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Behavioral interventions to enhance adherence to hormonal therapy in breast cancer survivors: A systematic literature review

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Abstract

Adjuvant hormonal therapy contributes to reductions in recurrence and mortality for women with hormone receptor positive breast cancer. However, adherence to hormonal therapy is suboptimal. This is the first systematic literature review examining interventions aimed at improving hormonal therapy adherence.

Researchers followed the PRISMA guidelines. PubMed-Medline, CINAHL, PsychInfo, Ovid-Medline, and EMBASE were searched for behavioral interventions that aimed to enhance adherence to adjuvant hormonal therapy in breast cancer survivors.

There were 376 manuscripts screened for eligibility. Five articles met criteria. All interventions presented adherence outcomes after one-year follow-up. None significantly enhanced adherence compared to the usual care in the primary analysis (OR ranged from 1.03 to 2.06 for adherence and from 1.11 – 1.18 for persistence). All targeted patients and three only included post-menopausal breast cancer patients. Three tested the same intervention consisting of educational materials. Only one was conducted in the US. Only one reported participants' ethnicity. Overall it was unclear whether the studies contained bias. The use of different terminology and operationalization of adherence made comparisons challenging.

Interventions to improve adherence to adjuvant hormonal therapy in US breast cancer populations that includes survivors who are ethnically diverse, premenopausal, and taking tamoxifen are necessary to inform future interventions. Adoption of consistent adherence definitions/measurements will provide a clearer framework to consolidate aggregate findings.

Given the limited efficacy of tested interventions, it is important to engage oncologists and academics to develop approaches that target different components associated with hormonal therapy adherence, such as doctor-patient communication or social support.

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Introduction

Breast cancer is the most commonly diagnosed cancer and the second highest cause of cancer death in women.¹ Luminal (A and B) or hormone receptor positive (estrogen and/or progesterone receptor positive; ER+, PR+) cancers are the most common subtypes of breast cancers.^{2, 3} Adjuvant hormonal therapy, through selective ER modulators (e.g., tamoxifen) and/or aromatase inhibitors (e.g., anastrozole), has contributed to significant reductions in recurrence and mortality in women with this diagnosis.^{4, 5} Adherence to the full course of treatment (one pill every day for at least 5 years) is necessary to obtain the full benefits of hormonal treatment.^{4, 5} Despite these benefits, between 31-73% of survivors discontinue adjuvant hormonal therapy in clinical practice,⁶ thereby reducing treatment efficacy.⁷⁻¹⁰ Due to the accuracy limitations of the methods to assess adherence (e.g., self-report, pill counts, pharmacy records, medical records, electronic medication caps),¹¹ there is no gold standard for measuring adherence.¹²⁻¹⁴ Moreover, given the challenges in measuring adherence behaviors¹¹ and overestimation of adherence by doctors and patients, published rates are probably an underestimation of the true adherence rates.¹⁵

Patient variables (e.g., age), social support, patient-provider communication, and healthcare factors (e.g., cost) have been associated with breast cancer survivor adherence to systemic therapies.^{6, 16-18} However, few interventions have been developed to improve adjuvant hormonal therapy adherence.⁶ This paper provides a systematic literature review of behavioral interventions designed to enhance adjuvant hormonal therapy adherence in breast cancer survivors. Study findings may be used to inform approaches used in addressing non-adherence to adjuvant hormonal therapy.

Methods

Search Strategy

The Preferred Reporting Items for Systematic Literature Reviews and Meta-Analysis (PRISMA)^{19, 20} was followed to conduct a systematic literature review about interventions to enhance adjuvant hormonal therapy adherence in breast cancer survivors. On October 9, 2014 two authors (AH, MC) searched PubMed-Medline, CINAHL, PsychInfo, Ovid-Medline, and EMBASE using the following key terms: (1) hormonal treatment medication (“hormone treatment,” “tamoxifen,” “aromatase inhibitors,” “endocrine therapy,” “adjuvant hormonal therapy,” and “systemic therapy”), (2) adherence (“treatment adherence,” “patient adherence,” “patient compliance,” “medication compliance,” “medication adherence,” “discontinuation,” and “persistence”), (3) breast cancer (“breast cancer,” “ductal carcinoma in situ,” and “breast neoplasms”), (4) survivors (“patients”), and (5) intervention (“interventions,” “clinical trial,” “behavioral interventions,” and “experimental studies”). All key terms were used to uncover the appropriate MeSH terms within each database's search engine, which were then exploded to include them in the results. Retrieved papers were imported into RefWorks to delete duplicates. An exemplary search with Ovid is provided in Table A1 (online only).

Inclusion and Exclusion Criteria

Papers were eligible if they included: (1) a behavioral intervention with (2) breast cancer survivors who are taking (3) hormonal treatment medication and (4) assessed adherence as a primary or secondary outcome. We did not limit the search by location, year, or language. Study protocols and studies that did not have the outcomes yet were excluded along with pharmacological clinical trials (testing the effectiveness of different types of drugs). In the first round of reviews, two authors (AH and MC) independently reviewed all the papers' titles and abstracts to check eligibility and categorized the papers as "Yes," "No," or "Maybe," based on whether they met the inclusion criteria. To classify reasons for excluding papers, AH and MC independently checked eligibility criteria in the order of breast cancer, intervention study, adjuvant hormonal therapy, and adherence outcomes and assigned the first eligibility criteria that papers did not meet as the reason for exclusion. Then the full text of all articles categorized as "Maybe" and "Yes" were independently reviewed by AH and MC. Consensus was reached through discussion, and a third author (VS), was consulted to resolve any disagreements on article status (see Figure 1).

Abstraction Process

The authors created a comprehensive data abstraction form to record and organize the characteristics of the papers (n=5) that met the eligibility criteria. AH and MC independently abstracted the data and two additional reviewers (CD and VS) resolved any discrepancies in data extraction. Information on the following variables were abstracted: sample size, age, type of intervention, intervention description, main findings, type of adjuvant hormonal therapy, study location, study design, intervention components, adherence outcomes, and adherence measures (see Tables 1 and 2). For the purpose of this systematic review, adherence was defined as the extent that a patient conforms to the prescribed frequency, timing, and dosage of treatment that a provider recommends, which is often operationalized as the "medication possession ratio" (number of doses dispensed in the overall dispensing period).²¹ Persistence was defined as the continuation of treatment for the specified length of treatment, which is often measured as the length of time between initiation and discontinuation.^{22, 23}

In papers that had multiple adherence outcomes reported, only the primary outcome was considered for this review. Adjuvant hormonal therapy adherence and persistence were expressed as proportions and were either abstracted^{14, 24} or calculated^{25, 26} based on reported data by two authors (TL and CD). Odds ratios (OR) and its 95% CI comparing adherence and persistence with adjuvant hormonal therapy in the intervention compared to the usual care group were also calculated from study results and are presented in Tables 3 and 4.

Risk of Bias Assessment

Studies were assessed for risk of bias using the Cochrane Collaboration's tool²⁷ that includes six potential biases: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other. Two authors (AH and MC) independently reviewed each bias and categorized

them as “Yes,” “No,” or “Unclear”. Discrepancies were solved by consensus and by consulting a third reviewer (CD) (see Table 5 and Supplemental Table 2A).

Results

Studies

A total of 587 records were identified after the initial search. After deleting duplicates, 376 records were screened for eligibility. Five papers met the eligibility criteria (see Figure 1 for additional details). Although English language was not an inclusion criterion, all articles that met eligibility criteria were in English.

As seen in Table 1 and Table 2, 80% (n=4) of papers included only breast cancer patients who were taking Aromatase Inhibitors (AIs) (three of them focused only on post-menopausal survivors). There was only one paper (20%) that included patients who were taking either AIs or tamoxifen and none of the studies were restricted to survivors taking tamoxifen only. Three papers (60%) measured adherence outcomes as both adherence and persistence. Adherence was measured by self-report in one paper (20%), by pharmacy records in two papers (40%), or by a combination of both in two papers (40%). Persistence was measured by case report forms (20%; n=1), pharmacy records (20%; n=1), or by a combination of both (20%; n=1). All interventions presented adherence follow-up at one year (n=5). Only one study was conducted in the US²⁸ and it was the only one that reported participants' ethnicity. In relation to the interventions, three of the studies tested the German-based PACT study intervention but in different contexts.^{14, 24, 25} In relation to the study design, 80% (n=4) of the papers consisted of randomized controlled trials (RCT; n=4), all included an educational component (100%; n=5), and 60% incorporated reminders (n=3). All interventions were targeted towards patients (100%; n=5). Only 40% of the interventions (n=2) presented were theory driven.^{26, 28} None of the studies yielded significant differences between the intervention and comparison arms in their primary analysis (see Tables 3 and 4).

Adherence Interventions Summary

The Patient's Anastrozole Compliance to Therapy (PACT) study (2013) tested the impact of an intervention consisting of educational materials and monthly reminders on adherence to anastrozole in ER+ postmenopausal breast cancer survivors in Germany.¹⁴ The educational materials were mailed to participants and comprised of nine pamphlets and ten personal letters written in layman terms with information about breast cancer, treatments, medication side effects, strategies for enhancing adherence, and information about diet and physical exercise. The primary endpoint analysis with 2,740 participants (usual care n=1,339; intervention n= 1,401) found no statistical differences between the intervention and usual care arms in adherence (OR: 1.03; CI: 0.81 – 1.30) and persistence (OR: 1.11; CI: 0.95 – 1.29).

The Compliance of Aromatase Inhibitors Assessment in Daily Practice through Educational Approach (CARIATIDE)²⁶ (2014) study tested in a RCT the impact of the PACT education materials on adherence to AIs in ER+ postmenopausal breast cancer survivors in 18 countries.²⁴ Although the materials were translated, there is limited information about the

type of adaptation conducted and the extent of how divergent the material became from the original PACT form. Findings from the final endpoint analyses (n=2,543) showed no significant differences in the odds of adherence (OR: 1.07; CI: 0.89 – 1.30) and persistence (OR: 1.18; CI: 0.95 – 1.46) between participants randomized to the intervention (n=1,268) and usual care arms (n=1,275). However, there were some significant differences in specific countries, as intervention had a significantly positive impact on overall adherence in Sweden/Finland (p=0.02) and a significantly negative impact in Austria/Switzerland (p=0.03).

Similarly, Yu and colleagues' (2012)²⁵ study tested the efficacy of the PACT education materials and a follow-up reminder service to improve AI medication adherence in ER+ postmenopausal breast cancer patients in China. It is not clear to what extent the PACT materials were changed in order to accommodate the Chinese context however (besides language). The study did not follow a RCT design; the intervention was implemented in 10 sites and compared to 10 matched sites receiving usual care. The operationalization of persistence in this study, as the proportion of days covered by prescription refills within a year, corresponds to our definition of adherence. The odds of adherence (OR: 1.01; CI: 0.42-2.43) were not significantly different in the intervention (n=241) and usual care (n=262) groups.

The Compliance in Adjuvant Treatment of Primary Breast Cancer Study (COMPAS) (2013) tested the efficacy of two interventions on AI adherence and persistence in ER+ breast cancer survivors using a three-arm RCT design in Germany.²⁶ The control arm received standard information. Participants in the letter arm received personalized motivational reminder letters with information including the importance and impact of disease, effects of AIs, and nurse contacts to answer questions. Participants also received a breast cancer leaflet with general information about cancer, sport, and nutrition. The telephone arm participants received calls from a nurse who used a semi-structured interview guided by motivational interviewing principles to provide motivation, reminders, and individualized information (e.g., feedback to questions regarding problems with medication). The primary analysis (n=171) found no statistically significant differences between the phone group and the usual care arms (OR 1.90; CI: 0.90-4.03) and between the letter group and usual care arms (OR: 2.06; CI: 0.97-4.36). Although no significant differences were found in the primary analysis, post-hoc pooled analysis suggested that the intervention groups had significantly higher rates of adherence (62.7% telephone, 64.7% letter) than the control group (48%; p=.039). In relation to persistence, there was a significant difference in mean persistence between the letter and the control groups, but there were no differences between control and phone or between phone and letter groups. Since persistence was measured as the duration (months) from initiation to discontinuation and only means were presented (not a cut-off criteria for considering participants persistent vs. not), ORs could not be calculated.

The Improving Patient Access and Adherence to Cancer Treatment (IMPAACT) (2009) trial tested the impact of a culturally tailored patient navigation model to enhance access and adherence to adjuvant treatment in a sample of breast (n=237) and gynecological cancer patients in a public safety net medical center with low-income, predominantly Hispanic patients in the US.²⁸ Adjuvant therapy included chemotherapy, radiation, and adjuvant

hormonal therapy (tamoxifen and AI). This two-arm trial randomized 237 breast cancer patients to an enhanced standard of care (EUC) arm or to a written information plus patient navigation (TPN) arm. EUC participants received enhanced standard oncology care (e.g., facilitation of medical treatment funding) and written resource navigation information. The health belief model and the socio-cultural explanatory theory informed the TPN intervention. Patients in the TPN arm received written information plus one initial structured phone interview facilitated by a patient navigator to assess adherence barriers, and provide health education, problem solving strategies, and self-management support. From the 44 patients that obtained tamoxifen or anastrozole, 59% were adherent and there was no significant difference in hormonal therapy adherence between the two arms. However, this study was excluded from the Odds Ratios tables due to lacking a definition of adherence, lacking adherence cut off criteria, and having potential missing data (the study only included hormonal adherence data for 44 out of the 153 breast cancer survivors taking adjuvant hormonal therapy). Thus, it was difficult to evaluate the results of this study regarding adjuvant hormonal therapy adherence per se.

Bias Analysis

Overall it was unclear whether the studies contained bias as they did not provide sufficient information to assess risk of bias such as sequence generation, allocation concealment, or blinding (see Table 5). All the studies were randomized except for Yu and colleagues'.²⁵ Only one study, by Ziller and colleagues,²⁶ explicitly mentioned blinding of the study staff (interviewers and analysts) although no details were presented regarding how blinding was achieved or whether participants were blinded (see Table 2A, only available as an online appendix, for more specific details about the bias analysis).

Discussion

Suboptimal adherence to hormonal therapy in ER+ breast cancer survivors has been well documented in the literature.^{5, 6, 10, 29} However, this systematic literature review only identified five behavioral interventions aimed at enhancing adherence in this population. None of the interventions significantly enhanced adherence outcomes in their primary analysis. All of the interventions included educational materials and were targeted to patients, mostly postmenopausal breast cancer survivors taking AIs. There was only one intervention conducted in the US, which was also the only one that focused on an ethnic minority group. Findings from this study suggest the need of developing and testing more interventions, targeting patients that have been underrepresented in the existing trials, and exploring other intervention targets that have been associated with limited adherence in the literature.

The finding that none of the interventions were effective at increasing adherence is at odds with other literature reviews (not focusing on hormonal therapy) that found approximately half of interventions significantly enhanced adherence in the context of chronic conditions,³⁰ medication prescriptions in general,³¹ and self-administered medications for chronic diseases.³² A reason behind the limited impact of the interventions we found may lay in the specific characteristics of hormonal therapy adherence patterns. Adherence rates were

generally high at year one in most studies, except in Ziller and colleagues', ranging from 81% to 96%. Most studies only presented one-year follow-up results. Since adherence to hormonal therapy tends to decrease over time,^{33, 34} expanding the time frame of data collection may provide further insights about the long-term impact of the interventions.

Another potential explanation of the limited efficacy of the interventions may rely on the intervention strategies. All the interventions were patient-focused (rather than physician-focused or patient-provider communication focused) and comprised of an educational and a reminder component.^{14, 24-26, 28} Three of the interventions tested the PACT educational materials that included information about hormonal therapy and strategies to adhere to the medication in addition to more general breast cancer information. Although the PACT intervention can be easily scalable as it is not resource intensive (mailing materials), educational materials alone may not be sufficient in impacting adherence outcomes. Nieuwlaat and colleagues' literature review (2014)³⁵ found that the most effective adherence interventions were more complex and multi-faceted (e.g., delivering education materials via both peers and nurses) and provided tailored, personal, and continuous education, counseling, and daily treatment support from health professionals (e.g., pharmacists) and supplemental support from family. Echoing this, Ziller and colleagues' (2013)²⁶ intervention, which included personalized motivational letters and motivational interviewing calls, was the only one with higher odds of enhancing adherence and that found a difference between the two intervention arms and the usual care arm in the pooled analysis.²⁶

The lack of consistency in the terms, definitions, and operationalization of adherence and persistence made comparisons challenging. For instance, some studies used the term "compliance" instead of "adherence,"^{14, 24, 25} which is currently favored due to the paternalistic connotations associated with the term compliance.³⁶ Yu and colleagues operationalized persistence as the proportion of days covered by prescription refills within a year, which is how adherence tends to be operationalized in the literature.³⁶ Persistence was measured in a plethora of different ways including self-report (i.e., still taking the medication-yes vs.no),²⁴ documented prescription of 365 tablets,¹⁴ or average number of months from initiation to discontinuation.²⁶ Such a lack of consistency in medical terminology and operationalization made the comparisons between various interventions challenging. Adoption of consistent definitions and measurements by researchers will provide a clearer framework and lexicon to better analyze across studies, consolidate aggregate findings, and therefore better understand which aspects of adherence interventions are effective.²²

In relation to the characteristics of the samples included in the studies, the target population in three of the studies was post-menopausal breast cancer patients taking AIs.^{14, 24, 25} Although studies have shown that adherence is problematic in both older and younger women similarly,⁶ the reasons for discontinuation or barriers to adherence may be different between the two groups. Frailty tends to be a concern in older women³⁷ while fertility issues uniquely impact younger premenopausal survivors.³⁸ Thus, designing interventions that take into account the unique needs of premenopausal survivors as well is warranted. Only one study included survivors taking tamoxifen.²⁸ A recent meta-analysis found that patients on tamoxifen had lower adherence rates compared to those taking AIs.³⁴ Thus, future studies

should include patients who are taking tamoxifen and test whether interventions should be targeted based on the type of adjuvant hormonal medication.

None of the studies conducted outside the US provided information about patients' race or ethnicity. Notably, Ell and colleagues' intervention focused predominantly on Latina breast cancer survivors in a public safety net medical center in the US. Although there is mixed evidence,^{39, 40} some research suggests that minority groups have lower adjuvant hormonal therapy adherence.^{8, 10, 29} Moreover, since some ethnic groups have the worst breast cancer mortality and morbidity outcomes,¹ it is key to assure that interventions include diverse populations.

In summary, findings from this literature reviews suggest that future interventions may benefit from: (1) providing clear definitions of adherence and adherence outcomes; (2) providing more details on the methods to facilitate bias analysis; (3) clearly outlining all aspects of the interventions; (4) designing interventions that can assess the differential impact of individual features in multifaceted interventions; (5) using more objective ways of measuring adherence (e.g., electronic monitors); (6) measuring the longer term effects of the interventions; and (7) utilizing diverse samples (e.g., accounting for race and ethnicity, medication type, and menopausal status).

Conclusion

The research on adjuvant hormonal therapy behavioral interventions in breast cancer patients has lagged behind in the US. Given the limited success of prior interventions tested thus far, there is a need for developing and testing more dimensional and innovative approaches that target other components that have been associated to hormonal therapy adherence such as doctor-patient communication and social support.

Good communication between doctors and patients is associated with higher adherence to hormonal therapy,²⁹ but this remains an unexplored intervention target. An observational linguistic study that analyzed doctor-patient communication around adjuvant hormonal therapy found that doctors tend to do monologues providing general information about adjuvant hormonal therapy, but do not spend enough time discussing with the patient about potential barriers and how the treatment may particularly impact them.⁴¹ There is also evidence that survivors who reported (1) lack of understandable information about treatment, (2) not being told about side effects in advance, (3) having limited opportunity to ask questions at the time of diagnosis, and (4) never having been asked about the difficulties of taking adjuvant hormonal therapy, exhibited lower rates of adherence to hormonal treatment.¹⁶⁻¹⁸ Conversely, patient-centered communication and patients' perceived self-efficacy in interacting with doctors has been associated with higher adherence to hormonal treatment.⁴⁰ Thus, designing interventions that enhance doctors' communication skills around adherence and managing side effects may be effective strategies.

While hormonal treatment related side effects such as hot flashes and osteoporosis⁴² represent one of the main reasons for discontinuation,⁶ none of the retrieved interventions had an explicit focus on side effects. We retrieved several studies that tested the impact of

interventions (e.g., acupuncture, exercise) on adjuvant hormonal therapy related side effects but they did not focus or measure adherence to the treatment.⁴³⁻⁴⁵ Thus, future intervention studies that aim to improve side effects would benefit from including adherence to adjuvant hormonal therapy as an outcome.

Social support has also been associated with higher adherence in a meta-analysis with various medical conditions⁴⁶ and in several adjuvant hormonal therapy studies with breast cancer survivors.^{16, 17, 47} Ergo, including other members, such as relatives or any other caregivers, in adherence interventions may also prove to be an effective strategy. Finally, the use of new technology (e.g., especially for reminders) has been proven to be effective in improving adherence rates in other chronic conditions such as HIV or diabetes.^{48, 49} This aspect was unexplored in the retrieved studies.

Limitations

As in any systematic literature review, it is not possible to assure that all the behavioral adjuvant hormonal therapy interventions were retrieved due to the limitations of using MeSH terms and publication bias.^{19, 20} However, the authors included five search engines and adapted the search strategy as necessary for each one. Since publication bias tends to occur when negative findings are not published,²⁰ if there were unpublished papers, they would probably confirm the limited efficacy of the interventions to improve adjuvant hormonal therapy adherence rates. Most information retrieved came from studies that had an unclear risk of bias. The limited information provided on some aspects of the study methods limited the authors' ability to judge the probability of some of the potential biases. Furthermore, since this review focused solely on studies regarding adjuvant hormonal therapy, caution must be used in extrapolating these findings to other types of diseases or treatments. Despite these caveats, this is the first systematic literature review on behavioral interventions aimed to increase adherence to adjuvant hormonal therapy in ER+ breast cancer patients.

Implications for Practice

It is important for oncologists and other medical providers to be aware about the dearth of tested interventions, especially in the US, and the fact that the intervention strategies tested have not proven to be effective in increasing adherence.^{14, 24-26, 28} Since the provision of educational materials alone may not be sufficient to enhance adherence, providers would benefit from having an active approach to assessing adherence and adherence barriers. Collaborations between providers and academics will be key in the future to develop and test new interventions that include underrepresented participants such as premenopausal survivors and ethnically/racially diverse populations and interventions that target different components that have been associated with adjuvant hormonal therapy adherence such as doctor-patient communication or social support.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Literature Review Method

Table 1

Study Characteristics

Papers	Sample Size	Age	Type of intervention	Intervention description	Main Findings
Ell et al., 2009	237 breast cancer patients randomized	Enhanced Usual Care: 55% 50 years old Intervention: 56% 50 years old	Education, patient navigation, problem solving, self management support, emotional support Focus: Patients Theory driven: Yes	Enhanced Usual Care: standard of care (supportive services) Intervention: structured phone interviews to assess adherence barriers, health education, problem solving, and self-management support. Assigns participants through an adherence risk algorithm to services of different intensity (levels 1-3)	Primary end point: Adherence: UC ↔ Intervention
Yu et al., 2012	503	Usual Care: Md=59, range=34-83 Intervention: Md=58, range=26-87	Education and reminders Focus: Patient Theory driven: No	Usual Care: standard therapy Intervention: welcome packet, quarterly newsletters, reminder calls	Primary end point: Adherence: UC ↔ Intervention
Hadji et al., 2013	4844 randomized	Usual Care: Md=64.9 Intervention: Md=65.1	Education materials and reminders Focus: Patient Theory driven: No	Usual care: standard therapy Intervention: UC + Educational Materials: nine mailed letters and brochures, monthly reminders on persistence to endocrine therapy, gift items (e.g. 7-day table box, pocket mirror)	Primary end point: Adherence: UC ↔ Intervention Primary end point: Persistence: UC ↔ Intervention
Ziller et al., 2013	181 randomized	Usual Care: M=62.5, SD=8.5 Phone Group: M=64.1, SD=9.8 Letter Group: M=63.2, SD=8.1	Education, motivation and reminders. Focus: Patient Theory driven: Yes	Usual care: Standard information Letter group: eight personalized motivational reminder letters over two years with information (e.g. AIs' side effects), and breast cancer info leaflet (e.g. nutrition, and cancer) Telephone group: eight calls in two years, motivational interviewing to address questions, challenges, and provide information and reminders	Primary end point: Adherence: UC ↔ Telephone UC ↔ Letter, Letter ↔ Telephone Pooled analysis: Intervention arms together ↑ adherence than UC Persistence: Letter group ↑ adherence than UC, UC ↔ Telephone, Letter ↔ Telephone
Neven et al., 2014	2758 randomized	Usual Care: M= 62.5, SD=9.4 Intervention: M=62.8, SD=9.4	Education materials Focus: Patient Theory driven: No	Usual care: standard therapy Intervention: UC + Educational Materials: welcome packet plus nine mailed letters and brochures	Primary end point: Adherence: UC ↔ Intervention (Only ↑ adherence in the intervention vs. US in Sweden/ Finland) Primary end point: Persistence: UC ↔ Intervention

Table 2
Summary Characteristics

Manuscripts' Characteristics N = 5	N (%)	References
Hormone Therapy		
Aromatase Inhibitors only	4 (80)	Hadji et al. 2013, Neven et al. 2014, Yu et al. 2012, Ziller et al. 2013
Tamoxifen only	0 (0)	
Aromatase Inhibitors and Tamoxifen	1 (20)	Ell et al. 2009
Location		
Single Country	4 (80)	Ell et al. 2009, Hadji et al. 2013, Yu et al. 2012, Ziller et al. 2013
Germany	2 (40)	Hadji et al. 2013, Ziller et al. 2013
US	1 (20)	Ell et al. 2009
China	1 (20)	Yu et al. 2012
Multiple Countries (Europe, America, Australia)	1 (20)	Neven et al. 2014
Design		
Randomized Controlled Trial	4 (80)	Ell et al. 2009, Hadji et al. 2013, Neven et al. 2014, Ziller et al. 2013
Non-randomized Controlled Trial	1 (20)	Yu et al. 2012
Intervention Components		
Educational (provision of educative material)	5 (100)	Ell et al. 2009, Hadji et al. 2013, Neven et al. 2014, Yu et al. 2012, Ziller et al. 2013
Motivation	1 (20)	Ziller et al. 2013
Reminders	3 (60)	Hadji et al. 2013, Yu et al. 2012; Ziller et al. 2013
Patient Navigation	1 (20)	Ell et al. 2009
Problem Solving	1 (20)	Ell et al. 2009
Self-management Support	1 (20)	Ell et al. 2009
Emotional Support	1 (20)	Ell et al. 2009
Adherence Outcomes		
Adherence only	2 (40)	Ell et al. 2009, Yu et al. 2012
Adherence and Persistence	3 (60)	Hadji et al. 2013, Ziller et al. 2013; Neven et al. 2014
Adherence measures		
Pharmacy records only	2 (40)	Ell et al. 2009; Yu et al., 2012;
Self-report only	1 (20)	Neven et al., 2014
Pharmacy records and self-report	2 (40)	Hadji et al. 2013, Ziller et al. 2013
Persistence measures		
Pharmacy records only	1 (20)	Ziller et al., 2013
Case report form only	1 (20)	Hadji et al., 2013
Case report form and self-report	1 (20)	Neven et al., 2014

Table 3

Adherence

		Total subjects in study	Adherence (N %)	OR	95% LCI	95% UCI	p value
Ziller (Phone)	Intervention	114	36	1.90	0.90	4.03	0.0915
	Control (ref)		27				
Ziller (Letter)	Intervention	114	37	2.06	0.97	4.36	0.0605
	Control (ref)		27				
Yu	Intervention	503	231	1.01	0.42	2.43	0.9781
	Control (ref)		251				
Neven (overall)	Intervention	2543	1036	1.08	0.88	1.32	0.457
	Control (ref)		1027				
Hadji PACT	Intervention	2740	1244	1.03	0.81	1.30	0.8078
	Control (ref)		1185				

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Table 4

Persistence

		Total subjects in study	Persistence (N %)		OR	95% LCI	95% UCI	p value
Neven (persistence)	Intervention	2543	1086	86%	1.18	0.95	1.46	0.1396
	Control (ref)		1065	84%				
Hadji PACT	Intervention	2740	603	43%	1.11	0.95	1.29	0.174
	Control (ref)		542	40%				

Summarized Bias Table

Table 5

Bias Items	Hadji et al., 2013	Neven et al., 2014	Yu et al., 2012	Ziller et al., 2013	Ell et al., 2009
Sequence Generation	Unclear	Unclear	No	Unclear	Unclear
Allocation Concealment	Unclear	Unclear	No	Unclear	Unclear
Blinding of Participants, Personnel, and Outcomes	Unclear	Unclear	Unclear	Unclear	Unclear
Incomplete Outcome Data	Unclear	Yes	Unclear	Unclear	Yes
Selective Outcome Reporting	Unclear	Unclear	Unclear	Unclear	Unclear
Other (e.g., Goodwill bias, Recall bias)	Unclear	Unclear	Unclear	Unclear	Unclear