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Factors influencing five-year adherence to adjuvant endocrine therapy in breast cancer patients: A systematic review

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ABSTRACT

Purpose: This systematic review aimed to determine the rate and identify correlates of adherence and persistence over five years of treatment with adjuvant endocrine therapy in female breast cancer patients.

Methods: Relevant articles were identified from Medline, Embase, AMED, PsycINFO, International Pharmaceutical Abstracts, and APA PsycArticles. Studies that measured patient adherence in the implementation or persistence phase for a period of at least five years using objective or multiple measures of adherence and investigated correlates of adherence were included. The titles, abstracts and full articles were screened and reviewed by two authors and any discrepancies were discussed with a third author.

Results: Twenty-six studies were included. Mean rate of adherence at five-year for implementation phase was 66.2% (SD = 17.3%), and mean persistence was 66.8% (SD = 14.5%). On average, adherence decreased by 25.5% (SD = 9.3%) from the first to fifth year. Higher rate of adherence was observed through self-report in comparison to database or medical record. Older age, younger age, higher co-morbidity index, depression and adverse effects were associated with lower adherence. Treatment with aromatase inhibitors, received chemotherapy, and prior medication use were associated with improved adherence.

Conclusion: Adherence to adjuvant endocrine therapy decreased from the first to fifth year of treatment. On average, one-third of patients were not adherent to treatment by the fifth year. Nineteen recurring factors were found to be significantly associated with long-term adherence in multiple studies. Further research using objective or multiple measures of adherence are needed to improve validity of results.

Contents

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1. Introduction

In the year 2020, female breast cancer surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases worldwide [1]. Available data in multiple countries demonstrated a rise in estrogen receptor (ER)-positive breast cancer, which may be attributed to the obesity epidemic and the impact of mammographic screening program as it preferentially detects slow-growing ER-positive cancers [1,2]. For these women, adjuvant endocrine therapy (AET) is routinely recommended to prevent recurrence or death, for five to ten years after the initial treatment of breast cancer [3]. AET prevents the growth of tumor cells by inducing estrogen deprivation. For many years, tamoxifen was the gold standard for AET, but in the past 15 years, third-generation aromatase inhibitors (AI) have emerged as an alternative to tamoxifen, exhibiting clear benefits with better side-effect profiles [4–6].

Despite its long-established benefits, previous studies have shown that AET adherence was often suboptimal and decreased in each subsequent year [7–9]. The World Health Organization (WHO) reported that poor adherence to long-term treatment is a worldwide problem with striking magnitude, leading to poor health outcomes and increased health care costs [10]. Due to the suppression of female hormones, AET also comes with significant side effects that may result in early menopause and negatively affect sexuality. Despite having strong beliefs on benefits of AET, concerns over adverse effects may influence patients' attitude towards their treatment [11]. Suboptimal adherence is a major barrier in realizing the benefits of medication, as benefits exhibited in the closely-controlled environment of clinical trials are often reduced or nullified in usual clinical practice, where adherence rates are low [12].

In order to tackle the problem of AET non-adherence, it is essential to understand the multifaceted factors faced by patients during their treatment. Several systematic reviews were conducted to elucidate the problem, and the first was published by Murphy et al. comprising 29 studies with various designs and duration [7]. Cahir et al. and Toivonen et al. focused on identifying potentially modifiable determinants of AET medication taking behavior [8,13], and Mausbach et al. focused on the effect of depression on AET adherence [14]. With increasing interest in this topic, a considerable number of new studies have been published, and the more recent reviews included over 60 studies [9,13]. However, because of the heterogeneous nature of included studies, it was difficult to draw a conclusion from the reviews as they included studies with various measures of adherence with different duration of assessment. Newer reviews have explored qualitative evidence to delve deeper into individual experiences [15,16]. However, qualitative synthesis may be subjected to bias due to individual preconceptions and the results may not be generalizable to the wider population.

Methods to measure adherence can be divided into objective or subjective, and direct or indirect [17]. Existing systematic reviews included cross-sectional studies using subjective measures of adherence behavior through patient self-report, which are considered less reliable and highly prone to bias compared to objective methods [10,17]. A study comparing a direct method of adherence assessment through biochemical measurement versus an indirect method using self-report showed that adherence was overestimated in the latter [18]. Imprecise adherence measurement may lead to inaccurate determination of factors affecting adherence. However, subjective methods are usually conducted through surveys, which are useful in determining the beliefs and identifying the barriers to adherence and should not be completely excluded in adherence studies. As there is no gold standard in adherence measurement, a multi-measure approach has been suggested to attain more accurate results [10,17]. Another issue to consider is that cross-sectional studies that assess adherence at only one point of time may be inappropriate as AET adherence tends to change over time, and it may be inappropriate to estimate patient adherence only at the early phase of treatment. We would like to address this by focusing our systematic review on studies that assess long-term adherence with more reliable methods of adherence assessment. Therefore, the objective of this study is to determine rate of adherence over five years of treatment in female breast cancer patients quantified using objective method or multiple measures of adherence, and to identify correlates of adherence.

2. Methods

2.1. Search strategy

Studies that measured adherence among breast cancer patients using AET were identified from Medline (1946 – present), Embase (1947 – present), AMED (1985–October 2020), PsycINFO (1967 – present), International Pharmaceutical Abstracts (1970–October

2020), and APA PsycArticles Full Text. Search was limited to English, human and female patients. The last search was run on November 21, 2020. In addition, we searched the reference lists of past systematic reviews on similar topics and monitored updates of new articles until July 31, 2021 via Ovid auto alerts. Search terms used included a combination of terms related to breast cancer, AET and adherence or persistence, such as: (non)adheren*, (non)complian*, (non)persisten*, discontinu*, adjuvant hormon* and adjuvant endocrine. Detailed search strategies are shown in Appendix A.

2.2. Study selection

The review was initially conducted in reference to the preferred reporting of systematic reviews and meta-analysis (PRISMA) 2009 statement guideline [19], and updated according to the PRISMA 2020 guideline [20]. Studies were considered eligible for review if they fulfilled the following criteria: published in a peer-reviewed journal; written in English; involved quantitative, observational studies in clinical practice; investigated the factors affecting adherence of AET in female breast cancer; and measured patient adherence for a period of five years or more using objective or multiple measures of adherence. We excluded studies that determined adherence exclusively using self-reported method; included other oral anticancer drugs without sub-analysis for AET; did not specify duration of patient follow up; as well as qualitative studies, commentaries, essays, study protocols, literature reviews, conceptual papers and conference abstracts. We only included studies in clinical practice settings as adherence rates in clinical trials were often higher [21]. Studies that had more than 20% of patients not followed up for a full five-year period due to end of data collection period or loss to follow-up were also excluded. This cut-point was chosen as loss to follow-up of more than 20% is considered to pose serious threats to validity [22].

The titles and abstracts were screened and reviewed independently by two authors to determine their eligibility. The abstracts were coded as “Yes”, “No” and “Maybe”. Abstracts identified as “Yes” and “No” were included and excluded accordingly. Those that were identified as “Maybe” were discussed until a consensus was reached, which consisted of approximately 2.8% of all abstracts. Full articles were further screened according to the inclusion and exclusion criteria by the same two authors. A third author resolved discrepancies and also further reviewed 5.5% of the full articles. If any information was unclear, the study authors were contacted for further details.

2.3. Data extraction

The main outcomes for this study were five-year adherence rates and factors associated with them. Following the recommendations from the International Society for Medication Adherence (ESPACOMP) Medication Adherence Reporting Guidelines, adherence was defined as “the process by which patients take their medications as prescribed”, covering the phases of initiation, implementation (e.g., late, skipped, extra, or reduced doses), and persistence [23]. There was a large variability in the terminology and definition used to describe adherence and persistence (e.g.: adherence, persistence, compliance, discontinuation), and we categorized these as either implementation or persistence. Factors associated with adherence were identified from significant variables in final adjusted analysis, if available.

A standardized data extraction sheet was developed based on discussions among the authors. Two authors extracted the required information, which includes: general details of study (author, year of publication and country); participant characteristics (including age, breast cancer stage, estrogen receptor status); study characteristics (study design, duration); type of outcome measure (method of adherence measurement); and reported outcomes (rate of adherence, associated factors). Factors that were found to significantly affect adherence in two or more studies were grouped according to the WHO multidimensional model for drug adherence consisting of social/economic factors; condition-related factors; therapy-related factors; health system/health care team-related factors; and patient-related factors [10].

2.4. Quality assessment

Methodological quality and risk of bias were assessed according to a checklist used by Murphy et al. in their review on AET adherence [7], which was revised with added items from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [24], International Society of Pharmacoeconomics and Outcomes Research (ISPOR) checklist on database studies [25] and a related checklist developed by Peterson et al. [26]. The checklists from ISPOR and Peterson et al. were chosen as long-term adherence studies typically measured adherence using administrative databases.

Risk of bias was assessed based on completeness and reliability of data source; method of adherence measurement (objectivity of measurement and provision of clear definition); and methodological quality, determined based on items from STROBE and ISPOR checklists. Adherence calculated based on prescription database was considered as objective, and those based on patient self-report and physician-report were considered as subjective [10]. Completeness and reliability of data source was graded as “Good”, “Intermediate” and “Poor”. Other items were coded as Yes “Y”, No “N” or Not Applicable “N/A”. Studies were considered to have low risk of bias if they used complete and reliable databases, used an objective measure of adherence with explicit definition, and had good methodological quality with all relevant items reported. A summary of categorization for risk of bias can be referred from Appendix B.

3. Results

A total of 3814 reports were identified from the database search, and 2875 reports remained after removing duplicates. Of these, 2613 reports were removed following title and abstract screening as they did not meet the inclusion criteria. The full text of 278 reports identified from database search, citation searching and Ovid auto-alerts were retrieved and examined in more detail. From the full articles examined, 249 reports were removed for reasons specified in Fig. 1, and 26 studies were included in the systematic review. We provided explanations for excluding 21 studies despite almost fulfilling our inclusion criteria in characteristics of excluded studies table (Appendix C).

3.1. Study characteristics

A summary of study characteristics with adherence rate and associated factors is shown in Table 1. Of the 26 studies included, 25 were cohort studies that utilized administrative databases to estimate adherence. Databases used by the studies include pharmacy prescription collection records, insurance claims database, and hospital information system. One study used self-reported adherence via survey, which was verified with physician reports in patient medical charts [27]. Two studies reported adherence rate measured through multiple methods including database, self-report and physician-report to compare the differences in measurement within the same cohort [28,29]. Six other studies also included surveys in addition to database analysis to collect patient

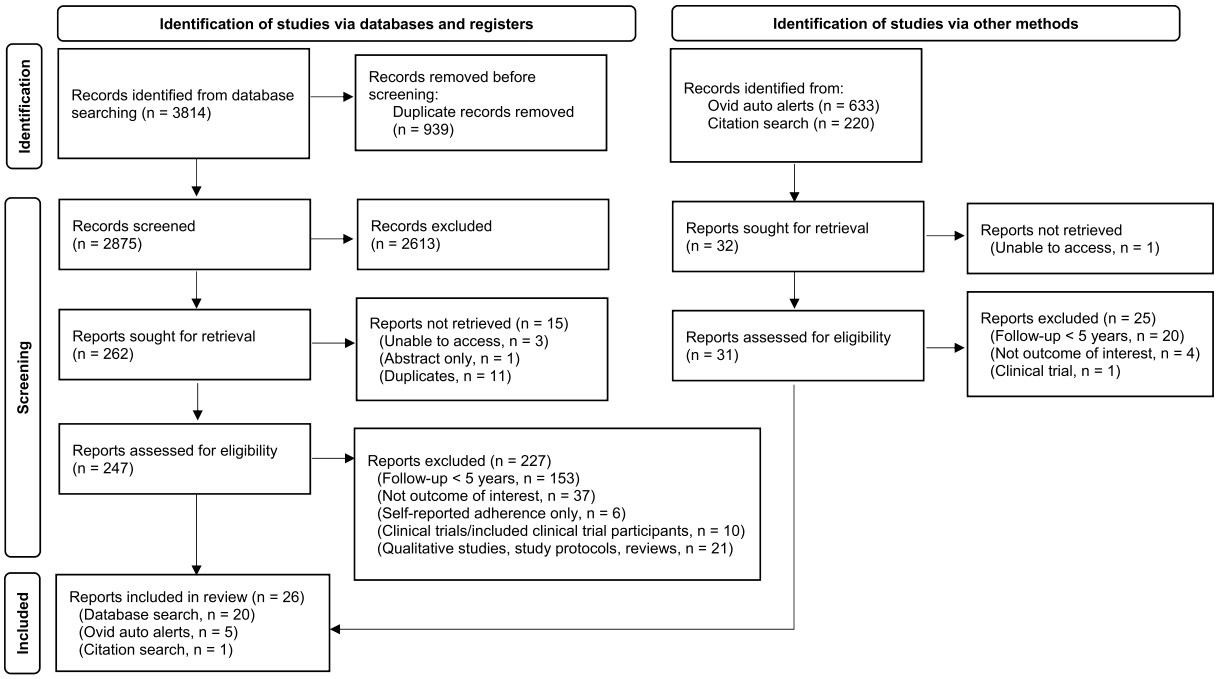

Fig. 1. PRISMA Flow Chart for study selection.

information and factors affecting their adherence to AET [30–35].

The mean sample size was 5392 (range 138–33,260). Studies were conducted in Europe (n = 14), North America (n = 9), Asia (n = 2) and South America (n = 1). Most of the studies included participants taking both tamoxifen and AI (n = 21), two studies with tamoxifen only and three studies with AI only. Eight studies measured adherence in the implementation phase, eleven studies measured persistence, and seven studies measure both, with varying definitions. For studies using databases, adherence was defined as having a medication supply of 80% or more during the measured time period, assessed using Medication Possession Ratio (MPR) or Proportion of Days Covered (PDC). Non-persistence was defined as gaps in treatment or medication supply of 60, 90 or 180 days.

3.2. Study quality and risk of bias

Majority of the studies had high or moderate risk of bias, as summarized in Table 2. The completeness and reliability of data source for 15 studies were considered to be good, with multiple databases linked together at national or regional level. Studies that used databases from private insurance or healthcare systems [34,40,41,46,47] and hospital or pharmacy databases without linkage to other databases [30,38,42] were rated as intermediate quality. One study was considered to have poor data source, as information was based on survey and incomplete data collection from medical charts [27]. Many studies did not sufficiently control for confounders, and did not report efforts to reduce potential biases associated with database studies. Eight studies had poor methodological quality, with omission of ≥50% of items relevant for their studies (e.g.: did not specify how MPR≥80% was handled, did not determine continuous eligibility for insurance claims database, did not control for confounders), and were subsequently classified as high risk of bias [27–30,42,43,49,53]. One study was classified to have high risk of bias as the study did not have explicit definition of persistence, and less than 50% of the participants had their persistence verified with a refill database [48].

3.3. Rate of adherence

Excluding patient-reported rate and adherence measured only among persistent patients, adherence at five years of AET treatment ranged from 33.3% to 88.6% (mean = 66.2%, SD = 17.3%) for implementation phase, and persistence ranged from 45.2% to 87.4% (mean = 66.8%, SD = 14.5%). On average, adherence fell by 25.5% (SD = 9.3%) from the first to fifth year. Higher rates of adherence were observed through self-report in comparison to databases (92% vs 74.7%) [28] or medical records (97.4% vs 87.4%) [27]. Similarly, non-persistence was lower based on self-report compared to database (7% vs 25%) [29]. The highest rate of five-year adherence based on dispensing record was 91.5%, which was calculated only among those that persisted to treatment [45].

3.4. Correlates of adherence and persistence

Over 50 different factors were found to significantly affect patients' long-term adherence to AET (see Table 1). Majority of these factors were identified through multivariate analysis of available demographic information in the databases used for the study, with or without adjustment for confounders. Factors found to be significant only in univariate analysis but non-significant in the subsequent multivariate analysis were excluded. Table 3 consists of factors that were found to be significant in two or more studies, grouped according to the WHO framework of factors influencing medication adherence [10]. We also included studies that found no significant association in both univariate and multivariate analysis for comparison. A total of 19 factors were identified, with the majority being in the 'Social and economic factors' domain.

3.4.1. Social and economic factors

Older age (N = 7) [31,36,39,44,46,48,52], younger age (N = 3) [31,38,43], and lower financial status (N = 2) [30,47] were associated with lower adherence in AET treatment. Various age ranges were used in the included studies. For the purpose of this review, older age referred to the age range of >65–80 and younger age

Table 1
Summary of studies and adherence rate at five years.

Author, Year (Country)	Study Design/Approach	Participant Characteristics	AET Type, Number of Participants	Definition of Adherence	Rate of Adherence	Factors that Increased Adherence	Factors that Decreased Adherence
Bhatta, 2013 (US) [27]	Retrospective cohort/ cross-sectional. Self-administered survey and medical record for verification of adherence.	Stage I-III BC, no BRCA1/2 germ-line mutation.	TAM & AI. N = 254	Implementation Self-report taking ≥80% of prescribed pill Persistence Completion of 5 years of therapy as verified by chart review	Implementation (Self-report): 97.4% Persistence (Chart review): 87.4%	1) Perceived importance of AET 2) Value placed on their doctor's opinion about the importance of AET	–
Blanchette, 2020 (Canada) [36]	Retrospective cohort. Linked health administrative database – cancer registry, health insurance, physician database.	Post-menopausal women aged ≥66 years with early-stage breast cancer. Median age = 73.	TAM & AI. N = 5692	Implementation High: MPR ≥80% Intermediate: MPR 40–79% Low: MPR <40% (based on availability of prescription)	High: 74% Intermediate: 13% Low: 13%	1) Received adjuvant chemotherapy 2) Oncologist follow-up in the first 4 months of starting AET 3) Initiated with AI (vs TAM)	1) Older age 2) Dementia
Bosco-Levy, 2016 (France) [37]	Retrospective cohort. Reimbursement database from French public-funded health system.	Women aged ≥20 years. Mean age = 62.	TAM & AI. N = 600	Non-persistence Treatment discontinuation of at least 90 days.	Persistence Year 1: 88% Year 5: 69.4%	1) Initiated with AI (vs TAM) 2) Co-payment exempt status 3) Received chemotherapy	1) Switching AET 2) Metastasis to other organs
Cahir, 2017 (Ireland) [38]	Retrospective cohort. National cancer registry linked to pharmacy claim data.	Stage I-III, ER+/ PR+ BC who had received tumor-directed surgery. Mean age = 61.4.	TAM & AI. N = 3415	Implementation Proportion of days with supply of AET≥80% Non-persistence Treatment gap of ≥180 days	Implementation: 88.6% Persistence: 80.1%	1) Married 2) Prior medication use	1) Younger age (<50) 2) Prescribed with antidepressants
Cavazza, 2020 (Italy) [39]	Retrospective cohort. Regional, patient-linked health administrative database.	Non-metastatic BC and an inpatient stay for mastectomy in Lombardy region. Age≥30.	TAM & AI. N = 8400	Implementation Proportion of days with supply of AET≥80% Non-persistence Gap >180 days between two prescription refills	Implementation: Year 1: 93%; Year 2: 84%; Year 3: 82%; Year 4: 78%; Year 5: 57% Persistence: 82%	1) Continued care in same surgical hospital 2) Received chemotherapy 3) Earlier AET initiation	1) Older age (>70) 2) Took TAM 3) Concomitant depression
Emerson, 2021 (US) [40]	Retrospective cohort. Regional cancer registry with pharmacy information system (Kaiser Permanente of Northern California).	Women diagnosed with a first HR+ BC, stage I to III.	TAM & AI. N = 19551	Implementation PDC≥ 80%	Year 1: 76.4%, Year 2: 72.1%, Year 3: 68.4%, Year 4: 65.7%, Year 5: 58.5%	1) Asian/Pacific Islander ethnic groups	1) Hispanic 2) Black
Farias, 2018 (US) [41]	Retrospective cohort. Regional Cancer Registry and Medicaid claims database.	Women with local or regional breast cancer who initiated AET within 1.5 years after the date of cancer diagnosis. Age 20–64.	TAM & AI. N = 300	Implementation MPR≥ 80%	Year 1: 56.9%, Year 3: 42.3%, Year 5: 33.3%	–	1) Higher comorbidity index (Comorbidity score of 3 or more)
Font, 2012 (Spain) [28]	Retrospective cohort. Patient self-reported (telephone survey), physician-reported, administrative drug reimbursement database.	Women with HR+ BC in stages I, II or IIIa.	TAM & AI. N = 673	Implementation Database prescription coverage ≥80% Self-report: How often patients have difficulties in taking medicine/forget to take it. Answered 'never' or 'sometimes'. Persistence Reported adherent in physician report	Database: 74.7% Self-report: 92% Physician report: 94.7%	1) Age 50–74 (vs < 50) 2) Received chemotherapy 3) Sequential TAM & AI (vs TAM only)	–

Table 1 (*continued*)

Author, Year (Country)	Study Design/Approach	Participant Characteristics	AET Type, Number of Participants	Definition of Adherence	Rate of Adherence	Factors that Increased Adherence	Factors that Decreased Adherence
Gao, 2018 (China) [30]	Retrospective cohort. Hospital database, and survey to determine factors associated with AET.	Women with ER+ and/or PR+ status, T stage < T4 & absence of distant metastasis.	TAM & AI. N = 1110	Persistence Continuous use of AET with interruption of <180 days	Overall: 63.1% -AI: 75.7%, -TAM: 69.2%	1) Switching AET	1) Financial constraints 2) Adverse effects 3) Skeptical attitude towards AET
Guedes, 2017 (Brazil) [42]	Retrospective cohort. Hospital Database analysis - pharmacy and electronic medical record.	Women aged >18 years with BC treated in a tertiary hospital. Age range 31–88, mean age 58.2.	TAM & AI. N = 182	Implementation MPR≥ 80% Non-persistence ≥60 days gap since last medication supply	Implementation: 85.2% Persistence Year 1: 83.5%; Year 2: 66.5%; Year 3: 53.4%; Year 4: 51.6%; Year 5: 45.2%	1) Had surgery	1) Advanced stage at diagnosis (III & IV) 2) More hospitalization
Hagen, 2019 (Norway) [29]	Prospective cohort. 4 surveys within 1–12, 24, 36 and 48–60 months after surgery (modified MMAS-8), prescription database for adherence, and medical record, for demographic and cancer-related data.	Postmenopausal women with HR+ BC. Age range 49–67, mean age 58.	TAM & AI. N = 138	Implementation MPR≥ 80% Non-persistence ≥180 days gap since last prescription refill prior to the completion of 54 months of therapy	Overall persistence: 62% Comparison of non-persistence Self-reported: 7%; Database: 25%	1) Lymph node involvement 2) Being employed (not significant when BMI included in the model)	1) Overweight or obese
He, 2015 (Sweden) [31]	Prospective cohort. Regional cancer registry linked to national drug register and survey.	Women with non-metastatic ER+ BC diagnosed in Stockholm.	TAM & AI. N = 3395	Non-persistence ≥180 days gap since last prescription refill	Persistence: Year 1: 86% Year 3: 64% Year 5: 46%	1) Lower Charlson comorbidity index	1) Family history of ovarian cancer; 2) Age <40 3) Age ≥65 4) Use of analgesics, hypnotics/sedatives, GI drugs, and HRT at baseline 5) Use of analgesics, hypnotics/sedatives, antidepressants, GI drugs concurrent with AET 6) Switching AET (either direction)
He, 2019 (Sweden) [32]	Prospective-retrospective cohort. Regional Breast cancer registry linked to national drug database, Stockholm Mammography Screening Program, and survey.	Women with non-metastatic (and non-in situ) BC who were invited for mammography 2 years before their diagnosis. Age range 40–69.	TAM & AI. N = 5098	Non-persistence ≥180 days gap since last prescription refill	Persistence (in relation to mammography screening): Overall: 47.4% Participants: 49.1% Non-participants: 40.0%	–	1) Non-participation in mammography screening
He, 2020 (Sweden) [33]	Prospective-retrospective cohort. Regional Breast cancer registry linked to national drug database, Stockholm Mammography Screening Program, and survey.	Women with stages I to III breast cancer using TAM.	TAM only. N = 1309	Non-persistence ≥180 days gap since last prescription refill	Persistence: 50% (Approximate from Kaplan Meier curve)	–	1) Ultrarapid CYP2D6 metabolisers (significantly low persistence only during early treatment)
Huiart, 2011 (UK) [43]	Retrospective cohort. Data analysis from GP Research Database.	Women with non-metastatic BC. Mean age 63.7 (mean age in TAM group 62, and AI was 70.8).	TAM & AI. N = 13479	Implementation MPR≥ 80% (based on availability of prescription) Non-persistence ≥3 months of treatment gap	Persistence: 70.2% - AI: 81.1% - TAM: 69.0% - TAM (age<40): 49.3%	–	1) Taking TAM 2) Age <40
Kroenke, 2018 (US) [34]	Prospective cohort. Regional cancer registry with pharmacy information system (Kaiser Permanente of Northern California),	Women diagnosed with stages I-III HR+ BC.	TAM & AI. N = 2682	Implementation MPR≥ 80% Non-persistence ≥90 days gap since last prescription refill	Implementation: 78% Persistence: 76%	–	1) Low personal social support 2) Low clinical social support

(*continued on next page*)

Table 1 (*continued*)

Author, Year (Country)	Study Design/Approach	Participant Characteristics	AET Type, Number of Participants	Definition of Adherence	Rate of Adherence	Factors that Increased Adherence	Factors that Decreased Adherence
	survey given 2 & 8 months after diagnosis.						
Lailler, 2021 (France)[a] [44]	Retrospective cohort. National Cancer Institute Database.	Women with non-metastatic BC who underwent a mastectomy or a lumpectomy. Mean age 61.	TAM & AI. N = 33260	Implementation PDC≥ 80%	Year 1: 87% Year 5: 71%	1) Received chemotherapy	1) Switching AET 2) Using TAM 3) Older age (>70) 4) Self-employed insurance scheme
Lambert-Cote, 2020 (France) [35]	Retrospective cohort. National administrative databases (hospital, outpatient and pharmacy) & survey (for baseline characteristics).	Women diagnosed with first non-metastatic BC and took AET within 12 months after diagnosis. Mean age 50.1.	TAM & AI. N = 674	Implementation PDC≥ 80% Persistence Covered by an AET in the 60 days before the 365th day of the year	Implementation Year 1: 82.9% Year 2: 79.9% Year 3: 74.5% Year 4: 65.9% Year 5: 59.7% Persistence Year 1: 95.1% Year 2: 92.7% Year 3: 89.1% Year 4: 85.9% Year 5: 75.7%	–	1) No chemotherapy 2) No personalized care plan
Lundgren, 2018 (Sweden) [45]	Retrospective cohort. National Breast Cancer Registry & prescribed drug register.	Women with ER+ BC in Region Jonkoping County.	TAM & AI. N = 271	Implementation MPR≥ 80% (measured only among those that remained on treatment)	Year 3: 91.2% Year 5: 91.5%	–	–
Ma, 2020 (US) [46]	Retrospective-prospective cohort. Surveillance, Epidemiology, and End Results-Medicare linked database.	Women with HR+ BC (stage I-III), age >65.	TAM & AI. N = 5684	Implementation MPR≥ 80%	Year 5: 35%	1) Introduction of generic AI 2) Being in the low-income subsidiary group 3) Asian 4) Married 5) Living in Northeast region	1) Older age (>80) 2) Black 3) Hispanic 4) Living in Southern region
Ma, 2021 (US) [47]	Retrospective cohort. Surveillance, Epidemiology, and End Results-Medicare linked database	Women with HR+ BC (stage I-III), age >65.	TAM & AI. N = 1133	Implementation MPR≥ 80% Non-persistence ≥90 days gap since last prescription refill	Implementation Year 1: 79.8% Year 2: 69.9% Year 3: 66.1% Year 4: 64.3% Year 5: 53.8%	1) Longer duration of zero co-payment 2) Higher income areas	1) Higher number of concomitant medications
Owusu, 2008 (US) [48]	Retrospective cohort. Cancer registry, administrative, and clinical databases from integrated health systems. Medical records and automated pharmacy record.	Women with stage I-IIB ER+ or indeterminant breast cancer, age >65.	TAM only. N = 961	Non-persistence ≥60 days medication discontinuation	Persistence: Year 1: 85% Year 2: 76% Year 3: 67% Year 4: 60% Year 5: 51%	–	1) Older age 2) Increase in comorbidity index 3) Increase in the number of cardiopulmonary comorbidities 4) Indeterminant ER status 5) Received breast-conserving surgery without radiotherapy
Pineda-Moncusi, 2020 (Spain) [49]	Prospective cohort. Regional Primary Care Research Database - Information System for the Development of Research in Primary Care	Women with HR+ BC. Mean age 67.6.	AI only. N = 18455	Non-persistence ≥6 months gap since last prescription refill	Year 1: 99.8% Year 2: 98.3% Year 3: 95.8% Year 4: 92.9% Year 5: 87.0%	1) Using bisphosphonates	–
Sella, 2019 (Israel) [50]	Retrospective cohort. Prescription record & electronic medical record of health service provider, national cancer registry.	Women with non-metastatic BC.	TAM & AI. N = 4178	Implementation PDC≥ 80% (over the period of persistence) Persistence ≥180 days gap since last prescription refill/follow up	Mean PDC: 82.9% Persistence: 77%	1) Age 45.01–85 (vs ≤ 45) 2) Hypertension	1) Underweight BMI 2) Unknown smoking status (vs never smoked)
Trabulsi, 2014 (Canada) [51]	Retrospective cohort. Provincial insurance claims database, cancer	Women with non-metastatic BC, insured, initiated	TAM & AI. N = 4715	Implementation MPR≥ 80% Persistence	Implementation: 79% Mean MPR	1) Prior medication use 2) Late switching	1) DCIS 2) More hospitalization 3) Newly added

Table 1 (*continued*)

Author, Year (Country)	Study Design/Approach	Participant Characteristics	AET Type, Number of Participants	Definition of Adherence	Rate of Adherence	Factors that Increased Adherence	Factors that Decreased Adherence
	registry, medical and pharmaceutical services and hospital discharge databases.	AET within a year, age ≥65 years. Mean age 72.9.		≥60 days gap in medication supply	Year 1: 90% Year 5: 75% Persistence: 66.2%	3) Non-surgeon as prescriber	medications (after starting AET) 4) Use of antidepressants 5) Using TAM 6) Switching AET during 1st year
Wulaningsih, 2018 (Sweden) [52]	Retrospective cohort. Regional breast cancer registry, Swedish Prescribed Drug Register, Patient Register and integration database for health insurance and labour market studies.	Women with non-metastatic stage I-III ER+ BC.	TAM & AI. N = 4645	Implementation MPR≥ 80%	Implementation: 79%	1) Mastectomy (vs BCS) 2) No surgery (vs BCS) 3) Lymph node involvement 4) Higher tumor grade & size 5) HER-2 positivity 6) Received chemotherapy 5) Taking AIs 6) Uppsala-Orebro region & Northern region (vs Stockholm-Gotland) 7) Baseline use of GI drugs	1) Older age (>65) 2) Greater increase in comorbidity burden 3) Baseline use of hormone replacement therapy, analgesics, hypnotics & sedatives, 4) Single/divorced/ widowed 5) High educational level 6) Concurrent use of analgesics, hypnotics and sedatives, antidepressant, GI drugs, vaginal estrogen

AI: Aromatase inhibitor; BC: Breast cancer; BCS: Breast-conserving surgery; DCIS: Ductal carcinoma in situ; ER+: estrogen-receptor positive; GI: gastro-intestinal; HR+: hormone-receptor positive; HRT: Hormone-replacement therapy; MPR: Medication Possession Ratio; PDC: Proportion of Days Covered; PR+: progesterone-receptor positive; TAM: Tamoxifen.

[a] Had different factors associated with 5 trajectories of non-adherence. Factors included here are those that were found to be significantly associated in three or more trajectories.

Table 2
Quality assessment and risk of bias.

Authors, Year	Completeness and Reliability of Data Source	Measure of Adherence		Methodological Quality							Risk of Bias
		Objective measure	Explicit definition	Examined pre-enrolment period	Verified continuous eligibility (claims database)	Explanation for MPR values of >1	Clear definition of outcomes, predictors, confounders	Explain how missing data were addressed	Addressed potential sources of bias	Attempted to control for confounders	
Bhatta, 2013 [27]	Poor	N	N	N/A	N/A	N/A	N	Y	N	Y	**High**
Blanchette, 2020 [36]	Good	Y	Y	Y	N/A	N	Y	Y	Y	Y	**Moderate**
Bosco-Levy, 2016 [37]	Good	Y	Y	Y	Y	N/A	Y	Y	Y	Y	**Low**
Cahir, 2017 [38]	Intermediate	Y	Y	Y	Y	N	Y	N	N	Y	**Moderate**
Cavazza, 2020 [39]	Good	Y	Y	Y	N/A	N/A	Y	N	N	Y	**Moderate**
Emerson, 2021 [40]	Intermediate	Y	Y	Y	Y	N/A	Y	Y	Y	Y	**Moderate**
Farias, 2018 [41]	Intermediate	Y	Y	N	Y	Y	Y	N	Y	Y	**Moderate**
Font, 2012 [28]	Good	Y	N	N	N/A	N	Y	N	Y	Y	**High**
Gao, 2017 [30]	Intermediate	Y	N	N	N/A	N/A	N	N	N	Y	**High**
Guedes, 2017 [42]	Intermediate	Y	Y	N	N/A	N	N	N	N	Y	**High**
Hagen, 2019 [29]	Good	Y	Y	N	N/A	N	Y	Y	N	Y	**High**
He, 2015 [31]	Good	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	**Low**
He, 2019 [32]	Good	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	**Low**
He, 2020 [33]	Good	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	**Low**
Huiart, 2011 [43]	Good	Y	Y	Y	N/A	Y	N	N	N	N/A	**High**
Kroenke, 2018 [34]	Intermediate	Y	Y	Y	Y	N	Y	Y	Y	Y	**Moderate**
Lailler, 2021 [44]	Good	Y	Y	Y	Y	N/A	Y	Y	Y	N	**Moderate**
Lambert, 2020 [35]	Good	Y	Y	Y	Y	N/A	Y	Y	N	N	**Moderate**
Lundgren, 2018 [45]	Good	Y	Y	N	N/A	N	N	Y	N	Y	**High**
Ma, 2020 [46]	Intermediate	Y	Y	Y	Y	Y	Y	Y	Y	Y	**Moderate**
Ma, 2021 [47]	Intermediate	Y	Y	Y	Y	N	Y	Y	Y	Y	**Moderate**
Owusu, 2008 [48]	Intermediate	Y	N	Y	N	N/A	Y	Y	Y	Y	**High**
Pineda-Moncusi, 2020 [49]	Intermediate	Y	Y	N	N/A	N/A	N	N	N	Y	**High**
Sella, 2020 [50]	Good	Y	Y	Y	N	Y	Y	N	N	Y	**Moderate**
Trabulsi, 2014 [51]	Good	Y	Y	Y	N/A	Y	Y	Y	N	N	**Moderate**
Wulaningsih, 2018 [52]	Good	Y	Y	Y	N/A	N	Y	Y	Y	Y	**Moderate**

included <40–50 years old. Having a partner or being married was associated with better adherence in three studies [38,46,52]. In terms of racial differences, it was noted that Hispanic and Black patients were associated with lower adherence [40,46], and Asian

Table 3
Factors affecting non-adherence in two or more studies.

Variable	Association with Non-adherence in the Implementation Phase	Association with Non-adherence in the Persistence Phase	No Significant Association
Social and economic factors			
Older age	Blanchette [36]: OR 1.03 (1.02–1.05); Ma 2020 [46]: RR 1.03[a]; Wulaningsih [52]: OR 1.23 (1.05–1.43); Lailler [44]: OR 1.62 (1.40–1.87); Cavazza [39]: OR 3.33 (2.63–4.17)	He 2015 [31]: HR 1.39 (1.08–1.78); Owusu [48]: HR 2.02 (1.53–2.66)	Cahir, Lundgren
Younger age		He 2015 [31]: HR 1.15 (1.03–1.28); Cahir [38]: RR 1.41 (1.16–1.70); Huiart [43]: RR 1.52[a]	Bosco-Levy, Cavazza, Wulaningsih, Lambert
Married/has partner	Wulaningsih [52]: OR 0.70 (0.61–0.81); Ma 2020 [46]: RR 0.98[a]	Cahir [38]: RR 0.82 (0.70–0.94)	Hagen, Ma 2021
Lower financial status	Ma 2021 [47]: OR 1.60 (1.04–2.45)	Gao [30]: OR 1.82 (1.12–2.94)	Bhatta, Blanchette, Cahir, Farias, Sella, Trabulsi, Lambert
Hispanic (vs White)	Ma 2020 [46]: RR 1.066[a]	Emerson [40]: OR 1.15 (1.03–1.28)	Farias
Black (vs White)	Ma 2020 [46]: RR 1.067[a]	Emerson [40]: OR 1.20 (1.05–1.39)	Bhatta, Blanchette, Cahir, Farias, Owusu
Condition-related factors			
Metastatic breast cancer (vs early breast cancer)		Guedes [42]: HR 2.24 (1.45–3.45); Bosco-Levy [37]: HR 3.07 (1.73–5.46)	
Regional, later stage breast cancer (vs early breast cancer)	Wulaningsih [52]: OR 0.51 (0.40–0.65) (lymph node involvement); Wulaningsih [52]: OR 0.58 (0.47–0.73) (higher tumor grade & size)	Hagen [29]: HR 0.42 (0.18–0.97) (lymph node involvement)	Font, He 2015, Ma 2021
Higher comorbidity (Charlson)	Ma 2020 [46]: RR 1.056[a]; Wulaningsih [52]: OR 1.43 (1.08–1.88)	He 2015 [31]: HR 1.35 (1.03–1.76); Owusu [48]: HR 1.52 (1.18–1.95); Farias [41]: OR 2.87 (1.31–6.29)	Blanchette, Guedes, Ma 2021, Trabulsi, Lailler
Therapy-related factors			
Received chemotherapy	Cavazza [39]: OR 0.38 (0.29–0.50); Blanchette [36]: OR 0.42 (0.30–0.59); Wulaningsih [52]: OR 0.43 (0.35–0.52); Lambert [35]: OR 0.48 (0.28–0.84); Lailler [44]: OR 0.78 (0.70–0.87)	Font [28]: OR 0.63 (0.41–0.95); Bosco-Levy [37]: HR 0.65 (0.48–0.89)	Cahir, Farias, Hagen, He 2015, Lundgren, Owusu
Treatment with AI vs tamoxifen	Lailler [44]: OR 0.40 (0.34–0.47); Blanchette [36]: OR 0.70 (0.59–0.83); Cavazza [39]: OR 0.69 (0.57–0.83); Wulaningsih [52]: OR 0.72 (0.58–0.89)	Font [28]: OR 0.50 (0.30–0.85); Huiart [43]: RR 0.61[a]; Bosco-Levy [37]: HR 0.62 (0.46–0.83)	Cahir, Gao, Guedes, Lundgren
Switching AET (any switch)		He 2015 [31]: HR 1.50 (1.23–1.83); Bosco-Levy [37]: HR 3.10 (2.20–4.36)	Wulaningsih
Switching tamoxifen to AI	Lailler [44]: OR 0.53 (0.38–0.65)	Gao [30]: OR 0.35 (0.13–0.98); Font [28]: OR 0.44 (0.26–0.75)	Lundgren
Adverse effects/Using drugs related to adverse effects	Wulaningsih [52] (vaginal estrogen): OR 1.33 (1.08–1.64); Wulaningsih [52] (analgesics): OR 1.43 (1.24–1.66); Gao [30]: OR 4.55 (2.70–7.69)	Pineda-Moncusi [49] (bisphosphonates): HR 0.53 (0.47–0.60); He 2015 [31] (analgesics): HR 1.22 (1.08–1.37)	
Health care team and system-related factors			
Co-payment exempt status	Ma 2021 [47]: OR 0.52 (0.45–0.59)	Bosco-Levy [37]: HR 0.21 (0.13–0.32)	Bhatta
More hospitalization	Trabulsi [51]: 0.7 (−1.3, −0.2)[b]	Guedes [42]: HR 6.06 (2.53–14.54)	Cavazza
Patient-related factors			
Depression	Wulaningsih [52]: OR 1.27 (1.08–1.50); Cavazza [39]: OR 1.47 (1.28–1.67); Trabulsi [51]: 4.7 (−7.9, −1.5)[b]	Cahir [38]: RR 1.22 (1.04–1.45); He 2015 [31]: HR 1.22 (1.06–1.40)	
Prior medication use	Trabulsi [51]: 0.6 (0.4, 0.9)[b]	Cahir [38]: RR 0.61 (0.50–0.75)	
Use of hypnotics and sedatives	Wulaningsih [52]: OR 1.49 (1.28–1.74)	He 2015 [31]: HR 1.21 (1.07–1.37)	Trabulsi

[a] RR value estimated from proportion of adherence reported.
[b] Multivariate Regression analysis used to assess association. Positive value indicate association with higher adherence.

patients were associated with better adherence in comparison to White patients [46]. In addition, it was found that patients with low personal or clinical social support had higher AET non-adherence [34].

3.4.2. Condition-related factors

Higher comorbidity burden, measured using Charlson comorbidity index [54], was found to be associated with lower adherence in five studies. Patients with metastatic (stage IV) breast cancer were associated with lower adherence [37,42]. However, among those with non-metastatic breast cancer, adherence was higher among patients with higher tumor grade and lymph node involvement in comparison to patients in earlier stages of breast cancer [29,52].

3.4.3. Therapy-related factors

Seven studies reported that using AI instead of tamoxifen was associated with better adherence. In addition, better adherence was also associated with patients who had sequential treatment or switched their AET from tamoxifen to AI [28,30,44]. Conversely, switching from AI to tamoxifen was associated with lower adherence when compared to patients taking AI only [44]. Switching AET was also associated with lower adherence in studies that included both directions of switching (tamoxifen to AI and AI to tamoxifen)

[31,37]. In the study by Trabulsi et al. early switching was associated with better adherence, but late switching was associated with lower adherence compared to patients with no switching [51]. Seven studies reported that receiving chemotherapy was correlated with better adherence. Experiencing adverse effects and concomitant use of drugs that were typically used in treatment of AET side effects such as analgesics and vaginal estrogen were associated with lower adherence. However, using bisphosphonates to prevent loss of bone mass with AI was associated with increased adherence.

3.4.4. Health care team and system-related factors

Lower out of pocket cost for AET treatment was associated with higher adherence [37,47]. The study by Ma et al. also found that the decreasing trend of adherence to therapy over five-year treatment was attenuated with the introduction of generic AI [46]. It was also found that patients that had more hospitalizations were associated with lower adherence [42,51]. Continued care in the same hospital [39], personalized care plan [35], and follow-up with a medical oncologist within four months of AET initiation [36] were also associated with better adherence.

3.4.5. Patient-related factors

Patients who took antidepressants, hypnotics and sedatives or known to have pre-existing depression were found to have an increased risk of non-adherence [31,38,39,51,52]. Having prior medication(s) before taking AET was associated with better adherence [38,51]. Ultrarapid CYP2D6 metabolizers were found to be associated with lower adherence, though the association was only significant in early non-adherence [33]. Perceived importance of AET, and high value on doctor's opinion were found to be associated with higher persistence in the study by Bhatta et al. [27]. Gao et al. found that doubt and disbelief in AET efficacy correlated with lower persistence [30].

4. Discussion

This review included 26 studies assessing the rate of and factors significantly associated with adherence in patients taking AET over a period of five years. This systematic review attempted to improve from previous reviews by focusing on methodological quality of adherence assessment. Notably, most included studies used prescription database analysis to estimate adherence. None of the studies used other objective methods such as pill counts, electronic monitoring and biochemical measures, likely due to the difficulty of using these measures over a five-year period. We have also summarized correlates identified in multiple studies in a quantifiable manner, and categorized these according to five interacting dimensions affecting patient adherence. The large degree of variability in the studies made it difficult to pool the data, but there was a clear decreasing trend of patients' adherence over the five-year treatment period. On average, approximately one-third of patients did not adhere to treatment at the fifth year of treatment.

Social and economic factors were the most studied as these variables can be easily retrieved from health administrative databases. It was found that patients in the extreme age groups (older or younger) may be less adherent than the mid-range age group. However, it was difficult to quantify this association as variable age ranges and comparison were used in different studies. This trend was also observed in previous systematic reviews on adherence to AET and other oral anticancer treatment [9,55]. Lower adherence in the younger age group may be due to fertility concern in reproductive-age breast cancer survivors [56], as well as greater quality of life disturbance, with greater impact on emotional well-being and disease-related concerns [57]. Lower adherence in older age group may be attributable to various other inter-dependent factors including comorbidities, health-literacy, cognitive function, and lack of social support [58,59]. Although age itself is not a modifiable factor, our finding highlights that these age groups may be at higher risk. Therefore, healthcare personnel involved in their care should address related issues such as fertility concern, quality of life, cognitive problems and social support.

Having more advanced cancer was thought to instill a high motivation to remain adherent [52]. Similarly, patients who undertake more 'aggressive' treatments may perceive their condition as more serious and consider AET as more essential [60], which may explain the higher adherence observed in patients receiving chemotherapy compared to those who did not. However, perception of condition severity and treatment importance is subjective and a lot of other factors may influence patients' willingness to continue treatment. For patients with metastases and much more advanced cancer, benefit of AET may be low and it may be possible that treatment was stopped due to unfavorable risk-benefit profile [37].

Based on our findings, AI was often associated with better adherence compared to tamoxifen. Clinical trials comparing AI to tamoxifen showed better efficacy with significantly prolonged disease-free survival, time-to-recurrence and reduced metastasis, as well as improved adherence and improved side effect profile, with fewer thromboembolic events and less endometrial cancer, hot flashes and vaginal bleeding [4–6]. However, patients receiving AI had more skeletal events, with increased arthralgia and fractures [4,5,61]. Our review found that patients who used symptom-relieving drugs such as analgesics and vaginal estrogen were associated with lower adherence [31,52]. Adverse effects can have profound effects on quality of life, and it was found that those with more severe symptoms that affect their quality of life have a higher likelihood of non-adherence [18], although direct association with quality of life was not measured by the studies included. Side effects are usually an inevitable part of treatment, and the key to tackle this problem is through better management. For example, the study by Pineda-Moncusi et al. showed that the use of bisphosphonates in patients using AI was associated with improved persistence, which was also associated with reduced fracture and mortality [49]. Recent qualitative syntheses on AET adherence reported that patients perceived AET side effects as 'worse than the disease', and highlighted the importance of education and support to help breast cancer survivors manage the adverse effects of the treatment and improve their quality of life [15,16,62]. They believed that more information on side effects and management strategies would help them adhere and persist with AET [15,16,62]. This highlights the importance of patient education at the early stage of therapy, as adverse effects often caused early rather than late discontinuation, particularly for tamoxifen [33,48].

Co-payment exemption was found to significantly improve adherence in two studies [37,47], but this result should be interpreted with caution. A recent randomized controlled trial showed improved adherence in patients receiving free chronic medications, but it did not affect surrogate health outcomes such as hemoglobin A1c levels, blood pressure, and low-density lipoprotein levels [63]. The conflicting results suggested that many participants did not take all prescribed treatments as directed despite receiving free medications, indicating that factors other than out-of-pocket cost are important contributors to non-adherence [63]. Association between number of hospitalizations and non-adherence could be attributed to burden of existing comorbidities, disease severity and side effects [42,64], but more importantly it could also be due to errors in medication reconciliation at discharge [51]. It was reported that there were up to 60% discrepancies in discharge prescriptions for drugs targeting chronic conditions due to errors and omissions [65], indicating a room for intervention to improve

treatment continuity. Our review found that better clinical social support [34] and personalized care plan at diagnosis was associated with better adherence [35]. This highlighted the importance of effective communication between physician and patient, which allows the physician to understand the patient's expectations and perceptions regarding their treatment [66].

Patient-related factors have often attracted substantial interest in adherence research as they provide various opportunities for intervention. In this review, depression was found to be associated with decreased adherence. This agrees with a previous systematic review, which found that depression was a significant predictor of AET adherence, particularly in younger women during the early stage (<18 months) of treatment [14]. Hypnotics use was also associated with non-adherence, possibly reflecting quality of life influences in AET adherence [52]. Prior medication use may help to improve adherence as patients with existing medications may have developed existing habits that promote adherence [51]. We identified several modifiable factors, such as perceived importance of AET and belief in AET efficacy, which can be potentially modified through patient education. Another factor that may need to be addressed is the value placed on doctor's opinion, which emphasizes the importance of effective communication between healthcare personnel and patients [27]. Ultrarapid CYP2D6 metabolizers had a higher rate of discontinuation compared to normal metabolizers. They were found to have higher plasma concentration of endoxifen following a standard dose of tamoxifen and higher use of symptom-relieving drugs, indicating that they experienced more intense adverse effects [33]. This may necessitate dose adjustment in combination with concentration monitoring of tamoxifen metabolites for this subgroup of patients to improve treatment tolerability and adherence [33].

From the reports extracted, we found a considerable increase in the number of studies utilizing large prescription databases after 2010, with more focus on long-term adherence in studies published after 2015. Considering that the dose-response phenomenon is a continuous function and a binary definition of adherence using 80% cut-point over extended periods may result in loss of information [10], there was an increased interest in longitudinal patterns of adherence in recent studies. Our review included two studies using group-based trajectory modeling (GBTM) [35,44], which is able to identify homogeneous patient group profiles and changes in medication use as a function of time, and ascertain crucial moments when adherence is likely to decline [67]. The studies included were able to identify up to seven trajectories in patients using AET, including those with immediate discontinuation, late non-adherence, continuous suboptimal adherence, and continuous optimal adherence [35,44]. Information about longitudinal patterns may help healthcare professionals to develop tailored adherence-enhancing interventions, as the determinants that lead to non-adherence may be unique in the different trajectories. For example, the immediate discontinuation trajectory was associated with having anti-HER2 treatment, indicating cancers with poorer prognosis; those with continuous suboptimal adherence was associated with belonging to insurance scheme with less benefit and living in a deprived area, indicating that financial difficulties may have affected their adherence [44].

4.1. Limitations

Some limitations need to be considered. Variability in definitions of adherence, methods of measurement and study population made it difficult to pool the data. Although all studies used 80% cut-point to indicate good adherence, this measurement was either based on medication supply, prescription availability or patient self-report. Some studies considered patients to be non-adherent if AET medication was changed, and some measure of adherence was only based on prescription rather than medication availability. Definition of non-persistence was also varied in terms of duration of gap and definition, counted from the date of last dispensing or date of medication supply run out. Patients who eventually restarted AET may be censored even though AET was later continued, and most studies did not address this subgroup of patients. There was considerable variation in terms of how adherence and persistence were used in relation to each other. Some studies measured adherence only among those that were considered to be persistent to treatment, and some calculated them over the five-year period. Most included studies were observational studies using prescription databases, which are known to have various limitations [25,26]. As there is no guarantee that patients with medication supply would actually take them as prescribed, it has been argued that adherence measure using prescription databases is more suitable to assess adherence in the persistence rather than the implementation phase [68]. Patients were assumed to be non-adherent when they stopped collecting their medication, although reasons for cessation could be due to emigration, prescribers' recommendation, recurrence or death; and this information would be missed in studies using incomplete localized databases. Many studies used the same population-based administrative database, providing significant potential for data overlap. The search for relevant articles may have not been exhaustive as it was limited to English publication and did not include gray literature. Full-article assessment and data extraction was dually conducted only for 50% of articles due to time constraint. Nevertheless, we are confident that these methodological limitations would not change the overall conclusions of this review.

4.2. Implications & future research

As the review is limited to studies assessing five-years adherence, few modifiable factors were identified because most long-term adherence studies focused on database analysis. However, this review highlights several sociodemographic predictors of long-term adherence that may help healthcare professionals to identify populations with higher risk of AET non-adherence. Ever-increasing demands for health-care services resulting from improved life expectancy and growing population emphasize the importance of targeted care, thus identifying high-risk populations and providing early intervention and counseling may be important for improved long-term prognosis. Issues pertaining to adverse effect management, quality of life and fertility need to be discussed early in the treatment phase.

It must be understood that factors affecting adherence are varied and complex, and interpersonal aspects of medication adherence may be more appropriately investigated through qualitative research or validated questionnaires. To better understand long-term adherence of AET treatment, future studies may need to employ a multi-measure approach that combines subjective and reasonable objective measures such as combination of pharmacy database analysis and questionnaire with validated scales to measure specific determinants of adherence. Direct methods that measure the level of drug or its metabolites in the blood or urine can capture information missed by indirect measures, and may be considered when accurate evaluation of adherence is critical for outcome measurement. Any self-reported measures of adherence should be cross-checked with objective methods, as several studies included in this review have shown that AET adherence may be overestimated through self-reported measures. Future studies may want to utilize GBTM to identify longitudinal patterns in patient medication-taking behavior, as different factors can be identified for groups of patients with different adherence patterns, and

include measures of quality of life to further understand issues related to long-term AET adherence.

5. Conclusions

This systematic review shows that adherence decreased substantially from the first to fifth year of treatment, and provides an insight into factors that potentially affect long-term adherence in patients taking AET. Various factors relating to patient condition, therapy, healthcare-system, and socioeconomic condition were reported, indicating the dynamic and complex nature of medication adherence. Recurring factors identified to be associated with poor adherence include older and younger age, being single, depression, higher comorbidity index and adverse effects. Using AI instead of tamoxifen, received chemotherapy, and prior medication were associated with increased adherence. However, caution is needed in the interpretation and generalizability of the results, as the studies were heterogeneous and it was difficult to pool the data and make a clear conclusion. Several opportunities for intervention to improve adherence were identified, including patient education to improve knowledge of medication benefits, adverse effects and their management; discussion on fertility issues, quality of life and social support; as well as ensuring proper medicine reconciliation during hospital discharge. It was found that self-reported adherence was often higher when compared to adherence determined using prescription databases. Future studies may consider conducting multiple approaches to measure adherence and include longitudinal surveys to better understand modifiable factors affecting patients' adherence over the full duration of treatment.

Registration/protocol

Protocol for this systematic review was not registered or published elsewhere.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix

Appendix A: Details of Database Search

Results Generated From:
Embase Classic + Embase <1947 to 2021 September 02>
APA PsycInfo <1967 to August Week 5 2021>
AMED (Allied and Complementary Medicine) < 1985 to August 2021>
International Pharmaceutical Abstracts <1970 to August 2021>
Ovid MEDLINE(R) < 1946 to September 02, 2021>
Database APA PsycArticles Full Text.
001 *breast tumor/
002 *breast cancer/
003 *breast carcinoma/
004 (Breast cancer or Breast carcinoma or Breast tumo?r).mp. [mp 39485.
= ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh]
005 *Breast Neoplasms/
006 1 or 2 or 3 or 4 or 5.
007 *cancer hormone therapy/
008 *Antineoplastic Agents, Hormonal/
009 exp Selective Estrogen Receptor Modulators/
010 exp Tamoxifen/
011 exp Aromatase Inhibitors/
012 exp Anastrozole/
013 exp Letrozole/
014 exp Toremifene/
015 exp tamoxifen citrate/
016 exp exemestane/
017 (Adjuvant endocrine or Adjuvant hormon*).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh]
018 (Tamoxifen or Toremifene or Selective ?estrogen receptor modulator* or SERM).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh]
019 (Aromatase inhibitor* or Anastrozol* or Letrozol* or Exemestane).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc,id, tm, mh]
020 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19.
021 exp Morisky Medication Adherence Scale/
022 exp patient compliance/
023 exp Medication Adherence/or exp "Treatment Adherence and Compliance"/
024 exp Patient Compliance/or exp Compliance/
025 (Non?adhere* or Adhere*).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh]
026 (Non?complian* or Complian*).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh]
027 (Persisten* or Non?persisten*).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh]
028 Discontinu*.mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh]
029 Pharmacoadheren*.mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh]
030 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29.
031 6 and 20 and 30.
032 limit 31 to english language.
033 limit 32 to human.
034 limit 33 to female.
035 remove duplicates from 34.

Appendix B. : Categorisation of risk of bias

High Risk of Bias:
If data source reliability was Poor OR used non-objective measure of adherence/persistence OR adherence/persistence was not explicitly defined.
If data source reliability was Good/Intermediate AND used objective measure of adherence/persistence AND adherence/persistence was explicitly defined BUT methodological quality was low with ≥50% relevant items not reported.
Moderate Risk of Bias:
If data source reliability was Good/Intermediate AND used objective measure of adherence/persistence AND adherence/persistence was explicitly defined but methodological quality was moderate with <50% relevant items not reported.
Low Risk of Bias:
If data source reliability was Good AND objective measure of

adherence/persistence used AND adherence/persistence was explicitly defined and methodological quality was good with all relevant items reported.

Appendix C. : Characteristics of Excluded Studies

No	Study	Reason for exclusion
1	Bowles, 2012	Cross sectional study validated with pharmacy database, but the actual duration of use was unclear and largely based on self-report.
2	Brito, 2014	Large proportion of patients not analysed for full 5 years of follow up.
3	Guth, 2012	Include patients enrolled in clinical trial.
4	Haskins, 2018	Large proportion of patients not analysed for full 5 years of follow up.
5	Haskins, 2020	Unclear proportion of patients followed up for 5 years.
6	Jacob, 2016	Some patients not analysed for full 5 years of follow up. First prescription between 2004 and 2013, follow-up ended in 2015.
7	Kemp 2014	Some patients not analysed for full 5 years of follow up. Patient intiated between 2003 and 2008, follow-up ended in 2011.
8	Kim, 2018	Some patients not analysed for full 5 years of follow up. Diagnosed between 2008 and 2012, available data only until 2013.
9	Krotneva, 2014	24.8% patients not analysed for full 5 years of follow up. Diagnosed between 1998 and 2005, available data only until 2007.
10	Kuo, 2021	Some patients not analysed for full 5 years of follow up. Diagnosed 2010–2017, available data only until 2018.
11	Lee, 2014	Initiated 2002–2011, follow up until 2013. Only 20.6% followed up for 5 years
12	Llarena, 2015	Patients not analysed for full 5 years of follow up.
13	Mao, 2020	Large proportion of patients not analysed for full 5 years of follow up.
14	Moscetti, 2015	Focused on the toxicity and reasons for discontinuation, not factors affecting adherence.
15	Nekhlyudov, 2011	Patients were followed between 1 and 5 years. Two analyses of adherence predictors were made, for 1 year and 2–5 years. None for only 5 years.
16	Peng, 2016	Focused on tolerance towards AET, focusing on completion rate of different AET. Reason for discontinuation for <5 year. Did not focus on correlates/factors affecting adherence or persistence.
17	Pineda-Moncusi, 2019	Focused on the change in Quality of Life and joint pain over 5 years of treatment, not on factors affecting adherence. Part of a clinical trial.
18	Riley, 2011	SEER data were linked to Medicare data only after a certain years, therefore adherence were not assessed for full 5 years.
19	Schwartzberg, 2009	Unable to determine the number of patients followed up until 5 years. Focused more on time until discontinuation or drug switching among patients who were prescribed tamoxifen or an AI.
20	Seneviratne, 2015	Patients not analysed for full 5 years of follow up. Diagnosed 2005–2011, follow-up until 2013. 51% followed up until 5 years.
21	Tervonen, 2019	Study using group-based trajectories. Determination of factors affecting adherence was not a study objective.

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