

Title: Factors Associated with Intentional and Unintentional Non-adherence to Adjuvant Endocrine Therapy Following Breast Cancer

Brett J, Fenlon D, Boulton M, Hulbert-Williams N, Walker F, Donnelly P, Lavery B, Morgan A, Morris C, Watson E.

Brett J, Senior Research Fellow, Faculty of Health and Life Sciences, Oxford Brookes University, Jack Straws Lane, Marston, Oxford OX3 OFL 01865 482696
jbrett@brookes.ac.uk;

Fenlon D, Associate Professor, Faculty of Health Sciences, University of Southampton 104 Building 67 Highfield Southampton SO17 1BJ. 02380 595515 dfenlon@soton.ac.uk

Boulton M, Professor, Faculty of Health and Life Sciences, Oxford Brookes University, Jack Straws Lane, Marston, Oxford OX3 OFL 01865 485298 mgboulton@brookes.ac.uk

Hulbert-Williams NJ, Professor, Chester Research Unit for the Psychology of Health (CRUPH), Department of Psychology, University of Chester Riverside Campus Castle Drive Chester CH1 1SL 01244 511950 n.hulbertwilliams@chester.ac.uk

Walter FM, Reader, Primary Care Cancer Research, Lucy Cavendish College, Cambridge University Box 113 Cambridge Biomedical Campus Cambridge CB2 0SR 01223 762514 fmw22@medschl.cam.ac.uk

Donnelly P, Breast Care Consultant Surgeon, South Devon Healthcare NHS Foundation Trust, Torbay Hospital, Lowes Bridge, Torquay, Devon, TQ2 7AA 01803 614567 Peter.donnelly@nhs.net

Lavery B, Consultant Oncologist, Cancer Services, Churchill site, Oxford University Hospitals Foundation NHS Trust, Old Road, Headington, Oxford, OX3 7LE 01865 235268 Bernadette.lavery@ouh.nhs.uk

Morgan A, Patient Representative, Independent Cancer Patient Voice 17 Woodbridge Street, London, EC1R 0LL. adrienne@icpv.org.uk

Morris C, Patient Representative, Independent Cancer Patient Voice 17 Woodbridge Street, London, EC1R 0LL. carolynxmorris@gmail.com

Watson E, Professor, Faculty of Health and Life Sciences, Oxford Brookes University Jack Straws Lane, Marston, Oxford OX3 OFL 01865 482665 ewatson@brookes.ac.uk

Abstract:

Adherence to adjuvant endocrine therapy (AET) following breast cancer is known to be sub-optimal despite its known efficacy in reducing recurrence and mortality. This study aims to investigate factors associated with non-adherence and inform the development of interventions to support women and promote adherence. A questionnaire survey to measure level of adherence, side effects experienced, beliefs about medicine, support received and socio-demographic details was sent to 292 women 2-4 years post breast cancer diagnosis. Differences between non-adherers and adherers to AET were explored, and factors associated with intentional and unintentional non-adherence are reported. Approximately one quarter of respondents, 46 (22%), were non-adherers, comprising 29 (14%) intentional non-adherers and 17 (8%) unintentional non-adherers. Factors significantly associated with intentional non-adherence were: the presence of side effects ($p<0.03$), greater concerns about AET ($p<0.001$), and a lower perceived necessity to take AET ($p<0.001$). Half of the sample (105/211) reported that side effects had a moderate or high impact on their quality of life. Factors associated with unintentional non-adherence were: younger age (<65), ($p<0.001$), post-secondary education ($p=0.046$), and paid employment ($p=0.031$). There are distinct differences between intentional non-adherence and unintentional non-adherence. Differentiation between the two types of non-adherence may help tailor support and advice interventions

Key words: Adjuvant endocrine therapy, breast cancer, non-adherence, intentional non-adherence, BMQ, side effects

Background:

In the UK, approximately two thirds of breast cancers diagnosed are oestrogen receptor positive (ER +ve) and for these women use of adjuvant endocrine therapy (AET), such as tamoxifen or an aromatase inhibitor, reduces the risk of breast cancer recurrence and mortality (Davies *et al.* 2013; Hind *et al.* 2007). To gain the potential benefits of AET, women need to adhere to the medication as prescribed, yet studies report sub-optimal adherence, with almost half of all women not completing the currently recommended 5-year course of treatment (Makubate *et al.* 2013; McCowan *et al.* 2008). A systematic review of studies in clinical practice found persistence over 5 years as between 31% and 73% (Murphy *et al.* 2012). Other reviews report that up to 50% of women either do not take the correct dosage at the prescribed frequency or discontinue therapy (Banning 2012; Gotay & Dunn 2011; Hadji 2010; Chlebowski & Geller 2006). Low adherence to adjuvant endocrine therapy is associated with reduced quality-adjusted life years (QALYs), increased medical costs and a 30% increased risk of mortality due to recurrence (Makubate *et al.* 2013; Murphy *et al.* 2012; McCowan *et al.* 2008). It has been calculated that, in the UK setting, encouraging women to take their full course of AET could save 400 to 500 lives every year and bring substantial benefit to health service budgets by potentially freeing up nearly £30 million per year (Makubate *et al.* 2013; Hershman *et al.*, 2011). High adherence to AET would also benefit both patients and health care services internationally (Yang *et al.*, 2010; Delea *et al.*, 2006; Glaziou 1994).

Factors previously associated with low adherence to medication include side effects, anxiety and depression, poor patient- clinician relationships, forgetfulness, medication concerns, limited belief in the efficacy of the medication, and demographic factors (Wickersham *et al.*, 2012; Wouter *et al.*, 2013; Khan *et al.*, 2009; Fink *et al.*, 2004). Horne & Wienman (1999) developed a useful conceptual model for understanding patients' perspectives and beliefs on prescribed medicines (Horne & Weinman 1999). He also distinguished between two broad categories of non-adherers: intentional and unintentional non-adherers. Unintentional non-adherence occurs when a patient finds it difficult to schedule, administer or remember the treatment, or lack capacity to self-manage the medication themselves (Horne *et al.*, 2013). Intentional non-adherence occurs when a patient consciously decides not to follow the recommendations. This is best understood in terms of perceptual factors (e.g. beliefs around the medication and preferences to avoid side effects) influencing motivation to start and continue with treatment (Clifford *et al.*, 2008; Aikens *et al.*, 2005). How patients' beliefs

about medication affect intentional and unintentional adherence has been explored in other disease groups (Molloy 2014; Horne et al, 2013; Clifford et al, 2008).

While previous evidence has reported on factors affecting non-adherence to AET, such as side effects, concerns around toxicity, and psycho-social factors (Cahir 2015, Van Liew 2014, Hadji 2013, Harrow 2013), none have identified the extent to which behaviour is intentionally non-adherent or unintentionally non-adherent. However, characterisation by the different behaviours is important to inform the development of interventions to improve adherence. This study therefore aims to identify factors associated with non-adherence (both intentional and unintentional) to AET to inform interventions to support women, promote adherence and ultimately improve outcomes for women with breast cancer.

Methods

Design

The study is a cross sectional survey of a sub-group of participants in an existing cohort study

Recruitment

Women from the Joint Aches Cohort study (JACS) (Fenlon et al, 2014) were invited to participate. The JACS study was set up in 2010 to explore the onset of joint pain following breast cancer treatment. All patients diagnosed with primary breast cancer within a set time frame were invited at surgery and prior to adjuvant treatment, to participate in a questionnaire study. 543 women took part, representing 57% of the eligible cohort. Of these women 292 had been prescribed AET and were invited to participate in the current study, by a letter from the original study research team (Fenlon et al, 2014). All had previously indicated consent to participate in future research.

Those who wished to take part were asked to complete and return a postal questionnaire which addressed their experiences and beliefs about AET. Postal questionnaires were sent out in July 2014, with a single reminder sent to non-responders after 3 weeks. Ethics approval was gained through Oxford Brookes University, supplementing NRES approval for the original cohort study.

Questionnaire

The questionnaire comprised the following validated measures and additional questions to address areas of interest where no existing measures were available. The final questionnaire took approximately 20 minutes to complete.

The Beliefs about Medicine Questionnaire (BMQ) (Horne & Weinman 1999) assesses individuals' specific beliefs and understanding of the medication they are taking as well as general attitudes to taking medicines (Horne & Weinman 1999). The measure comprises two sections, each divided into two subscales. The BMQ-Specific comprises two five item subscales: the 'Specific Necessity' subscale (i.e. beliefs about the necessity of taking that specific medication to remain healthy) and the 'Specific Concerns' subscale (i.e. concerns about the negative effects of taking that specific medication). The BMQ-General comprises two 4-item subscales: the 'General Harm' subscale which assesses beliefs about medicines as harmful, addictive, poisons which should not be taken continuously and the 'General Overuse' subscale which assesses beliefs that medicines are overused by doctors. For this study the wording of the items in the BMQ-Specific section were modified, as advised by Horne et al (1999), to be more specific to women taking AET after breast cancer and to ensure face validity.

All items of the BMQ are rated on a 5-point likert scale where 1 represents strongly agree, and 5 represents strongly disagree. Scores obtained for the individual items are summed to give a total score for each subscale. A lower score equals a stronger belief. For example, a lower score on the Specific Necessity scale is a stronger belief in the necessity of taking the medication; a lower score on the Specific Concerns scale implies stronger belief of concerns about taking the medication (Horne et al, 2013; Horne et al, 2006). Total scores for the Necessity and Concerns subscales range from 5 to 25 and total scores for the Harm and Overuse subscales range from 4 to 20. The two sections of the BMQ can be used in combination or separately, but are reported separately in this paper. Psychometric evaluation of the BMQ in this population has been tested (Brett J et al, 2016).

The Medical Adherence Report Scale (MARS-5) (Thompson 2000) assesses adherence to treatment. The MARS-5 consists of five general statements about suboptimal adherence behaviour (I forget to take my AET medicine, I alter the dose of my AET medicine, I stop taking my AET medicine for a while, I decide to skip one of my AET tablets, I take AET less than prescribed) answered on a 5 point scale where 1 represents 'always', and 5 represents

‘never’. We included an additional item ‘I don’t order my prescription on time’ as this was raised as an issue by patient representatives in a pre-test of the questionnaire. Items were not summed but used individually in determining types of adherence and non-adherence.

Four additional questions to assess levels of adherence were also included: 1) Are you still taking AET? (Yes, no stopped completely, no stopped temporarily); 2) Have you ever taken a break from AET? (Yes I have taken a break [length of time], Yes I have considered stopping but have not actually done so, No I have never taken a break or considered stopping), 3) In the last week have you taken AET every day? (Yes, no, not sure, not applicable), and 4) How frequently do you take AET? (Daily, Most days, At least three times a week, less than once a month).

MARS and the additional questions were combined to overcome issues of under-reporting of non-adherence (Molloy et al, 2014; Hamilton 2003; Sewitch et al, 2003). Items 1 and 6 of the MARS refer to unintentional non-adherence, and items 2-5 refer to intentional non-adherence (Molloy 2015). Single item questions about adherence have been shown to correlate with the MARS in identifying the nature of adherence (Hamilton 2003).

Using the MARS and the four independent questions about level of adherence, the sample was divided into three groups. Two non-adherer groups (unintentional non-adherers and intentional non-adherers) and adherers:

- Adherers (Still taking AET, never had a break from AET, never considered stopping taking AET, taking AET daily in the last week, score ≥ 4 on all MARS items);
- Intentional non-adherence (have stopped taking AET permanently, have stopped taking AET temporarily, have taken a break from AET, score ≤ 3 on MARS statements ‘I change my dose of my hormone treatment’, ‘I stop taking my hormone treatment for a while’, ‘I decide to skip one of my treatments’, ‘I take the treatment less than prescribed’)
- Unintentional non-adherence (Intending to adhere: Still taking AET, never had a break from AET, never considered stopping taking AET. But not taking as prescribed: not taken daily, score ≤ 3 on MARS statements ‘I forget to take my AET, and I don’t order my prescription on time);

Additional questions were included on side effects experienced and their impact on daily life, and whether AET was discussed at hospital follow-up appointments or with the General Practitioner (GP) in primary care. Demographic data were collected, including age, marital status, employment status, education, and ethnic group.

Statistical Analysis:

Data were analysed using SPSS version 21. Descriptive statistics were performed for the sample as a whole. T-tests were conducted to explore differences between adherers and non-adherers for the BMQ. Factors significantly associated with intentional and unintentional non-adherence were explored using Pearson chi-square test of independence, with $p < 0.05$ as the chosen level of significance, and using adherers as the comparison group. A final logistic regression was performed to identify predictors of non-adherence, comparing all non-adherers vs all adherers.

Results

Two hundred and eleven completed questionnaires were returned, a response rate of 73%. The majority of women (165, 78%) were adherers to AET, although 20 (9%) had contemplated stopping. Approximately one quarter of respondents, 46 (22%), were non-adherers, comprising 29 (14%) intentional non-adherers and 17 (8%) unintentional non-adherers.

Demographic and clinical characteristics of the sample are summarised in Table 1.

Side effects of AET and the impact on adherence

A total of 127 (60%) women reported side effects, with a significantly higher proportion of non-adherers (41/49, 84%) than adherers 86/165 (52%) reporting them ($p < 0.001$). The most common side effects reported were hot flushes, joint ache or pain, weight gain, fatigue and tiredness and depression/low mood. Other side effects reported were vaginal dryness and vaginal discharge, lack of concentration, low esteem and low confidence, and low libido. Of those who reported a side effect, 83% (105/127) stated this had a moderate to high impact on their lives. Table 2 reports the total number reporting side effects, the proportion reporting the most common side effects, and the proportion reporting that these side effects had a moderate to high impact on their lives

A significant association between 'having side effects' and 'intentional non-adherence' was reported ($\chi^2 = 0.178$, 1 df, $p < 0.03$). The relationship was stronger between 'having side effects with moderate to high impact on life' and 'intentional non-adherence' ($\chi^2 = 0.290$, 1 df, $p < 0.01$). No significant association between having side effects and unintentional nonadherence ($\chi^2 = 0.038$ (1 df), $p = 0.962$) was found.

Beliefs about medicine and impact on adherence

Table 3 presents the mean scores for adherers and non-adherers of AET for each of the BMQ Specific Beliefs and Specific Necessity and Concerns subscale items and for the summary scores. Non-adherers had significantly greater concerns and significantly lower belief in the necessity of taking AET for the summary scores and for all individual items, except for one item, 'Hormone treatment is a mystery to me', where both adherers and non-adherers were similarly 'uncertain'.

A significant association was found between intentional non-adherence and both greater concerns about AET (BMQ Concerns) ($\chi^2=0.542$ (1df), $p<0.001$), and lower belief in the necessity to take AET (BMQ Necessity ($\chi^2= 0.443$ (1df), $p<0.001$). No significant associations were found between unintentional non-adherence and concerns about the medication or belief in the necessity to take AET.

General Beliefs of taking medication and impact on adherence

Table 4 presents the mean scores for adherers and non-adherers for each of the BMQ General Harm and BMQ General Overuse subscale items and for the summary scores.

No significant differences between adherers and non-adherers were found for mean BMQ harms scores or mean BMQ overuse scores either for the individual items or the summary scores. No significant association was found between intentional and unintentional non-adherence and the BMQ General Harms or BMQ General Overuse items or summary scores.

Support from health professionals and impact on adherence:

Of those still attending hospital clinic appointments, 51% (92/179) reported AET was always discussed, 34% (60/179) reported AET was sometimes discussed, and 16% (29/179) reported AET was never discussed. 41% (86/210) of the total sample reported having discussed AET with their GP. No significant associations were found between response to ‘discussed at hospital appointments’ or ‘discussed with GP’ and non-adherence.

Demographic factors and adherence

Younger age (<65 years) ($\chi^2= .0.283$ (df 1), $p=0.01$), higher education (completed college education and above) ($\chi^2= .0.140$ (df 1), $p=0.046$), and in paid employment ($\chi^2= .0.174$ (df 1), $p=0.031$) were significantly associated with unintentional non-adherence.

No significant associations between demographic factors and intentional non-adherence were found.

Multivariate analysis of factors predicting non-adherence

Logistic regression was performed to identify predictors of non-adherence to AET. The factors included were: BMQ Necessity (continuous total scores), BMQ Concerns (continuous total scores) BMQ Harm (continuous total scores) and BMQ Overuse (continuous total scores), side effects (yes/no), age (in years), education (post-secondary/secondary or less), and employment status (in paid employment/not in paid employment) (see Table 5).

Only two variables were found to be significant predictors of non-adherence: side effects (OR 4.383 CI 1.601-12.002, $p < 0.04$) and BMQ Concerns (OR: 1.181 CI 1.033-1.350, $p < 0.015$). Eliminating non-significant factors from the model had little effect on the model. The sample size was not large enough to allow separate predictors of intentional and unintentional non-adherence to be calculated

Discussion:

This study explored differences between non-adherers and adherers to AET in women with breast cancer, with regard to medication beliefs, side effects, and support provided, and reports factors associated with intentional and unintentional non-adherence. The strongest predictors of non-adherence in the sample as a whole were the presence of side effects, and having significant concerns about taking AET. Intentional non-adherence was significantly associated with concerns about taking AET, side effects, and lower belief in the necessity of taking AET. Unintentional non-adherence was associated with younger age (<65), in paid employment, and a higher level of education.

AETs are known to have a significant side effect profile which can adversely affect quality of life and have previously been cited as barriers to continuing with treatment (Harrow et al, 2013; Morgan & Fenlon 2013; Fenlon et al, 2009; Cella & Fallowfield 2008). In our study, nearly two thirds of women reported side effects they attributed to AET, with most reporting a moderate to high impact on their daily lives. The association between side effects and intentional non-adherence was calculated using the total number of women reporting any side effects. The relationship with intentional non-adherence was stronger for women whose side effects had a moderate or high impact on their lives. With an increasing number of women surviving breast cancer, and increasing periods of time on AET now being recommended (Gray 2013), there is a pressing need for effective interventions to manage symptoms for this patient group. Side effects can sometimes be managed by switching to another preparation or to another agent, if appropriate to women's menopausal status. Pharmacological treatment

may alleviate the symptoms of AET, including small doses of the selective serotonin reuptake inhibitor (SSRI) anti-depressants, such as venlafaxine and citalopram (Archer et al, 2009), anti-epileptic drugs (gabapentin) (Pandya et al, 2005, and progesterones (Bertelli et al, 2002). Some women may prefer use of complementary therapies, although there is limited evidence of their effectiveness (Chiu et al, 2015).

The influence of concerns with taking AET on non-adherence have also been explored in other studies (Wouter et al, 2013; Grunfeld et al, 2005; Stanton et al, 2014). Alongside the relatively well known side effects that women can experience, such concerns may include fear of long-term risks of taking AET, such as deep venous thrombosis, pulmonary embolism or endometrial cancer from tamoxifen and osteoporotic fracture from AIs. Furthermore, women may be reluctant to take additional ‘toxic’ medication following surgery, chemotherapy and radiotherapy particularly if they lack confidence in the value of the medication.

Factors associated with unintentional non-adherence have not previously been identified in this population. A review of the evidence exploring common factors causing therapeutic non-compliance reported that younger working women are more likely to be poor adherers due to juggling work and family (Jin et al, 2008). This may relate to women in this study too, although further investigation is needed.

The results of this study also support studies that have explored non-adherence to a broad spectrum of medications. A meta-synthesis of qualitative studies looking at adherence to medications in general reported that the main reason people do not adhere is because of concerns about the medicines themselves, such as worries of dependence, tolerance and addiction, the potential harm from taking medicines on a long-term basis and the possibility that medicine masks other symptoms (Pound et al, 2005). Furthermore, a meta-analysis of studies which have used the necessity-concerns framework (Horne et al, 2013) found that higher adherence was associated with fewer concerns about treatment, and stronger perceptions of necessity of treatment.

While results of this study supports previous qualitative studies that have explored themes relating to non-adherence to AET (Wouter et al, 2013, Harrow et al, 2013; Vergbrugge et al, 2015; Cahir et al, 2015; Flanagan et al, 2012; Pellefrini et al, 2010), the study adds to the

literature by dividing non-adherers into intentional and unintentional non-adherence categories, and by identifying the most significant factors associated with these categories. Strategies to improve adherence will have to recognise that implicit unconscious processes (such as unintentional non-adherence) and the more explicit conscious (intentional) processes exist (Strack & Deutsch 2004). It may prove useful for health professionals to distinguish between those who are intentional non-adherers and those who are unintentional non-adherers to tailor support and interventions.

While fostering tailored interventions that address non-adherence to AET are needed, further research is also needed around who is best placed to deliver these interventions. Currently there is no formal monitoring of adherence or standardised protocol for discussing AET, either in hospital or community (Harrow et al 2013). The trend towards shorter hospital follow-up further reduces the availability of hospital specialist advice and support for women, suggesting innovative models of community-based follow-up are required. While ongoing prescriptions for AET are provided by the GP in the UK, only 41% of women in this study had discussed AET with their GP. We know of no interventions designed to help the GP in supporting women taking AET, highlighting the need for research in this area. More recently, the growing role of the community pharmacist has been recognised to alleviate pressure from GPs (NHS 2013). Positive relationships between women taking AET and community pharmacies could aid frequent monitoring, support and feedback, and aid changes in beliefs about the medication. Pharmacy interventions such as electronic prescription service (EPS), online repeat prescriptions and reminders of repeat prescriptions, extended intervals between prescriptions, home delivery and blister packs may help improve adherence in the unintentional adherers (Claxton et al, 2001; Omran et al, 2012).

In the UK, the Cancer Reform Strategy in 2007 and the All Party Parliamentary Group in their report on inequalities in cancer published in December 2009 recognised the importance of follow-up strategies for cancer survivors. The Cancer strategy (2015) recommends more tailored care in this phase as this has the potential to reduce costs through reducing recurrences, better managing side-effects and supporting people to live well (Independent Cancer Force, 2015). Stratified follow-up pathways – which comprise holistic needs assessment, support for patients to self-manage, and remote monitoring could offer a more effective approach to aftercare for this group of women than traditional medical models of follow-up. There is evidence in breast and colorectal cancer that stratified follow-up

pathways deliver improved quality of care. Outpatient follow-up appointments and the Cancer Care Review GPs are recommended to conduct at 6 months post diagnosis represent potential opportunities for assessing concerns about AET and the impact of side-effects as part of follow-up.

Alongside these more practical interventions, novel ways in which health professionals could improve adherence through e-health interventions such as tailoring of messages through smart phones and tablets as a method of developing communication to influence specific health-related behaviours have been suggested (Dayer et al, 2013) [58]. The evidence to date suggests that these tailored health messages can improve medical adherence (Mosa et al, 2012).

Limitations of this study include those common to postal surveys, including the potential for non-response bias and accuracy of self-report. Participants are a self-selected sample, who had previously taken part in the JACS study. Furthermore, the sample size of non-adherers was too small to perform logistic regression separately for the intentional and unintentional non-adherers. However, the strengths include a good response rate providing a sufficient sample size to conduct a range of analyses. Association with co-morbidities was not calculated. Eighty three percent of women reported having ‘other health conditions’, but the data presented a diverse range of ‘other health conditions’ and the severity of these co-morbidities and whether medication was taken for these conditions was not reported. Future studies should explore the impact of co-morbidities and polypharmacy on patients’ lives and the extent to which these groups adhere to AET.

Conclusions:

This study has highlighted factors that influence intentional and unintentional non-adherence in women taking AETs following treatment for breast cancer, and points to the need for interventions to support and monitor these women throughout their five to 10 years of AET. Future development of interventions to improve adherence to medication would benefit from paying particular attention to both intentional and unintentional aspects of non-adherence; interventions both to manage the side effect profile of AET and to modify particular medication-based beliefs seem especially relevant behaviour change strategies for this population. Novel approaches to improve adherence to AET through GP practices,

community pharmacists, or via e-health interventions may be useful. As increasing numbers of women are diagnosed with breast cancer, it is essential we optimise the management of women prescribed AET and find strategies which help women persist with therapy in order to reduce recurrence of disease and mortality.

References:

- Aikens J.E., Nease D.E. Jr., Nau D.P., Klinkman M.S., Schwenk T.L. (2005) Adherence to maintenance-phase antidepressant medication as a function of patient beliefs about medication. *Annals of Family Medicine*. **3**, 23–30.
- Archer D.F., Dupont C.M., Constantine G.D., Dupont C.M., Constantine G.D., Pickar J.H., Olivier S. (2009) Desvenlafaxine for the treatment of vasomotor symptoms associated with menopause: a double-blind, randomized, placebo-controlled trial of efficacy and safety. *Am J Obstet Gynecol*. **200**, 2381
- Banning M. (2012) Adherence to adjuvant therapy in post-menopausal breast cancer patients: a review. *Eur J Cancer Care* **21**: 10-19
- Barron T.I., Connolly R., Bennett K., Feely J., Kennedy M.J. (2007) Early discontinuation of tamoxifen: a lesson for oncologists. *Cancer*. **109**(5), p. 832-839.
- Bertelli G., Venturini M, Del Mastro L., Bergaglio M., Sismondi P., Biglia N., Venturini S., Porcile G., Pronzato P., Costantini M., Rosso R. (2002) "Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study." *Ann Oncol* **13**(6), 883-8.
- Brett J., Hulbert-Williams N Fenlon D, Boulton M, Walter FM, Donnelly P, Lavery B, Morgan A, Morris C, Watson E. (2016) Psychometric properties of a modified Beliefs about Medicine Questionnaire (BMQ) for Women taking Adjuvant Endocrine Therapies (AET) following early-stage breast cancer. Submitted to Health and Psychology
- Cahir C., Dombrowski S.U., Kelly C.M., Kennedy J.M., Bennett K., Sharp L. (2015) Women's experiences of hormonal therapy for breast cancer: exploring influences of medication-taking behaviour, *Journal of Cancer Survivorship* **23**, 3115-3130
- Cella D., Fallowfield L.J. (2008) Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. *Breast Cancer Res Treat*, **107**, 167-180
- Chiu H.Y., Shyu Y.K., Chang P.C., Tsai P.S. (2015) Effects of Acupuncture on Menopause-Related Symptoms in Breast Cancer Survivors: A Meta-analysis of Randomized Controlled Trials *Cancer Nursing* **Jun 3**.
- Chlebowski R.T., Geller M.L. (2006) Adherence to endocrine therapy for breast cancer. *Oncol*. **71**, 1-9
- Claxton A. J., Cramer J., & Pierce C. (2001) A systematic review of the associations between dose regimens and medication compliance. *Clinical Therapeutics* **23**(8), 1296-1310.
- Claxton A.J., Cramer J., Pierce C. (2001) A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. **23**, 1296–1310

Clifford S., Barber N., Horne R. (2008) Understanding different beliefs held by adherers, unintentional nonadherers, and intentional nonadherers: Application of the Necessity-Concerns Framework. *Journal of Psychosomatic Research*. **64**, 41-46

Davies C., Pan H., Godwin J., Gray R., Arriagada R., Raina V., Abraham M., Alencar V.H.M., Badran A., Bonfill X., Bradbury J., Clarke M., Collins R., Davis., Peto R. (2013) Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* **381**:805–16.

Dayer L., Heldenbrand S., Anderson P., Gubbins P.O., Martin B.C. (2013) Smartphone Medication Adherence Apps: Potential benefits to patients and providers. *J Am Pharm*, **53** (2), 172-181

Delea T.E., Karnon J., Smith R.E., Johnston S.R., Brandman J., Sung J.C., Gross P.E. (2006) Cost-effectiveness of extended adjuvant letrozole therapy after 5 years of adjuvant tamoxifen therapy in postmenopausal women with early-stage breast cancer. *Am J Manag Care*. **12**(7), 374-86.

Demissie D., Silliman R.A., Lash T.L. (2001) Adjuvant tamoxifen: predictors of use, side effects and discontinuation in older women. *J Clin Oncol* **19**(2), 322-328

Fenlon D., Powers C., Simmonds P., Clough J., Addington-Hall J. (2014) The JACS prospective cohort study of newly diagnosed women with breast cancer investigating joint and muscle pain, aches, and stiffness: pain and quality of life after primary surgery and before adjuvant treatment. *BMC Cancer*, **14** (1), 467.

Fenlon D.R., Corner J.L., Haviland J. (2009) Menopausal hot flushes after breast cancer. *European Journal Of Cancer Care*, 2009 **18**(2), 140-148.

Fink A.K., Gurwitz J., Rakowski W., Guadagnoli E., Silliman R.A. (2004) Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. *Journal of Clinical Oncology*. **22**(16), 3309-3315

Flanagan J., Winters L.N., Habin K., Cahavelly B. (2012) Women's experiences with anitestrogen therapy to treat breast cancer. *Oncology Nursing Forum* **39**, 70-77
Garreau J.R., DeLaMelena T., Walts D. et al. (2006) Side-effects of aromatase inhibitors versus tamoxifen: the patients' perspective. *Am J Surg* **192**, 496-498

Glasziou P., Haas M. (1994) An Economic Evaluation of the Use of Tamoxifen in the Treatment of Early Breast Cancer. CHERE, University of Technology: Sydney

Gotay C., Dunn J. (2011) Adherence to long-term adjuvant hormonal therapy for breast cancer. *Expert Rev Pharmacoeconomics Outcomes Res*. **11** (6), 709-715.

Gray R. (2013) 10 years of tamoxifen better than 5 in reducing breast cancer recurrence and death. Annual Meeting of the American Society of Clinical Oncology.

Grunfeld E.A., Hunter M.S., Sikka P., Mittal S. (2005) Adherence beliefs among breast cancer patients taking Tamoxifen. *Pat Educ Couns* **59**, 97-102.

Guth U., Myrick M.E., Schotazau A., Kilic N., Schmid S.M. (2011) Drug switch because of treatment-related adverse side-effects in endocrine adjuvant breast cancer therapy: how often and how often does it work? *Breast Cancer Res Treat* **129**, 799-807

Hadji P. (2010) Improving compliance and persistence to adjuvant tamoxifen and aromatase inhibitor therapy. *Critical Rev Oncol/Haematology* **73**, 156-166

Hamilton G.A. Measuring adherence in a hypertension clinical trial. (2003) *Eur J Cardiovasc Nurs.* **2**:219–28.

Harrow A., Dryden R., McCowan C., Radley A., Parsons M., Thompson A.M., Wells M. (2013) A hard pill to swallow: a qualitative study of women's experience of adjuvant endocrine therapy for breast cancer. *BMJ Open*, **4**:e005285 doi:10.1136/

Hershman D., Shao T., Kushi L., Buono D., Tsai W., Fehrenbacher L., Kwan M., Gomez S., Neugut A. (2011) Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Research and Treatment* **126**, 529-537

Hind D., Ward S., De Nigris E., Simpson E., Carrol C., Wyld L. (2007) Hormonal therapies for early breast cancer: systematic review and economic evaluation. NIHR Health Technology Assessment programme: Executive Summaries.

Horne R., Chapman S., Parham R., Freemantle N., Forbes A., Cooper V. (2013) Understanding Patients' Adherence-Related Beliefs about Medicines Prescribed for Long-Term Conditions: A Meta-Analytic Review of the Necessity-Concerns Framework. *Plos. Dec.*

Horne R., Weinman J. (1999) Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res.* **47**(6), 555-67

Horne R., Weinman J., Barber N., Elliott R.A., Morgan M. (2006) Concordance, Adherence and Compliance in Medicine Taking: A conceptual map and research priorities. *National Co-ordinating Centre for NHS Service Delivery and Organisation R&D*, London.

Independent Cancer Force, 2015. Achieving world-class cancer outcomes. A strategy for England 2015-2020 <http://www.cancerresearchuk.org/about-us/cancer-taskforce>

Ingersoll K.S., Cohen J. (2008) The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med.* **31**(3), 213–224

Jin J., Sklar G., Vernon S.O., Chuen Li S. (2008) Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag.* Feb **4**(1), 269–286

- Khan M., Song X., Williams K., Bright K., Sill A., Rakhmaninal N. (2009) Evaluating adherence to medication in children and adolescents with HIV. *Arch Dis Child*, 94:970-973 doi:10.1136/adc.
- Makubate B., Donnan P., Dewar J.A., Thompson A., McCowan C. (2013) Cohort study of adherence to adjuvant endocrine therapy, breast cancer recurrence and mortality. *British Journal of Cancer* **108**, 1515-1524.
- McCowan C., Shearer J., Donnan P., Dewar J.A., Crilly M., Thompson A., Fahey TP. (2008). Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *British Journal of Cancer* **99**, 1763-1768
- McCowan C., Wang S., Thompson A., Makubate B., Petrie D. (2013) The value of high adherence to tamoxifen in women with breast cancer: A community-based cohort study. *British Journal of Cancer* **109**, 1172-1180
- Molloy G.J., Mersserl-Burgy N., Hutton G., Wikman A., Perkins-Porra L., Steptoe A. (2014) Intentional and unintentional non-adherence to medications following an acute coronary syndrome: a longitudinal study. *J Psychosom Res.* **76**(5), 430-2
- Morgan A., Fenlon D.R. (2013) Is it me or is it hot in here? A plea for more research into hot flushes *Clinical Oncology* **25** (11), 681–683
- Mosa A.D.M., Yoo I., Sheets L. (2012) A systematic review of healthcare applications for smartphones. *BMC Medical Informatics and Decision Making*, **12**, 67
- Murphy C., Bartholomew L., Carpentier M., Bluethmann S., Vernon S. (2012) Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: A systematic review. *Breast Cancer Research and Treatment* **134**, 459-478
- NHS Confederation. Health on the high street. Re-thinking the role of the community pharmacist. Report 2013
- Omran D., Guirguis L., Simpson S.H. (2012) Systematic Review of Pharmacist Interventions to Improve Adherence to Oral Antidiabetic Medications in People with Type 2 Diabetes *Canadian Journal of Diabetes* **36** (5), 292-299
- Pandya K.J., Morrow G.R., Roscoe J.A., Hickok J.T. (2005) Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet.* **3366**(9488), 818–824
- Pellegrini I., Sarradon-Eck A., Soussan P.B., Lacour A.C., Largillier R., Tallet A., Tarpin C., Julian-Reyneir C. (2010) Women’s perceptions and experience of adjuvant tamoxifen therapy account for their adherence: breast cancer patients’ point of view. *Psycho-Oncology* **19**, 472-479
- Pound P., Britten N., Morgan M., Yardley L., Pope C., Daker-White G., Campbell R. (2005). Resisting medicines: a synthesis of qualitative studies of medicine taking. *Soc Sci Med* **61**, 133-155.

- Salgado B., Zivian M.T. (2007) Aromatase inhibitors: side effects reported by 622 women. *Breast Cancer Res Treat* **106** (Suppl 1): S168
- Sewitch M.J., Abrahamowicz M., Barkun A., Bitton A., Wild G.E., Cohen A., Dobkin P.L. (2003) Patient nonadherence to medication in inflammatory bowel disease. *The American Journal of Gastroenterology*. **98**, 1535-1544
- Stanton A.L., Petrie A.J., Partridge A.H. (2014) Contributors to non-adherence and non-persistence with endocrine therapy in breast cancer survivors recruited from an online registry. *Breast Cancer Res Treat* **145**, 525-534
- Strack F., Deutsch R. (2004) Reflective and impulsive determinants of social behaviour. *Personality and Social Psychology Review*. **8**, 220-247
- Thompson K., Kulkarni J., Sergejew A.A. (2000) Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophrenia Research*, **42**(3), 241–247
- Vergbrugge M., Verhaeghe S., Decoene E., De Baere S., Vandendorpe B., Van Hecke A. (2015) Factors influencing the process of medication (non-) adherence and (non-) persistence in breast cancer patients with adjuvant antihormonal therapy: a qualitative study. *European Journal of Cancer Care*, online June 2015.
- Wickersham K., Happ M.B., Bender C.M. (2012) “Keeping the Boogie Man Away”: Medication self-management among women receiving anastrozole therapy. *Nursing Research and Practice*, doi:10.1155/2012/462121
- Wouter H., van Geffen E., Baas-Thijssen B., Warmerdam E., Stiggelbout A., Belitser S., Bouvy M.L., van Dijk L. (2013) Disentangling breast cancer patients' perceptions and experiences with regard to endocrine therapy: Nature and relevance for non-adherence. *The Breast*. **22** (5), 661-666
- Yang J.J., Park S.K., Cho L.Y., Han W., Park B., Kim H., Lee K.S., Hahn S.K., Cho S.I., Ahn S.H., Noh D.Y. Cost-effectiveness analysis of 5 years of postoperative adjuvant tamoxifen therapy for Korean women with breast cancer: retrospective cohort study of the Korean breast cancer society database. *Clin Ther*. **32**(6), 1122–1138.
- Ziller V., Kalder M., Albert U.S., Holzhauer W., Ziller M., Wagner U., Hadji P. (2009) Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. *Ann Oncol*. **20** (3), 431-6

