missing	1 (0.1 %)
Nationality	
Australian	86 (8.18 %)
Canadian	15 (1.42 %)
German	11 (1.05 %)
Italian	15 (1.42 %)
New Zealand	33 (3.14 %)
Other	72 (6.85 %)
UK/Ireland	194 (18.46 %)
USA	236 (22.45 %)
Missing	389 (37.01 %)
Marital status	
Married	723 (69.2 %)
Widowed	27 (2.6 %)
Divorced	141 (13.5 %)
Separated	24 (2.3 %)
Never married	130 (12.4 %)
Missing	6 (0.6 %)
Employment status	
Full-time	514 (49.1 %)
Part-time	192 (18.3 %)
Unemployed seeking work	20 (1.9 %)
Unemployed not seeking work	83 (7.9 %)
Retired	194 (18.5 %)
Student	8 (0.8 %)
Disabled	36 (3.4 %)
Missing	4 (0.4 %)
Education	
High school (4 years)	132 (12.7 %)
High school (5 years)	37 (3.6 %)
High school (6 years)	59 (5.7 %)
College (HND/HNC)	225 (21.6 %)
Bachelor's degree	319 (30.6 %)
Master's degree	225 (21.6 %)
Doctorate	44 (4.2 %)
Missing	10 (1 %)
Treatment stage	
Will receive	1 (0.1 %)
Currently undergoing	546 (52.3 %)
Finished treatment	497 (47.6 %)
Missing	7 (0.7 %)
BC stage at diagnosis	
Stage I (A or B)	444 (42.6 %)
Stage II (A or B)	348 (33.4 %)
Stage III (A or B or C)	169 (16.2 %)
Stage IV	29 (2.8 %)
Don't know	53 (5.1 %)
Missing	8 (0.8 %)
BC grade at diagnosis	
Grade 1	163 (17.5 %)

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Frequency (%)
Grade 2	351 (37.7 %)
Grade 3	247 (26.5 %)
DCIS	171 (18.3 %)
Don't know	0 (0 %)
Missing	155 (11.9 %)
Menopausal status	
Pre-menopause	404 (38.5 %)
Peri-menopause	150 (14.3 %)
Post-menopause	485 (46.2 %)
Prefer not to say	11 (1 %)
Missing	1 (0.1 %)
Comorbidities present	
Yes	480 (46.3 %)
No	556 (53.7 %)
Missing	15 (1.4 %)
Chemotherapy	
Will receive	3 (0.3 %)
Have received	519 (49.6 %)
Currently receiving	32 (3.1 %)
Undecided	7 (0.7 %)
Not offered	419 (40 %)
Decided against	67 (6.4 %)
Missing	4 (0.4 %)
Radiotherapy	
Will receive	13 (1.2 %)
Have received	768 (73.1 %)
Currently receiving	7 (0.7 %)
Undecided	7 (0.7 %)
Not offered	214 (20.4 %)
Decided against	41 (3.9 %)
Missing	1 (0.1 %)
Surgery	
Will receive	10 (1 %)
Have received	1022 (97.3 %)
Currently receiving	3 (0.3 %)
Undecided	1 (0.1 %)
Not offered	13 (1.2 %)
Decided against	1 (0.1 %)
Missing	1 (0.1 %)
Endocrine therapy	
Currently receiving	890 (84.7 %)
Have received	161 (15.3 %)
Tamoxifen	363 (34.8 %)
Tamoxifen and OFS	64 (6.1 %)
AI	453 (43.4 %)
AI and OFS	148 (14.2 %)
Unsure/prefer not to say	15 (1.4 %)
Missing	8 (0.8 %)

Table 2
Self-reported nonadherence according to endocrine therapy type.

ET type	Total *N* (%)	Unintentionally nonadherent *N* (%)	Intentionally nonadherent *N* (%)
Tamoxifen	363 (34.44 %)	204 (56.35 %)	122 (33.7 %)
Tamoxifen and OFS	64 (6.09 %)	35 (54.69 %)	18 (28.13 %)
Aromatase Inhibitor	453 (43.1 %)	217 (47.9 %)	144 (31.79 %)
Aromatase inhibitor and OFS	148 (14.08 %)	70 (47.3 %)	39 (26.35 %)
Unsure/prefer not to say/Missing	23 (2.19 %)	8 (34.78 %)	3 (13.04 %)

more likely to be classed as adherent than those in the High symptoms cluster, based on both unintentional ($B = 0.284$, SE = 0.124, Wald = 2.289, OR = 1.32, 95 % CI [1.04, 1.69], p = 0.022) and intentional ($B = 0.441$, SE = 0.134, Wald = 3.292, OR = 1.55, 95 % CI [1.19, 2.02] p = 0.001) MARS item scores.

4. Discussion

Nonadherence to ET treatment is related to higher risk of breast cancer recurrence and mortality [5]. Identifying factors underlying nonadherence could inform development of targeted interventions, promoting adherence and improving breast cancer outcomes. This study measured the scale of self-reported unintentional and intentional non-adherence and assessed clinical levels of common symptoms in a large, international sample of patients with breast cancer. We then used a data-driven approach to explore participant symptom clusters and investigated the impact of these on self-reported nonadherence.

4.1. Rate of nonadherence

The rate of nonadherence was 50.8 % (unintentional), and 31.01 % (intentional). This is consistent with a review by Moon et al. [8] finding that unintentional nonadherence was more frequent than intentional ($M = 31$ % vs 15 %). This indicates a higher rate of intentional non-adherence than studies published after this review [23,25], although unintentional nonadherence (50.8 %) was comparable to Moon's (2019) study (35–47 %). Studies which differentiate between intentional and unintentional nonadherence tend to report frequency of specific non-adherence behaviours [28–30] or reasons for nonadherence [31], rather than overall frequency. This limits effective comparison of these results with past research and highlights the need to utilise a consistent, reliable measure of ET adherence.

4.2. Symptoms in endocrine therapy patients

We utilised validated measures of common ET side effects [15] to identify the scale of clinical significance. Sleep problems emerged as the most frequently troubling symptom (over 70 % of participants met criteria for probable insomnia disorder), reflecting the high prevalence of insomnia among patients with breast cancer, particularly those prescribed ET [32]. Fatigue was also common, with almost 40 % of participants reporting moderate to severe levels. Over 25 % of the current sample reported clinically significant levels of anxiety, and 43 % reported clinical moderate to severe levels of depression, which aligns with previous estimates of 20–50 % and >30 %, respectively [33]. Participants reported being more troubled by musculoskeletal pain than either cognitive impairments or vasomotor symptoms.

4.3. Cluster analysis of self-reported endocrine therapy side effects

K-means cluster analysis identified two clusters within the dataset. Those in the High symptoms cluster reported scores indicating all symptoms were highly troublesome, whereas the Low symptoms cluster reported lower levels of all measured symptoms. The results and number of clusters identified can vary according to clustering methodology and treatment stage [16]. However, previous studies of patients with breast cancer during chemotherapy [34,35] also identified clusters based on symptom severity, rather than different symptom types.

The identification of overall symptom clusters, differentiated by severity, supports the existence of connections between different ETside effects, commonly referred to as 'symptom clusters'(16). Studies consistently demonstrate a relationship between symptoms such as sleep problems, depression, anxiety, hot flashes, and fatigue [36]. Understanding interrelationships between symptoms could aid in identifying efficient targets for intervention, as targeting a 'central symptom' may alleviate overall side effect burden, presenting a cost-effective method of improving ET adherence [37].

4.4. Influence of side effects on endocrine therapy nonadherence

Logistic regression analysis found that cluster membership (High or Low ET symptoms) significantly predicted likelihood of both intentional

Table 3
Descriptive statistics for side effect measures and self-reported adherence.

Measure	*M*(*SD*) total score			Proportion meeting cut-off score		
	Overall sample	High side effects cluster	Low side effects cluster	Overall sample	High side effects cluster	Low side effects cluster
SCI	12.79 (7.3)	8.8(5.61)	16.28(6.82)	73.83 %	42.63 %	31.21 %
PHQ-9	9.41 (5.66)	13.71(4.75)	5.65(3.14)	43.39 % (Moderate-severe)	37.58 %	5.8 %
GAD-7	6.80(5.3)	10.2(5.2)	3.82(3.18)	26.36 % (Moderate-severe)	23.31 %	3.04 %
FFS	13.6 (6.57)	18.23(4.5)	9.53(5)	39.49 % (Moderate-severe)	33.21 %	6.28 %
BESS cognitive subscale	5.46 (3.16)	7.79(2.51)	3.41(2.08)	N/A	N/A	N/A
BESS musculoskeletal subscale	6.69 (3.71)	8.41(3.19)	5.18(3.47)	N/A	N/A	
BESS vasomotor subscale	4.24 (3.28)	5.66(3.28)	2.99(2.73)	N/A	N/A	
MARS unintentional (Item 1)	4.35(0.76)	4.27(0.81)	4.42(0.70)	50.8 %	25.5 %	25.31 %
MARS intentional (Items 2–5)	18.68(2.69)	18.41(2.91)	18.92(2.47)	31.02 %	16.84 %	14.18 %

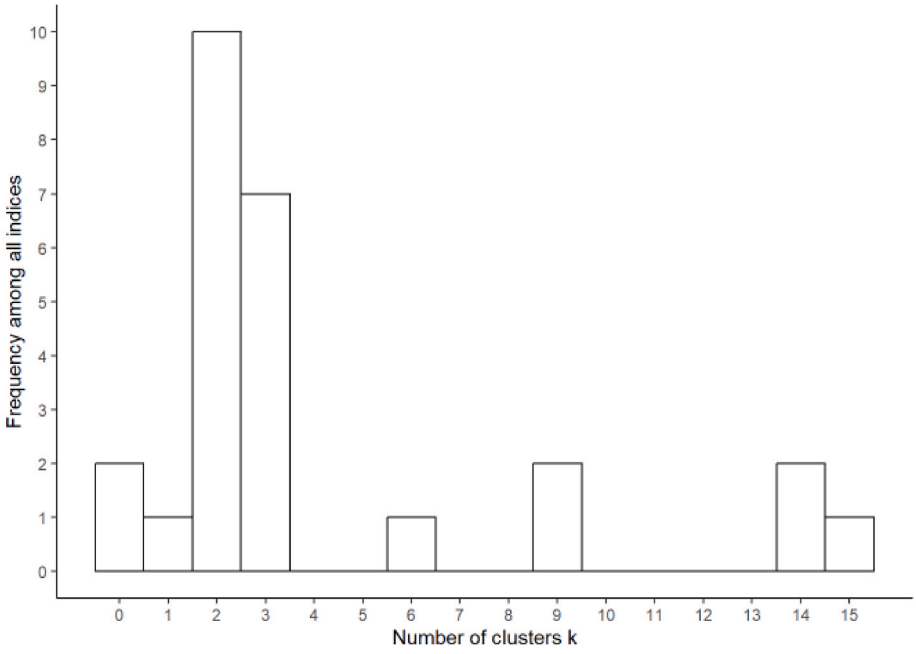

Fig. 1. Histogram showing the optimal number of clusters based on 30 indices.

Table 4
Summary of cluster centres (means) based on target variables (standardized (z-scores).

Cluster	N	SCI	PHQ	GAD	FFS	Cog	Musc	Vas
1	560	0.48	−0.67	−0.56	−0.62	−0.65	−0.41	−0.38
2	491	−0.55	0.76	0.64	0.71	0.74	0.46	0.43

and unintentional nonadherence. This is supported by research consistently identifying side effects as a significant predictor of nonadherence [38]. Fleming's [15] review identified only 8 studies which specified the nature of nonadherence (intentional vs unintentional). Across these studies, they report conflicting findings regarding the influence of side effects. Furthermore, several studies considered the presence or number of reported side effects as a predictor of nonadherence, rather than capturing symptom severity. A lack of studies specifying the nature of nonadherence, in addition to variation in measurement of ET side effects, therefore impedes direct comparison of the current results with previous research.

4.5. Strengths and limitations of the current study

This study addresses several gaps identified in Fleming's recent review. We explored the influence of common symptoms on ET adherence in a large, international sample of patients with breast cancer. We used a validated adherence measure that distinguishes between intentional and unintentional nonadherence and validated clinical tools to measure the magnitude of symptoms. This study also used a data-driven approach to capture a comprehensive symptom profile of this sample and explored the predictive value of symptom clusters on intentional and unintentional nonadherence behaviours, crucial for the identification of intervention targets to improve ET adherence. To the best of our knowledge, this is the first study to conduct a cluster analysis on a sample solely

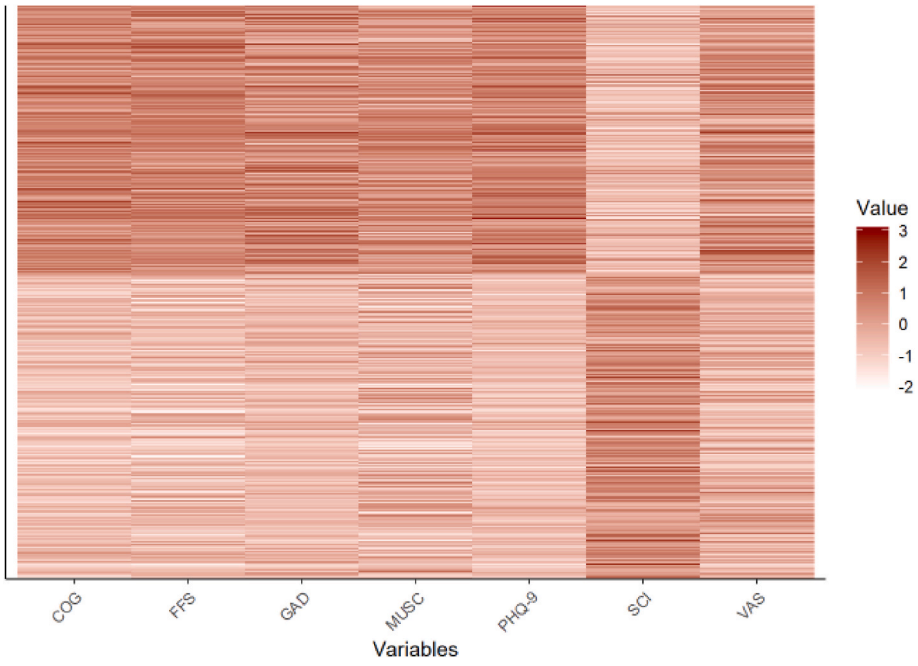

Fig. 2. Heat map of self-reported symptoms in High and Low symptom cluster.

comprised of patients currently or previously prescribed ET, measuring a comprehensive range of common ET side effects using validated measures. Existing research has not consistently identified specific side effects as predictors of intentional and unintentional nonadherence. Therefore, this approach allowed exploration of self-reported symptoms with no a-priori assumptions, prior to examining the influence of these symptoms on nonadherence.

Despite these strengths, we acknowledge the following limitations of the current study. Compared to 'objective' measures (such as blood serum level), self-report measures may underestimate nonadherence, as they are subject to social desirability and recall bias [39]. To address this, we applied a strict cut-off score for classifying participants as nonadherent based on previous research [23,24]. The MARS-5 is also designed to reduce social desirability bias by including a statement to normalise nonadherence, and, crucially, permits identification of the nature of nonadherence, which objective measures do not allow [40]. Despite these mitigations, we recognise that reported nonadherence in the current sample may be conservative. Furthermore, despite efforts to widen recruitment, the current sample may not be representative of the entire patient population.

The current study did not differentiate between symptom profiles of Tamoxifen and AIs, or patients who were prescribed ET alone versus ET combined with ovarian function suppression. It also did not account for demographic and clinical factors which may contribute to nonadherence behaviour. Finally, due to the cross-sectional nature of the study, the influence of symptoms on long-term adherence and persistence (duration of medication use, from initiation to discontinuation [12] could not be captured. As both nonadherence and non-persistence are linked to higher risk of and breast cancer recurrence and shorter disease-free survival [13], identifying mechanisms to improve long-term persistence should be a clinical priority.

4.6. *Recommendations for future research and clinical implications*

Although the current study could not capture long-term ET persistence, ET may be prescribed for up to 10 years [2], and both nonadherence and non-persistence have been linked to poorer outcomes [5]. Future research should therefore consider both nonadherence and non-persistence, potentially using longitudinal design to assess the long-term impact of side effects, accounting for demographic and clinical factors which may also influence nonadherence. This should incorporate adherence measures which distinguish between intentional and unintentional nonadherence (such as the MARS), to determine a more precise estimation of the magnitude of nonadherence. Studies should also consider the potential for different symptom clusters to emerge depending on the type of ET prescribed (i.e., Tamoxifen, AI, alone or in combination with ovarian function suppression). Efforts should be made to recruit samples including those more likely to be nonadherent or disengage from treatment, such as minority ethnic groups [23]. Future research should explore targeted interventions for a 'central symptom' such as sleep problems, a transdiagnostic symptom which may reduce overall side effect burden, potentially promoting better adherence.

Based on the results of the current study, and our previous systematic reviews [11,15], we suggest the recommendations for clinical practice outlined in Table 5.

Table 5
Recommendations for clinical practice.

1	The current study reports high rates of ET nonadherence, particularly unintentional nonadherence, among patients with breast cancer. Clinicians should be aware of the potential for patients to struggle with taking ET as prescribed, inform patient expectations about potential side effects, and encourage honest discussion of potential barriers to ET adherence.
2	Follow-up cancer care should pro-actively assess for common ET side effects and facilitate their management by offering evidence-based treatments or signposting to appropriate support when required. Clinicians should be aware of the scale of ET side effects, especially anxiety, depression, pain, and insomnia (the most troublesome side effect).
3	Patients presenting with insomnia should be signposted to appropriate treatment such as cognitive behavioural therapy. Treatment for insomnia may act as a gateway to reduce the impact of comorbid symptoms such as depression and pain (which is known to disrupt sleep) on quality of life. Improved sleep may therefore help to ease the cumulative burden of ET side effects, potentially promoting better medication adherence.
4	We recommend that validated, reliable self-report adherence measures be routinely used in clinical practice to facilitate honest discussion and develop a clearer understanding of the reasons for treatment nonadherence so that appropriate, targeted interventions can be developed.

CRediT authorship contribution statement

Sommer Agnew: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Megan Crawford:** Writing – review & editing, Visualization, Supervision, Funding acquisition, Conceptualization. **Iain MacPherson:** Writing – review & editing, Visualization, Supervision, Funding acquisition, Conceptualization. **Victor Shiramizu:** Writing – review & editing, Visualization, Supervision, Software, Methodology, Formal analysis, Data curation. **Leanne Fleming:** Writing – review & editing, Visualization, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank the various organisations who collaborated with us to circulate this study, including but not limited to: So Brave Australia, Irish Cancer Society, Penny Brohn UK, and Breast Cancer Network Australia, with special thanks to Breast Cancer Now and Cancer Association of South Africa for their collaboration. We would also like to thank everyone who took time to participate in the study and provide feedback on our research, their contributions have been invaluable. We would also like to acknowledge the contribution of Holly Finesy, Leanne MacLarty, Katelyn Jones, Claire Malone, Stephanie Powell, Lara Strawbridge, and Molly Taylor to recruitment for this study. Finally, we would like to thank the Economic and Social Research Council for funding this work (ES/P000681/1) and declare that the funding body had no involvement in study design, implementation, or writing of the manuscript.

References

[1] Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: an overview. Int J Cancer 2021 Aug 15;149(4):778–89.
[2] Bradley R, Braybrooke J, Gray R, Hills RK, Liu Z, Pan H, et al. Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol 2022 Mar;23(3):382–92.
[3] Early Breast Cancer Trialists' Collaborative Group (Ebctcg). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011 Aug;378(9793):771–84.
[4] Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015 Oct;386:1341–52. 10001.
[5] Cahir C, Dombrowski SU, Kelly CM, Kennedy MJ, Bennett K, Sharp L. Women's experiences of hormonal therapy for breast cancer: exploring influences on medication-taking behaviour. Support Care Cancer 2015 Nov;23(11):3115–30. 11.
[6] Montagna E, Zagami P, Masiero M, Mazzocco K, Pravettoni G, Munzone E. Assessing predictors of tamoxifen nonadherence in patients with early breast cancer. Patient Prefer Adherence 2021 Sep;15:2051–61.
[7] Pan Y, Heisig SR, Von Blanckenburg P, Albert US, Hadji P, Rief W, et al. Facilitating adherence to endocrine therapy in breast cancer: stability and predictive power of treatment expectations in a 2-year prospective study. Breast Cancer Res Treat 2018 Apr;168(3):667–77.
[8] Moon Z, Moss-Morris R, Hunter MS, Carlisle S, Hughes LD. Barriers and facilitators of adjuvant hormone therapy adherence and persistence in women with breast cancer: a systematic review. Patient Prefer Adherence 2017 Feb;11:305–22.
[9] Condorelli R, Vaz-Luis I. Managing side effects in adjuvant endocrine therapy for breast cancer. Expert Rev Anticancer Ther 2018 Nov 2;18(11):1101–12.
[10] Ibrar M, Peddie N, Agnew S, Diserholt A, Fleming L. Breast cancer survivors' lived experience of adjuvant hormone therapy: a thematic analysis of medication side effects and their impact on adherence. Front Psychol 2022 May 6;13:861198.
[11] Peddie N, Agnew S, Crawford M, Dixon D, MacPherson I, Fleming L. The impact of medication side effects on adherence and persistence to hormone therapy in breast cancer survivors: a qualitative systematic review and thematic synthesis. Breast 2021 Aug;58:147–59.
[12] Wassermann J, Rosenberg SM. Treatment decisions and adherence to adjuvant endocrine therapy in breast cancer. Curr Breast Cancer Rep 2017 Jun;9(2):100–10.
[13] Inotai A, Ágh T, Maris R, Erdősi D, Kovács S, Kaló Z, et al. Systematic review of real-world studies evaluating the impact of medication non-adherence to endocrine therapies on hard clinical endpoints in patients with non-metastatic breast cancer. Cancer Treat Rev 2021 Nov;100:102264.
[14] Toivonen K, Williamson T, Carlson L, Walker L, Campbell T. Potentially modifiable factors associated with adherence to adjuvant endocrine therapy among breast cancer survivors: a systematic review. Cancers 2020 Dec 31;13(1):107.
[15] Fleming L, Agnew S, Peddie N, Crawford M, Dixon D, MacPherson I. The impact of medication side effects on adherence and persistence to hormone therapy in breast cancer survivors: a quantitative systematic review. Breast 2022 Aug;64:63–84.
[16] Chow S, Wan BA, Pidduck W, Zhang L, DeAngelis C, Chan S, et al. Symptom clusters in patients with breast cancer receiving radiation therapy. Eur J Oncol Nurs 2019 Oct;42:14–20.
[17] Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: a measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol 2020 Jul;86(7):1281–8.
[18] Espie CA, Kyle SD, Hames P, Gardani M, Fleming L, Cape J. The Sleep Condition Indicator: a clinical screening tool to evaluate insomnia disorder. BMJ Open 2014 Mar;4(3):e004183.
[19] Kroenke K, Spitzer RL, Williams JBW, Löwe B. The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. Gen Hosp Psychiatr 2010 Jul;32(4):345–59.
[20] Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092.
[21] Cameron K, Williamson P, Short MA, Gradisar M. Validation of the flinders fatigue scale as a measure of daytime fatigue. Sleep Med 2017 Feb;30:105–12.
[22] Stanton AL, Bernaards CA, Ganz PA. The bcpt symptom scales: a measure of physical symptoms for women diagnosed with or at risk for breast cancer. JNCI J Natl Cancer Inst 2005 Mar 16;97(6):448–56.
[23] Moon Z, Moss-Morris R, Hunter MS, Norton S, Hughes LD. Nonadherence to tamoxifen in breast cancer survivors: a 12 month longitudinal analysis. Health Psychol 2019 Oct;38(10):888–99.
[24] De Vries ST, Keers JC, Visser R, De Zeeuw D, Haaijer-Ruskamp FM, Voorham J, et al. Medication beliefs, treatment complexity, and non-adherence to different drug classes in patients with type 2 diabetes. J Psychosom Res 2014 Feb;76(2):134–8.
[25] Brett J, Fenlon D, Boulton M, Hulbert-Williams NJ, Walter FM, Donnelly P, et al. Factors associated with intentional and unintentional non-adherence to adjuvant endocrine therapy following breast cancer. Eur J Cancer Care 2018 Jan;27(1):e12601.
[26] Tibshirani S, Friedman H. Valerie and patrick hastie..
[27] Charrad M, Ghazzali N, Boiteau V, Niknafs A. NbClust: an R package for determining the relevant number of clusters in a data set. J Stat Software 2014 Nov 3;61(6):1–36.
[28] Brier MJ, Chambless D, Gross R, Su HI, DeMichele A, Mao JJ. Association between self-report adherence measures and oestrogen suppression among breast cancer survivors on aromatase inhibitors. Eur J Cancer 2015 Sep;51(14):1890–6.
[29] Henry NL, Speth K, Lintermans A, Kidwell KM, Carlson R, Hayes DF, et al. Associations between patient and anthropometric characteristics and aromatase inhibitor discontinuation. Clin Breast Cancer 2017 Aug;17(5):350–355.e4.
[30] Kimmick G, Edmond SN, Bosworth HB, Peppercorn J, Marcom PK, Blackwell K, et al. Medication taking behaviors among patients with breast cancer on adjuvant endocrine therapy. Breast 2015 Oct;24(5):630–6.
[31] Spencer JC, Reeve BB, Troester MA, Wheeler SB. Factors associated with endocrine therapy non-adherence in breast cancer survivors. Psycho Oncol 2020 Apr;29(4):647–54.
[32] Kwak A, Jacobs J, Haggett D, Jimenez R, Peppercorn J. Evaluation and management of insomnia in women with breast cancer. Breast Cancer Res Treat 2020 Jun;181(2):269–77.
[33] Carreira H, Williams R, Müller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. JNCI J Natl Cancer Inst 2018 Dec 1;110(12):1311–27.
[34] Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs 2010 Apr;14(2):101–10.
[35] Gwede CK, Small BJ, Munster PN, Andrykowski MA, Jacobsen PB. Exploring the differential experience of breast cancer treatment-related symptoms: a cluster analytic approach. Support Care Cancer 2008 Aug;16(8):925–33.
[36] Hwang Y, Knobf MT. Sleep health in young women with breast cancer: a narrative review. Support Care Cancer 2022 Aug;30(8):6419–28.
[37] Windgassen S, Moss-Morris R, Goldsmith K, Chalder T. The importance of cluster analysis for enhancing clinical practice: an example from irritable bowel syndrome. J Ment Health 2018 Mar 4;27(2):94–6.
[38] Franzoi MA, Agostinetto E, Perachino M, Del Mastro L, De Azambuja E, Vaz-Luis I, et al. Evidence-based approaches for the management of side-effects of adjuvant

endocrine therapy in patients with breast cancer. Lancet Oncol 2021 Jul;22(7):e303–13.

[39] Pistilli B, Paci A, Ferreira AR, Di Meglio A, Poinsignon V, Bardet A, et al. Serum detection of nonadherence to adjuvant tamoxifen and breast cancer recurrence risk. J Clin Oncol 2020 Aug 20;38(24):2762–72.

[40] Kwan YH, Weng SD, Loh DHF, Phang JK, Oo LJY, Blalock DV, et al. Measurement properties of existing patient-reported outcome measures on medication adherence: systematic review. J Med Internet Res 2020 Oct 9;22(10):e19179.