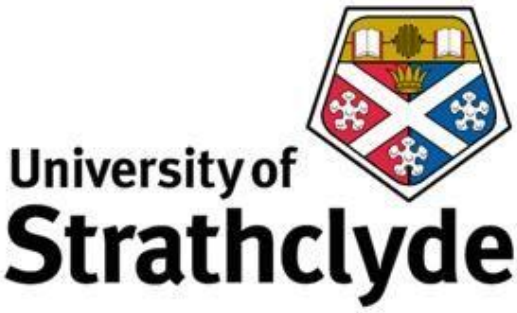

Department of Psychological Sciences and Health

A mixed methods investigation of the impact of insomnia on adherence to endocrine therapy treatment in patients with breast cancer

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Doctor of Philosophy (PhD)

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Declaration of Authenticity and Author's Rights

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:

Date: 01/08/2025

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Abstract

Approximately 70% of breast cancer cases are hormone receptor positive, therefore treatable with Endocrine Therapy (ET). When taken as prescribed, ET is effective in reducing the risk of breast cancer recurrence and mortality. However, research indicates that many patients struggle to take ET consistently. The most consistent, modifiable predictor of nonadherence to ET is treatment side effects. However, to date, research has not identified a specific side effect which consistently predicts nonadherence. This means we lack knowledge of potential targets for intervention to improve ET adherence. Insomnia is highly prevalent among patients with breast cancer (particularly those prescribed ET), and treatment of insomnia is known to have transdiagnostic benefits. Therefore, insomnia may be a sensible target symptom which, if treated, could reduce the overall burden of ET side effects and improve adherence.

The aims of this thesis are 1) investigate the impact of side effects on intentional and unintentional nonadherence to ET, identifying potential targets for intervention to improve adherence, 2) investigate the effect of improved sleep on unintentional and intentional nonadherence to ET, and 3) explore the potential role of insomnia in nonadherence to ET and gain insight into patient perceptions of how improved sleep could potentially improve adherence.

A cross-sectional survey study was conducted to explore the presentation of ET side effects in a large sample of patients with breast cancer (*N*=1051) prescribed ET. Using a data-driven approach, two symptom clusters emerged based on severity of all measured symptoms. Participants in the cluster with severe levels of all symptoms were significantly more likely to be both intentionally and unintentionally nonadherent to ET (based on self-reported

measures). The symptom most frequently reaching clinical levels in the sample was insomnia, and insomnia was significantly correlated with severity of all other symptoms.

To investigate the potential for improved sleep to improve ET adherence, a pilot randomised controlled trial was conducted of cognitive behavioural therapy for insomnia (CBT-I) in patients prescribed ET (*N*=32). Participants who received CBT-I reported a significantly greater improvement in unintentional nonadherence, depression, and musculoskeletal pain than the control group.

A qualitative study using semi-structured interviews (*N*=21) was conducted to explore patient perspectives of the potential role of insomnia in nonadherence, and potential for improved sleep to improve adherence. Participants reported that insomnia affected their ability (unintentional nonadherence) and willingness (intentional nonadherence) to take ET consistently. Participants reported that, following CBT-I, they felt better able to remember to take their medication, and less inclined to deliberately miss doses due to perceived improvement in overall quality of life.

This thesis provides a novel contribution to the literature and addresses key limitations of past research in this area. Overall, this thesis suggests that CBT-I may have transdiagnostic benefits for patients prescribed ET, which could potentially help to reduce intentional and unintentional nonadherence to ET, and provides direction for future research in this area.

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List of Abbreviations

Abbreviation	Full name
AASM	American Academy of Sleep Medicine
ACP	American College of Physicians
ACT	Acceptance and Commitment Therapy
AI	Aromatase Inhibitor
AIE pathway	Attention, Intention, Effort pathway
ANOVA	Analysis of Variance
APA	American Psychiatric Association
ASCO	American Society of Clinical Oncology
ATLAS	Adjuvant Tamoxifen: Longer Against Shorter
aTTom	Adjuvant Tamoxifen Treatment - Offer More
BAP	British Association for Psychopharmacology
BC	Breast Cancer
BCPT	Breast Cancer Prevention Trial
BESS	Breast Cancer Eight Symptom Scale
BMQ	Beliefs about Medicine
CANTO	CANcer Toxicities study
CBT-I	Cognitive Behavioural Therapy for Insomnia
CT	Cognitive therapy
CONSORT	Consolidated Standards of Reporting Trials
COREQ	COnsolidated criteria for REporting Qualitative research
DCIS	Ductal carcinoma in situ
DPA	Delaware Psychological Association
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EORTC QLQ-30	European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire
ESRS	European Sleep Research Society
ET	Endocrine Therapy
FACT-B	Functional Assessment of Cancer Therapy-Breast
FFS	Flinders Fatigue Scale
GAD-7	General Anxiety Disorder Assessment

HBM	Health Belief Model
HCP	Healthcare Practitioner
HDI	Human Development Index
ICD-11	International Classification of Diseases, 11th edition
IDEAL	Investigation on the Duration of Extended Adjuvant Letrozole
ISI	Insomnia Severity Index
LH	Luteinizing Hormone
MA.17 trial	Letrozole in the extended adjuvant setting: MA.17
MARS-5	Medication Adherence Report Scale
MEM	Medication Monitoring Device
MENQOL	Menopause-Specific Quality of Life Questionnaire
MSAS	Memorial Symptom Assessment Scale
NCF	Necessity Concerns Framework
OFS	Ovarian Function Suppression
PACT programme	Patient's Anastrozole Compliance to Therapy programme
PBC	Perceived Behavioural Control
PHQ-9	Patient Health Questionnaire
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomised controlled trial
SAT	Self-Affirmation Theory
SCI	Sleep Condition Indicator
SC Theory	Social Cognitive Theory
SCT	Stimulus control therapy
SERM	Selective Oestrogen Receptor Modulators
SH	Sleep hygiene
SOFT	Tamoxifen and Exemestane
SOLE trial	Study of Letrozole Extension trial
SRT	Sleep restriction therapy
TEXT	Tamoxifen and Exemestane
TIB	Time in bed
TPB	Theory of Planned Behaviour
WHO	World Health Organization

Chapter 1-treatment of hormone receptor-positive breast cancer

1.1 Breast cancer aetiology, incidence, and prevalence

Breast cancer is a form of cancer which originates in one or both breasts. This begins when abnormal cells in the breasts begin to grow out of control in spite of the homeostatic mechanisms which would normally regulate cell division and grow together to form a tumour (Feng et al., 2018). Breast cancer is the second most common cancer diagnosed in women, and the leading cause of cancer-related death in women worldwide (Trayes et al., 2021). In the year 2020, there were approximately 2.3 million new diagnoses (approximately 24.5% of all new cancer cases) and 685,000 deaths (accounting for 15.5% of deaths due to cancer) due to breast cancer worldwide (Arnold et al., 2022). Incidence of breast cancer is relatively higher in economically developed countries (Lei et al., 2021). Specifically in the UK, breast cancer is the most common cancer: there are around 55,900 new breast cancer cases in the UK every year (Cancer Research UK, 2015), accounting for 15% of new cases yearly. In the US, the lifetime risk of developing breast cancer is 12.38% (Akram et al., 2017), whereas breast cancer is estimated to affect 1 in 10 women in Europe (Lundqvist et al., 2016), and 1 in 7 specifically in the UK (Breast Cancer UK, 2018).

Lei et al. (2021) examined changes in breast cancer incidence over time across 185 countries, using the GLOBOCAN database, reporting that global burden of breast cancer has increased over the past 2 decades. Examination of the Global Burden of Disease 2017 database found that the incidence of newly diagnosed cases increased from 870.2 thousand to 1.9 million from 1990-2017 (Chen et al., 2020), with a further increase to 2.3 million cases worldwide in 2020 (Lei et al., 2021). This increase is occurring in both developed and developing countries, partly due to ageing populations and higher prevalence of risk factors (Sung et al., 2021). It is predicted that, by the year 2040, newly diagnosed breast cancer cases will increase by over 40% to approximately 3 million cases every year (Arnold et al., 2022).

Risk factors for breast cancer include reproductive and hormonal factors such as female sex, menstruation at a young age, later menopause, less breastfeeding, having fewer children, advanced age at birth of first child, hormone therapy medication, and oral contraception. Risk factors related to lifestyle include alcohol consumption, excess body weight, smoking, and lack of physical activity. Other risk factors include: carrying the BRCA1/2 gene, family history,

dense breast tissue, older age, history of radiation therapy to the chest, and exposure to environmental toxicants (Trayes et al., 2021; Kashyap et al., 2022). The increase in breast cancer incidence is partially attributable to societal and economic changes which increase prevalence of these risk factors, such as postponing childbearing, having fewer children, higher rates of obesity, reduced exercise, and increasing rates of women in industrial workforces (Sung et al., 2021).

Although incidence rates of breast cancer have risen (Sung et al., 2021), mortality rates have been decreasing in the past decades. In countries in the European Union (including the UK), overall breast cancer mortality declined from 17.9 to 15.2 in 100,000 from 2002 to 2012. This was most pronounced in younger women, with a 22% decline in mortality (Carioli et al., 2017). This was predicted to decrease further to 13.4 per 100,000 by 2020 (Dafni et al., 2019). Specifically in the UK, survival has doubled in the past decade; mortality rates are projected to fall by 13% from 2023-2025 and from 2038-2040 (Breast Cancer UK, 2018). This may be due to improved early detection through increased population screening, improved monitoring for breast cancer returning following treatment (potentially improving the duration of survival after cancer returns), and developments in treatments such as targeted therapies and ET (Caswell-Jin et al., 2018; Saadatmand et al., 2015). Despite a higher incidence of breast cancer in developed countries, developing countries are disproportionately represented in mortality statistics. Lei et al. (2021) report that while countries scoring low in the HDI make up only 18.4% of cases, they account for 30.1% of breast cancer deaths. The higher incidence in developed countries may partially be attributed to wider screening and better early detection, however the difference in mortality rates may be due to less accessibility to screening and effective treatment compared to countries scoring higher in the HDI (Lei et al., 2021).

Higher survival rates mean that there has been an increase in the number of people living with breast cancer, and that these people are living for longer after diagnosis. From 1975 to 2006, the 5-year survival rate increased from 74.6% to 90.6% for US patients diagnosed in 2006. Between 2005 and 2011, the 5-year survival rate was 89% in the USA. The primary contributors to this improvement are thought to be improved screening and advances in systemic treatment, especially adjuvant ET (Chen et al., 2014). In Europe, the average 5-year survival rate was almost 80% for women diagnosed from 1995-1999 and reached over 90% for women in the US in 2000. From 2000-2004, 5-year survival ranged from 71-87% in European countries without comprehensive screening programmes, and 83-91% for those with established programmes (Rosso et al., 2010). Data from 2010-2014 indicates 5-year survival

ranging from 79%-93% across countries in the EU (Dafni et al., 2019). In 2016, there were approximately 3.5 million women in the US living with breast cancer. In cases of metastatic breast cancer (where treatment does not have curative intentions), Mariotto et al. (2017) estimated a 2-fold increase in 5-year relative survival rate (from 18-36%) for women diagnosed with metastatic breast cancer from 1992-1994 and 2005 to 2012. At the end of 2020, 7.8 million women were alive who had been diagnosed with breast cancer within the past 5 years (WHO, 2023).

1.2. Breast cancer diagnosis and treatment

1.2.1. Breast cancer diagnosis and staging

Diagnosis of breast cancer usually involves clinical examination, imaging (through ultrasonography or mammography), and needle biopsy. Imaging may be administered through a population screening programme, or due to reporting of symptoms such as a lump, localised pain, or changes to the nipple or skin. Ultrasonography is used to observe localised symptoms, characterise abnormalities, and guide biopsy performed through the skin. If invasive cancer is found, a pathology report will detail the type of tumour, size, and presence of hormone receptors within the cancer cells (Harbeck et al., 2019).

Following diagnosis, the stage and characteristics of breast cancer are identified. Cancer cells will be tested for the presence of hormone receptors. In addition to the presence (or absence) of hormone receptors, staging is determined by tumour size), nodal involvement, and presence of metastases. Staging refers to identifying how much cancer is present within the body, i.e., whether the cancer has spread from the breast, past the lymph nodes to other parts of the body. The earliest stage is referred to as ‘Stage 0’ or DCIS. At this stage, breast cancer is non-invasive and has not spread. Early invasive stages (where cancer has spread from the ducts into surrounding breast tissue) include I, IIa, and IIb. Locally advanced stages include IIIa, IIIb, and IIIc. These states are non-metastatic, meaning the cancer has not spread to other parts of the body, whereas Stage IV breast cancer is metastatic (Trayes et al., 2021).

1.2.2. Breast cancer subtypes

Breast cancer is conceptualised as a group of diseases, as it includes multiple subtypes. These are categorised according to whether the cells express hormone receptors and a cell surface protein called Human Epidermal Growth Factor 2 (HER2). The major breast cancer subtypes are hormone-receptor positive, HER2 positive, and Triple Negative (Harbeck et al., 2019). A

case is classified as hormone-receptor positive when at least 1% of tumour cells contain oestrogen and/or progesterone receptors (meaning the cancer cells grow in response to these hormones) (Kashyap et al., 2022). Tumours which express HER2 are classed as HER2 positive. When cancer cells do not express oestrogen, progesterone, or HER2 receptors, the case is categorised as Triple Negative breast cancer.

Breast cancer treatment requires a multidisciplinary team including specialists in medical, surgical, and radiation oncology. The recommended treatment will be informed by the stage and breast cancer subtype (i.e., presence or absence of hormone receptors) (Trayes et al., 2021). Approximately 70% of cases are hormone receptor positive and HER2 negative, 15-20% are HER2 positive, and 15% are triple negative. Therefore, the most prevalent form of breast cancer is hormone-receptor positive (Waks & Winer, 2019). The following section will outline the intention of treatment for each stage of breast cancer and detail the treatment pathway for the hormone-receptor positive subtype.

1.2.3. Treatment of breast cancer according to stage at diagnosis

Treatment for non-metastatic breast cancer focuses on eradication of the tumour and prevention of recurrence (Waks & Winer, 2019). In the case of a recurrence (when cancer returns following treatment), treatment is guided by potential options for achieving the best possible outcome. For a local recurrence after the patient has already received a lumpectomy and radiation, further radiation is not recommended, therefore mastectomy is the standard treatment (Trayes et al., 2021). Following recurrence of metastatic (Stage IV) breast cancer, treatment options are guided by hormone receptor status. The treatment of metastatic breast cancer focuses on extending life, minimising symptoms, and preserving quality of life. This may involve ET, chemotherapy, and immunotherapy (Gennari et al., 2021).

1.2.4 Treatment of hormone receptor-positive breast cancer

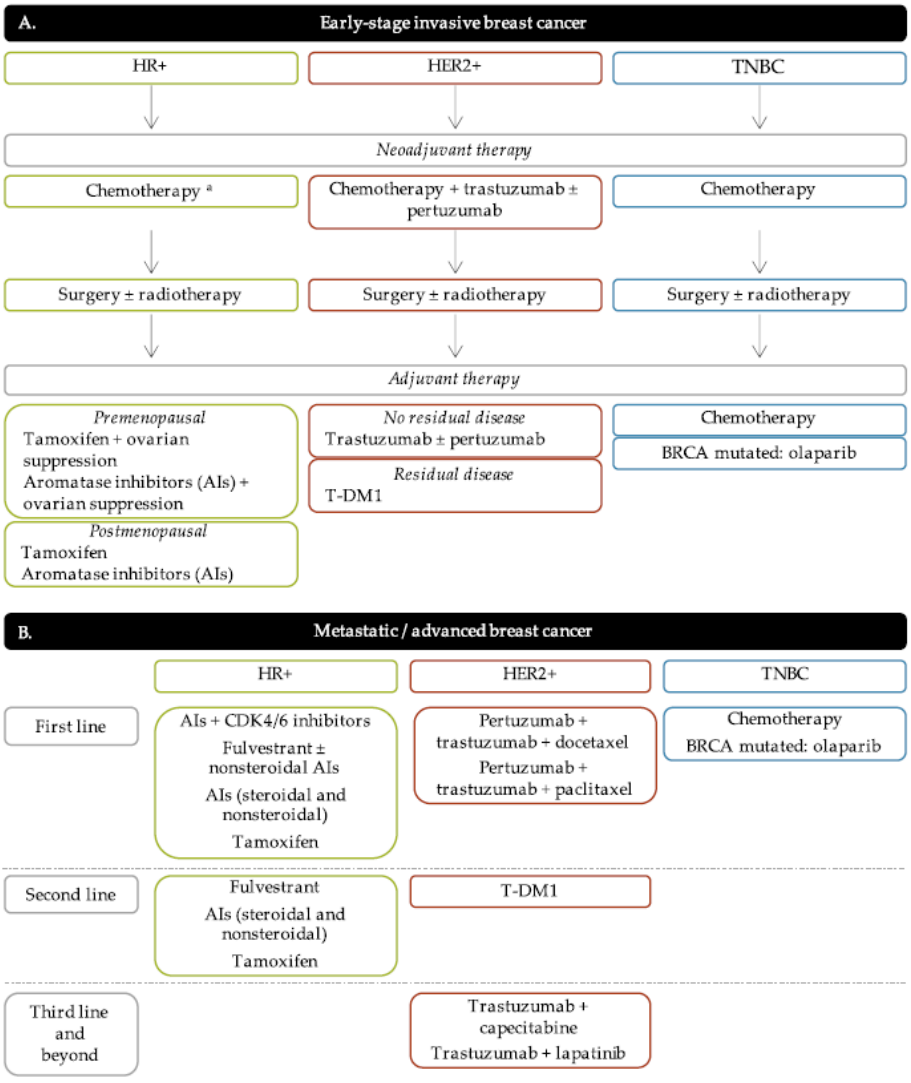
Breast cancer treatment usually involves complimentary strategies of surgery, radiotherapy, and chemotherapy. However, the order in which these are administered, and treatment administered following these, depends on the breast cancer subtype. The recommended treatment pathway for each breast cancer subtype is shown below in Figure 1 (Burguin et al., 2021, p.5).

The treatment pathway for hormone receptor-positive breast cancer includes systemic therapy: drugs which operate by spreading through the whole body to target cancer cells wherever they are. This may be administered in a neoadjuvant (before surgery) or adjuvant (post-surgery)

setting (Burguin et al., 2021). Neoadjuvant chemotherapy may be administered to reduce the size of the tumour. Following this, surgery may involve total removal of the breast (mastectomy), or removal of the tumour with a margin of normal tissue (lumpectomy, or breast-conserving surgery). Adjuvant (post-surgery) radiation therapy is then used to eliminate cancer cells which remain after surgery but may not be identifiable through testing or imaging. This is routinely offered following a lumpectomy but may be offered after mastectomy in high-risk cases (Waks & Winer, 2019; Yeo et al., 2014).

Where chemotherapy is administered as a neoadjuvant systemic therapy, hormone receptor-positive cases are also treatable with adjuvant ET. This involves taking daily tablets which operate by either lowering the volume of oestrogen produced in the body, or preventing oestrogen from binding to its receptors (Gnant et al., 2021).

Figure 1: Breast cancer treatment pathway acording to subtype (Burguin et al., 2021, p.5).



1.2.5 Endocrine therapy treatment

In cases of non-metastatic breast cancer, the aim of ET treatment is to reduce the risk of breast cancer recurrence. In metastatic breast cancer cases, ET is administered to inhibit tumour growth (Burstein et al., 2021).

Types of Endocrine Therapy

ET drugs can be classified into SERMS and AIs. The most commonly used SERM is Tamoxifen. AIs can be divided into steroidal (Exemestane) and non-steroidal (Anastrozole, Letrozole). These are 3rd generation AIs, which have higher specificity and efficacy than the preceding 1st and 2nd generations (Robertson et al., 2021).

The different types of ET work in slightly different ways. SERMS bind with hormone receptors in the cancer cells, which prevents oestrogen from binding to them. This prevents the oestrogen from stimulating the cancer cells to divide and grow. AIs prevent aromatase from converting other hormones into oestradiol, blocking the last step in the oestrogen sequence. This stops oestrogen production within the body, therefore preventing oestrogen from stimulating the cancer cells to grow (Miller, 2004).

The method of oestrogen suppression influences suitability of ET for an individual, depending on their menopausal status. Pre-menopause, oestrogen is mainly produced by the ovaries, although at certain points in the menstrual cycle up to 50% is produced in other sites (fat cells, breasts, liver, brain). After menopause, these other sites are primarily responsible for oestrogen production. The ovaries still produce androgens, which are synthesised into oestrogen in these sites. Therefore, oestrogen is still present in those without ovaries, or post-menopause. (Joshi & Press, 2018).

Previously, only Tamoxifen was suitable for premenopausal patients, as AIs cannot prevent the ovaries from producing oestrogen, and only block production from other parts of the body. The use of AIs in pre-menopausal women can actually lead to a compensatory feedback loop and increase oestrogen synthesis (Miller, 2004). However, in recent years, premenopausal women have been treated using a combination of AIs and OFS. This includes an AI (which blocks oestrogen production outside of the ovaries) and an agent to prevent the ovaries from producing oestrogen. OFS prevents the pituitary gland from releasing LH, the hormone which stimulates the ovaries to produce oestrogen. This is achieved by injection with a LH agonist, preventing the production of LH (Pistelli et al., 2018).

Efficacy

When taken as prescribed, ET is highly effective in reducing the risk of breast cancer recurrence and mortality (Shien & Iwata, 2020). Five years of tamoxifen reduces annual risk of recurrence by 39%, and mortality risk by 31%. The benefits of tamoxifen are similar for pre and post-menopausal patients (Karn et al., 2010), and have been supported by meta-analysis . AIs are thought to be even more effective than tamoxifen in reducing risk of breast cancer recurrence (Corona et al., 2019). A (2015) meta-analysis by the EBCTCG reported that the recurrence rate ratio of AIs for 5 years was significantly lower than tamoxifen in years 1-4. AIs were found to reduce recurrence by 30% and death by 15% in comparison to tamoxifen. RCTs have found improved disease-free survival compared to Tamoxifen in those prescribed Anastrozole (Fallowfield et al., 2004), Letrozole (Goss, 2007), and Exemestane (Morden et al., 2017). The TEXT and SOFT trials found that a combination of Exemestane and OFS in premenopausal patients resulted in significantly reduced risk of breast cancer recurrence compared to Tamoxifen and OFS (Francis et al., 2018).

Extended use

Despite the efficacy of ET in reducing the risk of breast cancer recurrence, there is a risk of the cancer returning following completion of ET treatment (Sella et al., 2020). Research has therefore considered the potential benefits of extending the duration of ET past the initial 5 years, for up to a decade. The ATLAS and aTTom trials found that extending tamoxifen from 5 to 10 years significantly reduced breast cancer recurrence and mortality (Davies et al., 2013; Gray et al., 2013). A combined analysis of these trials suggests that 10 years of tamoxifen could reduce breast cancer mortality by approximately 50% in comparison to no tamoxifen (Davies et al., 2013).

Although extending the use of tamoxifen seems to improve clinical outcomes, the potential benefits of extending AI treatment, and implications of extending the use of specific AI drugs, are therefore unclear (Li et al., 2018). Extending the use of an AI past 5 years can significantly reduce the risk of breast cancer recurrence, but not overall survival (Blok et al., 2018; Mamounas et al., 2019; Tjan-Heijnen et al., 2017). The ASCO recommends ET treatment including an AI for up to 10 years in cases where cancer was found in the lymph nodes (node-positive), and that extended treatment should be considered in node-negative cases. However, this must consider the individual patient prognosis and tolerability of the drugs (Burstein et al., 2019).

To maximise the benefits of extended ET therapy, a combination of tamoxifen and AIs has been explored. A meta-analysis by the EBCTCG confirmed that the extended use of an AI was associated with improved disease-free survival and modest improvement in overall survival only for those who took AIs following 2-3 years of tamoxifen (Dowsett et al., 2010). Taking extended letrozole following tamoxifen has been found to lead to significant improvement in recurrence and overall survival compared to placebo (Goss, 2007), however another study found no benefit for overall survival (Goss et al., 2016). The precise benefits of extending AI treatment are therefore unclear, and the optimal time to introduce an AI is unknown. However, sequential treatment with an AI following tamoxifen seems to present more relative benefit than extended AI or tamoxifen monotherapy (Burstein et al., 2019). Extended ET treatment (whether extending Tamoxifen use or switching to an AI following Tamoxifen) is recommended by ASCO panellists for patients who are tolerant of ET, and at high risk of late breast cancer recurrence (EBCTCG, 2015). However, this should be considered in balance with individual risk of recurrence, potential side effects, and implications for quality of life (Sella et al., 2020).

1.3 Challenges of adjuvant Endocrine Therapy treatment

1.3.1. Transition from hospital-based treatment to adjuvant endocrine therapy

When patients are prescribed adjuvant ET, they are required to take on more responsibility for their own care, as they become responsible for self-management of their own treatment. The completion of intensive, hospital-based treatment represents a complex practical and psychological shift from ‘patient’ to ‘survivor’, in terms of the care received, responsibilities undertaken, and expectations of other people. Patients report a perceived loss of support as they no longer have the safety net of regular checkups to detect potential breast cancer recurrence (Allen et al., 2009).

Patients are also referred from the care of an oncology team to their primary care physician, which can be seen as a loss of specialist care. Patients can be reluctant to discuss any questions or concerns about ET treatment with their primary care physician, as they perceive them to have apathetic to their side effects or possess insufficient specialist knowledge (Ahlstedt Karlsson et al., 2020; Ibrar et al., 2022). This can lead to a feeling of abandonment where patients are now responsible for managing their own prescriptions and medication administration, without sufficient specialist support for subsequent challenges (Peddie et al., 2021).

In addition to taking on more responsibility for their own treatment, patients begin to return to pre-diagnosis life. They may return to work and take on previous family and social responsibilities, which they were not able to engage in during active treatment. Despite expressing a desire to return to normality and go back to life the way it was before diagnosis, patients report difficulty in resuming their previous social, personal, and professional roles. While they may perceive that colleagues and loved ones expect them to return to their previous life with ease, now that primary treatment has been completed, patients report significant challenges making this transition (Chao et al., 2020). Allen et al. (2009, p. 71) refer to this as a 're-entry' phase, where patients try to return to life as it was before diagnosis, despite experiencing physical and emotional barriers they may be unprepared for.

Struggling to return to work and resume previously enjoyable activities creates a sense of loss and identity confusion as patients attempt to reintegrate back to life as it was before breast cancer diagnosis and treatment (Moon, Moss-Morris, et al., 2017). Patients report feeling excluded from social activities as people assume they will feel too unwell to attend, or they actively withdraw due ongoing physical symptoms from cancer treatment. This creates a sense of isolation which is worsened by feeling that friends and family do not truly understand the challenges of diagnosis and treatment. Strain on relationships is exacerbated by perceiving that people expect the individual to return to 'normal', despite feeling unable to return to life as it was (Keesing et al., 2018; Moon, Moss-Morris, et al., 2017). A desire to return to life before breast cancer diagnosis is an integral challenge during ET treatment, as this medication is seen as a reminder of the experience. Patients report feeling that ET as an inhibitor preventing them from returning to 'normal' life, due to ongoing treatment side effects and the act of continuously taking the medication itself (Moon, Moss-Morris, et al., 2017).

1.3.2. Residual effects of primary cancer treatment

Patients affected by breast cancer may experience residual side effects for years following completion of primary treatment. Long-term physical effects of treatment include loss of mobility, musculoskeletal pain (caused by surgery and/or radiation), reduced grip strength (common in those who received chemotherapy) and reduced aerobic capacity (due to deconditioning during treatment) (Lovelace et al., 2019). A highly prevalent side effect of radiotherapy and chemotherapy is fatigue, which has physical (reduced energy) and cognitive (reduced concentration) effects (Ruiz-Casado et al., 2021).

The likelihood of fatigue is influenced by factors such as sleep difficulties (Boscher et al., 2020). Sleep disturbance is a prevalent symptom among breast cancer survivors, with 62% reporting poor sleep quality (Cheng et al., 2023), and a pooled prevalence of 40% experiencing sleep disturbance across studies (Leysen et al., 2019). Sleep disturbance is also a persistent symptom, with 42% reporting symptoms of insomnia 3 years after breast cancer diagnosis (Beverly Hery et al., 2023). Sleep problems correspond with both physical and psychological effects of breast cancer treatment, being associated with fatigue (Lourenço et al., 2021) and cognitive complaints among breast cancer patients (Boscher et al., 2020).

In addition to significant physical impairment, a direct psychological consequence of primary treatment is cognitive dysfunction, which often arises as a result of chemotherapy (Lovelace et al., 2019). A meta-analysis by Whittaker et al. (2022) estimated that 1 in 3 breast cancer patients may experience clinically significant cognitive impairment following chemotherapy, and this may continue for 2-3 years following treatment. However, likelihood of cognitive impairment is also influenced by other psychological factors such as sleep difficulties, and symptoms of post-traumatic stress following treatment (Boscher et al., 2020). Whittaker et al. (2022) therefore propose that psychological and emotional effects of treatment must also be considered when evaluating the scale of cognitive impairment.

In addition to treatment side effects, the emotional impact of diagnosis and treatment is also persistent over time. While the completion of successful primary treatment may seem a positive milestone, patients report feeling depressed and anxious at this time, and that their strength has been depleted by the experience (Drageset et al., 2016). Following successful primary treatment, patients report a debilitating fear of their cancer returning, describing this fear of recurrence as “a sword dangling above your head” (Moon, Moss-Morris, et al., 2017, p. 990). A sense of uncertainty surrounding the future creates reluctance to make long-term plans (Drageset et al., 2016) and contributes to emotional distress and lower quality of life (Tran et al., 2022). Although this anxiety may lessen over time, severe fear of recurrence has been found to remain stable or worsen in one third of breast cancer patients through the first 5 years after diagnosis (Schapira et al., 2022). Fear of recurrence has a significant impact on the emotional wellbeing of patients with breast cancer, being significantly associated with depression, anxiety, and emotional distress, according to a recent meta-analysis (Podina et al., 2023). These are prevalent issues among breast cancer survivors, with 29% displaying depressive symptoms (Haque et al., 2021), and 20-50% experiencing anxiety (Carreira et al., 2018).

1.4. Side effects of adjuvant endocrine therapy

ET treatment is associated with a range of side effects, as oestrogen deprivation affects multiple systems within the body. This affects the reproductive, musculoskeletal, and central nervous systems, in addition to psychological effects on mood and cognitive capabilities. Physiological side effects of endocrine therapy treatment include musculoskeletal pain, vasomotor symptoms (hot flashes, cold sweats, and night sweats), fatigue, weight gain, and headaches. Psychological effects include sleep difficulties, depression, anxiety, and cognitive dysfunction (memory deficits and difficulty concentrating) (Condorelli & Vaz-Luis, 2018).

While the main types of ET (Tamoxifen and AIs) can present with similar side effects, the most common symptoms differ depending on which treatment is prescribed. Patients prescribed AIs are more likely to experience musculoskeletal disorders (e.g., arthralgia, osteoporosis), due to systemic oestrogen deprivation, than those prescribed Tamoxifen. AIs are associated with higher incidence of vaginal dryness, whereas Tamoxifen is associated with higher risk of vaginal bleeding (Condorelli & Vaz-Luis, 2018). Hot flashes and cognitive impairments are not particularly associated with one specific type of ET: higher incidence of hot flashes, and deficits in verbal memory and processing speed have been found in patients prescribed both Tamoxifen and AIs in comparison to healthy controls (Cella & Fallowfield, 2008; Ganz et al., 2016).

The addition of OFS to ET treatment further intensifies side effects. In a comparison of ET treatments, the SOFT trial found that patients prescribed a combination of Tamoxifen and OFS reported greater worsening of vaginal dryness, bone and joint pain than those prescribed Tamoxifen alone. Those prescribed Tamoxifen and OFS also reported more severe sleep problems at 6 months, although this difference did not remain significant at 24-month follow-up. Patients receiving both an AI and OFS reported that night sweats and hot flashes worsened more than those receiving Tamoxifen alone, and bone and joint pain worsened more than those receiving Exemestane alone (Ribi et al., 2016).

The ATAC trial (Cella et al., 2006) compared 5 years of Tamoxifen to 5 years of the AI Anastrozole. The most frequent side effect was hot flashes (reported by 26.6% of those on Anastrozole, and 28.5% of those on Tamoxifen). The second most frequent side effect was sleeping difficulties (19% Anastrozole, 18.9% Tamoxifen). Other psychological effects included mood swings (10.3% Anastrozole, 11.35% Tamoxifen), irritability (8.7% Anastrozole, 9.1% Tamoxifen), and nervous feeling (6.6% Anastrozole, 8.6% Tamoxifen). A systematic

review by Cella and Fallowfield (2008) considered that clinical trial data may not reflect the true prevalence of side effects, due to discrepancies between physician and patient reports in clinical trials. Therefore, the scale of ET side effects in clinical practice, and potential impact on quality of life, must be considered.

Research set in clinical practice indicates higher rates of vasomotor symptoms than identified in the ATAC trial, reported by up to 95% of premenopausal patients, and 30% of menopausal patients (Cucciniello et al., 2023). Cella et al. (2006) reported that 15.9-18.35% of ATAC participants experienced lack of energy, whereas Brett et al. (2018) reported that fatigue was experienced by 43% of patients prescribed ET. The ATAC trial reported sleep problems were one of the most common symptoms, which is reflective of studies set in clinical practice (Kwak et al., 2020). However, prior to initiating ET, 47.9% of breast cancer patients report poor sleep quality (Kidwell et al., 2014), whereas 19% reported sleep problems in the ATAC trial (Cella et al., 2006). As sleep difficulties are known to persist through the course of ET treatment (Ferreira et al., 2019), the prevalence of insomnia is likely to be higher than indicated in clinical trials.

A cross-sectional study using established, validated measures identified depression rates of 12.3% (moderate) and 12.9% (severe), and found that 41.1% of patients reported significant anxiety after 5 years of ET treatment (Kus et al., 2017). This potentially indicates higher levels of psychological distress than the ATAC trial, however, these estimates are not directly comparable as Cella et al. (2006) reported the prevalence of 'nervous feeling' (rather than anxiety) and did not measure depressive symptoms. Another prevalent symptom among breast cancer patients prescribed ET is musculoskeletal symptoms, which are reported by 46% of patients prescribed AIs, reaching similar levels in Tamoxifen users within 24 months (Cucciniello et al., 2023). However, the ATAC trial did include a specific measure of musculoskeletal pain (Cella et al., 2006).

A combined analysis of the SOFT and TEXT trials (Ribi et al., 2016) reported changes in symptom scores, including musculoskeletal pain, over time, however, this did not report the frequencies of these symptoms. This highlights the need for studies to utilise validated measures of these symptoms, to establish a consistent estimate of the scale of these issues among breast cancer patients, and allow comparison across different types of ET.

1.4.1. Impact of endocrine therapy on breast cancer recovery following primary treatment

Studies have found that overall quality of life, physical, social, and role functioning improve significantly from diagnosis and primary treatment to 18-month (Montazeri et al., 2008) and 5-year (Schmidt et al., 2018) follow-up. However, some residual side effects of breast cancer treatment can persist for years after treatment completion (Lovelace et al., 2019; Schapira et al., 2022). Specifically, fatigue, sleep problems, pain, and shortness of breath have been found to worsen from primary treatment to 18 months post-diagnosis (Montazeri et al., 2008). At 5 years post-diagnosis, breast cancer patients report significantly higher sleep problems and poorer cognitive functioning than healthy controls (Schmidt et al., 2018).

As ET may be prescribed for up to 10 years following primary treatment (Bekes & Huober, 2023), the potential impact on long-term recovery from breast cancer and its treatment must be considered. The side effects of ET can be challenging for patients to manage not only upon completion of intense primary treatment, but also long-term (Condorelli & Vaz-Luis, 2018). It can be difficult for patients to determine which symptoms are directly related to ET, which are residual effects of primary treatment, or which are due to natural ageing (Peddie et al., 2021). However, the trajectory of adverse effects following primary treatment indicates that ET may perpetuate existing symptoms and make long-term physical and psychological recovery from breast cancer more difficult.

Studies comparing patients who receive ET to those who do not receive this treatment have found differences in how side effects from primary treatment vary over time. Ganz et al. (2016) reported both cognitive and physical functioning are impacted by previous chemotherapy at 2 years post-diagnosis. However, participants who received ET reported significantly more severe hot flashes and cognitive complaints at 6 and 12 months after ET initiation than those who did not receive ET. Notably, these symptoms improved over time in patients who did not initiate ET, but remained persistent in those who did.

A later study by Ferreira et al. (2019) found that both premenopausal and postmenopausal patients who initiated ET reported significantly worse role and social functioning 2 years after breast cancer diagnosis than those who did not receive ET. Postmenopausal patients who received ET also reported significantly worse overall quality of life. Symptoms associated with systemic therapy (arm symptoms, breast symptoms, body image, and sexual functioning) and pain were significantly more severe in patients who received ET. Over time, insomnia

symptoms improved in patients who did not receive ET, but not in those who initiated ET treatment. The authors concluded that the effects of chemotherapy on quality of life may be more transient, whereas for patients who receive ET, symptoms persist over time. Therefore, ET seems to inhibit recovery from breast cancer and primary treatment, where these symptoms may otherwise stabilise and lessen over time.

1.4.2. The impact of endocrine therapy side effects on wellbeing

A review by Mioranza et al. (2016) examined the impact of ET side effects on quality of life across clinical trials, concluding that effects on quality of life are not significant in most patients. However, Cella and Fallowfield (2008) proposed that, as participants in trials (such as MA.17) elected to undergo extended treatment with Letrozole following 5 years of Tamoxifen, these patients may be especially tolerant of ET treatment. Furthermore, Mioranza et al. (2016) acknowledge that their results could be influenced by dropout of patients experiencing the most severe side effects. Therefore, clinical trials like this may not reflect the side effects many patients experience in clinical practice. Furthermore, the nature of clinical trials means these patients were likely under close observation. This does not necessarily reflect the nature of ET treatment, where responsibility is shifted from the oncology team to the patient to manage their own care more independently than during active breast cancer treatment.

To understand the implications of ET treatment for quality of life, qualitative studies have aimed to capture the patient experience and gain insight into its potential challenges. (Peddie et al.'s (2021) qualitative systematic review identified side effects as a significant challenge of ET treatment, describing how they present a multi-faceted and overwhelming challenge to many patients. Patients describe being surprised by the intensity of their side effects, feeling unprepared and unequipped to manage the impact on their daily lives. Side effects such as musculoskeletal pain, hot flashes, fatigue, sleep problems, low mood, and anxiety present a significant challenge to patients both in navigating everyday life, and in adjusting to life after completion of primary breast cancer treatment.

Daily functioning is hindered by an overall lack of energy, and symptoms which present obstacles to aspects of everyday life. Patients report difficulty socialising and reduced productivity at work due to a lack of energy, as fatigue persists over time and creates challenges keeping up with daily responsibilities (Peddie et al., 2021). Patients also report struggling to complete everyday tasks as musculoskeletal pain restricts their movement and impedes normal

daily activities like household chores and personal care such as washing and dressing. This causes previously effortless movements like standing up become straining (Peddie et al., 2021).

Functioning is also affected by vasomotor symptoms (such as hot flashes, night sweats, and cold flashes), as the working environment can become uncomfortable due to unpredictable hot or cold flashes. Discomfort and perceived embarrassment from visible hot flashes also makes patients reluctant to socialise, and enjoyment of social activities is lessened by worry about the unpredictable nature of their side effects. Activities such as travelling with loved ones are less enjoyable due to the added stress of bringing various items to manage side effects, such as chill pillows, spare clothing, medications, and painkillers (Ibrar et al., 2022).

Another symptom which can exacerbate a lack of energy in patients prescribed ET is sleep problems. As discussed in Sections 1.5-1.5.1, sleep problems are highly prevalent among patients with breast cancer (Kidwell et al., 2014), and persist for years following primary treatment in those prescribed ET (Ferreira et al., 2019; Montazeri et al., 2008; Schmidt et al., 2018). Sleep difficulties may be a direct effect of ET medication, however, other contributors include physical symptoms such as musculoskeletal pain and hot flashes (Kwak et al., 2020), and ongoing psychological distress due to fear of cancer recurrence and social isolation (Kwak et al., 2020; Lowery-Allison et al., 2018). Poor sleep contributes to an overall lack of energy and low mood, where patients struggle to function optimally (e.g., struggling to wake up for work). This also exacerbates cognitive side effects of both primary and adjuvant treatment, contributing to increased forgetfulness and reduced concentration (Ibrar et al., 2022).

Sleep problems also have a significant impact on mental wellbeing. The exacerbation of fatigue means patients have even less energy for work, daily chores, and social activities. This further contributes to a sense of social isolation and loss of identity, as patients report that poor sleep leads to emotional distress and extreme low mood (Ibrar et al., 2022; Johnsson et al., 2023). In addition to qualitative reports (Ibrar et al., 2022; Peddie et al., 2021), recent quantitative research has also found sleep problems related to higher fatigue (Momayyezi et al., 2021), lower quality of life, and depressive symptoms (Gabra & Hashem, 2021) in patients with breast cancer.

Whilst patients report intense psychological effects of ET treatment (including sleep problems, anxiety, and irritability) low mood may also present due to the strain of living with various side effects and the resultant detriment to quality of life. Patients describe feeling irritable, having

a less patient temperament when dealing with loved ones, placing strain on relationships, and severely impacting their overall mental health (Ibrar et al., 2022).

1.4.3. Challenges of managing endocrine therapy side effects and clinical implications

Because side effects of breast cancer treatment (both residual effects of primary treatment, and ongoing symptoms prolonged by ET) can cause significant impairment to quality of life long-term ET treatment can be challenging (Peddie et al., 2021). When beginning adjuvant ET treatment, patients report being highly motivated to reduce their risk of breast cancer recurrence and persist with the treatment even when experiencing side effects. However, they report a perceived lack of support from HCPs in managing these symptoms, and a sense of loss as they no longer have the safety net of check-ups and specialist care as frequently as during primary treatment. The absence of continuous monitoring and support (which was previously present during primary treatment), in managing ET side effects was described in a recent study as "an incredibly large void" (En-nasery - De Heer et al., 2022, p. 8) A perceived lack of support in managing these side effects has emerged consistently across studies, in addition to a lack of forewarning where patients report being surprised by the range and intensity of side effects (Johnsson et al., 2023; Peddie et al., 2021).

Although patients report understanding the importance of the medication, and a desire to continue adjuvant treatment to reduce the risk of breast cancer recurrence, this is complicated by the impact of these symptoms on their quality of life and their desire to feel healthy again following completion of primary treatment. Although some report determination to persist, the burden of side effects can become too great, where patients no longer feel able to continue their treatment (AlOmeir et al., 2020). Desire to resume 'normal' life and regain quality of life can lead them to take breaks from the medication, miss doses, or even contemplate cessation of the treatment (En-nasery - De Heer et al., 2022; Johnsson et al., 2023; Moon, Moss-Morris, et al., 2017; Peddie et al., 2021)

As ET may be prescribed for up to 10 years (Bekes & Huober, 2023), the success of this treatment is dependent on the patient's willingness to take medication long-term. The decision to stop treatment early has implications for the risk of breast cancer recurrence and mortality (Inotai et al., 2021). Factors which influence medication-taking behaviour must therefore be examined to identify potential means to support patients prescribed ET and facilitate their ability to continue with the treatment.

The following chapter will introduce the concept of treatment adherence (the extent to which patients follow treatment as it is prescribed (Wassermann & Rosenberg, 2017)). This will consider the reasons why patients may not take ET as prescribed, or decide to discontinue the treatment early, and the role that challenges such as side effects play in making these decisions. Limitations of our current understanding of this topic will be discussed, identifying gaps in our knowledge regarding the influence of side effects on adherence to ET.

Chapter 2: The challenge of adherence to Endocrine Therapy

2.1 Adherence in chronic conditions

2.1.1 Introduction of concepts and definitions used in this chapter

The WHO defines treatment adherence as "the extent to which a person's behaviour – taking medication, following a diet, and or executing lifestyle changes – corresponds with the agreed recommendations from a provider" (WHO, 2003, p.3). Medication adherence is a significant factor in the management of long-term chronic health conditions, which is often reliant on the patient following the prescribed course of treatment over longer periods of time (Costa et al., 2015). As the prevalence of chronic diseases rises, so does the importance of the patient's decision to follow prescriber recommendations to receive the benefits of their treatment and manage their own condition (Shahin et al., 2019).

The question of patient adherence was first pondered by Hippocrates, who stated that physicians should "keep watch also on the fault of patients which often make them lie about the taking of things prescribed". While Hippocrates emphasised the role of both the physician and patient in addressing sickness, and accepted this must be a collaborative process to some extent, later work by Robert Koch (1882) described tuberculosis patients who did not follow doctors' advice as "vicious consumptives, careless and/or irresponsible" (Lerner, 1997, p. 1424). Research into this concept led to the introduction of the term 'patient compliance' as a MESH term in the US National Library of Medicine in 1975. In 1987, the term 'Pharmionics' was introduced, to describe the discipline focused on studies of ambulatory patients who did not take their medication as prescribed (Ferlay et al., 2021).

The concept of 'patient compliance' refers to the extent to which a patient's behaviour aligns with the prescribed treatment, as recommended by the provider (Horne et al., 2005)**.** However, this term was criticised for undervaluing the attitudes and input of the patient, neglecting to take the complexity of their decisions about their own treatment into consideration. This has led the term 'adherence' replacing 'compliance' the literature, to avoid the potential paternalistic connotations of 'compliance'. The shift from use of 'compliance' to 'adherence' reflects a more patient-centred viewpoint where the patient and clinician work in partnership together, rather than the patient simply following instructions without completely understanding the necessity of following the clinician's recommendations. This also reflects

an increased demand on the patient to take responsibility for their own medical care, with an increased reliance on self-administered medication such as daily tablets (Atkins & Fallowfield, 2006).

The term 'concordance' is also used to reflect the relationship between patient and provider. This focuses on to the concept of shared perspective and the need for collaboration between patient and provider. However, this term has sometimes been incorrectly used as a synonym for 'adherence' or 'compliance' (Horne et al., 2005; Vrijens et al., 2012). The term 'adherence' reflects more quantifiable measures, regarding timing, dose, frequency, and duration of medication administration (Vrijens et al., 2012). Therefore, the term 'adherence' will be used throughout this thesis to describe the extent to which the patient's day-to-day behaviour reflects the instructions of the provider with regards to medication administration. This will be used as a distinct term from the concept of 'persistence' which refers to the duration of medication use from initiation to discontinuation, and 'non-persistence', which refers to discontinuation of treatment before the recommended duration is complete (Vrijens et al., 2012; Wassermann & Rosenberg, 2017).

When a patient does not take their medication in accordance with instructions, this behaviour is commonly referred to as 'nonadherence'. Morisky et al. (1986) proposed that this may occur due to passive reasons such as forgetfulness, or misunderstanding instructions (e.g., due to believing it was only required when symptoms are present or stopping medication when feeling unwell), or a deliberate action by the patient. Therefore, nonadherence can also be separated into intentional (deliberately not taking medication as prescribed), or unintentional (such as forgetting a dose or misunderstanding the instructions) (Moon et al., 2019).

This introductory chapter will briefly introduce the prevalence, consequences, and predictors of nonadherence to medication. This is necessary in order to understand fundamental concepts prior to discussing nonadherence to ET treatment in patients with breast cancer. The estimated prevalence of nonadherence, implications for clinical outcomes, and measures used to capture nonadherence in this population will then be discussed. Previous interventions aiming to improve ET adherence will be evaluated, examining the limitations of the existing research. Finally, potential future targets for intervention to improve ET adherence will be discussed, and a possible mechanism for improving adherence will be identified.

2.1.2 The prevalence of medication nonadherence

Medication nonadherence is a significant problem in the treatment of chronic health conditions (Gast & Mathes, 2019), with a recent meta-analysis by Foley et al. (2021) identifying a pooled estimate of 42.6% nonadherence across studies. This review also identified a prevalence of nonadherence ranging from 7-83.5% across studies. The prevalence of nonadherence was found to differ according to the method of measurement, and the nature of nonadherence (unintentional [46.9-62.9%] was more frequent than intentional [13.1-19.2%]). This highlights the need to identify a more reliable estimate of the frequency of nonadherence to medication, so that the potential scale and consequences of this issue can be more precisely identified.

2.1.3 Consequences of medication nonadherence

Nonadherence is particularly concerning in the context of chronic health conditions, as long-term treatment success is reliant on correct implementation through the patient's continued actions. Therefore, nonadherence can limit the effectiveness of the medication and, importantly, prevent the patient from receiving full benefit of their treatment (Gast & Mathes, 2019). This has serious implications on an individual level for the patient, as medication nonadherence is related to poorer outcome such as increased hospitalisation, morbidity, and mortality (Anderson et al., 2020). In older adults, good adherence to medication has been related to a 21% reduction in long-term mortality risk for patients prescribed medications for hypertension, depression, cancer, osteoporosis, and cancer (Walsh et al., 2019).

In addition to individual patient outcomes, nonadherence also places an additional burden on society. Costs of nonadherence include the need for additional resources due to hospitalisation, extra medical visits, and additional outpatient care (Kvarnström et al., 2021). It has been estimated that nonadherence could account for account for 125,000 deaths and 10% of hospitalisations annually in the US. Furthermore, the estimated cost per person of nonadherence in 2015 (adjusted across diseases), ranged from 949-44,190 US dollars (Kini & Ho, 2018).

2.1.4 Predictors of medication nonadherence

Throughout the literature, several factors have been explored in relation to medication adherence, with varying results. Socioeconomic factors such as education, employment, marital status, age, and ethnicity (Gast & Mathes, 2019; Hyvert et al., 2023) have not been consistently associated with adherence across studies. Higher medication costs have been related to higher risk of nonadherence; however, this effect was not consistent for anticancer

medications (Gast & Mathes, 2019). Across reviews, treatment side effects consistently emerge as a negative predictor of adherence (Konstantinou et al., 2020; Kvarnström et al., 2021), whereas better-quality relationships with prescribers and fewer obstacles to treatment have been related to higher adherence (Foley et al., 2021).

Although some factors are consistently related to medication adherence across different health conditions (such as side effects, relationship and communication with HCPs (Konstantinou et al., 2020; Kvarnström et al., 2021), the nature of the illness, its treatment, and specific patient beliefs must be considered in the development of appropriate interventions. In relation to cancer treatment, fear of the consequences of nonadherence may be a powerful motivation for patients to take their medication (Ibrar et al., 2022; Peddie et al., 2021). However, predictors of ET adherence may be influenced by different factors than other chronic health conditions, as this treatment is preventative in nature. A desire to minimise symptoms and maintain a 'normal' life as much as possible is related to higher adherence in some populations (Kvarnström et al., 2021). However, the benefits of endocrine therapy may be less tangible than treatment for other conditions, as ET can cause or exacerbate bothersome symptoms and patients can feel like this prevents them from returning to 'normal' life after breast cancer treatment (Peddie et al., 2021). Therefore, to inform the development of evidence-based, appropriate interventions to improve adherence, potential barriers and facilitators of adherence must be examined within the context of this specific patient population.

2.1.5 Interventions to improve medication adherence

A recent overview by Anderson et al. (2020) summarised the results of 25 systematic reviews assessing medication adherence interventions. The authors categorised the types of interventions included in these reviews (from most to least frequent) as: nonrestricted (any type of intervention), special meds packaging, dose simplification, cognitive behaviour change techniques, electronic reminders, text messaging reminders, monitoring, psychosocial or educational, and technology focused. Half of the included reviews concluded that interventions were effective, whereas half reported they were ineffective, or there was a lack of high-quality evidence from which to draw conclusions about specific interventions.

Educational interventions may involve explaining to patients how to take their medication, informing them of potential consequences of nonadherence, and reinforcing the benefits of following the treatment regimen (Costa et al., 2015). These have had some modest success in improving treatment adherence (Anderson et al., 2020; Kini & Ho, 2018). However, Costa et

al. (2015) reported that improved patient knowledge does not necessarily translate into altered behaviour. Furthermore, these interventions are rarely based on patients' prior knowledge, meaning patients may not receive any new information from the intervention. Some reviews have found interventions reminding patients to take their medication effective, however this is effect is not consistently found across the literature (Anderson et al., 2020). Inconsistent results have also been found for behavioural strategies (Costa et al., 2015), although positive results have been found for self-management training and motivational interviewing (Kini & Ho, 2018). However, these results vary depending on the patient group (Costa et al., 2015).

The variation in effectiveness between patient groups (Costa et al., 2015), and reported lack of consistency between systematic reviews examining adherence interventions in general (Anderson et al., 2020) reinforces the need to examine adherence behaviour, and potential strategies, in specific patient groups to identify appropriate targets for intervention.

2.2 Nonadherence to endocrine therapy in patients with breast cancer

Endocrine therapy differs from other forms of breast cancer treatment (surgery, radiotherapy, and chemotherapy), as, when delivered as adjuvant treatment, this medication is taken long-term. In cases of non-metastatic breast cancer, this relies on the patient's ability and willingness to take the medication for up to 10 years following primary treatment. Therefore, despite the efficacy of ET treatment in reducing the risk of breast cancer recurrence and mortality, suboptimal adherence and persistence to this medication may reduce its success (Corona et al., 2019; Shien & Iwata, 2020). Due to the high proportion of breast cancer cases which are classed as hormone-receptor positive, and the predicted continual increase in the number of patients living after breast cancer diagnosis (Breast Cancer UK), a large proportion of breast cancer patients will be prescribed ET at some point. As the reduction in breast cancer mortality is partially attributed to advances in systemic therapies such as ET (Caswell-Jin et al., 2018; Saadatmand et al., 2015), maximising the success of this treatment (and therefore patient adherence to the medication) should be a clinical priority.

2.2.1 Prevalence of nonadherence to endocrine therapy

Given the established implications of nonadherence on clinical outcomes in breast cancer patients (Inotai et al., 2021; Pistilli et al., 2020), it is important to identify how frequently patients are nonadherent to their medication. An early review by Murphy et al. (2012) identified wide-ranging estimates of 41-72% ET adherence across 29 papers. More recent reviews also found significant variation in reported prevalence of adherence across the

research. Moon et al.'s (2017) review identified 61 papers exploring ET adherence and persistence, finding the prevalence of adherence ranged from 47-97%, falling from an average of 79% to 56% from year 1 to the 4th or 5th year of treatment. In a review of 12 real-world studies, Inotai et al (2021) found adherence ranging from of 52.4-84.84%. It is difficult to draw conclusions about the prevalence of adherence from these reviews, partly due to wide-ranging estimates across studies, and also due to the use of various measurements and definitions of adherence which prevents effective comparison of these estimates across studies. Potential reasons for the range in the prevalence of adherence identified across studies, and challenges of synthesising this data, will be discussed below.

Large-scale clinical trials indicate that ET nonadherence is not an issue of significant concern (Chlebowski et al., 2014). However, early works in the field of ET adherence propose that the prevalence of nonadherence identified in clinical trials may not be truly reflective of those in clinical practice (Partridge, 2002; Partridge et al., 2003). The differences in prevalence of adherence in studies of clinical practice compared to clinical trials may be due to the close observation and voluntary nature of these trials. Compared to real-world practice, clinical trial conditions are highly controlled and strictly monitored. This means that clinical trial data may not reflect the prevalence of ET adherence in clinical practice, as this is reliant on patients' adherence to the medication regime outside of these strict protocols. Clinical trials may also be likely to attract individuals who are particularly concerned by the risk of breast cancer recurrence, and therefore highly motivated to take their medication (Inotai et al., 2021; Leventhal et al., 1991).

The discrepancy between estimates of adherence in clinical trials compared to clinical practice is further complicated by the conflation of 'adherence' and 'persistence'. Chlebowski et al., (2014) summarised ET adherence rates in the ATLAS and IDEAL trials as 84% at 5 years and 81.6% at 2.5 years, respectively. However, these statistics reflect the proportion of patients who completed the course of treatment, rather than the extent to which they followed instructions during implementation of the treatment. These figures therefore more accurately reflect long-term persistence of patients in these trials, rather than adherence to their medication.

Comparison of the prevalence of adherence across studies is further complicated by use of the term 'compliance' in clinical trials (Blok et al., 2018; Davies et al., 2013; Goss, 2007). While Chlebowski's (2014) review refers to 'adherence' (which could more accurately be described as 'persistence'), large scale trials tend to use the terminology of 'compliance'. As discussed

in Section 2.1, this term is being used less frequently in favour of ‘adherence’ to imply a more active role of the patient in decision-making (Gould and Mitty). This contributes to a lack of clarity regarding the prevalence of adherence in clinical trials, as the distinction between ‘adherence’, ‘persistence’, and ‘compliance’ is unclear.

The definition of ‘noncompliance’ used in the IDEAL trial included switching from one type of ET to another (Blok et al., 2018). However, switching ET type has actually been used as a management strategy to help patients continue despite severe side effects and could be viewed as an attempt to extend ET treatment (Lailler et al., 2021; Markopoulos et al., 2015). Therefore, estimates of adherence based on clinical trial data may not reflect the reality of clinical practice.

As discussed above, systematic reviews of studies set in clinical practice identify wide-ranging estimates of ET adherence (Inotai et al., 2021; Moon, Moss-Morris, et al., 2017b; Murphy et al., 2012). Effective comparison of adherence across the research is difficult, as the method of measurement, definition of adherence (i.e., criteria used to classify participants as ‘adherent’), and reported metrics vary between studies. Dependent on the method used to measure ET adherence, studies may report the proportion of participants classed as adherent based on the amount of time they are in possession of medication (Helland et al., 2019), meeting an established cut-off score for a self-reported measure (Moon et al., 2019), or they may be dichotomised depending on responses to a single-item question (Grunfeld et al., 2005). However, studies may also report the average proportion of the time participants are in possession of medication (Partridge et al., 2003) or average scores on self-reported adherence measures (Moon et al., 2019)**,** in addition to (or in favour of) classifying them as ‘adherent’ or ‘nonadherent’. Estimates of nonadherence have been found to vary according to the method of measurement used (Moon, Moss-Morris, et al., 2017b). Therefore, identifying a reliable, optimal method measurement is vital to establish a consistent estimate of nonadherence, and identify the scale and the potential impact of nonadherence on patient clinical outcomes.

It has been proposed that the absence of a consistent estimate could be attributed to reliance on self-reported adherence data, and a high proportion of cross-sectional studies which may mean previous reviews have not captured an accurate estimate of long-term adherence to ET (Yussof et al., 2022). However, Yussof’s (2022) systematic review excluded papers reliant on self-reported data (potentially subject to memory and social desirability bias), yet also identified wide-ranging estimates of 33.3-88.6% adherence at year 5 (based on the proportion of time covered by prescription, and gaps of significant duration between filling prescriptions). This

demonstrates a lack of consistency even across papers employing more 'objective' measures of adherence.

Measurement of endocrine therapy nonadherence

The identification of an optimal method to capture ET nonadherence is important in establishing: a reliable estimate of the scale of nonadherence, the impact of this nonadherence on long-term clinical outcomes, and accurate assessment of any intervention which aims to improve adherence. Accurate measurement of adherence is vital in ensuring that the efficacy of the treatment demonstrated in clinical trial data is reflected in effectiveness in clinical practice. This is also important for ensuring patients are prescribed the correct dosage, as nonadherence may lead to underestimating the potency of the medication.

Broadly, adherence measures can be classified into objective and subjective methods. Subjective methods may include patient and clinician report, whereas objective measures include pill counts, electronic monitoring devices, secondary database analysis of electronic prescription services or pharmacy insurance claims, and biochemical measures (such as measuring the metabolite concentration of medication in a patient's blood or urine) (Lam & Fresco, 2015).

Adherence measures can also be categorised as direct (biochemical measures) and indirect (pharmacy records, pill counting, MEMS, and self-report) (Lam & Fresco, 2015). Indirect measures may include using prescription refill data to identify the proportion of time a patient had access to their medication (referred to as medication possession ratio, or proportion of days covered, depending on the calculation), or electronic monitoring devices. These record the dates where a patient opens the container for their medication, presuming that they took their medication on this date. Identifying an optimal method of adherence measurement (based on both accuracy and practicality), requires consideration of both strengths and weaknesses of these types of measures.

Comparison of endocrine therapy adherence measurements

Systematic reviews indicate that the most frequently used methods of adherence measurement have changed over time. Murphy et al. (2012) noted that most studies in their review used pharmacy refill data or records from hospital databases to assess whether patients were filling their prescriptions for ET. Moon et al. (2017) noted a more equal frequency of studies using self-report compared to pharmacy refill data (21 vs 27), although Inotai et al. (2021) noted that 7 of 12 studies calculated adherence based on prescription refill data. In a recent review by

Fleming et al. (2022), examining the impact of side effects on ET adherence, authors reported that subjective (self-report methods) were most frequently used (71% of studies measuring adherence used self-reported measures). The most common indirect measures in this review were pharmacy records, and no studies applied a direct measure of adherence.

Although self-report measures of adherence are frequently used, they do present limitations. Yussof et al. (2022) focused their review of factors predicting adherence on studies which did not rely solely on subjective data, to reduce the potential for recall and social desirability bias to influence results in subjective measures. However, Murphy et al. (2012) highlighted in their earlier review that indirect measures such as prescription records also have limitations, as they only indicate the rate patients fill their prescription, not whether they ingest their medication as it was prescribed.

To investigate the difference between self-report and objective measures of ET adherence, the CANTO study compared the prevalence of ET nonadherence identified by self-report and objective measures (blood serum level). When measuring tamoxifen serum levels, the prevalence of ET non-adherence was 16%. However, the prevalence of nonadherence was only 8.8% according to self-report. Therefore, the prevalence of nonadherence based on self-report was approximately half of that identified by blood serum level (Pistilli et al., 2020). This indicates that subjective reports underestimate nonadherence in comparison to objective measures. However, Moon et al. (2017) reported that studies using MEMS found the highest level of adherence (93%), followed by self-report (82%) and prescription refill rates (75%). The advantages of 'objective' measures are not guaranteed, as drugs such as Anastrazole may be detected for days after taking a dose and may vary depending on individual differences in metabolic rate (Oberguggenberger et al., 2012). This means they are not guaranteed to accurately capture the consistency of medication-taking.

In addition to accuracy, is important to consider the level of insight a measurement affords. Objective measures such as electronic monitoring devices and biochemical tests may indicate whether a patient took their medication but cannot indicate the reasons why they may not have taken it. Self-report measures have the advantage of permitting identification of the nature of nonadherence (e.g., intentional or unintentional), which is not possible with objective measures (Kwan et al., 2020). A lack of understanding the nature of nonadherence is highlighted in Fleming's (2022) review, which identified only 8 studies which distinguished between intentional and unintentional nonadherence, despite the most common measurement being self-

reported data. Therefore, the measures often used to capture self-reported data also have significant limitations. However, self-reported measures are frequently used as they are more pragmatic than more objective measures. Monnette et al. (2018) concluded that self-report measures remain the most practical method of assessing adherence due to ease of administration, efficiency, and cost effectiveness.

It is difficult to accurately capture ET nonadherence due to the varying nature of the behaviour (intentional or unintentional), and measures potentially being subject to bias. Each method presents with advantages and disadvantages, which must be carefully considered. However, an element of pragmatism is also required to consider which methods are appropriate and can be effectively administered.

2.2.2. The consequences of nonadherence to endocrine therapy

A recent review (Inotai et al., 2021) examined the impact of nonadherence and early discontinuation on breast cancer outcomes across 12 good quality, community-based studies. Of these, 8 studies identified a significant relationship between medication nonadherence and mortality (Hazard/Odds Ratio 1.2-9.5). Both nonadherence and early discontinuation were associated with worse disease-free survival (Hazard Ratio of 4.24). This review also found significant associations between nonadherence and risk of distant metastasis (Hazard Ratio from 1.6-5) and breast cancer recurrence (Hazard Ratio of 1.7-2.9). Studies published outside of Inotai's (2021) review also identified a significant association between nonadherence, non-persistence, and clinical outcomes in breast cancer patients. Nonadherence has been identified as a significant predictor of mortality (Hershman et al., 2010; Hsieh et al., 2014), and patients with low adherence have been found at greater risk of all-cause mortality (Makubate et al., 2013). More recently, a study (Pistilli et al., 2020) found that patients classed as adherent to ET medication lived for significantly longer without their cancer having spread than nonadherent patients.

Although research indicates that ET adherence is significantly related to long-term treatment outcomes (Inotai et al., 2021), these studies could possibly be subject to 'healthy adherer bias'. This refers to the idea that patients who strictly adhere to treatment may demonstrate healthier lifestyle habits (Pack et al., 2021), and the benefits of these underlying behaviours may be attributed to the treatment. Patients who are especially adherent to ET may also demonstrate other health behaviours which are related to lower risk of cancer recurrence (such as less

frequent smoking, lower alcohol consumption, more physical activity, and healthy diet) (Kreklau et al., 2021; Tollosa et al., 2019).

2.2.3 Predictors of endocrine therapy adherence

This section will discuss factors which influence adherence to ET treatment, identified in both quantitative and qualitative research. This will include clinical and demographic, care-related, psychosocial factors, and treatment side effects. First, clinical, and demographic factors will be considered. However, identification of a target for intervention to improve adherence must consider factors which i) are consistently associated with nonadherence across the literature, and ii) are potentially modifiable. Although demographic and social factors such as age, ethnicity, and financial status are consistently related to adherence, these are not amenable to intervention. Therefore, this section will expand further on the potentially modifiable factors associated with adherence, considering the potential mechanism through which they may improve adherence, in the context of theoretical models of health behaviour.

Clinical factors

Moon et al. (2017b) reported that clinical factors such as previous chemotherapy, tumour size, and lymph node status were not consistently associated with ET adherence. However, more recent reviews have reported that higher tumour grade and lymph node involvement are related to ET nonadherence among metastatic patients (Yussof et al., 2022). Not having received chemotherapy prior to surgery (Montagna et al., 2021) or at all (Yussof et al., 2022) has also been related to higher adherence. A higher number of hospitalisations has been related to lower adherence across systematic reviews (Moon, Moss-Morris, et al., 2017b; Yussof et al., 2022). However, studies tend not to report the exact nature of these hospital admissions. Other clinical factors associated with lower adherence include higher burden of comorbidity, metastatic breast cancer, use of hypnotics, sedatives, and pre-existing depression (Yussof et al., 2022).

Studies report inconsistent findings on the impact of 'switching' (changing from one type of ET to another). Moon et al. (2017b) reported that the patients who switched from one ET to another were likely to have lower adherence than those who remained on the same type, supported by Murphy's (2012) previous review. However, this finding was not consistent across studies. More specifically, Yussof's recent (2022) review reported that switching from tamoxifen to an AI was associated with higher adherence, but patients who switched from an AI to tamoxifen had lower adherence than those treated with an AI only. The impact of

switching on adherence also varied according to timing: early switching was associated with higher adherence, whereas late switching was related to nonadherence (Yussof et al., 2022).

Demographic factors

Both older and younger age have been associated with increased risk of ET nonadherence (Moon, Moss-Morris, et al., 2017b; Murphy et al., 2012; Paranjpe et al., 2019; Yussof et al., 2022). Financial factors such as not having insurance, medication costs (Moon, Moss-Morris, et al., 2017b; Murphy et al., 2012), and lower financial status (Yussof et al., 2022) have been related to nonadherence. Being unmarried or not having a partner (Yussof et al., 2022) has been related to lower adherence. Ethnicity also influences likelihood of nonadherence: black or Hispanic ethnicity is associated with lower adherence than in white patients, whereas Asian ethnicity is associated with higher adherence than in white patients (McGuinness et al., 2022; Moon, Moss-Morris, et al., 2017b; Yussof et al., 2022).

Structural/care-related factors

The type of care received by a patient is related to their ET adherence. Patients who receive continuous follow-up care (Lambert et al., 2018), a personalised care plan, and continuous treatment in the same hospital (Yussof et al., 2022) are more likely to be adherent. Furthermore, the type of HCP they receive care from influences their adherence. Patients who see a specialist, such as breast cancer nurse, mastologist, or oncologist (Lambert et al., 2018; Moon, Moss-Morris, et al., 2017b; Murphy et al., 2012) demonstrate higher adherence than those who only receive care from a GP. Yussof et al. (2022) reported that follow-up consultation with an oncologist within 4 months of ET initiation was associated with higher adherence.

The relationship between patients and HCPs and perceived nature of their interactions has consistently been related to ET adherence across systematic reviews. Lambert et al. (2018a) identified that patients who were dissatisfied with the patient-HCP relationship were less likely to be adherent. The quality of this relationship was associated with adherence 83% of the time in univariate statistical models (Toivonen et al., 2020). A poor relationship with HCPs and lack of opportunity to ask questions is associated with interruption of ET treatment (Paranjpe et al., 2019). In qualitative research, patients report that HCPs play an important role in encouragement, emotional and practical support. Facilitators of adherence include regular follow-up care, effective communication and a trusting relationship with HCPs (Clancy et al.,

2020; Lambert et al., 2018). Some patients cite a loss of trust in HCPs as a factor in stopping the medication (AlOmeir et al., 2020).

In addition to the quality of the patient-HCP relationship, the nature of communication regarding ET influences the likelihood of adherence. Patient-centred communication, frequency of communication from HCPs, both in general (Moon, Moss-Morris, et al., 2017a) and about the importance of ET (Lambert et al., 2018) are positively related to adherence. Poor communication (in terms of the amount, type, and quality of information given) has been related to lower adherence (Lambert et al., 2018). Conversely, patients who perceive the information received as understandable are more likely to adhere (Toivonen et al., 2020). A lack of shared decision-making, where the patient does not feel involved in decisions about ET treatment, has been associated with lower adherence (Lambert et al., 2018; Montagna et al., 2021).

The role of HCP communication in ET adherence can be interpreted through the HBM (Rosenstock, 1974), as difficulty communicating with HCPs about medication, and lack of resources (e.g., lack of access to specialists) could act as barriers to the desired behaviour (ET adherence). We can also view this through the lens of SC theory (Bandura, 1999), where lack of self-efficacy (i.e., belief in their own ability to communicate) in HCP-patient interactions makes it difficult for the patient to raise concerns. Interventions offering support to patients in speaking to doctors about concerns related to their medication (Wagner et al., 2016), and tailored support based on level of need (Ziller et al., 2013) did not find significantly improved adherence, although one study found a significant pooled effect of intervention and control arms (Ziller et al., 2013). This indicates that facilitating communication with HCPs may not be sufficient to support patients with adherence, and other potential means to improve adherence should be considered.

Social support:

As discussed above, the patient-HCP relationship is one path through which perceived support from others can facilitate ET adherence. In addition to the quality of the relationship with HCPs, social support from loved ones is also related to higher adherence (Lambert et al., 2018): this may include emotional or material support (Toivonen et al., 2020). Support from family and friends is consistently cited as an aid to adherence, in addition to peer networks of other patients with breast cancer (AlOmeir et al., 2020; Lambert et al., 2018; Xu, Zhang, et al., 2020).

A supportive and understanding partner, particularly in relation to side effects, is helpful in navigating drawbacks of the medication. Peer networks are also viewed as a valuable resource for emotional support, a sense of understanding, and practical advice in managing side effects of the medication, thus facilitating adherence (Clancy et al., 2020). According to the TPB (Ajzen, 1991), the influence of others may also affect the patient's perception of ET by affecting perceived social norms, i.e., the attitudes of those around the patient towards their medication (Toivonen et al., 2020).

Self-efficacy:

Discussion of patients' perceptions of communication with HCPs must consider the psychological and social constructs underlying these interactions. The patient's confidence in navigating these interactions is an important factor. Several systematic reviews have found that self-efficacy in communicating with HCPs (Lambert et al., 2018; Moon, Moss-Morris, et al., 2017b; Toivonen et al., 2020) is positively associated with ET adherence. Patients who feel they have less influence over their health, or that others have more influence over their health decisions, are more likely to be nonadherent (Lambert et al., 2018). A recent meta-analysis identified self-efficacy as one of the most consistent predictors of ET adherence, being positively associated with adherence in 75% of studies (Toivonen et al., 2020). However, a lack of theory-driven interventions means the potential value of applying SC theory to ET adherence is not well understood. A recent pilot study explored the feasibility of an intervention informed by SC theory, but did not explore efficacy of the intervention (Ahlstedt Karlsson et al., 2022)

Attitudes towards treatment:

Beliefs about the necessity of the medication are known to influence adherence, as nonadherent patients report more scepticism regarding the necessity of the treatment (Lambert et al., 2018). Some patients report that they believe taking the medication for some time affords them enough protection to discontinue early, believing that it is no longer necessary. In contrast, adherent patients report a strong belief in the necessity of the medication, and in its ability to reduce risk of recurrence (Xu, Jin, et al., 2020).

In addition to beliefs about the necessity and efficacy of medication, adherence is influenced by perceived drawbacks of taking ET. This may include negative emotions related to the medication, negative beliefs about the medication (e.g., concerns about potential overuse, side effects, long-term health consequences), and perceived barriers to medication-taking. According to the HBM, if the perceived benefits are outweighed by these barriers (i.e., the

disadvantages are prioritised more than the necessity and efficacy), patients are less likely to adhere (Lambert et al., 2018). Even patients who reportedly struggle with severe side effects are influenced to continue because of their belief in the necessity of treatment (Xu, Jin, et al., 2020).

Lower perceived need for ET and higher concerns (e.g., addiction and long-term side effects), have been related to higher intentional nonadherence (Paranjpe et al.,2019). However, another review (Toivonen et al., 2020) reported that specific beliefs about overuse or harmful effects of ET were not associated with adherence. A recent study by Tan et al. (2021) also found that neither necessity nor concern beliefs were significant predictors of adherence. This discrepancy may be due to Paranjpe's (2019) review including both qualitative and quantitative research. A previous study (Wouters et al., 2014) found that validated instruments such as the BMQ (Brett et al., 2017) do not necessarily apply to patients' individual experiences and perceptions of the medication. Therefore, qualitative research may provide more insight into how individual patients' beliefs and concerns could influence their adherence to ET.

Qualitative research indicates that necessity beliefs about ET are informed by the patient's perception of their own risk of breast cancer recurrence, and their fear of recurrence. Some patients who struggle with side effects report that these are preferable to recurrence and having to go through subsequent intensive treatments (namely, chemotherapy and surgery) again. Patients report a desire to do everything they can to reduce the risk of recurrence, feeling ET gives them a sense of control and helps reduce worry about anticipated regret (AlOmeir et al., 2020).

Barriers:

Perceived barriers to adherence may arise from the patient themselves. Forgetfulness is frequently identified as a barrier to nonadherence, as ET relies on the patient's own initiative to take medication every single day (Tan et al., 2021). This may be especially problematic in ET treatment as patients report the medication itself contributes to brain fog and forgetfulness (Ganz et al., 2016; Peddie et al., 2021). Interventions involving reminders to take medication have found mixed results (Park et al., 2022; Hadji et al., 2013; Markopoulos et al., 2015). According to the HBM, heath behaviours are also influenced by factors such as perceived severity and susceptibility (i.e., consequences of nonadherence) and perceived benefits. This

may explain why addressing one barrier (forgetfulness) through reminders is not sufficient to promote adherence. Other intervention components may also be needed if barriers other than forgetfulness are present, as reminders would only address unintentional, and not intentional, nonadherence.

Reminder interventions tend to include the additional component of information provision, which may increase their effectiveness given the superiority of multicomponent interventions (Dang et al., 2022) This may be especially important in addressing intentional nonadherence, which may be influenced by the patient's beliefs about the medication. Information provision may facilitate behaviour change by addressing components of the HBM such as perceived benefits of the treatment, and perceived severity of not taking the medication. However, although necessity beliefs and fear of cancer recurrence have been associated with higher adherence (Murphy et al., 2012; Toivonen et al., 2020), information provision alone does not seem to facilitate greater adherence (Finitsis et al., 2019). This aligns with SC theory, which states that knowledge alone is not sufficient to create a change in behaviour (Bandura, 1999).

Decisional balance

Adherence may also be influenced by 'decisional balance', which is a key element of the NCF (Horne & Weinman, 1999). According to this framework, the likelihood of adherence is dependent on the perceived balance of positives and negatives of the medication. Toivonen et al. (2022) found that a positive decisional balance (i.e., a more positive than negative attitude towards ET) was related to higher adherence at least 75% of the time. The balance between perceived advantages and disadvantages of taking ET is also influenced by coping strategies, such as positive self-talk about the necessity of ET (Lambert et al., 2018). Several reviews also point towards time orientation as a factor in adherence. Adherent patients tend to focus their actions and thoughts on the future and prioritise long-term benefits of taking ET (such as avoiding breast cancer recurrence), whereas nonadherent patients tend to have a present orientation where they focus on avoiding the negative aspects of the medication, such as unpleasant lifestyle changes and associated side effects (Montagna et al., 2021; Moon et al., 2019). The following section will consider how these side effects could impact decisional balance towards ET, and their potential influence on treatment adherence.

Treatment side effects

As discussed in Chapter 1, ET side effects can have a serious detriment to patients' quality of life and daily functioning, creating a significant challenge as they are prescribed this treatment

for up to 10 years (Peddie et al., 2021). Common side effects include hot flashes, sleep problems, anxiety, depression, musculoskeletal pain, and cognitive dysfunction (Condorelli & Vaz-Luis, 2018). These side effects rarely occur in isolation, often sharing a common cause or aetiology, meaning patients with side effects are likely to experience several of these symptoms (So et al., 2021).

Treatment side effects have been identified as a predictive factor in ET adherence across numerous systematic reviews (Fleming et al., 2022; Lambert et al., 2018; Montagna et al., 2021; Murphy et al., 2012). Specifically, the number and severity of side effects influences nonadherence (Toivonen et al., 2020), as the lowest adherence is found in patients with severe side effects, and likelihood of nonadherence increases by 20% for every additional side effect (Lambert et al., 2018). Side effects may affect the likelihood of nonadherence by influencing decisional balance, where the negative impact of side effects could outweigh perceived effectiveness of ET medication, and potential consequences of nonadherence (Murphy et al., 2012). The anticipated severity of side effects has been found to influence adherence negatively (Montagna et al., 2021; Toivonen et al., 2020), and self-efficacy to manage side effects is associated with higher adherence (Montagna et al., 2021)

Although some reviews of quantitative research reported that side effects did not always predict adherence (Moon, Moss-Morris, et al., 2017b; Toivonen et al., 2020), side effects are the most frequently cited barrier to ET adherence by patients (Toivonen et al., 2020). Furthermore, systematic reviews frequently cite variation in the measurement of adherence and side effects as a barrier to synthesising research into the impact of side effects (Fleming et al., 2022; Moon, Moss-Morris, et al., 2017b; Toivonen et al., 2020; Yussof et al., 2022), which may contribute to the lack of consensus across the literature. This is further complicated by the fact the patient must be taking their medication to experience potential side effects. Therefore, patients who are frequently nonadherent or discontinued their medication prematurely due to side effects may no longer experience these side effects, creating uncertainty regarding the initial cause of their nonadherence. Moon, Moss-Morris, et al. (2017b) identified that in some studies, nonadherent patients reported fewer side effects than adherent patients, proposing that this could possibly be a result of not taking the medication.

Ability to manage side effects consistently emerges as a theme across reviews of qualitative literature. Patients report difficulty reconciling that medication intended to extend cancer-free

life also impacts their quality of life negatively, creating the need to balance side effects against benefits of the medication (Lambert et al., 2018). Nonadherent patients report frequent, severe, unpredictable side effects, which are viewed as a hindrance to returning to 'normal' life (i.e., life before cancer diagnosis) (AlOmeir et al., 2020; Xu, Zhang, et al., 2020). This contributes to feeling powerless and lacking support and knowledge to manage side effects. In contrast, adherent patients report strong motivation to manage side effects and regain a sense of control over their bodies (Xu, Zhang, et al., 2020). This highlights the importance of self-efficacy in relation to managing side effects, which is linked to higher adherence in quantitative studies (Montagna et al., 2021).

A systematic review of 17 qualitative studies (Xu, Zhang, et al., 2020) identified four categories of patients, and suggest that the 'bearing/suffering' and 'hesitation/adjustment' types should be identified, and their support needs in relation to adherence should be addressed. Patients described as 'bearing/suffering' strive to persevere with ET treatment despite severe side effects but would seriously contemplate discontinuing if symptoms became unbearable. Patients described as 'hesitation/adjustment' hesitate to take ET medication (despite understanding its importance) due to side effects and may adjust their level of adherence or even discontinue. The authors report that, despite high motivation to adhere, no participants expressed an intention to continue with ET regardless of the severity of side effects.

Patients report that there is a 'tipping point', where, if side effects become severe enough, they will prioritise quality of life over the sense of security from cancer recurrence, and seriously contemplate discontinuing ET (Clancy et al., 2020, p. 4). This aligns with the NCF, indicating that altering decisional balance (by increasing perceived benefits or reducing perceived negative consequences of the medication) would improve the likelihood of adherence. This may be more effective than strategies such as information provision, as knowledge alone is not necessarily enough to readdress decisional balance (Toivonen et al., 2020).

Support in management of side effects would address a major barrier to ET adherence, which may promote adherence according to the HBM. Reducing side effect burden could address unintentional nonadherence, if an intervention helped with cognitive side effects such as brain fog and memory deficits (Peddie et al., 2021), leading to forgetfulness. This could also potentially influence intentional nonadherence by reducing negative attitudes and beliefs about ET. This could promote positive decisional balance, which could encourage adherence according to both the TPB (Ajzen, 1991) and NCF (Horne & Weinman, 1999). Another element

of the TPB which side effect management could address is PBC, which can be likened to self-efficacy. Toivonen et al. (2020) propose that the perceived ability to manage side effects, rather than actual presence of side effects, has a significant impact on adherence. Therefore, supporting patients in self-management of their side effects may improve their perceived control over their own adherence behaviour, and self-efficacy in relation to taking fthe medication. Side effects therefore represent a modifiable predictor of nonadherence which could potentially be amenable to intervention (Fleming et al., 2022).

2.2.4 Interventions to improve endocrine therapy adherence

Previous ET adherence interventions have included patient education, reminders, tailored patient support, and symptom management. The following section will summarise previous attempts to improve ET adherence and evaluate the limitations of existing research in this area.

Educational and reminder interventions

The PACT study investigated a programme designed to promote ET adherence. The PACT programme was developed in a German context, in close collaboration with patients with breast cancer. This includes both educational materials, (delivered through letters and brochures) and monthly reminders (Hadji et al., 2013). The educational materials include information about ET, breast cancer groups, mental wellbeing, impact of breast cancer on sexuality, sports and nutrition advice, and personal stories of other patients with breast cancer. Participants who scored at least 80% on a self-report questionnaire were deemed adherent, with no significant differences found between intervention and control arms (Hadji et al., 2013). A similar programme adapted for Chinese patients with breast cancer found no significant difference in persistence between intervention and control arms (Yu et al., 2012). In an evolution of the PACT study, Neven et al. (2014) conducted a large-scale investigation spanning 18 different countries, finding no significant differences in the proportion of adherent participants (through self-reported adherence questionnaires) between intervention and controls. This null result has been found both one (Hadji et al., 2013) and two years after ET initiation (Markopoulos et al., 2015). However, the 2-year follow-up study (Markopoulos et al., 2015) classed participants as ‘noncompliant’ (i.e. nonadherent) who switched ET type, rather than using a self-reported questionnaire. In a recent study, Park and colleagues (2022) investigated using an electronic pill bottle synced with their mobile phone, to prompt participants to take their medication. They reported that the intervention group opened their pill bottles significantly more than controls (indicating higher adherence). This indicates that reminder interventions may be helpful in promoting consistent medication-taking.

Studies have also investigated the influence of verbal information provision on ET adherence. Wagner et al., (2016) delivered informational phone calls to patients prescribed ET, to address any concerns about the medication, provide guidelines for its use, and offered support in speaking to doctors about any concerns. Adherence was calculated by assessing the proportion of time participants had access to ET based on prescription records. Among patients who received these phone calls, 50% were covered by a prescription at least 80% of the time (classed as adherent), compared to 25% of those who could not be reached. However, this difference was not statistically significant. Heisig et al. (2015) investigated the impact of both written and verbal information on the mechanism and benefits of ET, and common and serious adverse effects. Patients reported satisfaction with the information provided and improved relevant knowledge after receiving enhanced written information. However, this single-arm study did not allow comparison of adherence with any control group. Furthermore, information comprehension and recall were not significantly associated with likelihood of adherence (scoring 80% on a self-reported questionnaire) at 3-month follow-up.

Patient support interventions

A study by Ziller et al. (2013) investigated an intervention incorporating information provision, reminders, and direct support to promote adherence. This study found higher rates of adherence (based on self-report scores and 80% medication possession ratio) in intervention compared to control participants. Ell et al. (2009) also investigated a patient support intervention which involved telephone interviews designed to identify barriers to adherence and provide self-management support, tailoring the intensity of support to the patients' needs. Adherence data extracted from medical charts indicated that a higher proportion of the intervention group (69%) were classed as adherent than controls (67%), however, this difference was not significant.

A combination of information provision, reminders, and tailored patient support (delivered through phone calls) was delivered by Ziller et al. (2013). Similarly to other interventions using this individualised approach (Ell et al., 2009; Graetz et al., 2018), both intervention groups (information and reminder provision, and a combination of information, reminders, and phone calls to discuss specific patient concerns and adherence strategies) displayed higher adherence than controls. This difference was not statistically significant comparing individual intervention arms but was significant when combining a pooled effect of intervention arms compared to controls. Ziller et al. (2013) suggest that the study may be underpowered to detect a significant effect (each arm included 57 participants). A technology-based intervention

delivered by Graetz et al. (2018) also included a relatively small sample of 47 participants, finding a significantly higher proportion of the intervention group were adherent based on self-reported scores than control participants. This study involved using a web-based app to report treatment side effects, which was followed up by a phone call to signpost to appropriate support when symptoms were reported.

The success of patient support interventions (Graetz et al., 2018; Ziller et al., 2013) compared to verbal (Wagner et al., 2016) and written information provision (Hadji et al., 2013; Neven et al., 2014) could potentially be due to the different nature of these interventions. These patient support interventions provided personalised materials, contact details for a practitioner (Ziller et al., 2013), and allowed patients to report troublesome symptoms so that they could receive appropriate support (Graetz et al., 2018). This indicates that reactive interventions tailored to the individual may be more effective in improving adherence than providing the same information to all patients.

Acceptance and Commitment Therapy interventions

Several studies have utilised principles of ACT within ET adherence interventions. Studies applying this framework aim to facilitate patient awareness of their long-term goals and values, attempting to align their behaviour with their long-term goals of adherence despite challenges of taking the medication, such as treatment side effects. Hall et al. (2022) developed a workshop including components of ACT to promote medication adherence and quality of life in breast cancer patients. This intervention was found highly acceptable, with participants reporting this could be helpful in easing the transition from breast cancer 'patient' to 'survivor'. Another recent study (Arch et al., 2022a) tested an intervention informed by ACT and SAT, finding that intervention participants demonstrated significantly higher adherence (based on proportion of days they opened an electronic medication storage device) in the first month of follow-up. Although this difference was not maintained from months 2-6, adherence began to decline significantly more quickly in the control than the intervention participants. In their feedback, participants expressed a desire for more specific side-effect management strategies. Studies applying ACT principles therefore demonstrate acceptability and initial efficacy in maintaining ET adherence (Arch et al., 2022a; Hall et al., 2022), although this effect is not maintained at longer term follow-up (Arch et al., 2022a). Further ongoing studies have developed interventions based on ACT principles (Green et al., 2022), and began investigating their feasibility (Smith et al., 2023).

Symptom management interventions

Symptom management was the focus of a technology-based study by Graetz et al. (2018). Participants used a web-based app to report any symptoms related to ET, followed by a response through telephone support and appropriate referral. Adherence was significantly higher in intervention (100%) than control (72.7%) participants at 8 weeks. However, a more recent study implementing a similar intervention found no significant differences between intervention and control groups, based on an electronic pillbox which monitored adherence (Graetz et al., 2024).

To maximise acceptability of a potential intervention to promote ET adherence, Jacobs et al. (2020) qualitatively explored patient attitudes towards ET, barriers and motivations in relation to taking the medication. Following on from this, they investigated and collected feedback from an intervention designed to directly address known barriers to ET adherence. This included modules focused on symptom management and reducing distress related to ET side effects. These included education about the need for ET, identifying barriers, medication-taking goals, and support in identifying and managing troublesome side effects. Although this pilot study did not include a measure of preliminary efficacy, the intervention was rated highly acceptable by participants. Participants expressed a desire for more focus on side effect management, and rated the sessions focused on symptom management most highly.

An overview of systematic reviews by Dang et al. (2022) found that multicomponent interventions including an element of symptom management were most effective in improving adherence to anticancer medications. Therefore, symptom management interventions are acceptable (Jacobs et al., 2021) and could potentially provide an opportunity for effective behaviour change.

Limitations of previous endocrine therapy adherence interventions

A 2016 systematic review (Hurtado-de-Mendoza et al., 2016) identified only 5 studies of interventions aiming to improve ET adherence. This highlighted a lack of research into potential means to improve adherence. More recent systematic reviews also identified similar limitations, and a relatively small body of research, identifying 5 (Ekinci et al., 2018) to 7 (Finitsis et al., 2019) papers. Heiney et al. (2019) identified only 4 RCTs of ET adherence interventions.

Studies of ET adherence interventions are also subject to the same challenges in relation to definition and measurement of adherence as other research in this area. As discussed in Section

2.2, terminology and the measures used to capture adherence vary widely across studies. This variation has been identified as an obstacle to effective comparison of interventions in several systematic reviews (Ekinci et al., 2018; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016). Furthermore, previous interventions have not distinguished between intentional and unintentional nonadherence to ET.

The majority of studies investigating ET adherence interventions are not theory-based. This lack of theoretical underpinning has been reported across systematic reviews (Ekinci et al., 2018; Finitsis et al., 2019; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016). Additionally, several intervention studies included patients beginning their prescription of ET (Yu et al., 2012.; Ziller et al., 2013; Hadji et al., 2013; Markopoulos et al., 2015), rather than identifying those who may be at risk of nonadherence, or already struggling to take their medication. Therefore, these studies may not allow us to observe the effect of the intervention in addressing known barriers to ET adherence.

The most frequently used behaviour change strategies focus on education provision, which does not seem sufficient to facilitate behaviour change on its own, as studies administering educational materials were found to have an overall null effect in Finitsis' (2019) meta-analysis. However, a significant medium effect size was detected for studies including a bidirectional flow of information (i.e., tailored to the needs of individual participants, such as providing support with their reported barriers to adherence, rather than simply giving all participants the exact same information). Multi-component interventions which include both information provision and more practical support, such as symptom management, are more likely to improve adherence (Dang et al., 2022). Therefore, it has been suggested that patients would benefit from individually tailored approaches guided by established barriers to ET adherence. This aligns with theories of health behaviour which indicate that knowledge alone is not sufficient to facilitate behaviour change (Finitsis et al., 2019).

2.3. Future directions for ET adherence research

Side effects present a potential means to promote ET adherence, based on research finding they significantly predict nonadherence (Fleming et al., 2022), and act as a major barrier to medication-taking (Peddie et al., 2021). Effective support with side effects could alter the balance between perceived benefits and disadvantages of the medication, shifting positive decisional balance in favour of adherence. This can be understood through the lens of several models of health behaviour, including social cognitive models (TPB, HBM, SC theory), and

the NCF. The applicability of multiple models of health behaviour further highlights the potential for side effects to be an effective target for intervention, as one single model may not capture the complexity of adherence behaviour (Green et al., 2022). Taking several models into account may allow the intervention to address multiple barriers to adherence and potentially facilitate greater success (Holmes et al., 2014). This also addresses a lack of theoretically supported interventions, a significant limitation of previous research in this area (Ekinci et al., 2018; Finitsis et al., 2019)

Self-management of treatment side effects emerges as a common theme throughout qualitative literature, indicating that patients prescribed ET are willing to incorporate practical strategies to manage their own symptoms. Patients with breast cancer are proactive in identifying management strategies, and report lifestyle changes in relation to diet and exercise, 'pacing' activities around reduced energy levels, and adapting clothing and bedding to minimise the impact of side effects on everyday life (Peddie et al., 2021). This indicates that behavioural strategies to manage side effects may be particularly acceptable.

To date, few existing interventions have evaluated the impact of side effect management on ET adherence. A technology-based symptom support intervention did find a significantly higher proportion of intervention participants were adherent than controls (Graetz et al., 2018). Furthermore, feedback from recent interventions indicates a desire for focus on symptom management, and more specific management strategies (Arch et al., 2022b; Jacobs et al., 2021). A lack of specific, targeted symptom management interventions means we cannot draw conclusions about the potential to promote ET adherence. However, feedback from these recent interventions, in addition to qualitative research (Peddie et al., 2021), indicates that intervention focused on symptom management would be highly acceptable to patients with breast cancer, and address a major barrier to ET adherence.

2.3.1 Identifying a specific symptom target for intervention

Interventions including symptom management have included advice on a range of treatment side effects. However, to-date, no study has explored the effect of a specific, symptom-targeted intervention on ET adherence. Side effects of breast cancer treatment are complex, and it can be difficult for the patient to disentangle residual side effects of primary treatment, symptoms caused specifically by ET, and natural ageing processes (Peddie et al., 2021). Patients express a desire for more specific, practical advice in managing symptoms such as pain, sleep problems, and hot flashes (Jacobs et al., 2021). This indicates that symptoms treatable through

behavioural intervention, such as insomnia (Ma et al., 2021), may provide appropriate targets. A targeted behavioural intervention aiming to address a specific symptom (or symptoms) would therefore directly address patient feedback from previous interventions.

Identification of a target symptom for intervention should consider which symptoms are most frequently reported and can also be effectively managed. This also should consider which symptoms may have the most significant impact on adherence behaviour and therefore present the best opportunity to promote behaviour change. Common symptoms in patients with breast cancer include fatigue, insomnia, cognitive dysfunction (e.g., memory and concentration problems), musculoskeletal pain, and vasomotor symptoms (e.g., hot flashes and night sweats) (Mokhtari et al., 2020). These may be related directly to ET treatment, or residual side effects of primary treatments (Lovelace et al., 2019). Patients report these symptoms are detrimental to their quality of life, restricting day-to-day activity and preventing them from returning to 'normality' after completing primary breast cancer treatment (Ibrar et al., 2022; Peddie et al., 2021). In particular, insomnia, vasomotor symptoms, pain, and fatigue have been related to psychological distress and identified as manageable symptoms (Syrowatka et al., 2017). Therefore, these may present sensible targets for intervention to promote adherence. However, the potential impact of addressing these symptoms on ET adherence must be considered in context of previous research.

To explore potential options for a targeted intervention, Fleming et al. (2022) conducted a systematic review of 62 papers investigating the influence of side effects on ET adherence. This review reported that, although a general side effect profile was consistently related to lower ET adherence, individual side effects produced mixed findings across the research. The side effects most frequently related to nonadherence were low mood/depression and musculoskeletal pain. However, almost twice as many studies (*N*=22) were identified exploring these side effects than others, such as Anxiety and Sleep problems (*N*=12), and some found no significant relationship with nonadherence.

Research published since Fleming's (2022) review has identified some specific symptoms which are related to ET non-persistence. Worsening of endocrine symptoms (vasomotor symptoms, changes in weight, sexual symptoms, mood changes, joint pain) (Smith et al., 2022), sleep disturbance (Balazard et al., 2023; Smith et al., 2022) and fatigue (Balazard et al., 2023) have been related to higher likelihood of discontinuing ET treatment. However, another study

reported that hot flashes were associated with lower likelihood of discontinuation (Rosenberg et al., 2023).

Previous research has not identified any one individual symptom as a consistent predictor of ET nonadherence (Fleming et al., 2022). However, an overall side effect profile emerges as a predictor across systematic reviews (Fleming et al., 2022; Moon, Moss-Morris, et al., 2017a; Murphy et al., 2012), and the burden of side effects is identified by patients as a major challenge of ET treatment (Peddie et al., 2021). It may be the case that individual symptoms do not consistently predict adherence because symptoms rarely occur in isolation. Patients with breast cancer tend to experience a range of different symptoms, which may present as 'clusters' which share common aetiology and can influence the severity of one another (So et al., 2021). Therefore, examining side effects in isolation may not accurately capture the burden placed on the individual, and subsequent implications for their adherence to the medication. Identification of a 'central symptom' within these clusters may provide an efficient target which, if treated, could also alleviate the severity of related symptoms (Jing et al., 2023) and therefore reduce overall side effect burden.

2.3.2. Limitations of previous research and for direction for future studies

The nature of nonadherence is not well understood in previous studies of the influence of side effects on ET adherence. Fleming's (2022) review identified only 8 papers which made a distinction between intentional and unintentional nonadherence. This highlights a frequent limitation of ET adherence literature, where methods of measurement such as prescription and pharmacy databases (despite being efficient and allowing a large sample size to be easily obtained) do not provide any insight into the patient's behaviour beyond collecting their prescription (Murphy et al., 2012).

Recent studies investigating the impact of side effects on ET persistence measured the point where patients discontinued the treatment, rather than day-to-day adherence (Balazard et al., 2023; Smith et al., 2022; Rosenberg et al., 2023)**.** This is important to consider as patients report nonadherence as a management strategy to gain relief from side effects and avoid early discontinuation (Peddie et al., 2021). Therefore, it is imperative that future studies identify the nature and frequency of nonadherence during treatment, rather than only identifying whether patients have discontinued the medication.

The following research study will attempt to address the limitations of previous ET research identified in these introductory chapters. Self-reported symptoms of patients with breast cancer

prescribed ET will be explored, using validated measures which have been previously used in breast cancer research to allow comparison with previous studies. As previous research has not identified any individual symptom as a consistent predictor of ET adherence, this study will explore the potential influence of symptom clusters on self-reported adherence. An adherence measure will be employed which allows identification of the nature of nonadherence, and has been previously used in the literature, allowing comparison with previous studies.

Chapter 3: The impact of symptom clusters on endocrine therapy adherence in patients with breast cancer

The research study detailed in this chapter was published in The Breast journal. This can be cited as follows:

Agnew, S., Crawford, M., MacPherson, I., Shiramizu, V., & Fleming, L. (2024). The impact of symptom clusters on endocrine therapy adherence in patients with breast cancer. The Breast, 75, 103731. https://doi.org/10.1016/j.breast.2024.103731

3.1. Introduction

Breast cancer is the most prevalent form of cancer worldwide, and the leading cause of cancer-related death in women (Ferlay et al., 2021). Approximately 70% of cases are hormone-receptor positive, therefore treatable with ET in the form of a SERM (such as Tamoxifen), or 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 OFS or ablation (Bradley et al., 2022). 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 (EBCTCG, 2011). AIs can reduce breast cancer recurrence by a further 30% and mortality by 15% relative to tamoxifen (EBCTCG, 2015).

Despite these clinical advantages, ET is associated with a range of treatment side effects (Cahir et al., 2015; Montagna et al., 2021; Moon, Moss-Morris, et al., 2017b; Pan et al., 2018). 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) (Condorelli & Vaz-Luis, 2018; Ibrar et al., 2022; Peddie et al., 2021). These symptoms can impact patients' ability or motivation to take their medication as prescribed (Peddie et al., 2021), and there are reports of poor adherence rates in this population. In a review of 12 community-based, real-world studies, Inotai et al. (2021) 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 (Inotai et al., 2021), and a 49% increased risk of all-cause mortality (Toivonen et al., 2020).

Despite the relationship between ET nonadherence and poorer breast cancer outcomes (Inotai et al., 2021), previous systematic reviews have identified wide-ranging estimates of adherence (Inotai et al., 2021; Moon, Moss-Morris, et al., 2017b; Murphy et al., 2012). As previously discussed in Chapter 2, variation in definition and measurement of ET adherence inhibits effective comparison across studies. This makes it difficult to establish a consistent estimate of the prevalence of nonadherence, identify specific targets for intervention, or investigate of the effect of any intervention on ET adherence. To quantify the magnitude of ET nonadherence, Fleming et al. (2022) recommended the consistent use of validated self-report adherence measures, which differentiate between intentional and unintentional nonadherence, such as the MARS-5 (Chan et al., 2020).

As discussed in Chapter 2 (Section 2.3.1.), the existing literature does not consistently point to any specific treatment side effect as a predictor of ET nonadherence, despite a general side effect profile being consistently related to nonadherence (Fleming et al., 2022). Lack of clarity over the contribution of specific ET side effects to nonadherence and non-persistence prevents identification of patients who may be at particular risk of nonadherence, and prevents delivery of appropriate, targeted intervention strategies.

Fleming et al. (2022) observed that many studies report the presence of individual symptoms, or an overall side effect profile (based on measures incorporating several symptoms into one overall score). This may not capture the complex interrelationships among symptoms, as they rarely occur in isolation. Patients typically experience at least 10, co-occurring symptoms (Chow et al., 2019) which may share common aetiology and influence the presence and severity of one another, referred to as a ‘symptom cluster’. Symptoms within a cluster are more strongly related to one another than symptoms in different clusters (Dodd et al., 2010).

Symptom clusters are detrimental to quality of life and overall functioning (Gwede et al., 2008; Nho et al., 2018; Whisenant et al., 2022), more so than individual symptoms (Nho et al., 2018). Targeting a ‘central symptom’ may influence the severity of other symptoms, providing a more efficient target for intervention than treating one symptom individually (Chow et al., 2019; Windgassen et al., 2018). Exploration of these clusters in patients with breast cancer may therefore allow greater understanding of side effect burden than capturing symptoms in

isolation. This could allow identification of targets for potential intervention to improve quality of life and promote ET adherence.

Previous studies of patients with breast cancer have frequently identified clusters of pain, sleep, and fatigue, clusters of gastrointestinal or psychological symptoms, with fatigue and sleep disturbance also being related to anxiety and depression (So et al., 2021). However, these studies tend to include patients receiving chemotherapy (Dodd et al., 2010; Gwede et al., 2008) or radiotherapy (Chow et al., 2019). One study which focused solely on patients prescribed ET identified only one cluster of menopausal symptoms (Glaus et al., 2006). However, this study did not measure psychological symptoms such as anxiety, depression, or insomnia, which are known to be highly prevalent among patients with breast cancer (Carreira et al., 2021; Kwak et al., 2020). Therefore, our understanding of symptom clusters in patients prescribed ET is limited, preventing identification of an efficient target to relieve symptom burden in this population.

In order to identify symptom clusters that may offer the most promise as intervention targets, this study aims 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, 3) identify symptom clusters in patients prescribed ET 4) investigate the relationship between these symptom clusters and ET nonadherence.

3.2. Methods

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.

Participants and recruitment

Recruitment took place from September 2021 to July 2022. The study was advertised through websites, social media pages and mailing lists of breast cancer support organisations. Participants were aged 18 or over, had previously received a breast cancer diagnosis, and had internet access. No other inclusion / exclusion criteria were set.

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 minutes to complete. Following survey completion, a written debrief was provided online.

Measures

Demographic information was collected regarding gender, age, ethnicity, nationality, marital status, employment, and education level. 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 ET adherence (MARS-5 (Chan et al., 2020)), insomnia (SCI (Espie et al., 2014)), depression (PHQ-9 (Kroenke et al., 2010)), anxiety (GAD-7 (Spitzer et al., 2006)) fatigue (FFS (Cameron et al., 2017)), and menopausal symptoms (BESS (Stanton et al., 2005)).

The MARS-5 comprises 5 statements intended to measure self-reported medication adherence. Item 1 measures unintentional nonadherence, whereas 2-5 represent intentionally not taking medication as prescribed. Items are scored from 1 (never)-5 (always), with 1 representing optimal adherence behaviour. This scoring method is designed to minimise the potential influence of social desirability on participants' answers. For this purpose, the MARS-5 is preceded by a statement which is intended to normalise nonadherence behaviours: "Many people find a way of using their medicines which suits them. This may differ from the instructions on the label or from what their doctor had said. Here are some ways in which people have said they use their medicines. For each statement, please tick the box which best applies to you". Scores of ≤ 4 (unintentional nonadherence subscale) and ≤ 19 (intentional nonadherence subscale) were used to classify participants as nonadherent, in accordance with previous studies of ET adherence (De Vries et al., 2014; Moon et al., 2019). The MARS-5 has also been used in several previous studies examining ET adherence (Brett et al., 2018; Henry

et al., 2017; Moon et al., 2019; Wouters et al., 2014); in the current study, internal consistency for MARS intentional items was good (α=0.87).

The SCI includes 8 items which measure symptoms of insomnia disorder, such as time taken to fall asleep, nighttime awakenings, daytime functioning over the past month, and frequency and duration of sleep problems. This includes items such as "How long does it take you to fall asleep", and "To what extent has poor sleep…Affected your mood, energy, or relationships?" (Espie et al., 2018, p.3). Items are measured on a 5-point scale from 0-4, and responses are summed to create a total score, which ranges from 0-32. Higher scores indicate better sleep, with a total score ≤ 16 representing probable insomnia disorder (Espie et al., 2014). Scores from 0-2 for each individual question represent threshold criteria for insomnia disorder according to the DSM-5 (APA, 2013). The SCI has been previously utilised in numerous studies which included patients with breast cancer (Donohoe et al., 2021, 2024; Lin et al., 2020). High internal consistency was found for this measure in previous research (Espie et al., 2014) and in the current study (α=0.87).

The PHQ-9 includes 9 items, with higher scores indicating more severe depressive symptoms. Participants are asked how much each symptom has bothered them over the past 2 weeks, from 0 (not at all)-3 (nearly every day). This measure is informed by the DSM-4 diagnostic criteria for depression (APA, 2000); the 9 relevant items are still present in the DSM-5 (APA, 2013), therefore it remains relevant to current diagnostic criteria. A score of ≥ 10 is recommended as a threshold for moderate depression (Kroenke et al., 2010). This measure is widely used, has identified as highly reliable (Costantini et al., 2021), and been applied in several recent studies involving patients with breast cancer (Ganz et al., 2021; Juanjuan et al., 2020; Schulte et al., 2021). The PHQ-9 had high internal consistency in the current study (α=0.86).

The GAD-7 measures symptoms of General Anxiety Disorder using 7 ordinal items with higher scores indicating worse symptoms. Participants are asked how often each problem has affected them over the past 2 weeks, scored on a scale from 0 (not at all)-3 (nearly every day). Items include symptoms such as "Feeling nervous, anxious, or on edge", and "Becoming easily annoyed or irritable". Responses are summed to create a total score ranging from 0-21. Cut-off scores of 5 (mild), 10 (moderate), and 15 (severe) are recommended (Spitzer et al., 2006). This measure was used in several recent studies of patients with breast cancer (Elimimian et al., 2020; Kang et al., 2021; Yang et al., 2022). The GAD-7 has been

found to have excellent internal consistency in previous research (α=0.88) (Johnson et al., 2019) and in the current study (α=0.91).

Fatigue was measured using the FFS. This scale asks participants to what extent they experienced 7 symptoms of fatigue over the past 2 weeks, including items such as "Did fatigue cause you distress?", and "Was your fatigue caused by poor sleep?". For clarification, the measure is preceded by a statement which distinguishes between fatigue and general sleepiness. Each item is scored from 0 (Not at all) to 4 (Extremely), except for item 5 (which asks at which times of day participants experienced fatigue). Higher scores indicate more severe fatigue, with scores of ≥ 16 indicating moderate to severe (≥ 21=severe) fatigue (Cameron et al., 2017). The FFS has previously been found to have good internal consistency (Cronbach's alpha ranging from 0.75-0.88), and excellent discriminant validity (Cameron et al., 2017). Internal consistency in the current sample was good (α=0.88).

Cognitive, musculoskeletal and vasomotor subscales of the BESS were used to measure menopausal symptoms. The BESS, developed from the 42-item BCPT checklist (Terhorst et al., 2011), includes eight subscales. Each subscale includes 3 items, with higher scores representing more severe symptoms. This measure was developed specifically for side effects of ET treatment and has been applied in samples taking Tamoxifen (Cella et al., 2008) and AIs (Schover et al., 2014). 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.

Statistical analysis

All analyses were carried out using R (R Core Team, 2021). All outputs, packages, and code are publicly available at OSF. Data will be made 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 groups based on similarity: data points within the same group are more similar to one another than to those in another group (Ding et al., 2004; Jain et al., 1999). This strategy allows groups to be identified where the researcher makes no a-priori assumptions about the data (Hastie et al., 2009). Although there is no established rule for the sample size required to conduct a cluster analysis, the current sample exceeded recommendations of 200 or 500 from previous research (Windgassen et al., 2018).

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, the NbClust package was used (Charrad et al., 2014). This package temporarily applies K-means clustering to solutions with different numbers of clusters and evaluates the clustering solutions by calculating 30 different indices. These indices reflect the default and recommended set provided by the package, and are intended to provide a more comprehensive evaluation of cluster quality than relying on a single criterion. The NbClust package applies the 'majority rule', where the cluster solution supported by the highest number of indices is selected. K-means clustering is then performed to assign participants to the final clusters (Charrad et al., 2014). This approach has been used in several previous cluster analysis studies (Asgarizadeh et al., 2023; Han et al., 2019; Soh et al., 2024).

Following the approach of Graham et al. (2013), an additional post-hoc analysis was carried out to assess the stability of the clusters. This followed the same procedure as the original cluster analysis, using a random 50% of the sample, to assess the proportion of participants who were then reclassified into the same clusters as in the initial analysis.

Logistic regression

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

3.3. Results

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 45-54 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).[1] 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).

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%)

[1] 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.

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%)
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%)

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.

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%)

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.

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)	45.58% (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%

Relationship between cluster membership and nonadherence

Cluster analysis

According to the majority rule, 10 among 30 indices selected 2 as the optimal number of clusters (Figure 2). Therefore, 2 clusters were deemed optimal in the *k*-means cluster analysis. These clusters were stable, as 97.9% (514 of 525) were successfully reclassified in the post-hoc validation using a random 50% of the sample.

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. Mean scores in each cluster for all symptoms measured are presented in Table 4; Figure 3 shows the heatmap for both clusters, and their features.

Figure 2: Histogram showing the optimal number of clusters based on 30 indices

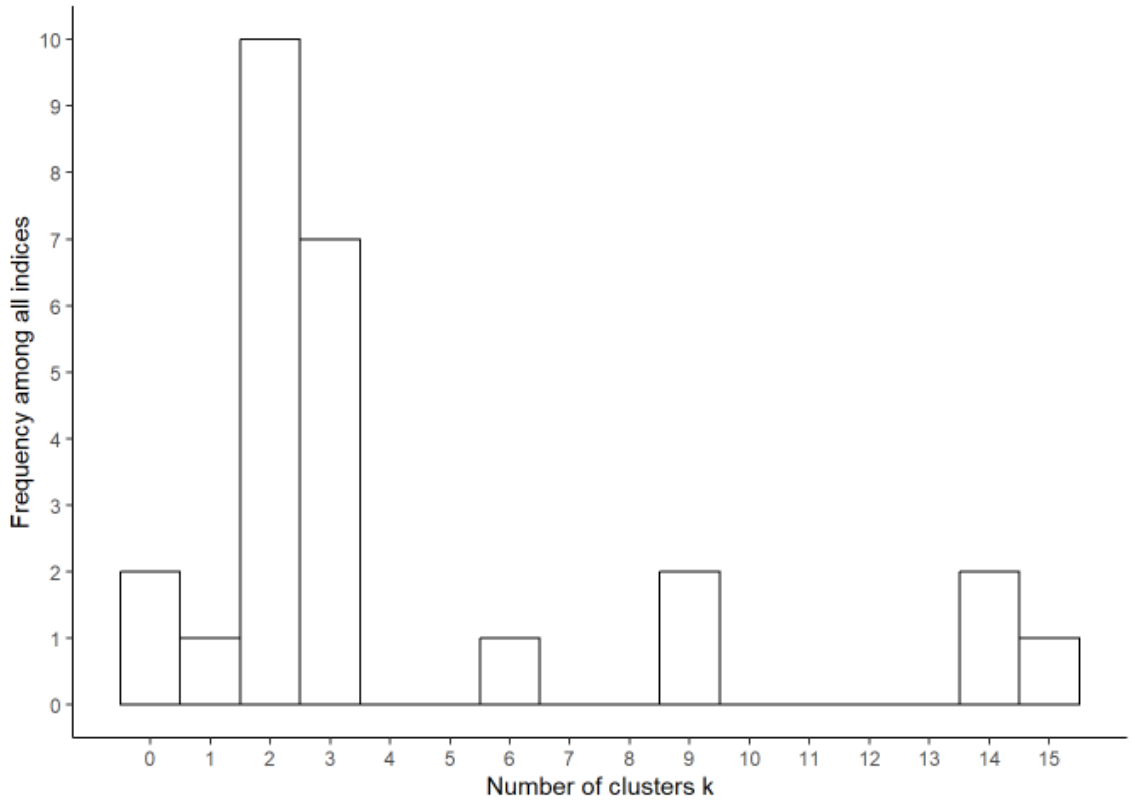
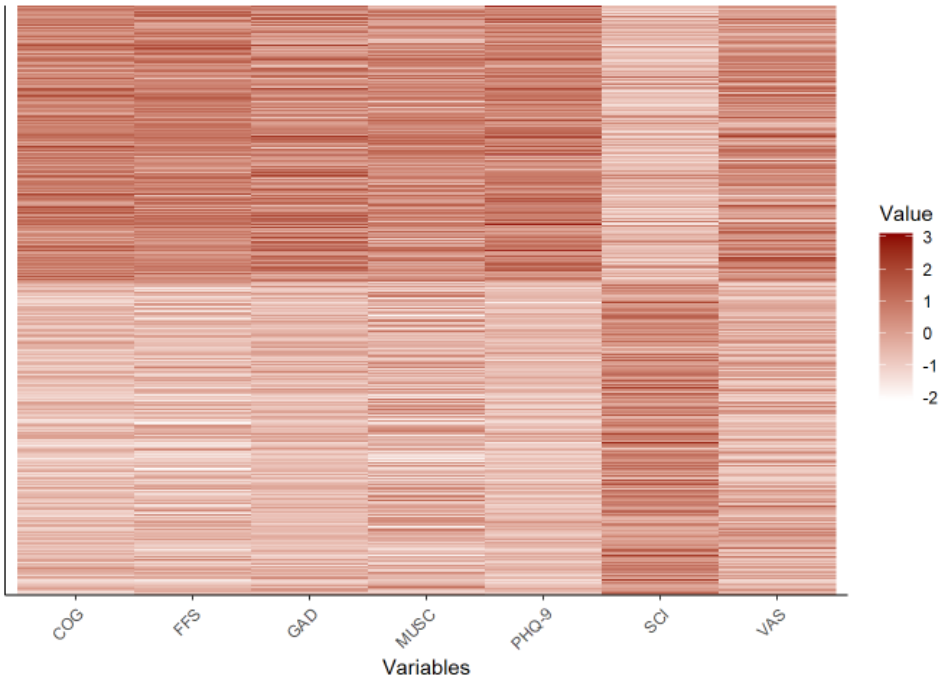


Table 4: Summary of cluster centres (means) based on target variables (standardized (z-scores)

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

Figure 3: Heat map of self-reported symptoms in High and Low symptom cluster



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 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.

3.4. Discussion

3.4.1. Summary of study aims

Nonadherence to ET treatment is related to higher risk of breast cancer recurrence and mortality (Inotai et al., 2021). Identifying factors underlying nonadherence could inform the development of targeted interventions, promoting adherence and improving breast cancer

outcomes. This study measured the scale of self-reported unintentional and intentional nonadherence 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.

3.4.2. Results in the context of previous research

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. (Moon, Moss-Morris, et al., 2017a) finding that unintentional nonadherence was more frequent than intentional (31% vs 15%). This indicates a higher rate of intentional nonadherence than studies published after this review (Brett et al., 2018; Moon et al., 2019), although unintentional nonadherence (50.8%) was comparable to Moon's (2019) (35-47%), study. Studies which differentiate between intentional and unintentional nonadherence tend to report the frequency of specific nonadherence behaviours (Brier et al., 2015; Henry et al., 2017; Kimmick et al., 2015) or reasons for nonadherence (Spencer et al., 2020), 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.

Severity of symptoms in patients prescribed Endocrine Therapy

We utilised validated measures of common ET side effects (Fleming et al., 2022) to identify the scale of clinical significance. 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 (Kwak et al., 2020). 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 (Carreira et al., 2018). Participants reported being more troubled by musculoskeletal pain than either cognitive impairments or vasomotor symptoms.

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. Some previous studies have also identified clusters of overall high and low symptoms in patients with breast cancer receiving chemotherapy (Dodd et al., 2010; Gwede et al., 2008), whereas others identified clusters based on physical or psychological symptoms (Browall et al., 2017; Nho et al., 2018). Glaus' (2006) study explored symptom clusters specifically in patients prescribed ET, identifying one cluster of menopausal symptoms (comprised of hot flashes, weight gain, tiredness, decreased sexual interest and vaginal dryness), whereas the current study found menopausal symptoms were encompassed in an overall cluster.

These differing results may be due to the use of principal component analysis (Nho et al., 2014) and factor analysis (Browall et al., 2016) in studies which identified clusters based on symptom type. Previous studies have also frequently used measures of overall quality of life such as the EORTC QLQ-30 (King, 1996) , or MSAS (Chang et al., 2000), rather than specific, validated measures for individual symptoms (which the current study utilised). Comparison of the current results with these previous studies is therefore limited, as the results and number of clusters can vary according to clustering methodology, treatment stage, and instruments used (Chow et al., 2019).

The identification of overall symptom clusters, differentiated by severity, supports the existence of connections between different ET side effects, commonly referred to as 'symptom clusters' (Chow et al., 2019). Studies consistently demonstrate a relationship between symptoms such as sleep problems, depression, anxiety, hot flashes, and fatigue (Hwang & Knobf, 2022). 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 (Windgassen et al., 2018). So et al. (2021) reported that across 32 studies, the most frequently reported symptom clusters among patients with breast cancer are fatigue/sleep disturbance and psychological symptoms. As the current study found that insomnia was highly prevalent among participants (and was included within the overall High symptoms cluster), further exploration of symptom clusters which include insomnia could potentially indicate appropriate targets for intervention.

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 and unintentional nonadherence. This is supported by research consistently identifying side effects as a significant predictor of nonadherence (Franzoi et al., 2021). Fleming's (2022) 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.

3.4.3. Strengths and limitations of the current study

This study addresses several limitations of previous research, including gaps identified by Fleming's (2022) review. We explored the influence of common symptoms on ET adherence in a large, international sample of patients with breast cancer, using a validated adherence measure which distinguishes between intentional and unintentional nonadherence, and validated clinical tools to measure the magnitude of symptoms. Previous studies of symptom clusters have mainly focused on patients receiving primary breast cancer treatment (Dodd et al., 2010; Gwede et al., 2008) and used global measures rather than specific instruments for each symptom. This study therefore measured a wider range of symptoms than previous research, allowing more detailed measurement as we used instruments which could capture severity rather than the presence or absence 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 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. Although efforts were made to widen recruitment, the current sample may not be representative of the entire patient population. The majority of the sample (99.7%) were white and identified as female (94%). Being part of a of minority ethnic group is significantly related to likelihood of nonadherence (Moon et al., 2019), and research has found significantly higher rates of ET discontinuation in male than female participants (Berkowitz et al., 2021; McGuinness et al., 2022). Therefore, individuals more likely to be nonadherent may not be well-represented in this sample. Furthermore, participants were mainly recruited through mailing lists and social media pages related to breast cancer organisations and charities. Patients prescribed ET are known to use these resources to seek advice and peer support when struggling with treatment side effects (Peddie et al., 2021), therefore these individuals may be particularly engaged and motivated to adhere to their ET treatment despite their symptoms. This means that the current study may underestimate the rate of nonadherence in the overall patient population.

The rate of nonadherence may also be influenced by the use of self-report measures in 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 (Pistilli et al., 2020). However, self-report measures are the most practical and cost-effective method of adherence measurement (Monnette et al., 2018), and crucially, permit identification of the nature of nonadherence, which objective measures do not allow (Kwan et al., 2020). The use of measures such as the MARS was recommended by Fleming's (2022) review, to distinguish between unintentional and intentional nonadherence, and facilitate comparison across studies, as the MARS has been utilised in previous studies of ET adherence (Brett et al., 2018; Moon et al., 2019; Wouters et al., 2014).

To address the potential for self-reported data to underestimate the rate of nonadherence, we applied a strict cut-off score for classifying participants as nonadherent based on previous research (De Vries et al., 2014; Moon et al., 2019). The MARS-5 is also designed to reduce social desirability bias by including a statement to normalise nonadherence. However, despite these mitigations, we recognise that reported nonadherence in the current sample may be conservative.

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 (Wassermann & Rosenberg, 2017)) 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, identifying mechanisms to improve long-term persistence should be a clinical priority.

3.4.4. 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 (Bradley et al., 2022), and both nonadherence and non-persistence have been linked to poorer outcomes (Inotai et al., 2021). 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 (Moon et al., 2019). Future research should explore targeted interventions for a ‘central symptom’ such as insomnia: a transdiagnostic symptom which may reduce overall side effect burden, potentially promoting better adherence.

Based on the results of the current study, and previous systematic reviews (Fleming et al., 2022; Peddie et al., 2021), recommendations for clinical practice are 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.

Chapter 4: Insomnia as an intervention target to relieve symptom burden and improve endocrine therapy adherence

The previous chapter (Study 1) explored clusters of common symptoms among patients prescribed ET, and the influence of these symptom clusters on self-reported ET adherence. Data-driven analyses identified two clusters of overall high and overall low symptoms: participants in the High Symptoms cluster were more likely to be both unintentionally and intentionally nonadherent. Study 1 also recommended treatment of a 'target symptom' within clusters which may promote ET adherence. Identification of the target symptom should consider which symptoms within these clusters are most clinically significant and may have transdiagnostic benefits if treated. Outcomes reported in Study 1 highlight why insomnia may be an appropriate target symptom.

First, insomnia was a highly prevalent symptom in the sample. Using the SCI, scores of 16 or below indicate probable insomnia disorder. Applying this cutoff, 74% of participants displayed probable insomnia disorder, with the average score for the SCI being 12.79. For comparison, in the original publication of the SCI, the average score for those with probable insomnia was 10.7 (Espie et al., 2014). Second, there was a strong correlation between all symptoms measured in study 1. The cluster analysis (see figure 3 of Study 1: Chapter 3, page 12.) demonstrates that individuals with more severe insomnia scores also reported worse depression, anxiety, fatigue, musculoskeletal pain, and vasomotor symptoms.

This chapter will provide a rationale for why insomnia has been identified as a target symptom to improve ET adherence. In Section 4.1, the severity of insomnia will be compared to the other symptoms measured in Study 1. In Section 4.2., the relationship between insomnia and these other symptoms will be discussed in context of previous research. Section 4.3. will discuss the transdiagnostic benefits of insomnia treatment. Finally, Section 4.4. will provide an overview of the prevalence, measurement, and development of insomnia disorder. This will provide context for the recommended treatment of insomnia, which will be discussed in-depth in Chapter 5 and delivered in the intervention study detailed in Chapter 6.

4.1 Severity of insomnia in Study 1

Study 1 used validated measures of insomnia, depression, anxiety, and fatigue, to accurately measure common symptoms of ET, facilitate comparison with previous research, and allow identification of prevalent symptoms based on established cut-off scores. Insomnia was measured using the SCI (Espie et al., 2014). This measure uses higher scores to indicate better sleep, with a score of 16 or below indicating probable insomnia disorder. Using this threshold, 73.54% of our sample displayed probable insomnia disorder.

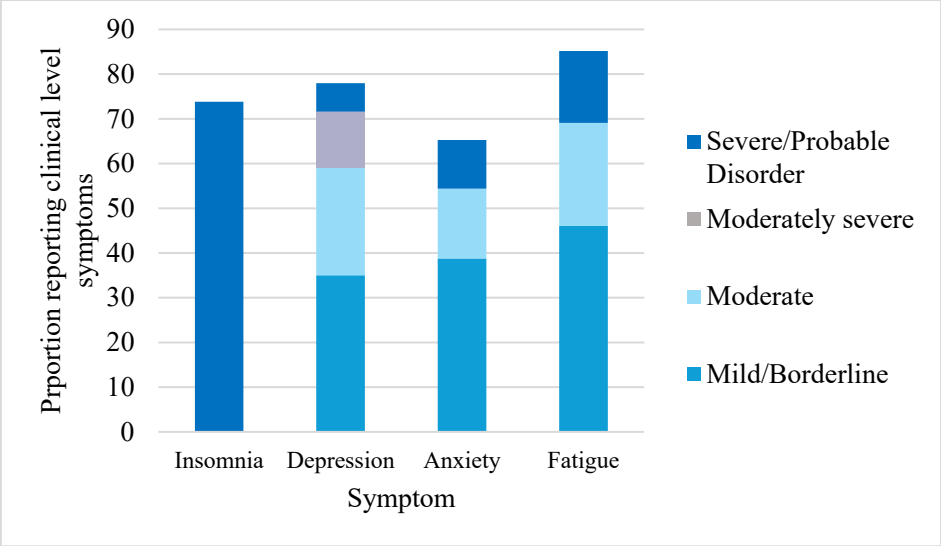
To further assess the severity of insomnia symptoms in our sample, SCI scores can be compared directly to diagnostic criteria for insomnia disorder, based on the DSM-5. Table 6 shows the proportion of participants in our sample who met each of the diagnostic criteria for insomnia disorder. In total, 68.6% of participants met all diagnostic criteria.

Table 6: Proportion of sample displaying each domain of diagnostic criteria for insomnia

Criteria	Frequency	Proportion of sample
Sleep onset latency ≥ 30 minutes OR wake after sleep onset ≥ 30 minutes OR sleep quality' ≤ 'Average'	945	89.91%
Sleep problems at least 3x per week for ≥ 3 months	936	89.06%
Sleep problems causing impairment in daily functioning at least 'somewhat'	841	80%

In addition to insomnia, the measures of depression, anxiety, and fatigue used in Study 1 allowed identification of participants who reported severe levels of each symptom using established cut-off scores. The proportion of participants whose scores indicated mild to severe levels of each of these symptoms is shown below in Figure 4.

Figure 4: Proportion of sample displaying clinical symptom levels



4.2 Relationship between insomnia and other ET symptoms

4.2.1. Correlation between insomnia and other symptoms measured in Study 1

To explore the potential relationship between insomnia and other symptoms common in those prescribed ET, a Spearman's correlation analysis was conducted using the data from Study 1 (as data was not normally distributed) (see Table 7).

Table 7: Correlation coefficients between insomnia and other side effects

Symptom	Correlation coefficient with Insomnia
Depression	-.56**
Anxiety	-.40**
Fatigue	-.50**
Vasomotor symptoms	-.33**
Musculoskeletal pain	-.33**
Cognitive symptoms	-.42**

**Significant at .01 level (1-tailed)

This analysis indicates a significant relationship between insomnia symptoms and all other ET symptoms. Worse insomnia symptoms were related to worse depression, anxiety, fatigue, and menopausal symptoms. The highest correlations were found between sleep, depressive

symptoms, and fatigue. This is supported by recent research finding significant correlations between sleep difficulties and depression (Emre & Yılmaz, 2024; Gabra & Hashem, 2021), anxiety (Emre & Yılmaz, 2024), and fatigue (Martin et al., 2021).

4.2.2 Relationship between insomnia and other ET symptoms in previous research

Previous research indicates a bidirectional relationship between ET symptoms and sleep difficulties. The odds of sleep disturbance are significantly higher in patients who report symptoms such as hot flashes, depression, and fatigue, indicating that these symptoms contribute to sleep difficulties. However, whilst emotional distress, anxiety, and depression have been found to lessen following the completion of primary breast cancer treatment, insomnia remains persistent over time (Schieber et al., 2019).

Insomnia has also been found to influence the odds of the onset of psychological symptoms such as depression, cognitive complaints, and anxiety in patients with breast cancer. Even after adjusting for potential confounders such as clinical characteristics and perceived stress, the odds of depression are 6 times greater in patients with breast cancer displaying insomnia symptoms (Haque et al., 2021). Current insomnia has been found to predict likelihood of depression 5 years after breast cancer diagnosis, indicating that this relationship is sustained over time (de la Torre-Luque et al., 2021). Sleep difficulties also predict increased odds of cognitive complaints (Boscher et al., 2020; Matthews & Wang, 2022), and the severity of cognitive impairment in patients with breast cancer has also been found to increase in accordance with insomnia severity (Liou et al., 2019).

Additionally, insomnia is related to various physical symptoms. Poor sleep quality predicts worse fatigue and perceived disability in patients with breast cancer (Bean et al., 2021; Lourenço et al., 2021). More specifically, significant correlations have been found between fatigue and sleep parameters including WASO, SE, and SOL (Martin et al., 2021). Poor sleep quality is also associated with increased pain and hot flashes among patients with breast cancer (Rumble et al., 2010).

A bidirectional relationship between insomnia and other symptoms is highlighted in qualitative research exploring the experience of ET treatment. As discussed in Chapter 1, patients prescribed ET report a range of symptoms which rarely occur in isolation. The cumulative impact of physiological symptoms (such as hot flashes, musculoskeletal pain, and fatigue)

hinders daily activity and creates a psychological burden where the individual feels unable to return to life as it was before breast cancer treatment. This can contribute to low mood, anxiety, and feelings of isolation. Hot flashes and joint pain are detrimental to sleep as patients report struggling to get comfortable enough to sleep and being woken through the night by hot flashes. A lack of sleep then leads to further fatigue and exacerbates low mood, adding further detriment to their daily functioning (Peddie et al., 2021).

This overlap between insomnia and other common symptoms in patients with breast cancer justifies the selection of insomnia as an intervention target to improve ET adherence. As discussed above, insomnia persists over time and influences the likelihood of other psychological and physical symptoms in patients with breast cancer (Haque et al., 2021; Lourenço et al., 2021; Schieber et al., 2019). Furthermore, sleep disturbance has been found to mediate the relationship between depression, vasomotor symptoms (Accortt et al., 2015; Hwang & Knobf, 2022), and anxiety (Hwang & Knobf, 2022). This indicates that improving insomnia may alleviate the impact of other symptoms on emotional wellbeing and could potentially improve ET adherence. Previous research found that treatment of insomnia led to improvements in functional symptoms and general psychiatric symptoms, indicating transdiagnostic benefits for mental health problems (Harvey et al., 2021). A transdiagnostic approach may also benefit individuals with comorbid physical health problems, as this approach considers the complex relationship between sleep and other health problems (Harvey, 2022). Therefore, insomnia may act as an efficient ‘target symptom’ within the clusters previously identified in Study 1.

4.3. Transdiagnostic benefits of insomnia treatment

Depression and fatigue

Meta-analysis (Squires et al., 2022) found that CBT-I improved not only sleep quality and insomnia severity, but also had significant effects on anxiety, depression, fatigue, and quality of life. These effects appear to be maintained in patients with breast cancer at 36-month follow-up, indicating durable benefits to other symptoms in addition to insomnia (Amidi et al., 2022).

The potential for improving sleep to alleviate fatigue is also highlighted by Dean et al.'s (2022) systematic review of 20 studies (7 focused on patients with breast cancer). This review reported that 75% of interventions that significantly improved insomnia also found significant

improvements in fatigue. The importance of improving sleep quality is further supported by research finding a significant relationship between sleep quality (rather than quantity) and self-reported fatigue in patients with cancer (Martin et al., 2021).

The potential for CBT-I to address depression and fatigue is reinforced by Haque et al.'s (2021) study which examined predictors of insomnia, depression, and fatigue in a sample of 315 patients with breast cancer. This study found that the likelihood of fatigue and depression increased in participants who had a history of using antidepressants. Depressive symptoms and fatigue persisted, even among participants who had used antidepressants since breast cancer diagnosis, and use of antidepressants was not associated with lower likelihood of depressive symptoms or fatigue. The authors propose that antidepressants may not be sufficient to address these symptoms alone. As the odds of depression and fatigue were 6 times greater in those reporting current insomnia symptoms, Haque et al. (2021) propose that CBT-I may present an efficient intervention to treat a cluster of symptoms including depression, fatigue, and insomnia.

Anxiety

Recent meta-analyses (Alimoradi et al., 2022; Lee et al., 2023) identified that CBT-I significantly reduces anxiety in individuals without major comorbidities. However, to date, the potential impact of CBT-I on anxiety in patients with breast cancer is not well understood. A (2022) meta-analysis by Squires et al. found that CBT-I led to small but significant effects on anxiety in patients with cancer. However, this review was not focused specifically on patients with breast cancer, and the authors noted that effects may differ based on patient characteristics. A recent pilot study of 40 patients with cancer (26 were diagnosed with breast cancer) found that CBT-I did not lead to significant improvement in cancer-related rumination or a general tendency to worry (Arditte Hall et al., 2025). However, this study did not report the change in general anxiety symptoms over time, and the authors highlighted a need for future research to further explore the impact of CBT-I on anxiety in patients with cancer.

Cognitive symptoms

A lack of research into the potential benefits of CBT-I for cognitive functioning in patients with cancer was noted in the (2022) meta-analysis by Squires et al., where the authors were unable to assess the effect on other symptoms such as cognitive dysfunction. However, a systematic

review by Herbert et al. (2018) reported evidence for a small to moderate effect of CBT-I on cognitive functioning in the general population. In studies of patients with breast cancer, McCarthy et al. (2018) found small but statistically significant improvement in cognitive functioning following a CBT-I intervention, whereas Matthews et al. (2014) identified a non-significant trend towards cognitive improvement, which reached significance in post-hoc analyses. A recent study of patients with cancer (41% diagnosed with breast cancer) found significantly greater improvement in cognitive abilities in participants who received CBT-I (Garland et al., 2024). As research has consistently identified a relationship between insomnia, depression, fatigue, and cognitive dysfunction, further research is needed to explore the potential transdiagnostic benefits of CBT-I across these symptoms (Duivon et al., 2022; Haque et al., 2021).

Pain

CBT-I has been found effective in the treatment of insomnia in individuals with chronic pain, although no significant effect has been found for improvement in pain itself at follow-up. However, these meta-analyses (Salazar-Méndez et al., 2024; Selvanathan et al., 2021) excluded studies of patients with cancer. The effect of CBT-I on pain in patients with cancer (31% diagnosed with breast cancer) was investigated by Garland et al. (2019), finding a non-significant change from baseline to weeks 8 and 20. However, this study was not limited to patients with breast cancer, and cannot not provide insight into how this treatment may impact pain in those prescribed ET treatment. Squires et al. (2022) identified Garland's (2019) study as the only investigation of CBT-I treating pain in patients with cancer, stating there was insufficient research in this area for meta-analysis. Therefore, our understanding of the potential benefits of CBT-I on pain in patients with cancer is limited.

Vasomotor symptoms

A recent systematic review of 12 studies (Carmona et al., 2023) found support for the use of CBT interventions including elements of CBT-I in the treatment of insomnia and vasomotor symptoms in peri and post-menopausal individuals. This review identified 3 studies of patients with breast cancer which investigated interventions including sleep hygiene, relaxation, and behavioural strategies to reduce wakefulness, finding significant improvement in hot flashes and night sweats in comparison to controls. The authors noted rigorous designs and use of intention to treat analysis as strengths of the studies included in this review, however stated that

there was a lack of research to synthesise in this area. A later study by Donohoe et al. (2024) investigated a multimodal intervention including medication, digital CBT-I, self-management strategies, and partner support in 120 patients with breast cancer. Significant improvement was seen in the frequency of vasomotor symptoms, and degree that participants felt bothered by these symptoms throughout the day. This indicates that CBT-I may help reduce the burden of vasomotor symptoms in patients with breast cancer, including those prescribed ET. Although these effects cannot be attributed specifically to CBT-I (due to the other intervention components and lack of control arm) this indicates a need for further research to investigate the potential effect of CBT-I on vasomotor symptoms, particularly among women prescribed ET.

As discussed in Section 4.2.2., treatment of insomnia has been found to have transdiagnostic benefit in individuals with comorbidities including Schizophrenia, Bipolar disorder, and Major Depressive disorder (Harvey et al., 2021). These benefits may extend to treatment of other health problems (Harvey, 2022). Studies indicate that improving insomnia also improves depression and fatigue in patients with breast cancer (Haque et al., 2021). However, there is a lack of research investigating potential benefits of insomnia treatment for anxiety, pain, and vasomotor symptoms in patients with breast cancer, particularly those prescribed ET. Therefore, further research is needed to explore the transdiagnostic benefits of insomnia treatment in patients with breast cancer prescribed ET, and the potential for this to reduce overall symptom burden, thus facilitating ET adherence. The following section will therefore provide an overview of insomnia disorder for context, as the next 2 chapters of this thesis will detail the recommended treatment for insomnia and an intervention study investigating the impact of this treatment on ET adherence.

4.4. Overview of insomnia disorder

4.4.1. Prevalence and impact

Insomnia is the most prevalent sleep disorder worldwide, characterised by persistent difficulty falling or staying asleep. Estimates of the prevalence of insomnia vary depending on the measurements used and whether full diagnostic criteria or specific symptoms are reported. The estimated prevalence of insomnia in the adult population is approximately 10%, and population-based data indicates that 30-36% of adults report at least one nighttime symptom of insomnia (Morin & Jarrin, 2022).

Diagnostic criteria for insomnia state that sleep difficulties (specifically trouble initiating or maintaining sleep) must result in daytime dysfunction (such as mood disturbance, irritability, detriment to professional or academic performance, or reduced energy), and occur at least 3 times per week, for at least 3 months. This must occur despite the individual having adequate opportunity for sleep (meaning they have adequate time and a comfortable sleeping environment) and not be better explained by any other sleep disorder (APA, 2013, WHO, 2019). Insomnia may appear as a comorbidity with another physical or mental health problem; however, it often presents as an independent disorder which requires specific evaluation and treatment (Riemann et al., 2022).

Diagnosis of insomnia disorder is based on subjective report of the above symptoms. This should include a sleep diary (where the individual keeps a daily record of their sleep for 1-2 weeks), and validated instruments such as the SCI (Espie et al., 2014) or ISI (Morin et al., 2011). The ESRS recommends that in cases where an individual does not experience improvement following appropriate psychological or pharmacological treatment, polysomnography should be used to objectively assess their sleep through physiological measures. This may identify other sleep pathologies such as sleep apnoea or periodic limb movement disorder (Riemann et al., 2017).

Insomnia has significant implications at an individual and societal level. Compared to healthy controls, individuals with untreated insomnia are significantly more likely to experience mental and physical health problems including anxiety, depression, hypertension, and obesity. People with insomnia also report significantly higher levels of drowsiness, disorientation, dizziness, and fatigue than healthy controls (Grandner et al., 2023). Individuals presenting 2 or more symptoms of insomnia have significantly higher odds of emergency hospital visits and hospital admissions even after adjusting for demographic and health variables (Tzuang et al., 2021). The annual cost of insomnia is estimated to exceed 100 billion US dollars, mainly due to indirect costs such as poorer workplace performance, increased risk of accidents, and healthcare utilisation (Wickwire et al., 2016).

4.4.2. Prevalence of insomnia in patients prescribed ET

In patients with cancer, insomnia is up to three times more prevalent than in the general population, and especially prevalent among patients with breast cancer (Kwak et al., 2020). A recent meta-analysis of 51 studies identified a global prevalence of 62% for poor sleep quality among patients with breast cancer, noting that 70% experienced poor quality sleep during

treatment. However, the prevalence of poor sleep after treatment remained high at 60% (Cheng et al., 2023). Leysen et al. (2019) identified a pooled prevalence of 40% for sleep disturbance in patients with breast cancer at least 3 months after primary treatment completion, while a recent study identified that 42% reported symptoms of insomnia 3 years after breast cancer diagnosis (Beverly Hery et al., 2023). As discussed in Chapter 1 (Section 1.3.2.), research indicates that insomnia is a prevalent and persistent condition that continues to affect patients for years following primary breast cancer treatment, and rarely remits without intervention (Schieber et al., 2019). Insomnia seems to be especially persistent in patients prescribed ET. Ferreira et al.'s (2019) study reported that insomnia persisted 2 years post-diagnosis in patients who received ET, whereas significant improvement in insomnia was seen over time in those who were not prescribed ET.

Sleep difficulties were identified as the one of the most prevalent adverse events among patients prescribed ET in large-scale trials of Tamoxifen (Cella et al., 2006), Anastrozole (Cella et al., 2006), and Letrozole (Colleoni et al., 2018). The ATAC trial found that sleep difficulties were reported by 19% of those prescribed Anastrozole, and 18.9% of those prescribed Tamoxifen, whereas the SOLE trial reported that 40% of participants prescribed Letrozole experienced insomnia. However, these trials did not explore the severity of insomnia symptoms and used measures which encompassed various adverse effects, rather than an instrument designed to measure specific insomnia symptoms. Furthermore, as discussed in Section 1.5.2, clinical trials of ET may naturally attract and retain patients who are particularly tolerant to these drugs and therefore reflect a lower prevalence of side effects than in clinical practice (Cella & Fallowfield, 2008; Mioranza et al., 2016).

Studies conducted in clinical practice have identified a higher estimated prevalence of insomnia than RCTs of ET. A study assessing the prevalence of insomnia in patients prescribed Tamoxifen (Aiello Bowles et al., 2012) found that 39.1% reported insomnia, whereas Ziller et al. (2009) reported that 62% experienced ‘sleep disorders’. Comparing patients with and without an interruption to their Tamoxifen use, Cluze et al. (2012) found that 54.9% of patients with interruptions reported ‘fatigue/insomnia’, compared to 48.1% without interruptions. In patients prescribed AIs, studies report that 44.2-50% (Aiello Bowles et al., 2012; Desai et al., 2013) of patients reported sleep problems, with 19% exceeding threshold for clinically significant insomnia (Desai et al., 2013). A study of 32,311 patients prescribed ET reported a lower estimated prevalence of 7.9%. However, this study did not measure insomnia directly, as the proportion of participants using medication to manage sleep problems was used as a proxy

measure for insomnia (Hsieh et al., 2015). In studies of specific AIs, sleep problems were reported by 54% of patients prescribed Anastrozole (Ziller et al., 2009), and 4.6% of those prescribed Letrozole (Nabieva et al., 2018). Kyvernitakis et al. (2014) studied 180 patients prescribed AIs, reporting a prevalence of 17% mild, 32.7% moderate, 18.9% severe, and 6.3% extremely severe sleep problems.

More recent studies have investigated the difference in symptoms between patients prescribed different cancer treatments. These studies reported that 37.6% of patients who received ET without chemotherapy reported sleep problems (Mandelblatt et al., 2020), and that patients receiving ET report significantly more difficulty falling asleep than those who did not receive this treatment (Mandelblatt et al., 2020; Scher et al., 2022). However, similarly to clinical trials of ET (Cella et al., 2006; Colleoni et al., 2018), these studies used measures that encompassed a range of symptoms and only captured the presence or absence, rather than severity, of insomnia symptoms. There is a significant lack of research focused on insomnia in patients taking ET: very few recent studies have focused on investigating sleep problems specifically in this population.

Leysen et al.'s (2019) meta-analysis identified wide-ranging estimates of 14-93% poor sleep quality among patients with breast cancer. Research that focused on patients prescribed ET has identified rates of sleep problems from 4.6-62% (Nabieva et al., 2018; Ziller et al., 2009). Wide-ranging sample sizes and variation in assessment tools used to measure sleep disturbance have been identified as barriers to establishing a consistent estimate of insomnia prevalence. This highlights the need for studies to utilise adequate sample sizes and validated measures designed to measure insomnia (Cheng et al., 2023; Leysen et al., 2019), to establish a consistent estimate of insomnia prevalence among patients prescribed ET and identify factors contributing to insomnia in this population.

4.4.3. Measurement of insomnia disorder in patients prescribed Endocrine Therapy

Leysen’s (2019) meta-analysis identified 20 articles that used validated questionnaires to measure insomnia, and 7 that used study-specific measures of sleep disturbance in patients with breast cancer. Among those that used validated questionnaires, the most frequently used were the PSQI (Buysse et al., 1989), ISI, and EORTC QLQ-30. A more recent meta-analysis by Cheng et al. (2023) identified 51 studies of sleep disturbance in patients with breast cancer, finding that the most frequently used measures were the PSQI (76%) and ISI (15.7%). Although

Cheng et al. (2023) found a greater proportion of studies that used validated measures than the earlier review, they also identified heterogeneity across studies as a barrier to establishing a consistent estimate of insomnia. The authors propose that the variation in cut-off scores based on symptom severity may also contribute to differences reported across the literature.

In clinical trials of ET, the prevalence of sleep problems has often been measured using a single item from overall measures of health-related quality of life or an individual item from a list of symptom indicators. For example, the FACT-B (Fallowfield et al., 1999) (used in the ATAC trial) asks participants whether they have been sleeping well within the past week, whereas the MENQOL (MA.17 trial) asks whether they had trouble sleeping within the past month. The SOLE trial (Ribi et al., 2019) reported the proportion of participants who experienced sleep disturbance as an adverse event, however this trial used a single item from the BCPT symptom scales to measure trouble sleeping. The use of single items to measure the prevalence of insomnia was highlighted by Leysen's (2019) meta-analysis, where 26% of included studies used a single item from the EORTC QLQ-30. The relevant item asks the participant to rate whether they have had trouble sleeping over the past week on a 4-point scale, from 'Not at all' to 'Very much'. Comparison of this single-item measure to a 4-item measure concluded that the EORTC-QLQ insomnia scale was suitable for use in gathering an estimate of sleep problems in a group sample (Hofmeister et al., 2020). However, the authors also noted that this only accounts for one dimension of sleep (ability to fall asleep) and does not account for nighttime awakenings or quality of sleep. Measures such as the EORTC-QLQ and others used in ET trials (listed above) also do not capture the frequency or duration of sleep problems sufficiently to establish a diagnosis of insomnia disorder. Therefore, the prevalence of insomnia among patients prescribed ET may not be accurately captured by these trials.

A systematic review by Fleming et al. (2022) highlighted a lack of validated measures and inconsistency in the reporting of insomnia in patients prescribed ET. This review identified 12 studies which investigated the relationship between sleep problems/insomnia and ET adherence/persistence. Of these, only 1 used a validated, sleep-specific measure (the PSQI). The remaining 11 papers used individual items from global quality of life questionnaires, individual symptom severity scales, or medical records. The method of reporting insomnia also varied, as some studies reported the proportion of participants who experienced a non-specific 'sleep disorder', some specifically asked participants if they had experienced insomnia, and some reported mean scores from a single item. A review of exercise interventions in patients

prescribed ET (McGrorry et al., 2023) identified only 2 studies which focused on insomnia; however, both utilised the PSQI, a recommended, validated measure. Three papers which were not included in these reviews have used validated measures to measure sleep problems in patients prescribed ET. However, of these, 2 (Bhave et al., 2018; Desai et al., 2013) used different insomnia-specific instruments (PSQI and ISI, respectively), whereas one (Scher et al., 2022) created its own instrument, which also included symptoms and risk factors for sleep apnoea.

As discussed above, systematic reviews have consistently noted that a lack of validated, sleep-specific measures is a barrier to identifying a consistent estimate of insomnia prevalence and severity in patients with breast cancer (Cheng et al., 2023; Costa et al., 2014; Leysen et al., 2019). To date, no systematic review has been conducted to synthesise the existing literature focused on insomnia specifically in patients prescribed ET, to evaluate the overall prevalence and consequences of the disorder in this population.

4.4.4. Using the 3P Model to explain the development of insomnia disorder in patients using Endocrine Therapy

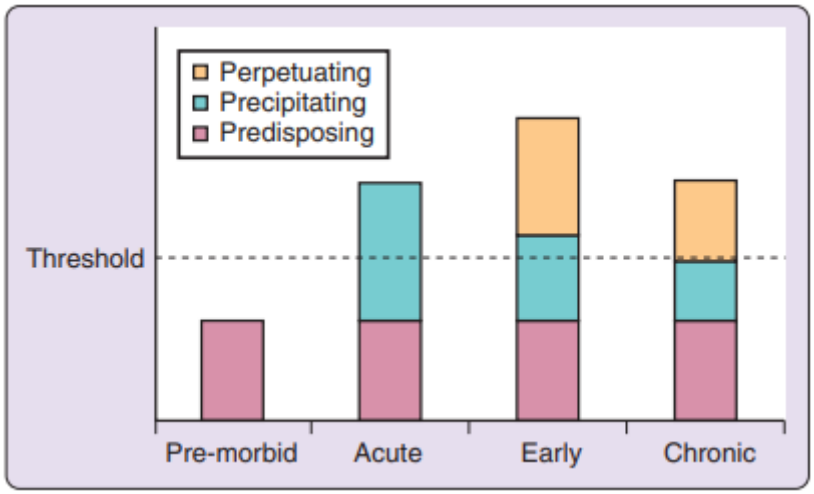
The prevalence of insomnia in patients prescribed ET is related to multiple factors that contribute to development and maintenance of the disorder in this population. This includes pre-existing sleep problems, psychological distress related to diagnosis and treatment, treatment side effects, and cognitive-behavioural factors (Van Dyk et al., 2021). As discussed above in Section 4.2.2., to date, the contributing factors to insomnia in patients prescribed ET have not been assessed through systematic review or meta-analysis. However, previous research has consistently identified a relationship between symptoms related to ET and insomnia (Costa et al., 2014; Van Dyk et al., 2021). The prevailing model of insomnia development, known as the '3P model' (Spielman et al., 1987), is shown below in Figure 5. The 3P model provides an overview of factors contributing to the onset and development of insomnia in patients prescribed ET.

Based on the 3P model (Spielman, 1987), individuals who may be vulnerable to insomnia often develop acute sleep disturbance around diagnosis, or during primary treatment (such as surgery, radiotherapy, or chemotherapy) due to intense physiological side effects and psychological distress (Fleming et al., 2019). Although side effects of primary treatment may subside over time, side effects of adjuvant ET treatment (such as musculoskeletal pain, hot flashes, and night

sweats) can contribute to chronic insomnia by inhibiting sleep onset and disrupting sleep (Van Dyk et al., 2021). Counterproductive strategies to cope with the resultant lack of sleep (such as daytime napping, increasing caffeine consumption, reduced physical activity) and self-prescribed sleep promotion strategies (such as spending excessive time in bed awake and unstable bed/rising times) may also perpetuate insomnia (Garland, Barg, et al., 2019; Reynolds-Cowie & Fleming, 2021).

Insomnia is considered a psychophysiological disorder, meaning that both psychological and biological factors play a role in the development and maintenance of the condition long-term. This includes heightened arousal (through biological and cognitive mechanisms) and learned associations, which prevent or interrupt sleep (Wilson et al., 2019). The prevailing model for understanding the development and maintenance of insomnia is the '3P' model (Spielman, 1987). This stress-diathesis model proposes that acute insomnia occurs due to a combination of predisposing vulnerabilities to sleep disturbance and a precipitating event. Predisposing factors include genetics, discordance between the homeostatic sleep drive and circadian rhythm, early childhood adversity, personality traits (neuroticism, perfectionism, and tendency to internalise problems), depression, and an emotional preoccupation with sleep (Ellis et al., 2021; Riemann et al., 2010). Spielman proposes that acute insomnia develops when these predisposing factors interact with precipitating factors, such as a bereavement, relationship breakdown, or illness. The response to this precipitating event may be short-term, however symptoms often persist long-term, leading to chronic insomnia disorder (Riemann et al., 2010).

Figure 5: Spielman's (1987) 3P Model of Insomnia (Perlis et al., 2011, p. 852)



According to Spielman, insomnia symptoms persist, despite the impact of the initial stressor lessening, due to perpetuating factors. These factors are often behavioural changes made by the individual to promote good sleep (such as increased alcohol use, or rigid bedtime routines), or maladaptive coping strategies to manage the effects of poor sleep (such as prolonged time in bed, or increased daytime napping) (Dressle & Riemann, 2023). These behaviours contribute to the maintenance of insomnia by weakening the association between the bed (stimulus) and sleep (desired behaviour). Sleep intention and subsequent effort creates a cyclical association between bedtime, distress, and a state of arousal, which is counterproductive to falling and staying asleep (Dressle & Riemann, 2023).

4.4.5. Precipitating and perpetuating factors in patients prescribed Endocrine Therapy

Precipitating factors

In patients with breast cancer, diagnosis is often a precipitating factor for the onset of insomnia. This is supported by Fleming et al.'s (2019) study, which explored the trajectory of insomnia in this population. The proportion of patients with insomnia increased from 24.9% pre-diagnosis to 46.1% at diagnosis, then remained stable at around 50% after 12 months. A recent meta-analysis reported that sleep quality declined from 4 months to 1-year after breast cancer diagnosis (Chang & Chang, 2020), in addition to patient reports that sleep problems often began due to the distress of initial cancer diagnosis (Hwang et al., 2024).

In addition to diagnosis, breast cancer treatment can also be a precipitating factor. Early research found that symptoms related to treatment (including hot flashes, pain, and emotional distress) contributed to the development or worsening of insomnia in patients with breast cancer (Savard et al., 2001, 2004). This is supported by later systematic reviews which found that radiotherapy, chemotherapy, and ET treatment is associated with significantly higher odds of sleep problems (Costa et al., 2014; Leysen et al., 2019).

Perpetuating factors

As discussed in Chapter 1 (Section 1.5.1.), treatment side effects can persist for years after completion of primary breast cancer treatment (Lovelace et al., 2019; Schapira et al., 2022), and symptoms such as hot flashes, cognitive complaints (Ganz et al., 2016) and pain (Ferreira et al., 2019) may persist for longer in those prescribed adjuvant ET treatment. A systematic review by Costa et al. (2014) concluded that the cumulative impact of psychological distress (due to breast cancer diagnosis and treatment), side effects of primary treatment, and ET-related

symptoms contribute to both the development and long-term maintenance of insomnia in patients with breast cancer.

A study of patients prescribed ET found that those reporting severe joint pain, mild, moderate, or severe hot flashes, anxiety, or depression were significantly more likely to report insomnia (Desai et al., 2013). The role of ET symptoms in maintaining disturbed sleep is also highlighted by qualitative research finding that patients report their sleep is interrupted by hot flashes, night sweats, and musculoskeletal pain (Peddie et al., 2021). However, a recent study of patients with breast cancer (80% of participants were prescribed ET) noted that patients also report seemingly waking for no reason during the night and being unsure why their sleep is broken (Hwang et al., 2024).

Research has also identified cognitive factors which encourage the maintenance of insomnia in patients with cancer after completion of primary treatment. Hwang et al. (2024) identified that a busy mind occupied with everyday worries (e.g., finances, family, and professional responsibilities) contributes to trouble falling asleep, in addition to worries related to breast cancer. In previous qualitative studies, patients with cancer reported a pre-occupation with sleep, tendency to catastrophise about the daytime impacts of poor sleep, and 'clock watching' (Fleming et al., 2010; Garland, Barg, et al., 2019; Reynolds-Cowie & Fleming, 2021). These increase psychological distress, resulting in heightened psychological and physiological arousal. According to the 3P model of insomnia, patients can become conditioned to associate bedtime and their sleeping environment with this distress, perpetuating a cycle of arousal at bedtime which inhibits sleep onset (Riemann et al., 2022).

Studies in those with breast cancer have also identified maladaptive behaviours known to maintain disordered sleep. This includes maladaptive strategies to help cope with poor sleep, such as spending excessive time in bed to increase opportunity for sleep, daytime napping (which interferes with homeostatic sleep drive, causing a lack of 'sleep pressure' at bedtime), and increased caffeine consumption to manage the effects of poor sleep (this stimulates the nervous system, increasing physiological arousal, which inhibits sleep onset) (Garland, Barg, et al., 2019; Reynolds-Cowie & Fleming, 2021). Participants in these studies also reported having a strict, ritualistic bedtime routine; according to the AIE pathway (Espie et al., 2006), this level of focus and intentional effort towards sleep is counterproductive and helps to maintain sleep problems.

4.4.6. Treatment of insomnia in relation to the 3P model

The 3P model informs the rationale for the recommended treatment for insomnia, which is CBT-I. CBT-I targets the perpetuating factors that prolong insomnia after the initial precipitating event, (i.e. dysfunctional thoughts, feelings, and behaviours related to sleep) (Ellis, 2019). The following chapter will provide an overview of CBT-I, detailing the treatment components, efficacy in patients with breast cancer, and reasons why this is likely to be an acceptable intervention for people prescribed ET. This will provide context for the research study detailed in Chapter 6, which investigates the potential for CBT-I to improve adherence to ET.

Chapter 5: Cognitive Behavioural Therapy for Insomnia

5.1. Overview of Cognitive Behavioural Therapy for Insomnia

The purpose of this chapter is to provide context regarding the components of CBT-I, treatment efficacy, and present the rationale for investigating CBT-I as a potential intervention to improve ET adherence. First, the components of CBT-I will be explained. Next, the evidence base for CBT-I as a multicomponent intervention and its individual components will be summarised. Based on the results of Study 1, feedback from previous interventions aiming to improve ET adherence, and the potential acceptability of CBT-I, a rationale for using CBT-I to improve ET adherence will then be presented.

As outlined in Chapter 4, CBT-I is the recommended treatment for insomnia according to the ACP, AASM, ESRS, and BAP (Ma et al., 2021; Riemann et al., 2022). Updated European Insomnia Guidelines state that CBT-I should be the first-line treatment for adults of any age with insomnia, even if comorbidities are present. The individual should then be offered pharmacological treatment (such as Benzodiazepines or antidepressants) only if CBT-I is not sufficiently effective (Riemann et al., 2023).

CBT-I is a multi-component, evidence-based intervention which includes the behavioural components SRT and SCT, and CT. Additionally, relaxation techniques and SH are frequently included as elements of this intervention (Edinger & Means, 2005).

Often, the first treatment offered for insomnia is pharmacotherapy such as benzodiazepines, benzodiazepine receptor agonists, and some sedating antidepressants (Baglioni et al., 2023; Ferini-Strambi et al., 2021). However, in comparison to pharmacotherapy, CBT-I leads to greater improvement in overall insomnia severity, SE, and WASO (Zhang et al., 2022). Some support has been found for other non-pharmacological treatments for insomnia, namely Mindfulness (Gong et al., 2016) and ACT (Salari et al., 2020). However, there is a lack of evidence for long-term efficacy of ACT (Salari et al., 2020), Mindfulness (Wang et al., 2020), and pharmacotherapy (De Crescenzo et al., 2022), whereas the effects of CBT-I have been found to last up to 10 years (Baglioni et al., 2023).

5.2. Rationale and mechanism of treatment components

Sleep Restriction Therapy

According to the 3P model, one of the behaviours which can perpetuate insomnia is extending time spent in bed (by going to bed early, staying in bed after awakening, and napping) to increase the opportunity for sleep and compensate for lost or broken sleep (Riemann et al., 2022; Spielman et al., 1987). This behaviour inadvertently leads to an inconsistent sleeping pattern and increased wakefulness at night (Maurer et al., 2018). SRT therefore reduces the opportunity for sleep, which leads to consolidation of broken sleep, a more consistent sleep-wake pattern, and improved sleep quality (Spielman et al., 1987).

A systematic review was conducted by Maurer et al. (2018) to investigate specific mechanisms of SRT, which informed formulation of the 'Triple R' Model. This model states that SRT works by: "1. Restricting time in bed awake 2. Regularising timing of sleep and wake, and consequently 3. Re-conditioning the association between bedroom factors and sleep." (Maurer et al., 2018, p. 134). TIB is restricted by prescribing a specific bedtime and risetime, so that the amount of time the individual spends in bed is equal to the duration of sleep they usually receive. They are instructed to avoid daytime naps or spending extended periods in bed outside this window of time. The prescribed TIB is reviewed and gradually extended over time as the duration of sleep becomes more proportionate to the individual's TIB (Spielman et al., 1987).

Stimulus Control Therapy

Factors which can perpetuate insomnia include weakening of the psychological association between the bed/bedroom environment and sleep. Based on operant conditioning, Bootzin (1972) proposed that insomnia may be perpetuated by poor stimulus control. This means that for individuals with insomnia, the bedroom environment is not a discriminative stimulus for sleep, i.e. the individual does not associate the bed with sleepiness. The bed-sleep association may be weakened due to spending time in bed waiting for sleep onset (potentially feeling frustrated or worrying about the effects of poor sleep) and carrying out activities such as watching television or using social media which can inhibit sleep. SCT aims to strengthen the association between bed and sleep and establish the bedroom as a discriminative stimulus for sleep. This helps the individual to fall asleep more quickly once they go to bed and return to sleep more quickly if they awake during the night (Jansson-Fröjmark et al., 2024; Verreault et al., 2024).

To implement SCT, the individual is instructed to avoid all activity in bed except from sleep and intimacy. If they wake during the night, or initial sleep onset does not occur, they are instructed to follow the '15-minute rule' and leave the bed (and sleep environment if possible), after 15 minutes (Riemann et al., 2022). They are instructed to avoid daytime napping and only go to bed when they feel truly ready for sleep, to reinforce the association between bed and sleepiness, establishing the bedroom as a discriminative stimulus for sleep (Jansson-Fröjmark et al., 2024; Verreault et al., 2024).

Cognitive Therapy

Perpetuating factors of insomnia include maladaptive beliefs or attitudes towards sleep, which can lead to worry and create psychological distress (Harvey et al., 2005). These thoughts/beliefs may occur throughout the day, as the individual worries they will have difficulty sleeping later, or around bedtime as they worry about the possible daytime consequences of poor sleep. As the bedroom is often a quiet environment with little distraction, troubling cognitions may be especially prevalent at night, and the individual may become conditioned to associate bedtime with psychological distress (Tang et al., 2023). Maladaptive cognitions may also lead to counterproductive 'safety behaviours' intended to reduce the impact of insomnia (Harvey, 2002). For example, an individual who believes they will be unable to function with less than 8 hours of sleep may go to bed early to extend sleep opportunity yet become concerned when they are unable to fall asleep (Lancee et al., 2015). This leads to further cognitive and physiological arousal, which is counterproductive to sleep onset (Riemann et al., 2022).

CT includes multiple strategies which aim to address maladaptive beliefs about sleep and alleviate anxiety related to bedtime. Maladaptive beliefs are the focus of cognitive reappraisal, which aims to address misconceptions about the cause of insomnia and alter dysfunctional beliefs about sleep. Cognitive control encourages individuals to process and deal with troublesome thoughts before bed, by instructing them to write down their worries and lingering thoughts about the next day. Paradoxical Intention aims to reduce anticipatory anxiety around falling asleep to facilitate sleep onset. To apply Paradoxical Intention, the individual is instructed to try to remain awake for as long as they can: this relieves perceived pressure for fall asleep, allowing them to relax so that sleep onset can occur (Riemann et al., 2022).

Relaxation

As discussed above, individuals with insomnia often experience psychological distress around bedtime, due to concerns about their ability to sleep and the potential consequences of

sleeplessness (Tang et al., 2023). This psychological distress can lead to a physiological stress response, where activation of the sympathetic nervous system causes symptoms such as increased heart rate, body temperature, and more rapid, shallow breathing. As the early stages of sleep involve the body gradually slowing down (the heart rate slows, breathing becomes lengthened and deeper, and body temperature reduces), this stress response inhibits sleep onset (Wuyts et al., 2012). This can create a cyclical association between bedtime, distress, and a state of physiological and cognitive arousal counterproductive to sleep (Dressle & Riemann, 2023; Tang et al., 2023). Relaxation strategies (such as progressive muscle relaxation, breathing exercises, or guided imagery) aim to reduce autonomic arousal and intrusive thoughts, making it easier for the individual to fall asleep and weakening the association between bedtime and psychological distress over time (Morin & Buysse, 2024; Riemann et al., 2022).

Sleep Hygiene

SH is a psychoeducational component which aims to promote behaviours that encourage good sleep and reduce behaviours which perpetuate insomnia (Campbell et al., 2014). This is intended to minimise behaviours which can have a harmful effect on sleep, rather than actively treat insomnia symptoms (Jansson-Fröjmark et al., 2019). SH includes general advice about relevant lifestyle (e.g. diet, substance use, regular exercise) and environmental factors (e.g. noise, light levels, and distractions in the sleeping environment). This also involves educating the individual regarding the biological basis of sleep, factors which can influence sleep, and what normal sleep looks like (Edinger et al., 2021). This may allow them to identify and address behaviours which can contribute to insomnia such as excessive caffeine use, exercising late in the day, and watching television in bed (Harvey, 2002).

5.3. Efficacy

5.3.1. Efficacy of CBT-I

The efficacy of CBT-I has been supported by early (Murtagh & Greenwood, 1995) and recent (Furukawa et al., 2024) meta-analyses. An extensive meta-analysis of 87 papers was conducted by Van Straten et al. (2018): 43% included behavioural and cognitive components of CBT-I, 11% included only a behavioural component, 19% included relaxation, and 26% included one aspect of cognitive or behavioural strategies. Large effects were found for overall measures of insomnia severity, SE, WASO, and SOL, whereas small-moderate effects were found for number of nighttime awakenings, and sleep quality. AASM guidelines do not recommend a

specific mode of delivery (i.e. individual vs group, or face-to-face vs online) of CBT-I (Edinger et al., 2021). However, research indicates that CBT-I is effective when delivered individually or in groups, directly by a therapist, or in a digital format (Gao et al., 2022; Scott et al., 2025).

CBT-I is also the recommended first line treatment for insomnia in patients with breast cancer (Kwak et al., 2020; Ma et al., 2021). A recent meta-analysis of 22 articles (7 focused on patients with breast cancer, whereas 15 included mixed cancer samples) found significant small to large effects of CBT-I on insomnia symptoms (Squires et al., 2022). Specifically in patients with breast cancer, a meta-analysis of 14 randomised controlled trials found medium to large effects of CBT-I on insomnia symptoms based on the PSQI, ISI, and sleep diary variables (TST, SE, SOL, WASO, and sleep quality). Importantly, these effects were maintained at 6- and 12-month follow-up (Ma et al., 2021). The long-term efficacy of CBT-I is further highlighted by a study which found insomnia scores in patients with breast cancer were significantly lower at post-intervention than at baseline, and remained lower at 36-month follow-up, using two validated measures of insomnia symptoms (Amidi et al., 2022). Previous studies have found that CBT-I is rated as acceptable by patients with breast cancer when delivered face-to-face (Palesh et al., 2018), and through videoconferencing (Oswald et al., 2022).

5.3.2. Multicomponent vs single-component therapy

Multicomponent CBT-I is strongly recommended as the first-line treatment by the AASM (Edinger et al., 2021) and ESRS (Riemann et al., 2017, 2023). A lack of high-quality research investigating the efficacy of single-component interventions was highlighted by Edinger's (2021) systematic review. However, of the individual components, some support has been found for SRT, SCT, and relaxation (Edinger et al., 2021). For context, the evidence for delivery of individual treatment components as standalone interventions will be detailed below.

Of the individual CBT-I components, SRT is best supported as a standalone intervention. Meta-analyses have found SRT leads to improvements in overall insomnia severity (based on validated measures) and individual insomnia symptoms. Specifically, SRT has been found to reduce SOL, WASO, and improve SE (Furukawa et al., 2024; Maurer et al., 2021). However, SRT can be difficult to implement as it requires consistency and may require lifestyle changes (Kyle et al., 2011; Miller et al., 2014). Implementation of SRT can initially lead to a decrease in the overall duration of sleep, and have side effects such as increased sleepiness, fatigue,

and decreased motivation (Edinger et al., 2021; Kyle et al., 2011). However, adverse effects have been found to return to normal 3 months after treatment (Miller et al., 2014).

Similarly to SRT, SCT can initially lead to a decrease in overall sleep duration and can be difficult to implement (Kyle et al., 2011). Post intervention, in comparison to control conditions, SCT leads to greater reductions in time taken to fall asleep and time spent awake in bed overall (Furukawa et al., 2024; Jansson-Fröjmark et al., 2024; Verreault et al., 2024). However, recent systematic reviews (Jansson-Fröjmark et al., 2024; Verrault et al., 2024) have noted a lack of high-quality studies investigating this component individually.

There is a lack of research that has assessed the efficacy of CT as a standalone intervention. A previous meta-analysis of 32 studies (Jansson-Fröjmark & Norell-Clarke, 2018) found support for CT and Paradoxical Intention, yet noted a lack of high-quality studies and variation across research as barriers to understanding the efficacy of these interventions. Due to a lack of studies meeting inclusion criteria for their systematic review, the AASM guidelines do not make recommendations about delivery of CT as a single-component intervention (Edinger et al., 2021). However, a recent meta-analysis identified cognitive restructuring as a critical component of CBT-I, particularly for improvement of subjective sleep quality (Furakawa et al., 2024).

Relaxation has been found significantly more effective in improving sleep quality compared to controls, although improvements in SOL and WASO did not meet threshold for clinical significance in this meta-analysis. Overall, the quality of evidence was low for this intervention component (Edinger et al., 2021). A later meta-analysis (Furakawa et al., 2024) found that relaxation could have detrimental effects on insomnia; the authors propose that relaxation exercises may lead to increased time spent in bed (e.g. practicing breathing exercises), which could be counterintuitive to behavioural components (SRT and SCT). However, the meta-analysis by Edinger et al. (2021) concluded that the potential benefits of relaxation outweighed potential harms, as this intervention poses minimal risk of adverse effects. The authors also noted potential benefits to the individual beyond sleep improvement, such as decreased overall stress or improved pain management.

Although SH is usually included within educational elements of CBT-I, it has often been used in RCTs as a control condition. Multicomponent CBT-I has been found significantly more effective than SH in improving SOL, WASO, SE, and overall insomnia (Chung et al., 2018),

and a recent meta-analysis concluded that SH was not an essential component of CBT-I (Furakawa et al., 2024). It has been proposed that SH may be useful within a 'stepped care' approach, providing the least restrictive treatment to people with less severe symptoms (Espie, 2009). However, a reported limitation of this model is the lack of high-quality evidence for SH as a standalone intervention (Edinger et al., 2021; Riemann et al., 2017).

5.4. Future Directions: using CBT-I to improve ET adherence

As discussed in Chapter 2 (Section 2.2.4), previous interventions to improve ET adherence have had limited success. Limitations of previous research in this area include a lack of theoretical underpinning, and inconsistency in the definition and measurement of adherence (Hurtado-de-Mendoza et al., 2016; Ekinci et al., 2018; Heiney et al., 2019). Interventions including support with symptom management have had some success (Graetz et al., 2018), and patients with breast cancer have expressed a desire for practical symptom management strategies (Arch et al., 2022; Jacobs et al., 2021). As discussed in Chapter 2 (Section 2.3.), addressing symptom burden could address a significant barrier to ET adherence, aligning with several prominent theories of behaviour change. However, to date, no intervention has explored the impact of addressing a specific symptom on adherence. The research study outlined in Chapter 3 identified two findings which led to identification of insomnia as a potential target symptom to improve ET adherence: 1) insomnia was a highly prevalent and severe symptom in a large sample of patients prescribed ET, 2) insomnia was significantly related to all other measured symptoms, and targeting insomnia should have transdiagnostic benefits.

Study 1 found that participants in the High Symptoms cluster were significantly more likely to be both unintentionally and intentionally nonadherent to ET treatment. A significant correlation was found between insomnia and all other symptoms including cognitive dysfunction, which is well-supported by previous research (Boscher et al., 2020; Haque et al., 2021; Matthews & Wang, 2022). Furthermore, previous research has found that CBT-I leads to improvements in cognitive functioning (Herbert et al., 2018) and overall quality of life (Squires et al., 2022). Therefore, CBT-I could potentially reduce the likelihood of forgetting medication (unintentional nonadherence) and reduce the impact of ET on quality of life, improving motivation to adhere (intentional nonadherence).

The following chapter will detail a mixed-methods investigation to explore the potential for CBT-I to improve self-reported ET adherence in patients with breast cancer. This will be

conducted through two research studies. First, a pilot RCT will be conducted to investigate the effect of CBT-I on intentional and unintentional ET adherence. Secondly, qualitative interviews will be conducted to explore patients' perspectives on the potential role of sleep in ET adherence, and the perceived benefits of this intervention.

Chapter 6: Mixed methods investigation of the role of insomnia in nonadherence to endocrine therapy

6.1. Introduction

As outlined in Chapter 1, approximately 70% of breast cancer cases are classed as hormone-receptor positive, meaning they are treatable with ET. ET is usually prescribed following primary treatment (typically surgery, chemotherapy and/or radiotherapy), as a daily tablet for 5-10 years, to reduce the risk of breast cancer recurrence (Waks & Winer, 2019). When taken as prescribed, ET is highly effective in reducing the risk of breast cancer recurrence and mortality (EBCTCG, 2011; 2015). However, despite these clinical advantages, suboptimal adherence and persistence are a concern. Research indicates that up to half of those prescribed ET take less than 80% of their prescribed dose, and up to half discontinue before completing the recommended course of treatment (Moon et al., 2019). This is worrying, as nonadherence and non-persistence are related to increased risk of breast cancer recurrence and mortality (Inotai et al., 2021a; Pistilli et al., 2020). Therefore, to further improve breast cancer outcomes, adherence to this medication should be maximised.

The most consistent predictor of ET nonadherence is treatment side effects, which include insomnia, low mood/depression, anxiety, fatigue, vasomotor symptoms, musculoskeletal pain, and cognitive deficits. These symptoms often originate at the point of breast cancer diagnosis or primary treatment, and the psychological impact of diagnosis and treatment often worsens existing issues. However, symptoms such as pain, insomnia, hot flashes, and cognitive complaints are more persistent over time in patients who receive ET than those who do not (Ferreira et al., 2019; Ganz et al., 2016). These symptoms have severe implications for quality of life, sense of identity, and the desire to return to normality following cancer treatment (Ibrar et al., 2022; Peddie et al., 2021). Unlike demographic predictors of nonadherence (such as age, ethnicity, and socioeconomic status), ET side effects may be amenable to intervention, and patients express a desire for support in managing their side effects (Peddie et al., 2021). This indicates that reducing the burden of side effects may improve patient wellbeing and facilitate greater ET adherence.

Despite an overall side effect profile being consistently related to ET nonadherence, previous research has not identified any individual side effects as consistent predictors (Fleming et al.,

2022). Therefore, Study 1 (detailed in Chapter 3) explored symptom clusters in patients prescribed ET, with the aim of identifying a potential target to relieve overall symptom burden. This study identified two clusters of overall high and overall low severity for all symptoms. Participants in the High Symptoms cluster were significantly more likely to be both intentionally and unintentionally nonadherent than those in the Low Symptoms cluster.

Validated measures were used to assess the symptoms measured in study 1, and insomnia was identified as a prominent, clinically significant symptom in the sample, with 74% displaying probable insomnia disorder. Further analysis identified a significant relationship between insomnia and the severity of all other symptoms, indicating that participants with more severe insomnia also experience more severe symptoms overall. As detailed in Chapter 4 (Section 4.2.1.), previous research has consistently found a significant relationship between insomnia and other common symptoms in patients with breast cancer, such as hot flashes, night sweats, musculoskeletal pain, depression, and anxiety (Kwak et al., 2020; Van Dyk et al., 2021). CBT-I has transdiagnostic benefits, leading to improvements in anxiety, depression, fatigue, and quality of life in patients with cancer (Squires et al., 2022). Therefore, CBT-I could potentially reduce the burden of several different symptoms and improve overall quality of life in patients with breast cancer (Haque et al., 2011), promoting better medication adherence in those prescribed ET.

Previous research investigating the impact of insomnia on ET adherence is limited. A recent review by Fleming et al. (2022) identified 12 studies which investigated the impact of sleep difficulties on ET adherence, with half of these finding a significant negative relationship between sleep problems and adherence. However, none of these studies distinguished between intentional and unintentional nonadherence, and only one study used a validated, specific measure of insomnia, rather than a sleep item from overall quality of life measures. Furthermore, Fleming et al. (2022) noted significant variation in the definition and measurement of adherence across the literature, preventing effective comparison across studies. As discussed in Chapter 2, Section 2.2.4., limitations of previous interventions include this variation in measurement of adherence, a lack of RCTs, and lack of consideration of theories of health behaviour (Ekinci et al., 2018; Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016). This is important because a lack of theoretical grounding makes it difficult to identify mechanisms of change and understand why an intervention is successful or unsuccessful (Green et al., 2022; Holmes et al., 2014).

Exploration of qualitative research indicates a perceived lack of support for patients in managing side effects (Peddie et al., 2021), and participant feedback from intervention studies highlights a desire for practical support with symptom management (Jacobs et al., 2021). Unlike other symptoms such as hot flashes and musculoskeletal pain, insomnia can be effectively treated non-pharmacologically using CBT, which is considered the gold standard treatment (Riemann et al., 2022). This has been found to improve not only insomnia but also depression, anxiety, and fatigue in patients with breast cancer (Squires et al., 2022). To date, no study has explored the effects of a symptom-specific intervention on ET adherence, therefore the potential for treatment of insomnia to improve adherence has not been explored. As discussed in Chapter 4 (Section 4.3.), treatment of insomnia using CBT-I would address patients' desire for practical, evidence-based support and could potentially reduce overall symptom burden, reducing a significant barrier to ET adherence.

Therefore, the following two studies report on the potential for CBT-I to improve ET adherence, using a sequential mixed methods approach. First, a pilot RCT (Study 2) investigates the preliminary effectiveness of CBT-I on self-reported intentional and unintentional ET nonadherence. Next, a qualitative study (Study 3) uses semi-structured interviews to 1) identify factors that influence ET adherence 2) explore the potential role of insomnia in ET nonadherence, and 3) gain insight into participants' perceptions of how improved sleep may have impacted their adherence.

6.2. Study 2

6.2.1. Methods

The current study was pre-registered on the ClinicalTrials. gov website (NCT05887297). Reporting was guided by the CONSORT 2010 statement, specifically the extension guidelines for pilot and feasibility trials (Eldridge et al., 2016a) (see Appendix 1 for completed checklist).

Study design

A pilot randomised controlled trial was conducted, including 32 patients with breast cancer. Participants were randomly assigned (2:1) to CBT-I delivered via videoconferencing (*N*=21) or to a sleep monitoring control condition where they kept a sleep diary for 4 weeks but had no active intervention (*N*=11).

Participants and Recruitment

Participants were individuals who had been diagnosed with breast cancer, experienced symptoms of insomnia (defined as difficulty falling asleep or staying asleep, at least 3 times per week for 3 months), self-reported as nonadherent to their ET medication, were fluent in English, and had access to videoconferencing software. Exclusion criteria were being currently pregnant or breastfeeding, having received CBT-I within the past 12 months, received chemotherapy or radiotherapy within the past 4 weeks/had chemotherapy/radiotherapy planned, substance misuse, or having an unstable physical or mental health condition (e.g. psychosis) which may be incompatible with CBT-I treatment. Participants were not excluded based on a diagnosis of another sleep disorder, providing they reported that this was stable and well-managed. Participants were not excluded based on a palliative breast cancer treatment plan. However, during screening interviews, the nature of CBT-I treatment was explained, and potential participants were asked if they felt well enough to participate.

A-priori power analysis was conducted using G*Power version 3.1.9.7 (Faul et al., 2007) to determine the minimum sample size required to test the study hypothesis using a repeated measures ANOVA (within-between interaction). Results indicated the required sample size to achieve 80% power for detecting a medium effect (significance criterion α=.05) was N=28. Therefore, a recruitment target of 40 participants was set to account for participant attrition.

Preliminary analyses indicated that a key assumption of the ANOVA test, homogeneity of variance, was violated, therefore multilevel modelling was used to investigate the effect of group and time on outcome variables. To determine the statistical power of the sample for multilevel modelling, post-hoc power analyses were conducted based on effect sizes (Cohen's f^2) which calculated from fixed effect t values and residual degrees of freedom obtained from the multilevel models. Power analyses were conducted in R Studio using the 'pwr' package, generating 70 power estimates (5 fixed effects across 14 variables). Statistical power to detect significance (α<.05) was relatively low for all models, ranging from 5-20%. Full results of the post-hoc power analysis are reported in Table 8 (Appendix 2).

Recruitment was conducted from April to December 2023. Recruitment was stopped at this point to allow sufficient time for data collection, analysis, and reporting in line with the intended timeline for thesis submission. The study was concluded once participants who had been recruited up until this point had completed follow-up measures.

Recruitment involved emailing participants from Study 1 (detailed in Chapter 3) whose responses indicated they may meet the inclusion criteria for study 2. The study was also advertised via relevant social media pages and mailing lists. Individuals who were interested in participating were advised to contact the researcher and were then invited to a screening interview to determine eligibility.

Piloting materials and procedures

Intervention materials were piloted on 2 individuals who expressed interest in participating. Pilot participants (both female; aged 50-52), had been diagnosed with breast cancer, were prescribed ET treatment, and reported insomnia symptoms. However, at screening, both reported being completely adherent to ET and were therefore ineligible to participate in the main study. However, these individuals were happy to participate in a pilot study to assess the appropriateness of the data collection and intervention protocol. Therefore, they completed baseline measures, attended 4 weekly CBT-I sessions, and were asked to provide feedback on the study protocol after completing these sessions. Based on their feedback, instructions for accessing the daily sleep diary were amended to recommend participants save the link for ease of access.

Procedures

The study was approved by the Strathclyde University Ethics Committee (UEC23/09). Individuals who wished to participate in the RCT were emailed a link to a virtual consent form via the Qualtrics survey platform. Following informed consent, screening interviews were carried out via Zoom to check that participants met inclusion criteria (see Appendix 3), to explain the rationale for the study, and to clarify what was involved in participation. Any points of uncertainty regarding eligibility were clarified through discussion with academic supervisors. Those who met inclusion criteria following screening were sent a link to the baseline assessment. All further assessments (post treatment and 3-month follow up) were sent via email at the appropriate time and completed using the Qualtrics survey platform.

Following enrolment in the study, participants were assigned a unique identifier, and following completion of the baseline assessment, they were randomised to either the intervention or sleep monitoring condition. Randomisation was carried out by a PhD student unrelated to the study, using an online randomisation tool (Sealed Envelope Ltd., 2024) to generate an allocation

sequence. Participants were allocated on a 2:1 basis in blocks of 10 to the intervention or sleep monitoring group. Following randomisation, participants in the intervention group were sent a Zoom link used to access the 4 weekly CBT-I sessions (delivered by the PhD student). Participants in the sleep monitoring control condition kept a daily sleep diary for 4 weeks. All participants then completed post-intervention measures 5 weeks after randomisation, and follow-up measures after a further 8 weeks (follow-up data was collected between October 2023 and April 2024). Control participants then received the CBT-I sessions and afterwards completed another set of post-intervention and follow-up measures. The trajectory of each group throughout the study is shown in Figure 6. Descriptive data for control participants before and after CBT-I is presented in Section 6.2.2.

Intervention

CBT-I is a multi-component, evidence-based intervention, which incorporates both cognitive and behavioural techniques to improve sleep quality and duration (Riemann et al., 2022). The intervention was delivered by SA (PhD student). In preparation, SA was trained to criterion standards by attending a 2-day training workshop delivered by the Delaware Psychological Association (DPA). CBT-I sessions were recorded and 10% of sessions were assessed by supervisors to monitor treatment fidelity.

The protocol for the CBT-I intervention was adapted from previous CBT-I training manuals (Ong et al., 2012; Perlis et al., 2005). Four weekly sessions (each lasting approximately one hour) were delivered via videoconferencing in groups of 2-3 participants. This included the key components of CBT-I (SRT, SCT, SH) and relaxation, which is often included (Riemann et al., 2022). The rationale and mechanisms of these key components are detailed in Chapter 5 (Section 5.2). The structure of the sessions (beginning with psychoeducation and SRT, then including SRT, SH, and CT in separate sessions) followed the training manual developed by Ong et al. (2012). Content of the individual weekly sessions is summarised below in Table 9.

Sessions were mostly didactic in format, however, opportunities for reflection and discussion were incorporated throughout. At the beginning of the session, participants were encouraged to reflect on the previous week, and they were asked to share their thoughts on the CBT-I strategies once the instructions had been explained. For example, CT was done by explaining the relationship between thoughts, the physiological stress response, and behaviours. The researcher provided an example of how a common maladaptive cognition about sleep (e.g. “I’m

going to be too tired to function in the morning.") could be challenged by reflecting on participants' own experiences of insomnia, and the knowledge they had gained about the homeostatic sleep drive. Participants were then encouraged to challenge other examples of common maladaptive cognitions about sleep.

Each session allowed time to reflect on the previous week, to cover the CBT-I strategies, and address immediate questions from participants. However, after each session, participants were sent a copy of the materials which had been presented and advised that they could contact the researcher between sessions if they had any further questions.

Table 9: Content of weekly CBT-I sessions

Session	Contents
1	Psychoeducation about sleep (biological basis of sleep, misconceptions about sleep, causes of insomnia). Relaxation: breathing techniques (square breathing), progressive muscle relaxation, and guided imagery. SRT (reviewed baseline sleep diary and prescribed bedtime and risetime based on this data).
2	Review sleep diary, titrate prescribed bedtime and risetime. SCT: rationale, aims, and 'troubleshooting' questions. Advised to follow the '15-minute rule': to leave the bed and do something they found relaxing if they were unable to fall asleep or return to sleep within approximately 15 minutes.
3	Review sleep diary, titrate prescribed bedtime and risetime. SH: discussed aims, misconceptions, diet, lifestyle, and environmental influences on sleep. Participants encouraged to share existing knowledge with one another.
4	Review sleep diary, titrate prescribed bedtime and risetime. CT: challenging maladaptive thoughts (e.g. "I'm going to be too tired to function in the morning"), thought blocking, and paradoxical intention. Relapse prevention: asked to reflect on how content of the sessions could help improve sleep in future; shown how to calculate TIB, TST, and SE using a sleep diary.

Materials/measures

Primary outcomes were self-reported intentional and unintentional nonadherence to ET. This was measured using the adherence MARS-5. As discussed in Chapter 3 (Section 3.2), the MARS-5 includes 1 item measuring unintentional nonadherence, and 4 items measuring

intentional nonadherence. A total score of ≤ 4 (on the unintentional nonadherence subscale) and ≤ 19 (on the intentional nonadherence subscale) was applied to classify participants as nonadherent based on previous research (De Vries et al., 2014; Moon et al., 2019).

Secondary outcomes included common symptoms in patients with breast cancer who are prescribed ET treatment. Standardized and validated questionnaires were used to measure insomnia (SCI), depression (PHQ-9), anxiety (GAD-7), fatigue (FFS), musculoskeletal pain, and vasomotor symptoms (BESS). As previously discussed in Chapter 3, each of these measures has been identified as reliable, valid, and applied in previous studies of patients with breast cancer.

The consensus sleep diary was used to collect self-report sleep data for each participant. These were completed daily (to reflect the previous night's sleep) for one week at a time. Sleep diary data included SE, SOL, WASO, TST, TIB, and number of night-time awakenings. All participants (intervention and sleep monitoring group) completed a baseline sleep diary for one week prior to the intervention period, completed sleep diaries throughout the 4-week intervention period, then for 1-week post-intervention, and 1 week at follow-up (13 weeks post-randomisation).

Missing data

The intention to treat (ITT) principle was applied, meaning all participants were analysed within their randomised groups even if they withdrew from the study. This aims to maintain sample size and reduce the risk of Type 1 error (overestimating the efficacy of the intervention) (McCoy, 2017; Tripepi et al., 2020). Where possible, participants were recontacted and asked to complete measures to minimise missing data. Where missing data could not be completed, it was replaced using multiple imputation (MI). MI uses the available information about individuals to estimate the missing data and generate multiple datasets, which are pooled to create one complete dataset (Woods et al., 2024). Twenty imputed datasets were generated, and results were pooled using Rubin's rules (Rubin, 1996). This allowed all participants to be included in the final analysis within their randomised groups, even if they had withdrawn from the study.

There are various methods for handling missing data, depending on the mechanism of missing data (i.e. the presumed reason for missingness), and the amount of missing data (Woods et al., 2024). MI was selected as this has been found to replace missing data more accurately than other methods, particularly when the proportion of missing data increases (Shrive et al., 2006), and is recommended over single imputation methods such as last observation carried forwards because MI can account for the other available information in the dataset (Little et al., 2012; National Research Council, 2010). The risk of bias and inaccuracy is higher when data is missing not at random (meaning due to factors not included in the data), even when using MI (McNeish et al., 2017). However, overall, MI is still recommended as a justifiable approach when data is missing not at random, and is preferable to listwise deletion methods (Woods et al., 2023).

Missing questionnaire data was replaced for 7 intervention participants at post-intervention, and 6 at follow-up. Missing sleep diary data was replaced for 7 intervention participants at post-intervention, and 10 at follow-up. Sleep diary data was replaced for one control participant at baseline (this participant did not complete the baseline sleep diary but completed all post and follow-up measures).

Statistical analysis

All data analyses were carried out using SPSS Version 27.

The method of analysis conducted deviates from the plan detailed in the study pre-registration. As stated in Section 6.2., preliminary analyses indicated that a key assumption of the ANOVA test, homogeneity of variance, was violated. The F-test (used to compare means) is sensitive to heterogeneity of variance, particularly in unbalanced designs where one group is bigger than another (Gaugler & Akritas, 2012), such as the current study. Therefore, multilevel modelling was selected as an alternative method of analysis.

Multilevel modelling was selected to investigate the effect of group and time on outcome variables. This approach has been used in numerous previous RCTs of CBT-I (Arnedt et al., 2021; Savard et al., 2014; Zachariae et al., 2018). Multilevel modelling assumes homogeneity of variance, however, it has been found to be fairly robust when this assumption is violated (Schielzeth et al., 2020). Multilevel modelling is also recommended when analysing data from studies with unbalanced designs (Armstrong, 2017). Therefore, this method was deemed

appropriate for the design of the current study, as it can consider both between and within group factors (allowing investigation of the interaction between treatment group and time) (Armstrong, 2017).

As the CBT-I intervention was delivered in groups, it is possible that clustering could occur within the intervention group data. In RCTs, this may occur due to participants receiving an intervention delivered by the same provider, or the group dynamics when the intervention was delivered (Candlish et al., 2018). To investigate the potential for clustering to occur within CBT-I groups, a null multilevel model including a random intercept for therapy group was run for the primary outcomes of the current study (MARS unintentional and intentional scores) at post-intervention. The estimated ICC for both outcomes was 0, indicating minimal clustering occurred within therapy groups. Due to the low ICCs for both primary outcomes, therapy group was not included as a random effect within the final multilevel models.

Models were fitted using full information maximum likelihood estimation. Fixed factors included in the models were group and timepoint, and all outcome variables were treated as continuous. In total, 14 multilevel models were evaluated.

6.2.2. Results

Participants

Between April and December 2023, 53 potential participants were screened for eligibility. Of these, 17 were excluded as they did not report ever missing a dose of ET (either intentionally or unintentionally), and 1 was excluded because their ET treatment would be complete before the study period finished. In total, 35 participants were recruited. However, 3 participants became unresponsive after screening, therefore 32 completed baseline measures and were randomised. These 32 participants were included in the analysis (21 intervention, 11 sleep monitoring control). The trajectory of participants throughout the study is shown in Figure 6.

Demographic and clinical characteristics of all participants are presented in Table 10. All participants were female, with ages ranging from 43 to 72 (M=55.87, SD=7.37). The majority (96.9%) of participants were white and the most frequent nationality was UK (84.38%). Time since beginning ET treatment ranged widely (from 3 months to 24 years), as one patient had been diagnosed with metastatic breast cancer and was therefore prescribed ET long-term. All other participants had been prescribed ET for 5-10 years. Of these participants, the average duration since beginning ET was 3 years and 7 months. Some patients had originally been

diagnosed long ago and had since experienced a recurrence (although this was not metastatic). In these cases, the timepoint where their most recent course of ET began was recorded. Most participants (81.3%) had received radiotherapy treatment, and 40.6% had received chemotherapy. All participants had previously received breast cancer surgery and were currently prescribed ET. Most were prescribed an AI (43.8%) or Tamoxifen (40.6%) without the addition of OFS.

Attrition

In total, 32 participants completed baseline measures. Of these, 8 (all from the intervention group) withdrew from the study. Of the 8 participants who withdrew, 2 were successfully recontacted, and agreed to complete follow-up measures (1 of these participants had not initiated CBT-I, and 1 had attended 1 session).

No adverse events related to the intervention were reported, although one participant withdrew from the study as they felt unwell due to side effects of targeted breast cancer treatment. Reasons for withdrawal from the study are reported in Figure 6.

Following the intention to treat principle, all participants were included in the final analysis, as missing data was replaced.

CBT-I session attendance

Of the 21 intervention participants, 18 (85.71%) initiated CBT-I sessions. Twelve (57.14%) attended 4 sessions, three (14.29%) attended 3 sessions, two (9.52%) attended 2 sessions and one (4.76%) attended only 1 session. The average number of sessions attended by intervention participants was 2.95.

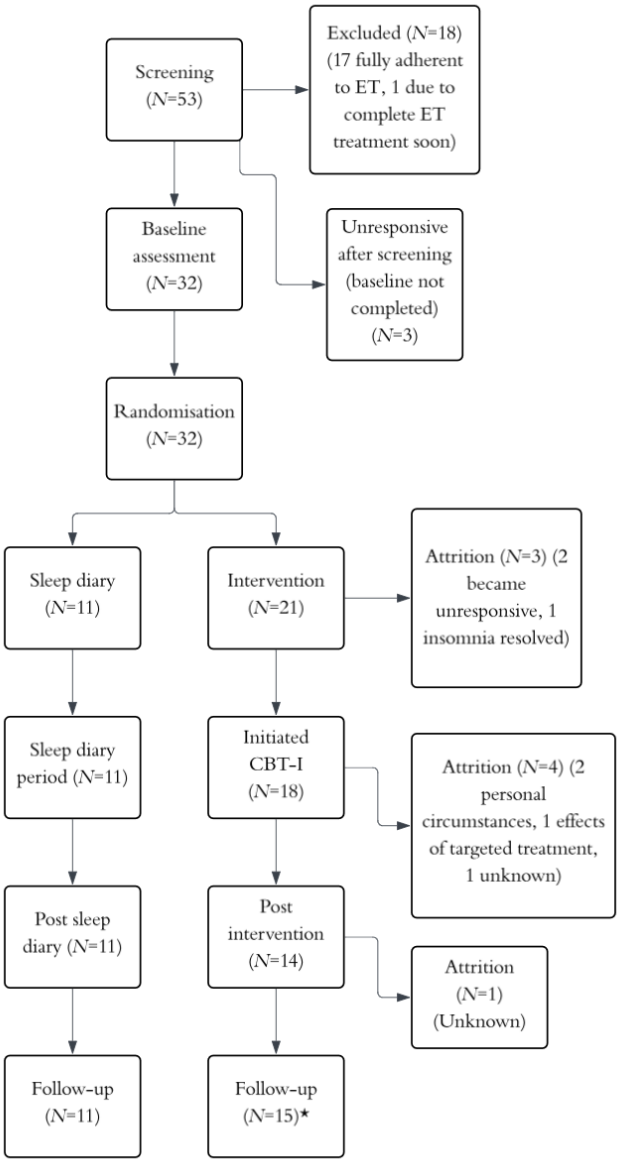
One of the participants who attended 2 sessions received the rest of the materials in written form and completed post-intervention and follow-up measures.

Descriptive statistics

To assess potential differences between groups at baseline, average scores for each of the measures were compared for intervention and sleep monitoring control participants. At baseline, participants in the sleep monitoring control condition reported worse insomnia, depression, anxiety, fatigue, and musculoskeletal pain than the intervention group. To identify whether these differences were statistically significant, scores for each group were compared using independent samples t-tests for normally distributed data, and Mann-Whitney tests for

data for non-normally distributed variables. No significant differences were found between intervention and control groups at baseline (see Appendix 4, Table 11, for full output). Average scores for each outcome at each timepoint are presented in Table 12.

Figure 6: Participant flow diagram



*2 participants who withdrew from the study without completing CBT-I sessions completed follow-up measures.

Table 10: Demographic and clinical characteristics of participants

Characteristic	Intervention *(N*=21)	Sleep monitoring control (*N*=11)	Overall sample (*N*=32)
Gender *N* (%)			
Female	21 (100)	11 (100)	32 (100)
Age *M* (*SD*)	56.3 (7.51)	55.09 (7.38)	55.87 (7.37)
Race/ethnicity *N* (%)			
White	20 (95.24)	11 (100)	31 (96.9)
Asian	1 (4.76)		1 (3.13)
Nationality *N* (%)			
UK	18 (85.71)	9 (81.82)	27 (84.38)
Ireland	1 (4.8)		1 (3.13)
USA	1 (4.8)		1 (3.13)
Spain		1 (9.1)	1 (3.13)
Canada	1 (4.8)		1 (3.13)
Mixed		1 (9.1)	1 (3.13)
Marital status *N* (%)			
Married	10 (47.6)	6 (54.5)	16 (50)
Widowed		1 (9.1)	1 (3.13)
Divorced	3 (14.3)	2 (18.2)	5 (15.6)
Separated	1 (4.8)	1 (9.1)	2 (6.3)
Never married	7 (33.3)	1 (9.1)	8 (25)
Employment status *N* (%)			
Full-time	8 (38.1)	5 (45.5)	13 (40.6)
Part-time	6 (28.6)	1 (9.1)	7 (21.9)
Unemployed seeking work	1 (4.8)	1 (9.1)	2 (6.3)
Unemployed not seeking work	2 (9.5)		2 (6.3)
Retired	3 (14.3)	4 (36.4)	7 (21.9)
Missing	1 (4.8)		1 (3.1)
Education *N* (%)			
High school (4 years)	1 (4.8)		1 (3.1)
High school (6 years)	2 (9.5)		2 (6.3)
College (HND/HNC)	2 (9.5)	2 (18.2)	4 (12.5)
Bachelor's degree	9 (42.9)	7 (63.6)	16 (50)
Master's degree	6 (28.6)	2 (18.2)	8 (25)
Doctorate	1 (4.8)		1 (3.1)
BC stage at diagnosis *N* (%)			
Stage I (A or B)	5 (23.8)	3 (27.3)	8 (25)
Stage II (A or B)	9 (42.9)	3 (27.3)	12 (37.5)
Stage III (A or B or C)	3 (14.3)	3 (27.3)	6 (18.8)

Stage IV			
Don't know	4 (19)	2 (18.2)	6 (18.8)
BC grade at diagnosis *N* (%)			
Grade 1	2 (9.5)	1 (9.1)	3 (9.4)
Grade 2	7 (33.3)	5 (45.5)	12 (37.5)
Grade 3	7 (33.3)	4 (36.4)	11 (34.4)
Menopausal status *N* (%)			
Pre-menopause	5 (23.8)	3 (27.3)	8 (25)
Perimenopause	4 (19)	3 (27.3)	7 (21.9)
Post-menopause	12 (57.1%)	5 (45.5)	17 (53.1)
Comorbidities* *N* (%)			
Musculoskeletal issues (Peripheral neuropathy, pain, arthritis, osteoporosis, osteopenia)	8 (38.1)	6 (54.55)	14 (43.75)
Chronic physical health problem (Hypertension, Diabetes/pre-diabetes, high cholesterol, thyroid issue)	5 (23.81)	6 (54.55)	11 (34.38)
Chronic Fatigue Syndrome		2 (18.18)	2 (6.25)
Glaucoma		1 (9.09)	1 (3.13)
Migraines	1 (4.76)	1 (9.09)	2 (6.25)
Asthma	1 (4.76)		1 (3.13)
Lymphedema	1 (4.76)	1 (9.09)	2 (6.25)
Liver problems	1 (4.76)		1 (3.13)
Heart condition	1 (4.76)	1 (9.09)	2 (6.25)
Depression	1 (4.76)	1 (9.09)	2 (6.25)
Anxiety	1 (4.76)		1 (3.13)
Treatment-related trauma	1 (4.76)	1 (9.09)	2 (6.25)
Breast cancer treatments			
Chemotherapy *N* (%)			
Yes	7 (33.3)	6 (54.5)	13 (40.6)
No	14 (66.7)	5 (45.5)	19 (59.4)
Radiotherapy *N* (%)			
Yes	16 (76.2)	10 (90.9)	26 (81.3)
No	5 (23.8)	1 (9.1)	6 (18.8)
Surgery *N* (%)			
Yes	21 (100)	11 (100)	32 (100)
No	0 (0)	0 (0)	0 (0)
Endocrine therapy *N* (%)			

Tamoxifen	10 (47.6)	3 (27.3)	13 (40.6)
Tamoxifen and OFS		1 (9.1)	1 (3.1)
AI	10 (47.6)	4 (36.4)	14 (43.8)
AI and OFS	1 (4.8)	2 (18.2)	3 (9.4)
Unsure/prefer not to say		1 (9.1)	1 (3.1)

*Comorbidities were self-reported during screening interviews.

Self-reported Endocrine Therapy adherence

Table 13 shows the proportion of participants in each group classed as unintentionally and/or intentionally nonadherent at each timepoint, based on MARS scores. Participants were classified as nonadherent based on a total score of ≤ 4 on the unintentional nonadherence subscale (Item 1) and ≤ 19 on the intentional nonadherence subscale (Items 2-5) (Moon et al., 2019; de Vries et al., 2014). The proportion of intervention participants classed as unintentionally nonadherent decreased at each timepoint; the proportion intentionally nonadherent decreased from baseline to post-intervention, then increased at follow-up, but remained lower than at baseline. The proportion of sleep monitoring participants classed as unintentionally nonadherent remained the same (100%) throughout the study, whereas the proportion classed as intentionally nonadherent remained the same from baseline to post-intervention, then increased from post to follow-up.

Proportion of sample displaying severe symptoms and probable insomnia disorder

Figures 7 and 8 show the proportion of intervention and sleep monitoring control participants who reported moderate to severe level symptoms, based on established cutoff scores. All participants displayed probable insomnia at baseline. However, in the intervention group the proportion displaying probable insomnia decreased at each timepoint. In the control group, this only decreased slightly from post-intervention to follow-up. The proportion of intervention participants displaying moderate-severe depression and anxiety decreased from baseline to post-intervention, increased at follow-up, yet remained below baseline level. In the control group, the proportion reporting moderate-severe depression increased at each timepoint, whereas anxiety decreased throughout the study. The proportion reporting moderate-severe fatigue decreased throughout the study in the intervention group yet remained the same over time in the control group. These figures are reported fully in Table 14 (see Appendix 5).

Table 12: Mean scores for each outcome in intervention and sleep monitoring control groups

		SCI *M* (*SD*)	PHQ-9 *M* (*SD*)	GAD-7 *M* (*SD*)	Fatigue *M* (*SD*)	Vasomotor *M* (*SD*)	Musculoskeletal *M* (*SD*)	TIB *M* (*SD*)	TST *M* (*SD*)	SE (%) *M* (*SD*)	SOL *M* (*SD*)	WASO *M* (*SD*)	Awakenings *M* (*SD*)	MARS Intentional *M* (*SD*)	MARS Unintentional *M* (*SD*)
Group	Timepoint														
Intervention	Baseline	8.33	8.62 (3.53)	5.86 (4.54)	16.71 (6.14)	4.95 (3.84)	6.57 (2.69)	544.60 (76.65)	386.22 (59.09)	71.66 (11.20)	45.14 (39.60)	45.31 (34.44)	3.23 (1.72)	17.24 (2.57)	3.43 (0.68)
	Post-intervention	17.24 (7.59)	5.27 (5.03)	3.31 (5.61)	11.56 (7.43)	3.91 (4.64)	4.33 (3.48)	454.16 (83.85)	370.74 (64.47)	82.88 (11.62)	21.58 (37.55)	29.85 (36.61)	2.47 (1.89)	18.09 (3.20)	3.93 (1.05)
	Follow-up	19.59 (6.36)	4.12 (4.29)	4.20 (5.91)	9.03 (7.34)	3.72 (4.48)	3.64 (3.22)	481.81 (67.82)	393.64 (49.92)	82.39 (10.17)	9.12 (34.63)	27.07 (38.20)	2.28 (1.72)	17.88 (3.59)	3.83 (1.09)
Control	Baseline	6.73 (4.47)	11.45 (4.50)	9.73 (5.76)	17.00 (5.33)	4.36 (3.59)	7.09 (3.27)	556.26 (62.69)	359.75 (85.48)	64.10 (11.84)	56.79 (43.00)	63.88 (33.31)	2.80 (0.80)	17.00 (3.29)	3.45 (0.52)
	Post-intervention	11.18 (3.63)	11.55 (4.68)	8.00 (5.87)	15.73 (6.50)	4.00 (3.07)	7.45 (1.92)	542.56 (82.46)	411.40 (116.39)	75.00 (16.86)	40.84 (36.04)	58.19 (40.11)	2.73 (0.75)	18.18 (2.32)	3.36 (0.67)
	Follow-up	9.64 (5.73)	12.45 (4.46)	8.45 (4.03)	15.91 (5.56)	5.00 (2.83)	7.36 (2.62)	534.31 (92.73)	401.73 (102.39)	74.87 (13.04)	35.59 (45.42)	47.86 (32.98)	2.58 (1.00)	17.36 (2.62)	3.36 (0.67)

TIB=Time in Bed, TST=Total Sleep time, SE=Sleep Efficiency, SOL=Sleep Onset Latency, WASO=Wake after Sleep Onset

Figure 7: Proportion of Intervention group reporting moderate-severe symptoms

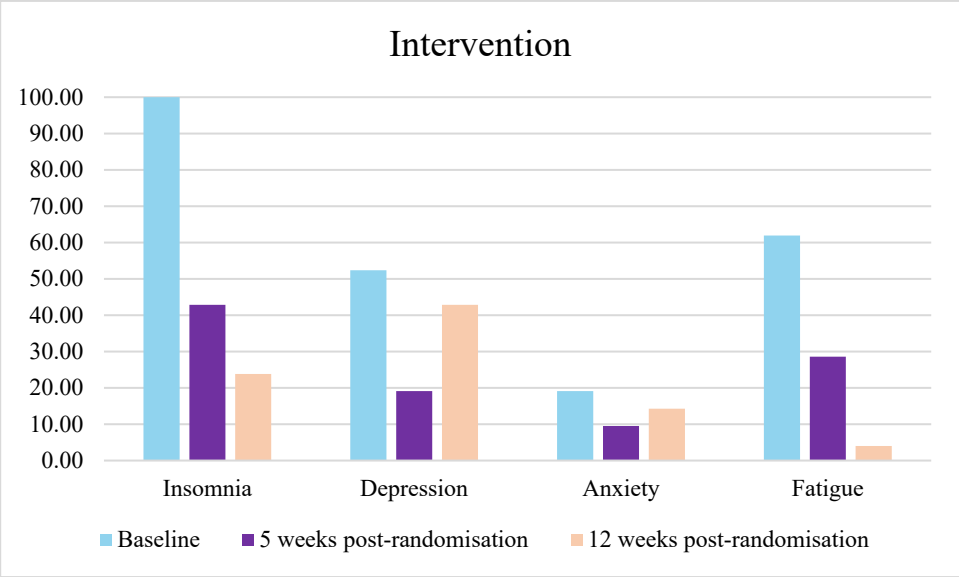


Figure 8: Proportion of control group reporting moderate-severe level symptoms

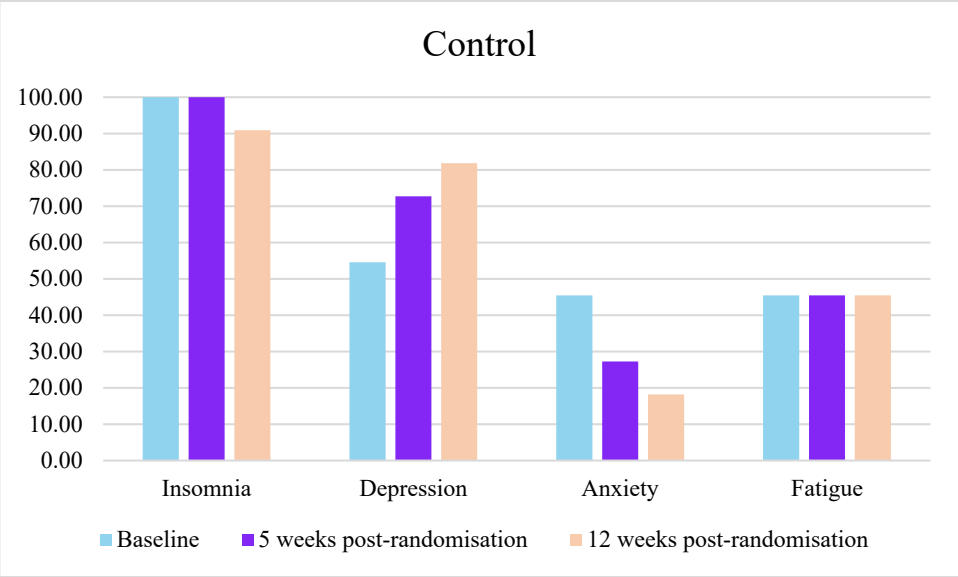


Table 13 Proportion of participants classed as intentionally and unintentionally nonadherent

		Unintentional nonadherence items % (*N*)	Intentional nonadherence items % (*N*)
Intervention	Baseline	90.48 (19)	76.19 (16)
	Post	66.67 (14)	38.10 (8)
	Follow-up	47.62 (10)	61.91 (13)
Control	Baseline	100 (11)	63.64 (7)
	Post	100 (11)	63.64 (7)
	Follow-up	100 (11)	72.73 (8)

Effect of group and time on outcome variables

The effects of group, time, and potential group/time interaction were investigated for all variables using fixed effects, multilevel models. As stated in Section 5.2.2., no significant differences were found between intervention and control participants at baseline, therefore secondary outcome variables were not included as covariates within these models. Random intercepts were investigated to consider individual variation in baseline scores, but did not significantly improve model fit for any variables. The results of multilevel models investigating group/time interaction for all variables are presented in Table 15. The results of fixed effects of group and time for all variables are shown in Table 16 (Appendix 6).

Primary outcome-Endocrine Therapy adherence

Intentional nonadherence

Multilevel modelling did not identify a significant effect of group (B = -.09, SE = 1.19, t = −.08, p = .0938, 95% CI -2.42-2.24]), or time from baseline to post (B = -1.18, SE = .92, t = -1.29, p = .198, 95% CI [-2.98-.062]) or post to follow-up (B = -.82, SE = .71, t = -1.15, p =.25, 95% CI [-2.21-.58]) on intentional nonadherence. This indicates that intentional nonadherence did not differ significantly between groups or change significantly over time.

A significant group/time interaction was not found from baseline to post-intervention (B = .33, SE = 1.23, t = .27, p = .789, 95% CI [-2.09-2.75]), or from post to follow-up (B = .61, SE = .99,

t = .62, p = .537, 95% CI [-1.33-2.56]). This indicates that any change in intentional nonadherence scores over time did not differ significantly between groups.

Unintentional nonadherence

Multilevel modelling identified a significant group/time interaction from baseline to post-intervention, indicating that unintentional nonadherence scores improved significantly more in the intervention compared to the control group (B = −0.59, SE = 0.28, t = −2.11, p = .035, 95% CI [−1.15, −0.04]).

Secondary outcomes

Insomnia

A significant main effect of group (B = 6.06, SE = 2.61, t = 2.32, p = .022, 95% CI [0.89, 11.22]). indicated that intervention participants reported less severe insomnia than those in the control group overall. A significant main effect of time indicated that insomnia improved over time in both groups from baseline to post-intervention (B = −4.46, SE = 2.16, t = −2.07, p = .039, 95% CI [−8.68, −0.23]).

Depression

A significant main effect of group (B = −6.27, SE = 1.81, t = −3.47, p < .001, 95% CI [−9.83, −2.72]) indicated that intervention participants reported less severe depression than those in the control group overall. A significant group/time interaction was found from baseline to post-intervention, indicating that depression scores improved significantly more in the intervention compared to the control group (B = 3.44, SE = 1.62, t = 2.13, p = .034, 95% CI [0.25, 6.62]).

Anxiety

A significant main effect of group indicated that anxiety was overall lower in the intervention group (B = −4.69, SE = 2.16, t = −2.18, p = .030, 95% CI [−8.93, −0.45]).

Musculoskeletal pain

A significant main effect of group indicated that musculoskeletal pain was lower in intervention participants overall (B = −3.12, SE = 1.24, t = −2.52, p = .012, 95% CI [−5.56, −0.68]). A significant group/time interaction was found from baseline to post-intervention, indicating that musculoskeletal pain scores improved significantly more in the intervention compared to the control group (B = 2.60, SE = 1.30, t = 2.00, p = .046, 95% CI [0.05, 5.16]).

Sleep diary variables

Significant main effects of group indicated that intervention participants reported significantly lower TIB ($B = -88.40$, $SE = 29.50$, $t = -2.30$, $p < .003$, 95% CI [−146.24, −30.56]) and WASO ($B = -28.34$, $SE = 13.76$, $t = -2.06$, $p = .040$, 95% CI [−55.33, −1.35]) than control participants overall.

A significant interaction was found between group and time indicated that TIB ($B = 76.74$, $SE = 32.51$, $t = 2.36$, $p = .018$, 95% CI [13.00, 140.49]) and TST ($B = 76.74$, $SE = 32.51$, $t = 2.36$, $p = .033$, 95% CI [13.00, 140.49]) decreased more in the intervention than control group baseline to post-intervention.

A significant time effect indicated that, in the overall sample, TST ($B = -51.66$, $SE = 25.03$, $t = -2.06$, $p = .039$, 95% CI [−100.73, −2.58]), and SE ($B = -10.89$, $SE = 3.43$, $t = -3.18$, $p = .001$, 95% CI [−17.61, −4.18]) increased from baseline to post-intervention.

Table 15: Multilevel model results for group*time interaction (unadjusted for multiple comparisons)

Variable	Effect	*B*	SE	*t*	*p*	CI
Unintentional nonadherence	Group*time interaction from baseline-post	-.59	.28	-2.11	.035	-1.15--.04
	Group*time interaction from post-follow-up	-.10	.29	-.036	.722	-.68-.47
Intentional nonadherence	Group*time interaction from baseline-post	.33	1.23	.27	.789	-2.09-2.75
	Group*time interaction from post-follow-up	.61	.99	.62	.537	-1.33-2.56
Insomnia	Group*time interaction from baseline-post	-4.45	3.12	-1.43	.155	-10.60-1.70
	Group*time interaction from post-follow-up	3.89	2.92	1.34	.184	-1.87-9.66
Depression	Group*time interaction from baseline-post	3.44	1.62	2.13	.034	.25-6.62

	Group*time interaction from post-follow-up	-2.06	1.74	1.18	-.238	-5.50-1.38
Anxiety	Group*time interaction from baseline-post	.82	1.87	.44	.66	-2.86-4.51
	Group*time interaction from post-follow-up	.04	1.90	.23	.816	-3.30-4.18
Fatigue	Group*time interaction from baseline-post	3.88	2.64	-1.47	.143	-1.32-9.08
	Group*time interaction from post-follow-up	-2.71	2.65	-1.02	.308	-7.94-2.52
Musculoskeletal pain	Group*time interaction from baseline-post	2.60	1.30	2.00	.046	.05-5.16
	Group*time interaction from post-follow-up	-.60	.14	-.53	.598	-2.85-1.65
Vasomotor symptoms	Group*time interaction from baseline-post	.68	1.08	.63	.527	-1.43-2.80

	Group*time interaction from post-follow-up	-1.19	1.22	-.097	.332	-3.61-1.23
TIB	Group*time interaction from baseline-post	76.74	32.51	2.36	.018	13.00-140.49
	Group*time interaction from post-follow-up	35.91	26.92	1.37	.172	-15.68-87.49
TST	Group*time interaction from baseline-post	32.58	24.68	1.32	.187	15.80-80.96
	Group*time interaction from post-follow-up	32.58	24.68	1.32	.187	15.80-80.96
SOL	Group*time interaction from baseline-post	7.61	16.04	.48	.635	-23.87-39.10
	Group*time interaction from post-follow-up	-7.20	16.05	-45	.654	-38.72-24.31
WASO	Group*time interaction from baseline-post	7.55	8.92	1.06	.29	-8.41-27.95

	Group*time interaction from post-follow-up	7.55	8.92	.85	.398	-9.99-25.09
SE	Group*time interaction from baseline-post	-.33	4.40	-.07	.941	-8.96-8.30
No. awakenings	Group*time interaction from post-follow-up	-.38	4.36	-.087	.931	-8.93-8.18
	Group*time interaction from baseline-post	.70	.44	1.57	.118	-.18-1.57
	Group*time interaction from post-follow-up	-.04	.45	-.10	.923	-.94-.85

Additional Control group data following CBT-I

As discussed in Section 6.2.1., additional data was collected from sleep monitoring control participants. Follow-up data after the initial sleep monitoring period was used as a baseline. This was compared to additional post-intervention and follow-up measures which these participants completed after receiving CBT-I. Average scores for each of these timepoints are presented in Table 17.

Primary outcome-Endocrine Therapy adherence

The number of control participants classed as nonadherent following CBT-I is shown in Table 18. All control participants were classed as unintentionally nonadherent at baseline, post-intervention, and follow-up. The number of participants classed as intentionally nonadherent decreased slightly from baseline to post-intervention, then returned to baseline level at follow-up.

Secondary outcomes

The number of control participants who reported moderate to severe level symptoms at each timepoint (based on established cutoff scores) is shown below in Table 19. At baseline (prior to CBT-I), all control participants reported probable insomnia disorder. This decreased from baseline to post-intervention, and slightly from post-intervention to follow-up. The number reporting moderate-severe depression, anxiety, and fatigue also decreased from baseline to post-intervention. The number then increased from post-intervention to follow-up but remained below baseline level.

Table 17: Mean scores for each outcome in sleep monitoring control group following CBT-I

	SCI *M* (*SD*)	PHQ-9 *M* (*SD*)	GAD-7 *M* (*SD*)	Fatigue *M* (*SD*)	Vasomotor *M* (*SD*)	Musculoskeletal *M* (*SD*)	TIB *M* (*SD*)	TST *M* (*SD*)	SE (%) *M* (*SD*)	SOL *M* (*SD*)	WASO *M* (*SD*)	Awakenings *M* (*SD*)	MARS Intentional *M* (*SD*)	MARS Unintentional *M* (*SD*)
Timepoint														
Baseline	8.5 (4.55)	13.2 (3.91)	8.60 (4.22)	16.60 (5.34)	5 (2.98)	7.5 (2.72)	527.394 (96.76)	376.01 (91.08)	70.99 (8.90)	40.92 (46.64)	50.56 (34.20)	2.71 (0.87)	17.8 (2.30)	3.5 (0.53)
Post-intervention	17 (5.70)	5.6 (3.66)	3.60 (2.99)	12.60 (6.83)	4.1 (3.25)	6.1 (3.48)	428.55 (72.00)	369.70 (85.19)	85.77 (12.15)	15.52 (10.70)	37.66 (35.79)	2.39 (1.32)	17.9 (2.73)	3.9 (0.57)
Follow-up	17.6 (6.48)	5.8 (6.11)	4.60 (3.31)	14.40 (8.55)	3.3 (2.75)	6.6 (3.13)	483.46 (107.14)	399.05 (116.77)	81.41 (10.88)	21.71 (18.29)	41.16 (31.70)	2.22 (0.92)	17.7 (2.63)	3.8 (0.63)

TIB=Time in Bed, TST=Total Sleep time, SE=Sleep Efficiency, SOL=Sleep Onset Latency, WASO=Wake after Sleep Onset

Table 18: Number of control group participants classed as nonadherent following CBT-I

	Unintentional nonadherence items *N* (%)	**Intentional nonadherence items *N* (%)**
Baseline	10 (100)	7 (70)
Post	10 (100)	6 (60)
Follow-up	10 (100)	7 (70)

Table 19: Number of control group participants displaying moderate-severe level symptoms following CBT-I

	Insomnia *N* (%)	Depression *N* (%)	Anxiety *N* (%)	Fatigue *N* (%)
Baseline	10 (100)	9 (90)	2 (20)	5 (50)
Post-intervention	5 (50)	1 (10)	1 (10)	2 (20)
Follow-up	4 (40)	2 (20)	2 (20)	4 (40)

6.2.3. Discussion

Summary of study aims and results

This study investigated the impact of insomnia treatment on intentional and unintentional nonadherence to ET, by conducting a pilot RCT of CBT-I. To the best of my knowledge, this is the first study to investigate a targeted, symptom-specific intervention to improve adherence to ET. Results indicated a significantly greater improvement in unintentional nonadherence, depression, and musculoskeletal pain from baseline to post-intervention in participants who received CBT-I compared to the sleep monitoring control group. Additionally, TIB and TST both decreased significantly more in the intervention group from baseline to post-intervention.

Results in the context of previous research

As summarised above, the current study identified a significant effect of CBT-I on unintentional nonadherence (indicated by a significantly higher improvement in intervention participants from baseline to post-intervention), but no significant effect was found on intentional nonadherence. After receiving the CBT-I intervention, all control participants remained unintentionally nonadherent. The proportion classed as intentionally nonadherent decreased very slightly post-intervention, then increased to same level at follow-up. This differs from the pattern observed in intervention participants, however, inferential testing was not conducted as only 10 control participants received the intervention. Although these findings do not clearly support for the possible impact of CBT-I on nonadherence to ET, this does not necessarily refute the potential benefits of the intervention. These results must be considered in context of the wider literature and the limitations of the current study (discussed below).

As discussed in Chapter 2 (Section 2.4), previous interventions have aimed to support patients by addressing barriers to ET adherence (Ell et al., 2009; Ziller et al., 2013), yet few have specifically focused on symptom management. Graetz et al. (2018) investigated a symptom management intervention, finding significantly higher adherence post-intervention in intervention participants than in control participants. However, Graetz's (2018) study did not report the impact of addressing specific symptoms, therefore cannot inform our understanding of the impact of insomnia treatment specifically on ET adherence. Furthermore, whilst Graetz's (2018) study used an established measure of self-reported adherence (the MMAS-4), it did not distinguish between intentional and unintentional nonadherence. Therefore, there is a lack of targeted symptom management interventions to effectively compare with the current results.

Comparison of symptoms scores in each group indicated greater improvements in depression and musculoskeletal pain in intervention participants from baseline to post-intervention. This is supported by previous research identifying transdiagnostic benefits of CBT-I (Squires et al., 2022). Insomnia was significantly lower in the intervention group overall yet improved from baseline to post-intervention in both groups. This does not align with previous research, as significant effects of CBT-I on insomnia have been found in numerous RCTs (Ma et al., 2021). In the current study, the ability to detect a significant group/time interaction may have been impaired by the use of sleep diaries as an active control, potentially contributing to the observed improvement in insomnia in control participants. Furthermore, based on the post-hoc power analysis discussed in Section 6.2.1., the current sample may have been underpowered to detect a statistically significant intervention effect for insomnia.

Strengths and limitations of the current study

This study builds upon previous research and addresses the limitations of previous interventions identified in Chapter 2, Section 2.2.4. As discussed in Section 5.3.3., previous systematic reviews noted a lack of RCTs investigating ET adherence interventions (Ekinci et al., 2018; Finitsis et al., 2019). Heiney et al., 2019; Hurtado-de-Mendoza et al., 2016). Therefore, by conducting a pilot RCT (an RCT is considered the 'gold standard' for evaluating treatment effect (Concato et al., 2017), the current study addressed a significant gap in the literature. However, the limitations of the current study must also be acknowledged. The following section will evaluate strengths and limitations of the design, recruitment strategy, sample, and method of measuring ET adherence.

The design of the current study presents both advantages and disadvantages. Using a waitlist control design allows comparison between groups to assess treatment effect, while ensuring all participants have the opportunity to receive the intervention (Cuijpers, 2025). Furthermore, this may reflect the reality of waiting times for support with mental health (Hart, Fann, & Novack, 2008). However, the use of sleep diaries as an active control condition could have also led to improvements in insomnia. A recent study by Tollanes et al. (2025) found some support for improved sleep following a week of sleep diaries; however, this occurred in a small sample of 17 poor sleepers (based on PSQI scores). It is possible that keeping sleep diaries during the control period caused participants in the current study to become more aware of their sleeping patterns, potentially leading to changes in their behaviour during the control period and reducing the ability to detect a significant intervention effect when comparing the two groups over time.

While past interventions have often included participants at or near the beginning of ET treatment, regardless of whether they are nonadherent to their medication (Hadji et al., 2013; Neven et al., 2014; Graetz et al., 2018), this study purposefully recruited individuals who reported difficulty taking ET consistently (whether intentionally or unintentionally). The study included participants with a range of comorbidities, who were prescribed both Tamoxifen and AIs, and at varying times since they began breast cancer treatment. As noted in Chapter 2, Section 4.1.2., RCTs of ET may include participants who are especially tolerant of ET treatment, and therefore not give an accurate idea of the challenges patients may experience (Cella & Fallowfield, 2008; Mioranza et al., 2016). Therefore, the current study provided insight into the potential benefits of CBT-I for patients who experienced insomnia (one of the most prevalent symptoms in this population) and had trouble adhering to ET treatment.

This study reported recruitment and retention of participants, and CBT-I session attendance, reflecting several key aspects of feasibility (Eldridge et al., 2016b). Although retention was 100% in sleep diary control participants, 6 of 21 intervention participants withdrew (71.42% retention). This is lower than other RCTs of CBT-I in patients with breast cancer with retention rates over 90% in all study arms (Oswald et al., 2022; Starling et al., 2024). However, it is comparable to studies of CBT-I and a stimulant (Peoples et al., 2017) and brief behavioural therapy modelled on CBT-I in patients with breast cancer receiving chemotherapy (Palesh et al., 2018).

Of the participants who withdrew from the current study, only 3 provided reasons for withdrawal, and none cited the nature of the study or content of the CBT-I sessions as a reason. Therefore, although attrition was higher in the intervention group, this does not conclusively indicate acceptability or feasibility of the intervention in patients prescribed ET. Although participant retention and session attendance provide indications of feasibility, other aspects such as treatment fidelity or acceptability were not formally assessed, for example, through a structured checklist or standardised questionnaires (Borrelli et al., 2011; Sekhon et al., 2017).

The measure used to capture self-reported ET adherence (MARS-5) was selected based on several factors. This measure is relatively short, yet specifies the nature of nonadherence, and aims to encourage the participant to be honest regarding their medication-taking behaviour. This aims to address the tendency for self-report measures to underestimate nonadherence (discussed in Chapter 2, Section 2.2.1.). The use of validated self-report measures which

specify the nature of nonadherence (including the MARS) was also recommended by Fleming et al.'s (2022) systematic review. While this may be less reliable than objective measures of adherence (Pistilli et al., 2020), the MARS was selected due to these key strengths and will facilitate effective comparison of these results with future research. To date, no study has specifically assessed the impact of a targeted intervention on intentional/unintentional nonadherence. Therefore, the current study utilised a validated questionnaire which specifies the nature of nonadherence and has been applied in previous studies of patients prescribed ET (Brett et al., 2018; Henry et al., 2017; Moon et al., 2019; Wouters et al., 2014), to facilitate comparison with future research.

A potential limitation of this study is the method of recruitment, as participants were recruited by liaising with breast cancer charities, organisations, and support groups. As discussed in Chapter 3 (Section 3.4.3.), this strategy relies on reaching people who were either involved with these groups in some capacity or heard about the study from someone who was. Therefore, this study recruited from a sample of people likely to be actively engaged and motivated to continue with ET treatment, despite experiencing troublesome symptoms. The majority of participants were white, all were female, and 78% were educated to undergraduate level or higher. Previous research has identified being part of a minority ethnic group and lower socioeconomic status are significantly related to nonadherence (Moon et al., 2017; McGuinness et al., 2022). Therefore, this study may not have reached some individuals who may have especially benefited from an intervention to improve adherence. It must also be acknowledged that the study could not measure long-term adherence or identify whether participants continued to take ET after the follow-up period (13 weeks post-randomisation). Although both nonadherence and non-persistence are related to poorer breast cancer outcomes (Inotai et al., 2021; Pistilli et al., 2020), the current study could only capture adherence within this relatively short timeframe.

The current study included a relatively small sample of 32 participants. As discussed in Section 6.2.1., this would have provided adequate statistical power for the initial analysis plan but was underpowered for the multilevel model analysis which was conducted. Due to the lack of statistical power (and relatively low risk of Type 1 error), multilevel model results were not adjusted to account for familywise error. The results of the current study should therefore be interpreted with caution. However, as the current RCT was intended as a pilot study, statistical power was not imperative to addressing the study aims. Furthermore, a lack of statistical power does not negate the contribution of the current study to the literature, as an underpowered study

may still be included in meta-analyses and provide a basis for future research (Carnahan & Brown, 2024; Zitzmann et al., 2024).

Recommendations for future research

Future research should build upon these results by investigating the potential for CBT-I to improve ET adherence in a larger sample (to ensure adequate statistical power) and assessing key elements of feasibility (such as treatment fidelity, recruitment, and retention) and acceptability. Studies should utilise validated measures which distinguish between intentional and unintentional nonadherence to allow investigation of interventions on specific forms of nonadherence to ET and facilitate effective comparison between studies. A concerted effort should be made to recruit a diverse range of participants, including those who may be at greatest risk of nonadherence. It would also be beneficial for future research to investigate the effect of delivering CBT-I earlier during breast cancer treatment to explore whether addressing insomnia (or potentially providing this as a preventative treatment, before insomnia becomes chronic), helps to reduce the risk of nonadherence in future. This would also allow researchers to investigate the potential impact of CBT-I on long-term persistence to ET, which is a crucial factor in improving breast cancer outcomes.

6.2.4. Funding

This study was funded by the Economic and Social Research Council (ES/P000681/1). The funding body had no involvement in the study design, data collection, analysis, or writing of the manuscript.

6.3. Study 3

6.3.1 Methods

Design

A qualitative approach was used to gain further insight into nonadherence to ET and the potential role of insomnia. Semi-structured interviews were designed to explore the study aims (detailed in Section 6.1.), and thematic analysis (Braun & Clarke, 2006) was then used to generate themes and subthemes related to these aims.

Participants and recruitment

Following participation in Study 2, participants were invited to take part in an optional follow-up interview to explore the lived experience of adhering to ET medication. Recruitment ceased when it was agreed that data saturation had been reached. Saturation was defined as the point where the data was no longer yielding new ideas or themes (Braun & Clarke, 2021). This was identified through discussion between the PhD researcher and MSc students who attended the online interviews, by reflecting on the anonymised transcripts and whether new information had been gained from the most recent interview.

Participants had been informed of the opportunity to take part in follow-up interviews prior to beginning the RCT and were invited via email after completion of post-intervention measures. In total, 26 participants were invited to participate in interviews. Five declined: 4 chose not to participate due to personal reasons, and 1 became unresponsive. Therefore, 21 agreed to participate. Of these, 12 had been in the intervention group, and participated in interviews after completion of post-intervention measures. Nine had been in the sleep monitoring control group and participated in interviews after they had received CBT-I and completed additional post-intervention measures.

Procedures

Participants who indicated interest in participating were asked for availability, and an interview was arranged and conducted via Zoom. All interviews were attended by two researchers, the PhD student and attending MSc student. After observing the PhD student conducting an interview, the attending MSc student led future interviews under supervision of the PhD student. At the beginning of each interview, participants were introduced to the attending MSc student. The researcher explained that participants had the right to withdraw at any time, and that their data would be anonymised. Participants were then given the opportunity to ask any

questions. The researcher then asked for permission to record the interview for transcription. Interviews were conducted using a semi-structured topic guide (Appendix 7) which was developed based on the study aims. This topic guide was piloted on a convenience sample of individuals outside of the study (*N*=3) to assess the clarity and flow of the questions. Following this pilot, the first 2 questions were amended to make the language more accessible. Interviews lasted approximately 1 hour. Following each interview, participants were thanked for their participation in Studies 2 and 3. The researcher then asked for permission to retain their contact details in case of future studies which they may be suitable for.

Interviews were recorded via Zoom and transcribed verbatim using the Outlook transcription feature. All transcriptions were assessed for accuracy by the attending MSc student.

Data analysis

Themes were derived from the data through theoretical thematic analysis, following the steps set out by Braun and Clarke (2006). This process began during data collection, as the PhD student and attending MSc student both made notes during interviews of interesting points raised (e.g. if the participant responded differently to one of the questions than others in previous interviews).

Once anonymised, each transcript was then independently read and coded by the PhD student and 2 MSc students. The PhD student and 2 MSc students independently generated initial codes and constructed initial themes. The MSc students shared the initial themes they had constructed with the PhD student and explained how they had generated these themes from the data. The PhD student then compared their own initial themes to the themes generated by the MSc students to assess validity. The PhD student then revisited the transcripts to assess which themes best captured the data and addressed the research questions.

The PhD student refined and named the final themes and produced the report. The generation of codes and themes was a reflexive, active process which was led by the researchers. Rather than simply summarising the data, codes and themes were continuously evaluated and refined by referring to the transcripts and reflecting on the research questions throughout this process (Braun & Clarke, 2019). The preparation of transcripts and a detailed account of the stages of Thematic Analysis are reported in Table 20, Appendix 8.

6.3.2. Results

Participants

Participants (*N*=21) were all female, and the average age was 55.67 (SD=7.61). The majority were white (95.20%), British (80.95%), and prescribed Tamoxifen (42.86%). Sample characteristics are reported fully in Table 21 (see Appendix 9).

Thematic analysis results

Overall, 4 main themes were generated from the thematic analysis. The first theme describes the complexity of nonadherence to ET, including the challenges of this treatment, factors which influence unintentional and intentional nonadherence, and participants' perspectives of nonadherence. Theme 2 explores the impact of insomnia and perceived importance of sleep to participants. Theme 3 captures the impact of insomnia on intentional and unintentional adherence. The final theme explores the potential for a CBT-I intervention to improve adherence and reflects the improvements in ET side effects and overall quality of life experienced by participants following CBT-I. These themes and subthemes are presented in Table 22. The codes used to generate themes and subthemes through thematic analysis are presented in Table 23 (see Appendix 10).

Theme 1: Nonadherence is complicated

Theme 1 captures the challenges of ET treatment, complex perspectives participants held towards nonadherence, and factors participants felt led to intentionally and unintentionally missing doses of ET. This includes one subtheme focused on the challenges of ET treatment, two subthemes relating to unintentional and intentional nonadherence, and one subtheme about how, despite feeling relief when taking a break from ET, participants were highly motivated to continue the medication.

<u>Subtheme 1.1 Side effects are a major challenge of Endocrine Therapy</u>

Some participants stated that it was difficult to distinguish between side effects of ET, residual effects of primary breast cancer treatment, or pre-existing health problems. However, most noticed side effects within weeks of initiating ET. All participants reported symptoms of insomnia (difficulty falling or staying asleep, for at least 3 months) prior to inclusion in the study. During interviews, the other most frequently reported side effects were vasomotor symptoms (hot flashes/night sweats) (*N*=15), cognitive dysfunction (concentration, memory problems, brain fog, word finding difficulties (*N*=15), joint pain or stiffness (*N*=11) and fatigue (*N*=9).

Side effects of ET had a multi-faceted impact on participants' quality of life. Participants described the overall impact of side effects as "debilitating", and the particularly "crippling" effect of insomnia. Overall, side effects created a perception of rapid physical and cognitive ageing, which one participant compared to "being put into a rocket, aged as I was then 53, and then being shot 20 years into the future". Another stated, "I just felt like an old woman, to be honest…I feel old before my time." The cumulative impact of side effects caused a lack of energy, difficulty moving, and obstructed daily activities: "He has to push me in a wheelchair for a while when I'm when I'm shopping because I get tired, and I can't do it…The fatigue from it is horrific".

Side effects had a detrimental effect on employment, as participants struggled to follow conversations and maintain their thought process in a professional setting. This was especially challenging for those who worked in cognitively demanding or positions of high responsibility, such as teaching or healthcare settings "I was finding it really hard to concentrate in the day. I have clinics with like 6 patients one after the other and follow-ups…My concentration was going". Difficulty at work created a feeling of failure which affected participants' overall confidence "I couldn't remember things at work…It was really detrimental to my self-esteem, my self-confidence. I felt like I was failing at work…that was really devastating for me actually". They also reflected on instances of being short-tempered with their loved ones due to mood swings and irritability, describing themselves as "snappy" and "low", which added strain to their relationships: "I was arguing with my partner over nothing. You know, my poor stepson was getting it in the neck at times. I was really short with him and slamming doors and all the rest of it."

During interviews, when the overall topic of nonadherence to ET was raised, 67% of participants identified side effects as a barrier to adherence. When asked about the general experience of ET treatment, a further 24% of participants responded by describing the intensity of their side effects and the impact on their quality of life. Overall, participants identified side effects as a significant challenge of ET treatment and a major factor in nonadherence to the medication.

Subtheme 1.2. Driven to distraction: unintentional nonadherence

Participants described various ways that the side effects of ET made adherence more difficult. Some described struggling to remember due to feeling generally unwell, and some identified specific side effects such as brain fog and memory deficits which, in addition to lack of routine, made it difficult to consistently take their medication: “I was waking up at different times every day. So yeah, lack of routine and structure and…just brain fog and yeah, forgetfulness.” A lack of routine was exacerbated by side effects such as insomnia and fatigue, making it more difficult for some to consistently take their medication: “If I'm particularly fatigued, I wouldn't necessarily make it through to my bed. So, if I don't make it through to my bed, I don't take my medication.”

Twelve participants reported that they had unintentionally missed doses of ET due to forgetting, not being in their usual routine, or struggling to handle the medication and dropping their tablets. Forgetting to take medication was more likely when their routine was disrupted, they were particularly busy, or they were away from home. Several stated that they would initially intend to take their tablets, then become distracted by work or their family, and end up forgetting: “There are times where I forget because I have been busy in the morning or whatever with the kids and I, suddenly, ‘oh my God, I haven't taken my tablets’”. One participant attributed forgetting ET to a lack of routine after completing primary treatment, as they no longer had regular appointments to attend, “If you've got a routine and you know you're getting up at, at half seven and you've got to be ready for 8:00, cause you're going to the hospital…there's more of the system in place, whereas when everything stops that system’s gone”. Others initially found it difficult to establish the habit of taking daily medication: “All of a sudden you have to take this once a day, which in itself… There's like a big legacy issue of memory.”

Subtheme 1.3. Seeking relief through intentional nonadherence

Eleven participants described intentionally missing doses of ET to temporarily alleviate side effects including insomnia, hot flashes, cognitive dysfunction, fatigue, musculoskeletal pain, mood swings, and upset stomach. Some described ‘accidentally on purpose’ missing doses, where they subconsciously decided to miss a dose but preferred to think they had forgotten: “I would sometimes forget to take it. I would say it was…A decision to forget, but I was kind of pretending I was forgetting.”.

Two participants related instances of missing tablets to feeling “rebellious”. One of these individuals stated they had missed tablets when they became frustrated with the unfairness of

having gone through intensive breast cancer treatments and now experiencing further side effects due to ET: “There might have been a couple of, you know, three or four rebellious days where I was like, I'm not taking that. And I think it's just, like it's particularly when the side effects have been bad… I've kind of gone…Why me? The unfairness of it”. The other reported that nonadherence gave them a sense of control, “It was also a bit me taking control of how often I took it rather than just doing as I was told, so I take it… I take it because I'm told to, but I take it on my terms”.

Some described planning to take a short break in advance, so that they could feel well and enjoy special occasions, or simply to feel better at the weekend when they had time off work: “I was tired or stressed, or…I think I'm just not going to have it on the Saturday so I could have a restful Saturday”. One participant had taken a break of 3 months, to identify whether ET was causing their side effects. However, most described taking short breaks when they felt mentally low, particularly tired and especially burdened by the side effects: “Both times are actually, I've been off sick, low mood in terms of almost like depression, high anxiety. And just struggling and just wanted to kind of kick start my body a bit”. This was usually motivated by a desire to “Feel consistently good for a while”, as they reported feeling relieved and that their quality of life was better during these breaks from the medication.

Table 22: Themes, subthemes and relevant quotations generated from thematic analysis

Theme	Subthemes	Relevant extract
Theme 1: nonadherence is complicated	Side effects are a major challenge of Endocrine Therapy	"I saw that the reflection of myself one day. Who is that old woman? It was me. I was stooping like an old woman."
	Driven to distraction: unintentional nonadherence	"The main side effects that affect my ability to remember to take it are the brain fog and the sleep."
	Seeking relief through intentional nonadherence	"My brain was thinking, this is the Letrozole doing this. Let's have a little break. Let's just give yourself a little break and see if things can improve."
	In two minds about Endocrine Therapy	"There is an element of it where you think, well, this is just not fair. And I don't want to do it. But then, your rational brain goes, but actually, I need to take this."
Theme 2: Sleep impacts everything	Insomnia is detrimental to wellbeing	"I was looking forward to the end of the day so I could just come home and try and get a good night's sleep or just sit on the sofa and doze…that's all I was looking forward to, to the exclusion of not just work, but doing other stuff I'm interested in and engaging in like other stuff hobbies, activities."
	Soldiering on with insomnia	"I've never been to a healthcare professional or my GP or anyone…I'll just suck it up. That's the way it is."

Theme 3: Two sides of the same coin: sleep affects both forms of nonadherence	Can't or won't? Insomnia affects ability and willingness to consistently take medication	"I stopped taking Tamoxifen probably about three times… where it felt like just really critical. I'm not getting enough sleep, or I needed to reboot and then start again."
	Better sleep may help adherence and persistence	"Improving the sleep, I think is one more piece of the jigsaw that makes it easier to both take it regularly. And to get my head around the fact that I'm going to…continue to take it for another four years"
Theme 4: CBT-I is good for more than just sleep	Everything looks better after a good night's sleep	"It's completely changed my life, so before your study, if I wanted to do anything...It had to be at lunchtime cause I could never guarantee I'd be reliably awake. Last night I went to the theatre… I didn't think twice about it".
	Benefits of a CBT-I intervention	"Having appointments makes you turn up, makes you listen, makes you engage"
	CBT-I addresses patient support needs	"I have found it very useful, and I do think other women would benefit from it…The amount of women I see who are really, really struggling and an early intervention with sleep problems might actually stop women from giving up with it."

Subtheme 1.4. In two minds about Endocrine Therapy

The impact of ET side effects was perceived as a barrier to returning to life as it was before the distress of breast cancer diagnosis and treatment. Participants described a misconception that they could quickly return to 'normal' following hospital-based treatment: "There's this narrative that you have cancer, you have a treatment, and then you try to go back to the old you". This created a perceived pressure to get back to normal, but being held back by ET side effects, which led to a feeling of failure: "You're failing at living, you're failing at, you know. I should be able to do this. I should be able to just take this medication and live my life and go on". Participants expressed desire for ET to be over, hoping that life would resume as 'normal' once they completed the treatment "Hopefully once I'm done with this jail sentence, I can get some normalcy back."

Several participants stated they wanted to move on from the identity of 'breast cancer patient', for the good of themselves and their loved ones. They described the profound impact of breast cancer diagnosis and treatment on their loved ones as "Like a stone dropping into a pond. It has ripples on everybody else". As discussed in Subtheme 1, side effects created tension in relationships, which was exacerbated as others did not always understand that participants could not recover so quickly following treatment "There was the, the kind of knock-on effect, as I say, with my husband, who had been good when I've been acutely ill, but then he wanted to move on".

As discussed in Subtheme 1.3, some participants were tempted to miss doses of ET for relief from side effects. Despite feeling better during these breaks, participants were also anxious, and desired to resume the medication despite its challenges: "I thought I just don't want to take this stuff anymore. And I gave myself like a 3-4-day break, but then I started to get a bit scared … so I took it again". Some stated that they had contemplated discontinuing ET treatment completely because of the side effects but reconsidered due to fear of breast cancer recurrence. Nonadherence was viewed as a compromise, as this was less severe than complete discontinuation: "I was feeling quite rebellious about it but equally couldn't quite cope with the guilt of saying I'm never going to take it again."

Several participants had discussed nonadherence with their family, who discouraged them from further nonadherence, despite recognising the impact of the side effects, "When my kids found out I was off it, went absolutely through me, even though they realised that my quality of life was a bit better". However, some reported that their loved ones questioned the benefits of the

treatment due to its impact on their quality of life and reflected that their relationships had been strained by the long-term impact of breast cancer treatment: “That caused a lot of angst between me and my husband. So, I'm trying very hard to keep very calm. But if I, if I'm in too much of a bad mood for him, he'll respond by saying well, do you have to take these medicines? So that it's really hard for both of us.”

Overall, participants understood the importance of ET in reducing the risk of breast cancer recurrence, yet the detriment of side effects to their quality of life caused them to evaluate the overall value of taking the medication. They expressed that ET was different from primary breast cancer treatment, as the intent is preventative rather than curative, and saw the medication as a reminder that they were still being treated for the breast cancer in some way. Overall, they described having a “love-hate” relationship with ET. They experienced cognitive dissonance regarding a desire to move on from breast cancer (seeing the medication as a reminder they were still being treated for the disease in some way) yet felt motivated to continue with ET to reduce the risk of breast cancer recurrence: “This was also my security blanket…But on the other hand, I'm feeling like, you know what, f**k this”.

Theme 2: Sleep impacts everything

Of the challenges described in Theme 1, one of the most significant difficulties faced by participants was living with insomnia. While some felt their sleep problems began at the point of breast cancer diagnosis (or that existing sleep problems worsened at this point), over half (*N*=13) stated that ET specifically had either caused these issues or worsened existing sleep problems. The two subthemes of Theme 2 describe the impact of insomnia on quality of life and the importance of sleep to participants. Insomnia had a profound effect on overall functioning and was associated with the difficulty returning to ‘normality’ after breast cancer treatment. Participants reported feeling they had no choice but to bear the burden of insomnia as no real help was available. They perceived sleep as vital to overall wellbeing and reported numerous benefits of improved sleep.

<u>Subtheme 2.1 Insomnia is detrimental to wellbeing</u>

Several participants stated that insomnia was the most distressing side effect they experienced which created a feeling of general unwellness, placing a significant burden on everyday life. Poor sleep made participants more emotionally sensitive, exacerbating existing anxiety and stress: “If I don't get enough sleep, I'm terrible. I'm really snappy, get really low, my body aches…I can do that for, it feels like for so long and then I just can't cope any

longer…Everything becomes exacerbated, I suppose because your emotions become much more heightened, I suppose, with the lack of sleep… You get that brain fog, you can't process stuff".

Being awake at night left participants' minds free to wander, causing them to ruminate about their stresses and worry about the potential daytime consequences of a poor sleep. Lying in bed unable to sleep perpetuated this anxiety and frustration, which would continue the following day with further anxiety and low mood: "I was...lying there...wide awake...I couldn't get to sleep. And...really wound myself up frustrated then, so that it knocked me out for the day". The numerous effects of poor sleep were summarised by one participant: "Sleep is the most important part of your health, so if you're not sleeping then it affects just about everything else".

Participants reported that living with insomnia was "extremely difficult". Insomnia was a cause of low mood as they felt drained by living with this burden. They reported struggling to get up in time for work, remember appointments, and perform effectively in their work. Poor quality sleep was related to difficulty processing information, and a lack of sleep was related to brain fog which created difficulty concentrating. One participant described this pattern of struggling to get through the day, worrying they were not functioning or performing adequately, as "a hamster wheel. You basically, get up, you go to work, you try and function, and then you try to sleep or not sleep".

A lack of energy (related to insomnia and fatigue) led to reduced interest in social activities, as participants tired easily and struggled to commit to plans: "At one time I would just have stayed in all weekend…I might not have done anything all the previous week because I cancelled everything, all my social engagement." Planning the week around this lack of energy led to using weekends for household chores they did not have energy for during the week, which furthered this social isolation: "I have such a high-pressure job, I probably use up all my energy and focus for that. I'll spend my whole weekend doing my housework, cooking food for the week, so that in the week I don't have to do it because I'm so tired…The sort of main things I would say less, were less socialising."

Reserving all energy for work, to the detriment of other activities, made participants feel dissatisfied with their lifestyle: "I literally was just eat, sleep, work, repeat, eat, sleep work, and I just felt that…You've got to have some sort of social life it can't all be about work." Insomnia also had an impact on relationships, as loved ones observed the difference compared to before

breast cancer treatment and became frustrated by their lack of energy: “There were times where (husband) would say I just wish...you weren't so tired”.

As discussed in Subtheme 1.2., side effects such as insomnia were perceived to prevent participants from recovering fully from breast cancer treatment. Insomnia significantly added to a perception of failure, as participants could no longer fulfil professional or social roles as they did before diagnosis due to lack of energy and related daytime impairment: “I was connecting lack of sleep and feeling tired during the day, not being able to concentrate and this cycle of work, can't concentrate, feeling bad about that… this pattern of everything being suboptimal”.

Insomnia was seen as further impediment to returning to ‘normality’ following cancer treatment. Participants described an expectation that life would resume once they completed primary treatment and described how insomnia was a further impediment to returning to ‘normality’: “I started to get back to the new normal bit more like my old self. But I'd started taking Letrozole, it was this underlying oh, can't just quite get to sleep”. Managing the effects of poor sleep also became more difficult when they resumed their usual responsibilities after finishing hospital-based cancer treatment: “As I, you know, went back to like normal life and went back to work…I found it more difficult to deal with because, you know, when you're off sick, if you don't sleep, it doesn't matter too much because you're, you've got time to catch up during the day, but during, if you're working, that's a lot harder to do.” The completion of ET treatment was expected to bring relief from insomnia symptoms, and a return to normal life overall: “Once it's over, my perception of them [people who complete their ET treatment] is that they go back to being a normal person…You know, sleeping…Doing the things that human beings do.”

Subtheme 2.2 Soldiering on with insomnia

Despite the impact of insomnia on participants’ wellbeing, only half (*N*=11) had sought professional help to improve their sleep. HCPs suggested strategies such as acupuncture, taking a break from ET, or reducing ET dosage to relieve overall side effects, including sleep problems. Two participants reported being prescribed medication such as SSRIs, which helped alleviate hot flashes but did not address insomnia. Two had been prescribed sleeping tablets; one had discontinued these due to experiencing nightmares, and one used these infrequently due to concerns about addiction. None of the participants had ever received CBT-I for their insomnia, although one was offered sleep hygiene advice by their GP. Some reported that when

they did speak to HCPs, they denied that their insomnia could be related to ET or dismissed the importance of the issue: “My GP went well, how do you know it's anything to do with the drug? She says you know, 80% of people come into me have got sleep problems… basically, she told me to go away.”

Participants reported managing their lives around insomnia, employing coping strategies such as planning activities around their energy levels, hesitating to make plans in case they had a particularly bad night’s sleep, and planning days of low activity to ‘catch up’ on sleep. One participant explained “If I wanted to do anything…It had to be at lunchtime, because I could never guarantee I'd be reliably awake for anything”. Another described altering their work situation to navigate days where insomnia particularly affected them: “There was always the agreement if I'd had a really, really bad night, I could start work from home”.

Although some participants sought help for their insomnia, others reported a perception that they simply had to live with this problem: “If I hadn't known about the sleep study… I just would have thought that's just that's just how life is. You know, you're on this medication.” They reported a sense that other people simply dealt with insomnia on their own, and hesitated to discuss their sleep with HCPs, as this was seen as a personal issue. One participant related a lack of support to their decision to participate in the study: “I went on to the link and thought actually you know what, why not give something a go because I don't know where else to turn and I'm just going to just carry on like this”.

A perceived lack of support with insomnia aligned with an overall lack of support with ET side effects. Participants described feeling "lost and vulnerable” during the transition from active breast cancer treatment (which involves various HCPs and routine appointments) to being responsible for their own treatment (ET). As discussed in Theme 1, participants were highly motivated to persevere with ET treatment; they were therefore proactive in seeking management strategies for their side effects. However, prior to the study, several participants had believed sleep was out of their control and could not be improved like other aspects of health: “Sleep doesn't feel like you can control it because you're not conscious. You know what I mean? Whereas food is something literally put in your mouth? And exercise is something that you do.” Despite their best efforts, a lack of effective strategies to improve their sleep and alleviate the overall burden of insomnia was perceived to impact their ability to take their medication and persist with ET treatment.

Theme 3: Two sides of the same coin: sleep affects both forms of nonadherence

Two subthemes describe the perceived relationship between sleep and adherence to ET. Insomnia contributed to both intentional and unintentional nonadherence. This was partly due to difficulties establishing a consistent routine, and partly due to taking matters into their own hands to gain relief from the effects of poor sleep. Conversely, improved sleep led to improved adherence through intentional and unintentional effects.

Subtheme 3.1. Can't or won't? Insomnia affects ability and willingness to consistently take medication

As discussed in Subtheme 1.2, brain fog and memory problems contributed to unintentional nonadherence. Participants felt that insomnia either caused or exacerbated cognitive symptoms, stating that they were more likely to forget medication after a night of poor sleep: "It's the lack of sleep that makes my brain fog worse. So, I just forget", "My brain's just mush…I know now there's like a lot of correlation…A lack of sleep is, it is my trigger". Several participants highlighted that inconsistent sleep made it harder to take medication consistently as falling asleep during the day disrupted their routine, and they struggled to take ET consistently at bedtime as they did not know what time they would feel ready for sleep: "If I make it through to my bed, I'll take it. If I don't make it through to my bed, that's when I'll forget to take it".

Insomnia also influenced participants' decision to intentionally miss doses of ET. Several participants stated that insomnia was the most distressing symptom they experienced, and either attributed this directly to ET, or considered it a secondary result of hot flashes and musculoskeletal pain attributed to the medication. They described taking a short break from ET on particularly bad days when they were "Feeling tired, poor sleep and my joints aching and not being able to concentrate very well". One participant described taking their ET on alternate days only due to their insomnia, and that they worried taking it more often would further harm their sleep. After experiencing improvements in their sleep following CBT-I, they stated they would prefer to take it every single day, but would only be willing to do so once they had solidified a better sleeping pattern long-term: "I'm still not convinced that I'm feeling ready to sleep properly and take a higher dose of Exemestane".

Insomnia also prompted participants to consider their long-term commitment to ET. The effects on wellbeing and relationships prompted participants and their loved ones to consider whether they should complete the full duration of treatment: "There was quite a lot, especially prompted by my husband, of 'are you sure you want to take it for another five years'? Problems …Of

which sleep was one, and then the irritability cause of the not sleeping." During the day, participants were able to distract themselves from their side effects by keeping busy. However, when awake during the night, there were fewer distractions and their mind was free to wander, considering the prospect of living with these side effects for up to a decade: "If you do, waken up…you've got that frustration that you're, you're so uncomfortable that you can't get back to sleep. And you're doing that night in and night out. You're thinking like really, you know, nine years of this…Those hours, the frustration can be, can be overwhelming".

Subtheme 3.2. Better sleep may help with adherence and persistence

Overall, participants felt that they had taken their medication more consistently since receiving CBT-I. They reported their mood had improved, resulting in higher motivation to take their medication. Unintentional nonadherence also reduced, as they reported having a clearer head in the morning, helping them remember to take medication: "My mind's been more alert and…I've actually actively thought without, without seeing the box on the breakfast table… I've got to, you know, take my medication now". Participants also reported taking ET more consistently at night due to establishing a consistent bedtime routine which acted as a "trigger" to take their medication. One participant considered whether their adherence had also improved due to increased awareness as a natural consequence of taking part in the study, rather than specifically due to improved sleep.

Improved sleep also brought about a change in participants' mindset towards their medication. Participants reported being able to think more clearly and feeling they could make better decisions about their medication: "If you don't get sufficient sleep. You can't think rationally, sensibly, normally. And if you've got concerns, fears, paranoia is going to be compounded without a sleep." They felt better able to cope with other side effects, and that the overall burden of ET had been reduced. They reported having more energy, feeling more 'normal'. ET now took up less mental space than before the intervention: "I have this reminder. I take this tablet every day and I have this reminder. But then? It now it feels like a, a sort of five-minute reminder and then I forget about it and get on with my day and I'm not thinking, oh, you know, is this symptom due to it… Or should I even stop taking it all together?". This made them feel hopeful that they could see further improvement in future, and made the prospect of long-term persistence seem more realistic: "I've seen improvements. So that makes me think…I can still improve on this. That makes that part easier, to take the medication. Because you know that even on the medication you can improve your sleep".

Theme 4: CBT-I is good for more than just sleep

Theme 4 includes 2 subthemes which summarise the perceived benefits of the CBT-I intervention. Participants noted not only a marked improvement in their sleep but also improved overall wellbeing and a more positive outlook on long-term ET use. They also enjoyed the practical nature of CBT-I, and felt it addressed an important, often unmet need in patients prescribed ET.

Subtheme 4.1. Everything looks better after a good night's sleep

After receiving a CBT-I intervention, participants reported that the overall quality and their satisfaction with their sleep had improved. They noticed a decrease in nighttime awakenings and felt more refreshed upon waking in the morning. Several noted that they now worried less about their sleep, and that reduced psychological pressure allowed them to fall asleep faster: "When you stop worrying that you're not going to fall asleep…you relax and fall asleep."

Participants also reported additional benefits of improved sleep, which one summarised as "the difference between feeling ill and feeling well". This included increased energy and improved physical and cognitive functioning throughout the day, in addition to improved mood. They also reported physical benefits, as they felt less affected by night sweats, fatigue, musculoskeletal pain, and reported less stiffness upon waking in the morning: "It's a combination of more able to deal with them, but also that I don't have so much irritability cause I'm not sleep deprived and I don't have so much stiffness in the morning… I don't have so many symptoms".

Several participants reported increased energy levels, being able to enjoy a late performance at the theatre and attend exercise classes more regularly due to their newfound energy: "Prior to that, because I was so tired I would cancel quite a lot, and I'd get annoyed with myself…I wouldn't go to the gym. But now…I'm doing absolutely everything…I'm also meeting friends once or twice a week for coffee." Several noted improvements in physical fitness, which were perceived as beneficial to recovery from breast cancer: "I'm exercising now…I never thought that I could get to the point of exercise… That's nice to feel like I'm almost getting back to being a bit more normal than what I was before."

In addition to perceived improvement in physical side effects, participants reported they were less mentally aware of other side effects and felt more resilient in their ability to cope: "If I can get better sleep…It makes me feel better to deal with whatever I've got to deal with during the waking part of the day." Improvement in sleep gave participants hope that they could see further

benefits to their mental health over time, as they reported being better equipped to manage negative thoughts. One participant described feeling that “You can't fix it all at once, and if you can fix your sleep, though, it might influence other things”.

Subtheme 4.2. Benefits of a group-based and therapist-driven intervention

The group format of the CBT-I intervention was received positively by participants, who felt validated by seeing others experiencing similar challenges: “It actually gave you the chance to realise that other people are going through the same thing…It's good to know that you're not on your own cause sometimes you do feel isolated.”. They found the peer support they received “grounding and affirming”, creating a sense of synergy from reflecting on their experiences and comparing sleep diaries with one another.

Participants expressed a preference for receiving direct support through sessions rather than working through materials independently, although they stated they liked having a copy of the materials to look back on. They appreciated the input of the facilitator for support and practical advice: “Things that we spoke about are very common sense and were very basic, but the exchange was good…Perhaps, put the phone to one side. Perhaps work should be done during the day rather than in the evening, just gentle, gentle conversations like that.” Several participants expressed that they had not necessarily learned new information from the CBT-I, but the intervention helped them to put existing knowledge into practice and persevere with active support and guidance from the facilitator: “It hasn't told me anything I didn't already know. But perhaps it's, it's boosted me into taking action on it”.

Subtheme 4.3. CBT-I addresses patient support needs

Participants consistently expressed that there is a lack of support following primary treatment, particularly in managing side effects of ET, stating that any support with side effects could be beneficial to adherence. They desired information about expected side effects and management from reliable sources, including more focus on patient wellbeing and non-pharmacological symptom management options: “I’ve had enough stuff going inside my body. I don’t really want to take something else.” Participants felt validated by the study itself, which was viewed as acknowledgement of the challenges of ET treatment: “I was absolutely delighted…Somebody, somewhere was giving a consideration to, uh, this idea…That people have to take a medication for such a long period of time.”. One participant felt especially validated to learn that others taking ET also experienced insomnia, therefore insomnia did not reflect a personal failing on their part: “The validation that…you know, this definitely could be

affecting your sleep. So that validation made you feel like, okay well, I'm not crazy. This is not just me, and I can't, and I can't function in the world, and I should be able to".

Several participants stated that they had been given information about side effects when they began ET treatment, but information alone was not sufficient without management strategies. One participant explained how this was also driven by a desire to regain control over their own health after the uncertain and intensive nature of primary treatment: "Give me some practical solutions…what can I do to make myself feel better and to help my recovery?", and described a desire among their peers for "Things where they can feel in control…practical solutions that they can put in place and make sense to them". Participants were highly motivated to implement healthy behaviours, having already incorporated exercise and dietary changes since breast cancer treatment to become healthier and possibly reduce the risk of breast cancer recurrence. The strategies involved in CBT-I were therefore highly acceptable, as they valued the simple, practical nature of the advice given. Feeling in control of their own sleep and observing an improvement also gave participants a sense of confidence, stating they now had the tools to improve their own sleep and felt they could manage independently if they experienced insomnia relapse: "I feel like I've regained that control because I've got tools that I can use."

Participants indicated that several components of CBT-I were particularly helpful. This included SRT, SCT (specifically minimising non-sleep activity in bed, and the '15-minute rule'), cognitive therapy (particularly thought blocking), relaxation exercises, and sleep hygiene. They valued using the sleep diaries to observe quantitative changes in their sleep and felt this helped improve understanding of their own sleep. Several participants felt that CBT-I should be offered early in the course of ET treatment, as this could potentially prevent the development of chronic insomnia. They believed that psychoeducation about sleep would be important, as they had assumed their sleep would return to 'normal' following completion of active treatment. Sleep was viewed as a vital component of recovery, equal to diet and exercise, and was identified as necessary to make decisions about their treatment with a clear mind. One participant stated that they had initially hesitated to take ET and would have begun more quickly if they had received this support, as improving their sleep would have helped them to think more clearly about the decision, "I think sleep, it's a very important component of recovery. For restoration and revitalisation purposes, and to be able to think rationally and sensibly about medication, about the course of treatment". Participants described CBT-I as "validating and confidence building", as it appealed directly to their desire to take control over their own health, giving them "a sense of achievement, a sense of agency".

6.3.3. Discussion

Summary of study aims and results

This study qualitatively explored the potential relationship between insomnia and nonadherence to ET. Specifically, the study explored patient perspectives of nonadherence, the perceived importance of sleep, impact of insomnia on their adherence, and the effect of CBT-I on nonadherence. Semi-structured interviews indicated that insomnia severely affected participants' quality of life and contributed to nonadherence in several different ways. Conversely, participants reported improved sleep and adherence following CBT-I, in addition to benefits to other side effects and overall quality of life.

Role of insomnia in nonadherence to Endocrine Therapy

In accordance with previous research (Hwang et al., 2024; Ibrar et al., 2022), participants reported that insomnia had a severe impact on their overall quality of life and contributed to a general feeling of unwellness. Some reported missing doses of ET on days where they felt especially tired and bothered by fatigue and brain fog caused by insomnia, or taking a break to establish better sleep and improve their overall mood. This is supported by previous studies reporting that patients would intentionally miss doses of ET for relief from the overall burden of side effects (Brauer et al., 2016; Harrow et al., 2014; Humphries et al., 2018). However, the current study builds on previous research by providing insight into the specific role of insomnia in intentional nonadherence. Previous research indicates that insomnia is related to higher pain sensitivity in individuals with chronic pain (Selvanathan et al., 2021), and lower perceived resilience to stressors in patients with cancer receiving chemotherapy (Morse, 2024). Although these previous studies did not focus on patients with breast cancer, participants in the current study reported struggling to get through the day following a particularly poor night's sleep. This may explain why participants were more inclined to miss doses of medication when they felt particularly burdened by insomnia, as they were more sensitive and less able to cope with other side effects.

Insomnia was also viewed as a contributor to unintentional nonadherence, as it was related to forgetfulness and a lack of bedtime routine which made it difficult to consistently take medication. This is supported by previous research identifying a significant negative relationship between insomnia and cognitive functioning in patients with breast cancer (Liou et al., 2019), and qualitative studies reporting that a lack of routine and forgetfulness were barriers to ET adherence (Harrow et al., 2014; Humphries et al., 2018). Patients have also stated the importance of establishing a routine to minimise the influence of side effects (such as

memory problems) on their adherence (Ibrar et al., 2022). The current study therefore expands on this previous research by providing insight into the role of insomnia in patients' ability to remember their medication and establish the habit of taking ET.

Impact of CBT-I on intentional and unintentional nonadherence

Participants reported that their adherence to ET had improved since receiving CBT-I. This was partly due to improved sleep (which reduced brain fog and made it easier to remember their medication), and partly due to establishing a consistent bedtime routine (which helped maintain the habit of taking medication at nighttime). As noted in Chapter 4 (Section 4.3.), there is a lack of research into the potential for CBT-I to improve cognitive functioning in patients with breast cancer (Squires et al., 2022). The current study therefore provides some insight into perceived cognitive benefits following CBT-I. The improvement in unintentional nonadherence reported by participants could be interpreted through the perspective of the Health Belief Model (Rosenstock, 1974), as memory problems and lack of routine were identified as barriers to consistent adherence by participants. By improving their ability to remember their medication and promoting a consistent bedtime routine, CBT-I addressed these barriers and facilitated the desired behaviour (improved adherence).

Participants also reported that they had not felt tempted to intentionally miss medication since taking part in the study. Following CBT-I, they reported feeling less bothered by ET side effects, as increased energy and resilience (due to improved sleep) allowed them to feel closer to 'normality' despite taking the medication. As discussed above, insomnia is related to lower perceived resilience to stressors in patients with cancer during chemotherapy treatment (Schimmel et al., 2024), which may explain why improved insomnia increased participants' perceived ability to cope with other side effects. This could be understood by applying the TPB (Ajzen, 1991), as participants viewed ET as less of a burden: this change in attitude towards increased their willingness to take the medication every day. The NCF (Horne & Weinman, 1999) could also be applied here, as alleviating symptom burden altered the perceived balance between advantages and disadvantages of the treatment.

Impact of CBT-I on insomnia and other symptom measures

Participants reported various benefits of improved sleep following CBT-I sessions, including better mood and overall daily functioning as a direct benefit of poor sleep. They also reported improvements in night sweats, fatigue, and musculoskeletal symptoms. Increased energy levels allowed them to undertake enjoyable activities they would normally struggle with, which

facilitated further improvements in mood and overall perceived wellbeing. This is supported by previous research (summarised in chapter 4, Section 4.2.5) which identified significant improvements in insomnia (Ma et al., 2021) and additional transdiagnostic benefits of CBT-I, including depression, fatigue, anxiety, and overall quality of life (Donohoe et al., 2024; Garland et al., 2019; Squires et al., 2022).

Impact of CBT-I sessions on perceptions of persistence with Endocrine Therapy

An unexpected finding of the follow-up interviews was the impact of CBT-I sessions on participants' views of ET persistence. Insomnia was perceived to prevent participants from resuming normal life following breast cancer treatment, due to its impact on quality of life and daily functioning. In accordance with previous research, the cumulative impact of ET side effects (Brauer et al., 2016; Harrow et al., 2014), and specifically insomnia (Ibrar et al., 2022), led patients to question the prospect of taking the treatment long-term. Following the CBT-I intervention, participants felt hopeful that they would see further improvement in their sleep and overall wellbeing in future, reporting increased resilience when managing physical and psychological side effects. This made the prospect of long-term ET persistence feel less daunting, as they felt better equipped to cope with the challenges of this treatment. This aligns with theories of health behaviour including SC Theory (Bandura, 1999) and TPB (Ajzen, 1991), as these results indicate that improved self-efficacy/Perceived Behavioural Control in relation to managing side effects may help participants to continue with treatment for longer. Therefore, these results build upon previous research by providing insight into the specific impact of insomnia and its treatment on patients' views of long-term persistence with ET.

Results of the current study compared to results of the randomised controlled trial

Comparison of the results of the intervention reported in Study 2 and the follow-up interviews reported in Study 3 indicates some inconsistency between the quantitative and qualitative findings. Study 2 did not find a significant effect of CBT-I on intentional nonadherence, whereas participants in the follow-up interviews reported they felt less inclined to deliberately miss doses of their ET medication.

In Study 2, the proportion of intervention participants displaying probable insomnia, depression, and fatigue decreased noticeably after CBT-I (see Figure 7), although a significant effect was only found for depression and musculoskeletal pain. However, interview participants reported improved insomnia symptoms and transdiagnostic benefits including reduced fatigue and improved overall mood. As discussed in Section 6.2.3, Study 2

included a relatively small sample which may have been underpowered to detect significant results, therefore it may not have captured the improvements in intentional nonadherence or insomnia reported by participants.

In Study 3, semi-structured interviews allowed participants to describe the benefits of CBT-I in detail, reflect on improvements in overall quality of life and their perceived ability to cope with ET side effects following CBT-I. As Study 2 measured specific symptoms individually, and did not measure perceived coping with symptoms, this may not have captured the holistic benefits of CBT-I. Data was collected for both studies during a relatively short follow-up period, therefore neither study captures the potential long-term benefits of CBT-I for ET adherence and overall quality of life in this population.

Strengths and limitations of the current study

As discussed in Section 5.2.3., to the best of my knowledge, this is the first evaluation of an intervention targeting a specific side effect to improve ET adherence. This builds upon previous intervention studies finding that participants desired practical guidance on management of side effects including sleep problems (Arch et al., 2022; Jacobs et al., 2020).

The use of semi-structured interviews allowed exploration of themes raised by participants which the researchers had not anticipated, leading to the finding that the various benefits of CBT-I (beyond improved sleep) made participants feel more optimistic about the prospect of long-term ET treatment (however, we were unable to measure the effect of CBT-I on long-term ET use). The interview structure therefore allowed identification of possible long-term benefits beyond the scope of the initial RCT detailed in Study 2, although this could not be measured within the timeframe of the current study.

This study purposefully recruited individuals who reported probable insomnia disorder and whose self-report measures indicated nonadherence to ET, whereas most previous qualitative studies have not focused on nonadherent individuals (Peddie et al., 2022; Ibrar et al., 2022). This allowed exploration of the role of insomnia and effect of CBT-I for people who had struggled with adherence and could potentially benefit from the intervention. Furthermore, as discussed in Chapter 2, previous intervention studies have rarely specified the nature of nonadherence in their outcomes, whereas this study specifically explored the role of sleep and effect of CBT-I on intentional and unintentional nonadherence.

The sample included individuals with a variety of clinical characteristics (ET type, ET treatment duration, and comorbidities), including one individual with secondary breast cancer,

whereas previous intervention studies have often been restricted to those diagnosed with Stage I-III breast cancer (Neven et al., 2014; Wagner et al., 2016; Heisig et al., 2015; Ziller et al., 2013; Graetz et al., 2018). This sample therefore permitted insight into the factors contributing to nonadherence (including insomnia) and the impact of CBT-I in a range of individuals. However, a lack of diversity regarding education level and ethnicity is a limitation of this study. The recruitment strategy may also have led to a sample of participants who are especially motivated to continue with their ET treatment (see Section 6.2.3. for discussion of these limitations).

The dual role of the researcher as therapist and interviewer should also be considered, as this presented both advantages and disadvantages. As the PhD researcher, I undertook data collection and analysis during the RCT, delivered the CBT-I sessions, and conducted the follow-up interviews. I therefore had some prior knowledge of participants before interviews were conducted, which could have influenced my interpretation of the qualitative data. To address this (as detailed in Section 6.3.1.), each transcript was coded independently, and I discussed preliminary themes with 2 MSc students who contributed to data collection to check the validity of the themes. It is possible that having a pre-existing relationship with participants may have helped them to feel comfortable in the interview. The characteristics of the interviewers and participants may also have influenced this dynamic, as all participants and researchers (the attending MSc students and I) are female. It is possible that given the nature of the study (which included discussion of sensitive topics relating to mental and physical health), this could have contributed to their comfort in sharing personal experiences.

It is possible that participants were inclined to provide positive feedback regarding the CBT-I intervention, and potential benefits, because I had also delivered the CBT-I sessions in the previous study. To address this, participants were assured at the beginning of each interview that that there were no ‘wrong’ answers to any of the questions. Reflecting on these interviews, participants appeared to be honest about the challenges of implementing CBT-I, and (in some cases) initial skepticism about the strategies involved. However, I acknowledge that there may have been a perceived power dynamic in these discussions. As discussed in Section 6.3.21., the majority of interviews were led by the attending MSc student. This may have helped to change the dynamic established during the CBT-I sessions (of the researcher as the ‘expert’), to place participants as the expert of their own experience, as the student was learning about the participant’s experiences for the first time.

Reflections on the strengths and limitations of the methods and reporting of this study were informed by the COREQ guidelines (Tong et al., 2007). This discussion considers researcher reflexivity, including characteristics of the interviewer and attending MSc students, and the relationship between the PhD researcher and participants. The study reported the recruitment of participants (including non-participation), identification of data saturation, the process of data analysis (including the number of coders and software used) and derivation of themes. However, some elements of the CORE-Q guidelines were not fully addressed, as a detailed coding tree showing the process of data analysis was not presented, and methodological orientation and theory were not explicitly discussed.

Recommendations for future research

As the current study included participants who may be especially motivated to continue ET, therefore particularly open-minded regarding interventions, future studies should consider how to recruit individuals at particular risk of nonadherence, explore their perspectives of factors which influence their adherence, and the potential role of insomnia. Future research should explore the acceptability and potential benefits of CBT-I to different groups, as the current sample was mostly white and educated to degree level. Future studies should also explore the mechanisms through which CBT-I may influence decision-making regarding ET, such as perceived coping with symptoms, and seek further insight into the possible effect of CBT-I on patient perspectives of long-term persistence.

Chapter 7: Overall thesis discussion

7.1. Summary of studies conducted within this thesis and relation to overall aims

The introductory chapters of this thesis (Chapters 1-2) reviewed existing literature regarding challenges of ET treatment, factors which influence the likelihood of nonadherence to ET, and the impact of specific side effects on adherence. Chapter 1 detailed that ET presents a significant challenge, as many patients struggle to adhere due to side effects. Chapter 2 highlighted that the impact of specific side effects on adherence to ET is not well understood, as (despite an overall side effect profile being a predictor of nonadherence), previous research has not consistently found a relationship between individual side effects and nonadherence. Throughout the literature in this area, adherence is often poorly measured, and few studies have considered the difference between intentional and unintentional nonadherence (Fleming et al., 2022). This means that we lack knowledge of potential side effects which could act as effective targets for intervention to promote treatment adherence and improve quality of life. To date, no study has investigated the effect of an intervention targeting a specific side effect to improve adherence Therefore, aim 1 of this thesis was to investigate the impact of side effects on intentional and unintentional nonadherence to ET, identifying potential targets for intervention to improve adherence.

Study 1 (detailed in Chapter 3) used a cross-sectional survey to explore symptom clusters in patients prescribed ET, and their impact on self-reported adherence. The use of an adherence measure which distinguishes between intentional and unintentional nonadherence allowed investigation of the impact of side effects in more detail than most previous studies, as this measure considers the nature of nonadherence. Although this study only measured solicited side effects (rather than asking participants which side effects they experienced), using cluster analysis allowed exploration of how these side effects presented in the sample without a-priori assumptions. The finding that participants who reported more severe levels of all side effects were more likely to be unintentionally and unintentionally nonadherent indicated that a transdiagnostic side effect target may present the best opportunity to relieve overall side effect burden, promoting ET adherence (Aim 1).

The results of Study 1 showed that, based on the recommended cutoff scores, insomnia was a prevalent, clinically significant side effect in the sample. Insomnia appeared in the overall symptom clusters identified through cluster analysis and was significantly related to severity of all other side effects. Treatment of insomnia using CBT-I is known to have transdiagnostic benefits for patients with breast cancer (Dean et al., 2021; Squires et al., 2022). This presents the main rationale for selecting insomnia as a target side effect to improve ET adherence. This is further outlined and placed in the context of previous research in chapter 4. Chapter 5 provided further context regarding the recommended treatment for insomnia (CBT-I), and the potential for improved sleep to address unintentional and intentional nonadherence to ET. Therefore, Aim 2 of this thesis was to investigate the effect of improved sleep on unintentional and intentional nonadherence to ET.

Study 2 detailed a a pilot RCT of CBT-I to investigate the impact of improved sleep on ET adherence (Aim 2). This allowed investigation of whether participants who received CBT-I demonstrated improved adherence over time, in comparison to those who had not received the intervention. A specific strength of this study was the recruitment of individuals who self-reported as intentionally or unintentionally nonadherent, whereas (as stated in Chapter 6), previous interventions have often included individuals prescribed ET regardless of their level of adherence (Hadji et al., 2013; Neven et al., 2014; Graetz et al., 2018). This allowed the study to investigate the effect of CBT-I in a sample of participants most likely to benefit from an intervention to improve adherence (Aim 2). The results indicated that participants who received CBT-I (compared to the control group) reported a significantly greater improvement in unintentional nonadherence, musculoskeletal pain, and depression than those in the control group. Insomnia was significantly lower in intervention participants throughout the study yet improved significantly over time in both groups. However, the ability to detect a significant interaction between the effects of group and time may have been limited by the relatively small sample size of the study (N=32).

In Study 3, semi-structured interviews were conducted to explore the potential role of insomnia in nonadherence to ET, identify factors which patients felt led to nonadherence, and gain insight into participants' perceptions of how improved sleep may have impacted their adherence (Aim 3). Participants reported that insomnia contributed to unintentional (due to impaired memory and energy levels), and intentional (due to desire to improve functioning and feel more energised) nonadherence. Conversely, they reported that after CBT-I they were less likely to forget to take their ET and felt less inclined to deliberately miss doses due to

perceived improvements in insomnia, fatigue, mood, hot flashes, and musculoskeletal symptoms. The use of a semi-structured topic guide allowed participants to lead the discussion, which led to finding that perceived improvement in insomnia and overall quality of life helped participants to feel more optimistic about the prospect of long-term persistence to ET.

The role of each chapter included in this thesis, aims of each chapter, and a summary of key points/findings are presented in Table 24. In summary, the results of Study 1 led to the identification of insomnia as a prevalent, transdiagnostic side effect which, if targeted, may promote ET adherence. Study 2 provided insight into the possible transdiagnostic benefits of CBT-I and potential to improve nonadherence in patients prescribed ET. This was explored further in Study 3, where participants reported perceived improvements in adherence and several benefits of CBT-I. These results should be considered in context of the limitations of each individual study, which are detailed in their respective chapters. These limitations include recruitment of participants who may be especially motivated to continue ET treatment, lack of diversity in terms of sample demographics, and the relatively small sample included in Study 2.

7.2. Strengths and limitations of this thesis and future directions

The strengths and limitations of the individual studies 1-3 are discussed in detail within their respective chapters. Therefore, this section will focus on the strengths and limitations of the thesis project as a whole. Recommendations for future research will then be presented. Future research should aim to address these wider limitations, also considering the specific limitations of Studies 1-3 (detailed in Chapters 3 and 6).

A significant strength of this thesis is its mixed methods approach, which allowed the overall aims of the thesis to be addressed from different perspectives and provided greater depth of understanding than one method alone could provide. As discussed in Chapter 4, the role of insomnia in nonadherence to ET is not well understood, due to limitations of previous studies, and an overall lack of research investigating insomnia specifically in participants prescribed ET. Study 1 allowed investigation of common side effects in a large sample of patients prescribed ET and could specifically investigate their impact on intentional and unintentional nonadherence due to the self-report measure which was utilised. Subsequent reflection of the results in Chapter 4 identified insomnia as a potential transdiagnostic target. Study 2 allowed investigation of the potential for insomnia to improve adherence using a

pilot RCT. Although the ability to detect significant effects was limited by the relatively small sample size, follow-up interviews (Study 3) explored the potential benefits of CBT-I from participants' perspectives, allowing them to describe in their own words the perceived role of insomnia in nonadherence to ET. This also provided further insight into the results from Study 1, as participants described their experience of the overlap between insomnia and the various side effects they experienced. This provided greater depth of understanding of the possible mechanism by which the symptom clusters identified in Study 1 influenced nonadherence.

Another strength is the consideration of a transdiagnostic target for intervention to improve ET adherence. Chapter 2 outlined that, despite previous research identifying that an overall side effect profile is significantly related to ET nonadherence, studies have not consistently identified an individual side effect which may act as a target to improve adherence (Fleming et al., 2022). As discussed in Chapter 4, side effects in patients with breast cancer rarely occur in isolation (Chow et al., 2019), and a bidirectional relationship between insomnia and other common side effects has been established by previous research (Scheiber et al., 2019). Therefore, it is difficult to disentangle the influence of specific side effects on adherence. Exploration of symptom clusters in Study 1 captured the overlap between common side effects (including insomnia) and used the clusters which emerged to inform identification of a target side effect. The emergence of clusters of overall High and overall Low Symptoms indicated that an overarching target would be most beneficial. This was supported by Study 3, as, in response to being asked about reasons for nonadherence, participants described experiencing a range of side effects which contributed to overall side effect burden (for most, insomnia was the most severe and overarching side effect).

A limitation of this thesis is the lack of measurement of long-term persistence to ET. As discussed in Chapter 2, ET is prescribed for up to a decade. Many patients discontinue treatment early (Moon et al., 2017), which is associated with higher risk of breast recurrence and mortality (Inotai et al., 2021). Study 1 used a cross-sectional design, and Study 2 was restricted to a 13-week follow-up period. Therefore, this thesis was unable to investigate whether insomnia may predict nonadherence long-term, or the potential long-term benefits of CBT-I for adherence.

Recruitment for the studies detailed in this thesis largely relied on circulation of study advertisements by breast cancer charities and organisations. While this method was

successful in recruiting a large sample of participants for Study 1, and meeting the initial recruitment target for Study 2, the individuals recruited were engaged with these groups in some capacity and may be especially motivated to continue with ET. Although this point was raised in discussion of the individual research studies, it may also be considered a limitation of the contribution of the overall thesis to our understanding of nonadherence in this population. However, previous studies of patients prescribed ET have often recruited patients who were near the beginning of ET treatment directly from medical facilities (Hadji et al., 2013; Heisig et al., 2014; Graetz et al., 2018; Neven et al., 2014; Ziller et al., 2013). Therefore, the challenge of identifying specific individuals at risk of nonadherence, or those who have discontinued, is also present within wider research in this area.

Despite the limitations of the research, this thesis suggests that CBT-I could potentially lead to improved ET adherence and indicates possible benefits of CBT-I for overall quality of life in patients prescribed ET. Study 1 identified that 74% of the sample displayed probable insomnia disorder, which supports previous research finding insomnia is highly prevalent in patients with breast cancer (Kwak et al., 2020). Therefore, a large proportion of patients prescribed ET would likely benefit from insomnia treatment. However, CBT-I is often difficult to access, due to a lack of trained providers (Edinger et al., 2021). This is highlighted by the fact that no participant in Study 2 had previously received CBT-I (even among those who had sought help for their sleep). Furthermore, as discussed above, the individuals who participated in these studies were involved in some capacity with breast cancer groups/organisations and initiated their own participation by following the links provided in the study advertisements. Therefore, this thesis was unable to consider the feasibility of delivering CBT-I to a large number of patients prescribed ET, or how patients who are likely to require this treatment could potentially be identified within clinical practice.

Future research should utilise longitudinal designs to investigate the influence of insomnia on long-term persistence to ET. Studies should also investigate the potential for CBT-I to improve adherence in larger samples and incorporate longer follow-up periods to consider potential long-term effects. The feasibility of delivering CBT-I on wider scale should be considered, in addition to potential means of identifying patients who would benefit from CBT-I and are at risk of nonadherence or discontinuation from ET.

Table 24: Thesis chapter aims and key points/findings

Chapter number	Purpose	Aims	Summary/key findings
1	Literature review	Provide context for the reader regarding the role of ET in breast cancer treatment and challenges of ET treatment (including ET side effects).	Approximately 70% of breast cancer cases are treatable with ET, which is effective in reducing the risk of breast cancer recurrence and mortality. However, research indicates patients often struggle to take ET consistently and often do not complete the recommended 10 years of treatment. Side effects are a significant challenge to patients who are prescribed ET and have a detrimental impact on their quality of life. Therefore, these side effects have implications for patients' ability and willingness to adhere to this treatment long-term.
2	Literature review	Introduce the concept of treatment adherence, discuss the impact of nonadherence on breast cancer outcomes and predictors of nonadherence to ET. Identify gaps in our knowledge regarding the role of side effects in nonadherence to ET and limitations of previous interventions aiming to improve adherence to ET.	Nonadherence and non-persistence to ET are significantly related to risk of breast cancer recurrence and mortality. Based on previous research, the most consistent predictor of nonadherence is treatment side effects. The majority of previous interventions aiming to improve adherence have focused on reminders and educational interventions, with little success. To date, no study has evaluated an intervention targeting a specific side effect to improve ET adherence. However, previous research has not consistently identified a specific side effect which predicts nonadherence. This prevents identification of specific side effect targets for intervention to potentially improve ET adherence.
3	Study 1	1) Reliably estimate the rate of ET self-reported nonadherence in a large sample of patients with breast cancer 2) measure	Cross-sectional survey study. Measured self-reported adherence, insomnia, depression, anxiety, fatigue, musculoskeletal, vasomotor, and cognitive symptoms. Explored these symptoms using *K*-means cluster analysis.

		and quantify the scale of ET side-effect burden, and 3) explore the relationship between these side effects and ET nonadherence.	Investigated impact of symptom clusters on adherence using logistic regression. Identified 2 clusters of overall High Symptoms and overall Low Symptoms. Participants in the High Symptoms Cluster were significantly more likely to be intentionally and unintentionally nonadherent (based on MARS cutoff scores). Based on established cutoff scores, insomnia was a highly prevalent and clinically significant symptom in the sample (74% displayed probable insomnia).
4	Literature review and further analysis	Provide a rationale for the selection of insomnia as a target to improve ET adherence, based on results of Study 1 and previous research. Provide context for the reader regarding the aetiology and epidemiology of insomnia disorder among patients with breast cancer.	Insomnia was highly prevalent in the sample of Study 1, and worse insomnia was significantly correlated with severity of all other measured symptoms (this is supported by previous research finding a relationship between insomnia and depression, anxiety, fatigue, musculoskeletal pain, vasomotor symptoms, and cognitive symptoms). Treatment of insomnia is known to have transdiagnostic benefits, therefore insomnia may act as an efficient target with the potential to reduce the overall burden of side effects. Insomnia is highly prevalent among patients with breast cancer, and research indicates that ET may perpetuate insomnia following completion of hospital-based treatment. The development of insomnia in this population can be understood through Spielman's (1987) '3P' model. This model informs the recommended treatment for insomnia, which is CBT-I.

5	Literature review	Provide context for the reader regarding the efficacy of CBT-I, treatment components, and further rationale for the potential for CBT-I to improve ET adherence (based on prevalence of insomnia in the Study 1 sample, and relationship between side effects and nonadherence in Study 1).	CBT-I is considered the gold standard treatment for insomnia. This is a multi-component therapy which includes SRT, SCT, and CT (sleep hygiene and relaxation are often also included). CBT-I could potentially lead to improvements in nonadherence to ET by i) improving cognitive function and ability to remember to take medication (unintentional nonadherence), ii) improving overall quality of life, increasing willingness to take ET (intentional nonadherence).
6	Study 2	Investigate the effect of improved sleep on self-reported intentional and unintentional ET nonadherence.	Pilot RCT of CBT-I. Measured self-reported adherence, insomnia, depression, anxiety, fatigue, musculoskeletal, and vasomotor symptoms. Measures were taken at baseline, post-intervention, and 13-week follow-up. Multilevel modelling used to investigate between group differences, changes over time, and group/time interaction (indicating treatment effect). A significant interaction between the effects of group and time indicated greater improvement in unintentional nonadherence, depression, and musculoskeletal pain in those who received CBT-I compared to control group. Intervention participants reported significantly less severe insomnia and anxiety throughout the study, yet no significant group/time interaction was found.
6	Study 3	1) Identify factors which patients perceive as important to adherence 2) explore the potential role of insomnia in	Semi-structured interviews with participants of RCT after completing CBT-I intervention. Thematic analysis was used to generate themes and subthemes.

	nonadherence, and 3) explore the benefits of CBT-I to patients prescribed ET and potential for treatment of insomnia to improve adherence.	Participants reported that insomnia influenced willingness to take ET through the impact on their quality of life, and their ability to consistently take ET due to impact on memory and cognitive functioning. Following CBT-I intervention, participants felt they were less likely to forget taking ET, less inclined to deliberately miss doses, and more optimistic about the prospect of continuing ET treatment due to perceived overall improved quality of life.

7.3. Personal reflections

The aim of this section is to detail my personal reflections when I look back over the course of this PhD project. Firstly, I am immensely grateful not only to the individuals who took part in each of the studies detailed in this thesis, but also those who expressed interest yet were unable to participate. I was advised by my primary supervisor (Professor Leanne Fleming) before beginning this project that patients with cancer are often highly motivated to participate in research, willingly giving up their own time in pursuit of helping those who will go through the same intensive treatments and experience the same challenges in the future. However, I did not anticipate the level of interest and generosity of those who circulated these studies, reached out to provide feedback on the recruitment materials, and participated despite having their own commitments and busy lives to attend to.

The enthusiasm this research received from this community is partly due to the need for greater support for patients who are prescribed ET, which was highlighted in their responses during follow-up interviews (Study 3). Prior to beginning my PhD, I was aware of the challenges of ET, having worked on previous systematic reviews of the impact of side effects on treatment adherence (Fleming et al., 2022; Peddie et al., 2021). However, I was struck by hearing, in participants' own words, the difficulties they had faced. Following the distressing experience of breast cancer diagnosis and various intensive treatments, these individuals maintain the strength to carry on, to take ET despite its challenges, and actively pursue ways to manage the symptoms they experience (whether these are residual effects of cancer, treatment, or side effects of ET). Participants described how the transition from intensive, hospital-based treatments to taking ET and being discharged back to their GP left them feeling abandoned. Despite their best efforts to navigate the impact of insomnia and other side effects on their daily lives, and attempts to seek help, they did not feel supported or truly listened to.

During follow-up interviews, participants described how taking part in this research validated their experience and allowed them to see they were not alone, as other people had experienced similar challenges. The benefits of CBT-I extended beyond insomnia, as they felt empowered by having the tools to improve their sleep and ultimately their quality of life. I first studied insomnia when I undertook my MSc 6 years ago, therefore I was familiar with the importance of sleep to physical and mental health, and the transdiagnostic benefits of CBT-I (Harvey, 2022; Ramar et al., 2021). However, I did not anticipate how profound the impact of improved sleep would be to these individuals, or how moved I would be by hearing

in their own words how they had benefitted from this intervention. Participants shared stories of how they now had the energy to enjoy themselves, spend quality time with friends and family, and generally felt well again. This strengthened my conviction that insomnia in this population needs to be taken seriously and effectively treated within truly comprehensive, person-centred care. Engaging with these individuals has reinforced that they are resourceful and determined: they understand why they are prescribed this medication, and they will actively take steps to manage their side effects and facilitate their adherence. They are not helpless; however, they do need help, support, and understanding.

7.4. Concluding remarks

In summary, this thesis aimed to use a mixed methods approach to investigate the influence of specific side effects (including insomnia) on nonadherence to ET, the role of insomnia in nonadherence, and the potential for treatment of insomnia to improve nonadherence. Several recommendations have been proposed for future research to build upon this work, considering the wider implications of these findings. Ultimately, this thesis highlights the importance of insomnia treatment for the wellbeing of patients prescribed ET, the potential for CBT-I to promote ET adherence (and by extension, improved breast cancer outcomes), and the need for greater support for patients with breast cancer beyond completion of hospital-based treatment. As one participant aptly summarised,

> “From cancer care, they need to be looking way, way beyond the ‘we saved your life’”.

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Appendices

Appendix 1: Study 2 Consort extension checklist

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	106
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	5
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	106
	2b	Specific objectives or research questions for pilot trial	106
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	106
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	107
Participants	4a	Eligibility criteria for participants	106
	4b	Settings and locations where the data were collected	108

	4c	How participants were identified and consented	107
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	108-109
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	108-109
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	NA
Sample size	7a	Rationale for numbers in the pilot trial	107
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	108
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	108
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	108
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA

Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	106
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	113
	13b	For each group, losses and exclusions after randomisation, together with reasons	113
Recruitment	14a	Dates defining the periods of recruitment and follow-up	107,108
	14b	Why the pilot trial ended or was stopped	107
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	114
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	111
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	122-128
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	112
	19a	If relevant, other important unintended consequences	NA
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	134-136

Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	136
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	133-134
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	135, 137
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	106
Protocol	24	Where the pilot trial protocol can be accessed, if available	106
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	137
	26	Ethical approval or approval by research review committee, confirmed with reference number	108

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

Appendix 2: Study 2 post-hoc power analysis

Table 8: Post-hoc power analysis

	Effect	f^2	Power %
MARS_1	Group	0.001004746	6.04
MARS_1	TimeBL	4.29654E-06	5.00
MARS_1	TimeFU	1.82811E-60	5.00
MARS_1	TimeBL*	0.002214024	7.31
MARS_1	TimeFU*	1.97417E-06	5.00
MARS_intent	Group	4.61954E-09	5.00
MARS_intent	TimeBL	0.000328187	5.34
MARS_intent	TimeFU	0.000209406	5.22
MARS_intent	TimeBL*	6.3763E-07	5.00
MARS_intent	TimeFU*	1.78813E-05	5.02
SCI	Group	0.003202822	8.36
SCI	TimeBL	0.002056453	7.15
SCI	TimeFU	5.76907E-05	5.06
SCI	TimeBL*	0.00048745	5.50
SCI	TimeFU*	0.00037789	5.39
PHQ	Group	0.014117711	20.36
PHQ	TimeBL	5.4496E-09	5.00
PHQ	TimeFU	5.3711E-05	5.06
PHQ	TimeBL*	0.002295227	7.40
PHQ	TimeFU*	0.000235412	5.24
GAD	Group	0.002498914	7.62
GAD	TimeBL	0.000356751	5.37
GAD	TimeFU	1.77206E-06	5.00
GAD	TimeBL*	4.61903E-06	5.00
GAD	TimeFU*	3.59892E-07	5.00
FFS	Group	0.000560029	5.58
FFS	TimeBL	3.26275E-05	5.03
FFS	TimeFU	1.3742E-08	5.00
FFS	TimeBL*	0.000552674	5.57
FFS	TimeFU*	0.000131925	5.14
Musculoskeletal	Group	0.004341527	9.59
Musculoskeletal	TimeBL	2.85051E-06	5.00
Musculoskeletal	TimeFU	3.01587E-08	5.00
Musculoskeletal	TimeBL*	0.001825789	6.90
Musculoskeletal	TimeFU*	9.53103E-06	5.01
Vasomotor	Group	1.81069E-09	5.00
Vasomotor	TimeBL	5.23989E-06	5.01
Vasomotor	TimeFU	0.000290955	5.30
Vasomotor	TimeBL*	1.96605E-05	5.02
Vasomotor	TimeFU*	0.000108176	5.11

TIB	Group	0.008303383	13.91
TIB	TimeBL	1.01186E-05	5.01
TIB	TimeFU	3.6222E-06	5.00
TIB	TimeBL*	0.003411272	8.59
TIB	TimeFU*	0.0004124	5.43
TST	Group	0.000450066	5.47
TST	TimeBL	0.002044209	7.13
TST	TimeFU	7.88273E-06	5.01
TST	TimeBL*	0.002331972	7.44
TST	TimeFU*	0.000361045	5.37
SE	Group	0.000949745	5.99
SE	TimeBL	0.01030364	16.12
SE	TimeFU	1.98074E-10	5.00
SE	TimeBL*	3.77376E-09	5.00
SE	TimeFU*	7.00814E-09	5.00
SOL	Group	0.000284494	5.29
SOL	TimeBL	0.000312453	5.32
SOL	TimeFU	4.67321E-06	5.00
SOL	TimeBL*	6.2405E-06	5.01
SOL	TimeFU*	4.98017E-06	5.01
WASO	Group	0.002029501	7.12
WASO	TimeBL	6.65126E-05	5.07
WASO	TimeFU	0.000787187	5.82
WASO	TimeBL*	0.000151149	5.16
WASO	TimeFU*	6.22925E-05	5.06
No. awakenings	Group	4.74392E-06	5.00
No. awakenings	TimeBL	2.76412E-07	5.00
No. awakenings	TimeFU	6.27883E-06	5.01
No. awakenings	TimeBL*	0.000707089	5.73
No. awakenings	TimeFU*	1.0945E-08	5.00

Appendix 3: Study 2 screening questions

Screening Form Confidential

Name:

_____

Date of birth: _____

How did you hear about the study?

_____

Email:

_____

Before going through the questions, I'd like to confirm that you meet the basic criteria for participants.

Inclusion/exclusion criteria:

Do you have a current prescription for hormone therapy medication?

_____

Please answer the following questions about how you take your hormone therapy medication:

https://hass.eu.qualtrics.com/jfe/form/SV_74LBeVrEE9jQUVE

Do you have difficulty getting to sleep or staying asleep or wake too early and struggle to get back to sleep at least 3 nights per week?

_____

Have you ever received CBT for your sleep before? If so, how long ago was this?

_____

Can you confirm if any of the following apply to you? If so, which?

- Are you currently pregnant or breastfeeding?
- Do you do shift work? (If so, what type of shifts-early, late, nightshift, rotational)
- Have you received any chemotherapy or radiotherapy in the past 4 weeks?
- Is it part of your current treatment plan to receive any chemo or radiotherapy in future?

Medical characteristics

Have you ever received a diagnosis of secondary breast cancer?

(If yes to above) What is the treatment you've been prescribed for this? Has this treatment been prescribed with palliative intent?

_____

What was/were the dates of your diagnosis/diagnoses? Primary_____ Secondary_____

Sleep problems

When did your sleeping problems begin?

_____

Do you think you know the cause(s) of your sleeping problems?

_____

Have you tried anything to help your sleep? If yes, what have you tried before?

_____

Other sleep disorders

Have you ever been officially diagnosed with a sleep disorder? If so, how is this managed? Is it well controlled?

_____

Have you ever received a diagnosis of Obstructive Sleep Apnea? If so, how is this managed? Is it well controlled?

_____

Have you ever received a diagnosis of Restless Leg Syndrome? If so, how is this managed? Is it well controlled?

_____

(*If yes to one of the above*) If your OSA/RLS could be cured, do you think you would still have problems with your sleep?

_____

Other health issues

Except from sleep problems, have you been diagnosed with any other physical or mental health conditions? If so, how are these treated?

_____

Do you drink alcohol? If yes, what do you usually drink? How many of alcoholic drinks would you usually have per day?

Appendix 4: Table 11

Table 11: Tests of difference between groups at baseline

Variable	Test	*t* / U	*df*	*p*
SCI	t-test	1.080	14.44	.298
PHQ	t-test	–1.817	16.61	.087
Musculoskeletal	t-test	–0.453	17.28	.656
Vasomotor	t-test	0.430	21.71	.671
MARS_1	t-test	–0.120	25.46	.905
MARS_intentional	t-test	0.209	16.57	.837
TIB	t-test	–0.292	21.31	.773
TST	t-test	0.974	13.03	.348
SOL	t-test	–0.881	16.64	.391
WASO	t-test	–1.317	17.06	.204
Awakenings	t-test	2.744	28.99	.285
Sleep_efficiency	t-test	1.636	16.48	.121
GAD	Mann-Whitney U	74.5		.106

Appendix 5: Table 14

Table 14: Proportion of sample displaying moderate-severe level symptoms at each timepoint

		Insomnia % (*N*)	Depression % (*N*)	Anxiety % (*N*)	Fatigue % (*N*)
Intervention	Baseline	100 (21)	52.38 (11)	19.10 (4)	61.91 (13)
	5 weeks post-randomisation	42.86 (9)	19.10 (4)	9.52 (2)	28.57 (6)
	13 weeks post-randomisation	23.81 (5)	9.52 (2)	14.29 (3)	4 (19.05)
Control	Baseline	100 (11)	54.55 (6)	45.45 (5)	45.45 (5)
	5 weeks post-randomisation	100 (11)	72.73 (8)	27.27 (3)	45.45 (5)

	13 weeks post-randomisation	90.91 (10)	81.82 (9)	18.18 (2)	45.45 (5)

FFS	Mann-Whitney U	129	.605

Appendix 6: Table 16

Table 16: Multilevel model output for all variables (unadjusted for multiple comparisons)

Variable	Effect	*B*	SE	*t*	*p*	CI
Unintentional nonadherence (MARS item 1)	Group	.57	.33	1.72	.086	-.081-1.22
	Time (baseline-post)	.09	.21	.43	.665	-.32-.50
	Time (post-follow-up)	-2.32	.21	.00	1.00	-.41-.41
	Group*time interaction from baseline-post	-.59	.28	-2.11	.035	-1.15--.04
	Group*time interaction from post-follow-up	-.10	.29	-.036	.722	-.68-.47
Intentional nonadherence (MARS items 2-5)	Group	-.09	1.19	-.08	.0938	-2.42-2.24
	Time (baseline-post)	-1.18	.92	-1.29	.198	-2.98-.062
	Time (post-follow-up)	-.82	.71	-1.15	.25	-2.21-.58

	Group*time interaction from baseline-post	.33	1.23	.27	.789	-2.09-2.75
	Group*time interaction from post-follow-up	.61	.99	.62	.537	-1.33-2.56
Insomnia (SCI)	Group	6.06	2.61	2.32	.022	0.89-11.22
	Time (baseline-post)	-4.46	2.16	-2.07	.039	8.68-.23
	Time (post-follow-up)	-1.55	1.86	.83	.407	-5.20-2.10
	Group*time interaction from baseline-post	-4.45	3.12	-1.43	.155	-10.60-1.70
	Group*time interaction from post-follow-up	3.89	2.92	1.34	.184	-1.87-9.66
Depression (PHQ)	Group	-6.27	1.81	-3.47	<.001	-9.83--2.72
	Time (baseline-post)	-.091	1.12	-.08	.935	-2.28-2.10
	Time (post-follow-up)	.91	1.12	.82	.415	-1.28-3.10
	Group*time interaction from baseline-post	3.44	1.62	2.13	.034	.25-6.62
	Group*time interaction from post-follow-up	-2.06	1.74	1.18	-.238	-5.50-1.38
Anxiety (GAD)	Group	-4.69	2.16	-2.18	.030	-8.93-.45
	Time (baseline-post)	1.73	1.31	1.32	.188	-.85-4.30
	Time (post-follow-up)	.46	1.31	.35	.729	-2.13-3.03

	Group*time interaction from baseline-post	.82	1.87	.44	.66	-2.86-4.51
	Group*time interaction from post-follow-up	.04	1.90	.23	.816	-3.30-4.18
Fatigue (FFS)	Group	-4.17	2.82	-1.48	.141	-9.72-1.39
	Time (baseline-post)	1.27	1.77	.72	.472	-2.20-4.74
	Time (post-follow-up)	.18	1.77	.10	.918	-3.29-3.65
	Group*time interaction from baseline-post	3.88	2.64	-1.47	.143	-1.32-9.08
	Group*time interaction from post-follow-up	-2.71	2.65	-1.02	.308	-7.94-2.52
Musculoskeletal pain (BESS)	Group	-3.12	1.24	2.52	.012	-5.56--.68
	Time (baseline-post)	-.36	.93	-.39	.696	-2.19-1.46
	Time (post-follow-up)	-.09	.73	-.03	.901	-1.52-1.33
	Group*time interaction from baseline-post	2.60	1.30	2.00	.046	.05-5.16
	Group*time interaction from post-follow-up	-.60	.14	-.53	.598	-2.85-1.65
Vasomotor symptoms (BESS)	Group	.09	1.51	-.06	.951	-3.05-2.86
	Time (baseline-post)	.36	.80	.45	.65	-1.21-1.93

	Time (post-follow-up)	1.00	.80	1.25	.211	-.57-2.57
	Group*time interaction from baseline-post	.68	1.08	.63	.527	-1.43-2.80
	Group*time interaction from post-follow-up	-1.19	1.22	-.097	.332	-3.61-1.23
TIB	Group	-88.40	29.50	-2.30	<.003	-146.24-30.56
	Time (baseline-post)	13.70	25.57	.54	.592	-36.41
	Time (post-follow-up)	-8.25	19.92	-.41	.679	-47.31-30.80
	Group*time interaction from baseline-post	76.74	32.51	2.36	.018	13.00-140.49
	Group*time interaction from post-follow-up	35.91	26.92	1.37	.172	-15.68-87.49
TST	Group	-40.66	29.11	-1.40	.163	97.76-16.44
	Time (baseline-post)	-51.66	25.03	-2.06	.020	-100.73-2.58
	Time (post-follow-up)	-9.68	19.23	-.50	.615	-47.39-28.00
	Group*time interaction from baseline-post	32.58	24.68	1.32	.187	15.80-80.96
	Group*time interaction from post-follow-up	32.58	24.68	1.32	.187	15.80-80.96
SOL	Group	-19.26	15.50	-1.24	.214	-49.69-11.17
	Time (baseline-post)	15.95	12.53	1.27	.203	-8.63-40.51

	Time (post-follow-up)	-5.25	11.90	.44	.659	-28.58-18.07
	Group*time interaction from baseline-post	7.61	16.04	.48	.635	-23.87-39.10
	Group*time interaction from post-follow-up	-7.20	16.05	-45	.654	-38.72-24.31
WASO	Group	-28.34	13.76	-2.06	.040	-55.33-1.35
	Time (baseline-post)	5.69	6.61	.86	.390	-7.28-18.66
	Time (post-follow-up)	-10.33	6.41	-1.61	.107	-22.90-2.23
	Group*time interaction from baseline-post	7.55	8.92	1.06	.29	-8.41-27.95
	Group*time interaction from post-follow-up	7.55	8.92	.85	.398	-9.99-25.09
SE	Group	7.89	4.67	1.69	.091	-1.26-17.05
	Time (baseline-post)	-10.89	3.43	-3.18	.001	-17.61-4.18
	Time (post-follow-up)	-.12	3.34	-.036	.972	-6.66-6.42
	Group*time interaction from baseline-post	-.33	4.40	-.07	.941	-8.96-8.30
	Group*time interaction from post-follow-up	-.38	4.36	-.087	.931	-8.93-8.18
No. awakenings	Group	-.26	.60	-.44	.658	-1.43-.91
	Time (baseline-post)	.07	.32	.22	.828	-.56-.70

Time (post-follow-up)	-1.15	.31	-.48	.634	-.75-.46
Group*time interaction from baseline-post	.70	.44	1.57	.118	-.18-1.57
Group*time interaction from post-follow-up	-.04	.45	-.10	.923	-.94-.85

Appendix 7: Semi-structured interview topic guide

- For a bit of context, this is a follow-up to the study you just took part in. We'd like to find out a bit more, in people's own words, what it's like to be on a hormone therapy medication and get a better understanding of that experience. You were included in the first part of the study, and one of the reasons for that was that, like the other people in the study, is you said you were on some sort of hormone therapy medication, and that you'd found it tricky to take it 100% of the time, every single day. Can you tell me a bit about that?
    - Can you tell me a time when you didn't take it, for any reason?
- What has it been like being on HT?
    - What was it like when you started?
    - How do you feel about being on the HT?
    - How has being on HT affected you?
- You've mentioned [...] challenges/things that could be difficult. So why do you take your medication?
    - You've mentioned [...] How do you manage that?
- You've taken part in the study/you've mentioned sleep problems. Can you tell me about when you first weren't happy with your sleep/tell me a bit more about?
    - How does that affect you?
    - What did you think when you saw the study?

- Thinking back to the start, the overall goal of this study was to explore whether improving sleep could help people to take their hormone therapy medication. What are your thoughts on that?

Appendix 8: Table 20

Table 20: Phases of Thematic Analysis

	Phase	Description
1	Preparation of transcripts and familiarisation with the data	Interviews were transcribed verbatim using the Outlook transcription feature. All transcripts were then assessed for accuracy by the attending MSc student. The PhD student and two MSc students independently read and familiarised themselves with the data by reading the transcripts repeatedly, actively searching for patterns, and noting points which may be relevant to the research questions.
2	Generating initial codes	PhD student and 2 MSc students coded each transcript independently and each generated an initial list of codes. This was a partly deductive process driven by the aims of the study, therefore only text which was deemed relevant to the research questions were coded. However, open coding was used (no pre-defined list of codes), and codes were continually assessed and refined throughout analysis. Therefore, coding was an inductive process driven by the data. The 2 MSc students utilised NVivo to code the transcripts, whereas the PhD student used printed copies, manually highlighted interesting pieces of text, and added notes to the transcripts in Microsoft Word to assign relevant codes.
3	Searching for themes	PhD student and 2 MSc students independently grouped related codes together to each construct a set of preliminary themes. The codes within each theme were then evaluated to consider whether certain codes were more strongly related to each other. This allowed identification of potential subthemes. The 2 MSc students arranged codes into themes using Microsoft Word, whereas the PhD student used Microsoft Excel to collate all codes, then printed copies of all codes and manually arranged these to visualise inter-relationships, themes, and subthemes.
4	Reviewing themes	Through discussion, the PhD student compared their initial themes to themes generated by the 2 MSc students to assess validity. The MSc students shared how they had developed their themes, and how they felt their themes addressed the research question. The PhD student then evaluated similarities and differences between the 3 sets of themes, considering which themes were most relevant to the research questions, and whether each theme was sufficient alone or

		would fit better as a subtheme. The PhD student then revisited the transcripts independently to assess whether these themes accurately reflected the data.
5	Defining and naming themes	Following supervisor feedback, the PhD student a generated final list of themes and relevant codes. This involved revisiting the transcripts, assessing whether the themes accurately represented the data and addressed the research questions, and how each theme fit into the overall 'story' of the data. Theme names were chosen by identifying the key message of each theme and generating a name which made this clearly identifiable to the reader.
6	Producing the report	The first stage of writing the report entailed generating a descriptive summary of the codes included in each theme. The PhD student then revisited the transcripts to identify relevant quotations which illustrated the key ideas of this theme. During this process, the PhD student actively reflected on the key argument of each theme in relation to the research question. Based on these reflections, the write-up of each theme was refined to reflect how the data was interpreted in context of the research question, and the relationships between the themes.

Appendix 9: Table 21

Table 21: Demographic and clinical characteristics of interview participants

Characteristic	*N* (%)
Gender	
Female	21 (100)
Age	
Race/ethnicity	
White	20 (95.2)
Asian	1 (4.76)
Nationality	
UK	17 (80.95)
Ireland	1 (4.76)
USA	1 (4.76)
Spain	1 (4.76)
Canada	1 (4.76)
Marital status	
Married	12 (57.14)
Widowed	1 (4.76)
Divorced	2 (9.52)
Separated	2 (9.52)
Never married	4 (19.05)
Employment status	
Full-time	8 (38.10)
Part-time	4 (19.05)
Unemployed seeking work	2 (9.52)
Unemployed not seeking work	1 (4.76)
Retired	5 (23.81)
Missing	1 (4.76)
Education	
High school (4 years)	1 (4.76)
College (HND/HNC)	1 (4.76)
Bachelor's degree	15 (71.43)
Master's degree	3 (14.29))
Doctorate	1 (4.76)
BC stage at diagnosis	
Stage I (A or B)	5 (23.81)
Stage II (A or B)	9 (42.86)
Stage III (A or B or C)	3 (14.29)

Don't know	4 (19.05)
BC grade at diagnosis	
Grade 1	1 (4.76)
Grade 2	9 (42.86)
Grade 3	8 (38.10)
Menopausal status	
Pre-menopause	5 (23.81)
Peri-menopause	4 (19.05)
Post-menopause	12 (57.14)
Comorbidities present	
Musculoskeletal issues (Peripheral neuropathy, pain, arthritis, osteoporosis, osteopenia)	7 (33.33)
Chronic physical health problem (Hypertension, Diabetes/pre-diabetes, high cholesterol, thyroid issue)	3 (14.29)
Chronic Fatigue Syndrome	2 (9.52)
Glaucoma	1 (4.76)
Migraines	1 (4.76)
Lymphedema	1 (4.76)
Liver problems	1 (4.76)
Heart condition	2 (9.52)
Depression	1 (4.76)
Anxiety	1 (4.76)
Treatment-related trauma	1 (4.76)
Chemotherapy	
Yes	7 (33.33)
No	14 (66.66)
Radiotherapy	
Yes	17 (80.95)
No	4 (19.05)
Surgery	
Yes	21 (100)
Endocrine therapy	
Tamoxifen	9 (42.86)
Tamoxifen and OFS	1 (4.76)
AI	8 (38.10)
AI and OFS	2 (9.52)

Unsure/prefer not to say	1 (4.76)

Appendix 10: Table 23

Table 23: Codes used to generate themes and subthemes through thematic analysis

Theme	Subthemes	Relevant codes
Theme 1: nonadherence is complicated	Side effects are a major challenge of Endocrine Therapy	Cognitive side effects debilitating
		Not feeling in control of life due to ET.
		Desire to understand more about specific benefit of ET.
		Frustration at lack of answers to ET questions.
		Awkwardness from visible hot flashes.
		Side effects impact work.
		Unable to do previous hobbies
		Hard to distinguish between ET and residual treatment side effects.
		Difference between preventative ET and drugs for other conditions.
		Outdated advice on symptoms from GP
		Seeking specialist help with symptoms
		Pain makes it hard to move.
		Feeling of rapid ageing.
		Changing work setting due to side effects
		Harder to think under pressure
		Feeling of mentally ageing
		Difficulty with decision making
		Struggling to cope mentally due to cognitive dysfunction
		Frustration with side effects.
		Other people don’t understand what BC treatment is like.
		Work makes side effects worse.
		Poor quality of life.
		Like going through menopause again

	Fatigue means lack of energy for activities
	Embarrassed by memory problems
	Less patience due to side effects
	Side effects put strain on relationships
	Side effects are all linked
	Hard to distinguish ET from natural ageing effects
	Memory problems impact work
	Loss of identity
	Having to change work affects identity
	Anger at loss of identity
	Frustrated by treatment side effects
	Embarrassed by hot flashes
	Intense side effects of OFS
	Changing sleep environment to manage hot flashes
	Hot flashes triggered by everyday interactions
	Desire to avoid 'BC' identity
	ET extends effects of chemo
	Cognitive impact affects daily activities
	Employment endangered by effects of BC
	Family members want to move on from BC
	Taking longer to recover than others expect
	Recovery from BC affects relationships
	Mood swings impact loved ones
	Loss of community when cancer impacts work
	Fatigue makes work difficult.
	Time off work due to mental health.
	Being off work adds to psychological distress.

	Existing anxiety worse than before BC treatment.
	Existing MH problems worse after BC treatment.
	Loss of confidence in oneself since BC
	Side effects impact work
	Reduced self-esteem due to struggling at work
	Perception of failure due to side effects
	Fatigue especially distressing
	Side effects impact quality of life
	Loved ones can add pressure, making side effects harder to cope with
	Family members want to move on from BC
	ET is a reminder of BC
	Desire for BC treatment to be finished
	Feeling unhealthy on ET
	Lack of energy for social activity due to insomnia
	Expectation that you go through treatment then recover fully.
Driven to distraction: unintentional nonadherence	Getting distracted and forgetting
	Brain fog and memory make adherence harder
	Didn't previously take medication often
	Missed doses due to being away from home
	Importance of routine
	Bringing medication when travelling
	Setting a reminder on phone for meds.
	Visual cues to take meds.
	Loss of routine since primary treatment could impact adherence
	Forgetting despite strategies to remember

	Adherence worse when out of routine
	Forgetting due to busy schedule
	Not the same person after BC treatment.
Seeking relief through intentional nonadherence	Desire to feel well again
	Break due to low mood overall.
	Taking a break for a specific amount of time
	Just need a break for relief from side effects sometimes.
	Changing time of ET dose to try and improve side effects
	Intention to gradually take meds more consistently
	Feeling rebellious missing ET
	Missing doses to enjoy certain times more
	Contemplating nonadherence to feel better
	Contemplating discontinuation to feel better
	Tempted to miss doses for partner's benefit
	Break due to side effects
	Better quality of life during a break from ET.
In two minds about Endocrine Therapy	Balance between quality of life and risk of recurrence
	Desire to know exact benefits of ET to risk
	Aware that ET doesn't treat symptoms, it makes them worse
	Decision to adhere is logic vs emotion
	Taking a break until fear of recurrence comes back
	Missing doses accidentally on purpose
	Feeling compelled to keep going with ET.
	Wanting to take ET despite struggling.
	Wanting to continue ET even when on a break.
	Discontinuation would cause guilt
	Nonadherence has less guilt than discontinuation

		Nonadherence gives a sense of control
		Concern about overmedication
		Hard to comprehend being on meds long-term.
		Prospect of living with side effects affects mental health
		Motivated by avoiding recurrence
		Hard to comprehend being on meds for 10 years.
		ET isn't technically needed as treatment
		ET gives a sense of security
		Balance between quality of life and risk of recurrence.
		Planning to miss a dose in advance
		Pretending to consider nonadherence knowing dose will be missed
		Intense primary treatment means dislike of medication
		Love/hate relationship with ET.
Theme 2: Sleep impacts everything	Insomnia is detrimental to wellbeing	Expected sleep to improve after primary treatment Menopause symptoms impact sleep Hot flashes interrupt sleep Days without sleep Lack of sleep makes it hard to function ET made existing sleep problems worse Getting minimal sleep duration Pain interrupts sleep. Sleep began after initiating ET. More sensitive to pain when asleep than when awake. Sleep affects concentration. Insomnia adds to fatigue. Poor sleep makes cognitive functioning worse. Lack of sleep is a trigger. Tiredness exacerbates stress and anxiety Frustrated by sleep problems Insomnia makes you feel generally unwell Insomnia adds to feeling of 'failure' Impact of poor sleep on other symptoms Poor sleep makes cognitive functioning worse

	Cycle of wake, fatigue, sleep.
	Sleep problems worsen quality of life
	Struggling at work due to insomnia.
	Increased need for rest through the day
	Loved ones affected by lack of energy
	Interrupted sleep
	Jet lag having more effect than usual
	Others concerned about lack of energy
	Brain fog due to poor sleep
	Concentration issues
	Short temper from poor sleep
	Loss of interest in activities due to insomnia
	Harder to manage insomnia after going back to work
	Cycle of sleeplessness, rumination and anxiety
	Insomnia affects mood
	Lack of energy for daily activities
	Insomnia makes you feel unwell
	Poor sleep affects mental health
	Withdrawing due to poor sleep
	Sleep affects different aspects of wellbeing
	Sleep has a bigger impact now because of BC
	Completing treatment means sleep returning to normal
	Sleep associated with normality
	Joint pain impacts sleep
	Joint pain interrupts sleep
	Reminders to remember things.
	Forgetting appointments.
	Brain fog from not sleeping
	Short temper due to poor sleep
	Tired easily from activity due to lack of sleep
	Sleep an additional burden
	Struggling to manage on little sleep
	Tiredness exacerbates stress and anxiety
	Sleep problems make low mood worse
	Cycle of wake, fatigue, sleep.
	Sleep problems worsen quality of life
	Lying in bed frustrated by lack of sleep
Soldiering on with insomnia	Napping to recover
	Hoping insomnia will resolve itself

		Questioning whether insomnia is a real problem
		Others just deal with insomnia
		Not talking to anyone about insomnia
		Adapting work arrangements due to insomnia.
		Planning activities around fatigue/sleep.
		Plan in time to catch up on sleep.
		Perception that you have to live with sleep problems
		Early bedtime to extend sleep opportunity
		Never sought help for sleep
		Lack of support for sleep problems
		Sleep is out of our control
Theme 3: Two sides of the same coin: sleep affects both forms of nonadherence	Can't or won't? Insomnia affects ability and willingness to consistently take medication	Insomnia most distressing symptom
		Cumulative impact of sleep and menopausal symptoms
		Break due to tiredness, brain fog
		Break due to poor sleep-needed a 'reboot'.
		Changing time of ET dose to try and improve sleep.
		Sleep side effects make adherence difficult
		Considering discontinuing ET during sleepless nights.
		Unsure whether interrupted sleep can be tolerated for full treatment term.
		No distraction from thinking about discontinuation at night.
		Hesitant to increase adherence in case sleep is damaged
		Intention to adhere more gradually over time
		Cycle of ET affecting sleep, which then impacts adherence
		Falling asleep accidentally disrupts routine for taking meds.
		Bedtime routine is a cue to take meds.
		Forgetting due to poor sleep

		Attributing nonadherence to sleep and brain fog
		Forgetting due to poor sleep
		Lack of routine due to sleeping pattern
		Break from ET due to poor sleep.
	Better sleep helps with adherence and persistence	Hopeful seeing sleep can improve on the medication
		Improving sleep can help with other symptoms
		Can fix one thing at a time, including sleep
		Adherence better since sleep intervention
		Sleep helps decision-making
		Better mood and sleep motivate to continue ET
		Less doubt about ET persistence since improved sleep
		Remembering tablets more since CBTI
		Improved sleep makes long-term ET use seem more realistic
Theme 4: CBT-I is good for more than just sleep	Everything looks better after a good night's sleep	Improved sleep means better memory and functioning
		ET takes up less mental space since improved sleep
		Sleep is a start at improving wellbeing
		Sleep important to wellbeing
		Improved sleep means less cognitive burden
		More energy for activities
		Fatigue improved with better sleep
		Better sleep helps manage negative thoughts.
		Better sleep helps manage through the day better.
		Brain fog improved since CBTI
		Think about other symptoms less since improved sleep
		Hopeful sleep will facilitate better MH.
		Improved sleep improves quality of life
		Feeling healthier since CBT
		Better resilience to cope with other symptoms
		Less stiff in morning since CBT-I
		Improved sleep helps overall wellbeing

	Improved sleep means more energy
	Less anxiety about sleep since intervention
	Taking the pressure off self to sleep
	Night sweats improved
	Improved physical fitness
	Resilience in coping with lack of sleep
Benefits of a CBT-I intervention	Lack of control during primary treatment
	Information alone is not enough
	Desire for practical solutions
	Practical advice gives sense of control
	Improved sleep helps mood
	Function better with better sleep
	Negative experience with sleeping tablets
	Benefit of peers having similar experiences
	Online format widens accessibility
	Sleep scheduling was useful
	Improved quality of sleep
	Less interrupted sleep
	Validation from group dynamic
	Support with sleep early into ET would be beneficial
	Simple, practical instructions easy to remember
	Synergy from group dynamic
	Having tools to continue improving sleep
	Intervention gives a sense of control back
	Group dynamic addresses isolation
	Applied previously existing knowledge about sleep
	Benefit of peer networks

	Sessions hold you accountable
CBT-I addresses patient support needs	Told by HCPs that side effects are unusual
	HCPs dismissive of side effects
	Patients have to actively seek support if needed
	Lack of support after primary treatment
	Desire for validation about side effects.
	Desire for connection with other BC patients.
	Perception there is nothing to help with side effects.
	Desire for support in managing adherence vs side effects
	Desire for non-pharmacological management
	Support with sleep early into ET would be beneficial
	Loss of confidence in oneself since BC
	CBT-I should be offered on initiating ET
	CBT-I builds confidence
	Cancer care should include wellbeing support.
	Feeling of abandonment after primary treatment