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EFFECTS OF PRIOR MEDICATION REGIMEN FACTORS AND BIPOLAR AND PSYCHOTIC DISORDERS ON BREAST CANCER ENDOCRINE THERAPY ADHERENCE

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Abstract

Background: Endocrine therapy adherence remains a barrier to optimal estrogen receptor positive (ER+) breast cancer outcomes. We theorized that experience navigating difficult medication regimen factors, such as route of administration complexity, may improve subsequent adherence following stressful cancer diagnoses, but not in patients with bipolar and psychotic disorders at-risk for poor access and non-adherence.

Methods: We included 21,894 women aged 68 or older at their first surgically treated stage I-IV ER+ breast cancer (2007-2013) from the SEER-Medicare dataset, 5.8% having bipolar and psychotic disorders. We required continuous fee-for-service Medicare (Parts A and B) for at least 36 months before and 18 after cancer diagnosis. “Medication regimen factors” in the Part D claims

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four months prior included the number of all medications used, pharmacy visits, and administration complexity (Medication Regimen Complexity Index subscale). Cox regression was used to model time-to-initiation and discontinuation, with longitudinal linear regression for adherence to endocrine therapy.

Results: Women with more frequent prior medication use and pharmacy visits were more likely to initiate ["4+ Meds & 2+ Visits" vs "No Meds" HR 1.47 (95% CI 1.33-1.63)], adhere [+6.0% (95% CI 4.3-7.6)], and continuously use endocrine therapy [discontinuation HR 0.48 (95% CI 0.39-0.59)]. Medication administration complexity had modest effects. Difficult medication regimens were more common among patients with bipolar and psychotic disorders but had no statistically significant effects.

Conclusions: Experience with frequent prior medication use and pharmacy visits may increase likelihood of endocrine therapy use in most patients, but not in those with bipolar and psychotic disorders.

MicroAbstract:

Breast cancer endocrine therapy non-adherence can worsen survival and recurrence risk. We examined patient medication regimens prior to breast cancer diagnosis, which may impact readiness for future adherence. Patients who used more medication and frequently visited pharmacies before cancer were more likely to adhere, but subgroups with behavioral risk factors (bipolar and psychotic disorders) saw no significant benefit.

Introduction

Oral endocrine therapies are used to treat estrogen receptor positive (ER+) breast cancer, reducing recurrence and mortality, but few patients fully adhere to therapy [1-5]. Prior research has examined sociodemographic, treatment, and cost factors related to non-adherence. Medication regimen characteristics prior to cancer have been less-well studied, especially among patients with serious mental illness, such as bipolar and psychotic disorders, who often have limited social support, access to care, debilitating symptoms, and general non-adherence [6-9]. Patients with these barriers may not easily navigate difficult regimens, impacting readiness for future endocrine therapy adherence.

Treatment burden is a multidimensional concept describing factors associated with health care utilization [10]. While taking numerous medications could be burdensome, this experience may promote skills for managing future cancer treatments. In a study of women aged 65 or older with breast cancer, those using multiple medications at baseline were more likely to complete tamoxifen therapy [11]. However, difficult medication administration routes, measured with the medication regimen complexity index (MRCI), may decrease chronic illness treatment adherence [12, 13]. The physical act of obtaining medication may impact adherence; reducing necessary pharmacy visits is associated with improved cardiovascular medication adherence in Medicare patients [14].

Normalization Process Theory has been applied to the treatment burden concept, describing how experience taking medication can impact organization and formation of health behaviors [15, 16]. Experience with difficult regimens may normalize medication use,

altering long-term adherence. Medication regimen factors may differentially affect patients with mental illness. Negative mood before treatment was associated with endocrine therapy non-adherence [17]. Negative mood effects were amplified when combined with disease stage and symptoms, financial concerns, and complex medication regimens [17].

We previously examined preexisting mental illness and endocrine therapy adherence in Medicare enrolled women; initiation rates were suboptimal with 20% of women never initiating, and those with bipolar and psychotic disorders at increased risk [HR 0.93 (95% CI 0.87-0.99)] [18]. In the present study, we examined the relationship between prior medication regimen utilization factors (all prescription medications) and endocrine therapy initiation/adherence/discontinuation in a cohort of women from the Surveillance, Epidemiology and End Results (SEER)-Medicare database, including subgroup analyses of patients with bipolar and psychotic disorders. We defined “medication regimen factors” using burden-relevant claims-based variables likely to impact adherence, including number of medications and pharmacy visits, and ease of administration [12, 19].

Methods

Study Population

We used the SEER-Medicare database to identify 21,894 women with ER+ breast cancer, surgically treated and diagnosed between 2007 and 2013 at age 68 or older. The SEER cancer registries include approximately 28% of the US population [20]. We were able to identify cancer diagnoses and characteristics, and detailed fee-for-service Medicare claims including (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)), clinical procedures, and prescription drug claims (National Drug Codes (NDC)) [21].

This study included women with continuous fee-for-service Parts A and B Medicare coverage for at least 36 months prior to invasive breast cancer diagnosis and 18 months after, as well as Part D coverage at least four months before and 18 months after. Breast cancer diagnosis can take place over several health care encounters, so multiple diagnoses in a three-month span were defined by the earliest diagnosis date and highest stage (4.7% of cases). All breast cancers were diagnosed before death and SEER and Medicare files listed the same death date, as applicable. Patients with potentially inaccurate endocrine therapy Part D data were excluded, defined as greater than a 10:1 ratio of prescription fill size to days supplied (n=154). Censoring occurred at end of continuous Medicare coverage or claims, new breast cancer diagnosis, use of hospice care, or death.

Measures

SEER data provided baseline demographics and tumor characteristics (AJCC 6th edition stage, receptor status, diagnosis date) [21, 22]. General comorbidity was assessed in Medicare claims using a modified NCI index (excluding dementia) for a 36 month baseline period before breast cancer and reassessed every six months for 36 months after [23]. We measured function-related indicators of comorbidity in the year prior, such as mobility limitations, which have been associated with poor health outcomes in older adults [24, 25].

Patient home rurality was determined using county-level 2013 Rural-Urban Continuum codes [26]. Because the original study was aimed at exploring the effects of mental illness, we used the Diagnostic and Statistical Manual of Mental Disorders-IV to guide selection of groups such as bipolar and psychotic disorders (bipolar depression, schizophrenia, and other psychotic disorders) [18, 27]. We adjusted for anxiety, substance use, and cognitive-impairing dementia disorders because these were previously associated with endocrine therapy initiation, discontinuation, or adherence [18]. In the 36-month baseline period, we identified mental illness comorbidity using relevant ICD-9 diagnosis codes appearing at least once in an inpatient claim, or twice in outpatient claims 30 or more days apart.

Medicare Part D prescription drug claims were used to measure endocrine therapy initiation, occurring at the first claim following cancer diagnosis. Endocrine therapies included tamoxifen and toremifene (selective estrogen receptor modulators, SERMs), anastrozole, exemestane, and letrozole (aromatase inhibitors, AIs). We examined “medication regimen factors”, including the number of all prescription medications used, pharmacy visits, and medication administration complexity before breast cancer. A four-month lookback was selected to increase detection of prescriptions with greater than a one-month supply. Medications were identified by generic name, with unique medications counted once. We measured pharmacy visits by the number of unique dates of service, except dates within a three-day window of each other were considered the same pick-up event and counted only once. We measured administration complexity using the Medication Regimen Complexity Index (MRCI) subscale “A”, with oral tablet forms given the minimum score of “1” and higher scores assigned to difficult methods such as injections [13] (Appendix 1). We controlled for financial expenditure using total out-of-pocket medication costs.

Model Selection

Medication regimen factors influence on endocrine therapy initiation was assessed using Cox regression with follow-up starting at cancer diagnosis. Adjusted models also included stage, age, race, ethnicity, NCI comorbidity score, function-related indicators, rurality, mental illness, and year of diagnosis. The number of medications and pharmacy visits were combined into a summary variable representing these related concepts. In creating this “combined medication & visit score”, individual responses with significant hazard ratios were weighted and combined [“1-3 Meds”, “4+ Meds or 2+ Visits”, and “4+ Meds and 2+ Visits” (highest weight)], with “no medication use” as reference (Appendix 2). We performed a test for trend across medication regimen factor strata and subgroup analyses of patients with and without bipolar and psychotic disorders.

Endocrine therapy discontinuation was assessed using Cox regression models, with follow-up starting at initiation and concluding at a maximum five years of use. Discontinuation was defined as the day of no available medication, with no more fills in the remaining 90 or more follow-up days [29]. Adherence was analyzed using longitudinal linear regression models fit with generalized estimating equations (normal distribution, identity link, unstructured covariance matrix), with annually repeated Proportion Days Covered (PDC = days covered/days in follow-up) adherence [30]. If patients switched from SERM to AI endocrine therapies, residual medication was disregarded once the new medication was filled. Patient

follow-up spent in skilled nursing facilities or a hospital was not analyzed, as staff dispense medication and claims should not be available in Medicare Part D [31]. Adherence values in a given year were excluded if a patient was in such facilities for over six months. Patients with less than one year of endocrine therapy follow-up did not contribute to adherence analyses. Sensitivity analyses were performed to assess confounding risk from inclusion of high stage breast cancer (limiting analysis to patients with stage I-III), and treatment delays related to adjuvant chemotherapy use (adjustment for treatment receipt, based on HCPCS claims). Statistical analyses were conducted using SAS v9.4 statistical software (SAS Institute Inc, Cary, NC).

Results

We identified 21,894 female patients with stage I-IV ER+ breast cancer diagnosed from 2007 to 2013 who met eligibility criteria. Most patients were age 68-84 years old at diagnosis (86.6%), White (89.0%), non-Hispanic (94.7%), lived in metropolitan areas (82.5%), had progesterone receptor positive (85.8%) stage I tumors (60.3%), with no function-related indicators (59.0%). The majority used four or more medications in the four months prior to breast cancer (69.8%), had five or more pharmacy visits (62.5%), and had medication administration complexity in the lowest strata (54.8%) (Table 1).

Compared to patients without, the 5.8% of patients with bipolar and psychotic disorders were more likely to be younger at diagnosis (age 68-74 45.8% vs 42.3%, p=0.006), diagnosed after stage I (stage II 33.0% vs 29.7%, p<0.001), live in metropolitan areas (87.1% vs 82.2%, p<0.001), and have more function-related indicators (“3+” 29.0% vs 7.0%, p<0.001). Patients with bipolar and psychotic disorders more frequently used medication in the four months before breast cancer (“9+” medications 46.9% vs 21.0%, p<0.001), had eleven or more pharmacy visits (39.1% vs 16.4%, p<0.001), and administration complexity in the highest strata (22.1% vs 11.4%, p<0.001) (Table 1).

In multivariable adjusted models, patients with more medication and pharmacy visits remained more likely to initiate endocrine therapy [“4+ Meds & 2+ Visits” vs “No Meds” HR 1.47 (95% CI 1.33-1.63)], and those with moderate medication administration complexity [MRCI-A “2-4” HR 0.96 (95% CI 0.93-0.99)] were less likely. Patients with bipolar and psychotic disorders [HR 0.92 (95% CI 0.86-0.98)] were less likely to initiate after adjustment for these factors. Patients with more medication use and pharmacy visits were less likely to discontinue [HR 0.48 (95% CI 0.39-0.59)] and had 6.0% higher average adherence rates (p<0.001) (Table 2).

In multivariable tests for trend, patients with more medications and pharmacy visits were more likely to initiate [HR 1.11 (95% CI 1.08-1.13) per strata], less likely to discontinue [HR 0.82 (95% CI 0.79-0.86)], and had higher daily adherence [estimate +1.6% (95% CI 1.2, 1.9)]. As out-of-pocket costs increased, initiation decreased [HR 0.97 (95% CI 0.95-0.99)], discontinuation increased [HR 1.07 (95% CI 1.02-1.12)], and adherence decreased [estimate - 1.4% (95% CI −1.8, −1.1)]. Increasing administration complexity was associated with discontinuation [HR 1.06 (95% CI 1.01-1.11)], and adherence [estimate +0.6% (95% CI 0.2, 1.0)] (data not shown).

Among patients without bipolar and psychotic disorder diagnoses, prior medication use and pharmacy visits remained positively associated with endocrine therapy initiation [“4+ Meds & 2+ Visits” vs “No Meds” HR 1.47 (95% CI 1.33-1.64)], continuous use [discontinuation HR 0.49 (95% CI 0.39-0.61)], and adherence [estimate +5.4% (95% CI 3.7, 7.2)]. In contrast, patients with these mental illness diagnoses had no significant associations among these factors [“4+ Meds & 2+ Visits” vs “No Meds” HR 1.07 (95% CI 0.64-1.78); discontinuation HR 0.64 (95% CI 0.23-1.73); adherence +6.3% (95% CI −5.1, 17.8)], but high out-of-pocket costs were detrimental to initiation [“$500+” vs “$0 < $1” HR 0.73 (95% CI 0.57-0.93)] and adherence [−6.5% (95% CI −10.1, −3.0)] (Table 3).

In sensitivity analyses restricted to stage I-III breast cancer and adjusting for receipt of adjuvant chemotherapy, the statistically significant medication regimen associations in our primary adjusted initiation/discontinuation/adherence models remained significant with comparable effects in their corresponding sensitivity analyses (Table 4). Only one variable's statistical significance changed in sensitivity analyses: the association between medication cost and discontinuation in the subgroup with bipolar and psychotic disorders (out-of-pocket costs "$50 < $500"; primary analysis HR 1.43 p=0.10; sensitivity analysis HR 1.57 p=0.04). The use of adjuvant chemotherapy was independently associated with endocrine therapy initiation, (HR 0.48, p<0.001).

Discussion

Overview:

In this cohort of Medicare-enrolled women with stage I-IV ER+ breast cancer, 20.0% never initiated endocrine therapy. Patients with any prior medication use in the four months prior to breast cancer diagnosis were more likely to initiate, continuously use, and adhere, with maximum effects in those with frequent medication use and pharmacy visits. Complex prior medication administration was associated with modestly detrimental effects to initiation and discontinuation, with some potential benefit to adherence. Despite high rates of medication use and pharmacy visits in patients with bipolar and psychotic disorders, we did not detect any potentially protective medication effects, in contrast to the remainder of the cohort.

Prior Medication Regimen Factors

Patients using any medication in the four months prior to cancer were more likely to initiate endocrine therapy, consistent with reports suggesting tamoxifen adherence increases with more medications used before breast cancer [11]. Implementation and embedding of behavior can lead to sustained change. Therefore, experience using multiple medications may increase readiness to adhere [15]. While medication administration complexity has been identified as a non-adherence risk factor [12], in our study patients with the highest strata of prior regimen complexity had an 1.4% increase in adherence rates. Administration complexity during cancer treatment may be burdensome, whereas experiences prior to cancer may normalize chronic regimen behaviors to some extent. Because oral endocrine therapies are simple to administer, experience with complex medications may have a limited effect.

While experience with medication administration complexity did not improve endocrine therapy initiation, patients with many pharmacy visits were more likely to initiate. Prior work suggests “synchronization”, the ability to pick up all medications at the same time, may improve adherence by reducing travel and simplifying management [32]. The current study is not designed to assess synchronization, but frequent visits prior to cancer may reflect the ability and readiness to travel and initiate treatment. Additionally, pharmacist-patient interactions may increase initiation likelihood. In a study of adherence to diabetes mellitus medication and initiation of concomitant therapies, patients with supplemental pharmacist counseling and follow-up contact were 38% more likely to initiate [33]. These interactions and education may influence key beliefs, such as medication distrust and uncertainty of efficacy, which are associated with non-initiation of osteoporosis treatment [34]. Among breast cancer patients in the Detroit and Los Angeles SEER registries, those reporting inadequate endocrine therapy education were significantly less likely to initiate [35]. Interventions providing education and counseling may be valuable in improving endocrine therapy initiation rates.

Medication Regimen Factors in Patients with Bipolar and Psychotic Disorders

Although patients with bipolar and psychotic disorders were less likely to initiate endocrine therapy, and often struggle with general daily medication adherence [36], we observed high rates of prior medication utilization in this subgroup and no significant associations between these medication regimen factors and initiation, discontinuation, or adherence. The trend in discontinuation across levels of prior medication and pharmacy use mirrored that in patients without these conditions to some extent, but analytic power was limited because most patients with bipolar and psychotic disorders had high medication and pharmacy use.

Bipolar and psychotic disorder symptoms may compromise the ability to acquire beneficial health behaviors. Alternatively, social factors including stigma, limited access to care, and poor provider-patient relationships may affect receipt of guideline concordant cancer and general health care [6-8]. Medication regimens for patients with bipolar and psychotic disorders include more psychiatric medications, compared to patients without these conditions (Appendices 4 and 5). Therefore, prior medication use may capture a different behavioral concept in patients with mental illness (e.g., increased psychiatric treatment, not general medication adherence). These patients were diagnosed at later stages, consistent with evidence suggesting patients with mental illness have delays in initial breast cancer diagnosis and primary treatment [37]. Interventions to improve endocrine therapy use should consider unique approaches for these and other at-risk patients with individual and societal challenges.

Sensitivity Analyses

Our sensitivity analyses were performed to address confounding risk, including late stage cancer diagnosis as it may relate to symptom severity which could influence both baseline medication use and future endocrine therapy adherence. After excluding stage IV cancer patients, our medication regimen findings remained significant, with minimal change to the magnitude of effects. This suggests prior medication regimen factors are associated with

endocrine therapy use, even after acknowledging potential treatment differences in patients with stage IV cancer.

We also examined potential confounding from adjuvant chemotherapy use. Adjuvant chemotherapy may be more frequently used in healthier patients able to tolerate treatment, who may have used fewer medications in the past. Also, patients may delay endocrine therapy initiation until adjuvant treatment has concluded. In our adjusted models, adjuvant chemotherapy was strongly associated with a delay in endocrine therapy initiation, however medication regimen effects remained significantly associated with outcomes. We can conclude that adjuvant chemotherapy is related to delays in endocrine therapy initiation, but this relationship does not meaningfully confound the independent effects of prior medication regimen factors.

Other Patient Characteristics

Patients with an intermediate number of function-related indicators of comorbidity (Appendix 6) were less likely to initiate endocrine therapies. A cohort study of myocardial infarction patients found those with more function-related indicators were less likely to use preventive medications [25]. Patients with some limitations in daily functioning may minimize travel, reducing pharmacy access, but patients with a greater functional burden may receive family or social assistance, reducing the impact of individual limitations. Patients in rural counties were more likely to initiate therapy, which may represent practice-level, cultural, or other unmeasured factors in these patients.

High endocrine therapy costs have been associated with non-adherence in commercially insured women [38]. We found that high out-of-pocket costs for any medication were associated with reduced endocrine therapy initiation and adherence rates. This is consistent with a more general body of research indicating that increased patient costs are associated with lower medication initiation rates [39]. Although conceptually interrelated, the detrimental effects associated with medication cost and protective effects of prior medication use and pharmacy visits remained independently significant in adjusted models. The negative impact of high cost on initiation and adherence remained significant among patients with bipolar and psychotic disorders, even though other medication regimen factors were not. Medicaid patients with schizophrenia have reduced antipsychotic utilization and increased emergency service use when monthly drug reimbursement is capped [40]. Excessive costs may contribute to symptom exacerbations, further reducing likelihood of endocrine therapy initiation and adherence.

Extending previous findings [3, 18], patients with stage I cancer and older age at diagnosis were less likely to initiate, even after adjustment for medication regimen factors. Perception of a poor risk-benefit ratio may influence cancer treatment in older women with competing mortality risks and potential endocrine therapy side effects, while stronger provider recommendations may be given to women with advanced cancers [41-43].

Study Strengths and Potential Limitations

We utilized a large SEER-Medicare cohort of older women with stage I-IV breast cancers. Medicare Part D claims allowed for examination of detailed prescription medication

regimens, characterizing non-cancer treatments. We measured endocrine therapy initiation, adherence, and discontinuation in three separate models, as appropriate for these related but distinct outcomes. Our findings used variables reflective of clinically accessible data to predict preventable morbidity and mortality due to endocrine therapy non-adherence.

Potential study limitations are related to the nature of administrative claim studies. Medicare patients are not necessarily representative of younger women with other insurance providers, or managed care plans. However, breast cancers are often diagnosed in older women, making the disease burden relevant to the Medicare population [44]. We were unable to assess use of mail-order pharmacy services, which may simplify medication-taking behaviors [45]. While MRCI-A complexity calculations appropriately assess administration complexity, the remaining domains could not be reliably assessed: “additional instructions” are not included in claims and “dosing frequency” can only be partially estimated [13]. Administrative claims-based diagnoses risk potential misclassification and underestimation. Provider-level prescribing behaviors were not assessed but could affect medication utilization and the likelihood of initiation. Finally, our prior medication regimen variables may be correlated with factors that are unavailable or partially unmeasured in these data, for example we cannot tell if low rates of prior medication use are due to fewer medications prescribed, or a general lack of adherence/willingness to fill initial prescriptions.

Conclusions

Despite the established benefits of endocrine therapy, one-fifth of female Medicare beneficiaries with ER+ breast cancer did not initiate treatment. Prior medication regimen factors including frequent medication use and pharmacy visits increased likelihood of initiation, continuous use, and adherence. After adjustment, patients with bipolar and psychotic disorders remained at risk for endocrine therapy non-initiation and were not significantly affected by medication regimen factors. Interventions focused on health behavior development and provider-patient counseling may increase initiation rates in the general population, but patients with bipolar and psychotic disorders may require targeted efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- Breast cancer endocrine therapy non-adherence is known to reduce survival and increase recurrence risk. Therefore, identification of patients at risk for endocrine therapy non-adherence is critical to improve outcomes.
- Patients with regimens prior to cancer including more medication and pharmacy visits were significantly more likely to initiate, adhere, and continuously use endocrine therapy.
- In contrast to the general population, subgroups with bipolar and psychotic disorders had no significant association between extensive prior medication regimens and endocrine therapy adherence.
- Familiarity with chronic medication regimens may be helpful for the development of adherence behaviors. Providers should consider patients' prior experience with medication and relevant behavioral illnesses when identifying those at risk for endocrine therapy non-adherence.

Table 1:

Characteristics of breast cancer patients diagnosed 2007-2013, according to bipolar and psychotic disorder status

				Bipolar and psychotic disorder diagnosed				
Covariate	**Level**	**All N=21,894**		**No N=20,635 (94.2%)**		**Yes N=1,259 (5.8%)**		**p value***
Age at Diagnosis	68-74	9,308	42.5%	8,732	42.3%	576	45.8%	**0.006**
	75-84	9,659	44.1%	9,133	44.3%	526	41.8%	
	85-94	2,831	12.9%	2,685	13.0%	146	11.6%	
	95+	96	0.4%	85	0.4%	11	0.9%	
Race	Asian	[a]	[a]	910	4.4%	[a]	[a]	0.19
	Black	1,315	6.0%	1,233	6.0%	82	6.5%	
	Other	[a]	[a]	140	0.7%	[a]	[a]	
	White	19,480	89.0%	18,352	88.9%	1,128	89.6%	
Ethnicity	Hispanic	1,166	5.3%	1,090	5.3%	76	6.0%	0.25
	Non-Hispanic	20,728	94.7%	19,545	94.7%	1,183	94.0%	
Rurality	Metro	18,053	82.5%	16,957	82.2%	1,096	87.1%	**<.001**
	Non-metro, non-rural	3,361	15.4%	3,220	15.6%	141	11.2%	
	Rural	[a]	[a]	[a]	[a]	[a]	[a]	
	Unknown	[a]	[a]	[a]	[a]	[a]	[a]	
Year of Diagnosis	2007	1,961	9.0%	1,855	9.0%	106	8.4%	0.90
	2008	2,968	13.6%	2,801	13.6%	167	13.3%	
	2009	3,144	14.4%	2,954	14.3%	190	15.1%	
	2010	3,131	14.3%	2,953	14.3%	178	14.1%	
	2011	3,300	15.1%	3,119	15.1%	181	14.4%	
	2012	3,492	15.9%	3,279	15.9%	213	16.9%	
	2013	3,898	17.8%	3,674	17.8%	224	17.8%	
Stage at Diagnosis	I	13,194	60.3%	12,503	60.6%	691	54.9%	**<.001**
	II	6,534	29.8%	6,119	29.7%	415	33.0%	
	III	1,516	6.9%	1,397	6.8%	119	9.5%	
	IV	[a]	[a]	195	0.9%	[a]	[a]	

		Bipolar and psychotic disorder diagnosed						
Covariate	**Level**	**All N=21,894**		**No N=20,635 (94.2%)**		**Yes N=1,259 (5.8%)**		**p value***
	Unknown	[a]	[a]	421	2.0%	[a]	[a]	
Receptor Status	ER+PR+	18,789	85.8%	17,718	85.9%	1,071	85.1%	0.43
	ER+PR-	3,105	14.2%	2,917	14.1%	188	14.9%	
Endocrine Therapy Class	AIs	13,659	62.4%	12,889	62.5%	770	61.2%	**<.001**
	Both	1,903	8.7%	1,819	8.8%	84	6.7%	
	None	4,382	20.0%	4,074	19.7%	308	24.5%	
	SERMs	1,950	8.9%	1,853	9.0%	97	7.7%	
Adjusted NCI Comorbidity	Mean (Median)	2.1 (2.0)		2.0	2.0	3.1	3.0	**<.001**
Function-related Indicators	0	12,921	59.0%	12,741	61.7%	180	14.3%	**<.001**
	1	5,159	23.6%	4,718	22.9%	441	35.0%	
	2	1,995	9.1%	1,722	8.3%	273	21.7%	
	3+	1,819	8.3%	1,454	7.0%	365	29.0%	
Anxiety Disorder		2,086	9.5%	1,673	8.1%	413	32.8%	**<.001**
Dementia Disorder		1,017	4.6%	742	3.6%	275	21.8%	**<.001**
Substance Use Disorder		1,006	4.6%	846	4.1%	160	12.7%	**<.001**
Number of Medications[d]	0-3	6,617	30.2%	6,474	31.4%	143	11.4%	**<.001**
	4-8	10,358	47.3%	9,833	47.7%	525	41.7%	
	9+	4,919	22.5%	4,328	21.0%	591	46.9%	
Number of Pharmacy Visits	0-1	2,463	11.2%	2,414	11.7%	49	3.9%	**<.001**
	2-4	5,755	26.3%	5,602	27.2%	153	12.1%	
	5-10	9,799	44.8%	9,234	44.7%	565	44.9%	
	11+	3,877	17.7%	3,385	16.4%	492	39.1%	
MRCI-A Route Complexity	0-1	12,006	54.8%	11,488	55.7%	518	41.1%	**<.001**
	2-4	7,252	33.1%	6,789	32.9%	463	36.8%	
	5+	2,636	12.0%	2,358	11.4%	278	22.1%	
Combined Medication & Visit Score	No Meds	1,207	5.5%	1,182	5.7%	25	2.0%	**<.001**
	1-3 Meds	1,132	5.2%	1,115	5.4%	17	1.3%	
	4+ Meds or 2+ Visits	4,402	20.1%	4,294	20.8%	108	8.6%	
	4+ Meds & 2+ Visits	15,153	69.2%	14,044	68.1%	1,109	88.1%	

		Bipolar and psychotic disorder diagnosed						
Covariate	**Level**	**All N=21,894**		**No N=20,635 (94.2%)**		**Yes N=1,259 (5.8%)**		**p value***
Out-Of-Pocket Medication Cost	$0 < $1	2,266	10.3%	2,007	9.7%	259	20.6%	**<.001**
	$1 < $50	5,882	26.9%	5,596	27.1%	286	22.7%	
	$50 < $500	11,874	54.2%	11,353	55.0%	521	41.4%	
	$500+	1,872	8.6%	1,679	8.1%	193	15.3%	
Number Who Initiated		17,512	80.0%	16,561	80.3%	951	75.5%	**<.001**
Days to Initiation	Mean (Median)	156.6 (120.0)		156.7	120.0	156.6	120.0	0.68
Number Who Discontinued		4,503	25.7%	4,248		255		
[b]**Days to Discontinuation**	Mean (Median)	701.5 (521.0)		704.8	523.0	647.1	458.0	0.28
Number with 1+ Years		14,517	66.3%	13,739		778		
[c]**Average Adherence**	Mean (Median)	0.84 (0.90)		0.84	0.91	0.84	0.91	0.23
Follow-up Days	Mean (Median)	1377.9 (1280.0)		1,383.3	1,280.0	1,288.3	1,157.0	**<.001**
Number Censored at Death		1,376	6.3%	1,242	6.0%	134.0	10.6%	**<.001**

"Combined Medication & Visit" variable created from each variable's significant response levels in separate adjusted models (Appendix 2).

[a]Values under 11 and nearest strata censored to maintain confidentiality.

[b]Discontinuation analysis censored after five years continuous use.

[c]Adherence measured with the proportion of days covered (PDC), for patients with one or more years of observation with over half of this time outside hospitals and skilled nursing facilities.

[d]Medication variables describe utilization in the four months prior to breast cancer diagnosis.

*Parametric p value calculated by chi-square test, Wilcoxon for continuous variables.

Table 2:

Bivariable and adjusted multivariable models: medication regimen factors and endocrine therapy initiation, discontinuation, adherence

Parameter		Initiation n=21,894		[a]Discontinuation n=17,512		[b]Adherence n=17,512	
		Unadjusted HR (95% CI)	Adjusted Multivariable HR (95% CI)	Unadjusted HR (95% CI)	Adjusted Multivariable HR (95% CI)	Unadjusted Estimate (95% CI)	Adjusted Multivariable Estimate (95% CI)
[c]Intercept		-	-	-	-	-	**0.773 (0.754, 0.793)
MRCI-A Route Complexity	2-4	0.99 (0.96-1.03)	*0.96 (0.93-0.99)	1.01 (0.95-1.08)	1.07 (1.00-1.14)	0.004 (−0.002, 0.009)	0.001 (−0.004, 0.007)
(ref= 0-1)	5+	1.02 (0.98-1.07)	1.00 (0.95-1.05)	1.05 (0.95-1.15)	*1.12 (1.02-1.24)	**0.017 (0.009, 0.025)	**0.014 (0.006, 0.023)
Overall variable p value		0.57	0.08	0.62	0.04	<0.001	0.002
Combined Medication & Visit Score	1-3 Meds	**1.30 (1.19-1.43)	**1.34 (1.19-1.50)	0.87 (0.74-1.03)	*0.71 (0.56-0.89)	0.005 (−0.011, 0.022)	*0.024 (0.005, 0.044)
(ref= No Meds)	4+ Meds or 2+ Visits	**1.27 (1.18-1.37)	**1.36 (1.23-1.51)	**0.74 (0.65-0.84)	**0.56 (0.45-0.68)	*0.022 (0.009, 0.036)	**0.049 (0.032, 0.065)
	4+ Meds & 2+ Visits	**1.30 (1.22-1.40)	**1.47 (1.33-1.63)	**0.72 (0.64-0.81)	**0.48 (0.39-0.59)	**0.029 (0.016, 0.041)	**0.060 (0.043, 0.076)
Overall variable p value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Out-of-Pocket Medication Costs	$1 < $50	**1.19 (1.13-1.26)	0.98 (0.91-1.06)	**0.82 (0.74-0.92)	1.17 (0.99-1.39)	0.008 (−0.001, 0.017)	**−0.021 (−0.032, −0.009)
(ref= $0 < $1)	$50 < $500	**1.17 (1.11-1.23)	0.96 (0.89-1.03)	0.93 (0.84-1.03)	*1.31 (1.11-1.55)	−0.007 (−0.016, 0.001)	**−0.042 (−0.053, −0.031)
	$500+	1.03 (0.96-1.10)	*0.86 (0.79-0.94)	0.92 (0.81-1.06)	*1.25 (1.03-1.51)	0.000 (−0.012, 0.012)	**−0.037 (−0.050, −0.023)
Overall variable p value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage at Diagnosis	II	**1.13 (1.10-1.17)	**1.14 (1.10-1.18)	**0.81 (0.76-0.87)	**0.80 (0.75-0.85)	−0.001 (−0.007, 0.004)	−0.001 (−0.006, 0.005)
(ref= I)	III	*1.07 (1.01-1.13)	1.04 (0.99-1.10)	**0.74 (0.65-0.84)	**0.72 (0.64-0.82)	*−0.016 (−0.027, −0.006)	*−0.014 (−0.024, −0.004)
	IV	**1.50 (1.29-1.74)	**1.57 (1.36-1.82)	1.24 (0.96-1.61)	1.13 (0.87-1.47)	**−0.060 (−0.092, −0.029)	*−0.048 (−0.078, −0.017)
	Unknown	**0.82 (0.73-0.92)	*0.87 (0.77-0.97)	0.87 (0.70-1.09)	0.84 (0.67-1.05)	−0.006 (−0.025, 0.014)	−0.003 (−0.022, 0.017)
Overall variable p value		<0.001	<0.001	<0.001	<0.001	<0.001	0.003
Race	Asian	*1.11 (1.04-1.20)	*1.11 (1.03-1.19)	*0.81 (0.69-0.94)	*0.82 (0.70-0.95)	*0.015 (0.004, 0.026)	0.010 (−0.002, 0.021)
(ref= White)	Black	0.99 (0.93-1.05)	0.95 (0.89-1.01)	**0.72 (0.63-0.83)	**0.74 (0.64-0.86)	*−0.012 (−0.023, −0.001)	*−0.015 (−0.026, −0.004)
	Other	1.02 (0.85-1.22)	0.98 (0.82-1.17)	0.87 (0.59-1.29)	0.91 (0.61-1.35)	−0.033 (−0.067, 0.001)	*−0.039 (−0.073, −0.005)
Overall variable p value		0.03	0.01	<0.001	<0.001	0.001	0.002

Parameter		Initiation n=21,894		[a]Discontinuation n=17,512		[b]Adherence n=17,512	
		Unadjusted HR (95% CI)	Adjusted Multivariable HR (95% CI)	Unadjusted HR (95% CI)	Adjusted Multivariable HR (95% CI)	Unadjusted Estimate (95% CI)	Adjusted Multivariable Estimate (95% CI)
Ethnicity (ref= Non-Hispanic)	Hispanic	1.03 (0.97-1.10)	0.99 (0.93-1.06)	*0.80 (0.69-0.92)	*0.82 (0.71-0.95)	−0.004 (−0.015, 0.007)	−0.008 (−0.019, 0.003)
Age at Diagnosis	75-84	**0.91 (0.88-0.94)	**0.92 (0.89-0.95)	**1.24 (1.16-1.32)	**1.27 (1.19-1.35)	−0.003 (−0.008, 0.002)	−0.003 (−0.008, 0.003)
(ref= 68-74)	85-94	**0.64 (0.60-0.67)	**0.65 (0.61-0.68)	**1.50 (1.36-1.65)	**1.57 (1.42-1.73)	*0.010 (0.001, 0.018)	*0.012 (0.004, 0.020)
	95+	**0.44 (0.33-0.59)	**0.45 (0.34-0.60)	*2.33 (1.40-3.87)	**2.68 (1.61-4.48)	−0.036 (−0.099, 0.027)	−0.026 (−0.091, 0.039)
Overall variable p value		<0.001	<0.001	<0.001	<0.001	0.03	0.01
Adjusted NCI Comorbidity Score (6-month time varying)		0.99 (0.99-1.00)	1.00 (0.99-1.01)	1.01 (0.99-1.02)	1.01 (1.00-1.03)	**0.005 (0.004, 0.006)	−0.001 (−0.002, 0.000)
Function-related Indicators	1	0.98 (0.94-1.02)	1.00 (0.96-1.03)	1.06 (0.99-1.14)	1.03 (0.96-1.11)	*−0.010 (−0.017, −0.004)	**−0.011 (−0.017, −0.005)
(ref= 0)	2	**0.87 (0.82-0.92)	**0.91 (0.86-0.96)	*1.19 (1.07-1.31)	*1.13 (1.01-1.26)	−0.003 (−0.012, 0.006)	−0.005 (−0.014, 0.005)
	3+	**0.91 (0.86-0.96)	0.97 (0.91-1.03)	1.02 (0.91-1.14)	0.92 (0.81-1.05)	0.005 (−0.004, 0.014)	0.003 (−0.007, 0.013)
Overall variable p value		<0.001	0.01	0.009	0.04	0.004	0.002
Bipolar and Psychotic Disorder		*0.90 (0.84-0.96)	*0.92 (0.86-0.98)	1.13 (0.99-1.28)	1.12 (0.98-1.28)	0.001 (−0.010, 0.013)	−0.002 (−0.013, 0.010)
Anxiety Disorder		1.00 (0.95-1.05)	0.99 (0.94-1.05)	**1.24 (1.13-1.37)	**1.23 (1.11-1.36)	−0.004 (−0.013, 0.005)	−0.007 (−0.016, 0.003)
Dementia Disorder		**0.82 (0.76-0.88)	*0.89 (0.82-0.97)	1.09 (0.94-1.28)	1.02 (0.86-1.20)	0.008 (−0.005, 0.021)	0.005 (−0.009, 0.018)
Substance Use Disorder		1.00 (0.93-1.07)	0.98 (0.91-1.05)	**1.41 (1.24-1.61)	**1.44 (1.26-1.64)	**−0.026 (−0.040, −0.012)	**−0.024 (−0.038, −0.010)
Home Rurality	Metro	**0.82 (0.74-0.91)	**0.84 (0.76-0.92)	1.21 (0.99-1.49)	1.22 (0.99-1.50)	**−0.032 (−0.046, −0.018)	**−0.032 (−0.045, −0.018)
(ref= Rural)	Non-metro	*0.84 (0.76-0.93)	*0.86 (0.77-0.95)	1.15 (0.92-1.42)	1.15 (0.93-1.43)	*−0.022 (−0.037, −0.006)	*−0.020 (−0.035, −0.006)
	Unknown	1.59 (0.40-6.26)	1.54 (0.38-6.20)	3.38 (0.47-24.26)	3.33 (0.46-23.97)	−0.046 (−0.162, 0.071)	−0.040 (−0.143, 0.064)
Overall variable p value		<0.001	0.003	0.11	0.11	<0.001	<0.001
Year of Diagnosis	2008	0.99 (0.93-1.06)	0.98 (0.92-1.04)	0.95 (0.86-1.05)	0.95 (0.86-1.06)	0.002 (−0.009, 0.014)	0.002 (−0.009, 0.013)
(ref= 2007)	2009	1.01 (0.95-1.08)	1.01 (0.94-1.07)	0.91 (0.82-1.00)	0.91 (0.82-1.00)	**0.021 (0.010, 0.032)	**0.023 (0.012, 0.033)
	2010	**1.13 (1.06-1.20)	*1.10 (1.04-1.18)	*0.86 (0.77-0.97)	*0.86 (0.77-0.96)	**0.049 (0.038, 0.059)	**0.058 (0.048, 0.069)
	2011	**1.18 (1.10-1.25)	**1.16 (1.09-1.23)	0.91 (0.81-1.02)	0.91 (0.81-1.02)	**0.049 (0.038, 0.059)	**0.069 (0.059, 0.080)
	2012	**1.17 (1.10-1.25)	**1.15 (1.09-1.22)	0.92 (0.82-1.05)	0.92 (0.81-1.04)	**0.048 (0.037, 0.058)	**0.084 (0.073, 0.094)

Parameter		Initiation n=21,894		[a]Discontinuation n=17,512		[b]Adherence n=17,512	
		Unadjusted HR (95% CI)	Adjusted Multivariable HR (95% CI)	Unadjusted HR (95% CI)	Adjusted Multivariable HR (95% CI)	Unadjusted Estimate (95% CI)	Adjusted Multivariable Estimate (95% CI)
	2013	**1.21 (1.14-1.29)	**1.18 (1.11-1.26)	0.94 (0.82-1.08)	0.93 (0.81-1.06)	**0.024 (0.012, 0.035)	**0.082 (0.071, 0.094)
Overall variable p value		<0.001	<0.001	0.24	0.22	<0.001	<0.001
[c]Year of Endocrine Therapy Use	2	-	-	-	-	**0.061 (0.057, 0.065)	**0.067 (0.063, 0.071)
(ref= 1)	3	-	-	-	-	**0.079 (0.074, 0.084)	**0.089 (0.084, 0.094)
	4	-	-	-	-	**0.100 (0.095, 0.106)	**0.119 (0.113, 0.125)
	5	-	-	-	-	**0.102 (0.095, 0.109) <0.001	**0.131 (0.123, 0.139)
Overall variable p value		-	-	-	-	<0.001	<0.001

P value *<0.05, **<0.001, 95% confidence interval. Overall variable p value calculated for categorical variables with 3 or more strata. “Combined Medication & Visit” variable created from each variable’s significant response levels in separate adjusted models (Appendix 2).

[a,b]Follow-up began the day of endocrine therapy initiation, concluding at censoring or a maximum five years of endocrine therapy use. Discontinuation was assessed in Cox regression.

[a]Discontinuation analysis censored after five years continuous use.

[b]Adherence measured with the proportion of days covered (PDC), for patients with one or more years of observation with over half of this time outside hospitals and skilled nursing facilities. Estimate of 0.01 corresponds to 1%.

[c]Applicable to adherence only.

Table 3:

Prior medication regimen effects on endocrine therapy adherence, by subgroups with and without bipolar and psychotic disorders

Parameter		Initiation		[a]Discontinuation		[b]Adherence	
		Bipolar and Psychotic Disorder n=1,259	No Diagnosis n=20,635	Bipolar and Psychotic Disorder n=951	No Diagnosis n=16,561	Bipolar and Psychotic Disorder n=951	No Diagnosis n=16,561
		Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Estimate (95% CI)	Estimate (95% CI)
[c]Intercept		-	-	-	-	**0.711 (0.576, 0.846)	**0.777 (0.757, 0.797)
MRCI-A Route Complexity	2-4	1.00 (0.85-1.16)	*0.96 (0.93-1.00)	0.94 (0.69-1.27)	*1.08 (1.00-1.16)	0.007 (−0.018, 0.031)	0.001 (−0.005, 0.006)
(ref= 0-1)	5+	0.97 (0.81-1.17)	1.00 (0.95-1.06)	1.00 (0.69-1.44)	*1.14 (1.02-1.26)	0.016 (−0.013, 0.046)	*0.014 (0.005, 0.022)
Overall variable p value		0.95	0.06	0.89	0.03	0.56	0.005
Combined Medication & Visit Score	1-3 Meds	0.88 (0.42-1.85)	**1.34 (1.19-1.51)	1.01 (0.25-4.05)	*0.71 (0.56-0.90)	−0.035 (−0.206, 0.136)	0.020 (0.000, 0.040)
(ref= No Meds)	4+ Meds or 2+ Visits	0.87 (0.50-1.50)	**1.37 (1.23-1.52)	0.78 (0.27-2.22)	**0.56 (0.45-0.70)	0.032 (−0.089, 0.153)	**0.044 (0.026, 0.061)
	4+ Meds & 2+ Visits	1.07 (0.64-1.78)	**1.47 (1.33-1.64)	0.64 (0.23-1.73)	**0.49 (0.39-0.61)	0.063 (−0.051, 0.178)	**0.054 (0.037, 0.072)
Overall variable p value		0.42	<0.001	0.60	<0.001	0.19	<0.001
Out-of-Pocket Medication Costs	$1 < $50	1.04 (0.83-1.29)	0.98 (0.90-1.07)	1.18 (0.73-1.90)	1.16 (0.96-1.40)	−0.021 (−0.051, 0.009)	*−0.016 (−0.029, −0.004)
(ref= $0 < $1)	$50 < $500	0.96 (0.78-1.16)	0.96 (0.89-1.04)	1.43 (0.93-2.18)	*1.28 (1.07-1.54)	**−0.069 (−0.098, −0.039)	**−0.036 (−0.048, −0.024)
	$500+	*0.73 (0.57-0.93)	*0.88 (0.80-0.97)	1.36 (0.83-2.23)	1.22 (1.00-1.50)	**−0.065 (−0.101, −0.030)	**−0.029 (−0.044, −0.015)
Overall variable p value		0.02	0.01	0.36	0.006	<0.001	<0.001

P value *<0.05, **<0.001, 95% confidence interval. Overall variable p value calculated for categorical variables with 3 or more strata. “Combined Medication & Visit” variable created from each variable’s significant response levels in separate adjusted models (Appendix 2). Models adjusted for stage, age, race, ethnicity, NCI comorbidity score, function-related indicators, rurality, mental illness, year of diagnosis (Appendix 3).

[a,b]Follow-up began the day of endocrine therapy initiation, concluding at censoring or a maximum five years of endocrine therapy use.

[a]Discontinuation analysis censored after five years continuous use.

[b]Adherence measured with the proportion of days covered (PDC), for patients with one or more years of observation with over half of this time outside hospitals and skilled nursing facilities. Estimate of 0.01 corresponds to 1%.

[c]Applicable to adherence only.

Table 4:

Sensitivity analysis: medication regimen effects in multivariable models limited to stage I-III breast cancer patients with adjustment for adjuvant chemotherapy use, compared to primary analysis results

		Initiation		[a]Discontinuation		[b]Adherence	
		Full Cohort n=21,244	Bipolar and Psychotic Disorder n=1,225	Full Cohort n=17,020	Bipolar and Psychotic Disorder n=928	Full Cohort n=17,020	Bipolar and Psychotic Disorder n=928
Parameter		**Sensitivity Analysis Hazard Ratio (Primary Analysis)**	**Sensitivity Analysis Hazard Ratio (Primary Analysis)**	**Sensitivity Analysis Hazard Ratio (Primary Analysis)**	**Sensitivity Analysis Hazard Ratio (Primary Analysis)**	**Sensitivity Analysis Estimate (Primary Analysis)**	**Sensitivity Analysis Estimate (Primary Analysis)**
MRCI-A Route Complexity	2-4	*0.96 (*0.96)	0.98 (1.00)	1.07 (1.07)	0.93 (0.94)	0.002 (0.001)	0.008 (0.007)
(ref= 0-1)	5+	0.99 (1.00)	0.98 (0.97)	*1.12 (*1.12)	1.03 (1.00)	**0.015 (**0.014)	0.019 (0.016)
Combined Medication & Visit Score	1-3 Meds	**1.29 (**1.34)	0.78 (0.88)	*0.72 (*0.71)	0.96 (1.01)	*0.028 (*0.024)	−0.031 (−0.035)
(ref= No Meds)	4+ Meds or 2+ Visits	**1.33 (**1.36)	0.75 (0.87)	**0.56 (**0.56)	0.76 (0.78)	**0.052 (**0.049)	0.040 (0.032)
	4+ Meds & 2+ Visits	**1.43 (**1.47)	0.92 (1.07)	**0.49 (**0.48)	0.60 (0.64)	**0.062 (**0.060)	0.065 (0.063)
Out-of-Pocket Medication Costs	$1 < $50	1.02 (0.98)	1.14 (1.04)	1.16 (1.17)	1.23 (1.18)	**−0.022 (**−0.021)	−0.021 (−0.021)
(ref= $0 < $1)	$50 < $500	1.00 (0.96)	1.05 (0.96)	*1.30 (*1.31)	*1.57 (1.43)	**−0.043 (**−0.042)	**−0.069 (**−0.069)
	$500+	*0.91 (*0.86)	*0.78 (*0.73)	*1.23 (*1.25)	1.47 (1.36)	**−0.039 (**−0.037)	**−0.063 (**−0.065)
Adjuvant Chemotherapy Prior to Endocrine Therapy		**0.48 (n/a)	**0.52 (n/a)	**0.83 (n/a)	0.80 (n/a)	−0.003 (n/a)	−0.018 (n/a)

P value *<0.05, **<0.001. Models adjusted for same variables in primary analysis: stage, age, race, ethnicity, NCI comorbidity score, function-related indicators, rurality, mental illness, year of diagnosis.

[a,b]Follow-up began the day of endocrine therapy initiation, concluding at censoring or a maximum five years of endocrine therapy use.

[a]Discontinuation analysis censored after five years continuous use.

[b]Adherence measured with the proportion of days covered (PDC), for patients with one or more years of observation with over half of this time outside hospitals and skilled nursing facilities. Estimate of 0.01 corresponds to 1%.