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REVIEW ARTICLE

Adherence and discontinuation of oral hormonal therapy in patients with hormone receptor positive breast cancer

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Abstract *Background* Oral treatment in women with breast cancer has been increasingly used. However, a potentially negative side of oral medication is poor patient adherence and/or discontinuation, which reduces the treatment effectiveness, accelerating progression of the disease and reducing the patient survival rate. *Aim of the review* To compare the rates of adherence and/or discontinuation and the methodologies used to assess these outcomes. It was conducted an integrative review of original articles published from 2000 to 2012, in which their primary outcome was to quantify medication adherence and/or discontinuation of oral hormonal therapy in patients with hormone receptor positive breast cancer. *Methods* Original studies were searched in the PubMed/MEDLINE, Scopus, Embase and SciELO databases. The Medical Subject Heading was used to define descriptors. The descriptor "breast neoplasms" was used in all combinations. Each of the descriptors "medication adherence" and "patient compliance" were combined with each of the following descriptors "tamoxifen", "aromatase inhibitors", "selective estrogen receptor modulators", or the terms "letrozole", "anastrozole", and "exemestane". *Results* Twenty-four original articles were included. Our study showed a wide range of adherence and discontinuation rates, ranging from 45–95.7 and 12–73 %, respectively. Regarding the methodological development of the selected articles, a high prevalence (87.5 %) of prospective and/or retrospective longitudinal studies was found. In addition, there was a high prevalence of studies using a database (70.8 %). Among some of the studies, it was shown that patient adherence to hormonal therapy gradually reduces, while discontinuation increases during the treatment. *Conclusions* It was observed a great diversity among rates of adherence and/or discontinuation of hormonal therapy for breast cancer, which may be due to a lack of methodology standardization. Therefore, adequate and validated methods to ensure reliability of the results and allow comparison in the literature are needed. Furthermore, adherence decreases and discontinuation increases over time, suggesting the need for patient continuous education and a pharmacotherapeutic follow up by health professionals to improve these clinical outcomes.

Keywords Aromatase inhibitors · Breast cancer · Hormonal therapy · Medication adherence · Tamoxifen

Impacts on practice

- According to literature, there seems to be a wide variation in adherence and/or discontinuation rates to hormonal therapy in patients with breast cancer.
- To ensure reliability of the results, adequate and validated methods should be used to assess adherence and/or discontinuation rates to hormonal therapy in patients with breast cancer.
- Patients' adherence to hormonal therapy gradually reduces, while discontinuation increases during the treatment suggesting that a follow up by health professionals can be an interesting strategy to improve the outcomes.

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Introduction

Nowadays, it is estimated that each year more than one million women are diagnosed with breast cancer worldwide, and more than 410,000 die from the disease [1]. However, improvements in early diagnosis and correct treatment have significantly increased the survival of these women [2].

The prognosis and the choice of the most appropriate treatment are usually based on tumor stage, which consists of surgery for tumor removal followed by radiotherapy, chemotherapy and/or adjuvant therapy with targeted therapies that confer fewer systemic cytotoxic side effects [3]. Over expression of HER2/neu and hormone receptors status are important factors used in the decision-making process of the adequate targeted therapy. The humanized monoclonal antibody trastuzumab and oral endocrine therapy are examples of targeted therapies for HER2 positive breast cancer and for breast cancer with the presence of hormone receptors such as estrogen and progesterone receptors, respectively [4].

The main classes of oral endocrine therapy are aromatase inhibitors (AI) (letrozole, anastrozole and exemestane) and selective estrogen receptor modulators (SERMs) such as tamoxifen [5]. According to the Early Breast Cancer Trialists Collaborative Group [6], adjuvant treatment with tamoxifen for 5 years reduces the risk of disease recurrence by 41 % and of death by 34 % in women with estrogen receptor-positive early stage breast cancer.

During recent decades, a five-year treatment with tamoxifen represented the standard therapy for women with estrogen receptor-positive breast cancer. Recently, therapy with AI showed further reduction of the risk of recurrence and death in postmenopausal women [7, 8]. AI suppresses only the estrogen production amounts of peripheral tissues while in premenopausal women its major production site is the ovary [9]. Although generally well tolerated, side effects associated with tamoxifen and AI such as hot flushes, sleep disturbances, and depression were identified as significant causes for discontinuation and/or non-adherence to treatment [10–12].

Therefore, a potentially negative side of oral medication is poor patient adherence and/or discontinuation, which reduces the treatment effectiveness, accelerating progression of the disease and reducing the patient survival rate [13]. However, oral treatment in women with breast cancer has been increasingly used due to a reduced prevalence of side effects compared to chemotherapy, an increased convenience of drug administration and a decreased hospitalization length [14].

Although there are some studies evaluating adherence and/or discontinuation of hormonal therapy [15–18], works that compare the data obtained from these different studies, as well as the methodologies employed to assess adherence and/or discontinuation rates are scarce [19, 20]. Therefore, studies that address this subject are important as they are able to identify possible problems and to suggest measures to promote and improve adherence to medication.

Aim of the review

To quantify and compare the rates of adherence and/or discontinuation and the methodologies used to assess oral hormonal therapy in patients with hormone receptor positive breast cancer.

Methods

A literature review was performed of original articles published between 2000 and 2012.

Search strategy

We searched PubMed/MEDLINE, Scopus, Embase and SciELO databases, using Medical Subject Heading (MeSH) to define descriptors. The descriptor “breast neoplasms” was used in all combinations. Each of the descriptors “medication adherence” and “patient compliance” were combined with each of the following descriptors “tamoxifen”, “aromatase inhibitors”, “selective estrogen receptor modulators”, or the terms “letrozole”, “anastrozole”, and “exemestane”. The connector AND was used between terms, according to the example: “breast neoplasm” AND “medication adherence” AND “tamoxifen”. The limits established were publications between January 01, 2000 and December 31, 2012 and in English, Spanish or Portuguese languages.

An integrative review was conducted since it allows the inclusion of diverse methodologies, such as experimental and non-experimental studies, whereas the systematic review is focused primarily on experimental studies [21, 22].

Inclusion and exclusion criteria

The articles were identified and all duplicate records were excluded in the first stage. In the second stage, a prior reading of the title and abstract was conducted to include original articles in which their main objective was to evaluate the rates of adherence to or discontinuation of oral medication in patients with hormone receptor positive breast cancer in clinical practice. Therefore, original articles related to breast cancer chemoprevention, metastatic breast cancer patients since their awareness of the

consequences of not taking their medication is higher and they also use different treatment protocols, breast cancer in males, extended hormonal therapy, and clinical trials, were excluded, as well as those published as a review, note, correspondence, editorial, and letter. In the last stage, the selected articles were read in their entirety in order to be included.

Data analysis

The selected articles were subjected to a complete analytical reading to identify variables of interest: drug used, sample size, patient age, disease stage, follow up length, study design, source, method and adherence and/or discontinuation rates. These datas were collected and arranged in a table. Full reading of the articles and variable's results were analyzed and performed by three of the authors of this study. In the event of any disagreement, discussions continued until consensus was reached.

Adherence and discontinuation definitions

Patients are considered to be adherent when they follow the prescription guidelines correctly, in acting co-responsibly towards their treatment [23]. Compliance refers to the patient's obedience in following the prescription and guidelines made by the physician [24]. In order to standardize the terms used in the article, we decided to use the term adherence to refer to adherence and/or compliance.

Discontinuation occurs when the patient stops taking the prescribed medication for a reason and it is also defined by a lapse in treatment longer than a determined amount of time, which may vary from 45 to 180 days in some studies [25, 26]. In this case it is not considered as non-adherence, but as a decision to discontinue following poor response to the drug or as a result of adverse side effects, intolerance to the drug, difficult access to medicines, employment and socioeconomic status, social stigma of disease, and cognitive function [25]. Persistence is the length of time between the beginning of the treatment until the last dose, which immediately precedes discontinuation [26]. The term discontinuation was used in this review since it was the term used in the investigated studies.

Results

We identified 1,024 studies, of which 24 were included in this study (Fig. 1). All the articles that were in accordance with our inclusion criteria were available as full text and all the included studies were published in English and conducted in developed countries.

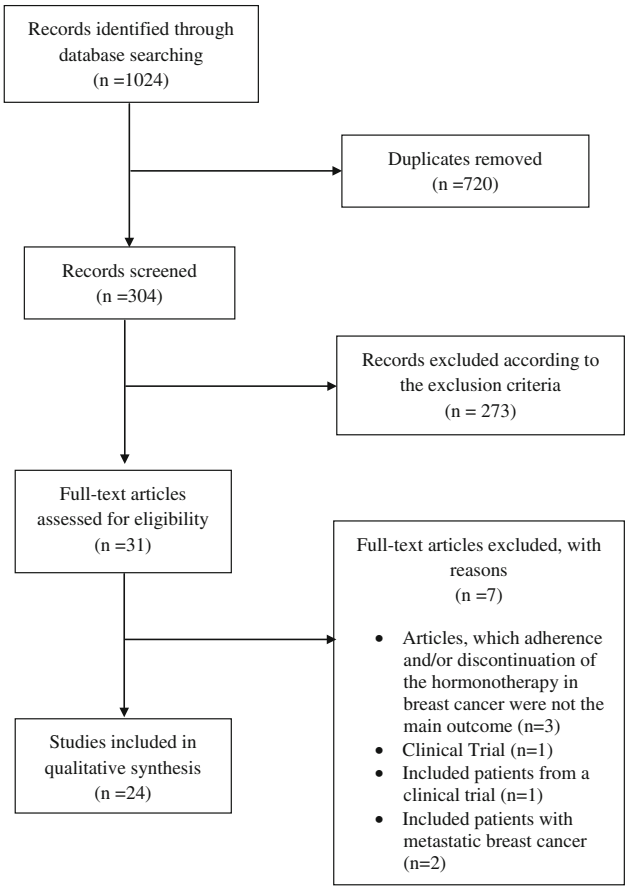

Fig. 1 Selection of the articles for the integrative review adapted from PRISMA flow diagram [27]

Among them, nine referred only to adherence, ten only to discontinuation and five to adherence and discontinuation (Table 1). In addition, 13 articles addressed the use of tamoxifen, three of AI and eight of both.

The rates of adherence in cancer patients ranged from 45 to 93.4 % among studies with tamoxifen (n = 7), from 62 to 94.7 % with AI (n = 3) and from 49 to 95.7 % with both (n = 4). The rates of discontinuation ranged from 15 to 60 % in studies with tamoxifen (n = 9), 18.9–24.7 % with AI (n = 3) and 12–73 % with both (n = 7). The same study may have been counted more than once since some of them analyzed adherence and/or discontinuation of tamoxifen and AI separately.

Regarding the methodological development of the selected articles, table 1 shows a high number (87.5 %) of prospective and/or retrospective longitudinal studies, and identified only two cross-sectional studies [11, 41]. In addition, seven studies used self-report (n = 1) [40] and interviews (n = 6) [10–12, 17, 41, 42] to access adherence and/or discontinuation and the majority of them (n = 18) used the information provided by professional routine databases, which includes medical records and registers of

Table 1 Published articles evaluating adherence and/or discontinuation during hormonal therapy for breast cancer

Reference, year of publication and country	Drug(s)	Subjects Number	Age (years)	Disease Stage	Follow-up length	Study design	Method of evaluation adherence (A) or discontinuation (D)	Adherence (A) or Discontinuation (D)
Font et al. [17], Spain	Tamoxifen and AI	692	≤49 years; 50–74 years; ≥75 years	I–IIIa stage	5 years	Retrospective cohort	Physician report and questionnaire (A) Refill prescription (D = coverage of prescribed medication less than 80 %)	A: Questionnaire: 92 % (tamoxifen: 88.8 %; IA: 92.6; Tamoxifen + IA: 93.8) Physician report: 94.7 % (tamoxifen: 93.4 %; IA: 94.7; tamoxifen + IA: 95.7) D: 25.3 % (tamoxifen: 31.4 %; IA: 24.5; tamoxifen + IA: 21.5)
Huiart et al. [18], France	Tamoxifen	246	39.6 mean	I–III stage	Median 2 years (1.0–3.3)	Prospective cohort	MPR (D = gap of more than 90 days)	A (first year) = 93.9 % D: 1st year = 17 % 2nd year = 29.7 % 3rd year = 39.5 %
Wigertz et al. [28], Sweden	Tamoxifen and AI	1,741	<40 years 40–49 50–59 60–69 70–79 ≥80	I–III stage	3 years	Prospective cohort	MPR (D = gap of more than 180 days)	A = 69 % D = 12 %
Cluze et al. [29], France	Tamoxifen and AI	196	37 mean	I–III stage	2 years	Prospective cohort	Pharmacy refill data (D = at least two consecutive months of interruption)	D = 42 %
Hershman et al. [30], USA	Tamoxifen and AI	8,769	<50 50–64 ≥65	I–III stage	4 1/2 year	Prospective cohort	MPR	A 4 1/2 year = 49 %
Huiart et al. [31], UK	Tamoxifen and AI	Total 13,479 Tamoxifen 10,806 AI 2,673	62.0 mean (Tamoxifen) 70.8 mean (AI)	I–III stage	5 years	Prospective cohort	MPR (D = gap of 90 days or more)	D = 29.8 % Tamoxifen D = 31 % AI D = 18.9 %
Nekhlyudov et al. [32], USA	Tamoxifen and AI	2,207	>18 years	Early stage	Median 923 days	Prospective cohort	MPR (D = gap of more than 60 days)	D: 21–73 % 1st year = 21 % 2nd year = 30 % 3rd year = 38 % 4th year = 47 % 5st year = 73 %

Table 1 continued

Reference, year of publication and country	Drug(s)	Subjects Number	Age (years)	Disease Stage	Follow-up length	Study design	Method of evaluation adherence (A) or discontinuation (D)	Adherence (A) or Discontinuation (D)
Neugut et al. [33], USA	AI	8,110 (< 65 years); 14,050 (≥ 65 years)	>50 years	Early stage	2 years	Retrospective cohort	MPR (D = gap of more than 45 days)	A = <65 years: 89.7 %; ≥65 years: 91.1. D: <65 years: 21 %; ≥65 years: 24.7 %
Sedjo et al. [34], USA	AI	13,593	55.5 mean	Primary and secondary breast cancer	1 year	Retrospective cohort	MPR	A = 77 %
Thompson et al. [9], UK	Tamoxifen	Cohort 1: 391 Cohort 2: 227	Cohort 1: 60.5 mean Cohort 2: 63.1 mean	I–III stage	Not available	Retrospective cohort	MPR	A = 85.6 %
Dezentjé et al. [35], Netherlands	Tamoxifen	1,962	59.6 mean	I–III stage	1 year	Retrospective cohort	MPR	A 1st year = 93 % A 3rd year = 84 %
Van Herk-Sukel et al. [36], Netherlands	Tamoxifenand AI	4,917	≤35 to ≥70	I–IIIa stage	5 years	Retrospective cohort	Medication count (D = gap of more than 60 days)	Tamoxifen: D 1st year = 17 % D 2nd year = 30 % D 3rd year = 45 % D 4th year = 50 % D 5th year = 60 % Tamoxifen/IA: D 1st year = 13 % D 2nd year = 22 % D 3rd year = 31 % D 4th year = 37 % D 5th year = 51 %
Kimmick et al. [37], USA	Tamoxifen and AI	1,491	67 median	Nonmetastatic	2 years	Not available	MPR (D = gap of more than 90 days)	A = 60 % D = 20 %
Ma et al. [38], USA	Tamoxifen	788	54–59	Not available	5 years	Retrospective cohort	Database (A = not follow physician recommendation)	A = 63 %
Owusu et al. [16], USA	Tamoxifen	961	>65	I–IIb stage	5 years	Prospective cohort	Medical record (D = gap of more than 60 days)	D = 46 %
Partridge et al. [15], USA	Anastrozole	7,132	>35 to >65	Early-stage	3 years	Retrospective cohort	MPR	A 1st year = 78–86 % A 3rd year = 62–79 %
Barron et al. [39], Ireland	Tamoxifen	2,816	>35	Not available	3.5 years	Retrospective cohort	Medical record (D = gap of more than 180 days)	D 1st year = 22.1 % D 3.5 years = 35.2 %

Table 1 continued

Reference, year of publication and country	Drug(s)	Subjects Number	Age (years)	Disease Stage	Follow-up length	Study design	Method of evaluation adherence (A) or discontinuation (D)	Adherence (A) or Discontinuation (D)
Kahn et al. [40], USA	Tamoxifen	881	<50 to >65	I–IIIa stage	4 years	Prospective cohort	Self-report (D = Stop taking medication after 4 years)	D = 21 %
Atkins et al. [41], UK	Tamoxifen	72	59.4 mean	Stable disease	–	Cross sectional	Interview	A = 45 %
Lash et al. [12], USA	Tamoxifen	462	>65	I–IIIa Stage	5 years	Ambispective cohort	Interview (D = stop taking medication)	D 5th year = 31 %
Grunfeld et al. [11], UK	Tamoxifen	110	56.3 mean	Primary breast cancer	–	Cross sectional	Interview [A = Medication Adherence Report Scale (MARS-5)]	A = 88 %
Fink et al. [42], USA	Tamoxifen	516	>65	I–IIIa stage	2 years	Prospective cohort	Interview (D = stop taking medication)	D 2nd year = 17 % D 2 1/4 year = 21 %
Partridge et al. [43], USA	Tamoxifen	2,378	75.4 mean	Early-stage	4 years	Retrospective cohort	MPR	A = 77 % A 1st year = 83 % A 2nd year = 68 % A 3rd year = 61 % A 4th year = 50 %
Demissie et al. [10], USA	Tamoxifen	189	67.7 mean	I–II stage	3 years	Ambispective cohort	Interview (D = stop taking medication)	D = 15 %

AI aromatase inhibitors, *MPR* Medication Possession Ratio (less than 80 % of days covered was defined as nonadherence)

Medication Possession Ratio (MPR) and pharmacy refill data. One study used both, database and interviews to collect data. Only one study described the use of a specific and validated instrument (Medication Adherence Report Scale MARS-5) [11]. None of the studies used direct methods, such as quantification of the concentration of the drug or metabolite in plasma or urine and quantification of biological markers to estimate adherence and/or discontinuation rates.

Considering the definition of adherence and discontinuation, ten studies evaluated adherence using MPR, which defined nonadherence as a less than 80 % of days covered by the medication [9, 15, 18, 28, 30, 33–35, 37, 43]. Discontinuation was defined by a lapse in treatment, which may vary from 45 to 180 days in seven studies using MPR [18, 28, 31–33, 36, 37]. Three studies that used interviews and one that used self-report considered discontinuation when a patient stops taking the medication [10, 12, 40, 42].

In relation to the studies that used self-report and interviews, 72–881 patients were investigated, while those using professional routine database could include a greater number of patients, as observed in two studies that included more than 13,000 women.

It is worth mentioning that the age range for all the studies varied from 18 to more than 80 years. The way age was arranged did not allow calculating a mean age for all the studies. However the majority of patients were from 50 to 70 years.

Considering the follow-up length of the longitudinal studies, it ranged from 1 to 5 years, with a mean of 3.3 years. Three studies compared adherence rates throughout time [15, 35, 43]. All of them showed a reduction in adherence rates over the years. Moreover, five studies compared the discontinuation rates in the same way and all of them showed that discontinuation gradually increases throughout the treatment period [18, 32, 36, 39, 42].

Side effects associated with tamoxifen and AI were identified as significant causes for discontinuation and/or non-adherence to treatment among three of the selected articles [10, 12, 29]. However the studies did not compare the side effect profiles of tamoxifen and AI have on patients behavior.

Discussion

Our review showed that all the studies analyzed are non-experimental and that they present a wide range of adherence and discontinuation rates, ranging from 45–95.7 and 12–73 %, respectively. However only three studies showed adherence rates below 60 % [30, 41, 43]. Analyzing the incidence and/or prevalence of adherence in this study it is possible to observe that patients with cancer, taking hormonal therapy, seem to have better adherence to treatment compared to patients with other chronic diseases, which is approximately 50 % in developed countries for the chronic patients [23]. One explanation for this can be that patients with cancer have a better understanding of the risks of not properly taking the drugs [44, 45].

Another review found rates of adherence and discontinuation in agreement with ours, ranging from 41 to 72 % and from 31 to 73 %, respectively [20]. That study was conducted in a similar period of time, from 1998 to May 2012, while ours was from January 2000 to December 2012. The study included 30 articles and from the 24 selected articles in our review, there were 21 matches with those included in that review. The contrast found between the numbers of articles selected in both reviews was due to distinct inclusion criteria, limits, terms to identify the articles and mainly because different databases were searched.

An interesting finding related to the years of publication is that from 2000 to 2007, studies were exclusively performed with tamoxifen in a clinical setting. This happened because the first AI to be approved by the Federal Drug Administration (FDA) was anastrozole in 2002, as an adjuvant treatment for postmenopausal women [46, 47]. Evaluation of its use takes at least 5 years as this is the standard period of treatment, therefore, the first study with anastrozole was from 2008.

All the selected articles in our study were originally from developed countries where it seems to have higher adherence rates compared to emerging countries [23]. However, even with the socioeconomic similarity, heterogeneity in adherence rates occurred. The causes of non-adherence are multifactorial and may be related to reduction of care during treatment due to lack of specific symptoms or because the patient might experience a cure sensation of the disease, and adverse reactions that may arise during treatment [48]. One of the reasons of the heterogeneity observed among the rates of nonadherence and/or discontinuation seems to be due to the period of treatment when data collection was performed, since patients seem to be more adherent at the beginning of treatment.

The length of follow up is relevant because according to the Early Breast Cancer Trials Collaborative Group [6], 5 years of tamoxifen treatment is a major factor in the reduced mortality rate from early stage breast cancer. In addition, the discontinuation and nonadherence to treatment can lead to breast cancer recurrence, disease progression, such as the development of metastasis, which may be related to an increased consumption of health resources, including an increased number of physician visits, higher hospitalization rates and longer hospital stays

[15, 48]. Moreover, as observed in longitudinal studies, it is noteworthy that patient adherence to hormonal therapy gradually reduces [15, 35, 43], while discontinuation increases over the years [18, 32, 36, 39, 42]. This suggests the need for pharmacotherapeutic follow up to the patient during the whole treatment to prevent recurrence and complications of the disease.

Methods to evaluate rates of adherence and/or discontinuation

The majority of the articles (87.5 %) used longitudinal studies to analyze adherence and/or discontinuation. It is important to note that longitudinal studies provide answers related to the incidence of adherence and/or discontinuation of medication prescribed during treatment, while cross-sectional studies allow the assessment of prevalence only. Considering the method, it is important to highlight that MPR was used in 54.2 % of the studies but it was used to analyze different variables, since six articles analyzed adherence, four adherence and discontinuation, and three only discontinuation.

Font and colleagues used a combination of methods [17], a questionnaire and a physician's report in which rates of adherence were 92 and 94.7 %, respectively. By analyzing their refill prescriptions, the problems related to adherence were more significant (discontinuation rate of 25.3 %). This difference found justifies the use of different instruments to estimate adherence incidence and/or prevalence. Besides, this approach reduced the biases inherent to each type of methodology [49].

Seventy-five percent of the studies used a professional routine database as the data collection source. The use of database in research tends to improve health care programs, as they provide a broad representation of the sampled population, and facilitate longitudinal studies to be performed in a shorter period of time [50]. This fact can be observed in two studies that used professional routine database as a source of information and could include more than 13,000 women in contrast with studies that used questionnaires and only interviewed 72–881 patients. Despite the advantages of the magnitude of information received from large databases, it is noteworthy that there are limitations to the analysis and interpretation of results, because it is difficult to confirm the reliability and validity of the database used [50]. To increase the reliability and validity of data from databases, researchers need to previously select the appropriate database and analyze how population data were created or inserted into the database [51].

This review has some limitations. Firstly, studies that used self-report (n = 1) and interviews (n = 6) as sources of data collection can lead to recall bias. Secondly, the majority of studies used database or medical records as data sources, which can overestimate the adherence rates, since collection of the medication at the pharmacy does not guarantee that the patient actually takes their medicine. Considering the MPR, patients might get their medication in another pharmacy without computerizing the medication in the same database which may underestimate the rates of adherence and/or discontinuation. In addition, in the literature there is a wide variety of definitions on adherence and discontinuation and a wide variety of terms that have been used to describe medication-taking behavior, such as persistence, concordance and medication adherence. Therefore there is a need to standardize these definitions to allow a better comparison among the studies. An European consensus was elaborated to face this diversity of concepts and terms and the various problems related to publications about adherence [26].

Suggestion to improve adherence and future recommendations

Patient education by the health care team has shown significant improvement in adherence in the treatment of various diseases and their complications [52]. However little is known about professionals' training, beliefs or practice in this area [53]. As observed in some studies [15, 35, 43], rates of adherence were decreasing gradually over the years, which may be due to a diminished frequency in physician visits. As patients have to go to the pharmacy often to acquire their drugs, the pharmacists are the health professionals who have more patient contact between the physicians' visits and as such they are able to remind them of the importance of taking their drug as prescribed. Therefore, this is a natural opportunity to monitor the progress of therapy [54]. In this context, a service of continuous patient education provided by pharmacists in collaboration with other healthcare professionals can be an interesting strategy to improve adherence to drug treatment, as already observed in pharmaceutical care studies [55–58].

Conclusion

In this review, we could observe differences among rates of adherence and/or discontinuation of hormonal therapy for breast cancer, ranging from 45 to 95.7 % and from 12 to 73 %, respectively. This diversity can be justified by data collection performed in different periods of treatment, since we could observe that patient adherence to hormonal therapy gradually reduces, while discontinuation increases during the treatment. Therefore further studies are important, especially those that compare adherence and/or

discontinuation rates throughout the whole treatment length. Besides, the need for further approaches on this topic in emerging countries was evident, since no studies were performed in such countries according to literature. These findings also suggest that patient education, and that a pharmacotherapeutic follow up by pharmacists and other health professionals can be an interesting strategy to improve these results.

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Conflicts of interest None to declare.

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