Accepted refereed manuscript of:

Cahir C, Guinan E, Dombrowski SU, Sharp L & Bennett K (2015) Identifying the determinants of adjuvant hormonal therapy medication taking behaviour in women with stages I-III breast cancer: A systematic review and meta-analysis, *Patient Education and Counseling*, 98 (12), pp. 1524-1539.

**Identifying the determinants of adjuvant hormonal therapy medication taking behaviour in women with stage I-III breast cancer: a systematic review and meta-analysis**

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**Running head:** Adjuvant hormonal therapy medication taking behaviour

**Key words:** Breast cancer, hormonal therapy, medication taking behaviour, Theoretical Domains Framework

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**Competing interests:** All authors have nothing to declare.

**Word Count:** 3,997

**Total number of figures:** 2

**Total number of tables:** 4

**Abstract (200 words)**

**Objective**

This systematic review and meta-analysis aimed to identify the modifiable determinants of adjuvant hormonal therapy medication taking behaviour (MTB) in women with stage I-III breast cancer in clinical practice settings.

**Methods**

We searched PubMed, EMBASE, PsycINFO and CINAHL for articles investigating determinants of adjuvant hormonal therapy. Potentially modifiable determinants were identified and mapped to the 14 domains of the Theoretical Domains Framework (TDF), an integrative framework of theories of behavioural change. Meta-analysis was used to calculate pooled odds ratios for selected determinants.

**Results**

Potentially modifiable determinants were identified in 42 studies and mapped to 9 TDF domains. In meta-analysis treatment side-effects (Domain: *Beliefs about Capabilities)* and follow-up care with a general practitioner (vs. oncologist) *(Social Influences)* were significantly negatively associated with persistence (p<0.001) and number of medications *(Behaviour Regulation)* was significantly positively associated with persistence (p<0.003). Studies did not examine several domains (including *Beliefs about Consequences, Intentions, Goals, Social Identity, Emotion* and *Knowledge)* which have been reported to influence MTB in other disease groups.

**Conclusions**

There is some evidence that the domains *Beliefs about Capabilities*, *Behaviour Regulation* and *Social Influences* influence hormonal therapy MTB.

**Practice Implications**

Further research is needed to develop effective interventions to improve hormonal therapy MTB.

**Highlights**

- This review identified modifiable determinants of hormonal therapy medication taking behaviour (MTB)

- Modifiable determinants were mapped to the Theoretical Domains Framework

- *Beliefs about Capabilities, Behaviour Regulation* and *Social Influences* influence MTB

- Several domains reported to influence MTB in other disease group**s** were not examined

## 1. Introduction

Breast cancer survival in women has increased due to improvements in early diagnosis and the use of adjuvant hormonal therapy.(1) Five to ten years of adjuvant hormonal treatment has been shown to reduce the relative breast cancer recurrence risk by up to 50% in women with hormone responsive early breast cancer.(2, 3) Despite the proven clinical efficacy of adjuvant hormonal therapy many women do not take their treatment as prescribed. Medication taking behaviour (MTB) can be defined in terms of two distinct variables; persistence which is continuing the treatment for the prescribed duration of time and adherence which is acting in accordance with the prescribed interval and dosage of the treatment.(4) Non-persistence to hormonal therapy ranges from 13.6% at 1 year to 40.9% at 5 years in routine clinical settings, while adherence ranges from 79.6% at 1 year to 68.3% at 5 years.(5, 6) Non-persistence and non-adherence to hormonal therapy have been associated with increased risks of early breast cancer recurrence and death.(7, 8)

MTB is influenced by a number of factors, including socio-economic factors, medical condition-related factors, therapy and treatment-related factors, health system-related factors and patient-related factors.(9) A systematic review published in 2012 reported that, despite the high prevalence of non-adherence and non-persistence with hormonal therapy, little is known about the factors associated with hormonal therapy MTB in women with breast cancer.(5) In particular, there is a critical need to identify potentially modifiable determinants that influence hormonal therapy MTB in order to develop behavioural interventions to improve it; no previous reviews have focussed on identifying the potentially modifiable determinants.(5) The aims of this systematic review were to; (i) identify the potentially modifiable determinants of adjuvant hormonal therapy MTB in women with stage I-III breast cancer in routine clinical practice settings and; (ii) to map these potentially modifiable

determinants to the Theoretical Domains Framework (TDF). The TDF is an integrative framework of multiple psychological theories of behaviour change designed to assess potential influences on individuals' behaviours and inform intervention design.(10-12) The TDF has been applied in systematic reviews to identify the barriers and facilitators to behaviour change in clinical practice and develop theory-informed behaviour change interventions.(13-15)

## 2. Methods

### 2.1.    *Eligibility, information sources and search strategies*

The study was conducted and reported in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) Statement guidelines.[16] An electronic database search of PubMed (via National Centre for Biotechnology Information), EMBASE (via Elsevier), PsycINFO (via EBSCO) and CINAHL (via EBSCO) was undertaken from database start to 31st March 2014 to identify studies that assessed determinants of adjuvant hormonal therapy MTB in women with stage I-III breast cancer in a clinical practice setting. Studies were considered eligible for review if they were; (i) published in a peer reviewed journal before 31st March 2014; (ii) reported data from a primary study (not a review, editorial or commentary); (iii) included female breast cancer patients who were prescribed adjuvant hormonal therapy; (iv) measured or assessed the determinants of adjuvant hormonal therapy MTB in clinical practice settings and; (v) were observational studies or randomised controlled trials (RCTs). Studies that examined adjuvant hormonal therapy MTB in women with ductal carcinoma in situ (DCIS) or in women with metastatic disease or exclusively after the initial 5 year period or after therapy switches or in clinical trials were excluded.

MTB included persistence, adherence and initiation of adjuvant hormonal therapy. Persistence was defined as continuous use of adjuvant hormonal therapy, with few gaps in treatment or in prescription refills. Adherence was defined as the degree of conformity to the prescribed dosage and daily frequency of the treatment.[4] Initiation was defined as whether or not the patient commenced their adjuvant hormonal therapy the first time it was prescribed.[17] Persistence, adherence and initiation could be measured objectively or through self-report or self-assessment. Determinants included socio-economic factors (e.g. age, education), medical condition factors (e.g. tumour grade), therapy and treatment factors

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(e.g. receipt of chemotherapy), health system factors (e.g. primary provider an oncologist) and patient factors (e.g. beliefs about treatment, doctor-patient communication). Adjuvant hormonal therapy included both selective estrogen-receptor modulators (e.g. tamoxifen) and aromatase inhibitors (e.g. letrozole). MeSH heading and text word searches were conducted as appropriate, with wildcards used to increase sensitivity. The search terms (non) complian*, (non) adherence, persist*, discontinu* were combined with various terms for hormonal therapy (e.g. antineoplastic agents, aromatase inhibitors, tamoxifen) according to the individual database requirements (Supplementary Table 1). The reference lists of eligible studies were scanned for additional studies.

## 2.2.    Study selection

The titles and abstracts of all potentially eligible articles were reviewed independently by two reviewers (CC, EG) to determine their eligibility. Each reviewer coded the abstracts as; (i) eligible; (ii) possibly eligible or; (iii) not eligible. Abstracts considered eligible by both reviewers were included for further review. Abstracts identified as not eligible were excluded. Abstracts considered as possibly eligible by either reviewer, and those considered as eligible by one reviewer only, were discussed until consensus was reached (approximately 3% of all abstracts were discussed).

## 2.3.    Data extraction

The full text articles for abstracts identified as eligible were reviewed independently by the two reviewers (CC, EG). The following data were extracted from each: author, year of publication, country, participant characteristics, eligibility criteria, time period, type of

adjuvant hormonal therapy, measures of MTB and measures of determinants of adjuvant hormonal therapy MTB (Supplementary Table 2).

## 2.4. Quality assessment

The Downs and Black scale was used to critically assess and appraise all eligible studies in a standardised way, including the measurement of MTB, study methodology and statistical analysis. The scale includes questions about: (i) study quality; (ii) external validity; (iii) study bias; (iv) confounding and selection bias; and (v) power of the study.(18) The scale was modified to include items from the International Society of Pharamcoeconomics and Outcomes Research (ISPOR) checklist for studies of medication compliance and persistence that use administrative databases.(19) Each reviewer independently recorded the extent to which the studies adhered to the checklist and any methodological issues that emerged.

## 2.5. Mapping determinants to the TDF

The TDF was developed by Michie *et al.* in 2005 to simplify and integrate a number of behaviour change theories to provide a comprehensive assessment of behavioural determinants to inform systematic intervention design. These authors mapped 128 explanatory constructs from 33 theories and identified 12 discrete domains of behaviour change synthesised into a single framework.(10, 12) The authors identified theories and theoretical constructs related to behaviour change and then grouped these constructs into overarching theoretical domains. Each domain is defined as 'a group of related theoretical constructs'.(10) The TDF has recently been validated and refined to include 14 domains (*Knowledge, Skills, Social and Professional Role and Identity, Beliefs about Capabilities, Optimism, Beliefs about Consequences, Reinforcement, Intention, Goals, Memory, Attention*

*and Decision Processes, Environmental Context and Resources, Social Influences, Emotion and Behaviour Regulation*).(11) In this review, the modifiable determinants of adjuvant hormonal therapy MTB abstracted from the eligible papers were categorised into the 14 domains by one reviewer (CC).(11) The categorisation process was independently reviewed by a second author (SD) with expertise in behavioural change theory. Categorisation was undertaken in a two-stage process. Firstly, if applicable the reported determinants were allocated to the domains suggested in the published frameworks.(10, 11) Secondly, some determinants were interpreted as proxy measures for a particular domain and allocated to that domain e.g. co-morbidities and number of medications were considered to be a proxy for behavioural regulation as managing a medication regime draws on an individuals' regulatory capacity. Studies have shown that patients who are medication naïve have a higher risk of medication discontinuation.(20, 21) Similarly treatment side-effects was allocated to the domain *Beliefs about Capabilities* as patient expectations about their treatment, as well as coping skills and emotional representations of their illness have been found to predict the incidence of treatment side-effects in breast cancer.(22)

Domains with more than two studies examining the association between a particular determinant and MTB, and where the studies were deemed sufficiently homogenous (e.g. similar in design, population, measure of MTB) for combination of results to be meaningful, were identified for potential meta-analysis. For these domains and their determinants, additional data extraction was undertaken independently by two reviewers (CC, KB); data was abstracted on statistical results of measures of association and also the details of any covariates adjusted for in the analysis. Authors of studies were contacted and asked to provide additional data or conduct further analysis where necessary.

## 2.6.    *Data synthesis*

Fixed and random effects models were used to calculate pooled odds ratios (ORs) for the association between the potentially modifiable determinants and the various measures of persistence, adherence and initiation. Tests for heterogeneity were conducted and the $I^2$ statistic was calculated to quantify the degree of heterogeneity between studies.(23) An $I^2$ value of 0% indicates no observed heterogeneity, values between 25%-50% indicate low heterogeneity and values between 50%-75% indicate moderate heterogeneity and values $\geq$ 75% indicate high heterogeneity.(24) Overall estimates of the association between the determinants and MTB are presented in forest plots (Figure 2). All statistical analysis was performed using STATA 11.0 (Stata, College Station, TX).

## 3. Results

### 3.1. Included studies

Database searches identified 767 potentially eligible studies, of which 45 met the inclusion criteria (Figure 1). In total 28 studies considered adherence to adjuvant hormonal therapy, 29 studies considered persistence and 3 studies considered initiation. Nineteen studies measured adherence to adjuvant hormonal therapy in administrative or prescription claims data or hospital/medical databases using a medication possession ratio (MPR) of ≥ 80%.(25-43) The MPR was generally calculated as the sum of the days supplied divided by the individual participant study period with a supply of 80% considered to be adherent.(44) Nine studies measured adherence using self-report measures.(34, 36, 45-51) Two studies used a combination of both the MPR and self-report measures.(34, 36) Two studies measured adherence using a medication event monitoring system (MEMS).(52, 53) Seventeen studies measured persistence using administrative or prescription claims data or hospital/medical databases. Persistence was generally defined as continuous use of adjuvant hormonal therapy with minimum treatment gaps ranging from 45 to 180 days.(26, 29-31, 33, 36, 38, 39, 42, 43, 54-60) Eleven studies measured self-reported (non-)persistence (discontinuing treatment) (47, 49, 61-69) and one study used medical chart review.(70) The three studies of initiation of hormonal therapy were based on self-report.(54, 66, 68)

### 3.2. Quality assessment

The majority of studies used standard methodology (e.g. MPR, treatment gaps, self-report) for measuring adherence, persistence and hormonal therapy initiation. No studies reported how anomalous values of MPR were accounted for in their analysis e.g. MPR > 100% or negative treatment gaps where patients may have been "hyper compliant/adherent" with their

treatment.(19) Studies differed in their choices of measures of determinants and covariates and some studies did not adjust for covariates in their analysis.(37, 46, 59) Some studies used selected patient groups (e.g. ≥70 years) and findings may not be generalisible to the general breast cancer population.(25, 42, 53)

### 3.3.    Mapping determinants to the TDF

The determinants of hormonal therapy MTB studied included socio-demographic, diagnostic, clinical, treatment, health system and psychosocial factors (Supplementary Table 2). Potentially modifiable determinants were identified in 42 of the 45 studies; these mapped to 9 of the possible 14 TDF domains (Table 1). No studies investigated determinants in the domains *Skills, Optimism, Reinforcement, Intentions* and *Goals*. Determinants were most frequently examined in the domains *Social Influences* (26 studies), *Behaviour Regulation* (25 studies)*, Beliefs about Capabilities* (13 studies)*, Emotion* (11 studies) and *Environmental Context and Resources* (11 studies). Fewer studies investigated modifiable determinants within the domains *Beliefs about Consequences* (8 studies)*, Knowledge* (5 studies)*, Memory, Attention and Decision Making* (5 studies) and *Social Identity* (4 studies) (Table 1).

The majority of the modifiable determinants within each domain had inconsistent or mixed associations with hormonal MTB (i.e. they were positively and negatively associated with MTB or unrelated) (Table 1). Only three determinants were identified for further investigation in meta-analysis; treatment side-effects (*Beliefs about Capabilities)*, number of prescriptions- managing medication *(Behaviour Regulation)* and follow-up care- GP vs. oncologist *(Social Influences)*. The studies concerning these three determinants were considered sufficiently homogenous for the combination of results to be meaningful.

### 3.4.    Beliefs about Capabilities- Treatment side-effects

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Ten studies examined the association between treatment side-effects and hormonal therapy MTB (Table 2). Three studies reported a negative association between treatment side-effects and adherence to hormonal therapy (36, 45, 50) and four studies a negative association with persistence with hormonal therapy (61-63, 65, 67). Two studies reported no association between treatment side-effects and hormonal therapy adherence (34, 52) and one study no association with persistence.(64)  Data were pooled for meta-analysis from two adherence studies and two persistence studies (Figure 2).(36, 45, 63, 65) Women who reported side-effects were significantly more likely not to persist with hormonal therapy (OR =5.73, 95% confidence intervals (CI) 3.87, 8.47, p<0.001). They were also less likely to adhere (OR= 1.98, 95% CI 0.56, 0.71) but there was considerable heterogeneity ($I^2$=78.6%) among the studies, with differences in study populations and follow up periods.(Figure 2)

*3.5.    Behaviour regulation- Number of prescription medications*

Thirteen studies examined the association between number of prescription medications and hormonal therapy MTB.(Table 3) Six studies reported no association between number of medications and adherence to hormonal therapy (29, 33, 35, 37, 47, 50) and two studies no association with persistence.(33, 56) Seven studies reported a positive association between number of medications and persistence with hormonal therapy.(29, 42, 43, 60, 61, 64, 68) Data were pooled for meta-analysis from two adherence studies and two persistence studies (Figure 2).(33, 35, 61, 64) Women who were prescribed a greater number of medications were significantly more likely to persist with their hormonal therapy (OR=0.58, 95% CI 0.40, 0.83, p<0.003). They were also less likely to be adherent (OR=0.98, 95% CI 0.96, 1.00) but there was substantial heterogeneity ($I^2$=59.8%) among the studies, with differences in study time periods and types of hormonal therapy (Figure 2).

*3.6.    Social Influences-Follow up care with general practitioner (GP) versus oncologist*

Six studies examined the association between follow-up care and hormonal therapy MTB (Table 4). One study reported a negative association between follow-up care with a GP versus an oncologist and adherence to hormonal therapy (29) and five studies a negative association with persistence with hormonal therapy.(29, 39, 54, 58, 66) One study reported no association between follow-up care and adherence to hormonal therapy.(48) Data were pooled for meta-analysis from three studies which measured the association between follow-up care and persistence with hormonal therapy (Figure 2).(29, 39, 54) Women whose follow-up care was with their GP were significantly more likely not to persist with their hormonal therapy (OR=1.32, 95% CI 1.14, 1.54, p<0.001).

## 4. Discussion and Conclusion

### 4.1. Discussion

This systematic review is the first to examine potentially modifiable determinants of hormonal therapy MTB in women with breast cancer in routine clinical settings. Potentially modifiable determinants were identified in 42 studies and were classified into 9 domains from the TDF but most of these domains and their associated determinants were only examined in one or two studies. There is some evidence that the domains *Beliefs about Capabilities* (side-effects), *Behaviour Regulation* (managing medication) *and Social Influences* (follow-up care) influence adherence and persistence with hormonal therapy. As other previous reviews have noted, the majority of studies to date have examined sociodemographic, clinical or treatment related factors which cannot be modified and which are therefore, of little value in informing the development of interventions to enhance hormonal therapy MTB.(5, 71)

Within the domain *Beliefs about Capabilities* treatment related side-effects were significantly associated with non-persistence in meta-analysis. Studies have shown that side-effects that affect quality of life in breast cancer patients are often not acknowledged or underestimated by clinicians.(72, 73) However studies have not identified whether it is the experience of side-effects per se or a lack of individual coping skills, self-efficacy, clinical support or coordination of care or a combination of these (or other) factors which lead to non-persistence. There is also a lack of evidence on interventions to effectively manage hormonal therapy side-effects in breast cancer patients in clinical practice.(22)

Medication beliefs have also been shown to influence patients' actual experience of treatment side-effects and coping behaviours via negative expectancies, suggesting that interventions to

enhance MTB may need to include both *Beliefs about Capabilities* and *Beliefs about Consequences*.(74) Within the domain *Beliefs about Consequences,* lack of belief in the efficacy of hormonal therapy or lower perceived necessity was identified as potentially associated with hormonal therapy non-adherence and non-persistence.(46, 49, 51, 61, 64) However, the studies used various different measures of beliefs and some did not adjust for covariates.(46, 51, 68) The Health Beliefs Model (HBM) has been applied as a framework to explain MTB across disease groups, with beliefs about disease severity, personal susceptibility to recurrence, efficacy of treatment, self-efficacy, barriers to treatment and cues to action influencing health behaviours.(75, 76) The model has been extended to include the necessity-concerns framework where patients conduct a cost-benefit analysis by weighing up the necessity of their prescribed medication against concerns regarding potential adverse effects; this has been shown to influence adherence across disease groups.(76, 77)  Meta-analyses has been conducted to test the power of the HBM to predict patient adherence and other health behaviours and has found that the relative importance of the components of the model (perceived susceptibility, severity, benefits, costs) vary between studies, but all components are related to better adherence.(76, 78) Patients' beliefs about their breast cancer and the value of their hormonal therapy treatment (e.g. risk, benefits, treatment efficacy) and the  relationships of these beliefs  with hormonal therapy MTB have not yet been established using this model.

In the domain *Behaviour Regulation* a greater number of medications was positively associated with persistence with hormonal therapy in meta-analysis. The number of medications was considered a proxy for medication management as studies have shown that patients who are medication naïve have a higher risk of medication discontinuation.(20, 21) Previous adherence has been reported to be the strongest predictor of future adherence suggesting that  identifying practical barriers to medication taking may improve adherence

and persistence.(79) Non-adherent women may benefit from the provision of aids (pill boxes) and action planning techniques e.g. set up of prompts or cues around the taking of hormonal therapy.(21) To date, few studies have investigated strategies for remembering to take hormonal therapy or the capacity to implement lifestyle modifications.(46, 50) Cognitive deficits also contribute to non-adherence, particularly in older breast cancer patients, suggesting that the domain *Memory, attention and decision-making* should be considered alongside the domain *Behaviour Regulation.*(80) There was mixed evidence that costs were associated with hormonal therapy MTB within the domain *Environmental, Context and Resources* (Table 1).

The domain *Social Influences* identified follow up care with an oncologist (versus GP) to be associated with greater persistent with hormonal therapy in meta-analysis. Cancer patients who develop a strong alliance and trust in their oncologists have been shown to have greater psychosocial well-being and better treatment adherence.(81, 82) Studies of hormonal therapy MTB need to investigate the direct role that the physician-patient relationship has on treatment adherence and breast cancer outcomes. This could be through factors such as communication styles, time spent with patients or emotional and cognitive aspects of care. Good physician-patient communication has been found to be highly positively correlated with treatment adherence across diseases and training physicians to communicate better enhances patients' adherence.(83) Moreover, a linguistic study of oncologist-breast cancer patient communication reported that while discussions about hormonal therapy were generally good they often did not address potential difficulties of remaining adherent with long-term therapy.(84)

Research is also needed on patient-physician collaboration and MTB; only three studies looked at patient participation in hormonal therapy decision making in the domain *Social Identity.*(43, 45, 63) A meta-analysis of 48 studies across chronic and acute conditions found

that greater physician-patient collaboration was significantly associated with better adherence and health outcomes.(85) Improvements in knowledge and understanding can also be achieved through effective patient-physician collaboration and communication.(21) Educational materials have been reported not to improve adherence and persistence with hormonal therapy but it is possible that more "active" rather than passive delivery of information would be effective. Studies on the amount and type of knowledge and patient understanding, as well as how this information is delivered are required within the domain *Knowledge*.(86, 87)

Depression has been suggested to lead to negative attitudes towards breast cancer treatment plans and unwillingness to engage in treatment plans.(88) In the current review, the association was unclear between depression and hormonal therapy MTB (Table 1). Anxiety and distress about medical treatments have been shown to reduce adherence and uptake of healthy behaviours (e.g. clinical breast exams).(21, 89) A recent study has found therapy related negative emotions to be significantly related to hormonal therapy MTB and are potentially modifiable through psychological intervention.(90) The domain *Emotion* and the constructs within it also need to be investigated further alongside the domains *Social Influences, Social Identity* and *Knowledge* with healthcare providers addressing women's apprehensions, uncertainty and reservations about hormonal therapy.

Potential determinants within five of the TDF domains – *Optimism, Skills, Intentions, Goals,* and *Reinforcement* - were not investigated in any studies. There is some evidence that personality related factors such as resilience and self-determination within the domain *Optimism* influence ability to persist with medical treatment.(91) Previous meta-analysis has shown that intentions are one of the most influential determinants of actual behaviour and yet no studies have assessed the influence of the domains *Intentions* and *Goals* or *Reinforcement* on hormonal therapy MTB. Studies have shown patient self-regulation to be associated with

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adherence to health-related behaviours with patients delaying short-term gratification in favour of long-term goals and overcoming numerous barriers and difficulties to achieve their long-term outcomes.(92) Non-adherence to medication has also been related to an inability to self-regulate with factors such as self-efficacy, attitudes and beliefs, perceived control, intentions, goal priority and action plans key determinants of MTB.(93, 94) Acceptability of hormonal therapy and motivation to persist with treatment may be influenced by women's goal priorities or quality of life preferences. Studies are needed to explore determinants within these domains and establish their influence on hormonal therapy MTB.

This review has identified potentially modifiable determinants of adjuvant hormonal therapy MTB in women with breast cancer using the TDF; however it has a number of limitations. There was considerable heterogeneity in studies included in the review, with various measures of MTB and its determinants considered. Only a small number of studies were included in the meta-analyses due to the lack of sufficiently homogenous studies and pooled estimates could be biased. Despite the small number of studies, the results of the meta-analyses point to areas worthy of further exploration.(95)  The majority of studies in this review measured MTB using administrative or prescription claims data and prescription refill data does not establish whether the patient actually takes the medication or not. Studies were also predominantly based on European and American populations with healthcare access and findings may not apply to populations outside of Europe or America or minority or uninsured populations. This review did not include qualitative studies but only one such study using a mixed-methods approach was identified at the study selection process.(50)

4.2.    Conclusion

As more and more patients survive breast cancer, hormonal therapy MTB becomes an increasingly important part of survivorship care in clinical practice.(1)  This is the first

systematic review to investigate potentially modifiable determinants of hormonal therapy MTB. This review has provided some evidence that the domains *Beliefs about Capabilities, Behaviour Regulation* and *Social Influences* influence adherence and persistence with hormonal therapy. However several other domains which have been reported to influence MTB in other disease groups – namely *Beliefs about Consequences, Intentions, Goals, Social Identity, Emotion* and *Knowledge* -have not been investigated in relation to hormonal therapy MTB in breast cancer.(21, 96) Moreover, the relationship between the various domains for MTB is unclear and needs to be tested in future studies.(15)

4.3.    Practice Implications

The application of the TDF in this review permitted a comprehensive and systematic assessment of the evidence on potentially modifiable determinants that influence hormonal therapy MTB. The application of this theoretical framework has highlighted the critical need for further research in particular behavioural domains in order to inform the development of interventions. Fewer than half of published adherence-enhancing interventions have demonstrated improved MTB or enhanced patient outcomes; this is likely to be largely due to the fact that most interventions were developed without a thorough theoretical understanding of the factors that influence the behaviour of interest.(97, 98) A number of effective behaviour change techniques for behavioural interventions have been identified to target particular theoretical domains and these may form the basis for future evidence-based interventions.(99, 100)

Hence, despite a relatively large evidence-base, the reasons why some women do not take their hormonal therapy as prescribed remain largely unclear. More concerted action is needed to identify potentially modifiable determinants of hormonal therapy MTB, to inform the development of effective interventions to promote adherence and persistence to hormonal

therapy; this would have considerable potential to improve clinical outcomes among women

with breast cancer.

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**Table 1: Summary of studies reporting potentially modifiable determinants of hormonal therapy MTB mapped to the TDF**

| TDF Domain | TDF Construct | Determinants | Adherence | Persistence | Initiation |
|---|---|---|---|---|---|
| Knowledge | Knowledge of treatment | Books/information leaflets about treatment | | * | |
| | | Inadequate information about treatment | | - | - |
| | | Discussion with physician about why treatment is needed | * | | |
| | Knowledge of side-effects | Inadequate information on side-effects | | - | |
| Social Identity | Patient role | Perceived self-efficacy in patient-physician interaction (low) | - | | |
| | | Perceived less than adequate role in the decision making about treatment | | - * | |
| | | Decision making about treatment without adequate provider input | | - | |
| | | Multidimensional Health Locus of Control (weaker) | - | | |
| Beliefs about capabilities | Coping with side-effects | Treatment side-effects (general) | --- ** | ---- * | |
| | | Weight concern | - | | |
| | | Menopausal effects (hot flushes) | | ++ | |
| | | Headaches | | - | |
| | | Loss of appetite | | - | |
| | | Nausea (vomiting) | | - | |
| | | Arthralgia (joint pain) | - | - | |
| Beliefs about consequences | Beliefs about treatment | Beliefs about treatment (benefit/drawback ratio) | --- * | --- * | * |
| | | Dislike taking medication | - | | |
| | Outcome expectancies | Belief treatment will prevent breast cancer recurrence | + | | |
| Behaviour regulation | Managing medication | Number of co-morbidities | ++ -- *** | ++++ --- *********** | * |
| | | Number of prescriptions (other medications) | ****** | +++++++ ** | * |
| | | Adding a new prescription (new medications) | | -- | |
| | | Longer prescription refill intervals | + | + | |
| | | Mail order pharmacy use | + | | |
| | Action planning | Strategies employed to remember to take treatment (e.g. dosage box) | + * | | |
| | | Time of day treatment is taken | * | | |
| Memory, attention and decision making | Memory | Forgetting | - | | |
| | | Figural memory (deficits) | * | | |
| | | Verbal memory (deficits) | - | | |
| | | Attention and working memory (deficits) | - * | | |
| | Attention | Cognitive function | * | | |
| | | Cognitive impairment | | ** | |
| Environmental context and resources | Cost | Type of drug programme/insurance | - ** | **** | |
| | | Monthly cost of treatment | | ** | |
| | | High out of pocket costs | -- | -- | |
| | | Low material/financial support | | * | |
| | Health system | Problems receiving prescriptions from physician | * | | |
| Social Influences | Personal support | Married/relationship vs. single/other | +++ - **** | + -- *** | |
| | | Receiving psychological support | | ** | |
| | | Support of friends and relatives | + | | |
| | | Insufficient social support | | --- | |
| | Clinical support | Pharmacy call back (follow up on hormonal therapy use) | | * | |
| | | Received psychological support since diagnosis | | ** | |
| | | Follow up care- general practitioner (GP) vs. oncologist | - * | ----- | - |
| | | Referral/seeing medical oncologist | + | ** | + |

| TDF Domain | TDF Construct | Determinants | Adherence | Persistence | Initiation |
|---|---|---|---|---|---|
| | | One primary physician involved in follow up care | | + | |
| | | Increasing number of oncology visits during treatment | - * | - * | |
| | | Frequency of physician communication (high/regular) | ++ | | |
| | | Poor patient-physician communication | - | ** | |
| | | No opportunity to ask questions | | - * | |
| | Social norms | Previous history of breast cancer | * | | |
| | | History of cancer in family and/or social circle | + *** | * | |
| Emotion | Negative affect | Depression | -- * | + *** | |
| | | Fatigue/inertia | * | | |
| | | Anxiety | * | | |
| | | Psychological distress | | -- | |
| | Fear | Fear of breast cancer recurrence | + | * | + |

Determinants were examined in relation to adherence, non-adherence, persistence, non-persistence, initiation, non-initiation. A determinant positively associated with non-adherence was considered to be negatively associated with adherence.

Each +, -, * represents one study. One study may include multiple determinants.

+ Determinant positively associated with hormonal therapy adherence, persistence or initiation

- Determinant negatively associated with hormonal therapy adherence, persistence or initiation

* Determinant has no association with hormonal therapy adherence, persistence or initiation

**Table 2:  Studies of treatment side-effects and adherence and persistence to adjuvant hormonal therapy among women with breast cancer in clinical practice settings (TDF domain Beliefs about Capabilities)**

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Side-effects | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Liu, 2013 (45) | Prospective cohort | US | 303 women; mean age 51 yrs; 49% less-acculturated Latinas, 41% not completed high school | Aged ≥18 years, newly diagnosed with BC, enrolled in the California Breast and Cervical Cancer Treatment Program (BCCTP) | 36 m | TAM, AI | Self-report | Not measured | Abstracted from patient medical records (multiple side effects classified Yes/No) | AOR = 0.26, 95% CI 0.11, 0.63, p = 0.003 | Age, ethnicity, educational level, marital status, health insurance, financial adequacy, discussion with physicians about why hormonal therapy would be needed,  low patient-doctor communication, low patient perceived self-efficacy in patient-physician interaction,  co-morbidity, tumour stage, treatment received for BC-radiation therapy, chemotherapy, mastectomy |
| Font, 2012 (36) | Cross-sectional | Spain | 692 women; 89% received chemotherapy and/or radiotherapy | Diagnosis of BC stages I-IIIa, HR+, at least one rx for adjuvant endocrine treatment | 5 yrs | TAM, AI | Physician report, self-report,  MPR ≥ 80% drug reimbursement database | ≤ 2 months between rx fills | Abstracted from patient medical records (multiple side-effects classified Yes/No) | Physician adherence report AOR=1.81, 95% CI: 0.81, 4.02  Patient self-report AOR=1.06, 95% CI 0.49, 2.28  Prescription refill AOR=1.25, 95% CI 0.81, 1.93 | Age, tumour stage, surgical treatment, type of surgical treatment (conservative breast surgery), radiotherapy, neoadjuvant chemotherapy, adjuvant chemotherapy, type of hormonal therapy |

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Side-effects | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ziller, 2009 (34) | Retrospective cohort | Germany | 100 women; random sample taken (50 TAM and 50 AI) out of database of 258 patients, mean age 65 yrs (TAM), 71 years (AI), Stage I-III BC | Treated with surgery for BC at author clinic; assigned to adjuvant endocrine therapy; tx started 12-24 months before interview; postmenopausal; | Median time 13.6 m (TAM), 16.6 m (AI) | TAM, AI | MPR ≥ 80% ; self-report | Not measured | Abstracted from patient medical records: sweating, muscular problems, sleep disorders, anxiety, depression, exhaustion, sexual disorders, vaginal dryness, urinary tract problems | Sweating OR=1.71, 95% CI: 0.36, 8.15 Muscular problems OR=0.64, 95% CI: 0.14, 2.86 Sleep disorders OR=0.34, 95% CI: 0.06, 1.80 Anxiety OR=0.38, 95% CI: 0.09, 1.57 Depression OR=1.22, 95% CI: 0.31, 4.89 Exhaustion OR=0.64, 95% CI: 0.14, 2.86 Sexual disorders OR=0.48, 95% CI: 0.12, 1.96 Vaginal dryness OR=1, 95% CI: 0.24, 4.11 Urinary tract problems OR=1.15, 95% CI: 0.37, 6.14 | No adjustment for covariates |
| Wickersham, 2013 (52) | Prospective cohort | US | 198 women, mean age 59 yrs, white (98.3%), educated (mean 15 yrs of schooling) | Aged < 75 yrs, English speaking, minimum 8 years of education, oral HT alone or in combination with chemotherapy | 6 m | TAM,AI | Medication Event Monitoring System (MEMS)- ≥ 80% | Not measured | Breast Cancer Prevention Trial (BCPT) Symptom Checklist | Correlation, r = 0.15 between BCPT overall score and adherence (p ≤ 0.20) Subscale weight concern scores (b=0.209 SE=0.039 p = .003) in multiple regression model. No association reported for other subscales or BCPT overall score. | Study membership, employment status, primary occupation (homemaker and related categories vs. other), DCIS tumour type, and menopausal status. |
| Simon, 2014 (50) | Prospective cohort | Canada | 161women; mean age 56.6 | One clinic, ER+ BC | 6 m | TAM,AI | Self-report- 80% adherence, 100% adherence | Not measured | Patient self-report | Qualitative analysis- side-effects reported to be related to non-adherence (N=7) | Not applicable |

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Side-effects | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lash, 2006 (61) | Prospective cohort | US | 462 women; 58% aged 70-79 yrs; 87% ER+ tumours | Diagnosed with stage I-IIIA BC; age ≥ 65 yrs; ER+/indeterminate tumours; initiated TAM | 63 m | TAM | Not measured | Self-report continuing with treatment at each interview 3, 6, 15, 27, 39, 51, and 63 months | Patient self-report: number of TAM side-effects at baseline (≥1) and follow up 3, 6, 15, 27, 39, 51, and 63 months | Initial severe side effects: HR per side effect=1.2, 95% CI 0.97, 1.5  Developed new side-effects: HR per new side effect=1.3, 95% CI 1.0, 1.6. | Age, enrolment site, estrogen receptor status, number of prescription medications taken, patients' decisional balance scores |
| Kahn, 2007 (63) | Cross-sectional | US | 881; 85% white, one third ≥ 65 yrs, 92% ER/PR+ tumour | Diagnosed with stage I-III BC, registered by ACoS hospital cancer registry; initiated TAM; age 21-80 yrs at dx | 4 yrs post dx | TAM | Not measured | Self-report continuing with treatment (no time gaps specified) | Patient self-report - classified as severe, moderate, mild or none | Severe side-effects AOR=5.95 95% CI 3.95, 8.99 | Age, ethnicity, insurance, HR status, stage at diagnosis, lymph node involvement, BMI, comorbidity, surgery, chemotherapy, radiation |
| Demissie, 2001(65) | Prospective cohort | US | 303 women; mean age 67.7 yrs, 50% married, 83% high school education | Aged ≥ 55 yrs, newly diagnosed with stage I-III BC, no history of prior BC | 33 m | TAM | Not measured | Self-report continuing with treatment at 21 months | Patient self-report. Two dichotomous variables (Yes/No); hot flashes alone and any side effects, including hot flashes. | Any side-effects AOR=4 95% CI 1.1-13.9 | Age, standard primary therapy, ER status , treatment decision making (sources of helpful information about BC and its treatment) |
| Guth, 2011(67) | Retrospective cohort | Switzerland | 427 women, mean age 65.9 , majority stage I-II | Diagnosed with non-metastatic BC, treated with surgery at author institution, ER/PR+ tumours, postmenopausal | Median follow up 16.5 m | TAM, AI | Not measured | Self-report continuing with treatment | Patient self-report | 37 non-persistent and 24 (64.9%) due to side-effects | No adjustment for covariates |

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Side-effects | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bowles, 2012 (62) | Cross-sectional | US | 538, mean age 64 yrs; 90% white; postmenopausal | Diagnosed with BC, received at least one TAM, AI rx within 12 m after dx, postmenopausal | 3 m | TAM, AI | Not measured | Self-report continuing with treatment for 5 yrs. Validated against pharmacy data. | Patient self-report | Headaches: AIs: AOR = 4.16; 95% CI, 2.16, 8.01 TAM: AOR =2.34; 95% CI, 1.24, 4.41. Loss of appetite, upset stomach, or vomiting TAM: AOR 2.45; 95% CI, 1.14, 5.28. Hormone or menopause-related adverse effects AIs: AOR 0.35; 95% CI,0.18, 0.70 TAM: AOR 0.45, 95% CI, 0.24, 0.83. | Age, year of diagnosis |
| Fink, 2004 (64) | Prospective cohort | US | 516; majority aged ≥ 70 yrs, high school graduates | Diagnosed with stage I-IIIA BC, no prior history of BC; age ≥ 65 yrs; ER+ tumours; prescribed and taking TAM | 27 m | TAM | Not measured | Self-report continuing with treatment at each interview. Subset validated against pharmacy records | Items from the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial13. Classified the number of reported severe side effects as 0, 1, or 2. | 1 side-effect: OR=1.3 95% CI 0.72, 2.3 ≥2 side-effects: OR=1.1 95% CI 0.64, 1.9 Recalculated as any side-effects: OR= 1.23 95% CI 0.74, 1.87 | No adjustment for covariates |

*BC* breast cancer, *m* months, *yrs* years, *AI* aromatase inhibitor, *TAM* tamoxifen, *MPR* medication possession ratio, *tx* treatment, *rx* prescription, *dx* diagnosis, *ER/PR+* estrogen or progesterone receptor positive, AOR adjusted odds ratios, OR odds ratio, HR hazard ratio, CI confidence intervals

**Table 3: Number of medications and adherence and persistence to adjuvant hormonal therapy among women with breast cancer in clinical practice settings (TDF domain Behaviour Regulation)**

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Number of medications | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neugut, 2011(29) | Retrospective cohort | US | 22,160 (8,110 <65 yrs, 14,050 ≥ 65 yrs)/mean age 67.4 yrs, postmenopausal: 89.5% white, 74.3% married | Diagnosed with early stage BC; filled at least two 90 day mail order rx for an AI bwt 2007 - 2008: age ≥ 50 yrs | 2 yrs | AI | MPR ≥ 80% | Minimum 45 days elapsed from prior rx without a refill, with no subsequent refills before end of study period | Total number of prescriptions filled or refilled for each patient within the prior 12 months | *< 65 years non-adherence:* 5-9 meds vs < 5: AOR= 0.93 95% CI 0.76, 1.14 10-14 meds vs < 5: AOR= 0.86 95% CI 0.70, 1.07 ≥ 15 meds vs < 5; AOR=0.85 95% CI 0.68, 1.07 <br><br> *≥ 65 years non-adherence:* 5-9 meds vs < 5: AOR= 1.10 95% CI 0.90, 1.34 10-14 meds vs < 5: AOR= 1.04 95% CI 0.85, 1.28 ≥ 15 meds vs < 5; AOR=0.85 95% CI 0.70, 1.04 <br><br> *< 65 years non-persistence:* 5-9 meds vs < 5: AOR= 0.92 95% CI 0.79, 1.07 10-14 meds vs < 5: AOR= 0.75 95% CI 0.64, 0.89 ≥ 15 meds vs < 5; AOR=0.57 95% CI 0.48, 0.67 <br><br> *≥ 65 years non-persistence:* 5-9 meds vs < 5: AOR= 0.84 95% CI 0.73, 0.96 10-14 meds vs < 5: AOR= 0.74 95% CI 0.64, 0.85 ≥ 15 meds vs < 5; AOR=0.60 95% CI 0.52, 0.68 | Age, race, marital status, income, region, 90 day out of pocket cost, follow up with primary care physician vs oncologist, comorbidities |

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Number of medications | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kimmick, 2009 (33) | Retrospective cohort | US | 1,491; mean age 67 yrs (range 29-102), 59% White, low income, insured via gov programmes, 60% ER/PR+ tumours | Non-metastatic invasive BC 1998-2002, HR+ or unknown BCs, continuously enrolled in Medicaid for the 24 months after dx, local or regional staging, breast-conserving surgery or mastectomy, non-missing data on radiation status | 1 yr | TAM, AI | MPR ≥ 80% | No more than 90 days between rx fills or in tx gaps | Number of unique prescription meds within 12 months | *Adherence:* AOR=1.01 95% CI 0.99, 1.02 per unit increase in meds *Persistence:* AOR=1.06 95% CI 1.05, 1.08 per unit increase in meds | Age, race, comorbidity, marital status, stage, HR status, type of surgery, chemotherapy, radiation, urban residence, type of hospital |
| Krotneva, 2014 (42) | Prospective cohort study | Canada | 3180; mean age 77 yrs | ER+, ≥ 1 year of medical service history, initiated HT within 1 year of BCS | 5 yrs | TAM, AI | MPR ≥ 80% | No more than 60 days between rx fills or in tx gaps | Number of prescription medications at baseline | *Non-persistence:* HR= 0.93 95% CI 0.92, 0.95 per unit increase in number of prescription items | Age, are of residence, comorbidity, new medication initiated, radiotherapy, hospital admissions |
| Markkula, 2012 (37) | Prospective cohort | Sweden | 417; median age 60 yrs, range 25-99 | Patients ≥1 yr of follow up, had not received neoadjuvant treatment, advised to use HT, ER+, not been treated for another type of cancer in the previous 10 years | 2 yrs | TAM,AI | Declined treatment, MPR>80% from medical chart, patient questionnaire | Stopped treatment upon follow up from medical chart, patient questionnaire | Number of medicines for comorbidities from questionnaire excluding complementary taken in the last week | *Adherence and persistence:* ≥2 v <2 at 1y: OR=1.01, 95% CI 0.54, 1.89 ≥2 v <2 at 2y: OR=0.84, 95% CI 0.12, 1.63 | No adjustment |
| Partridge, 2003 (35) | Retrospective cohort | US | 2,378; mean age 75.4 yrs; 83% White; 63% locally staged disease | Continuously enrolled in state Medicaid prgm during study period; age ≥ 18 yrs; fill at least one TAM rx; history of definitive BC surgery | 1-4 yr | TAM | MPR ≥ 80%, proportion of days before any evidence of recurrence or new BC or any TAM adverse event | Not measure | Number of other prescription drugs used | AOR= 1.03, 95% CI 1.0, 1.04 per item increase | Age, race, surgery, oncology provider, Charlson score, outpatient services, days hospitalised |
| Atkins, 2006 (47) | Cross-sectional - Semi-structured interviews | UK | 131;mean age 59.4, 63% married, 53% at least secondary level education | 2 yrs post dx, stable disease, English speaking | 2 yrs | TAM, AI | Self-report: Forgetting to take medication (non-intentional adherence) and choosing not to take medication (intentional adherence) | Not measured | Number of other prescription drugs used | No association | No adjustment |

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Number of medications | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Simon, 2014(50) | Cross-sectional | Canada | 161; mean age 56.6 yrs | One clinic, treated for ER+ BC | 6 m | TAM, AI | Self-report interview, 80% adherence intake, 100% adherence intake | Not measured | Chronic medication for comorbidities | 80% adherence: 0.001 (0.00, 100.00)<br><br>100% adherence: 0.28 (0.03, 2.43) | Age, menopause status, HT, chemotherapy, tumour status, node status, mastectomy, HRT, history of BC |
| Huiart, 2013(43) | Prospective cohort | France | 382 women, mean age 71.8 yrs | ≥ 1 rx for AI | Median period 3.2 yrs | AI | MPR ≥ 80% | First tx discontinuation lasting more than 3 consecutive months | Polypharmacy (> 4 meds) (Yes or No) | *Non-persistence:* HR= 0.40, 95% CI 0.18, 0.88 | Complementary/Alternative therapy, comorbidities |
| Lash, 2006 (61) | Prospective cohort | US | 462; 58% aged 70-79; 87% ER+ tumours | Diagnosed with stage I-IIIA BC; age ≥ 65 yrs; ER+/indeterminate tumours; initiated TAM | 63 m | TAM | Not measured | Self-report continuing with treatment at each interview 3, 6, 15, 27, 39, 51, and 63 months | Number of prescription medications at baseline | 3 meds vs ≤ 2: RR=0.79 95% CI 0.48, 1.3<br>4 meds vs ≤ 2: RR=0.59, 95% CI 0.33, 1.1<br>≥ 5 meds vs ≤ 2: RR= 0.62, 95% CI 0.40, 0.96<br><br>ARR= 1.20 95% CI 1.0, 1.4 per additional prescription | Age, enrolment site ER status, presence of severe TAM side effects, patients' decisional balance scale |
| Fink, 2004 (64) | Prospective cohort | US | 516; majority aged ≥ 70 yrs, high school graduates | Diagnosed with stage I-IIIA BC, no prior history of BC; age ≥ 65 yrs; ER+ tumours; prescribed and taking TAM | 27 m | TAM | Not measured | Self-report continuing with treatment at each interview. Subset validated against pharmacy records | Number of prescription medications, including TAM classified as 0 to 2, 3, 4, and ≥5 | 3 meds vs ≤ 2: RR=0.66 95% CI 0.34, 1.2<br>4 meds vs ≤ 2: RR=0.47, 95% CI 0.25, 0.88<br>≥ 5 meds vs ≤ 2: RR= 0.49, 95% CI 0.27, 0.98 | No adjustment |
| Friese, 2013 (68) | Prospective cohort | US | 743; mean age 58.9 yrs | Age 20-79 yrs, Stages I-III BC, ER+ or PR+ | 4 yrs | TAM, AI | Not measured | Self-report continuing with treatment | Number of medications taken in the week prior to the follow up survey (4 years since dx) classified as 0,1 and ≥2 | ≥2 vs 0 to 1: AOR=4.19 95% CI 2.28, 7.68 | Age, race, SEER stage, SEER grade, worry about recurrence, primary oncology provider |
| Van Herk-Sukel, 2010(56) | Retrospective cohort | Netherlands | 1,725; 1,451 TAM | BC Stage I-IIIa, HT within 1 yr dx, time period 1998-2006 | 5 yrs | TAM, AI | Not measured | No more than 60 days between rx fills or in tx gaps, also looked at < 90 days and < 180 days | Number of different drug classes (ATC level 1) | 2-3 vs <2: AOR=0.82 95% CI 0.62, 1.07<br>4-5 vs <2: AOR=0.89 95% CI 0.68, 1.17<br>6+ vs <2: AOR=1.15 95% CI 0.89, 1.49 | Age, tumour size, number of comorbidities |

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Number of medications | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Barron, 2007(60) | Retrospective cohort | Ireland | 2,816; one-third aged ≥ 75 | Aged ≥ 35 yrs, commenced TAM as initial HT between Jan 2001- Jan 2004 | 1- 3.5 yrs (median 2.7 yrs) | TAM | Not measured | No more than 180 days between rx fills after index date, excluded treatment switchers, those lost to follow up (no prescription for any item) | Mean number of pharmacological agents in year before Tam | 1-3 vs <=1: AOR= 0.84, 95% CI 0.71, 1.00 >3-5 vs <=1: AOR=0.76, 95% CI 0.61, 0.94 >5 vs <=1: AOR=0.72, 95% CI 0.58, 0.92 | Age, antidepressant use, number of cognitive or functional impairments |

*BC* breast cancer, *m* months, *yrs* years, *AI* aromatase inhibitor, *TAM* tamoxifen, *MPR* medication possession ratio, *tx* treatment, *rx* prescription, *dx* diagnosis, *ER/PR+* estrogen or progesterone receptor positive, AOR adjusted odds ratios, OR odds ratio, HR hazard ratio, CI confidence intervals

**Table 4: Follow up with GP vs oncologist and adherence and persistence to adjuvant hormonal therapy among women with breast cancer in clinical practice settings (TDF domain Social Influences)**

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Follow up | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neugut, 2011(29) | Retrospective cohort | US | 22,160 (8,110 <65 yrs, 14,050 ≥ 65 yrs)/mean age 67.4 yrs, postmenopausal: 89.5% white, 74.3% married | Diagnosed with early stage BC; filled at least two 90 day mail order rx for an AI bwt 2007 - 2008: age ≥ 50 yrs | 2 yrs | AI | MPR ≥ 80% | Minimum 45 days elapsed from prior rx without a refill, with no subsequent refills before end of study period | Follow up with primary care physician vs. oncologist | < 65 yrs: AOR=0.91 95% CI 0.71,1.16 (adherence)<br><br>> 65 yrs: AOR= 0.81 95% CI 0.69, 0.96 (adherence)<br><br>65 yrs: AOR=0.82 95% CI 0.69,0.99 (persistence)<br><br>> 65 yrs: AOR= 0.79 95% CI 0.71, 0.89 (persistence) | Age, race, marital status, income, region, 90 day out of pocket cost, no of other prescriptions, comorbidities |
| Danilak, 2013 (39) | Retrospective cohort | Canada | 346; majority aged 35-74 yrs | Initiated adjuvant endocrine therapy, HR+, node positive or intermediate to high-risk node negative patients, completed primary surgery and chemotherapy. | 2 yrs | TAM, AI | After ≥2 yrs; MPR ≥ 80% | Discontinued therapy within 3 m, 6 m, 1 yr and 2 yrs | Cross Cancer Institute follow-up times of less than 1 yr (discharged to family physician) | AOR= 2.4 95% CI 1.0, 5.5 (non-persistence) | Age, residence (near centre), Chemotherapy, menopausal status, nodal status, surgery, radiation, pharmacy call back |
| Alkhayyat, 2012 (48) | Case-control | Canada | 160; (80 in each cohort), median age 62.5 yrs | ER+, therapy ≥ 1 yr | 5 yrs | TAM, AI | Adherent >80%, non-adherent < 50%, semi-adherent 50-80% | Not measured | Follow up with primary care physician vs. oncologist | HR= 0.7 (p > 0.999) | No adjustment |

| Primary author, year | Study type | Country | Participant characteristics | Eligibility criteria | Time period | HT | Adherence | Persistence | Follow up | Results | Covariates |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Güth, 2008 (66) | Retrospective hospital based cohort | Switzerland | 325; mean age 67.3 yrs (range 47-95); majority stage I-IIA | Diagnosed with non-metastatic BC, treated with surgery at author institution, ER/PR+ tumours, postmenopausal | 5 yrs | TAM, AI | Not measured | Patients who discontinued per medical record | Follow up with primary care physician vs. oncologist | OR= 2.78 95% CI 1.29, 5.98 | No adjustment |
| Güth, 2012 (54) | Retrospective hospital based cohort | Switzerland | 685; mean age 60 yrs, diagnosed with ER+ BC 1997-2008 at a university teaching hospital | HR+ non-metastatic invasive BC, received surgical therapy between 1997-2008. | Minimum 36 m | TAM, AI | Not measured | Persistence-discontinue treatment except for BC recurrence, physician decided to stop treatment, patients who died per medical record | Follow up with primary care physician vs. oncologist | AOR= 0.66 95% CI 0.49, 0.88 | Year of the initial diagnosis, patient's age at diagnosis, primary surgical therapy, tumor stage, receipt of previous chemotherapy and/or postoperative radiation |
| Hadji, 2013 (58) | Cross-sectional | Germany | 12,412; mean age 62 yrs TAM, 66 yrs AI | BC, first rx for TAM, AI Oct 2001-Dec 2010 (follow up time ≥365 days before index date), ≥18 years | 3m to 3 yrs from index date | TAM, AI | Not measured | 90 days without hormonal therapy | Follow up with primary care physician vs. oncologist | HR=0.44 95% CI 0.42, 0.46 | Age, type of health insurance, patient and physicians residency, baseline co-morbidities (osteoporosis, diabetes, depression) and co-medication (bisphosphonates for osteoporosis) |

*BC* breast cancer, *m* months, *yrs* years, *AI* aromatase inhibitor, *TAM* tamoxifen, *MPR* medication possession ratio, *tx* treatment, *rx* prescription, *dx* diagnosis, *ER/PR+* estrogen or progesterone receptor positive, AOR adjusted odds ratios, OR odds ratio, HR hazard ratio, CI confidence intervals
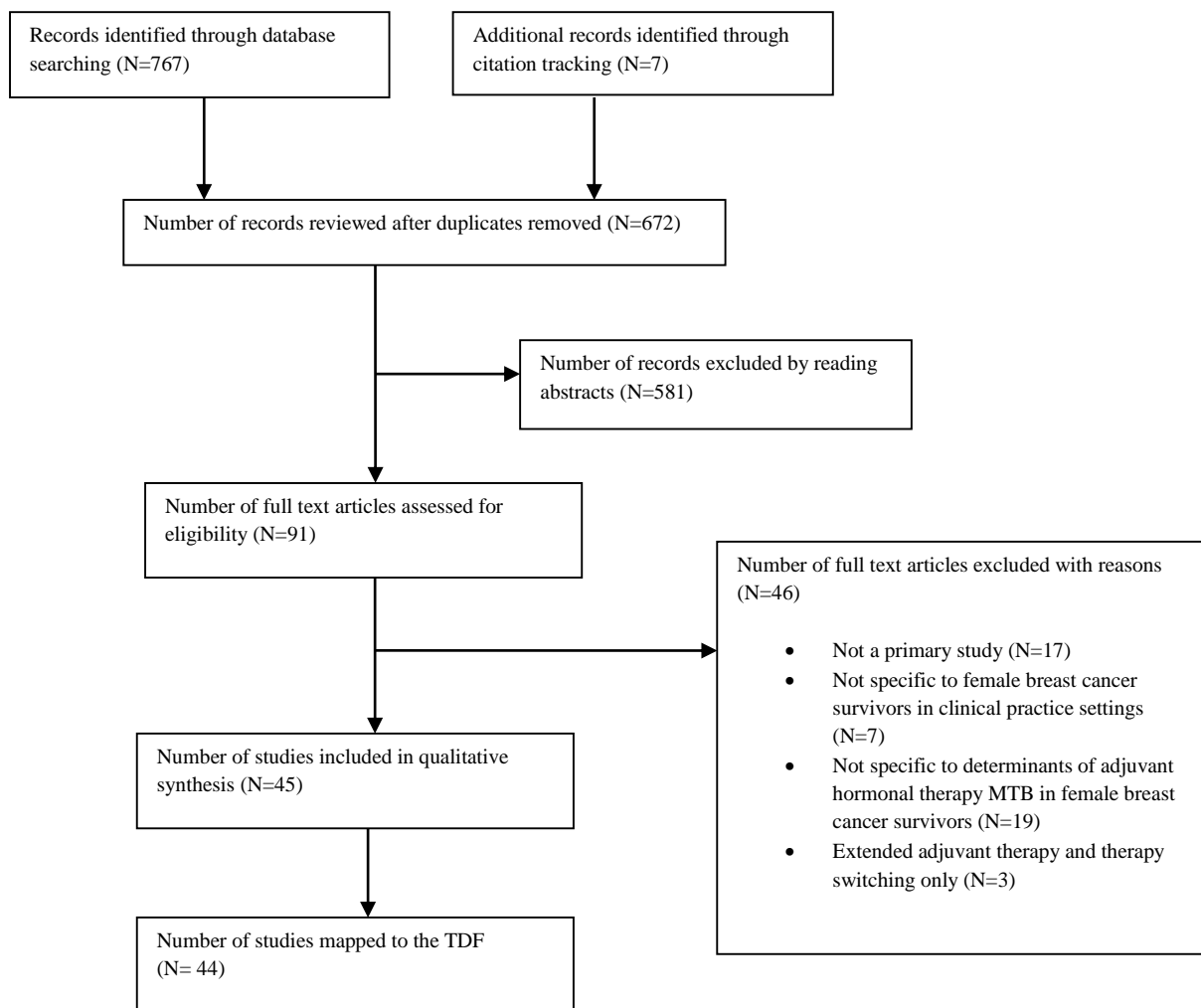
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                │                  │    survivors in clinical practice        │
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        │ Number of studies    │   │    female breast cancer survivors (N=19) │
        │ included in          │   │  • Extended adjuvant therapy and therapy │
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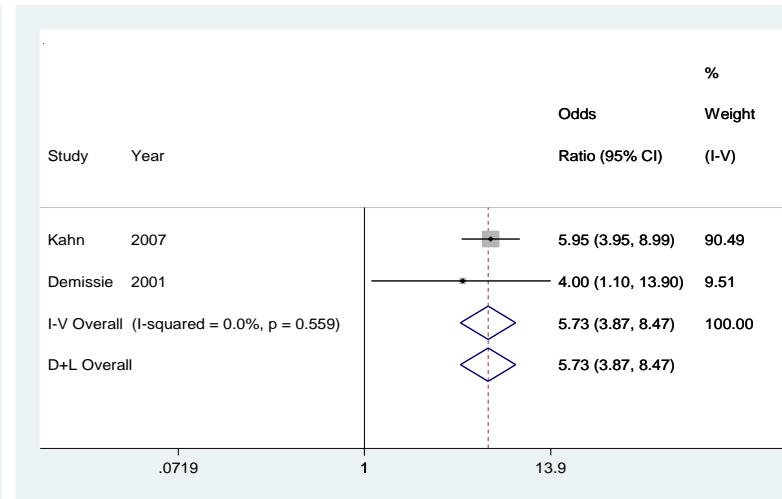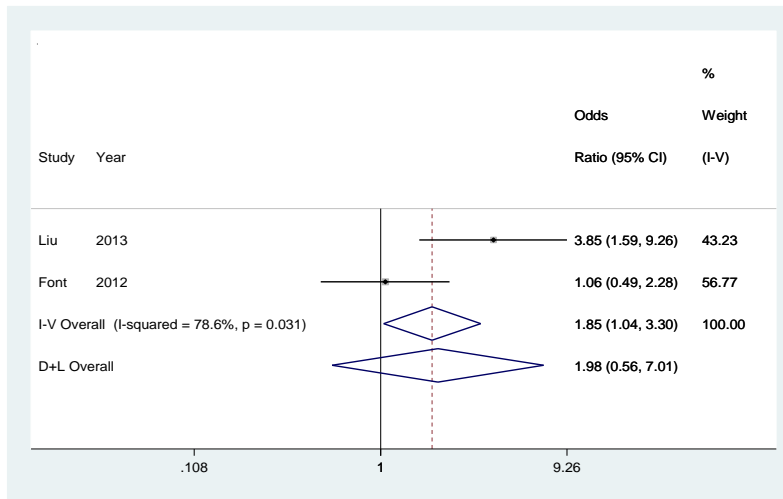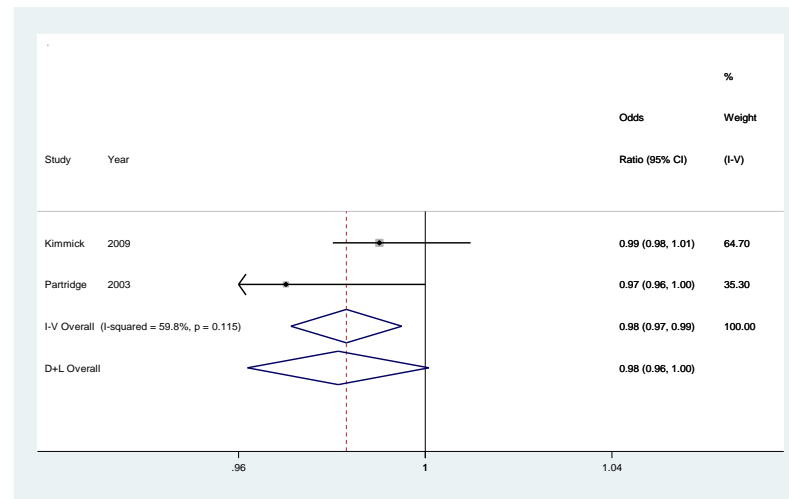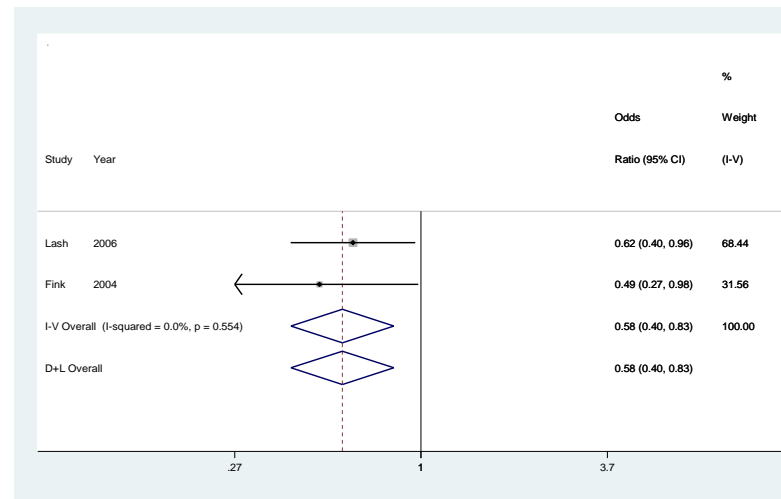
**Figure 1: PRISMA Flow Diagram: selection of studies for systematic review**

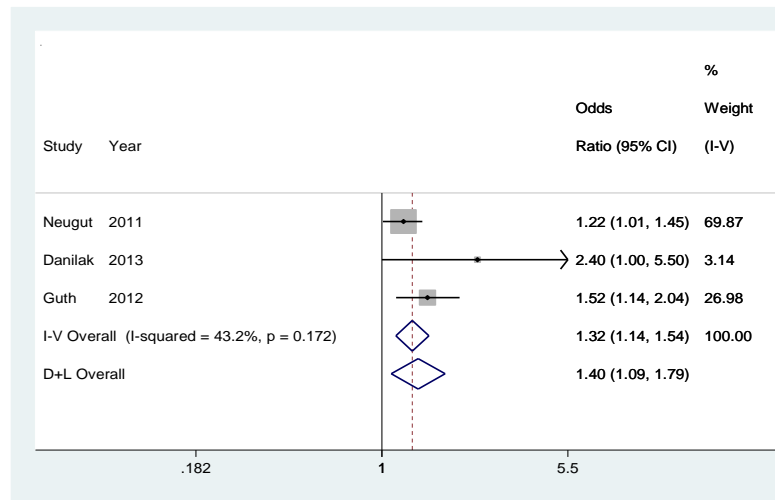**Self-report non-adherence and side-effects**



**Self-report non-persistence and side-effects**



**Non-adherence (MPR <80%) and number of medications**



**Self-report non-persistence and number of medications**

| Study | Year | Odds Ratio (95% CI) | % Weight (I-V) |
|---|---|---|---|
| Neugut | 2011 | 1.22 (1.01, 1.45) | 69.87 |
| Danilak | 2013 | 2.40 (1.00, 5.50) | 3.14 |
| Guth | 2012 | 1.52 (1.14, 2.04) | 26.98 |
| I-V Overall (I-squared = 43.2%, p = 0.172) | | 1.32 (1.14, 1.54) | 100.00 |
| D+L Overall | | 1.40 (1.09, 1.79) | |

**Non-persistence (treatment gaps) and follow up with GP vs oncologist**

**Figure 2: Forest plots: Side-effects, number of medications and follow up with GP vs. oncologist and non-adherence and non-persistence to adjuvant hormonal therapy**

**Notes: Non-adherence and side-effects:** Populations different- Liu 2013 study predominantly low education and low income. Different time periods, Liu 2013 study was 36 m vs. 5 yrs for Font 2012 study.
**Non-persistence and side-effects:** Different time periods, Kahn 2007 study was 4 yrs vs. 21 m for Demissie 2001 study. Kahn 2007study analysed severe side-effects only. Including Fink 2004 study and Bowles 2012 study: Heterogeneity chi-squared = 25.87 (d.f. = 3) p = 0.000, $I^2$= 88.4%. Test of ES=1 : z= 7.65 p = 0.000.Fink 2004 study did not adjust for any covariates and Bowles 2012 study measured specific side-effects (hormone, bone related)
**Non-adherence and number of medications:** Both studies measured per unit increase in number of medications. Kimmick 2009 study was 1 yr vs 1 to 4 yrs Partridge 2009 study. Kimmick 2009 study measured adherence to TAM, AI. Partridge 2009 measured adherence to TAM only.
**Non-persistence and number of medications:** Both studies measured ≥ 5 medications versus ≤ 2 medications. No adjustment for covariates.
**Non-persistence and follow-up with GP vs oncologist:** Neugut 2011 study included women < 65 years only as similar to mean age in Danilak 2013 and Guth 2012 studies