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The Use and Concurrent Use of Side Effect Controlling Medications Among Women on Aromatase Inhibitors

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Abstract

Background: Women on aromatase inhibitors (AIs) as part of their breast cancer treatment often experience difficult to control side effects. Although there are several medications to manage the side effects of AI therapy, many of them are associated with their own risk, particularly sedation. The objective of this study was to describe the prescribing practices for side effect managing (SE) medications among women with breast cancer on AI therapy and to assess for combinations of medications that may present a clinical risk to patients.
Methods: Retrospective data analysis using Surveillance, Epidemiology and End Results (SEER)-Medicare data of all women aged 66–90 years with stage I–III hormone positive breast cancer diagnosed between 2008 and 2014 who initiated AI therapy within 12 months of their diagnosis. We determined the percentage of patients prescribed an SE medication in the 12 months prior and in the 24 months after the initiation of AI therapy. We calculated the number of prescriptions and the number of days of overlapping (*i.e.*, >1 SE) prescriptions, and examined predictors of overlapping prescriptions.
Results: The use of SE medications was pervasive and increased after initiation of AI therapy. The most commonly prescribed medications were opiates (55.1%), selective serotonin reuptake inhibitors (22.6%), benzodiazepines (18.4%), tramadol (17.7%) and gabapentin (14.6%). In total 15.5% of patients had overlapping prescriptions; among those, 36.2% had three overlapping prescriptions. Prior use was the strongest predictor of overlapping prescriptions with an odds ratio of 7.9 (95% confidence interval: 7.17–8.77).
Conclusion: Among women on AI therapy, the use of SE medications is common and many have overlapping prescriptions raising concern for potential harm from polypharmacy.

Keywords: breast cancer, aromatase inhibitors, side effects, polypharmacy

Background

Breast cancer remains the most common malignancy in women with the American Cancer Society (ACS) estimating that in 2020 there will be 279,100 new diagnoses and 42,690 deaths.[1] More than 80% of breast cancer patients have hormone (*i.e.*, estrogen or progesterone receptor) positive cancer.[2] Increasingly postmenopausal women with hormone positive breast cancer are being placed on aromatase inhibitors (AIs) after initial treatment for up to 10 years to prevent distance recurrence and secondary occurrences of breast cancer.[3] Unfortunately, these medications are associated with several difficult to manage side effects, including vasomotor symptoms, vaginal dryness, and arthralgias. To improve adherence to AI therapy, several medications to manage the side effects, including gabapentin, selective serotonin reuptake inhibitors (SSRIs), serotonin norephedrine reuptake inhibitors (SNRIs), and clonidine have been studied. Several are now recommended by the ACS and American Society of Clinical Oncology (ASCO)[4] and National Comprehensive Cancer Network (NCCN),[5,6] yet little is known about how these medications are being used in clinical practice.

Although there are high-quality data to support the use of these medications,[7–10] there is an increasing body of literature raising concern about the harms of these medications.[11–14]

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Many are sedating, which could present a clinical risk for complications ranging from motor vehicle crashes to falls, particularly when used in combination with other frequently prescribed medications such as opiate therapy, tramadol, and anxiolytic medications. In addition, given the deleterious effects of AI therapy on bone mineral density, medications that increase the risk of falls and subsequent fractures in women on AI therapy[15,16] should be particularly concerning.

The objective of this study was to describe the patterns of medication use among breast cancer patients taking AIs. We earlier reported that 13% of women in a similar cohort had concurrent prescriptions for opioids and benzodiazepines,[17] but there has been little information on other medications and combinations of medications used in the adjuvant cancer setting.

Methods

Population

Using the population-based Surveillance, Epidemiology and End Results (SEER) Medicare-linked data, we identified all women aged 66–90 years with stage I–III hormone positive breast cancer diagnosis between January 1, 2008 and December 31, 2014. To be included in the cohort they were required to be enrolled in Medicare parts A, B, and D for the 12 months before diagnosis, to initiate AI therapy within 12 months of their diagnosis, and have Medicare part D coverage for 24 months after the initiation of AI therapy to allow us to track any new prescriptions of SE medications.

Outcomes

To describe the prescribing practices for SE medications we compiled a list of these medications using the guidelines from ACS/ASCO,[4] NCCN,[5,6] and the North American Menopause Society[18] for the treatment of menopausal symptoms, including SSRIs, SNRIs, gabapentin, pregabalin, tricyclic antidepressants (TCAs), clonidine, and added commonly prescribed medications for pain, including opiates, tramadol, and benzodiazepines. Although opioids, tramadol, and benzodiazepines are not guideline recommended for the treatment of AI side effects, they are commonly prescribed medications and potentially represent a clinical risk when used in combination with other guideline-recommended but sedating medications. We then generated a supply diary, which recorded whether a person had prescription drug supply available for each day using the prescription dispensing date and the days of supply from the prescription drug event file. If a person had any overlapping supply (*i.e.*, one or more days with supply) of two or more medications of interest, we created separate supply diaries for each drug.

We determined the percentage of patients prescribed these medications in the 12 months before initiation of AI therapy and in the 24 months after the initiation of AI therapy. To assess whether these medications were being used together, we calculated the number of overlapping prescriptions and the number of days of overlapping prescriptions. Although SSRIs and SNRIs are commonly prescribed for controlling the side effects of AI therapy, they are not associated with the same sedating properties as the other medications. We, therefore, excluded these medications when considering overlap, as we considered combinations with SSRIs/SNRIs to have much lower potential for harm.[19] In our primary analysis, we accounted for the possibility that physicians changed a patient's medications while they still had some medication supply by coding the presence of overlapping only if there was a minimum of 31 days of overlap between different drugs. Finally, we collected information on factors other than oral oncological medication use that could potentially be associated with use of overlapping prescriptions, focusing on prior use of any of the medications, age, race, comorbidity using the National Cancer Institute (NCI) algorithm.[20]

Analysis

We calculated the prevalence of SE-medication use, overall and by timing of use (*i.e.*, before or after AI initiation) by medication classes as well as overall medications. We performed all analyses on the cohort overall, as well as stratified by prior use, as patients who are not naive to treatments may have higher baseline risk of co-prescribing. Summary statistics for those with and without prior use were contrasted using standard *t*- and chi-squared tests. Finally, we used a multivariable logistic regression to examine factors associated with overlapping use. The Medical College of Wisconsin IRB deemed this study to not fit the criteria for human subjects' research.

Sensitivity analyses

Given the uncertainty about how best to measure clinically meaningful overlap, we conducted sensitivity analyses with variation in the definition of overlap. The minimum overlap of 1 day was chosen because even 1 day overlap of some medications, particularly if the overlap is with opioids and benzodiazepines, can result in clinical harm. The maximum overlap we considered was 91 days, to account for medications prescribed in 90-day increments (Appendix Table A1).

Results

We identified a total of 18,520 women in our cohort, of whom 7,436 (40.2%) had at least one prescription for one of the medications of interest in the 12 months before AI initiation (Table 1). The most commonly prescribed precancer medication classes were opioids (31.5%) followed by SSRIs (16.1%) and gabapentin (7.0%). Approximately half of the patients (49.3%) had no comorbidities.

Medication use in the 24 months after initiation of AI therapy, a total of 13,179 (71.2%) of the cohort filled a prescription for at least one SE medication. The most commonly prescribed medications for the total cohort included opiates (55.1%), SSRIs (22.6%), benzodiazepines (18.4%), tramadol (17.7%), and gabapentin (14.6%). Those with prior use of any medication had higher rates of prescriptions for all SE medications (p-value of <0.001 for all medications) (Table 2). Among those with prior use, 72.8% were prescribed an opiate, 29.8% were prescribed a SSRI, 28.8% were prescribed a benzodiazepine, 27.3% were prescribed tramadol, and 24.8% were prescribed gabapentin in the 24 months after initiation of AI therapy.

Medication overlap among women prescribed an SE medication, 15.5% of them had at least two prescriptions other than SSRIs/SNRIs that overlapped by 31 or more days. The median number of days of overlap was 155.0 (interquartile

Table 1. Demographics

	Total (n = *18,520*)	*No prior use* (n = *11,084*)	*Prior use* (n = *7,436*)	p
Age, *n* (%)				0.16
66–70	6,152 (33.2)	3,708 (33.5)	2,444 (32.9)	
71–75	5,304 (28.6)	3,154 (28.5)	2,150 (28.9)	
76–80	3,766 (20.3)	2,221 (20.0)	1,545 (20.8)	
81–85	2,308 (12.5)	1,425 (12.9)	883 (11.9)	
86–90	990 (5.4)	576 (5.2)	414 (5.6)	
Cancer stage, *n* (%)				0.789
I	10,747 (58.0)	6,438 (58.1)	4,309 (57.9)	
II	6,274 (33.9)	3,739 (33.7)	2,535 (34.1)	
III	1,499 (8.1)	907 (8.2)	592 (8.0)	
Race, *n* (%)				<0.001
White	16,208 (87.5)	9,715 (87.6)	6,493 (87.3)	
Black	1,257 (6.8)	611 (5.5)	646 (8.7)	
Other	975 (5.3)	705 (6.4)	270 (3.6)	
Unknown	80 (0.4)	53 (0.5)	27 (0.4)	
Comorbidity, *n* (%)				<0.001
0	9,128 (49.3)	6,208 (56.0)	2,920 (39.3)	
1	5,205 (28.1)	3,044 (27.5)	2,161 (29.1)	
2+	4,187 (22.6)	1,832 (16.5)	2,355 (31.7)	
Prior medications, *n* (%)				<0.001
SSRI	2,990 (16.1)	1,288 (11.6)	1,702 (22.9)	
SNRI	750 (4.1)	251 (2.3)	499 (6.7)	
Gabapentin	1,302 (7.0)	—	1,302 (17.5)	
Pregabalin	291 (1.6)	—	291 (3.9)	
Tricyclic	681 (3.7)	—	681 (9.2)	
Clonidine	468 (2.5)	—	468 (6.3)	
Tramadol	1,637 (8.8)	—	1,637 (22.0)	
Benzodiazepine	1,250 (6.8)	—	1,250 (16.8)	
Opiate	5,838 (31.5)	—	5,838 (78.5)	

SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

range: 68.0–360.0). Most of those with overlapping prescriptions (55.6%) had two overlapping prescriptions, but a third of patients (36.2%) had three overlapping prescriptions and 8.1% of patients had four or more overlapping prescriptions. Those with prior medication use were more likely to have overlapping prescriptions (31.3% vs. 4.9%, *p*-value <0.001). The most common medication class with any overlap with another class, again excluding SSRIs/SNRIs, was opioids (13.3% of all patients) followed by tramadol (7.6%), gabapentin (5.8%), and benzodiazepines (4.7%).

Multivariate results indicated that prior medication use, cancer stage, and number of comorbidities were positively and significantly associated with overlapping prescriptions (Table 3). The strongest predictor was prior use with an odds ratio of 7.93 (95% confidence interval: 7.17–8.77; $p < 0.01$). There was no association between a patient's age and receipt of overlapping prescriptions. Results of our sensitivity analysis showed that even when overlap was defined as ≥91 days, 10.2% of patients had overlapping prescriptions. Results of adjusted analyses were similar (Appendix Table A2).

Table 2. Percentage of Women with Breast Cancer Prescribed a Side Effect Controlling Medication in the 24 Months After Initiation of Aromatase Inhibitor Therapy

	Total (n = *18,520*)	*No prior use* (n = *11,084*)	*Prior use* (n = *7,436*)	p
Medications, *n* (%)				
SSRI	4,188 (22.6)	1,969 (17.8)	2,219 (29.8)	<0.001
SNRI	1,615 (8.7)	665 (6.0)	951 (12.8)	<0.001
Gabapentin	2,709 (14.6)	868 (7.8)	1,841 (24.8)	<0.001
Pregabalin	467 (2.5)	104 (0.9)	363 (4.9)	<0.001
Tricyclic	918 (5.0)	209 (1.9)	709 (9.5)	<0.001
Clonidine	746 (4.0)	201 (1.8)	545 (7.3)	<0.001
Tramadol	3,281 (17.7)	1,250 (11.3)	2,031 (27.3)	<0.001
Benzodiazepine	3,414 (18.4)	1,270 (11.5)	2,144 (28.8)	<0.001
Opiate	10,201 (55.1)	4,790 (43.2)	5,411 (72.8)	<0.001

Table 3. Adjusted Odds Ratio and 95% Confidence Intervals for Predicting any Overlapping Prescriptions

	OR (95% CI)
Prior use	
No	Reference
Yes	7.93 (7.17–8.77)
Age	
66–75	Reference
76–85	0.98 (0.89–1.08)
86–90	0.87 (0.71–1.05)
Cancer stage	
I	Reference
II	1.25 (1.14–1.37)
III	1.52 (1.30–1.77)
Race	
White	Reference
Black	1.08 (0.93–1.27)
Other	0.58 (0.46–0.74)
Unknown	1.24 (0.65–2.36)
Comorbidities	
0	References
1	1.51 (1.35–1.68)
2+	2.24 (2.01–2.49)

CI, confidence interval.

Discussion

In a large and geographic diverse cohort of female cancer survivors treated with AIs, we found high rates of prescriptions for SE-controlling medications as well as frequent overlapping of medications. Overlapping use was particularly evident among cancer survivors with prior use of such drugs where almost one-third of the population had overlapping prescriptions. The high rate of overlapping prescriptions raises concern about appropriate use and potential harm of these medications. To our knowledge, this is the first article to describe the use of these SE medications among breast cancer survivors on AI therapy.

AIs have only one recommended alternative in tamoxifen, which is less efficacious, causes many of the same side effects, and has a risk of venous thromboembolism not seen with AIs. Physicians, therefore, limited alternative adjuvant cancer treatments for most patients with AI side effects, so it is understandable that patients are sometimes put on combinations of medicines. Although the literature on risks associated with overlapping prescriptions of many of the medications used for AI symptoms is sparse, the few studies that do exist indicate an increased risk of harm when these medications are used together.[14,21,22] More than 3 out of 20 women in our cohort had overlapping prescriptions. We found that prior use of these medications was the strongest predictor of overlapping prescriptions. Although this is not surprising as these patients were on some of these medications before breast cancer diagnosis, it is an important reminder that prior prescriptions should be considered when initiating new medications to avoid potentially harmful combinations. We know from prior literature that providers often struggle to deprescribe medications that were initiated by other providers[23] or when multiple practitioners such as specialist and generalist are involved in care.[24] There may be opportunity for primary care providers and oncologist who are following these women to work together to eliminate unnecessary medications that may be resulting in more harm than good.

Our results revealed no association between the patient's age and overlapping medications, suggesting that elderly cancer patients are just as likely as their younger counterparts to have multiple overlapping prescriptions. This is concerning given that the risk of these medications is exacerbated in elderly patients. New data demonstrated an increased risk of fall and fractures among elderly patients prescribed TCAs and gabapentin.[14] Fractures can be a life-limiting event in elderly patients[25] and AI therapy is known to reduce bone mineral density,[15,16] which may exacerbate the risk of falls and fractures among breast cancer survivors. Physicians may want to focus their deprescribing efforts among those patients most at risk for side effects.

Beyond the concerns regarding overlapping prescriptions, there is a growing body of evidence that suggests that the medications we found were most commonly used, such as gabapentin, have more adverse side effects than had been appreciated. The use of gabapentin has more than tripled since 2008[26] much of which is for off-label use for which there is limited efficacy data.[26,27] Meta-analyses focusing on the use of gabapentin for noncancer pain syndromes have found consistent dose-dependent somnolence, sedation, dizziness, and gait difficulties among patients on the medicine.[28,29] These same dose-dependent adverse events have also been demonstrated in a meta-analysis among breast cancer survivors.[12] Our findings in users of AIs as adjuvant treatment, add to the literature regarding the risks of medications such as gabapentin, and thus are important to generalist as well as oncology-specialty physicians. Furthermore, most of the women in our study would be expected to go on to be long-term cancer survivors[1] and generalists are likely to play important roles in their long-term care.

In addition to gabapentin, tramadol was a frequently prescribed medication in this cohort. Although tramadol had previously been felt to be less risky compared with traditional opiates, newer literature suggests it may have substantial long-term risks. A recent study looking at the use of tramadol in patients with knee osteoarthritis found that those patients prescribed tramadol had an increased all cause 1-year mortality compared with those prescribed nonsteroidal medications but not compared with those prescribed codeine.[30] Another study found an increased risk of long-term opiate use among patients prescribed tramadol for acute pain compared with those prescribed hydrocodone or oxycodone.[31] Physicians may want to be more cautious in their use of tramadol and consider it in the same class as other opiates.

There are several limitations of our study. We were only able to track prescriptions and not actual use of these medications, but previous literature suggests strong concordance of prescription fills with measures of pill taking.[32–35] We had no information about reasons for prescriptions, and these could have included chemotherapy, diabetic neuropathy, or other indications. Future study should examine this in more detail, but does not change the implications of our study regarding the potential risks, particularly for overlapping medications. We attempted to be generous in our definition of overlapping prescriptions by not including SSRIs and SNRIs in our definition of overlap in an attempt to highlight those combinations of medications with the most potential for harm. If we had included these medications the number of

overlapping prescriptions would be even higher. In addition, in our primary analysis, we defined prescriptions as overlapping if there was a minimum of 31 days of overlap to account for transitions from one medication to another. Some patients could be harmed even with shorter overlap. Given the increased use of gabapentin, it is likely that physicians are encountering patients on gabapentin for unclear indications.

Our study demonstrates that the prescription of SE medications on women with breast cancer on AI therapy is common and that these medications are often used together, potentially increasing their risk. Future study should assess adverse clinical outcomes, such as falls and fractures, among breast cancer survivors prescribed SE medications.

Author Disclosure Statement

No competing financial interests exist.

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Appendix

Appendix Table A1. Sensitivity Analysis for Those Patients with Overlapping Medications, Number of Overlapping Prescriptions, and Days of Overlapping Prescriptions

	Any overlap	*91 days of overlap*
Any overlap, *n* (% of 18,520)	5,456 (29.5)	1,886 (10.2)
Maximum number of overlaps, *n* (%)		
2	3,929 (72.0)	903 (47.9)
3	1,291 (23.7)	767 (40.7)
≥4	236 (4.3)	216 (11.5)
Days of overlap, median (IQR)	36.5 (10.0–171.0)	277.0 (162.0–474.0)

IQR, interquartile range.

Appendix Table A2. Sensitivity Analysis Adjusted Odds Ratio and 95% Confidence Intervals for Predicting any Overlapping Prescriptions or 91 Days of Overlapping Prescriptions

	Any overlap OR (95% CI)	*91 days of overlap OR (95% CI)*
Prior use		
No	Reference	Reference
Yes	4.77 (4.45–5.11)	12.0 (10.4–13.8)
Age		
66–75	Reference	Reference
76–85	0.99 (0.92–1.07)	0.93 (0.82–1.03)
86–90	0.88 (0.760–1.03)	0.89 (0.71–1.11)
Cancer stage		
I	Reference	Reference
II	1.19 (1.10–1.28)	1.21 (1.09–1.35)
III	1.34 (1.21–1.55)	1.46 (1.22–1.74)
Race		
White	Reference	Reference
Black	1.14 (1.00–1.29)	1.11 (0.93–1.33)
Other	0.57 (0.47–0.68)	0.48 (0.34–0.66)
Unknown	1.20 (0.72–1.98)	1.37 (0.64–2.89)
Comorbidities		
0	References	References
1	1.34 (1.24–1.46)	1.50 (1.32–1.71)
2+	1.85 (1.70–2.02)	2.35 (2.01–2.66)

CI, confidence interval.