Adherence and Discontinuation of Endocrine Therapy among Egyptian Breast Cancer Patients Receiving Adjuvant Treatment: A Cross-sectional Study

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Abstract:

Background: Numerous studies have proven the survival benefit attained with the use of adjuvant hormonal therapy in breast cancer (BC) patients with hormone receptor-positive disease yet a percentage of women fail to comply with this effective therapy.

Objectives: We investigated the rate of adherence and discontinuation among Egyptian women with BC who were prescribed adjuvant oral hormonal therapy.

Methods: A cross-sectional, questionnaire-based study was performed at two Egyptian centers and recruited women with hormonal receptor-positive BC who received at least one adjuvant oral hormonal therapy prescription within 12 months from diagnosis.

Results: A total of 229 patients were included with a mean age of 54.2 ±11.1 years and 55.9% were from a governmental University hospital. Patients had at least a university degree in 59.4% of the cases. Less than half of the patients had stage II (45.4%) BC and 71.2% had received adjuvant chemotherapy. The most commonly prescribed hormonal therapy was aromatase inhibitors (48.5%). Ovarian function suppression was used in 15.3% of our cohort. Governmental funding (77.7%) was the main provider. A discontinuation of 10.9% and an adherence of 64.2% to adjuvant hormonal agents were recorded. Bothersome adverse events were the main reason for discontinuation (92%), whilst forgetfulness (30%), toxicity (17.5%) and COVID-19infection (12.5%) were listed as the main causes of non-adherence by the participants in the study.

Conclusion: Egyptian breast cancer patients displayed adherence and discontinuation rates similar to those reported worldwide. Future interventional strategies are encouraged to improve endocrinal therapy adherence and correlate it to outcome.

Keywords: Breast Cancer; Hormonal Therapy; Adherence; Compliance; Discontinuation.

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Introduction:

Hormonal positive expression represents the major molecular subtype of breast cancer prevalent in patients worldwide. Tamoxifen, aromatase inhibitors (A.I) +/- ovarian function suppression (OFS) have become established therapies in the adjuvant scene that have clearly improved outcomes in this malignancy and contributed substantially to survivorship. [1,2]

However, in order to achieve desired results these medications must be taken according to well-established doses and frequencies; adherence and for the required period set by trials; continuation. Although these therapies are in the oral form mostly and thus seem easy to comply with, nevertheless previous investigators have reported varying rates of adherence and discontinuation. [3] Consequently, the effectiveness of these treatments may be compromised as a result of this irregular dosing or premature cessation altogether. [4] Regional literature concerning this subject is sparse and deserves further research to shed light on the different socioeconomic and cultural diversities of breast cancer survivors globally. [5]

Therefore we set out to investigate the rate of adherence and discontinuation among Egyptian women with BC who were prescribed adjuvant oral hormonal therapy within 12 months from diagnosis. Furthermore, we aimed to assess the patient-specific factors that affect adherence to oral hormonal therapy.

Patients and Methods:

The present study gained ethical approval from the IRB committee of Helwan University Hospital (86-2020) before data collection. Verbal consent was obtained from all eligible patients before questionnaire administration. All study procedures were in strict compliance with the principles of the Declaration of Helsinki [6] and applicable regulatory laws. We followed the STROBE statement recommendations during the preparation of this report [7].

Study Design, Setting, and Participants:

We conducted a cross-sectional, questionnaire-based study from January to June 2021 at one University hospital (Helwan University Hospital) and one private oncology clinic from Cairo, Egypt. The study recruited women with hormonal-positive BC who were prescribed oral hormonal therapy within 12 months from diagnosis, with at least one prescription of oral hormonal therapy. Women with metastatic BC, secondary BC, recurrent disease, and/or psychiatric disorders were excluded from the present study.

Data Collection and Study's Outcomes

The study's investigators explained the study's objectives and procedures to all eligible patients and collected the data only after obtaining verbal consent from each patient. The following data were collected: age, educational status, employment status, tumor stage, presence of adjuvant chemotherapy, type of hormonal therapy, funding of hormonal therapy, date of start of hormonal therapy, occurrence and reasons of discontinuing hormonal therapy, data of discontinuation, occurrence and duration of interrupted treatment, and the need and the reasons for the switch from hormonal therapy.

The primary outcome was to investigate the rate of adherence and discontinuation of hormonal therapy. The adherence was defined as ≥80% medication coverage of the total days needing the medication or ≥80% medication coverage per month. While discontinuation was defined as ≥ six months of treatment stop from the last prescription within the first five years of starting hormonal therapy. At the same time, the secondary outcome was to investigate the patient's-specific factors that affect the adherence to oral hormonal therapy.[8–10]

Statistical Analysis:

Data analysis and interpretation were conducted using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22 for Microsoft Windows. Quantitative data were described as mean ±standard deviation (±SD), while qualitative data were expressed as frequencies and percentages. According to the type of data, the association between various patients' characteristics and adherence/discontinuation was tested using the Chi-square test with Fisher's exact or Mann-Whitney test. Variables with a p-value of less than 0.05 were considered statistically significant.

Results:

Two-hundred and twenty-nine patients were recruited with a mean age of 54.2 ±11.1 years old. Of them, 128 patients (55.9%) were recruited from the University hospital. Nearly half of the patients had a university education, while 8.7% of the patients had a post-graduate degree. Only 27 patients (11.8%) did not receive formal education. On the other hand, 97 (42.4%) were employed. Concerning tumor characteristics, the vast majority of the patients had stage II (45.4%) and stage III (43.8%) BC. More than two-thirds of the patients (71.2%) had received chemotherapy. The most commonly prescribed hormonal therapies were aromatase inhibitor single-agent (anastrozole or letrozole; 48.5%). Ovarian cancer suppression was used in 15.3% of our cohort. The treatment was mainly provided by governmental funding (78.2%). The mean duration of hormonal therapy was 31.2 ±21.2 months (Table 1).

Table 1: Characteristics of Eligible Patients (n =229)

Variables	Patients (n =229)
Age, mean ±SD	54.2 ±11.1
Site, No. (%)	
- University Hospital	187 (81.7%)
- Private Clinic	42 (18.3%)
Education, No. (%)	
- No formal education	27 (11.8%)
- Primary	22 (9.6%)
- Secondary	43 (18.8%)
- University	116 (50.6%)
- Postgraduate degree	21 (9.2%)
Employed, No. (%)	97 (42.4%)
Stage, No. (%)	
- I	26 (11.4%)
- II	104 (45.4%)
- III	99 (43.2%)
Chemotherapy, No. (%)	163 (71.2%)
Hormonal Therapy, No. (%)	
- AI	111 (48.5%)
- Tamoxifen	83 (36.2%)
- OFS/AI	8 (3.5%)
- OFS/Tamoxifen	27 (11.8%)
Funding, No. (%)	
- Governmental funding	179 (78.2%)
- Out of pocket	42 (18.3%)
- Private insurance	8 (3.5%)

Regarding discontinuation rate, 25 patients (10.9%) reported that they discontinued treatment due to side effects (n =23, 92%) or financial problems (n =2; 8%). The most commonly reported side effects were bone pain (n =8; 32%), gastrointestinal upset (n =3; 12%), hot flushes (n =4; 16%), fatigue (n =1; 4%), mood disturbance (n =8; 32%), and vaginal bleeding (n =3; 12%), Figure 1. The median duration from treatment start until continuation was 14 (IQR = 8 – 23) months. Forty-two patients (18.3%) reported treatment switch. Of them, 25 patients were switched as planned and 17 patients switched due to toxicity. All of the discontinued patients were from the university hospital (p =0.012). There were no significant associations between discontinuation and other variables (Table 2).

Out of the 204 patients who continued the treatment, a total of 73 patients (35.8%) reported treatment interruption, with a median duration of 90 (IQR = 150) days; the median days of interruption per month was ten (IQR =28) days. The reported reasons for treatment interruption included COVID-19 infection (12.5%), forgetfulness (30%), social problems (1.3%), toxicity (17.5%), travelling (1.3%), and unavailability (1.3%). Overall, the adherence rate was 64.2% (n =131). The association analysis demonstrated non-adherent patients were significantly older (p =0.005), more likely to be treated at university hospital (p <0.001), had lower level of formal education (p =0.021), unemployed (p <0.001), had lower stage (p <0.001), had not received chemotherapy (p =0.048), and that the treatment was funded out-of-pocket (p =0.012), Table 3.

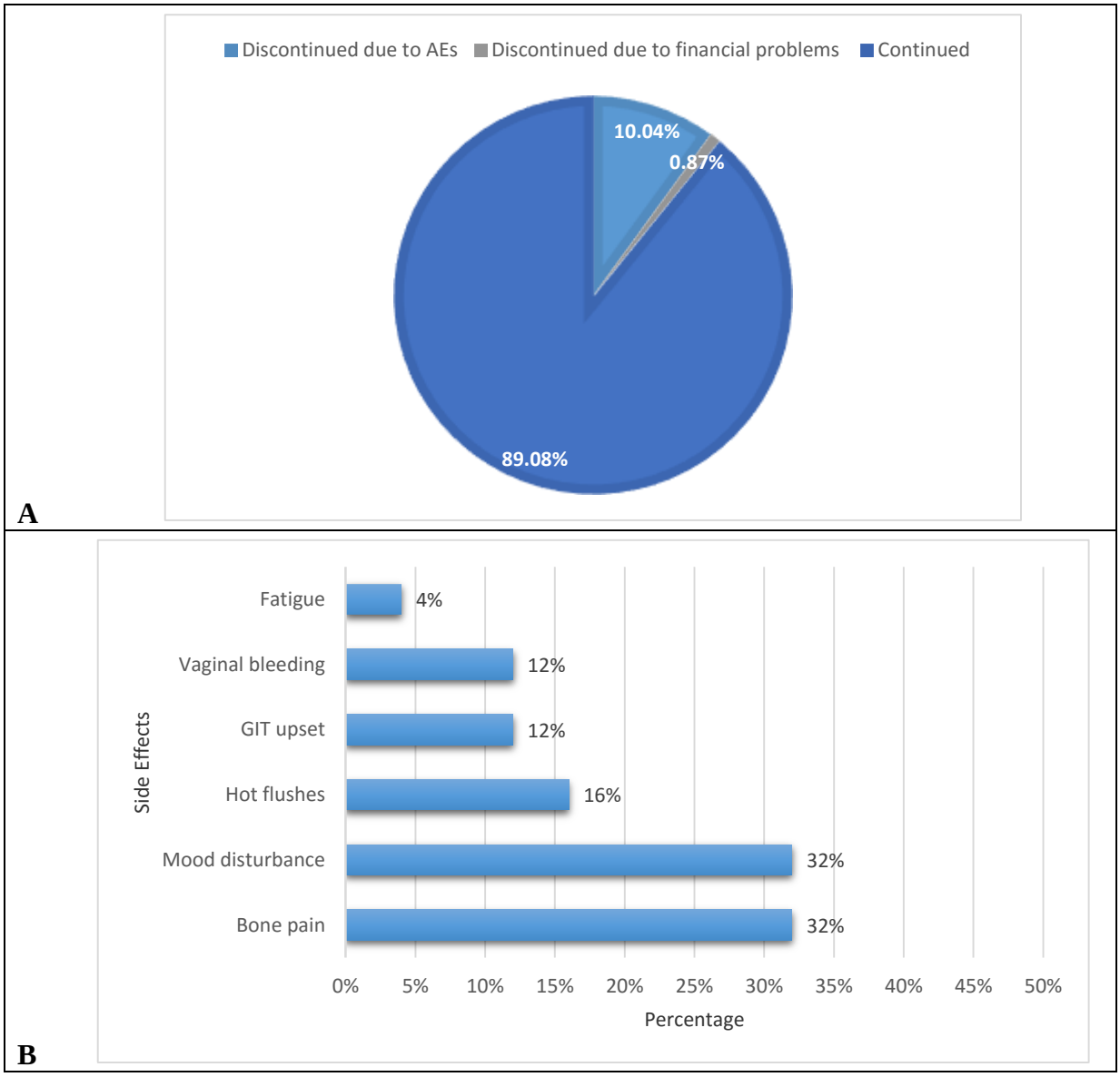

Figure 1: Reasons for treatment discontinuation (A) and side effects (B)

Table 2: The association between treatment discontinuation and characteristics of patients (n =229)

Variables	Discontinued (n =25)	Continued (n =204)	P-value
Age, mean ±SD	52.12 ±013.	52.9 ±11.01	0.84[@]
Site, No. (%)			
- University Hospital	25 (100%)	162 (79.4%)	0.012[#]
- Private Clinic	0	42 (20.6%)	
Education, No. (%)*			
- No formal education	4 (16%)	23 (11.4%)	0.83[#]
- Primary	2 (8%)	19 (9.4%)	
- Secondary	4 (16%)	39 (19.3%)	
- University	14 (56%)	102 (50.5%)	
- Postgraduate degree	1 (4%)	19 (9.4%)	
Employed, No. (%)	7 (28%)	90 (44.6%)	0.114[#]
Stage, No. (%)			
- I	4 (16%)	22 (10.8%)	0.54[#]
- II	9 (36%)	95 (46.6%)	
- III	12 (48%)	87 (42.6%)	
Chemotherapy, No. (%)	15 (60%)	148 (73.7%)	0.16[#]
Hormonal Therapy, No. (%)			
- AI	12 (48%)	99 (48.5%)	0.61[#]
- Tamoxifen	11 (44%)	72 (35.3%)	
- OFS/AI	0	8 (3.9%)	
- OFS/Tamoxifen	2 (8%)	25 (12.3%)	
Funding, No. (%)**			
- Governmental funding	20 (80%)	158 (78.6%)	0.92[#]
- Out of pocket	4 (16%)	37 (18.4%)	
- Private insurance	1 (4%)	6 (3%)	

AI= aromatase inhibitor; OFS= ovarian function suppression.
@= Mann-Whitnney test, # =Chi-square test.

Table 3: The association between adherence and characteristics of patients (n =204)

Variables	Not adherent (n =73)	Adherent (n =131)	P-value
Age, mean ±SD	55.6 ±10.9	51.3 ±11.4	0.005[@]
Site, No. (%)			
- University Hospital	44 (60.3%)	118 (90.1%)	<0.001[#]
- Private Clinic	29 (39.7%)	13 (9.8%)	
Education, No. (%)*			
- No formal education	12 (16.4%)	14 (10.7%)	0.021[#]
- Primary	10 (13.7%)	9 (6.9%)	
- Secondary	18 (24.7%)	22 (16.8%)	
- University	26 (35.6%)	75 (57.2%)	
- Postgraduate degree	7 (9.6%)	11 (8.4%)	
Employed, No. (%)	13 (17.8%)	77 (59.7%)	<0.001[#]
Stage, No. (%)			
- I	15 (20.5%)	7 (5.3%)	<0.001[#]
- II	37 (50.7%)	58 (44.3%)	
- III	21 (28.8%)	66 (50.4%)	
Chemotherapy, No. (%)	47 (64.4%)	101 (78.3%)	0.048[#]
Hormonal Therapy, No. (%)			
- AI	44 (60.3%)	55 (42%)	0.067[#]
- Tamoxifen	21 (28.8%)	51 (38.9%)	
- OFS/AI	1 (1.3%)	7 (5.3%)	
- OFS/Tamoxifen	7 (9.6%)	18 (13.7%)	
Funding, No. (%)			
- Governmental funding	50 (68.5%)	109 (84.2%)	0.012[#]
- Out of pocket	21 (28.8%)	17 (13%)	
- Private insurance	2 (2.7%)	5 (3.8%)	

AI= aromatase inhibitor; OFS= ovarian function suppression.
@= Mann-Whitnney test, # =Chi-square test.

Discussion:

For therapy to be effective, it needs to be taken diligently and properly addressing patient's medication-taking behavior is an integral part of achieving a successful treatment outcome. This cross- sectional study demonstrated a discontinuation of 10.9% and an adherence of 64.2% to adjuvant hormonal agents. Bothersome adverse events were the main reason for discontinuation (92%), whilst forgetfulness, toxicity and COVID 19 infection were also listed as reasons for non-adherence by the participants in the study.

In a systematic review by Murphy et al [11] discrepancy in treatment discontinuation in clinical practice (31–73%) contrasted to clinical trials (8–28%) clearly. One of the rationales provided for this inconsistency was that the primary provider in the clinical practice setting is sometimes ,through back referral, the primary care physician after completion of the more "active" form of breast cancer (surgery, radiotherapy and chemotherapy) with the clinical oncologist. The current patient cohort continued their therapy with their respective primary oncology teams thus explaining the proximity of the discontinuation rate to the clinical trial rate, where patients continue under the same provider underpinning the continuity of care in cancer patients.

Defining adherence was initially set at an arbitrary value range but has become generally accepted at 80%. [9] Retrospective analysis of non-adherence to tamoxifen with a <80% rate revealed an adverse effect on survival with a HR for all-cause mortality of 1.10 (95% CI, 1.0–1.2). [12] A variant definition of compliance was used by the Breast International Group 1-98 trial with letrozole that set it at 90%% and revealed a diminished disease free survival (multivariable model HR 1.61; 95% CI, 1.08–2.38). [13]

Moreover when reporting adherence various factors have to be considered. The collection method when inquiring about compliance can be either achieved through a direct approach like a survey to the patient or via reviewing medical health records of dispensing

bodies to record medication possession ratio (MPR) [14], a term accepted and adopted by many.

Hershman et al., [10] described a MPR cut- off 80% and found nonadherence at 28% in 8769 stage I to III breast cancer patients with a detrimental impact of 81.7% and 77.8% on 10 year survival in women who adhered and nonadhered respectively, serving as an independent predictor of mortality when adjustment of other variables was considered (HR 1.49).

Monitoring compliance via serum concentration of tamoxifen was reported and lower thresholds of the drug were associated with a significantly inferior distant DFS of 89.5% in patients alive with no distant recurrence at 3 years in the nonadherent versus 95.4% among adherent subjects. [15]

Whilst each method of inquiry has pros and cons, the self- reporting method utilized in the current study may be biased as it has been reported that patients asked to recall medication history can have a wish to please providers and over- estimate compliance, even the mere suggestion of observation can lead to the "Hawthorne effect." [16]

Non- adherent patients were slightly older in this survey in partial agreement with previous studies that found non-adherence and discontinuation of higher prevalence at the extremes of age, but reported it more troublesome in those less than 45 years of age. [10,16,17]

Although minimally represented in the current cohort treatment intensification (OFS + AI or tamoxifen) was described in 15.3% (35 cases) of the study population, after 2 discontinued therapy the majority adhered to their treatment (25 cases).The SOFT trial revealed more bothersome symptoms in the combination group [18], and in a combined analysis of SOFT/TEXT trials discontinuation rates were 16.1% and 11.2% for the respective OFS with exemestane versus tamoxifen in 4690 patients. [19]

Interestingly, the 10.9% that discontinued hormonal therapy were all in the governmental sector. Though they attributed stoppage to side effects but the previous period through the pandemic saw many patients prefer seeking their medical care in private facilities and not large crowded institutions fearing infection in densely crowded areas. A UK study found that reconfiguration of health services and lockdown during early 2020 resulted in 28% lower referrals for suspected breast cancer cases and 16% lower first time to treatment from diagnosis expected in that timeframe. [20] No direct comparative data on hormonal compliance during the COVID-19 pandemic can be described but further research is required to examine its impact on the cancer community regarding this area.

Additionally, the current analysis displayed non-adherent patients were more likely to be treated at the university hospital ($p < 0.001$), have a lower level of formal education ($p = 0.021$), be unemployed ($p < 0.001$), and that treatment expenses were out-of-pocket ($p = 0.012$). These factors can be counteracted by greater support from the medical team plus redirecting to social services and formulating a support system for these women.

Having a lower stage and not receiving chemotherapy likewise may be a reflection of a misconception the patient may have of her condition seeing it not worthy of strict compliance again reinforcing the concept of a deeper physician-patient communication on the benefits of timely drug adherence. These fairly simple tools may be used, and further predictors of possible non-adherence may be identified to construct targeted interventions as suggested by many groups. [17,21,22]

To our knowledge this is the first study to report on discontinuation and adherence to hormonal therapy from our region albeit having a moderate sample size and relatively short treatment duration and follow up it remains reflective of the different institutional and non-governmental sectors serving breast cancer patients in Egypt. It has displayed the main causes of incompliance to hormonal therapy subjectively reported; even with its flaws it is a valid parameter to base future strategies to tackle this area of concern. This study is also set at a unique timing, emerging from the post-COVID era where all aspects of healthcare have been disrupted to various degrees, making it of interest to examine how even the most convenient oral hormonal agents may have been affected and needless to say the outcome of such interruptions still lacks full correlation to outcome. Also, it does report a fairly low rate of discontinuation and non-adherence reflecting the lack of disruption in health care provider, as most patients continue in the initial facility providing treatment for their breast disease.

To conclude, whether survey or MPR, it is ultimately up to the patient to swallow the pill. The current study clearly identified higher discontinuation rates in the public sector, mainly as a result of side effects, thus setting support groups with empathetic communication and engaging patients in closer follow up care may solve this. Likewise this strategy should be implemented with adherence to the more likely subgroups to incur this identified in this study as being; slightly older , at the university hospital, having a lower level of formal education, unemployed, having a lower stage , not receiving chemotherapy, and those paying for their treatment. An alliance of governmental bodies and private facilities could easily navigate these patients to adequate financial aid, educational material and enhanced care if needed. The breast cancer team may mainly support by proactively encouraging and explaining the benefits of this fairly simple yet highly effective therapy in keeping disease relapse at bay and quickly addressing any concerns or toxicities arising to ensure a smooth treatment continuum.

Declarations of interest: none

Conflicts of Interest: All authors declare that they have no conflict of interest.

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