A Systematic Review and Meta-Analysis of Interventions to Promote Adjuvant Endocrine Therapy Adherence Among Breast Cancer Survivors

Emma E. Bright, PhD[1]; Lauren B. Finkelstein, MA[1]; Madeline S. Nealis, MPH[1]; Sarah R. Genung, BA[1]; Jordan Wrigley, MSLS, MA[1]; Heng Chao J. Gu, BA[1]; Sarah J. Schmiege, PhD[2]; and Joanna J. Arch, PhD[1,3]

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ABSTRACT

PURPOSE Adjuvant endocrine therapy (AET) adherence among breast cancer survivors is often suboptimal, leading to higher cancer recurrence and mortality. Intervention studies to promote AET adherence have burgeoned, more than doubling in number since this literature was last reviewed. The current aim is to provide an up-to-date systematic review and meta-analysis of interventions to enhance AET adherence and to identify strengths and limitations of existing interventions to inform future research and clinical care.

METHODS Systematic searches were conducted in three electronic databases. Studies were included in the systematic review if they examined an intervention for promoting AET adherence among breast cancer survivors. Studies were further included in the meta-analyses if they examined a measure of AET adherence (defined as compliance or persistence beyond initiation) and reported (or provided upon request) sufficient information to calculate an effect size.

RESULTS Of 5,045 unique records, 33 unique studies representing 375,951 women met inclusion criteria for the systematic review. Interventions that educated patients about how to manage side effects generally failed to improve AET adherence, whereas policy changes that lowered AET costs consistently improved adherence. Medication reminders, communication, and psychological/coping strategies showed varied efficacy. Of the 33 studies that met the inclusion criteria for the systematic review, 25 studies representing 367,873 women met inclusion criteria for the meta-analysis. The meta-analysis showed statistically significant effects of the adherence interventions overall relative to study-specified control conditions (number of studies [k] = 25; odds ratio, 1.412; 95% CI, 1.183 to 1.682; P = .0001). Subgroup analyses showed that there were no statistically significant differences in effect sizes by study design (randomized controlled trial *v* other), publication year, directionality of the intervention (unidirectional *v* bidirectional contact), or intervention type.

CONCLUSION To our knowledge, this is the first known meta-analysis to demonstrate a significant effect for interventions to promote AET adherence. The systematic review revealed that lowering medication costs and a subgroup of psychosocial and reminder interventions showed the most promise, informing future research, policy, and clinical directions.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Hormone receptor–positive (HR+) breast tumors are the most common form of breast cancer in the United States, accounting for approximately 83% of cases with known HR/human epidermal growth factor receptor 2 status.[1] Adjuvant endocrine therapies (AETs)—including tamoxifen and aromatase inhibitors (AIs)—are effective pharmacologic treatments for improving HR+ breast cancer prognosis, reducing the risk of recurrence up to 50%.[2,3] Despite the potential for improved prognosis, the benefits of AET are not fully realized because of patient nonadherence (ie, failure to take the medication as prescribed). AETs are typically prescribed for 5-10 years[4,5]; however, up to 40% of patients discontinue the medication early and 30% of patients take the medication less frequently than directed.[6,7] Poor medication persistence and adherence have substantial mortality costs: AET nonadherence is associated with a 49% increase in all-cause mortality.[8]

CONTEXT

Key Objective

What are effective intervention strategies for promoting adjuvant endocrine therapy (AET) adherence among women diagnosed with breast cancer?

Knowledge Generated

The meta-analytic subgroup findings indicated that a wide variety of approaches to increasing AET adherence can be effective. Effect sizes have not improved over time; more powerful approaches or more precision within existing interventions will be needed to advance efficacy.

Relevance *(K.D. Miller)*

The benefits of endocrine therapy are profound but attenuated in practice by poor adherence. Policies to lower out-of-pocket cost and reminders to patients increase adherence.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

The literature has documented a wide range of risk factors for AET nonadherence, including medication side effects, negative beliefs about the value of AET, and sociodemographic characteristics such as lower income.[9] Many of the barriers to improving AET adherence are sociobehavioral and potentially modifiable; thus, there is an urgent need for effective interventions that target these barriers to improve breast cancer survivors' prognosis.

Given suboptimal adherence and the large number of breast cancer survivors prescribed AET, research on interventions to increase AET adherence is burgeoning. Previous systematic reviews and meta-analyses[10-12] are older, including research published in 2017 or earlier, and the sole meta-analysis analyzed only seven studies. Since the publication of these reviews, the number of new studies has more than doubled, with 18 new studies published after 2017. The significant expansion of research focused on improving AET adherence warrants an updated systematic review and a meta-analysis that quantifies the effects of interventions aimed at promoting AET adherence. Developing a comprehensive understanding of the current status of AET interventions—what has worked, what has not worked, and for whom—is a critical next step in advancing researchers' and clinicians' knowledge about how best to support breast cancer survivors in taking AET and how to advance the research in this field.

The current study has two aims. First, we provide an updated systematic review of interventions that promote AET adherence among women diagnosed with breast cancer. This up-to-date review more than doubles the number of included studies compared with previous efforts,[10,12] and triples the number included in the sole previous meta-analysis,[11] leading to a more comprehensive and accurate understanding of intervention effectiveness. The systematic review also leverages the extensive research on risk factors for AET nonadherence to evaluate the extent to which extant interventions specifically address known risk factors (eg, a depression diagnosis). Second, we conduct a meta-analysis to determine the strength of the effect of interventions to date. Intervention subgroups are investigated in the meta-analysis to identify the most promising approaches. In brief, the goals of this systematic review and meta-analysis are to provide up-to-date evidence regarding interventions that promote AET adherence and to identify the strengths and weakness of current approaches to guide future research, policy, and clinical efforts.

METHODS

Eligibility Criteria

Included studies met the following eligibility criteria: (1) full text was published in English and available online by November 22, 2022; (2) separately analyzed a sample or subsample of adult (age 18 years and older) women with a diagnosis of breast cancer who were prescribed AET (tamoxifen and/or AIs); and (3) evaluated an intervention aimed at improving adherence to AET among women diagnosed with breast cancer. Beyond these systematic review criteria, additional inclusion criteria for the meta-analysis were (4) included a measure of AET medication adherence, defined as a measure of compliance or persistence beyond prescription initiation, and (5) provided sufficient information to calculate an effect size (or provided by the authors upon request). Eligible records were not required to be randomized controlled trials (RCTs) because many of the largest studies in real-world settings were observational and the goal was to identify a comprehensive set of promising intervention strategies and to increase the generalizability of the findings.

Data Collection

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[13] A research librarian who specializes in systematic reviews (J.W.) developed,

translated, and executed a search string in three databases: MEDLINE (PubMed), PsycINFO (EBSCO), and Embase (Elsevier). These databases were selected on the basis of their ability to return a comprehensive set of studies on the focal topic. The search string included a mix of keywords and subject headings related to breast cancer, AET, and adherence. No restrictions were placed on date or language of publication. Editorials, letters, and comments were excluded, as were animal-only studies. Reproducible search strategies can be found in Appendix Table A1 (online only). Additional references were identified by hand-searching the bibliographies of the included articles. The search was executed in October 2021 and updated in November 2022.

Meta-Analytic Statistical Approach

Because the majority of the focal studies used an 80% cutoff for AET adherence (ie, participants were considered adherent if adherence was ≥80% during the study), we used the same ≥80% cutoff as the definition of adherence in our meta-analysis. As the outcome was binary (adherent/nonadherent), odds ratios (ORs) were selected as the measure of effect size. Log ORs were extracted from the studies or calculated using the R package meta.gen.[14] A random-effects model was used to calculate pooled ORs and 95% CIs. Given the variability in study design and adherence measurement, we examined heterogeneity using the Q and I^2 statistics.[15] When multiple adherence outcome measures were available within a single study, the most objective measure was selected (eg, prescription records over self-report). If multiple follow-up points were included in the study, the 6-month follow-up, or the follow-up closest to that time, was selected to achieve greater consistency across studies. Four studies that included AET prescription initiation but not persistence or compliance were excluded from the meta-analysis to allow for a comparison of adherence over time.[16-19] If the manuscript contained insufficient data to calculate an OR, we contacted the authors to request it and included the estimate if the data were provided. Of the 33 studies identified for the systematic review, 25 were included in the meta-analysis (Fig 1). We conducted four subgroup analyses examining (1) study design, (2) publication date, (3) interventions that included interaction with cancer care providers/research team (*v* those that did not), and (4) policy (*v* nonpolicy) interventions. A random-effects model was used for all subgroup analyses apart from (3) because the interaction-based studies had limited heterogeneity, indicating that a fixed-effects model was appropriate.

RESULTS

Study Selection

As illustrated in Figure 2, the initial searches yielded a total of 8,900 citations across the three databases. All citations were imported into the online screening platform Covidence (Cochrane) via EndNote (Clarivate). After discarding duplicate citations (n = 3,855), two reviewers (among E.E.B., L.B.F., M.S.N., S.R.G., and H.C.J.G.) independently screened each unique article (n = 5,045) by title and abstract, excluding irrelevant articles that did not align with the screening criteria (n = 4,951). A third reviewer adjudicated disagreements regarding eligibility. Two independent reviewers then assessed the full text of the remaining articles (n = 94) to exclude irrelevant studies (n = 60), and a third adjudicated disagreements. Inter-rater reliability for study inclusion was 97.44%. Two of the study authors extracted the data from the final included unique studies (n = 33) and the first author established consensus on extracted information.

Risk of Bias

The Cochrane revised risk-of-bias tool[20] was used to categorize each study as low risk, moderate risk (termed some concerns), or high risk of bias. Of the included studies, six had a low risk of bias, 21 had some risk of bias, and seven had a high risk of bias overall (Table 1). The risk of bias differed

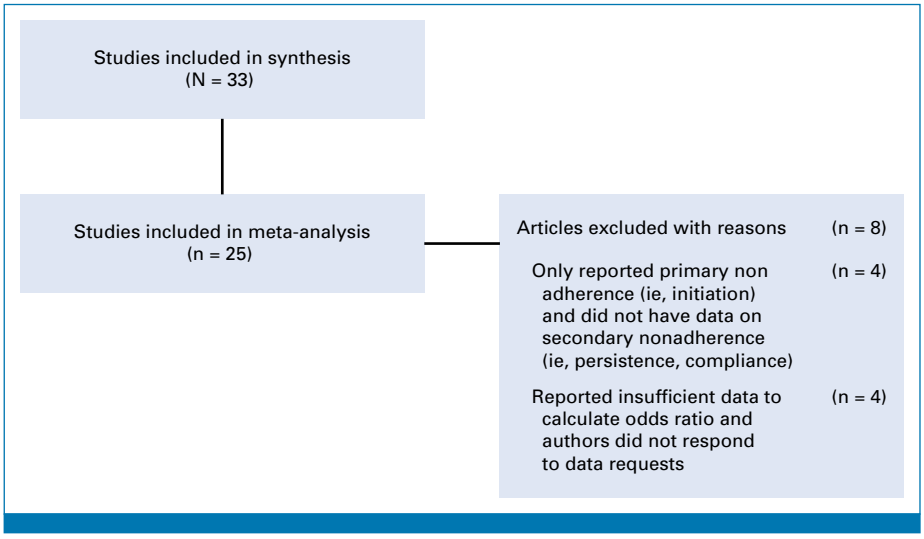

FIG 1. Flowchart of meta-analysis study selection.

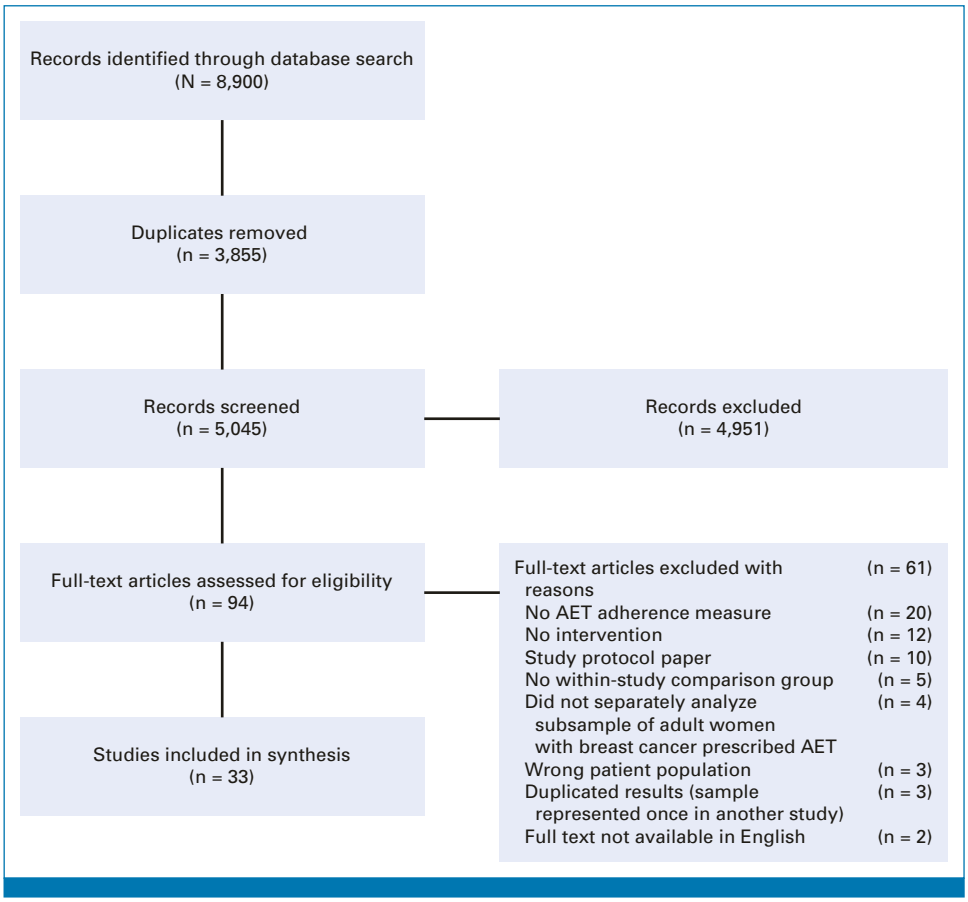

FIG 2. PRISMA flowchart of systematic review study selection. AET, adjuvant endocrine therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

significantly across studies because of variations in study designs (eg, RCT, pre-post, historical control) and sample size (eg, large trials, small pilots).

Participant Characteristics

This systematic review includes adherence data from 375,951 breast cancer survivors prescribed AET across 33 studies. Thirty-four records are represented in Table 2. All studies used unique samples with the exception of Markopoulos et al[28] and Neven et al,[71] which used the same sample. Only Markopoulos et al[28] was summarized in the systematic review because it was the most recent record with main effects reported. Only data from Neven et al[71] were used to calculate an effect size for the meta-analysis because they more closely conform to the measurement criteria of a 6-month follow-up. The meta-analysis represents a total of 367,873 participants across 25 studies.

Description of Adherence Measurement and Timing

Type of AET

Studies varied regarding included medication types. The majority (n = 21) included patients taking any type of AET, while a sizable minority focused exclusively on AIs (n = 10) or tamoxifen (n = 2). Of the 25 studies included in the meta-analysis, the majority (n = 14) included patients taking any type of AET, several focused exclusively on AIs (n = 9) or tamoxifen (n = 2).

Adherence Measurement

Most of the studies (n = 22) used dichotomous measures of adherence, with participants considered adherent if they received (confirmed via prescription records) or took (confirmed via electronic monitoring or self-report) ≥80% of the medication as prescribed during the study period.[16-19,21-38] Comparatively few studies (n = 8) used continuous measures of adherence.[39-46] Studies collected adherence data in various ways including self-report, medical chart records, prescription records, health insurance claims, electronic monitoring devices, and biological assays (urine or blood). Seven studies used more than one measure of adherence.[23,24,28,35,38,43,45]

Timing

Approximately half of the studies (n = 15) intervened early in patients' treatment trajectories, either at prescription initiation[16,17,23-26,30,36-38,43] or in the first year and a half

TABLE 1. Cochrane's Risk of Bias for Included Studies

Study	Sample Size	Randomization Overall Bias Risk	Missing Outcome Data Overall Bias Risk	Overall Bias Risk
Albert et al, 2011[a,21]	149	Some concerns	Some concerns	High
Alkhayyat et al, 2012[a,48]	160	High	Low	High
Arch et al, 2022[a,39]	88	Low	Low	Low
Castaldi et al, 2017[16]	117	High	Low	Some concerns
Chin et al, 2019[22]	6,900	Some concerns	Low	Some concerns
Ell et al, 2009[18]	153	Some concerns	Low	Some concerns
Getachew et al, 2022[a,23]	101	High	High	High
Graetz et al, 2018[a,24]	43	Low	Low	Some concerns
Hadji et al, 2013[a,25]	2,740	Low	Some concerns	Some concerns
Helzlsouer et al, 2016[17]	98	Some concerns	Low	Low
Hershman et al, 2020[a,49]	702	Low	Low	Low
Irwin et al, 2015[a,44]	121	Low	Low	Low
Jacob et al, 2015[a,26]	4,915	High	Low	Some concerns
Jacobs et al, 2022[a,45]	83	Some concerns	Some concerns	Low
Keating et al, 2022[a,42]	490,357	Some concerns	Some concerns	Some concerns
Krok-Schoen et al, 2019[43]	27	High	Some concerns	High
Lee et al, 2020[a,27]	7,867	High	Low	Some concerns
Markopoulos et al, 2015[28]	2,242	Low	Some concerns	Some concerns
McArthur et al, 2009[19]	838	Some concerns	Low	Some concerns
Moon et al, 2019[a,29]	27	High	Low	High
Mougalian et al, 2017[30]	189	High	Low	Some concerns
Neuner et al, 2015[a,31]	16,462	Some concerns	Low	Some concerns
Neuner et al, 2022[a,32]	18	High	Low	High
Neven et al, 2014[a,71]	2,543	Low	Some concerns	Some concerns
Park et al, 2022[41]	57	Low	Low	Some concerns
Qin et al, 2022[a,33]	20,677	High	Low	Some concerns
Ream et al, 2021[46]	59	Some concerns	High	Some concerns
Riis et al, 2020[a,47]	124	Low	Low	Some concerns
Singleton et al, 2022[a,34]	156	High	Some concerns	Some concerns
Tan et al, 2020[a,35]	242	Low	Low	Low
Wagner et al, 2016[a,36]	230	High	Low	High
Yu et al, 2012[a,40]	503	Some concerns	Low	Some concerns
Yu et al, 2021[a,37]	4,475	High	Some concerns	High
Ziller et al, 2013[a,38]	171	Low	Low	Some concerns

[a]Indicates that the study was included in the meta-analysis.

of adjuvant treatment.[28,34,40,47] Four of these studies examined only AET initiation.[16-19] Fifteen studies included women across the full trajectory of adjuvant treatment (0-5+ years).[22,27,29,32,33,35,39,41,42,44-46,48-50] One study included patients who had taken 4-5 years of tamoxifen at baseline and were eligible to continue with letrozole,[19] and two studies did not report any information regarding how long women had been taking AET.[18,21]

Participant Selection on the Basis of Risk Factors for Nonadherence

A minority of studies (n = 8) selected participants with a known risk factor for nonadherence: low income,[16,17,36] suboptimal baseline adherence or difficulties taking their medication,[29,32,39] significant AI-related pain,[44] or elevated AET distress about taking the medication or medication side effects.[45] Apart from studies that focused on low-income women,[16,17,36] no studies recruited participants on the basis of other known demographic risk factors for nonadherence (eg, age, race/ethnicity).

Cultural Tailoring of Interventions

Eighteen studies were conducted in the United States, four in Germany, two in Canada, and two in China; the remaining 16 studies were each conducted in a different country or were multinational. None of the studies reported

TABLE 2. Characteristics and Findings: Studies of Interventions to Promote AET Adherence Among Women With Breast Cancer

Author	Sample Size	Study Design	AET Type	Medication Timing at Enrollment	Patients Selected With a Risk Factor for Nonadherence	Adherence Measure	Study Conditions	Main AET Adherence Findings	Odds Ratio	Country
Albert et al, 2011[a,21]	149	Observational study	AIs; tamoxifen	No information	No	Self-report measures	1. Breast care nurse contact 2. No breast care nurse contact	Nurse contact led to significantly more adherence than no nurse contact (79% *v* 56%)	3.000	Germany
Alkhayyat et al, 2012[a,48]	160	Observational study	AIs; tamoxifen	Mixed (0-5+ years)	No	Self-report measures	1. Central cohort—follow-up visits at Regional Cancer Program 2. Peripheral cohort—follow-up through their family doctor or primary surgeon	No cohort differences in adherence	1.351	Canada
Arch et al, 2022[a,39]	88	Randomized controlled trial	AIs; tamoxifen	Mixed (0-5+ years)	Yes	Electronic monitoring device; self-report measures	1. Online education 2. Online/remote REACH: Education and values online intervention	REACH adhered significantly more than education for month 1 of follow-up but not thereafter	3.889	United States
Castaldi et al, 2017[16]	117	Observational study with historical control	AIs; tamoxifen	Prescription initiation	Yes	Medical records	1. Navigated care: Patients paired with navigator at the time of diagnosis who provided education, resources, appointment reminder calls, and met patients at appointments 2. Usual care	Navigated care significantly reduced days to AET initiation in an underserved minority community	—	United States
Chin et al, 2019[22]	6,900	Observational study	AIs; tamoxifen	Mixed (0-5+ years)	No	Health insurance claims	1. Patients residing in states enacting oral parity legislation in 2008-2013 who initiated AET with an index claim in the 12 months before the law was enacted 2. Patients residing in state enacting oral parity legislation in the 12 months after the law was enacted 3. Patients residing in states without oral parity legislation as of January 1, 2015	Oral parity legislation was associated with lower copayment amounts, which was in turn associated with greater adherence	—	United States
Ell et al, 2009[18]	153	Randomized controlled trial	AIs; tamoxifen	No information	No information	Prescription records	1. Written information plus patient navigation of phone call/assessment covering adherence barriers, health education, problem-solving, and self-management support. Then applied nonadherence risk algorithm to assign support intensity: Level 1 service (6- and 12-m FU calls), level 2 (phone or in-person navigation services), and level 3 (brief depression or anxiety counseling and/or counseling referral) 2. Enhanced usual care site—SC plus listings of supportive care resources educational pamphlets on depression and cancer	No significant difference in the adherence refills between conditions	—	United States
Getachew et al, 2022[a,23]	101	Randomized controlled trial	Tamoxifen	Prescription initiation	No	Prescription records; self-report measure	1. Breast nurses trained to deliver comprehensive service package of education about breast cancer, medication reminders, and patient support control group 2. Usual care	No statistically significant difference in treatment adherence between groups at 6-month follow-up. At 12 months, the intervention group had significantly higher adherence based on self-report but not for medication refill data	2.186	Ethiopia
Graetz et al, 2018[a,24]	43	Randomized controlled trial	AIs	Prescription initiation	No information	Self-report measure	1. App + reminder: In addition to app, received weekly reminders via text message and/or email to use the app 2. App: Used to report symptoms and medication use, with built-in alerts sent to care team	Significantly higher AI adherence in the app + reminder group (100%) than in the app group (72.7%)	16.939	United States
Hadji et al, 2013[a,25]	2,740	Randomized controlled trial	AIs	Prescription initiation	No	Self-report measures; pharmacy records	1. Standard AET + educational materials 2. Standard AET—1 mg anastrazole once daily	There was no difference between arms in either compliance or persistence rates	1.030	Germany
Helzlsouer et al, 2016[17]	98	Randomized controlled trial	AIs; tamoxifen	Prescription initiation	Yes	Medical records	1. Web-based navigation program with nurse/social worker support, AET information, and a netbook computer, and internet access 2. Web-based information access only	All patients in the intervention arm initiated AET, while three in the control condition did not. There was no statistically significant difference between groups	—	United States
Hershman et al, 2020[a,49]	603	Randomized controlled trial	AIs	Mixed (0-5+ years)	No	Urine assays	1. Text messaging—2×/week educational text messages for 3 years 2. Control—No text messages	No significant difference in time to adherence failure by study arm	0.814	United States
Irwin et al, 2015[a,44]	121	Randomized controlled trial	AIs	Mixed (0-5+ years)	Yes	Self-report measures	1. Exercise—A 12-month long 2×/week supervised resistance training program and a home-based aerobic exercise program 2. Usual care—Participants were not encouraged or discouraged from exercising	At 12 months, adherence was higher in the exercise group (80%) than in the usual care group (76%), but statistical significance was not tested	1.241	United States
Jacob et al, 2015[a,26]	4,915	Observational study	AIs; tamoxifen	Prescription initiation	No	Medical records	1. Disease management program 2. SC	Relative to those in the SC group, patients in disease management programs had significantly lower rates of discontinuation within 3 years of therapy initiation	1.348	Germany
Jacobs et al, 2022[a,45]	83	Randomized controlled trial	AIs; tamoxifen	Mixed (0-5+ years)	Yes	Electronic monitoring device; self-report measures	1. STRIDE—Usual care + medication monitoring with MEMS + relaxation training, cognitive reframing, acceptance skills, progressive muscle relaxation, mindfulness, and managing fears of recurrence 2. Control group—Medication monitoring and usual care	There was no statistically significant difference in adherence between the control and intervention groups	1.390	United States
Keating et al, 2022[a,42]	315,212	Pre/post design	AIs; tamoxifen	Mixed (0-5+ years)	No information	Prescription records	1a. Clinics participating in OCM before OCM 1b. Clinics participating in OCM after OCM 2a. Clinics that do not participate in OCM before OCM 2b. Clinics that do not participate in OCM after OCM	Adherence to AET was stable in OCM and comparison clinics, with no relative impact of OCM on adherence overall	0.967	United States
Krok-Schoen et al, 2019[43]	27	Pre/post design	AIs; tamoxifen	Prescription initiation	No	Blood serum; self-report measure	1. Before texting intervention—Daily text messages and weekly adherence surveys for 90 days focused on initiation, continuation, and adherence to prescribed dose 2. After texting intervention	Participants' self-reported adherence improved significantly from baseline to study end. Estradiol, estrogen, and estrone also decreased over this period, corroborating the accuracy of participants' self-reports	—	United States

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TABLE 2. Characteristics and Findings: Studies of Interventions to Promote AET Adherence Among Women With Breast Cancer (continued)

Author	Sample Size	Study Design	AET Type	Medication Timing at Enrollment	Patients Selected With a Risk Factor for Nonadherence	Adherence Measure	Study Conditions	Main AET Adherence Findings	Odds Ratio	Country
Lee et al, 2020[a,27]	7,867	Pre/post design	AIs; tamoxifen	Mixed (0-5+ years)	Yes	Prescription records	1. Before (2005-2007) program implementation—Nonadherent women received mailed reminder letters; health care provider contacted if nonadherence persisted after first letter 2. After intervention (2012-2014)	Patients had statistically significantly higher adherence after outreach program than before outreach	1.450	United States
Markopoulos et al, 2015[b,28]	2,242	Pre/post design	AIs	0-1 years	No	Prescription records; self-report measure	1. Standard AI treatment plus educational materials 2. Standard AI treatment	There was no statistically significant difference in adherence or persistence at 1 or 2 years	—	18 countries worldwide
McArthur et al, 2009[19]	838	Pre/post design	AIs	Prescription initiation: 4-5 years of tamoxifen were baseline for eligibility, while the study sought out women who were eligible for future treatment via letrozole	No	Prescription records	1. Before letter notification program—Letters sent to communicate a new treatment protocol for extended adjuvant letrozole in eligible women 2. After letter notification program	Letrozole prescriptions significantly increased after the letter mail-out	—	Canada
Moon et al, 2019[a,29]	27	Pre/post design	Tamoxifen	Mixed (0-5+ years)	Yes	Self-report measures	1. Before CBT-based intervention self-directed psychoeducational manual and two research team telephone calls 2. After intervention	Participants showed small statistically significant improvements in adherence over time	7.689	United Kingdom
Mougalian et al, 2017[30]	189	Pre/post design	AIs; tamoxifen	Prescription initiation	No	Self-report measures	1. A texting application that reminded participants to take and refill their medication, alerted health care providers of nonadherence, and recorded adherence and concerns about adverse effects in real time 2. Historical control group participants received usual care	Rates of discontinuation were not statistically significantly different between the intervention and control	—	United States
Neuner et al, 2015[a,31]	16,462	Pre/post design	AIs	Mixed (0-5+ years)	No	Prescription records	1. Before introduction of generic formulations of anastrozole, letrozole, and exemestane 2. After introduction of generic formulations	Regression-adjusted adherence probabilities were estimated to be 5.4% higher after generic anastrozole was introduced in 2010 and 11% higher after generic letrozole/exemestane was introduced in 2011. Subsidy recipients had higher adherence rates throughout the study	1.470	United States
Neuner et al, 2022[a,22]	18	Pre/post design	AIs; tamoxifen	Mixed (0-5+ years)	Yes	Prescription records	1. Before intervention—Meeting and follow-up with pharmacist trained on evidence-based AET symptom interventions 2. After intervention	Adherence increased after intervention but there was no statistically significant effect	29.952	United States
Neven et al, 2014[a,b,71]	2,543	Pre/post design	AIs	0-1 years	No	Self-report measures	1. SC plus educational materials 2. SC	At 1 year, there was no significant difference between the groups for adherence or persistence	1.070	18 countries worldwide
Park et al, 2022[41]	57	Randomized controlled trial	AIs; tamoxifen	Mixed (0-5+ years)	No	Electronic monitoring device; self-report measures	1. Smart pill bottle reminder intervention 2. SC	Medication adherence rates were higher among the experimental group than the control group		South Korea
Qin et al, 2022[a,51]	12,857	Observational study	AIs; tamoxifen	Mixed (0-5+ years)	No	SEER database	1. Medicare Part D LIS group—Reduced premiums, deductibles, or copayments 2. Non-LIS group	After generic entry, adherence without switching from one AI to another increased significantly for non-LIS but decreased for LIS. Adherence with switching significantly increased for both non-LIS and LIS	1.666	United States
Ream et al, 2021[a,46]	21	Randomized controlled trial	AIs; tamoxifen	Mixed (0-5+ years)	No	Self-report measures	1. CBT 2. Relaxation training 3. Health education	Compared with women receiving health education or CBT, women receiving relaxation training were less likely to (1) forget to take their AET and (2) intentionally miss doses of AET in the long term	0.913	United States
Riis et al, 2020[a,47]	123	Randomized controlled trial	AIs; tamoxifen	0-1 years	No	Prescription records	1. Individualized follow-up care 2. SC	There were no significant differences between SC and the intervention group	0.824	Denmark
Singleton et al, 2022[a,34]	97	Randomized controlled trial	AIs; tamoxifen	No information	No	Self-report measures	1. EMPOWER-SMS—Text message intervention including four text messages per week for 6 months regarding (1) physical activity and healthy diet, (2) social and emotional well-being, (3) medication adherence and side-effect management, and (4) general breast cancer information 2. Control group—Usual care	EMPOWER-SMS participants missed significantly fewer endocrine therapy doses than participants in the control group	0.889	Australia
Tan et al, 2020[a,35]	242	Randomized controlled trial	AIs	Mixed (0-5+ years)	No	Blood serum; self-report measures	1. SMS (text messages) 2. SC	The odds of adherence were higher in the SMS than in the SC at 6 months but were not significantly different at 1 year. There was no difference in serum hormone levels between groups	1.780	Singapore
Wagner et al, 2016[a,36]	38	Observational study	AIs; tamoxifen	Recent prescription initiation	Yes	Prescription records	1. Women who were contacted and completed the telephone script with care managers 2. Control group—Women who care managers were unable to contact or who refused to complete all components	There was no significant difference in adherence between the contacted and noncontacted groups	3.000	United States

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TABLE 2. Characteristics and Findings: Studies of Interventions to Promote AET Adherence Among Women With Breast Cancer (continued)

Author	Sample Size	Study Design	AET Type	Medication Timing at Enrollment	Patients Selected With a Risk Factor for Nonadherence	Adherence Measure	Study Conditions	Main AET Adherence Findings	Odds Ratio	Country
Yu et al, 2012[a,40]	503	Observational study	AIs	0-1 years	No	Prescription records	1. Standard treatment plus patient support program 2. Matched location and comparable medical care but without the systematic patient support program	There was no statistically significant difference in 1-year persistence rates	0.988	China
Yu et al, 2021[a,37]	2,689	Observational study with historical control	AIs; tamoxifen	Prescription initiation	No	Not reported	1. The app used cohort referred to patients who received a diagnosis between November 2017 and May 2019 and who had applied the smartphone-based app within the adjuvant treatment setting 2. The app nonused cohort included patients who received a diagnosis between November 2017 and May 2019 without using the app 3. The preapp cohort included patients who received a diagnosis between March 2013 and October 2017	There was no statistically significant difference in treatment adherence on the basis of application use	2.564	China
Ziller et al, 2013[a,38]	171	Randomized controlled trial	AIs	Prescription initiation	No	Prescription records; self-report measures	1. Letter group—Patients received motivational reminder letters and educational content via mail 2. Telephone group—Patients were called by a study nurse 3. Control group—Usual care	The differences between groups were not statistically significant for the primary end point	2.056	Germany

NOTE. Sample size only reflects the number analyzable for adherence.

Abbreviations: AET, adjuvant endocrine therapy; AIs, aromatase inhibitors; CBT, cognitive behavioral therapy; LIS, low-income subsidy; OCM, Centers for Medicare & Medicaid Services' Oncology Care Model, a payment model that provides structured incentives to oncology practices to improve the quality and efficiency of cancer care for Medicare beneficiaries; SC, standard care.

[a]Indicates that the study was included in the meta-analysis. Odds ratios are only reported for studies included in the meta-analysis, for which sufficient information was reported in the study or authors provided sufficient information upon request to calculate an effect size.

[b]All studies used unique samples with the exception of Markopoulos et al[28] and Neven et al,[71] which used the same sample. Only Markopoulos et al[28] was summarized in the systematic review because it was the most recent record with main effects reported. Only data from Neven et al[71] were used to calculate an effect size for the meta-analysis because they more closely conform to the measurement criteria of a 6-month follow-up.

implementing cultural adaptations to the focal interventions to promote adherence, apart from changing the language of the intervention. The delivery language of the interventions varied by target audience; English was the most common[17,19,24,27,29,30,34,39,43-46,49] and five were offered in multiple languages including English.[16,18,28,35,36]

Study Designs

Of the 33 studies in the systematic review, 15 were RCTs and 18 were non-RCTs (Table 2).

RCTs

The majority of the RCTs were small studies with analyzable sample sizes fewer than 100 (n = 6) or between 100 and 250 (n = 7). Two larger RCTs had analyzable sample sizes of 702[49] and 2,740.[25] Both of the larger RCTs and over half of the smaller RCTs had a standard care (n = 7) or enhanced usual care (n = 1) control group. The five remaining studies included active control groups—three included comparison groups that involved a subset of the full intervention components and two included three-group designs with at least one active control group. Among the 15 RCTs, 53.3% (n = 8) reported an intervention effect; however, among these, one study reported a pattern of improved adherence but did not test for statistical significance, two found an initial effect that attenuated over time, and one indicated that the effect was statistically significant when using a self-report adherence measure but not when using medication refill data.

Non-RCTs

The 18 non-RCT studies used pre/post, quasi-experimental, or observational designs. These studies varied in methodology, sample size, and intervention type. Over half were larger (n = 11), with sample sizes between 503 and 490,357, while the others were smaller or pilot studies (n = 8) with sample sizes between 18 and 230. Among the non-RCT studies, 57.9% (n = 11) reported an intervention effect. Notably, three of the largest non-RCTs found improvements in medication adherence after health system policy changes that lowered the cost of AET through either oral parity legislation (ie, cancer-specific legislation to limit the out-of-pocket costs of oral medications)[22] or the introduction of generic formulations.[31,51]

Intervention Targets for Known Adherence Barriers

Interventions targeted multiple previously identified adherence barriers and, in some cases, targeted more than one barrier simultaneously.

Medication Necessity and Importance

A common intervention was the delivery of breast cancer and AET education that addressed the necessity of AET in preventing recurrence. One study used this strategy exclusively[19] and found a significant intervention effect, while 12 studies used this strategy in combination with other components, with variable effectiveness (n = 5; 38.5% reported an intervention effect).[16,18,23,25,28,29,34,36,38-40,49]

Side Effects

Many interventions also targeted side effects. Five addressed side effects using education about strategies to manage them[17,25,28,34,45] but only one (16.7%) found a significant intervention effect.[34] Eleven studies targeted side-effect management via consultations with the oncology care team,[16,21,24,26,27,30,38,47] participants' pharmacists,[32] or the researcher,[29] and six (54.5%) revealed a significant intervention effect. One exercise-based intervention focused on reducing pain to improve AET adherence,[44] and did not test for statistical significance but found a pattern of greater adherence in the intervention group.

Forgetting

Another barrier to taking AET, forgetting to take the medication, was targeted in seven interventions via reminders in the form of letters,[27] texts,[30,35,43] mobile phone application notifications,[37] calls,[23] or smart pill caps.[41] Of these seven studies, four (57.1%) identified a significant intervention effect.

Affective Attitudes Toward AET

Two interventions were designed to reduce negative affective attitudes toward AET,[18,45] with one of these also using acceptance and relaxation training to target adherence.[45] However, neither found intervention effects. Another study sought to increase positive affective attitudes toward AET,[39] and one used cognitive behavioral therapy techniques to teach adaptive coping skills with an emphasis on reducing cancer-related stressors.[46] Both found significant intervention effects.[39,46]

Medication Costs and Health Systems

Three large studies examined interventions to reduce AET medication costs through oral parity legislation[22] and the introduction of generic medications.[33,50] Notably, all three of these studies identified intervention effects compared with baseline levels of adherence before the intervention. One study found no differences in AET adherence between clinics that participated in the Oncology Care Model (a multipayer model that focuses on improving coordination and quality of care) and those that did not.[42]

Quantitative Impact of Interventions: Meta-Analysis

Overall, the focal interventions showed statistically significant effects relative to their control groups (number of studies [k] = 25; OR, 1.412; 95% CI, 1.183 to 1.682; P = .0001; Fig 3). Because there was significant heterogeneity across studies (Cochrane's Q = 428.16 (24), P < .001; I^2 = 94.4% [92.8%-

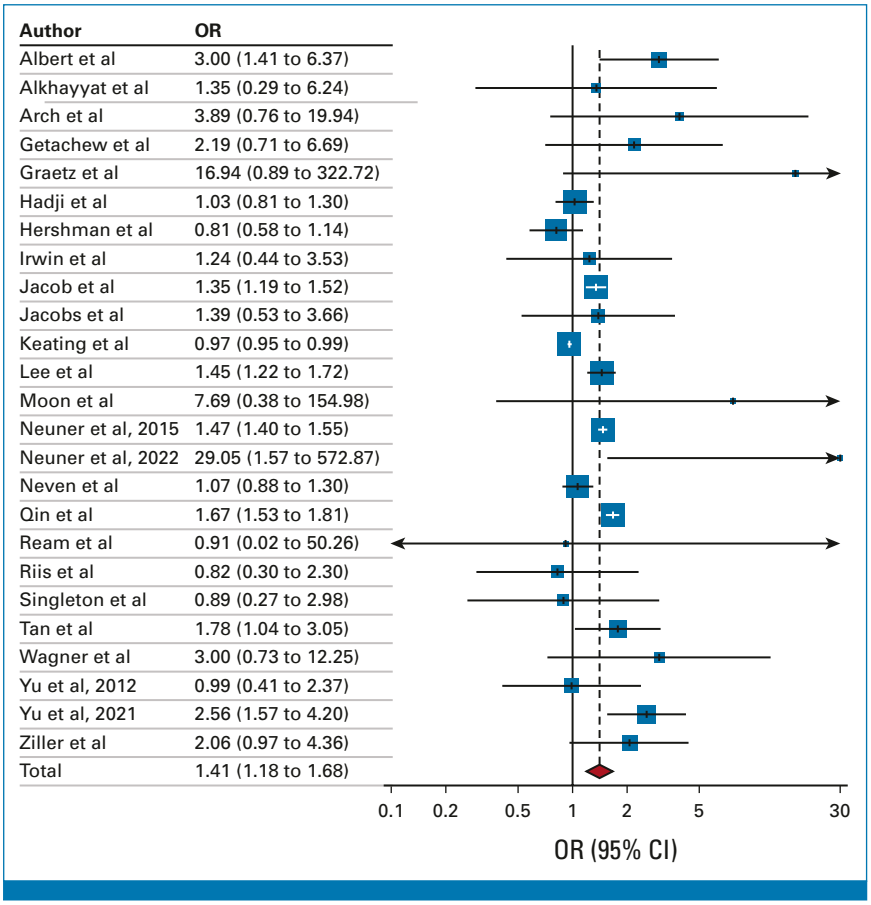

FIG 3. Forest plot of effect size by study. Box size corresponds with study weight (sample size). OR, odds ratio.

95.6%]), we examined a priori subgroups that may have contributed to the variability across studies, including study design, publication date, intervention directionality, and health system policy changes.

Study Design

There was greater heterogeneity within the non-RCT studies (k = 13), than within the RCTs (k = 12), as reflected in the I^2 values (non-RCT = 97.1%, RCT = 34.9%). However, there was not a statistically significant difference in effect sizes between the two types of studies (P = .301; Table 3).

Publication Date

There was no statistically significant difference in effect sizes between studies published on or before 2017 (k = 10) and studies published more recently (k = 15; P = .501; Table 3).

Intervention Directionality

Among RCTs, we examined whether there were any subgroup differences between interventions that involved interactions between patients and the oncology/research teams (k = 7; ie, bidirectional communication) compared with those that only provided one-way communication (k = 5; Table 3). There was no statistically significant difference in effect sizes between studies that used bidirectional communication (OR, 1.574; 95% CI, 0.990 to 2.500) versus unidirectional communication (OR, 1.105; 95% CI, 0.8102 to 1.507; P = .214).

Health System Policy Changes

We tested for subgroup differences between health system policy changes (k = 3), and nonpolicy interventions (k = 22). There was greater heterogeneity within the health systems policy changes studies (I^2 = 99.4%) than nonpolicy change interventions (I^2 = 54.3%); however, there was no statistically significant difference in effect size between them (P = .657; Table 3).

DISCUSSION

The primary aim of this up-to-date systematic review and meta-analysis was to summarize the existing evidence base and to describe and quantify the effects of interventions that promote AET adherence among breast cancer survivors. Given that suboptimal AET adherence is common and is associated with breast cancer recurrence and mortality,[6,8]

TABLE 3. A Priori Subgroup Analyses

Subgroup Comparison	k	OR	95% CI	I^2, %	$P_{subgroup}$
Study design					.181
RCT	12	1.247	0.953 to 1.631	34.9	
Other	13	1.512	1.180 to 1.938	97.1	
Publication date					.501
≤2017	10	1.329	1.111 to 1.589	63.2	
>2017	15	1.502	1.102 to 2.048	93.4	
Intervention directionality					
Unidirectional	5	1.105	0.812 to 1.507	52.8	.214
Bidirectional	7	1.576	0.990 to 2.500	0.0	
Healthy systems policy changes					
Policy change	3	1.331	0.964 to 1.837	99.4	.657
Other	22	1.453	1.172 to 1.801	54.13	

NOTE. A random-effects model was used for all subgroup analyses except for the intervention directionality subgroup analysis because the bidirectional communication studies had limited heterogeneity, indicating that a fixed effects model was appropriate.
Abbreviations: k, number of studies; OR, odds ratio; RCT, randomized controlled trial.

there is a vital need for effective interventions to promote adherence. Research has burgeoned in response to this need, with 18 new studies published since the previous meta-analysis.[11] Importantly, in contrast to the previous two systematic reviews and one meta-analysis that found overall null effects,[10-12] the current larger meta-analysis revealed a small but statistically significant effect of interventions relative to study control groups. Although subgroup analyses did not find a significant difference in effect sizes between studies published on or before 2017 and those published later, we included six additional pre-2017 studies not included in the one previous 2017 meta-analysis,[11] and also included 15 post-2017 studies, which together resulted in a significant overall intervention effect. The significant intervention effect in the meta-analysis indicates that behavioral and policy interventions that target modifiable risk factors for AET nonadherence led to a reliable increase in adherence, highlighting the benefit of these approaches. Taken collectively, these findings suggest that novel or multifaceted behavioral approaches will be required to increase the magnitude of the effect.

Although researchers have made significant recent contributions to interventions aimed at promoting AET adherence, the current systematic review and meta-analysis identified several limitations and recommendations for future research. First, AET adherence measures vary widely—self-report, medical chart records, prescription records, health insurance claims, electronic monitoring devices, and biological assays (urine or blood) were all used. Although self-report measures are positively correlated with more direct methods of adherence assessment, such as electronic monitoring,[52] they can be influenced by social desirability and recall biases.[53] In addition, most studies used a dichotomized version of a continuous adherence variable, thereby reducing the power to detect intervention effects or examine change in effects over time. Although 80% adherence is a commonly applied cutoff point and there is evidence that patients with <80% adherence have worse outcomes than those with >80% adherence,[8] lower levels of adherence may be sufficient in some settings.[54] Limiting the exclusive reliance on self-report adherence measures as well as better standardizing them across studies, and consistently integrating more objective measures of adherence (eg, electronic monitoring, assessing biological markers of adherence), are each warranted. A well-matched approach for balancing accurate assessment of adherence and patient acceptability and feasibility is real-time electronic adherence monitors.[55-58] In addition, as sufficient AET adherence levels appear to vary,[54] and dichotomizing a continuous adherence variable loses valuable information, we recommend using continuous (rather than dichotomized) measures of adherence whenever possible.

Second, with two exceptions, the targeted risk factor and meta-analytic subgroup analyses did not identify specific study or intervention features that reliably showed more success than others. Exceptions included the finding that approaches that focused on educating patients about how to manage AET side effect were largely ineffective, which is consistent with the findings from other meta-analyses on medication adherence across illnesses.[59,60] Approaches that focused on lowering medication cost through policy change were consistently effective (though were nonrandomized). Collectively, the meta-analytic subgroup findings indicated that a wide variety of approaches to increasing AET adherence can be effective, but also that effect sizes have not increased over time. As legislative changes focused on oral medication parity have largely been enacted in the United States and multiple interventions have shown promise for promoting AET adherence, future research should focus on identifying which unique components of the

interventions drive their efficacy. The Multiphase Optimization Strategy[61] offers researchers the methodology to disentangle the efficacy of a variety of intervention components (both alone and in combination); its use would advance knowledge of how best to improve AET adherence. In addition, novel multifaceted approaches and intervention foci are warranted.

Third, because of diverse ways of reporting sociodemographic characteristics, we could not quantify or evaluate sociodemographic subgroups for intervention effects. We strongly recommend that future research consistently report age (mean and range), socioeconomic status (eg, income and education), and race and ethnicity, at a minimum. There is evidence that AET adherence differs by these sociodemographic characteristics[62,63]; it is thus essential to report them to further illuminate which approaches work and for whom. We limited the current analysis to patients who identify as women because (1) this criterion conformed with the majority of interventions in this area and (2) the relative rarity of breast cancer among men compared with women.[64] Greater study of the experience of men taking AET and interventions to support them is also warranted. In addition, we limited our analysis to patients who identify as women because (1) this criterion conformed with the vast majority of interventions in this area and (2) breast cancer is rare among men as compared to women.[64] Greater study of the experience of men taking AET is warranted and further research should explore gender differences in intervention approaches.

Fourth, apart from a few notable trials,[18,38,39,45,46] previous research did not report on conceptualization within theoretical frameworks for behavior change (eg, Theory of Planned Behavior,[65] Health Belief Model[66]) or on following key principles of intervention development (eg, National Institutes of Health Stage Model[67]). The explicit application of theory and intervention development frameworks to inform AET interventions remains an area to expand in future work.[60]

Fifth, only a small number of interventions addressed key risk factors for nonadherence. Despite strong evidence that depression is a key predictor of AET nonadherence among women with breast cancer,[68] for example, only four of the 33 focal interventions targeted depression, anxiety, or negative affective attitudes toward AET. No studies aimed to leverage social support or strengthen patient-physician rapport, both of which are important factors for promoting medication adherence.[69,70] In addition, interventions were not tailored to the treatment trajectory (eg, initiation, years 2-3), known sociodemographic risk factors (eg, age) and did not report addressing cultural differences apart from delivery language. These findings lead to our recommending that future research capitalize on AET intervention targets identified in previous empirical work, ground interventions in theoretical frameworks of behavior change, and engage in a comprehensive process of intervention development, including steps before efficacy testing.

Strengths of the present systematic review and meta-analysis include the extensive investigation across a large number of breast cancer survivors prescribed AET and the examination of several subgroups of intervention types and study designs that facilitate AET adherence to guide future research and clinical efforts to improve adherence. A primary limitation of the study was the use of the 6-month follow-up period for the meta-analysis. There was significant variability in timing of study follow-up assessments; thus, to make meaningful inferences across studies, a 6-month follow-up point was selected to maximize the information presented in studies and calculate a meaningful pooled effect size. In addition, many studies focused early in the AET treatment trajectory, which did not provide the opportunity to promote AET adherence across the full duration of the prescription. Future research should closely consider the timing of intervention delivery and adherence assessment follow-ups and in light of the 5-10 years that AET is recommended, conduct follow-up assessments over a longer period.

To our knowledge, this meta-analysis is the first to find a significant effect of interventions to promote AET adherence compared with within study control groups. Collectively, the meta-analytic subgroup findings indicated that a wide variety of approaches to increasing AET adherence can be effective. However, as effect sizes have not improved over time, more powerful approaches or more precision within existing interventions will be needed to advance efficacy. We recommend the following to progress future research in this important area: (1) increase the standardization and rigor of AET adherence measures; (2) increase intervention efficacy and efficiency by conducting optimization trials[61]; (3) consistently report sociodemographic sample characteristics; (4) leverage established theory and intervention development frameworks; and (5) tailor interventions to address AET adherence risk factors identified in previous work (eg, depression), and relevant sociocultural contexts.

AFFILIATIONS

[1]Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO
[2]Department of Biostatistics and Informatics, Colorado School of Public Health at the Anschutz Medical Campus, University of Colorado Denver, Aurora, CO
[3]Cancer Prevention and Control, University of Colorado Cancer Center, School of Medicine, the Anschutz Medical Campus, Aurora, CO

CORRESPONDING AUTHOR

Joanna J. Arch, Department of Psychology and Neuroscience, University of Colorado Boulder, Box 345, Boulder, CO 80309; e-mail: joanna.arch@colorado.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Emma E. Bright, Madeline S. Nealis, Jordan Wrigley, Joanna J. Arch
Financial support: Joanna J. Arch
Administrative support: Madeline S. Nealis, Sarah R. Genung
Collection and assembly of data: Emma E. Bright, Lauren B. Finkelstein, Madeline S. Nealis, Sarah R. Genung, Jordan Wrigley, Heng Chao J. Gu
Data analysis and interpretation: Emma E. Bright, Lauren B. Finkelstein, Madeline S. Nealis, Heng Chao J. Gu, Sarah J. Schmiege, Joanna J. Arch
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

A Systematic Review and Meta-Analysis of Interventions to Promote Adjuvant Endocrine Therapy Adherence Among Breast Cancer Survivors

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jordan Wrigley
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Joanna J. Arch
Consulting or Advisory Role: AbbVie/Genentech, Bristol Meyers Squibb
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APPENDIX

TABLE A1. Search Strategy

Topic: Breast cancer, AET, adherence
Searcher: Jordan Wrigley
Date: October 23, 2021
Database (including vendor/platform): MEDLINE (via PubMed)

Set No.		Results
1. Breast cancer	"Breast Neoplasms"[Mesh] OR (("Neoplasms, Hormone-Dependent"[Mesh] OR "Cancer Survivors"[Mesh] OR "Neoplasm Staging"[Mesh]) AND "breast*"[tw]) OR "breast neoplasm*"[tw] OR "breast cancer*"[tw] OR "breast tumor*"[tw] OR "breast tumour*"[tw] OR "breast carcinoma*"[tw] OR "breast malignanc*"[tw] OR "malignant breast"[tw] OR "cancerous breast"[tw] OR "ductal carcinoma*"[tw] OR "DCIS"[tw] OR "lobular carcinoma*"[tw] OR "breast mass*"[tw] OR "mammary tumor*"[tw] OR "mammary tumour*"[tw] OR "mamma tumor*"[tw] OR "mamma tumour*"[tw] OR "breast gland tumor*"[tw] OR "breast gland tumour*"[tw]	434,100
2. AET	"Antineoplastic Agents, Hormonal"[Mesh] OR "Selective Estrogen Receptor Modulators"[Mesh] OR "Aromatase Inhibitors"[Mesh] OR "Triazoles"[Mesh] OR "Letrozole"[Mesh] OR "Anastrozole"[Mesh] OR "Tamoxifen"[Mesh] OR "Antineoplastic Agents Hormonal"[Pharmacological Action] OR "Selective Estrogen Receptor Modulators"[Pharmacological Action] OR "Aromatase Inhibitors"[Pharmacological Action] OR "AET"[tw] OR "adjuvant therap*"[tw] OR "adjunctive therap*"[tw] OR "adjunctive treatment*"[tw] OR "adjuvant treatment*"[tw] OR "aromatase inhibitor*"[tw] OR "hormone therap*"[tw] OR "hormonal therap*"[tw] OR "antihormone*"[tw] OR "antihormonal*"[tw] OR "anti hormone*"[tw] OR "anti hormonal*"[tw] OR "antiestrogen*"[tw] OR "antioestrogen*"[tw] OR "antiandrogen*"[tw] OR "adjuvant endocrine"[tw] OR "endocrine therap*"[tw] OR "antineoplastic*"[tw] OR "tamoxifen"[tw] OR "nolvadex"[tw] OR "soltamox"[tw] OR "triazoles"[tw] OR "Anastrozole"[tw] OR "anastrazole"[tw] OR "arimidex"[tw] OR "letrozole"[tw] OR "femara"[tw] OR "exemestane"[tw] OR "aromasil"[tw] OR "aromasin"[tw] OR "aromasine"[tw] OR "selective estrogen receptor modulator*"[tw] OR "SERM"[tw] OR "estrogen antagon*"[tw] OR "oestrogen antagon*"[tw] OR "anticancer*"[tw] OR "anti cancer*"[tw] OR "antitumor*"[tw] OR "anti tumor*"[tw] OR "antitumour*"[tw] OR "anti tumour*"[tw]	620,777
3. Adherence	"Medication Adherence"[Mesh] OR "Patient Compliance"[Mesh] OR "nonadherence"[tiab] OR "non-adherence"[tiab] OR "nonadherent"[tiab] OR "non-adhering"[tiab] OR "compliance"[tiab] OR "noncompliance"[tiab] OR "adherence"[tiab] OR "adhered"[tiab] OR "adherent"[tiab] OR "persistent"[tiab] OR "persistence"[tiab] OR "persistently"[tiab] OR "persistency"[tiab] OR "nonpersistent"[tiab] OR "non-persistent"[tiab] OR "nonpersistence"[tiab] OR "non-persistence"[tiab] OR "continuation"[tiab] OR "discontinuation"[tiab] OR "discontinued"[tiab] OR "refusal"[tiab] OR "patient cooperation"[tiab]	797,660
4.	1 AND 2 AND 3	2,895
5.	4 NOT (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	2,850
6.	5 NOT (animals[MeSH Terms] NOT humans[MeSH Terms])	2,796

Database (including vendor/platform): Embase (via Elsevier)

Set No.		Results
1. Breast cancer	"breast tumor"/exp OR (("neoplasm"/de OR "cancer staging"/de OR "cancer survivor"/de) AND breast*) OR "breast neoplasm*":ti,ab OR "breast cancer*":ti,ab OR "breast tumor*":ti,ab OR "breast tumour*":ti,ab OR "breast carcinoma*":ti,ab OR "breast malignanc*":ti,ab OR "malignant breast":ti,ab OR "cancerous breast":ti,ab OR "ductal carcinoma*":ti,ab OR "DCIS":ti,ab OR "lobular carcinoma*":ti,ab OR "breast mass*":ti,ab OR "mammary tumor*":ti,ab OR "mammary tumour*":ti,ab OR "mamma tumor*":ti,ab OR "mamma tumour*":ti,ab OR "breast gland tumor*":ti,ab OR "breast gland tumour*":ti,ab	716,489
2. AET	"antineoplastic hormone agonists and antagonists"/de OR "selective estrogen receptor modulator"/de OR "aromatase inhibitor"/de OR "triazole derivative"/exp OR "letrozole"/exp OR "anastrozole"/exp OR "tamoxifen"/exp OR "AET":ti,ab OR "adjuvant therap*":ti,ab OR "adjunctive therap*":ti,ab OR "adjunctive treatment*":ti,ab OR "adjuvant treatment*":ti,ab OR "aromatase inhibitor*":ti,ab OR "hormone therap*":ti,ab OR "hormonal therap*":ti,ab OR "antihormone*":ti,ab OR "antihormonal*":ti,ab OR "anti hormone*":ti,ab OR "anti hormonal*":ti,ab OR "antiestrogen*":ti,ab OR "antioestrogen*":ti,ab OR "antiandrogen*":ti,ab OR "adjuvant endocrine":ti,ab OR "endocrine therap*":ti,ab OR "antineoplastic*":ti,ab OR "tamoxifen":ti,ab OR "nolvadex":ti,ab OR "soltamox":ti,ab OR "triazoles":ti,ab OR "Anastrozole":ti,ab OR "anastrazole":ti,ab OR "arimidex":ti,ab OR "letrozole":ti,ab OR "femara":ti,ab OR "exemestane":ti,ab OR "aromasil":ti,ab OR "aromasin":ti,ab OR "aromasine":ti,ab OR "selective estrogen receptor modulator*":ti,ab OR "SERM":ti,ab OR "estrogen antagon*":ti,ab OR "oestrogen antagon*":ti,ab OR "anticancer*":ti,ab OR "anti cancer*":ti,ab OR "antitumor*":ti,ab OR "anti tumor*":ti,ab OR "antitumour*":ti,ab OR "anti tumour*":ti,ab	787,847

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TABLE A1. Search Strategy (continued)

Database (including vendor/platform): Embase (via Elsevier)		
Set No.		Results
3. Adherence	"adherence"/exp OR "patient compliance"/de OR "medication compliance"/exp OR "nonadherence":ti,ab OR "non-adherence":ti,ab OR "nonadherent":ti,ab OR "non-adhering":ti,ab OR "compliance":ti,ab OR "noncompliance":ti,ab OR "adherence":ti,ab OR "adhered":ti,ab OR "adherent":ti,ab OR "persistent":ti,ab OR "persistence":ti,ab OR "persistently":ti,ab OR "persistency":ti,ab OR "nonpersistent":ti,ab OR "non-persistent":ti,ab OR "nonpersistence":ti,ab OR "non-persistence":ti,ab OR "continuation":ti,ab OR "discontinuation":ti,ab OR "discontinued":ti,ab OR "refusal":ti,ab OR "patient cooperation":ti,ab	1,192,331
4.	1 AND 2 AND 3	6,855
5.	4 AND ("article"/it OR "article in press"/it OR "review"/it)	3,819
6.	5 AND [humans]/lim	3,674

Database (including vendor/platform): CINAHL (via EBSCO)		
Set No.		Results
1. Breast cancer	(MH "Breast Neoplasms") OR (MH "Carcinoma, Lobular") OR (MH "Hormone Receptor Positive Breast Neoplasms") OR (MH "Carcinoma, Ductal, Breast") OR (MH "Hereditary Breast and Ovarian Cancer Syndrome") OR TI ("breast neoplasm*" OR "breast cancer*" OR "breast tumor*" OR "breast tumour*" OR "breast carcinoma*" OR "breast malignanc*" OR "malignant breast" OR "cancerous breast" OR "ductal carcinoma*" OR DCIS OR "lobular carcinoma*" OR "breast mass*" OR "mammary tumor*" OR "mammary tumour*" OR "mamma tumor*" OR "mamma tumour*" OR "breast gland tumor*" OR "breast gland tumour*") OR AB ("breast neoplasm*" OR "breast cancer*" OR "breast tumor*" OR "breast tumour*" OR "breast carcinoma*" OR "breast malignanc*" OR "malignant breast" OR "cancerous breast" OR "ductal carcinoma*" OR DCIS OR "lobular carcinoma*" OR "breast mass*" OR "mammary tumor*" OR "mammary tumour*" OR "mamma tumor*" OR "mamma tumour*" OR "breast gland tumor*" OR "breast gland tumour*")	108,783
2. AET	(MH "Antineoplastic Agents, Hormonal+") OR (MH "Antineoplastic Agents, Combined") OR (MH "Antineoplastic Agents+") OR (MH "Aromatase Inhibitors+") OR (MH "Anastrozole") OR (MH "Letrozole") OR (MH "Selective Estrogen Receptor Modulators+") OR (MH "Estrogen Antagonists+") OR (MH "Tamoxifen") OR (MH "Estrogen Receptor Modulators+") OR TI (AET OR "adjuvant therap*" OR "adjunctive therap*" OR "adjunctive treatment*" OR "adjuvant treatment*" OR "aromatase inhibitor*" OR "hormone therap*" OR "hormonal therap*" OR antihormone* OR antihormonal* OR "anti hormone*" OR "anti hormonal*" OR antiestrogen* OR antioestrogen* OR antiandrogen* OR "adjuvant endocrine" OR "endocrine therap*" OR antineoplastic* OR tamoxifen OR nolvadex OR soltamox OR triazoles OR Anastrozole OR anastrazole OR arimidex OR letrozole OR femara OR exemestane OR aromasil OR aromasin OR aromasine OR "selective estrogen receptor modulator*" OR SERM OR "estrogen antagon*" OR "oestrogen antagon*" OR anticancer* OR "anti cancer*" OR antitumor* OR "anti tumor*" OR antitumour* OR "anti tumour*") OR AB (AET OR "adjuvant therap*" OR "adjunctive therap*" OR "adjunctive treatment*" OR "adjuvant treatment*" OR "aromatase inhibitor*" OR "hormone therap*" OR "hormonal therap*" OR antihormone* OR antihormonal* OR "anti hormone*" OR "anti hormonal*" OR antiestrogen* OR antioestrogen* OR antiandrogen* OR "adjuvant endocrine" OR "endocrine therap*" OR antineoplastic* OR tamoxifen OR nolvadex OR soltamox OR triazoles OR Anastrozole OR anastrazole OR arimidex OR letrozole OR femara OR exemestane OR aromasil OR aromasin OR aromasine OR "selective estrogen receptor modulator*" OR SERM OR "estrogen antagon*" OR "oestrogen antagon*" OR anticancer* OR "anti cancer*" OR antitumor* OR "anti tumor*" OR antitumour* OR "anti tumour*")	164,478
3. Adherence	(MH "Medication Compliance") OR (MH "Patient Compliance+") OR TI (nonadherence OR non-adherence OR nonadherent OR non-adhering OR compliance OR noncompliance OR adherence OR adhered OR adherent OR persistent OR persistence OR persistently OR persistency OR nonpersistent OR non-persistent OR nonpersistence OR non-persistence OR continuation OR discontinuation OR discontinued OR refusal OR "patient cooperation") OR AB (nonadherence OR non-adherence OR nonadherent OR non-adhering OR compliance OR noncompliance OR adherence OR adhered OR adherent OR persistent OR persistence OR persistently OR persistency OR nonpersistent OR non-persistent OR nonpersistence OR non-persistence OR continuation OR discontinuation OR discontinued OR refusal OR "patient cooperation")	211,808
4.	1 AND 2 AND 3	1,349
5.	Limiters—Human; Publication Type: Case Study, Clinical Trial, Journal Article, Meta Analysis, Meta Synthesis, Practice Guidelines, Randomized Controlled Trial, Review, Systematic Review	698

Database (including vendor/platform): PsycINFO, PsycArticles, PsycTests (via ProQuest)		
Set No.		Results
1. Breast cancer	(MAINSUBJECT.EXACT.EXPLODE("Cancer Screening") AND noft(breast*)) OR noft("breast neoplasm*" OR "breast cancer*" OR "breast tumor*" OR "breast tumour*" OR "breast carcinoma*" OR "breast malignanc*" OR "malignant breast" OR "cancerous breast" OR "ductal carcinoma*" OR DCIS OR "lobular carcinoma*" OR "breast mass*" OR "mammary tumor*" OR "mammary tumour*" OR "mamma tumor*" OR "mamma tumour*" OR "breast gland tumor*" OR "breast gland tumour*")	16,138

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TABLE A1. Search Strategy (continued)

Database (including vendor/platform): PsycINFO, PsycArticles, PsycTests (via ProQuest)		
Set No.		Results
2. AET	noft([STRICT])MJMAINSUBJECT.EXACT(Hormone Therapy) OR MAINSUBJECT.EXACT(Antineoplastic Drugs) OR MAINSUBJECT.EXACT.EXPLODE(Antiestrogens) OR noft(AET OR "adjuvant therap*" OR "adjunctive therap*" OR "adjunctive treatment*" OR "adjuvant treatment*" OR "aromatase inhibitor*" OR "hormone therap*" OR "hormonal therap*" OR antihormone* OR antihormonal* OR "anti hormone*" OR "anti hormonal*" OR antiestrogen* OR antioestrogen* OR antiandrogen* OR "adjuvant endocrine" OR "endocrine therap*" OR antineoplastic* OR tamoxifen OR nolvadex OR soltamox OR triazoles OR Anastrozole OR anastrazole OR arimidex OR letrozole OR femara OR exemestane OR aromasil OR aromasin OR aromasine OR "selective estrogen receptor modulator*" OR SERM OR "estrogen antagon*" OR "oestrogen antagon*" OR anticancer* OR "anti cancer*" OR antitumor* OR "anti tumor*" OR antitumour* OR "anti tumour*")	285,806
3. Adherence	MAINSUBJECT.EXACT.EXPLODE(Treatment Compliance) OR noft(nonadherence OR non-adherence OR nonadherent OR non-adhering OR compliance OR noncompliance OR adherence OR adhered OR adherent OR persistent OR persistence OR persistently OR persistency OR nonpersistent OR non-persistent OR nonpersistence OR non-persistence OR continuation OR discontinuation OR discontinued OR refusal OR "patient cooperation")	165,982
4.	1 AND 2 AND 3	236

Abbreviation: AET, adjuvant endocrine therapy.