Predictors for Non-Adherence and Non-Persistence to Adjuvant Hormone Therapy in Women with Breast Cancer: Literature Systematic Review

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Preditores para Não Adesão e Não Persistência à Terapia Hormonal Adjuvante em Mulheres com Câncer de Mama: Revisão Sistemática da Literatura

Predictores de la No Adherencia y la No Persistencia de la Terapia Hormonal Adyuvante en Mujeres con Cáncer de Mama: Revisión Sistemática de la Literatura

Fernanda Venâncio Soares de Sousa[1]; Anna Paula de Sá Borges[2]; Maria Ângela Ribeiro[3]

ABSTRACT

Introduction: Adjuvant hormone therapy reduces disease recurrence and mortality in women with hormone receptor-positive breast cancer. However, many studies suggest that breast cancer treatment with endocrine therapy is compromised by non-adherence and non-persistence. **Objective:** To identify the predictors of non-adherence and/or non-persistence that impair the good results of treatment with endocrine therapy in breast cancer patients. **Method:** Systematic Literature Review performed using MEDLINE/PubMed, Embase, and Scopus. Eligible studies for this review were selected using the Rayyan QCRI application, analyzed, and classified according to the Grading of Recommendations Assessment, Development and Evaluations (GRADE) hierarchy of levels of evidence, and inter-rater reliability (Kappa coefficient) was calculated. The study was filed in the International Prospective Register of Systematic Reviews (PROSPERO) and published under number CRD42021212788. **Results:** Predictors were identified in 21 articles with quantitative methodology. These predictors were grouped into seven categories as follows: adverse reactions, types of medications, duration of treatment, psychological factors, geographic location, polypharmacy/comorbidities and aspects related to monitoring by the multidisciplinary team, considered responsible for non-adherence and/or non-persistence with endocrine therapy. **Conclusion:** The predictors of adverse reactions, tamoxifen use, and long treatment duration were associated with non-adherence and non-persistence to endocrine therapy for breast cancer.

Key words: Breast Neoplasms/therapy; Treatment Adherence and Compliance; Tamoxifen; Aromatase Inhibitors.

RESUMO

Introdução: A terapia hormonal adjuvante em mulheres com câncer de mama receptor hormonal positivo reduz a recorrência da doença e a mortalidade. No entanto, muitos estudos sugerem que o tratamento para o câncer de mama com terapia endócrina é comprometido pela não adesão e não persistência. **Objetivo:** Identificar os preditores de não adesão e/ou não persistência que prejudicam os bons resultados do tratamento com terapia endócrina em pacientes com câncer de mama. **Método:** Revisão sistemática da literatura realizada por meio do MEDLINE/PubMed, Embase e Scopus. Os estudos elegíveis para esta revisão foram selecionados por meio do aplicativo Rayyan QCRI, analisados e classificados segundo a hierarquia dos níveis de evidência *Grading of Recommendations Assessment, Development and Evaluations* (GRADE) e a confiabilidade entre os examinadores (coeficiente Kappa). O trabalho foi protocolado no *International Prospective Register of Systematic Reviews* (PROSPERO) e publicado sob n.º CRD42021212788. **Resultados:** Foram identificados preditores em 21 artigos, com metodologia quantitativa. Esses preditores foram agrupados em sete categorias da seguinte forma: reações adversas, tipo de medicamento, tempo de tratamento, fatores psicológicos, localização geográfica, polifarmácia/comorbidades, aspectos relacionados ao acompanhamento da equipe multiprofissional, considerados responsáveis por não adesão e/ou não persistência à terapia endócrina. **Conclusão:** Os preditores reações adversas, o uso do tamoxifeno e o longo tempo de tratamento estiveram associados à não adesão e à não persistência à terapia endócrina do câncer de mama.

Palavras-chave: Neoplasias da Mama/terapia; Cooperação e Adesão ao Tratamento; Tamoxifeno; Inibidores de Aromatase.

RESUMEN

Introducción: La terapia hormonal adyuvante reduce la recurrencia de la enfermedad y la mortalidad en mujeres con cáncer de mama con receptores hormonales positivos. Sin embargo, muchos estudios sugieren que el tratamiento del cáncer de mama con terapia endocrina se ve comprometido por no adherencia y no persistencia. **Objetivo:** Identificar los predictores de baja adherencia y/o no persistencia que perjudican los buenos resultados del tratamiento con endocrinoterapia en pacientes con cáncer de mama. **Método:** Revisión Sistemática de la Literatura realizada en MEDLINE/PubMed, Embase y Scopus. Los estudios elegibles para esta revisión se seleccionaron mediante la aplicación Rayyan QCRI, se analizaron y clasificaron de acuerdo con la jerarquía de niveles de evidencia *Grading of Recommendations Assessment, Development and Evaluations* (GRADE), y se calculó la confiabilidad entre evaluadores (coeficiente Kappa). La obra fue archivada en el Registro Prospectivo Internacional de Revisiones Sistemáticas (PROSPERO) y publicada con el número CRD42021212788. **Resultados:** Se identificaron predictores en 21 artículos con metodología cuantitativa. Estos predictores se agruparon en siete categorías de la siguiente manera: reacciones adversas, tipos de medicamentos, duración del tratamiento, factores psicológicos, ubicación geográfica, polifarmacia/comorbilidades y aspectos relacionados con el seguimiento por el equipo multidisciplinario, considerados responsables de la no adherencia y/o no persistencia a la terapia endocrina. **Conclusión:** Los predictores de reacciones adversas, el uso de tamoxifeno y la duración prolongada del tratamiento se asociaron con la falta de adherencia y la falta de persistencia a la terapia hormonal para el cáncer de mama.

Palabras clave: Neoplasias de la Mama/terapia; Cumplimiento y Adherencia al Tratamiento; Tamoxifeno, Inhibidores de la Aromatasa.

[1]Universidade Federal de Uberlândia (UFU), Faculdade de Medicina, Programa de Residência em Área Profissional da Saúde (PRAPS). Uberlândia (MG), Brasil. E-mail: fvenancio2002@gmail.com. Orcid iD: https://orcid.org/0000-0003-1934-1254

[2]Universidade de São Paulo (USP), Faculdade de Ciências Farmacêuticas de Ribeirão Preto. Ribeirão Preto (SP), Brasil. Universidade Estadual de Goiás (UEG), Instituto de Ciências da Saúde e Biológicas, Curso de Farmácia. Itumbiara (GO), Brasil. E-mail: anna.borges@ueg.br. Orcid iD: https://orcid.org/0000-0002-0668-1957

[3]Universidade Federal de Minas Gerais (UFMG), Faculdade de Farmácia, Programa de Pós-Graduação em Medicamentos e Assistência Farmacêutica. Belo Horizonte (MG), Brasil. UFU, Hospital de Clínicas, Unidade de Farmácia Clínica e Dispensação Farmacêutica, Ebserh. Uberlândia (MG), Brasil. E-mail: maria.ribeiro.9@ebserh.gov.br. Orcid iD: https://orcid.org/0000-0002-1522-4299

Corresponding author: Anna Paula de Sá Borges. Rua Ronan Manoel Pereira Floriano Peixoto, 792, Apto. 101 – Segismundo Pereira. Uberlândia (MG), Brasil. CEP 38408-274. E-mail: anna.borges@ueg.br

INTRODUCTION

Breast cancer is the neoplasm with the highest incidence and mortality in women worldwide[1,2]. In Brazil, 73,610 new cases are estimated for each year of the triennium 2023-2025, with incidence rate of 41.89 cases per 100,000 women[3]. Nearly three quarters of breast cancers are positive hormone receptors and are treatable with endocrine therapy[4].

Endocrine therapy for breast cancer is a treatment that deprives hormone production or interferes in the signaling of the hormone receptor to prevent tumor growth and can be utilized for until ten years after diagnosis. Most common adjuvant endocrine hormone treatments for women with positive hormone receptor breast cancer include tamoxifen and aromatase inhibitors (AI)[5]. Tamoxifen blocks the signaling through estrogen receptor. On the other hand, aromatase inhibitors block the synthesis of estrogen, the most common drugs are third generation anastrozole, exemestane and letrozole[6].

Endocrine therapy increases patients global survival and is associated with reduced risk of breast cancer recurrence and mortality[5,7]. The therapy facilitates the treatment because it is administered orally, a non-invasive procedure that does not require sterile technique of administration nor the presence of a health professional. On the other hand, because the treatment is targeted to the patient alone, non-adherence and non-persistence are actual concerns[8]. Non-adherence occurs when the patient does not take the prescribed medication during the treatment and non-persistence occurs when a patient interrupts the treatment continuously for a lengthy time[9].

According to Teixeira et al.[8], patient and therapy-related aspects can interfere in non-adherence and non-persistence to the oral treatment of breast cancer. Patient-related aspects are age, cognitive impairment, education level, relation with the health professionals, complexity of the treatment, forgetfulness, difficulties of locomotion, emotional factors as depression and anxiety, poor information about the disease and time to take the medication. Adverse effects, drug interactions, food interactions, overdose, variation of the absorption of the medication and polypharmacy are medication-related aspects.

Rates of non-adherence and non-persistence to adjuvant endocrine therapy vary among the studies between 16.0% and 50.5%[10-14]. Yussof et al.[11] showed that adherence to adjuvant endocrine therapy reduces from the first through the fifth year of treatment and in the fifth year, in average, one third of the patients fail to adhere to the treatment. Pistilli et al.[12] and Collin et al.[13] associated non-adherence and non-persistence to adjuvant endocrine therapy with high recurrence and mortality by disease. These findings are socially, clinically and economically relevant because they increase the disease relapse, mortality and health costs.

The objective of this review is to identify the predictors of non-adherence and non-persistence that impair the good results of endocrine therapy treatment in patients with breast cancer and guide future studies, health policies and clinical services.

METHOD

Systematic review registered at the International Prospective Register of Systematic Reviews (PROSPERO[15]), published with number CRD42021212788 and elaborated according to the strategy Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[16] from 2017 to 2022.

Eight stages were followed for the review: 1 – definition of the research question, population and detailed intervention; 2 – identification of the databases, descriptors and key-words; 3 – elaboration of the search strategies for each medication corresponding to the endocrine therapy (tamoxifen, anastrozole, letrozole and exemestane); 4 – definition of inclusion and exclusion criteria; 5 – search at the databases; 6 – comparative search conducted by the examiners and definition of the initial selection of studies; 7 – application of inclusion and exclusion criteria and justification of exclusions of the studies; 8 – drafting of the text, summarizing the information collected from the studies included and evidences-based conclusion.

The research question was defined according to the strategy PICOS (patient-intervention-comparison-outcomes-studies): P, population (women using hormone therapy for breast cancer); I, intervention (evaluation of adherence and persistence during endocrine therapy); C, comparison (evaluation of the adherence among different clinical and social characteristics of these patients); O, (outcome): identification of predictors of non-adherence and non-persistence. S, (type of study): randomized clinical trial, non-randomized clinical trial, cohort study, retrospective cohort study, cross-sectional study, prospective cohort study, observational study and case control.

The research question was: What are the predictors of non-adherence and/or non-persistence to endocrine therapy available in the literature? MEDLINE/PubMed, Embase and Scopus were the databases selected as sources of data.

The search was based on eligibility criteria, with descriptors MeSH/DeCs and Boolean operators according to three strategies applied in all databases: strategy 1: "breast neoplasms" AND "Medication Adherence"

AND "Endocrine Therapy" OR Tamoxifen; strategy 2: "breast neoplasms" AND "Medication Adherence" AND "Endocrine Therapy" OR Anastrozole; strategy 3: "breast neoplasms" AND "Medication Adherence" AND "Endocrine Therapy" AND "medication therapy management" OR "Comprehensive Medication Management" OR tamoxifen OR anastrozole.

Quantitative studies with population of women aged 18 or older, with prescription of endocrine therapy for breast cancer that addressed adherence or persistence to treatment in the period 2017 to 2022 were included. Articles evaluating endocrine therapy as prevention for breast cancer, screening or diagnostic studies, out of the scope, annals of congresses, abstracts only, reviews, unavailable full articles and projects were excluded.

All the articles found after the initial search were analyzed by two skilled investigators to evaluate titles and abstracts, independently, through the applicative Rayyan Qatar Computing Research Institute (Rayyan QCRI)[17] between August 4 and September 3, 2022.

Rayyan QCRI helps authors to perform easy and fast systematic review, with exportation of data from one specific database into the software and exposure of titles and abstracts, blinding of the assignee investigator, which ensures reliability of the information, accuracy and methodological precision[17].

If discrepancies were found in the studies, a third investigator analyzed and decided the inclusion or exclusion. Next, full articles were critically analyzed.

Data were collected through a specific electronic form with the following variables: authors, year of publication, country, study design, sample and quality of the evidence. The studies were analyzed and rated according to the hierarchy of the evidence grades of the Grading of Recommendations Assessment, Development and Evaluations (GRADE)[18]: 1 – High evidence: well-designed clinical trials with representative sample. Strong reliability that the actual effect is close to the estimated. 2 – Moderate evidence: well-designed observational studies with consistent findings. Moderate reliability about the estimated effect. 3 – Low evidence: clinical trials with moderate limitations. Reliability of the effect is limited[18].

Kappa function was utilized to measure the concordance among examiners[19], reaching a Kappa value of 0.8, an excellent result.

RESULTS

In all, 451 articles were found at the databases investigated, 216 were removed in the identification phase, 214 did not meet the inclusion criteria, resulting in a final sample of 21 articles (Figure 1).

Of the 21 studies selected, three (14.3%) presented high quality of evidence, eight (38.1%), moderate and ten, (47.6%), low quality. Chart 1[20-40] portrays the articles selected, authors, methodology, sample size, country and level of scientific evidence.

Chart 2[20-40] presents the methodology of evaluation of adherence of the studies investigated and the predictors of non-adherence and non-persistence to drug therapy.

To evaluate the causes of non-adherence and non-persistence, ten (47.61%)[28,29,31,34-40] studies utilized the quantification of daily supply, rate of possession and dispensation as main method and nine (42.85%), tools of self-report[20-22,26,276,32,33]. Other two studies[23,25] utilized lab and outpatient parameters, one adopted serum dosing[23], and the other, outpatient evaluation of sleep parameter[25].

The main sources of data utilized to identify the daily supply, the medication possession rate and dispensation were the number of prescriptions and total supply of medicines per period of therapy. Among the self-reported studies, the main instruments utilized were the subscale Functional Assessment of Cancer Therapy-Endocrine Subscale (FACTES), present in four (44.44%)[23,26,27,33], the beliefs about medicines questionnaire (BMQ) in three (33.3%)[22,32,33] and in two (22.2%) the Morisky Medication Adherence (MMAS-8)[24,30]. Eight (38.1%)[20,22-24,26,27,32,33] of the 21 articles utilized more than one tool to identify the causes of non-adherence and non-persistence.

The main factors related to non-adherence and non-persistence were grouped in seven categories: 1 – adverse reactions (n=8), 2 – type of medication (n=3), 3 – time of treatment (n=3), 4 – psychological factors (n=2), 5 – geographical location (n=3), 6 polypharmacy/ comorbidities (n=1) and 7 – aspects related to follow-up by the multiprofessional team (n=1) (Chart 2).

Of the studies selected for the present review, eight (38.1%) (Chart 2) addressed the adverse reactions as one of the main causes of non-adherence and non-persistence to endocrine therapy. These studies utilized several methods of analysis of adverse reactions and with foci of investigation.

Xu et al.[30] identified that 30.3% of the women in use of endocrine therapy interrupted the treatment because of adverse reactions. According to Hagen et al.[24], the estimate of discontinuation of endocrine therapy in 60 months was 38.0% and emphasized overweight or obesity as significantly dependent adverse reactions of the time of endocrine therapy and a predictive factor for its interruption.

According to Berkowitz et al.[21], the most prevalent adverse reactions to endocrine therapy were musculoskeletal in women with initial stage cancer or metastatic (74.6% *vs.* 77.7%). The authors still report that the use of oral

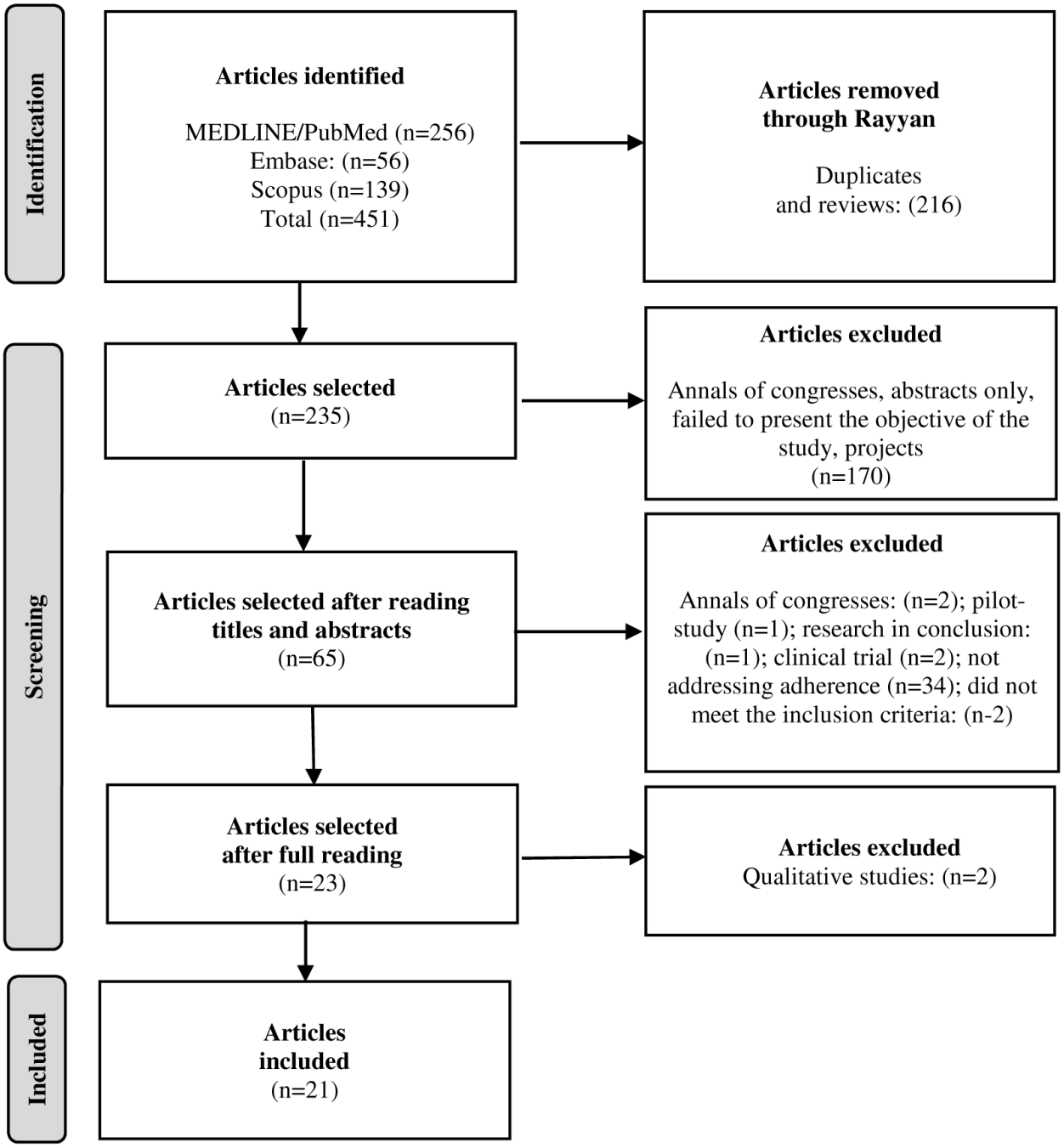

Figure 1. PRISMA 2020 flow diagram
Source: Adapted from PRISMA 2020[16].

endocrine therapy was associated with the aggravation of endocrine symptoms, fatigue and sleep disorders, which resulted in discontinuation of the therapy.

Sheppard et al.[22] identified gastrointestinal, gynecological, neuropsychological, vasomotor and bone symptoms as the main predictors of non-adherence to endocrine therapy. In addition, psychosocial factors as tangible support, beliefs of necessity of medications, concerns with medication and religiosity have also boosted this behavior. In all, 35.0% of the women reported at least one behavior of non-adherence, being the most common, not remembering to take the medication (26.4%). Women with highest scores of overall symptoms were less propense to adherence.

For Smith et al.[26], the most frequent adverse reactions in patients in 60 months were: sleep disorders (54.0%), endocrine symptoms (53.0%), sexual problems (48.0%) and fatigue (46.0%). The cumulative likelihood of discontinuation was 23.0% in 48 months. The treatment with aromatase inhibitor was associated with high odds

Chart 1. Characteristics of the studies included in the systematic review

Authors	Design	N	Country	Quality of the evidence
Conejo et al.[20]	Randomized clinical trial	40	Spain	High
Berkowitz et al.[21]	Cohort study	2,353	USA	Moderate
Sheppard et al.[22]	Prospective study	570	USA	Moderate
Helland et al.[23]	Prospective study	220	Norway	Moderate
Hagen et al.[24]	Prospective study	138	Norway	Moderate
Bhave et al.[25]	Clinical trial	49	USA	High
Smith et al.[26]	Prospective cohort study	321	USA	Moderate
Wagner et al.[27]	Randomized clinical trial	686	USA	High
Hwang et al.[28]	Retrospective study	338	USA	Low
Cavazza et al.[29]	Retrospective study	40,455	Italy	Low
Xu et al.[30]	Cross-sectional study	760	China	Low
Haskins et al.[31]	Cohort study	21,894	USA	Moderate
Salgado et al.[32]	Cross-sectional study	279	USA	Low
Sutton et al.[33]	Cohort study	592	USA	Moderate
Lee et al.[34]	Retrospective cohort study	3,580	USA	Low
Ternoven et al.[35]	Retrospective cohort study	2,656	Australia	Low
Heiney et al.[36]	Retrospective cohort study	1,532	USA	Low
Farias et al.[37]	Retrospective cohort study	1,240	USA	Low
Camacho et al.[38]	Observational study	18,054	USA	Low
Calip et al.[39]	Retrospective cohort study	40,009	USA	Low
Lopes et al.[40]	Case-control study	1,531	Australia	Moderate

of discontinuation than tamoxifen. Emerging endocrine symptoms of treatment and sleep disorders were associated with discontinuation of endocrine therapy.

Conejo et al.[20] analyzed the main adverse reactions related to the use of aromatase inhibitors and found the presence of articular pains on the cervical spine, shoulder, hand and wrists, pain in the shoulders and cervical spine were reported by more than 80% of the patients. For the authors, musculoskeletal toxicity can be one of the main causes of non-adherence and non-persistence due to pain.

Bhave et al.[25] observed that aromatase inhibitors therapy was closely related to fatigue, causing changes on patients activities of the daily life. In another study, Wagner et al.[27] identified that the main adverse reactions related to the use of aromatase, anastrozole and exemestane were respectively: articular pain (36.1% and 32.5%), heat waves (29.9% and 29.1%), decline in libido (23.7% and 24.07%), fatigue (15.2% and 24.0%), night sweats (17.7% and 17.2%). Articular pain is predominant for that class of medication and 36.2% of the patients discontinued the treatment before five years due to adverse reactions.

In addition, the study of Helland et al.[23] attempted to elucidate possible associations among adverse reactions, metabolic concentration of tamoxifen and adherence. The main adverse reactions found were heat waves (87.0%) in one year, and 40.0% presented this severe reaction in a three-year period, articular pain (30.2%), decline in libido (26.1%) and vaginal dryness (18.5%). The rate of treatment discontinuation obtained from the Norwegian prescription database (NorPD) was 17.9%, and the monitoring of metabolic concentrations of tamoxifen exhibited similar rate. The authors concluded that nausea, vaginal dryness and chemotherapy-naive were significant risk factors for discontinuation of tamoxifen.

Time of treatment of chemotherapy was also a factor associated with adherence and continuity of endocrine

Chart 2. Characteristics of the methods utilized to identify predictors of non-adherence and non-persistence

Authors	Methods of evaluation of adherence	Predictors of non-adherence and non-persistence
Conejo et al.[20]	Self-reported mental status questionnaires and Profile of Mood States (POMS), fatigue scale (Quickpiper) and quality of life (EORTC QLQ-C30)	Adverse reaction
Berkowitz et al.[21]	Survey Monkey tool with 33 objective questions and 13 questions with open comments	Adverse reaction
Sheppard et al.[22]	Functional assessment of cancer therapy-endocrine subscale (FACT-ES), Beliefs about medicines questionnaire subscale (BMQ) and Lukwago religiosity scale	Adverse reaction
Helland et al.[23]	Serum sample, questionnaires for side effects, Functional assessment of cancer therapy-endocrine subscale (FACT-ES)	Adverse reaction
Hagen et al.[24]	Morisky Medication Adherence Scale (MMAS); Subjective Health Complaints Inventory (SHC) and Quality of Patient Information Questionnaire (QPI)	Adverse reaction
Bhave et al.[25]	Measured by actigraphy	Adverse reaction
Smith et al.[26]	Patient reported outcome measurement information system (PROMIS), Functional assessment of cancer therapy-endocrine subscale (FACT-ES) and Medical Outcomes Study Sexual Problems (MOS-SP)	Adverse reaction
Wagner et al.[27]	Functional assessment of cancer therapy-endocrine subscale (FACT-ES), treatment related symptoms, trial outcome index (TOI)	Adverse reaction
Hwang et al.[28]	Daily supply (Proportion of Days Covered – PDC) in six months	Type of medication
Cavazza et al.[29]	Proportion of days covered (PDC) in 365 days	Time of treatment
Xu et al.[30]	Morisky Medication Adherence Scale (MMAS); some discomfort with this medicine?	Type of medication
Haskins et al.[31]	Proportion of days covered (PDC = days covered by endocrine therapy prescriptions/days in follow-up)	Time of treatment
Salgado et al.[32]	Beliefs about medicines questionnaire subscale (BMQ), assessment of survivor concerns scale (ASC), Personal Health Questionnaire depression scale (PHQ-8)	Psychological factors
Sutton et al.[33]	Beliefs about medicines questionnaire (BMQ), functional assessment of cancer therapy-endocrine subscale (FACT-ES), communication and attitudinal self-efficacy scale for cancer (CASE-cancer) and patient satisfaction	Psychological factors
Lee et al.[34]	Calculation of medication possession rate (MPR)	Type of medication
Ternoven et al.[35]	Period of dispensation. Non-adherence associated with no dispensing for a period greater than 180 days	Time of treatment
Heiney et al.[36]	Analysis of the variables race and geographical location per self-report. Adherence calculated, utilizing medication possession rate (MPR)	Geographical location
Farias et al.[37]	Adherence stratified by medication possession rate (MPR)	Geographical location
Camacho et al.[38]	Adherence to endocrine therapy by race and geographic region was evaluated by the medication possession rate (MPR)	Geographical location
Calip et al.[39]	Medication possession rates (MPR) estimated for 12 months subsequent intervals. Associations between polypharmacy and adherence for adjuvant endocrine therapy	Polypharmacy/ comorbidities
Lopes et al.[40]	Periods of dispensation were considered of low adherence if no dispensing occurred for a period greater than 180 days	Multiprofessional team follow-up

therapy of breast cancer. Xu et al.[30] indicated time of treatment as determinant for persistence. The study showed a non-persistence rate of 13.4% and, in the fifth year, 22.6% of the women discontinued treatment. 5-year adherence mean was 7.4% of the women with low, 42% with average and 50.7%, elevated adherence to the treatment.

Ternoven et al.[35] showed that 45.8% of the women discontinued endocrine therapy in five years; the average time of abandonment was around 2.6 years. The likelihood of discontinuation in one year was 11.3%; after two years, 19.2%, increasing to 47.9% after five years. Women who would potentially discontinue the treatment were young and usually were in treatment with tamoxifen (46.1 *vs.* 40.0). 45.8% of the women resumed treatment within 182 days.

Another factor of non-persistence and non-adherence to chemotherapy was associated with psychological factors related to the diagnosis of mental health, as depression or any other disorders and with belief[31-33]. Cavazza et al.[29] investigated the possibility of comorbidities influencing adherence. Women diagnosed with depression presented negative effect of adherence after five years (OR: 0.66; CI 95% 0.58-0.74) and two years (OR: 0.86; 95% CI 0.78-0.95).

Haskins et al.[31] conducted a cohort study to identify participants with diagnosis of breast cancer and pre-existing mental illness. Of the total participants selected, 24.9% presented some type of mental illness and one fifth, never initiated endocrine therapy. Both the beginning and continuity of endocrine therapy were low in individuals diagnosed with some type of mental illness. Patients with some kind of mental illness, unipolar depression, bipolar depression, dementia, delirium, non-schizophrenic psychosis presented low possibility of beginning the treatment. Discontinuation was more common in patients with some kind of mental illness, anxiety, depression, non-schizophrenic psychosis, use of illicit drugs, and alcohol-related disorders.

Salgado et al.[32] investigated the issue of belief associated with sociodemographic and clinic characteristics in women in use of aromatase inhibitors. Of the individuals investigated, 30.0% reported mild depression and 69.2%, adverse reactions with the class of medication. Women older than 70 years feared cancer recurrence less, had low concern with health and least propense to beliefs. Beliefs about medication appeared in the perspective of "necessity and concern". Beliefs about necessity were associated with increased number of medications prescribed. Beliefs of concerns were higher in women with mild and moderate to severe depression, with presence of adverse reactions and for those who interrupted the therapy due to other medication. Additionally, it was found the belief of concern was related to the status of the disease and health concerns.

On the other hand, the study of Sutton et al.[33], also about beliefs, revealed that women were relatively satisfied with the care they received. Age and race were not predictors of women's concerns. Beliefs of great concern were related to family income. Women with income above US$ 100.000 (B: 0.08; CI 95%: 0.06 to 0.10, $p< 0.001$) and high scores of religiosity (B: 0.05; CI 95%:0.01 to 0.08; $p=0.007$) were classified in the group of women more concerned than women with lower income.

Some studies investigated the geographical location as a factor of non-adherence and non-persistence[36-38]. Heiny et al.[36] observed that European and American women living in urban areas presented a medication possession rate statistically significant when compared with Afro-American women. The proportion of women with adherence to endocrine therapy was higher for those living in urban areas (75.9%) compared to those living in rural areas (24.1%). Another study showed that women living at the border with Mexico had less than 70.0% likelihood of continuing the endocrine therapy[37].

Camacho et al.[38] evaluated the aspects related to color and geographical location of the patients. Those self-claimed White, Black and others had a profile of adherence of 77%, 74% and 80%, respectively. Different rates of initiation and adherence to treatment were observed in relation to geographical location. Patients living far from medication distribution centers tend to present low adherence to endocrine therapy.

Polypharmacy is another condition that can influence the adherence and persistence to treatment. Calip et al.[39] conducted a study addressing polypharmacy to investigate whether this condition could impact the adherence to endocrine treatment in patients in treatment of breast cancer. 30.0% of the participants did not use other medications and 36.0% presented comorbidities and utilized other medications.

The multiprofessional team is among the predictors of adherence investigated in the articles selected. The study of Lopez et al.[40] investigated patients who sought several medical specialties. Patients who discontinued the endocrine therapy were not being followed-up by general clinicians and surgeons/oncologists (48.3% *vs*. 78.9%, $p < 0.001$). Finally, the author emphasizes the importance of these professionals for adherence and observed that 79.0% of the women who discontinued the medication were not being followed-up by clinicians.

In the study of Lee et al.[34], an integrated health system was offered (Kaiser Permanente Northern California – KPNC), attempting to help the patients in adhering to endocrine therapy. After the implementation of the

program, there was an absolute increase of the adherence rates in the first, second and third year of endocrine therapy of 4.2%, 4.6% and 4.9%, respectively.

DISCUSSION

There was a predominance of adverse reactions as the main factor of investigation of non-adherence and non-persistence to endocrine therapy in the studies selected. The rates of non-persistence to treatment of the studies which analyzed the adverse reactions varied from 17.9% to 38.8%. The results found corroborate the findings of other studies[41-43]. The main adverse reactions related to non-adherence and non-persistence are those related to the musculoskeletal system[20,21,23,27], in special women utilizing aromatase inhibitors.

According to Toivonen et al.[42], articular pain restrains activities of the daily life, personal care and even simple tasks as rising from bed in the morning. These data are also related to fatigue and muscular pain presented in the results of the category of adverse reactions.

Other adverse reactions mentioned in the articles and related with non-adherence and non-persistence were hot flash, night sweat, sleep disorders, decline in libido and vaginal dryness and were more present in patients using tamoxifen. These adverse reactions comprehend symptoms of breast cancer endocrine therapy-induced menopause.

Climacteric and premenopausal women can begin menopause induced by breast cancer endocrine therapy. Suffering associated with induced menopause and incidence of other adverse reactions contribute to increase the negative beliefs about hormone therapy of breast cancer and difficulties of tolerating the treatment leading to non-persistence[44-47]. According to Botelho et al.[10], non-persistence occurs most of the times because these events reduce the quality of life of these women.

Although adverse reactions are present in patients in use of aromatase inhibitors and in use of tamoxifen, several studies showed that patients who utilize aromatase inhibitors are more propense to adherence[22,28-30,39]. Time of treatment was related to increased non-persistence to endocrine therapy in both therapies[29,30,34,35].

A systematic review and meta-analysis[48] evaluated the ideal time of extension of endocrine therapy with aromatase inhibitor and showed reduction of recurrence of breast cancer when length of therapy increased from five to seven to eight years, especially in patients with estrogen receptor tumor size ≥ 2 cm, positive progesterone receptor, positive or negative human epidermal growth factor receptor 2 and previous chemotherapy. However, the analysis of adverse events revealed a significant increase of the incidence of arthralgia, osteoporosis, bone fractures and asthenia. As addressed before, adverse events are a barrier to endocrine therapy. According to Xu et al.[30], women in use of aromatase inhibitors tend to exhibit greater reduction of persistence to treatment in the first and second year. Ternoven et al.[35] demonstrated an increase of non-persistence of 11.3% in the first year of treatment to 47.9% in the fifth year. The identification of factors that may benefit the adherence of patients with breast cancer can reduce the rates of disease relapse.

Psychological factors can be co-responsible for non-adherence to endocrine therapy. For patients with mental diseases, adherence to endocrine therapy remains below the ideal, worsening cancer relapse and risk of mortality[31].

Mausbach et al.[49] identified depression as a predictor of successful adjuvant endocrine therapy. Another intervention study to improve the adherence to endocrine therapy in women with breast cancer concluded that those who had least anxiety and depression symptoms adhered better to endocrine therapy[50]. The early identification of mental diseases can help to tag patients with low adherence and high risk of abandonment of the treatment. In addition, can guide the health team to implement specific interventions for this subgroup of patients. Therefore, evaluate and support women with breast cancer diagnosed with previous mental diseases would positively impact the adherence to the treatment[31,49,50].

Geographical location can be an issue for patients in treatment of breast cancer and adherence to treatment. Because the treatment utilizes high expensive medications, these are concentrated in middle and large size municipalities in many countries. In Brazil, cancer treatment centers are located in regional hubs or capitals. This can block the access to the medication, although the treatment is funded by the National Health System (SUS) or private insured[51,52].

On the other hand, the study of Botelho et al.[10] showed that patients living in Great São Paulo presented lower adherence to tamoxifen. This finding shows that other factors are related to geographical location that can impact the adherence to therapy.

In addition, pre-existing comorbidities or acquired along the treatment with endocrine therapy can affect the behavior of adherence to hormone-therapy. According to Brito et al.[53], chronic diseases require behavioral changes that can affect the completion of the treatment. However, the disease diagnosed can be a predictor of adherence. Women with arterial hypertension and dyslipidemia had better adherence to endocrine therapy when compared to those with depression, anxiety among other mental diseases according to a study by Calip et al.[39].

Heiney et al.[36] affirm that if the health team is formed by physicians, the patients exhibit better adherence rates. Guedes et al.[14] found a direct relation between the number

of medical visits and persistence to treatment, because during the visits, it is possible to acquire information about the treatment, adverse reactions, management and emotional support. However, it is paramount that the team is multi-professional including various medical and non-medical specialties to treat breast cancer[36].

This review portrayed a scenario described in the literature about the predictors of non-adherence and/or non-persistence to endocrine therapy. Although containing all the elements of systematic literature reviews as research question, blinding with more than one investigator, search strategies and eligibility criteria to select the articles, there are many limitations still: the innumerous articles to be correlated with the study goal, many other studies not selected or undetected at the databases and the impossibility of performing a meta-analysis due to the heterogeneity of the studies.

CONCLUSION

The study identified seven categories of predictors of non-adherence and non-persistence. Adverse reactions were the most investigated variables and are directly associated with non-adherence and non-persistence. Another crucial topic was associated with the type of medication, it was possible to observe that women in treatment with tamoxifen presented high non-adherence and non-persistence rates compared with aromatase inhibitors. Time of treatment was also a negative predictor of adherence, as long the length of endocrine therapy, lower was the adherence and persistence.

More clinical trials should be conducted to clarify the actual influence of sociodemographics, psychological factors, comorbidities, and multiprofessional team on adherence and persistence to endocrine therapy further to studies addressing management of these predictors.

CONTRIBUTIONS

All the authors contributed substantially to the study conception and design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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Associate-editor: Fernando Lopes Tavares de Lima. Orcid iD: https://orcid.org/0000-0002-8618-7608
Scientific-editor: Anke Bergmann. Orcid iD: https://orcid.org/0000-0002-1972-8777