OXFORD

JNCI J Natl Cancer Inst (2022) 114(7): djac062

https://doi.org/10.1093/jnci/djac062
First published online March 25, 2022
Article

Hormonal Therapy Drug Switching, Out-of-Pocket Costs, and Adherence Among Older Women With Breast Cancer

Xuanzi Qin, PhD, MSPH [1,2,*] Peter Huckfeldt, PhD,[1] Jean Abraham, PhD,[1] Douglas Yee, MD [3] Beth A. Virnig, PhD, MPH[1]

[1]Division of Health Policy and Management, School of Public Health, University of Minnesota, Minneapolis, MN, USA; [2]Department of Health Policy, Vanderbilt University School of Medicine, Nashville, TN, USA; and [3]Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

*Correspondence to: Xuanzi Qin, PhD, MSPH, Department of Health Policy, Vanderbilt University School of Medicine, 2525 West End Ave, Ste 1250, Nashville, TN 37203, USA (e-mail: qinxx118@umn.edu).

Abstract

Background: Adherence to aromatase inhibitors (AIs) and tamoxifen has considerable survival benefits for postmenopausal women diagnosed with hormone receptor–positive breast cancer. Reduced out-of-pocket costs and treatment-related side effects could increase therapy adherence. Given that individuals' side effect profiles could differ across AIs, generic AI entry could facilitate switching between AIs to manage side effects and improve adherence. **Methods:** From Surveillance, Epidemiology, and End Results–Medicare, we selected women first diagnosed with hormone receptor–positive breast cancer at age 65+ years and initiated an AI within 1 year of diagnosis between January 1, 2007, and May 31, 2008, or June 1, 2011, and December 31, 2012, and followed them for up to 2 years (N = 20 677). We estimated changes in probabilities of adherence with and without switching for Part D enrollees with and without the low-income subsidy (LIS vs non-LIS) before and after generic entry using linear probability models. Tests of statistical significance are 2-sided. **Results:** After generic entry reduced out-of-pocket costs of AIs (larger reduction for non-LIS), the percentage of women who ever switched from one AI to another AI increased from 8.8% to 14.6% for non-LIS and from 7.3% to 12.5% for LIS. Adherence without switching increased by 8.0 percentage points (pp) for non-LIS ($P < .001$) but decreased by 4.9 pp ($P < .001$) for LIS. Adherence with switching increased for both non-LIS (6.4 pp, $P < .001$) and LIS (4.4 pp, $P < .001$). **Conclusions:** Increased switching after generic entry contributed to increased adherence, suggesting switching allowed better management of treatment-related side effects. Subsidized women also experienced increased adherence with switching after generic entry, suggesting that patients and physicians might not understand Part D benefit design when making decisions.

ARTICLE

Aromatase inhibitors (AIs) and tamoxifen are hormonal therapy drugs that improve disease-free and recurrence-free survival for postmenopausal women diagnosed with hormone receptor (HR)–positive breast cancer (1,2). Although AIs are more effective and better tolerated than tamoxifen (3–5), certain side effects of AIs, such as arthralgia or musculoskeletal symptoms, may lead to poor adherence and early discontinuation of therapy (6). Although the AI drugs, anastrozole, exemestane, and letrozole, have similar side effect profiles, some patients experience side effects with one AI but not another (7). Uncontrolled side effects are a major reason for nonadherence and early discontinuation (8,9), and switching among therapy drugs is an essential strategy for maintaining therapy while managing treatment-related side effects (4,5,10,11).

Three small studies found evidence that discontinuation of AIs could be prevented if women who experienced side effects with their initial AI switched to a different AI (12–14). However, in US clinical settings, drug costs may prevent women from trying another drug before skipping prescriptions or discontinuing therapy. It is not known whether reduced out-of-pocket (OOP) costs could promote switching and improve adherence.

To date, no population-based studies have examined how the interplay of reduced OOP costs for AIs and therapeutic switching promotes adherence to hormonal therapy. Before the introduction of generic AIs, OOP costs of AIs were increasing (15) and adherence to AIs was decreasing (16). The introduction of generic AIs in 2010 and 2011 lowered OOP costs of AIs for all older women enrolled in Medicare Part D (15) and was

Received: October 28, 2021; **Revised:** January 26, 2022; **Accepted:** March 17, 2022

accompanied by improved adherence to hormonal therapy (16–18). Two possible mechanisms underly the improved adherence after generic entry. First, with lowered copayments, more women could afford to refill their AI prescriptions. Second, due to lowered costs of hormonal therapy or perceptions of lowered costs (19), women might have been willing to try a different drug (switching) before discontinuing the therapy or skipping prescriptions.

We explore the role of OOP costs and drug switches on adherence by taking advantage of the natural experiment provided by generic entry of AIs (June 2010 for anastrozole, April 2011 for exemestane, and June 2011 for letrozole). We compare the experience of women with Medicare Part D low-income subsidy (LIS) with women without LIS (non-LIS) before and after generic AI entry. Eligible low-income beneficiaries who receive LIS have reduced premiums, deductibles, or copayments for their prescription benefits. Thus, the LIS group consistently had minimal OOP costs for all hormonal therapy drugs both before and after generic entry, whereas non-LIS had relatively high copayments before generic entry and considerably lower OOP costs after generic entry (16,19). Differential changes in drug switches and adherence after generic entry between LIS and non-LIS would be entirely due to the differences in cost reduction resulting from generic entry. Although drug switches are mostly due to treatment-related adverse events (12,13,20), the probability of women experiencing adverse events would not be affected by generic entry. Thus, we interpret changed switching rates after generic entry as a sign that generic entry has led to changes in the management of side effects.

We hypothesize that after generic entry the larger reduction in OOP costs for non-LIS women will result in larger increases in adherence both with and without drug switches (switching as an intermediary outcome was integrated to adherence) compared with LIS women. We interpret observed increases in adherence with drug switches as evidence that switching can increase adherence by improved management of side effects and that reduced OOP costs can promote this strategy. Comparisons between LIS and non-LIS may exhibit different patterns for adherence with drug switches vs adherence without drug switches, which could provide insights into different roles OOP costs played in decisions to refill the same drug vs switch to a different drug.

ARTICLE

Methods

Data Source and Study Sample

The Surveillance, Epidemiology, and End Results–Medicare database is population based and comprises 26% of the US population (21). We selected women who were first diagnosed with HR-positive breast cancer at age 65 years or older and initiated any of the 3 AIs within 1 year of their diagnosis between January 1, 2007, and May 31, 2008 (pregeneric entry period) or between June 1, 2011, and December 31, 2012 (postgeneric entry period). We followed those women until the end of 2 years after initiation, therapy discontinuation, death or loss of Medicare Part D coverage, whichever came the first (n = 6560 preperiod and n = 14 117 postperiod). We focused on the first and second years after initiation to avoid overinterpretation of switching because of guideline recommendations (1,2). All women's follow-up period did not fall between June 1, 2010, and May 20, 2011, where not all AIs had generic versions and women could switch based on costs. We included women who were enrolled in Medicare with a Part D prescription drug plan (PDP) or a Medicare Advantage plan that provided drug coverage (MAPD).

Study Variables

Outcome Variables

We used a common definition of adherence as the ratio of the total number of days of drug supply and the number of days of follow-up before discontinuation was greater than 80% (medication possession ratio >80%), a commonly used definition in the literature (8,9). We considered a woman as having discontinued the therapy when the difference between the total number of days of drug supply and the number of days of follow-up became greater than 180 days. Those who were nonadherent were those whose prescriptions only covered less than 80% of days of the follow-up period. We defined a drug switch as 2 contiguous prescriptions filled for different hormonal therapy drugs. All women in our study started with AIs and could switch to tamoxifen, among AIs, and from tamoxifen back to an AI. We did not differentiate generic vs brand-name use because brand-name use quickly decreased to very low levels after generic entry, and no evidence suggests clinical benefits of generic AIs and brand-name AIs differ.

We also categorized outcomes by the combination of switching and adherence to confirm that intermediary outcomes are not misinterpreted and created four binary outcome variables: 1) adherent to the therapy without drug switches, 2) adherent with drug switches, 3) nonadherent with drug switches, and 4) nonadherent without drug switches.

Independent Variables

Our key explanatory variable was an interaction term between the binary indicator for the postgeneric entry period and a binary variable indicating whether a woman received LIS for all the follow-up months. Our models controlled for demographic variables, including age at diagnosis, race or ethnicity, marital status, and urban or rural location. We adjusted for clinical factors, including HR status, grade, tumor size, lymph node, stage, surgery, and radiation. We controlled for whether women were enrolled in a PDP or an MAPD. Finally, we adjusted for cancer registry fixed effects to further account for time-invariant, geographic variation.

Statistical Analyses

We computed descriptive statistics for demographic characteristics, clinical factors, and Part D plan enrollment for those who initiated AIs before and after generic entry by their LIS status to confirm whether their characteristics changed considerably after generic entry.

To illustrate how patterns of drug switching changed after generic entry, we calculated the percentage of women with any switches by types of switching before and after generic entry by LIS status. We assessed the statistical significance of changes in the percentage of women switching after generic entry using 2-tailed z-tests.

We used a difference-in-differences approach and linear probability models (LPMs) to estimate the differential changes in probabilities of adherence after generic entry between non-LIS

and LIS. We used LPMs for the straightforward interpretation of results. We ran separate LPMs for each binary adherence outcomes, adjusting for demographics, clinical characteristics, and PDP vs MAPD. We computed predicted probabilities for the 4 binary outcomes by generic entry and LIS status. Difference-in-differences models assume that the "comparison group" (LIS women) displays the change in outcomes that the treated group would have exhibited in the absence of the policy (ie, parallel trends assumption). Thus, differences in changes of adherence after generic entry between the 2 groups are likely due to reduced costs (difference in cost reductions between the 2 groups). We confirmed that adherence trends were approximately parallel for LIS and non-LIS before generic entry (Supplementary Methods, available online).

We conducted several sensitivity analyses. First, we estimated predicted probabilities using multinomial logistic regressions (Supplementary Table 1, available online). Second, we used seemingly unrelated regressions to account for the correlation between categories of adherence. Third, we restricted our analysis to women in fee-for-service Medicare and controlled for Charlson comorbidity score. None of the sensitivity analyses altered our results or interpretation.

Results

We identified 20 677 women diagnosed with HR-positive breast cancer and initiated hormonal therapy with AIs within 1 year of their diagnosis. When AIs were all brand name (before June 2010), 6560 women initiated AIs and 24.1% received LIS for all follow-up months. When all AIs had generic versions available (after May 2011), 14 117 women initiated AIs, of whom 22.4% received LIS for all follow-up months (Table 1).

Non-LIS women were relatively younger and were more likely to be White, married, and residing in a large metropolitan area relative to the LIS group. They were also more likely to have less advanced cancers and to receive surgery and radiation than the LIS group. Finally, the non-LIS group had a higher proportion of women enrolled in MAPD plans than the LIS group.

For both non-LIS and LIS groups, we observed demographic changes between the pre- and post periods. Compared with those who initiated AIs before generic entry, those who initiated after generic entry were relatively younger, and those in the non-LIS group were more likely to be Black and enrolled in an MAPD. Clinical characteristics were similar before and after generic entry.

Table 2 summarizes the number and percent of women with different types of drug switches by generic entry and LIS status. Overall, 5.3% of women switched more than once. The most common switch for non-LIS women before generic AI entry was from AI to tamoxifen (tamoxifen already had generic versions), whereas the LIS group most commonly switched from one AI to another AI. After generic entry, the proportion of non-LIS women switching from AIs to tamoxifen decreased by 2.8 percentage points (pp) ($P < .001$). Switches from one AI to another AI increased substantially and became the most frequent type of switches for both groups. The proportion of non-LIS women who switched from one AI to another AI or from tamoxifen to AIs increased by 5.7 pp after generic entry ($P < .001$), and such increase was slightly smaller for the LIS group (5.3 pp, $P < .001$).

Median OOP costs for a 30-day supply of AIs for the non-LIS group were $42 before generic entry and $10 after generic entry. In contrast, the median OOP costs for the LIS group were $3.10 before generic entry and $1.15 after generic entry. The median OOP cost of a 30-day supply of tamoxifen did not change with generic entry and was approximately $9 for the non-LIS and $1 for the LIS groups in both periods. Differences in OOP costs between PDP and MAPD were minimal.

Table 3 shows the predicted probabilities of adherence with and without drug switches for non-LIS and LIS groups before and after generic entry, predicted changes after generic entry for the 2 groups, and predicted differential changes between the 2 groups (full results in Supplementary Table 2, available online). After generic entry, overall adherence increased for non-LIS but slightly decreased for LIS. Specifically, we observed a 6.4-pp (95% confidence interval [CI] = 5.5 to 7.4 pp) increase in the probability of being adherent with drug switches and an 8.0-pp (95% CI = 6.5 to 9.5 pp) increase in the probability of being adherent without drug switches among the non-LIS group. In contrast, the LIS group had a 4.4-pp (95% CI = 2.7 to 6.0 pp) increase in the probability of being adherent with drug switches but a 4.9-pp (95% CI = 2.4 to 7.3 pp) decrease in the probability of being adherent without drug switches after generic entry relative to before generic entry. Compared with the LIS group, the non-LIS group had a 12.8-pp (95% CI = 9.9 to 15.7 pp) larger increase in the probability of being adherent without switches and a 2.1-pp (95% CI = 0.2 to 4.0 pp) larger increase in the probability of being adherent with switches after generic entry.

Discussion

This study used the unique combination of generic entry of AIs and Medicare Part D subsidies for lower-income women to explore the role of OOP costs and therapeutic drug switching in medication adherence. Consistent with previous studies (16,17), we found overall adherence to hormonal therapy increased by 14.4 pp among non-LIS women after generic entry. We interpret switching as a proxy for management of therapy-related adverse events because clinical characteristics were stable before and after generic entry, making a woman's chance of experiencing therapy-related side effects unlikely to change after generic entry. Thus, the observed increases in switching after generic entry can likely be attributed to cost reductions after generic entry and suggest improved management of side effects. The increased switching likely resulted in increased adherence with drug switches after generic entry, which provides population-level evidence on the effects of drug switching on improving adherence.

Comparisons between LIS and non-LIS groups provide insights into the potentially different roles OOP costs may play in decisions to refill the same drug vs switch to a different drug. We found changes in outcomes for LIS women were not entirely consistent with changes in their OOP costs after generic entry. The LIS had minimal OOP costs for AIs before generic entry (median: $3.10 for a 30-day supply), which was reduced to $1.15 after generic entry. As demonstrated in a prior study and our data (16), adherence had been decreasing before generic entry. Unsurprisingly, LIS women's adherence without drug switches continued to decrease after generic entry, suggesting refilling the same drug was mostly unaffected by the minimal reduction ($1.95) in OOP costs due to generic entry. However, the LIS experienced increases in adherence with drug switches similar to non-LIS women who had a more than $30/mo reduction in their

Table 1. Characteristics of older women who initiated hormonal therapy with aromatase inhibitors before and after generic entry by Medicare Part D LIS status

Variables	Non-LIS[a]		LIS[a]	
	Pregeneric entry period (n = 4978)	Postgeneric entry period (n = 10 951)	Pregeneric entry period (n = 1582)	Postgeneric entry period (n = 3166)
Mean age at diagnosis, y	74.8	74.0	75.8	74.7
Age at diagnosis 85+ y	10.0	8.8	13.7	11.1
Race and ethnicity, %				
Asian	2.4	2.2	7.3	8.9
Black	4.8	5.7	19.5	19.0
Hispanic	0.8	0.7	6.4	6.6
Other	2.5	3.2	3.2	4.1
White	89.5	88.2	63.6	61.4
Married, %	47.8	48.7	20.7	21.5
Location, %				
Large metro	64.5	63.6	59.2	59.0
Urban	34.2	35.2	38.6	39.1
Rural	1.3	1.3	2.3	1.8
HR status, %				
ER−/PR+	0.6	0.5	1.0	0.6
ER+/PR−	18.0	15.0	16.4	13.7
ER+/PR+	81.4	84.5	82.6	85.7
Stage, %				
0	2.8	3.3	2.8	3.6
I	51.9	52.8	39.2	42.5
II	29.5	29.9	33.6	33.3
III	7.7	7.5	11.8	11.2
IV	4.0	3.9	7.5	5.3
Unknown	4.1	2.5	5.1	4.2
Tumor grade, %				
Low	74.7	76.4	69.0	71.5
High	18.3	18.2	21.9	21.9
Unknown	7.0	5.4	9.1	6.6
Tumor size, %				
0 to <1 cm	21.8	22.9	14.0	18.9
1-2 cm	43.8	42.5	39.5	36.0
>2 cm	30.4	31.6	40.8	40.7
Unknown	4.0	3.0	5.7	4.5
Lymph node involvement, %				
Negative	61.5	62.5	48.3	51.0
Positive	22.9	22.2	27.4	26.5
Not examined	15.6	15.3	24.3	22.5
Radiation, %	47.5	50.5	36.3	38.2
Surgery, %				
Lumpectomy	57.0	60.2	44.2	47.4
Mastectomy	36.2	31.8	42.8	39.0
No, other, unknown	6.9	8.0	13.0	13.6
Part D coverage, %				
PDP[a]	52.6	51.1	78.0	67.4
MAPD[a]	44.1	45.8	16.1	24.4
Mixed[a]	3.3	3.1	5.9	8.1

[a]ER = estrogen receptor; HR = hormone receptor; LIS = women who received the low-income subsidy for all follow-up months; MAPD = Medicare Advantage plan that offers prescription drug coverage; mixed = women had mixed months of PDP and MAPD during the follow-up period; non-LIS = women who did not receive Medicare Part D low-income subsidy for all follow-up months; PDP = stand-alone Medicare Part D prescription drug plan; PR = progesterone receptor.

OOP costs for AIs, which is inconsistent with their minimal cost change. Such inconsistency could be explained in several ways. First, LIS women might have had false expectations about the OOP costs of a drug they had not previously used. Second, LIS women might be sensitive to small cost changes because of their lower income. Third, physicians and pharmacists might respond to the availability of generic AIs and thus promoted switching among both groups. Likely, elements of all 3

Table 2. Patterns of drug switching among older women who initiated hormonal therapy with aromatase inhibitors

Drug-switching measures	Non-LIS[a]				LIS[a]			
	Pregeneric entry period (n = 4978) No. (%)	Postgeneric entry period (n = 10 951) No. (%)	Difference, percentage point	P[b]	Pregeneric entry period (n = 1582) No. (%)	Postgeneric entry period (n = 3166) No. (%)	Difference, percentage point	P[b]
Any switches	888 (17.8)	2184 (19.9)	2.1	.002	198 (12.5)	542 (17.1)	4.6	<.001
Any switches within 1 y	630 (12.7)	1637 (14.9)	2.3	.007	144 (9.1)	399 (12.6)	3.5	<.001
Any switches from TAX to AI[a]	58 (1.2)	151 (1.4)	0.2	.53	18 (1.1)	47 (1.5)	0.3	.33
Any switches from AI to TAX	526 (10.6)	851 (7.8)	−2.8	<.001	93 (5.9)	196 (6.2)	0.3	.67
Any switches from AI to another AI	437 (8.8)	1596 (14.6)	5.8	<.001	116 (7.3)	396 (12.5)	5.2	<.001
Any switches from AI to another AI or from TAX to AI[c]	488 (9.8)	1698 (15.5)	5.7	<.001	132 (8.3)	432 (13.6)	5.3	<.001

[a]Given that all women started with AIs, women who had switches from tamoxifen to AIs must first have switches from an AI to tamoxifen. AI = aromatase inhibitor; LIS = women who received low-income subsidy for all follow-up months; non-LIS = women who did not receive Medicare Part D low-income subsidy for all follow-up months; TAX = tamoxifen.
[b]Two-sided z test.
[c]One woman could have both types of switches (from AI to another AI and from TAX to AI), and thus percentages do not add up.

explanations apply, but the first may be the main driver. Due to the complexity of Part D plan design, including different cost-sharing across benefit phases, it is unlikely that any women would know their exact OOP costs or the cost reduction because of generic entry before ever using a drug, and generic entry might create perceptions of large cost reduction for LIS and non-LIS groups. The increase in initiation of hormonal therapy after generic AI entry among LIS women (19) supports this explanation. Also, studies have shown that Medicare Part D enrollees had limited knowledge about their drug coverage, especially those receiving LIS (22,23). LIS women might overestimate their cost-sharing liability for different AIs, and generic entry might create perceptions of cost reduction and address their concerns about facing an increase in OOP costs after switching.

To the best of our knowledge, this is the first population-based analysis to provide evidence that reducing OOP costs could increase drug switching, which could improve adherence when patients can switch to therapies that they experience fewer side effects. The probability of women being adherent to therapy with drug switches increased by more than 4 pp after generic entry regardless of their subsidy status. Given that the probability of experiencing treatment-related side effects is unlikely to change due to generic entry, the increased switching from one AI to another AI and/or from tamoxifen to AIs after generic entry suggests the management of side effects was improved with more generic options. Population-based studies often found switching was associated with increased nonadherence and early discontinuation of hormonal therapy by including switching (an intermediary outcome) as an independent variable (8,9). By integrating switching into our adherence outcomes, we demonstrated the benefits of switching while recognizing that they are still a sign of an adverse event.

Although our study has considerable strengths, some limitations must be acknowledged. First, we were unable to determine the specific mechanisms underlying increased switching among the LIS group with minimal cost-sharing. Second, due to the limitations of claims data, we were unable to determine the exact reasons for nonadherence and differentiate those who permanently discontinued vs those who temporarily stopped refilling their prescriptions. Third, some switches we captured were likely due to cost reasons. However, such switches only involve exemestane users and represent a very small proportion of all switches. We also excluded all follow-up in the time period where AIs were transitioning to generic versions and OOP costs were more variable. After generic entry, all hormonal therapy drugs had similar OOP costs except for exemestane, whose use was very low (19). Fourth, we could not examine factors other than drug costs, such as physicians' prescribing behaviors, patient–physician communications, or pharmacists' behaviors that might be correlated with generic entry and affect switching and adherence. Generic entry might trigger more communication between physicians and patients, and treatment adherence greatly depends on physician–patient communications (24,25). In some states, pharmacists are allowed to switch patients to a different drug, or they could request a new prescription from the prescriber (26). However, such practices should apply equally to LIS and non-LIS women. Despite these limitations, our study demonstrates important patterns that raise crucial questions about the role of cost-sharing and drug-switching behaviors for managing drug adherence and preventing discontinuation.

Before generic entry, 30.5% of postmenopausal women diagnosed with HR-positive breast cancer never started hormonal therapy, which decreased to 25.7% after generic entry (19). Our study demonstrated that generic entry substantially reduced OOP costs for non-LIS women, and overall adherence increased by 14.4 pp, with a 6.4-pp increase from adherence with drug switches and a 8.0-pp increase from adherence without drug switches. With generic entry, women appear to be more willing to try another therapy drug when experiencing side effects before they skip prescriptions or discontinue therapy. Such patterns are also observed for LIS women whose OOP costs declined only slightly after generic entry. Future research should investigate whether reducing OOP costs or improving understanding of costs should be promoted as a strategy for increasing adherence to beneficial therapies.

Table 3. Predicted probabilities of adherence with and without drug switches

	Non-LIS[a] (large cost reduction after generic entry)			LIS[a] (minimal cost-reduction after generic entry)			Group difference due to cost reduction	
Binary outcomes[b]	Pregeneric entry period (n = 4978) Predicted probability (95% CI[c])	Postgeneric entry period (n = 10 951) Predicted probability (95% CI)	Changes after Generic entry Predicted probability (95% CI)	Pregeneric entry period (n = 1582) Predicted probability (95% CI)	Postgeneric entry period (n = 3,166) Predicted probability (95% CI)	Changes after Generic entry Predicted probability (95% CI)	Group differential changes after generic entry[c] Probability (95% CI)	*P*
Adherent without switches	0.693 (0.656 to 0.730)	0.773 (0.737 to 0.808)	0.080 (0.065 to 0.095)	0.814 (0.775 to 0.853)	0.766 (0.729 to 0.803)	−0.049 (−0.073 to −0.024)	0.128 (0.099 to 0.157)	<.001
Adherent with switches	0.058 (0.032 to 0.083)	0.122 (0.097 to 0.147)	0.064 (0.055 to 0.074)	0.060 (0.034 to 0.087)	0.104 (0.078 to 0.130)	0.044 (0.027 to 0.060)	0.021 (0.002 to 0.040)	.03
Nonadherent[d] with switches	0.024 (0.010 to 0.038)	0.015 (0.002 to 0.028)	−0.009 (−0.014 to −0.004)	0.009 (−0.006 to 0.023)	0.017 (0.003 to 0.031)	0.009 (0.001 to 0.017)	−0.018 (−0.027 to −0.008)	<.001
Nonadherent without switches	0.225 (0.197 to 0.254)	0.090 (0.064 to 0.117)	−0.135 (−0.147 to −0.123)	0.117 (0.087 to 0.146)	0.113 (0.086 to 0.140)	−0.004 (−0.023 to 0.016)	−0.131 (−0.154 to −0.108)	<.001

[a]CI = confidence interval; LIS = women who received low-income subsidy for all follow-up months; non-LIS = women who did not receive Medicare Part D low-income subsidy for all follow-up months.

[b]No comparison was made across rows (different linear probability models and binary outcomes). Switching was integrated into adherence outcomes and not included as a right-hand side variable in regressions. If switching is included as a right-hand side variable, switching would be negatively associated with adherence, considering women switch mostly due to side effects and side effects reduce adherence. However, switching is an intermediary outcome that is likely a result of side effects but also could be a beneficial strategy that help managing side effects and thus improve adherence. Increased switching and increased adherence with drug switches together would demonstrate the benefits of switching.

[c]Comparisons between LIS and non-LIS (difference-in-differences [DID]) were for illustrating the potential different ways that costs could affect decisions to refill the same drug (adherence without switches) vs switch to a different drug (adherence with switches), and thus provide insights into designing interventions to improve adherence. Non-statistically significant DID estimator implies changes after generic entry could be attributed to factors other actual cost reduction.

[d]Adherence was defined as medication possession ratio (MPR) larger than 80%, and thus those with MPR smaller than 80% were nonadherent.

Funding

The authors did not receive funding for this study.

Notes

Role of the funder: Not applicable.

Disclosures: None exist.

Author contributions: XQ: Conceptualization, Methodology, Software, Formal analysis, Visualization, Writing—original draft, Writing—review and editing. PH: Methodology, Writing—review and editing, Supervision. JA: Methodology, Writing—review and editing. DY: Methodology, Writing—review and editing. BAV: Methodology, Writing—review and editing, Supervision.

Data Availability

We cannot share the original individual level data per our Data Use Agreement for using the Surveillance, Epidemiology and End Results (SEER)-Medicare 2016 linkage for this study. Researchers could apply for the access to the SEER-Medicare linked database.

References

1. Burstein HJ, Griggs JJ, Prestrud AA, Temin S. American Society of Clinical Oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer. *J Oncol Pract*. 2010; 6(5):243–246. doi:10.1200/JOP.000082.
2. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol*. 2014; 32(21):2255–2269. doi:10.1200/J Clin Oncol.2013.54.2258.
3. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol*. 2006;7(8):633–643. doi:10.1016/S1470-2045(06)70767-7.
4. Amir E, Seruga B, Niraula S, Carlsson L, Ocaña A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2011;103(17):1299–1309.
5. Roberts K, Rickett K, Greer R, Woodward N. Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early breast cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2017;111: 66–80. doi:10.1016/j.critrevonc.2017.01.010.
6. Dent SF, Gaspo R, Kissner M, Pritchard KI. Aromatase inhibitor therapy: toxicities and management strategies in the treatment of postmenopausal women with hormone-sensitive early breast cancer. *Breast Cancer Res Treat*. 2011;126(2):295–310. doi:10.1007/s10549-011-1351-3.
7. De Placido S, Gallo C, De Laurentiis M, et al. Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial. *Lancet Oncol*. 2018;19(4):474–485.
8. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Res Treat*. 2012;134(2): 459–478. doi:10.1007/s10549-012-2114-5.
9. Moon Z, Moss-Morris R, Hunter MS, Carlisle S, Hughes LD. Barriers and facilitators of adjuvant hormone therapy adherence and persistence in women with breast cancer: a systematic review. *Patient Prefer Adherence*. 2017;11:305–322.
10. Cella D, Fallowfield LJ. Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. *Breast Cancer Res Treat*. 2008;107(2):167–180. doi:10.1007/s10549-007-9548-1.
11. Nahm N, Mee S, Marx G. Efficacy of management strategies for aromatase inhibitor-induced arthralgia in breast cancer patients: a systematic review. *Asia Pac J Clin Oncol*. 2018;14(6):374–382.
12. Briot K, Tubiana-Hulin M, Bastit L, Kloos I, Roux C. Effect of a switch of aromatase inhibitors on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer: the ATOLL (articular tolerance of letrozole) study. *Breast Cancer Res Treat*. 2010;120(1):127–134.
13. Güth U, Myrick ME, Schötzau A, Kilic N, Schmid SM. Drug switch because of treatment-related adverse side effects in endocrine adjuvant breast cancer therapy: how often and how often does it work? *Breast Cancer Res Treat*. 2011; 129(3):799–807. doi:10.1007/s10549-011-1668-y.
14. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *J Clin Oncol*. 2012;30(9):936–942. doi:10.1200/J Clin Oncol.2011.38.0261.
15. Nattinger AB, Pezzin LE, McGinley EL, Charlson JA, Yen TW, Neuner JM. Patient costs of breast cancer endocrine therapy agents under Medicare Part D vs with generic formulations. *SpringerPlus*. 2015;4(1):54.
16. Neuner JM, Kamaraju S, Charlson JA, et al. The introduction of generic aromatase inhibitors and treatment adherence among Medicare D enrollees. *J Natl Cancer Inst*. 2015;107(8):djv130. doi:10.1093/jnci/djv130.
17. Hershman DL, Tsui J, Meyer J, et al. The change from brand-name to generic aromatase inhibitors and hormone therapy adherence for early-stage breast cancer. *J Natl Cancer Inst*. 2014;106(11):dju319. doi:10.1093/jnci/dju319.
18. Winn AN, Fergestrom NM, Pezzin LE, Laud PW, Neuner JM. The impact of generic aromatase inhibitors on initiation, adherence, and persistence among women with breast cancer: applying multi-state models to understand the dynamics of adherence. *Pharmacoepidemiol Drug Saf*. 2020;29(5):550–557.
19. Qin X, Huckfeldt P, Abraham J, Yee D, Virnig BA. Generic entry of aromatase inhibitors and pharmaceutical access: initiation of hormonal therapy, timeliness of initiation, and drug choice. *Res Soc Administr Pharm*. 2021;17(9): 1588–1595.
20. Kwan ML, Roh JM, Laurent CA, et al. Patterns and reasons for switching classes of hormonal therapy among women with early-stage breast cancer. *Cancer Causes Control*. 2017;28(6):557–562.
21. Engels EA, Pfeiffer RM, Ricker W, Wheeler W, Parsons R, Warren JL. Use of Surveillance, Epidemiology, and End Results-Medicare data to conduct case-control studies of cancer among the US elderly. *Am J Epidemiol*. 2011;174(7): 860–870. doi:10.1093/aje/kwr146.
22. Rudolph NV, Montgomery MA. Low-income Medicare beneficiaries and their experiences with the part D prescription drug benefit. *Inquiry*. 2010;47(2): 162–172.
23. Woelfel JA, Patel RA, Lee H, et al. An overview and study of beneficiaries' knowledge, attitudes, and perceptions of the Medicare part D benefit. *Consult Pharm*. 2015;30(2):101–111.
24. Zolnierek KBH, DiMatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care*. 2009;47(8):826–834.
25. Thompson L, McCabe R. The effect of clinician-patient alliance and communication on treatment adherence in mental health care: a systematic review. *BMC Psychiatry*. 2012;12(1):87.
26. Vanderholm T, Klepser D, Adams AJ. State approaches to therapeutic interchange in community pharmacy settings: legislative and regulatory authority. *J Manag Care Spec Pharm*. 2018;24(12):1260–1263. doi:10.18553/jmcp.2018.24.12.1260.