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Brief Communication

BRIEF COMMUNICATION

Concurrent Opioid and Benzodiazepine Prescriptions Among Older Women Diagnosed With Breast Cancer

Devon K. Check, Aaron N. Winn, Nicole Fergestrom, Katherine E. Reeder-Hayes, Joan M. Neuner, Andrew W. Roberts

See the Notes section for the full list of authors' affiliations.
Correspondence to: Devon K. Check, PhD, Department of Population Health Sciences, Duke University School of Medicine, Duke Cancer Institute, 215 Morris St., Durham, NC 27708 (e-mail: devon.check@duke.edu).

Abstract

Guidelines recommend using caution in co-prescribing opioids with benzodiazepines, yet, in practice, the extent of concurrent prescribing is poorly understood. Notably, no population-based studies, to our knowledge, have investigated concurrent prescribing among patients with cancer. We conducted a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) database linked with Medicare claims (2012–2016) for women diagnosed with breast cancer. We used modified Poisson regression to examine predictors of any concurrent prescriptions in the year post-diagnosis and Poisson regression to examine predictors of the number of overlapping days. We found that 13.0% of the 19 267 women in our sample had concurrent prescriptions. Women who underwent more extensive treatment and those with previous use of opioids or benzodiazepines were at increased risk for concurrent prescriptions (adjusted risk ratio of previous benzodiazepine use vs no previous use = 15.05, 95% confidence interval = 13.19 to 17.19). Among women with concurrent prescriptions, overlap was most pronounced among low-income, rural, and Hispanic women (adjusted incidence rate ratio of Hispanic vs non-Hispanic white = 1.25, 95% confidence interval = 1.20 to 1.30). Our results highlight opportunities to reduce patients' unnecessary exposure to this combination.

Over 20% of the 47 600 opioid overdose deaths in 2017 involved benzodiazepines (1), which exacerbate opioid-related respiratory depression. The risks of concurrent opioid and benzodiazepine use are compounded in older adults, who are prone to falls and other adverse consequences of impaired cognition resulting from this combination. Guidelines (2) and black box warnings (3) recommend that providers use caution in co-prescribing these two drug classes, but the extent of concurrent prescribing in practice is poorly understood.

Notably, no population-based studies, to our knowledge, have investigated concurrent opioid and benzodiazepine use in patients with cancer. Yet, opioids are the mainstay of pain management during treatment, and patients are frequently exposed to benzodiazepines to help manage common sequalae of cancer and its treatment, including anxiety and chemotherapy-related nausea. Moreover, patients with cancer—particularly those transitioning to survivorship—often have multiple physicians involved in their care, increasing the potential for uncoordinated prescribing (4–6). Examining patterns of concurrent opioid and benzodiazepine prescriptions after cancer diagnosis is a critical first step toward developing strategies to prevent harms potentially resulting from combination. The purpose of our study was to identify trends in, and predictors of, concurrent opioid and benzodiazepine prescriptions among older women diagnosed with breast cancer.

We conducted a retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (7) for years 2012–2016 for women with a first diagnosis of stage 0–III breast cancer between April 2013 and January 2015 who had no overlapping opioid and benzodiazepine prescriptions in the 3 months prediagnosis. Women were required to have continuous Medicare Parts A & B coverage in the 12 months before and after breast cancer diagnosis. Medicare Part D coverage was required from

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Table 1. Characteristics of sample, overall, and by any concurrent opioid and benzodiazepine prescriptions

Variable	All (n = 19 267) No. (%)	No concurrent prescriptions (n = 16 771) No. (%)	Concurrent prescriptions (n = 2496) No. (%)	P*
Age, y				<.001
66–75	11 877 (61.6)	10 097 (60.2)	1780 (71.3)	
76–85	6120 (31.8)	5501 (32.8)	619 (24.8)	
86–90	1270 (6.59)	1173 (6.99)	97 (3.89)	
Race/ethnicity				<.001
Non-Hispanic white	15 606 (81.0)	13 465 (80.3)	2141 (85.8)	
Non-Hispanic black	1496 (7.76)	1346 (8.03)	150 (6.01)	
Hispanic	1038 (5.39)	903 (5.38)	135 (5.41)	
Other	1127 (5.85)	1057 (6.30)	70 (2.80)	
Rural residence	4616 (24.0)	4013 (23.9)	603 (24.2)	.82
Percentage of residents with high school education in census tract of residence				.14
Quartile 1	2898 (15.0)	2513 (15.0)	385 (15.4)	
Quartile 2	4435 (23.0)	3904 (23.3)	531 (21.3)	
Quartile 3	5547 (28.8)	4825 (28.8)	722 (28.9)	
Quartile 4	6387 (33.1)	5529 (33.0)	858 (34.4)	
Median household income in census tract of residence				.09
Quartile 1	3206 (16.6)	2799 (16.7)	407 (16.3)	
Quartile 2	4426 (23.0)	3847 (22.9)	579 (23.2)	
Quartile 3	5267 (27.3)	4538 (27.1)	729 (29.2)	
Quartile 4	6368 (33.1)	5587 (33.3)	781 (31.3)	
Medicare part D low-income subsidy	3556 (18.5)	3052 (18.2)	504 (20.2)	.02
Charlson comorbidity index				.001
0	10 001 (51.9)	8792 (52.4)	1209 (48.4)	
1	5173 (26.8)	4450 (26.5)	723 (29.0)	
2+	4093 (21.2)	3529 (21.0)	564 (22.6)	
Previous use of opioids	2557 (13.3)	2097 (12.5)	460 (18.4)	<.001
Previous use of benzodiazepines	1724 (9.0)	852 (5.1)	872 (34.9)	<.001
Breast cancer stage†, No. (%)				<.001
0	2790 (14.5)	2502 (14.9)	288 (11.5)	
I	9670 (50.2)	8520 (50.8)	1150 (46.1)	
II	5522 (28.7)	4713 (28.1)	809 (32.4)	
III	1285 (6.67)	1036 (6.18)	249 (9.98)	
Tumor size, No. (%), cm				<.001
<2	13 137 (68.2)	11 567 (69.0)	1570 (62.9)	
2–5	5058 (26.3)	4311 (25.7)	747 (29.9)	
>5	1072 (5.56)	893 (5.32)	179 (7.17)	
Surgery				<.001
Minimal or no surgery	1846 (9.6)	1677 (10.00)	169 (6.9)	
Mastectomy	5571 (28.9)	4553 (27.1)	1018 (40.8)	
Partial mastectomy	11 850 (61.5)	10 541 (62.9)	1309 (52.4)	
Reconstruction	481 (2.50)	312 (1.9)	169 (6.8)	<.001
Radiation	10 600 (55.0)	9259 (55.2)	1341 (53.7)	.17
Hormone therapy	6935 (36.0)	6035 (36.0)	900 (36.1)	.96
Adjuvant chemotherapy	2819 (14.6)	2255 (13.5)	564 (22.6)	<.001
Length of active treatment (days)‡, mean (SD)	74.6 (80.7)	72.2 (79.2)	90.2 (88.6)	<.001

*Tests of statistical significance were two-sided.
†American Joint Committee on Cancer, 6th edition (8).
‡Beginning of active treatment was determined based on the earliest surgery, chemotherapy, or radiation claim within 6 months after diagnosis. The end of active treatment was defined as the last surgery, chemotherapy, or radiation claim occurring less than 90 days from the previous claim.

3 months prediagnosis through 12 months postdiagnosis. We excluded women who died or were diagnosed with a second primary cancer or who lacked a full year of follow-up. The institutional review board at the Medical College of Wisconsin determined that this study did not meet criteria for human participants research.

Our primary outcome was any concurrent opioid and benzodiazepine prescriptions, defined as having 1 or more days with overlap of opioid and benzodiazepine supplies during the 12-month follow-up period. We also assessed the number of overlapping days.

We described patient characteristics overall and by any concurrent prescriptions. Differences were assessed using *t* tests for continuous variables and χ^2 tests for categorical variables. Tests of statistical significance were two-sided and used *P* less than .05 as the cutoff for statistical significance. Using modified Poisson

Table 2. Adjusted* associations of patient characteristics with any concurrent prescriptions† and number of overlapping days‡

Variable	Any concurrent prescriptions (n = 19 267) aRR (95% CI)§	No. of overlapping days (n = 2496) aIRR (95% CI)‖
Age, y		
66–75	1.00 (Referent.)	1.00 (Referent.)
76–85	0.62 (0.55 to 0.70)	1.03 (1.01 to 1.06)
86–90	0.46 (0.36 to 0.58)	0.98 (0.93 to 1.02)
Race		
Non-Hispanic white	1.00 (Referent.)	1.00 (Referent.)
Non-Hispanic black	0.62 (0.50 to 0.76)	0.83 (0.80 to 0.86)
Hispanic	0.80 (0.63 to 1.01)	1.25 (1.20 to 1.30)
Other	0.43 (0.33 to 0.58)	0.73 (0.69 to 0.79)
Rurality		
Non-Rural	1.00 (Referent.)	1.00 (Referent.)
Rural	1.07 (0.93 to 1.22)	1.14 (1.11 to 1.17)
Percentage of residents with high school education in census tract		
Quartile 1	1.00 (Referent.)	1.00 (Referent.)
Quartile 2	0.92 (0.78 to 1.09)	0.90 (0.88 to 0.93)
Quartile 3	1.00 (0.85 to 1.20)	0.96 (0.93 to 1.00)
Quartile 4	1.10 (0.91 to 1.35)	0.95 (0.92 to 0.99)
Median household income in census tract		
Quartile 1	1.00 (Referent.)	1.00 (Referent.)
Quartile 2	1.06 (0.90 to 1.25)	0.92 (0.90 to 0.95)
Quartile 3	1.05 (0.89 to 1.25)	0.84 (0.82 to 0.87)
Quartile 4	0.91 (0.75 to 1.10)	0.86 (0.83 to 0.89)
Part D low-income subsidy		
No	1.00 (Referent.)	1.00 (Referent.)
Yes	1.09 (0.95 to 1.25)	1.26 (1.23 to 1.29)
Charlson comorbidity index		
0	1.00 (Referent.)	1.00 (Referent.)
1	1.13 (1.01 to 1.27)	1.23 (1.20 to 1.26)
2+	1.11 (0.98 to 1.27)	1.11 (1.08 to 1.14)
Prior benzodiazepine use		
No	1.00 (Referent.)	1.00 (Referent.)
Yes	15.05 (13.19 to 17.19)	1.49 (1.45 to 1.52)
Prior opioid use	2.57	3.21
No	1.00 (Referent.)	1.00 (Referent.)
Yes	2.57 (2.27 to 2.92)	3.21 (3.14 to 3.29)
Cancer stage		
0	1.00 (Referent.)	1.00 (Referent.)
I	1.21 (1.02 to 1.42)	1.08 (1.04 to 1.12)
II	1.23 (1.01 to 1.49)	1.16 (1.12 to 1.21)
III	1.38 (1.06 to 1.80)	1.07 (1.02 to 1.12)
Tumor size, cm		
<2	1.00 (Referent.)	1.00 (Referent.)
2–5	1.04 (0.88 to 1.24)	1.02 (0.99 to 1.06)
>5	1.11 (0.87 to 1.41)	0.96 (0.91 to 1.00)
Surgery		
No or minimal surgery	1.00 (Referent.)	1.00 (Referent.)
Partial mastectomy	1.07 (0.88 to 1.30)	0.64 (0.62 to 0.67)
Mastectomy	1.71 (1.40 to 2.08)	0.66 (0.64 to 0.69)
Hormonal therapy		
No	1.00 (Referent.)	1.00 (Referent.)
Yes	1.00 (0.89 to 1.11)	1.02 (1.00 to 1.04)
Radiation therapy		
No	1.00 (Referent.)	1.00 (Referent.)
Yes	0.86 (0.74 to 1.00)	0.91 (0.88 to 0.93)
Breast reconstruction		
No	1.00 (Referent.)	1.00 (Referent.)
Yes	2.74 (2.16 to 3.50)	0.90 (0.86 to 0.94)
Adjuvant chemotherapy		
No	1.00 (Referent.)	1.00 (Referent.)
Yes	1.28 (1.07 to 1.54)	1.07 (1.04 to 1.10)
Treatment duration	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)

*Models also adjusted for SEER region. aIRR = adjusted incidence rate ratio; aRR = adjusted risk ratio; CI = confidence interval; SEER = Surveillance, Epidemiology, and End Results.
†Adjusted associations of patient characteristics with any concurrent prescriptions assessed using modified Poisson regression.
‡Adjusted associations of patient characteristics with number of overlapping days assessed using zero-truncated Poisson regression.
§aRR and 95% CI.
‖aIRR and 95% CI.

regression (9), we estimated the probability of concurrent prescriptions for patients diagnosed in each calendar quarter of the study period (Q2: 2013 to Q4: 2015), adjusting for covariates. Also, using modified Poisson regression, we examined predictors of this outcome across the full study period. Among women with concurrent prescriptions, we assessed predictors of the number of days with overlapping opioid and benzodiazepine supplies using a zero-truncated Poisson regression model.

Across the entire study period, 13.0% of the 19 267 women in the cohort had concurrent opioid and benzodiazepine prescriptions (Table 1). The probability of having concurrent prescriptions was consistent across study quarters (Supplementary Figure 1, available online).

The risk of concurrent prescriptions increased with cancer stage and decreased with age (Table 2). Receipt of more extensive surgery and adjuvant chemotherapy was associated with an increased risk of having concurrent prescriptions. Use of opioids alone before breast cancer diagnosis increased the risk of receiving concurrent prescriptions after diagnosis by nearly threefold (adjusted risk ratio [aRR] = 2.57, 95% confidence interval [CI] = 2.27 to 2.92), whereas previous use of benzodiazepines increased this risk by 15-fold (aRR = 15.05, 95% CI = 13.19 to 17.19). Non-Hispanic black women were 38% less likely than non-Hispanic white women to have concurrent prescriptions (aRR = 0.62, 95% CI = 0.50 to 0.76).

Among women with concurrent prescriptions, the median number of days of overlap in opioid and benzodiazepine supplies was 6 (interquartile range = 3–16). The rate of overlapping days among Hispanic women was 1.25 times greater than that among non-Hispanic white women (95% CI = 1.20 to 1.29). Women with comorbidities, those living in rural areas, and those receiving the Part D low-income subsidy also experienced an increased rate of overlapping days (Table 2). With respect to clinical characteristics, receipt of adjuvant chemotherapy was associated with an increased rate of overlapping days (adjusted incidence rate ratio [aIRR] = 1.07, 95% CI = 1.04 to 1.10) as was previous opioid use (aIRR = 3.21, 95% CI = 3.14 to 3.29) and prior benzodiazepine use (aIRR = 1.49, 95% CI = 1.45 to 1.52).

In our sample, one in eight older women received concurrent opioid and benzodiazepine prescriptions in the year following breast cancer diagnosis. This combination was especially common among women who underwent more extensive cancer treatment. Among women with concurrent prescriptions, overlap was most pronounced among vulnerable subgroups.

Our findings highlight the need for strategies to reduce potentially hazardous opioid and benzodiazepine combinations. These strategies should include limiting the combination of these drug classes to situations where simultaneous possession of opioids and benzodiazepines is clinically beneficial, such as in a patient with both severe postoperative pain and refractory chemotherapy-induced nausea. In such circumstances, it is important to limit the amounts of prescribed drugs to those needed to control treatment-associated symptoms and to consider prescription of naloxone (10). Our findings also indicate a need for heightened monitoring of opioid or benzodiazepine use for chronic conditions that predate cancer diagnosis. In our sample, 13.3% and 9.0% of women, respectively, used opioids or benzodiazepines before diagnosis, and previous use of either drug substantially increased the risk of having overlapping prescriptions in the year postdiagnosis. Prescription drug-monitoring program databases are a valuable tool for assessing existing use of opioids and/or benzodiazepines at cancer diagnosis.

Our study has some limitations. First, we measured overlapping opioid and benzodiazepine prescription claims, which may not equate to concurrent use. Relatedly, we could not observe whether concurrent use occurred during clinician-led de-prescribing of either drug. Second, opioids and benzodiazepines are often taken as needed, meaning patients may use them beyond the Part D claim's minimum days' supply. This may have resulted in underestimation of overlapping days for some patients. Third, estimating the prevalence of concurrent opioid and benzodiazepine prescriptions in the year following breast cancer diagnosis required that we exclude women who died during this period, which may have excluded women who died from overdose. Future research should examine the association of this drug combination with mortality among patients with cancer. Finally, our findings may not generalize to other cancer types or younger populations with cancer.

Overlapping opioid and benzodiazepine prescriptions occur frequently among older women with breast cancer. Providers must use caution to mitigate the risks for serious adverse clinical outcomes stemming from this combination.

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Notes

Affiliations of authors: Department of Population Health Sciences, Duke University School of Medicine, Duke Cancer Institute, Durham, NC (DKC); Department of Clinical Sciences, School of Pharmacy, Center for Advancing Population Science, Medical College of Wisconsin, Wauwatosa, WI (ANW); Center for Advancing Population Science, Medical College of Wisconsin, Wauwatosa, WI (NF); Division of Hematology and Oncology, Department of Medicine, University of North Carolina at Chapel Hill (UNC-CH) School of Medicine, UNC-CH Lineberger Comprehensive Cancer Center, Chapel Hill, NC (KERH); Department of Medicine, Division of General Internal Medicine, Center for Advancing Population Science, Medical College of Wisconsin, Wauwatosa, WI (JMN); Department of Population Health and Department of Anesthesiology, University of Kansas Medical Center (KUMC), KU Cancer Center, KUMC, Kansas City, KS (AWR).

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