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A systematic review of interventions to improve adherence to endocrine therapy

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Introduction

Approximately two-thirds of diagnosed breast cancers (BrCas) in the United States are hormone-receptor positive. Endocrine therapy (ET), the recommended adjunct treatment for hormone-receptor positive BrCa, can reduce recurrence by 40% and lower the risk of dying by one third.[1] Despite these survival benefits, adherence to ET is a major problem;[2–13] 50 to 75% of all women prescribed ET prematurely discontinue or do not maintain adherence after five years. [6,9,14–17] Even lower rates of ET adherence occur among sub-groups of financially-disadvantaged women;[18] and, in some cases, are significantly lower among women who are both African American and are of low-income status.[19,20] With more recent findings indicating the need to continue ET for 10 years, adherence may be even more problematic.[14,21] Therefore, identifying effective interventions to improve maintenance of ET in women with BrCa is vital.[17,22,23]

Previous studies have extensively documented socio-demographics e.g., race, age, disease, and treatment-related factors are associated with ET adherence, and provided limited evidence about modifiable factors, e.g, psychosocial, behavioral, which can be targeted with interventions.[13,24,2526] A systematic review by Hurtado-de-Mendoza et al. (2016) confirmed

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Compliance with Ethical Standards

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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that few behavioral intervention studies were conducted on improving adherence to ET therapy. Therefore, the purposes of this systematic review were to explore studies that examined the impact of interventions or strategies to improve ET adherence among women with BrCa, and identify studies offering insights for future researchers designing interventions to improve ET adherence. Given the known health disparities of BrCa survivors that may contribute to lack of ET adherence,[18,27,28] we additionally sought to examine whether any studies discussed adaptations or considerations aimed to target the unique needs of disparate populations.

Methods

Inclusion and Exclusion Criteria.

Studies included in this review met the following criteria: original research in peer-reviewed journals, full-text available online, clearly stated descriptions of samples and methodology, human subjects, adults, and articles available in English. We focused on papers that examined strategies and approaches for improving adherence to ET among women with BrCa. We defined ET as tamoxifen and/or aromatase inhibitors, the two major classes of drugs used for hormone positive BrCa. We included studies with a broad range of designs to capture data that examined a direct relationship between adherence and any strategy that could be replicated in an intervention. For example, if a study reported modifiable factors e.g., self-efficacy, patient-provider communication)in association with adherence as an outcome, we included the study. We excluded any descriptive manuscripts which did not document strategies to improve adherence.

Search Strategy.

Articles from 2006 to 2017 were retrieved from the following databases: PubMed, CINAHL, PsychInfo, Web of Science, and Cochrane Library. The MeSH terms and keywords included *patient compliance* [MeSH Terms] OR *patient compliance* [All Fields] OR *medication adherence* [MeSH Terms] OR "*medication adherence*"[All Fields] OR "*treatment adherence*"[All Fields]) AND ("*breast neoplasms*"[MeSH Terms] OR "*breast neoplasms*" [All Fields] OR "*breast cancer*"[All Fields]) AND ("*antineoplastic agents, hormonal*"[All Fields] OR "*antineoplastic agents, hormonal*"[MeSH Terms] OR "*aromatase inhibitors*"[All Fields] OR "*aromatase inhibitors*"[MeSH Terms] OR *aromatase inhibitors*[Text Word] OR "*endocrine therapy*"[All Fields].

Study screening.

We imported and managed all study citations identified from our search strategy with the Covidence systematic review platform [29] Two reviewers (P.H., S.H.) independently screened titles and abstracts for study eligibility, and identified studies for full-text review. Reviewers independently read the full text and selected studies for inclusion. Following this review, the two reviewers met to reach consensus on the final selection of studies to be included.

Data abstraction.

Data selected for extraction and included in Table 1 are author/date, sample size, inclusion criteria, drug type, adherence measure, design, intervention detail, results and cultural

aspects. We based our risk-of-bias assessment on work by Chad-Friedman and colleagues who used a checklist adapted from STROBE recommendations[30] to review studies in their systematic review.[31]

Results

Study selection

Figure 1 provides a flowchart of the identification, screening, and article selection process, which initially resulted in 1254 original articles about strategies to improve ET adherence. After removing duplicates (n=304), we screened 950 titles and abstracts for study eligibility. From this process, 38 articles were selected for the full-text review. A total of 16 articles were included in the final review; one of the 16 papers reported on the same study at different time intervals, i.e. 1 year and final report.[32,33]

Overview of study characteristics

We observed a variety of study designs, adherence definitions and measurement approaches that are presented in Table 1. Eight studies reported inclusion of either tamoxifen or aromatase inhibitors, seven reported inclusion of only aromatase inhibitors, and one study examined tamoxifen only.

Risk of Bias

The risk of bias varied considerably due to the diverse nature of the study designs, e.g. RCT, cross sectional, and quasi-experimental. All studies reported inclusion criteria; sampling methods were appropriate to the design (randomized or convenience). As expected sample size was quite large in the database studies (range from 4915 to 22,160). Large samples were also reported in several of the RCT studies (about 2,700 participants). Human subjects review according to US or international standards was reported in 10 papers (n=16). Four papers used publicly available de-identified data from a claims database and may have been exempt from review.[34–37] Two papers did not report on human subjects protection.[33,38] However, one of the papers was from the same study[33] in which the final paper reported the ethics review.[32] The population was adequately described in the studies. Most of the studies addressed bias usually through a discussion of limitations. Only two studies omitted any discussion of bias.[35,39]

Study Designs

We used the authors' description of their study design as published in their paper. Two designs (RCT and retrospective) were most commonly used with four papers each.[32,33,40,41] Other designs reported included three prospective, [39,42,43] two cross sectional,[38,44] and one each of observational,[37] quasi-experimental,[45] and historical usual care versus an intervention.[46] Table 2 shows studies by design that was significantly associated with adherence and provides information on intervention strategies.

Definitions and Measurement of Adherence

Authors differed as to terminology about adherence and used adherence or compliance/compliant,[32,33,36,40,41,45] non-adherence,[43,44] persistence[32,39], non-persistence[35,36] and discontinuation.[32,34,35,39] Also, authors may have measured two different constructs within one study, commonly whether the patient was taking the drug, e.g. adherence and the time period of taking the drug, e.g. persistence. Compliance and adherence had similar definitions whether by self-report or objective measures such as prescription refill. Participants were considered adherent if they had received or taken 80 % of the drug dispensed and in some cases for analyses this was dichotomized to 80% as being adherent and below 80 % as not adherent.[36,43] Discontinuation was defined as lack of continuation of hormone therapy within a specified study time period, e.g. 90 days.[34,35] The definition of non-persistence was similar; but the author used a time period within which the drug had not been refilled.[36] Persistence was defined as the ongoing use or continuation of hormonal therapy within the specified study time period from initiation to discontinuation; studies lasted from 1 to 4 years.[42,46]

Data were obtained from self-report exclusively (n=3)[37,44,47], self-report and other corroborating data (n=8),[32,33,38–40,42,43,47,48] only medical records (n=1)[46] de-identified data sets from electronic medical records (n=2)[34,35] and claims data (n=2).[36,45] Regardless of the source of data, half of the authors used 80% as the standard for adherence as determined by a calculated medication possession ratio or a self-report that provided a similar score.[32,33,36,39,40,43,45]

Impact of Interventions to Improve ET Adherence

The most frequent intervention strategy reported was patient information/education (n=5). Other strategies included communication between the patient and health care team members (n=5), education and communication (n=2), patient navigation (n=2), and financial changes (n=3). All educational interventions used similar components such as educational materials on various aspects of ET, which were mailed to patients at intervals; although, none of these reported significant results.[32,33,39–41] However, one of these studies did show significant results in Sweden and Finland.[33] Two studies combined education and communication and both of these studies had significant results.[34,43] Similarly, patient navigation, facilitating the patient's process from diagnosis through treatment showed significant ET adherence.[46,47] Details about the interventions are provided in Table 1.

The majority of the studies (n=9) were conducted outside the United States: Germany (n=6)[34,35,40,41,43,47] China (n=1)[39] and several European/Scandinavian countries in multi-site cooperative studies (n=2).[32,33] Of the seven studies conducted in the US, the majority of the participants were white (n=5) with white participants ranging from 54% to 89.5 %.[36,38,42,44,45] One study had relatively high African American participation (45%).[46] The majority of participants in one study, based in California, were Latina (54%).[37] An examination of these studies that included African American and Latina populations did not find any evidence that any cultural adaptations were made. An exception[46] used navigated care for a racially diverse cohort of participants. The description of navigation suggested that

cultural adjustments were made, such as using bilingual (Spanish and English) navigators, and additional support was provided by American Cancer Society volunteer navigators.[46]

Discussion

This systematic review extended previous work by identifying and describing a broader range of studies on approaches to improve adherence to ET in women with breast cancer. Of the sixteen studies included in this review, only four were RCTs. While the RCT design yields the highest quality of scientific evidence, we found that the researchers who used this design proposed “educational only” interventions that did not lead to statistically significant improvements in ET adherence; except one study reported significant differences in adherence by country. This finding supports the notion that while education may be a necessary part of an intervention, it is not sufficient for behavior change.[49] In fact, the two interventions that combined education and communication reported significant results.

Our findings of inconsistent definitions and measurement of treatment adherence were similar to Hurtado-de-Medoza and colleagues.[50] This lack of consistency limited interpretation of findings. Further, the source of the data in four studies was self-reported which decreased credibility of the findings.[51] Approaches to increase the scientific rigor of future studies could include longitudinal designs,[52] electronic monitoring,[53] valid and reliable self-report measures[54] and biomarkers such as measurement of tamoxifen in a dried blood spot.[55]

Health care provider interaction, positive communication, and education are important to patient understanding and adherence.[37,38,43,46,47] A standardized program of patient navigation[46] or disease management[34] had significant impact on adherence. In the disease management program patients received tailored information and individual consultation as well as assistance with transition between inpatient and outpatient care.[34] In the patient navigation program, patients received information in English or Spanish and were supported through care transitions.[46] In both these cases, the approach was patient centered and adaptable to specific needs of the patient through the continuum of care. In contrast, six studies used well developed educational materials that were provided over time via mail and phone.[32,33,39–41,43] While the exact education about the hormonal therapy was not detailed in the papers, in general the educational materials covered benefits, side effects, and other pertinent details about cancer treatment. However, this information was not individualized to the patient. Specific content about the BrCA diagnosis may be needed to help patients understand the critical reason for taking hormonal therapy, such as hormone receptor status.[47] Therefore, researchers and provides should determine what content and delivery method works best.

A theoretical approach was used in only one study to frame and direct the components of the intervention.[41] Use of theory leads to better design of intervention components and outcomes.[56–59] Theories that could be used in adherence interventions include planned behavior,[60]and self regulation.[61] Additionally, frameworks, such as the World Health Organization’s Multidimensional Adherence model,[62] could also be useful for planning and evaluating multi-level intervention approaches to improving long-term adherence to ET.

Another weakness of all studies is that none of reported on treatment fidelity[62] which is a critical component to improve the quality of interventions.[63–65] Treatment fidelity includes an evaluation of the intervention to determine if it was delivered as planned and an assessment of participants' to establish exposure to the intervention. Even interventions that have been pilot tested may not show an effect and this could be due to problems with fidelity.[66] We speculate that treatment fidelity might account for differences found in a multi-site trial where significant changes were demonstrated in the intervention group by country.[33]

Conclusions

Based on this review, much work remains in the development and testing of interventions to improve ET adherence and adapt interventions to diverse cultures and ethnicities. In this review, of the US studies, none described any cultural adaptation even though both diverse cultures were represented in the samples. Yet, research shows that cultural adaptation is necessary for interventions to be well accepted and adopted by various cultural groups.[67–69] Further, cultural adaptation strengthens the effects of the intervention.[22,70–72] For example, our work with STORY (Sisters Tell Others and Revive Yourself) demonstrates the effectiveness of a culturally sensitive intervention that improved mood and social connection. Further, secondary analysis of this work found that although adherence was not an outcome of the original study, we documented that intervention participants significantly increased treatment specific knowledge.[73]

More research is needed in the US where individual health care plans may particularly impact ET adherence. Future interventions should address potential financial and economic barriers to adherence including access to discount pharmaceutical programs.[74]

We observed a need for standardization of terminology, definitions, and measurement in order to compare findings across studies. Although an 80% medication possession ratio (MPR) is considered adherent, it remains unknown whether this reaches a therapeutic drug level. Measures to determine ET adherence should be used as crosschecks against measurement error, e.g. self-report combined with automated electronic monitoring. Well planned RCTs that include effective intervention components such as communication and education should be implemented. Finally, cancer researchers and clinicians should learn from existing literature on successful intervention in other chronic conditions. Notably, AIDS/HIV work shows theories and models that could be applicable to cancer.[75–77]

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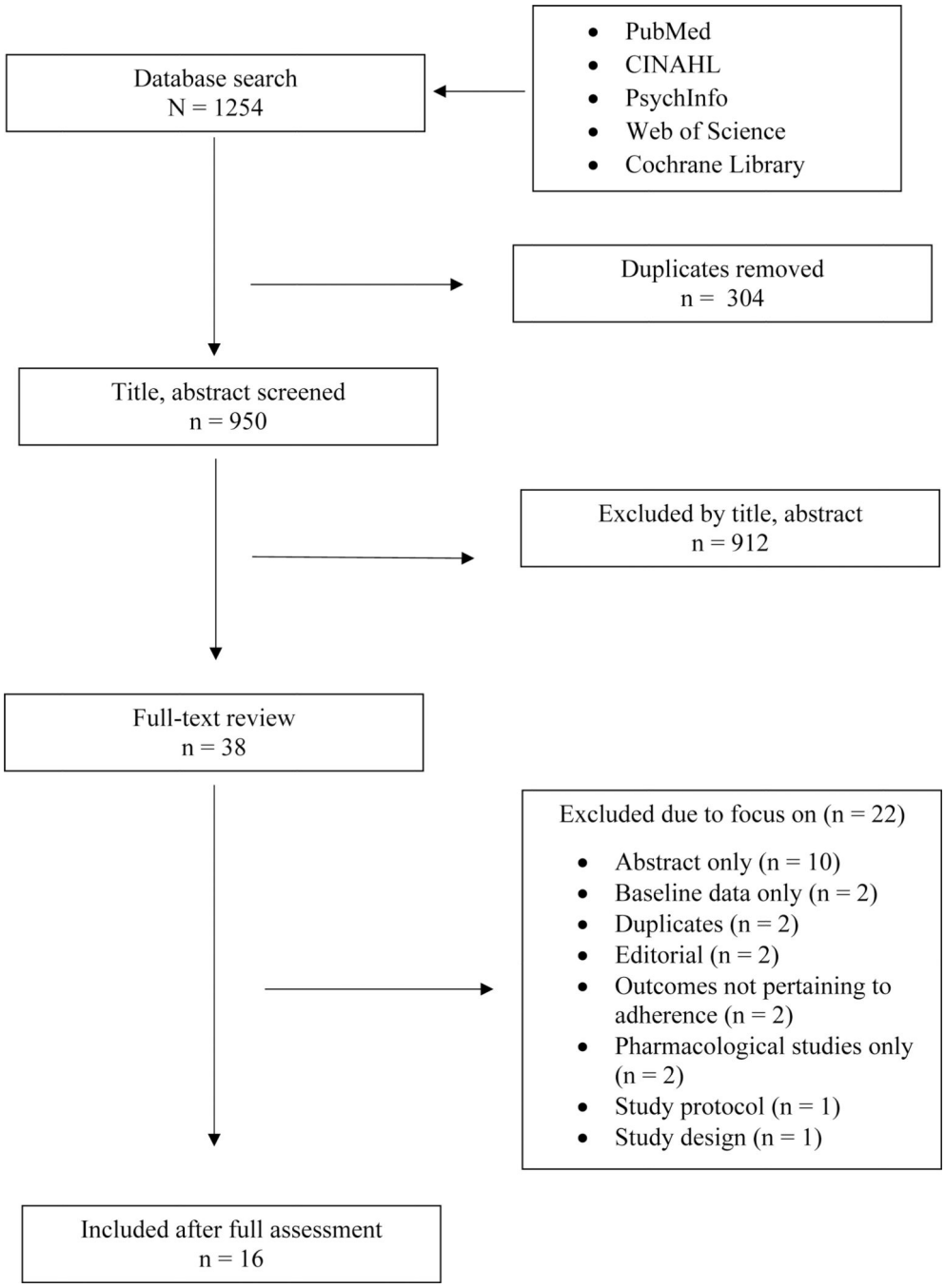

Figure 1.
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Chart

Table 1.

Data Extraction Table for Intervention Approaches to Adherence

Source	Sample Size	Drug Type	Measurement	Design	Type of Manipulation	Results	Cultural Aspects
Albert, 2011[47]	207	Tam & AI	Self report of medication adherence from questionnaire	retrospective descriptive	patient's interaction with the breast care nurse	nurse navigator contact and knowledge of hormone receptor status significantly correlated ($p < 0.001$)	Germany
Arriola, 2014[38]	200	Tam & AI	MARS (4 items), Drug Attittude Inventory (6 items) higher score greater adherence	cross sectional	physician communication frequency	Frequency of physician communication was significantly associated with medication adherence ($p < 0.05$)	US White, 54.5%
Castaldi, 2017[46]	117	Tam & AI	Days to ET start using National Quality Forum 2	non-randomized historical usual care versus navigated care	SC vs. Multi-disciplinary Patient Navigation program	SC (68.6 %) vs. navigation (100%) P < .0001)	US AA 45% Hispanic 28.5% Asian 8% white 8.5 %
Hadji, 2013[40]	Treatment (2442) / SC (2402)	AI	self-report questionnaire and percentage of patients adherent at 12 month based on prescription given	RCT	SC vs. Educational materials	SC (52.3%) vs. Educational materials (50.9%) P = 0.37.	Germany
Heisig, 2015[43]	137	Tam & AI	Self-assessment question of number of tablets taken in the last 12 weeks	prospective single cohort	SC vs. enhanced education with printed materials & verbal instruction	Adherence significant for satisfaction with ET information (ρ = 0.17, OR 1.55 p = 0.03, n = 133) and associated problems (ρ = 0.22, OR 1.77, p = 0.006)	Germany
Jacob, 2015[34]	1874 (DMP); 3041 (SC)	Tam & AI	90 days without medication refill over 3 year period	retrospective	SC vs. disease management program	SC (39.6 %) vs. Disease Management (32.7 %) adjusted HR = 0.91, 95 % CI: 0.85–0.98	Germany
Kahn, 2007[42]	881	Tam	Self-report survey; medical record	prospective cohort	patient-centered care	Three factors, amount of support, role in decision making and pre-treatment information on side effects was significantly associated with tamoxifen adherence	US Hispanic& other 5% Non-Hispanic white 85 % Non-Hispanic other 4 % black 7 %
Kostev, 2013[35]	3,620	Tam	90 days without medication refill	retrospective	conversion vs no conversion to a rebate	44.2% of women who used a rebate process and 33.8% of patients who continued with same process discontinued their treatment ($p < 0.01$) after one year.	Germany
Lin, 2017[44]	100	Tam & AI	MARS (4 item)	cross sectional	Patient provider communicatoin	Physician communication not associated ($p > .05$) with adherence	USA

Source	Sample Size	Drug Type	Measurement	Design	Type of Manipulation	Results	Cultural Aspects
Liu, 2013[37]	303	Tam & AI	Self report 3 years post diagnosis	observational	patient-provider communication	Patient centered communication by oncologist significantly predicted adherence at 3 years post diagnosis (AOR = 1.22, P = 0.006)	US Latina 49 % White 34 %
Markopoulos, 2015	1379 per group	AI	Self report number of pills taken; number of Rx written	RCT	Educational materials versus SC	SC (82 %) vs. Education (82%) no significant difference 1 year and similar at 2 years	Lead country Belgium, International study across 18 countries
Neugut, 2011[36]	Pre-medicare 8,110; Medicare 14,050	AI	minimum 45-day supply gap with no AI on hand and no refills	retrospective cohort	co-payment amount	90-day co-payment ($90 or more) in younger women compared to a co-payment of $30 (OR= 0.82; 95% CI, 0.72 to 0.94). Older women had similar negative findings regarding the co-payment amounts of $30 or more compared with co-payment amounts of less than $30 OR= 0.72=95% CI, 0.65 −0.80) respectively.	USA White 89/5 % Black 4.7 % Hispanic 3% Asian 1.8%
Neuner, 2015[36]	16, 462	AI	Number of days prescription received for 3 months	quasi-experimental pre-post	Amount of Copay	Generic anastrozole introduction increased probabilty of adherence by 5.4 % and with letrozole/ exemestane 11 % higher probability	USA
Neven, 2014[33]	1379 per group	AI	how many tablets taken during the past year (nearly all)	RCT	SC vs. Educational materials	SC (81%) vs. Educational Materials p = 0.4524	Austria Switzerland Sweden/ Finland
Yu, 2012[39]	Treatment (252) /SC (264)	AI	proportion of days covered by prescription refills over the 364 days following the initiation of AI	prospective, controlled, observational	SC vs. standard treatment plus patient support program group	SC (95.9%) vs. Educational materials and reminder calls (95.8%) P = 0.95	China
Ziller, 2013[41]	181	AI	Self reported adherence and an MPR of 80% or more	RCT, 3 arms	SC vs. reminder letters, information booklets vs. reminder letter, telephone calls	SC (48.0%) vs. letter group (64.7%) vs. phone call group (62.7%) P = .75	Germany

Abbreviations: SC, standard care; Tam, tamoxifen; AI, Aromatase inhibitors; RCT, randomized controlled trial; CI, confidence interval; OR, odds ratio; ET endocrine therapy; AOR, adjusted odds ratio

Table 2:

Intervention Type and Study Design with Results

Author	Intervention Type	Type of Manipulation	Measure	Design	Results
Arriola, 2014[38]	Communication	physician communication frequency	SR	Cross sectional	S - Frequency of physician communication was significantly associated with medication adherence ($p < 0.05$)
Lin, 2017[44]	Communication	Patient provider communication	SR	Cross sectional	NS - Endocrine therapy adherence was not associated ($p > .05$) with physician communications although the majority of the patients reported positive physician communications.
Castaldi, 2017[46]	Patient Navigation	Multi-disciplinary Patient Navigation program vs. SC	Other	non-randomized historical usual care versus navigated care	S - Navigation Program clearly demonstrated improved compliance with follow-up and adjuvant therapy in a predominantly minority population. Compliance for NQF measure 1 in NC is 100% versus 57.1% in UC ($P = .005$). Compliance for NQF measure 2 in NC is 100% versus 68.6% in UC ($P < .0001$).
Liu, 2013[37]	Communication	patient-provider communication	SR	Observational	S- The use of endocrine therapy 3 years after diagnosis was positively predicted (AOR = 1.22, $P = 0.006$) by women's report that their oncologist used patient-centered communication which was assessed at 18 months after diagnosis.
Kahn, 2007[42]	Communication	patient-centered care	SR & other	prospective cohort	S - Tamoxifen use was significantly higher ($P = 0.0051$) in those women who reported receiving the right amount of support (79%). Adherence was lower when women (81%) were less satifasfied with decision making role ($P = 0.0001$) and when decision made alone (56%) ($P = 0.0003$). Adherence lower ($P < 0.0001$) in women who were not informed about side effects prior to experiencing them (62% vs. 85%)
Heisig, 2015[43]	Education	SC versus enhanced education (printed materials & verbal instruction)	Other	Prospective single cohort	S - Adherence significant for satisfaction with ET information ($\rho = 0.17$, OR 1.55 $p = 0.03$, $n = 133$) and associated problems ($\rho = 0.22$, OR 1.77, $p = 0.006$)
Yu, 2012[39]	Support group	SC versus standard treatment plus patient support program group	Other	prospective, controlled, observational	NS - Patients in the standard care group stopped use of endocrine therapy at 213.2 days and in the intervention group at 227.8 days; there was no significant difference in the length of time for discontinuation ($P = 0.96$).
Neuner, 2015[45]	Financial	Amount Copay	Other	quasi-experimental pre-post	S - Generic anastrozole introduction increased increased probabilty of adherence by 5.4 % and with letrozole/exemestane 11 % higher probability
Hadji, 2013[40]	Education	SC versus educational materials	SR & Other	RCT	NS- no difference in rates between the standard and EM arms (50.9% and 52.3%, respectively, $P = 0.37$).
Markopoulos, 2015	Education	Educational materials versus SC	SR & Other	RCT	NS- end of study results (CARIATIDE) Educational materials did not signiificantly impact adherence in any country.
Neven, 2014	Education	Educational materials versus standard	SR	RCT	S by country - Year 1 Results (CARIATIDE): Educational materials only improved overall adherence with AI in Sweden/Finland; ($p = 0.0246$)
Ziller, 2013	Education	reminder letters, information booklets versus reminder letter,	SR and Other	RCT, 3 arms, partially-blinded parallel group	NS - No differences were found in adherence at one year post treatment initiation among control group (48.0%) letter group 64.7% or phone call group 62.7%. Post hoc analysis of combined

Author	Intervention Type	Type of Manipulation	Measure	Design	Results
		telephone calls versus SC			intervention groups versus control was significantly different (p = 0.039).
Jacob, 2015	Education	disease management program versus SC	Other	retrospective	S - DMP patients vs SC showed significant difference (p=0.001) in discontinuing endocrine therapy within 3 years (32.7 % versus 39.6 %). Risk for discontinuing endocrine therapy was lower in DMP patients than standard care (adjusted HR = 0.91, 95 % CI: 0.85–0.98).
Kostev, 2013	Financial	conversion vs no rebate conversion	Other	retrospective	NS - Switching patients to a rebate pharmaceutical process had a significantly negative effect on adherence at one year and 3 years. Discontinuation of treatment was significantly higher at three years (HR:1.27, CI: 1.05 – 1.53, p = 0.014) 44.2% of women who used a rebate process and 33.8% of patients who continued with same process discontinued their treatment (p < 0.01) after one year.
Neugut, 2011[36]	Education	co-payment amount	Other	Retrospective cohort	S - In younger women, the amount of a 90-day co-payment ($90 or more) was significantly associated with non-adherence when compared to a co-payment of $30 (OR= 0.82; 95% CI, 0.72 to 0.94). Older women had similar negative findings regarding the co-payment amounts of $30 or more compared with co-payment amounts of less than $30 OR= 0.72=95% CI, 0.65 −0.80) respectively.
Albert, 2011[47]	Patient Navigation	patient's interaction with the breast care nurse	SR	retrospective descriptive	S - Adherence was significantly correlated (p < 0.001) with nurse navigator contact (79 contact vs. 56% no contact) and knowledge of hormone receptor status

Abbreviations: SC, standard care; Tam, tamoxifen; AI, Aromatase inhibitors; RCT, randomized controlled trial; CI, confidence interval; OR, odds ratio; ET endocrine therapy; AOR, adjusted odds ratio; S, significant, NS, not significant