Concurrent prescribing of opioids with other sedating medications after cancer diagnosis: a population-level analysis

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Abstract

Purpose Cancer is a major reason for concurrent prescription of opioids with other sedating medications—particularly benzodiazepines and gabapentinoids—yet population-based assessments of the extent and predictors of concurrent prescribing among clinically and demographically diverse patients with cancer are lacking.

Methods We conducted a retrospective cohort study of patients with non-metastatic cancer using North Carolina cancer registry data linked with Medicare and private insurance claims (2013–2016). We used modified Poisson regression to assess associations of patient characteristic with adjusted relative risk (aRR) of new concurrent prescribing of opioids with benzodiazepines or gabapentinoids after diagnosis.

Results Overall, 15% of patients were concurrently prescribed opioids with benzodiazepines or gabapentinoids. Characteristics independently associated with an increased risk of concurrent prescribing included cancer type (e.g., aRR cervical vs. colorectal cancer: 1.55, 95% CI: 1.12–2.14); prior use of opioids (aRR: 2.43, 95% CI:2.21–2.67), benzodiazepines (aRR: 4.08, 95% CI: 3.72–4.48), or gabapentinoids (3.82, 95% CI: 3.31–4.39), and premorbid mental health conditions, including substance use disorder (aRR: 1.27, 95% CI: 1.05–1.54). Black and Hispanic patients were less likely to experience concurrent prescribing (aRR, Black vs. White: 0.35, 95% CI: 0.15–0.83; aRR, Hispanic vs. White: 0.75, 95% CI: 0.66–0.85).

Conclusion Approximately 1 in 7 patients with cancer was concurrently prescribed opioids with other sedating medications. Associations between patient characteristics and risk of concurrent prescribing highlight predictors of concurrent prescribing and suggest a rationale for systematic assessment of substance use history at diagnosis. Future research could explore inequitable pain and symptom management and investigate risk of adverse medication-related events.

Keywords Cancer · Concurrent prescriptions · Opioids · Sedating

Introduction

Studies have shown that, in the general population, concurrent use of opioids with other sedating medications is associated with an increased risk of adverse outcomes. In particular, concurrent use of opioids with benzodiazepines [1–3] or gabapentinoids [4, 5] has been shown to increase the risk of opioid overdose. Most studies examining the risks associated with concurrent use of opioids and other sedating medications have specifically excluded patients diagnosed with cancer. Yet a cancer diagnosis is a major reason why patients may be newly co-prescribed opioids with benzodiazepines and/or gabapentinoids [6, 7]. Opioid therapy has long been a mainstay of cancer-related pain management, and gabapentinoids are frequently used to specifically help manage treatment-related neuropathic pain [8]. Benzodiazepines are commonly prescribed for the management of other cancer-related symptoms, including anxiety, insomnia, and chemotherapy-related nausea [9].

Although patients with cancer have generally been excluded from prior studies assessing risks associated with concurrent use of opioids with other sedating medications,

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these risks may be compounded by cancer and its treatment. For example, an estimated 50% of all patients with cancer experience dyspnea or shortness of breath [10]. As a result, they may be particularly vulnerable to co-prescribing effects on respiratory function. Further, due to the neurological effects of chemotherapy—which affect up to 75% of patients [11]—patients with cancer may also be more prone to the effects of these medications and their combinations on postural stability and cognition.

Population-based assessments of the extent and predictors of concurrent prescribing among clinically and demographically diverse patients with cancer are lacking, but are critically needed to inform targeted interventions aimed at reducing avoidable harms for patients most at risk for using opioids with other sedating medications. To address this need, we leveraged unique state cancer registry data linked with multipayer insurance claims to (1) assess the prevalence of concurrent prescribing of opioids with benzodiazepines or gabapentinoids after a cancer diagnosis and (2) identify patient characteristics associated with concurrent prescribing.

Methods

Data source and population studied

We conducted a retrospective cohort study using the University of North Carolina's Cancer Information and Population Health Resource (CIPHR) [12]. CIPHR consists of data from the North Carolina Central Cancer Registry (NCCCR) linked with insurance claims from Medicare, North Carolina (NC) Medicaid, and private insurance. The present analysis is limited to Medicare and private insurance beneficiaries only, as, at the time of our analysis, state Medicaid data were only available through 2012, and our analysis starts in 2013, when Medicare part D began to cover benzodiazepines. We used the NCCCR data to select the study cohort, which included cancer survivors diagnosed at age 19 years or older, with a first primary diagnosis of a non-metastatic solid tumor (breast, cervical, colorectal, endometrial, esophageal, head/neck, lung, melanoma, ovarian, prostate, testicular) between April 1, 2013, and December 31, 2015 (most recent data available at the time of analysis). Recognizing that the benefits and risks of concurrent prescribing of sedating, symptom-directed medications may be weighed differently in the context of a life-limiting diagnosis, and we restricted inclusion to patients with non-metastatic disease at diagnosis with the goal of limiting our analytic cohort to patients with longer prognoses.

Patients were required to have continuous medical insurance coverage from 12 months prior to cancer diagnosis (to ascertain comorbidities) through 12 months following cancer diagnosis (to ascertain treatment). They were required to have continuous pharmaceutical coverage from 3 months prior to cancer diagnosis through 12 months following cancer diagnosis to ascertain medication use. We included patients who switched insurance types (e.g., private to Medicare).

Measures

Our primary outcome was a binary indicator of new concurrent prescribing of opioids with 1 of 2 sedating medications (benzodiazepines or gabapentinoids). Because we were focused on new concurrent prescribing after a cancer diagnosis, we excluded cancer survivors who used opioids concurrently with benzodiazepines or gabapentinoids in the 3 months before diagnosis. Consistent with prior research [2, 6, 7], we define concurrent prescribing as having 1 or more days with overlapping opioid/benzodiazepine supplies or overlapping opioid/gabapentinoid supplies during the 12-month period following cancer diagnosis. To ascertain overlapping supplies, we used the dispensing date and days' supply information from prescription drug claims to create daily indicators for whether a patient possessed an opioid, benzodiazepine, and/or gabapentinoid prescription supply. Secondary outcomes were concurrent prescribing of opioids with benzodiazepines and concurrent prescribing of opioids with gabapentinoids.

Factors evaluated for their associations with concurrent prescribing were the following: (1) demographic characteristics, including age at diagnosis, gender, race/ethnicity, urban/rural residence, area-level measures of income and education, and insurance provider (Medicare or private); (2) cancer- and treatment-related factors, including cancer type and stage (local or regional), receipt of surgery, radiation, and/or chemotherapy [6], and cancer treatment setting (academic or community); (3) other health-related characteristics, including baseline comorbidity burden (Charlson Comorbidity Index) [13], prior mental health and substance use disorder diagnoses, and prior chronic pain diagnoses [14]; and (4) use of opioids, benzodiazepines, or gabapentinoids in the 3 months before cancer diagnosis.

Analysis

We used descriptive statistics to characterize the analytic cohort overall and by any concurrent prescribing. Unadjusted differences between cancer survivors who did and did not experience concurrent prescribing were assessed using chi-squared tests for categorical variables and t-tests for continuous variables. Multivariable analysis used modified Poisson regression [15] to assess the adjusted relative

risk (aRR) of concurrent prescribing associated with patient characteristics.

Results

Characteristics of the analytic cohort

A total of 14,376 patients met inclusion criteria, 56% of whom were female and 16% of whom were Black (Table 1). The mean age at diagnosis was 68 years ($\pm$ 11), and most (76%) cancer survivors were insured by Medicare. The most common cancer diagnoses were breast (34%) and prostate (27%). The most common cancer affecting both men and women was colorectal cancer (13%). Nearly half of patients (46%) had 2 or more medical comorbidities. About 10% of patients had a prior diagnosis of chronic pain. With respect to prior mental health conditions, 12% had a depression diagnosis, 10% had an anxiety diagnosis, and 2% had a substance use disorder diagnosis.

Factors associated with concurrent prescribing

Roughly 15% of patients experienced any concurrent prescribing (i.e., prescribing of opioids with benzodiazepines and/or gabapentinoids). In unadjusted analysis, demographic factors associated with any concurrent prescribing included younger age, female gender, White race, and private insurance (Table 1). Cancer type was also strongly associated with concurrent prescribing, with incidence reaching 31%, 26%, and 23% for patients with cervical, ovarian, and lung cancer, respectively. The rates of concurrent prescribing were lowest for patients with testicular, prostate, and melanoma skin cancer (10%, 9%, and 8%, respectively) (Fig. 1).

With respect to other health characteristics, more advanced stage, increased comorbidity burden, and prior depression, anxiety, chronic pain, and substance use disorder were all associated with concurrent prescribing, as were receipt of surgery, radiation therapy, or chemotherapy. In addition, the use of opioids, benzodiazepines, or gabapentinoids prior to cancer diagnosis was associated with concurrent prescribing after cancer diagnosis. For example, among the 936 patients with prior benzodiazepine use, 58% ($N = 550$) received concurrent prescriptions after cancer diagnosis. Cancer treatment setting was not associated with any concurrent prescribing.

Examining each concurrent prescribing outcome (opioids/benzodiazepines and opioids/gabapentinoids) separately, about 12% of patients received concurrent opioid/benzodiazepine prescriptions, and approximately, 5% received concurrent opioid/gabapentinoid prescriptions. Overall, associations of patient characteristics with each separate concurrent prescribing outcome were similar to those observed for the composite outcome of any concurrent prescribing, with some exceptions. Specifically, comorbidity burden was not associated with receipt of concurrent opioid/benzodiazepine prescriptions, nor were area-level measures of education and income. Insurance provider was not associated with receipt of concurrent opioid/gabapentinoid prescriptions.

Multivariable analysis of factors associated with any concurrent prescribing

After adjustment, demographic differences in any concurrent prescribing persisted (Table 2). Specifically, compared to patients aged 60 to 69 years, those aged 19 to 49 years were 47% more likely (95% CI: 1.27–1.70), and those aged 50–59 years were 19% more likely (95% CI: 1.05–1.34) to experience concurrent prescribing. Conversely, patients aged 70–79 years were 23% less likely to experience concurrent prescribing (95% CI: 0.70–0.86). Further, women were 15% or more likely than men to experience concurrent prescribing (95% CI: 1.01–1.31). With respect to race/ethnicity, compared to non-Hispanic White patients, Black patients were 65% less likely (95% CI: 0.15–0.83), and Hispanic patients were 25% less likely (95% CI: 0.66–0.85) to experience concurrent prescribing. In addition, patients insured by Medicare were 14% less likely than those with private insurance to receive concurrent prescriptions (95% CI: 0.77–0.96). Area-level indicators of education and income were no longer associated with concurrent prescribing after adjustment.

Several health characteristics were independently associated with concurrent prescribing after adjustment. These included increased comorbidity burden (aRR, Charlson Comorbidity Index of 2 vs. 0: 1.12, 95% CI: 1.02–1.22), prior diagnosis of anxiety (aRR: 1.18, 95% CI: 1.07–1.32), prior diagnosis of a substance use disorder (aRR: 1.27, 95% CI: 1.05–1.54), and prior diagnosis of chronic pain (aRR: 1.19, 95% CI: 1.06–1.33). With respect to prior medication use, patients who used opioids before being diagnosed with cancer were more than twice as likely to experience concurrent prescribing after diagnosis (aRR: 2.43, 95% CI: 2.21–2.67), and those who used benzodiazepines or gabapentinoids before diagnosis were about 4 times as likely to experience concurrent prescribing after diagnosis (aRR for benzodiazepines: 4.08, 95% CI: 3.72–4.48; aRR for gabapentinoids: 3.82, 95% CI: 3.31–4.39). We also observed differences by cancer type. Compared to patients with colorectal cancer, those with cervical (aRR: 1.55, 95% CI: 1.12–2.14), head/neck (aRR: 1.59, 95% CI: 1.27–1.99), or lung cancer (aRR: 1.34, 95% CI: 1.14–1.57) were more likely to experience concurrent prescribing. Regional vs. local disease (aRR: 1.20, 95% CI: 1.10–1.31), receipt of surgery (aRR: 1.19, 95% CI: 1.05–1.34), and receipt of adjuvant

**Table 1** Cohort characteristics, overall and by any concurrent use in 12-month post-diagnosis

Variable	All patients ($N=14{,}376$)		Concurrent use ($N=2111$)		No concurrent use ($N=12{,}265$)		p value
	n	%	n	%	n	%	
Sociodemographic characteristics							
Age, y	68.2 (mean)	11.1 (SD)	64.9 (mean)	11.8 (SD)	68.8 (mean)	10.9 (SD)	<.0001
Age, categorized							<.0001
Category 1 (19–49)	919	6.4	236	11.2	683	5.6	
Category 2 (50–59)	1842	12.8	383	18.1	1459	11.9	
Category 3 (60–69)	4670	32.5	724	34.3	3946	32.2	
Category 4 (70–79)	4965	34.5	563	26.7	4402	35.9	
Category 5 (80+)	1980	13.8	205	9.7	1775	14.5	
Gender							<.0001
Male	6356	44.2	674	31.9	5682	46.3	
Female	8020	55.8	1437	68.1	6583	53.7	
Race/ethnicity							<.0001
Non-Hispanic White	11,565	80.5	1779	84.3	9786	79.8	
Non-Hispanic Black	2271	15.8	266	12.6	2005	16.4	
Hispanic	118	0.8	-	-	113	0.9	
Other	422	2.9	-	-	361	2.9	
Rural/urban residence							0.227
Rural	3868	27.4	545	26.3	3323	27.6	
Urban	10,250	72.6	1527	73.7	8723	72.4	
Percentage of residents with high school education in census track of residence							0.001
Quartile 1	3450	24.5	529	25.6	2921	24.4	
Quartile 2	3499	24.9	540	26.2	2959	24.7	
Quartile 3	3534	25.1	542	26.3	2992	24.9	
Quartile 4 (the highest education)	3575	25.4	452	21.9	3123	26.0	
Median household income in census track of residence							0.006
Quartile 1	3570	25.3	466	22.5	3104	25.8	
Table 1. Continued							
Quartile 2	3525	25.0	511	24.7	3014	25.1	
Quartile 3	3515	24.9	542	26.2	2973	24.7	
Quartile 4 (the lowest education)	3494	24.8	551	26.6	2943	24.5	
Insurance provider							<.0001
Any BCBS	3510	24.4	662	31.4	2848	23.2	
Medicare only	10,866	75.6	1449	68.6	9417	76.8	
Clinical characteristics							
Cancer type							<.0001
Breast	4822	33.5	875	41.5	3947	32.2	
Prostate	3856	26.8	338	16.0	3518	28.7	
Testicular	50	0.4	-	-	45	0.4	
Colorectal	1880	13.1	272	12.9	1608	13.1	
Lung (NSCL)	1135	7.9	260	12.3	875	7.1	
Cervical	90	0.6	28	1.3	62	0.5	
Ovarian	140	1.0	-	1.7	-	0.9	
Endometrial/uterine	773	5.4	97	4.6	676	5.5	
Melanoma	1117	7.8	93	4.4	1024	8.4	
Head/neck	392	2.7	81	3.8	311	2.5	
Esophageal	121	0.8	26	1.2	95	0.8	
Cancer stage							<.0001

Table 1 (continued)

Variable	All patients (N=14,376)		Concurrent use (N=2111)		No concurrent use (N=12,265)		p value
	n	%	n	%	n	%	
Local	10,569	73.5	1323	62.7	9246	75.4	
Regional	3807	26.5	788	37.3	3019	24.6	
Charlson Comorbidity Index							<.0001
0	6576	45.7	870	41.2	5706	46.5	
1	1188	8.3	170	8.1	1018	8.3	
2+	6612	46.0	1071	50.7	5541	45.2	
Prior diagnosis of depression and/or anxiety							
Anxiety	1412	9.8	422	20.0	990	8.1	<.0001
Depression	1770	12.3	424	20.1	1346	11.0	<.0001
Substance use disorder	351	2.4	94	4.5	257	2.1	<.0001
Table 1. Continued							<.0001
Prior diagnosis of fibromyalgia or chronic pain	1305	9.1	316	15.0	989	8.1	
Prior opioid use							<.0001
Yes	1524	10.6	483	22.9	1075	8.8	
No	12,852	89.4	1628	77.1	11,190	91.2	
Prior benzodiazepines use							<.0001
Yes	936	6.5	550	26.1	386	3.2	
No	13,440	93.5	1561	74.0	11,879	96.9	
Prior gabapentinoids use							<.0001
Yes	351	2.4	222	10.5	129	1.1	
No	14,025	97.6	1889	89.5	12,136	99.0	
Cancer treatment							
Adjuvant chemotherapy							<.0001
Platinum only	734	5.1	181	8.6	553	4.5	
Taxane only	1117	7.8	289	13.7	828	6.8	
Platinum and taxane	902	6.3	249	11.8	653	5.3	
Other	1537	10.7	237	11.2	1300	10.6	
None	10,086	70.2	1155	54.7	8931	72.8	
Adjuvant chemotherapy							
Yes	4290	29.8	956	45.3	3334	27.2	<.0001
No	10,086	70.2	1155	54.7	8931	72.8	
Surgery and radiation							
Surgery	10,164	70.7	1625	77.0	8539	69.6	<.0001
Radiation	6362	44.3	1111	52.6	5251	42.8	<.0001
Treatment setting							0.472
Major medical center	2717	18.9	413	19.6	2304	18.8	
Community-based cancer center	11,659	81.1	1698	80.4	9961	81.2	

chemotherapy (aRR: 1.53, 95% CI: 1.40–1.67) were also associated positively with concurrent prescribing.

Overall, results from the secondary model examining associations of patient characteristics with concurrent prescribing of specifically opioids/benzodiazepines were similar (Supplemental Table 1). However, surgery was not independently associated with concurrent opioid/benzodiazepine prescribing (aRR: 1.12, 95% CI: 0.99-–1.28). Esophageal cancer emerged as a statistically significant predictor of concurrent prescribing (aRR, esophageal vs. colorectal: 1.51, 95% CI: 1.04–2.20). For the secondary model examining associations of patient characteristics with concurrent prescribing of opioids with gabapentinoids, results diverged from the primary model in several respects (Supplemental Table 2). First, neither race/ethnicity nor insurance provider was independently associated with the outcome (aRR, Black vs. non-Hispanic White: 0.57, 95% CI: 0.18–1.80; aRR, Hispanic vs. non-Hispanic White: 1.04, 95% CI: 0.86–1.25).

Fig. 1 Percentage of patients with new concurrent prescriptions in the year after cancer diagnosis by cancer type
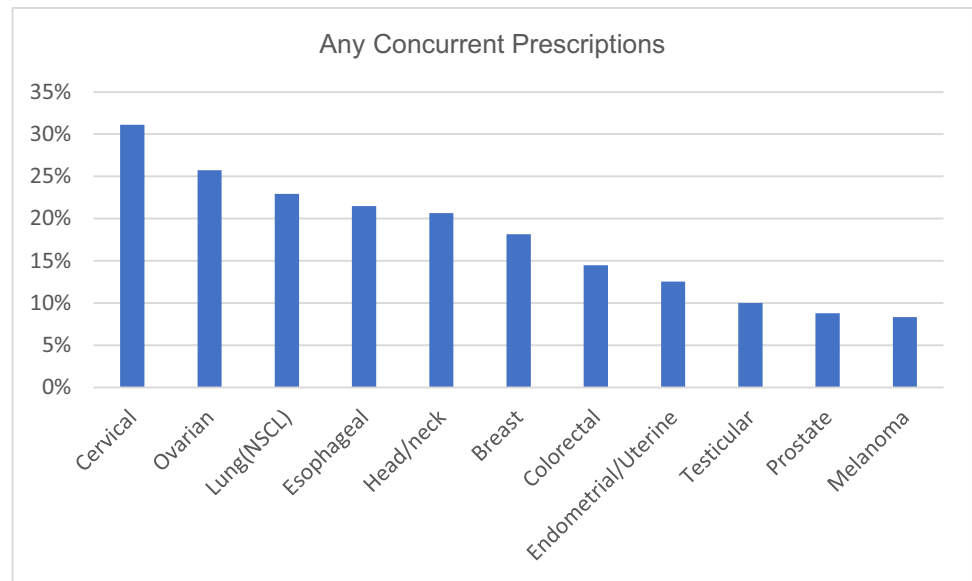
Further, cervical and lung cancer were the only cancer diagnoses independently associated with concurrent prescribing (aRR, lung vs. colorectal: 1.34, 95% CI: 1.04–1.74; aRR, cervical vs. colorectal: 1.72, 95% CI: 1.05–2.82). Chronic pain was the only previously diagnosed health condition associated with this outcome (aRR: 1.40, 95% CI: 1.18–1.66). In addition, living in an area with a lower level of education was associated with an increased likelihood of concurrent opioid/gabapentinoid prescribing (aRR lowest vs. highest education: 1:49, 95% CI: 1.14–1.95).

Discussion

In our study, we found that roughly 1 in 7 (15%) of patients received opioid prescriptions that overlapped with benzodiazepine and/or gabapentinoid prescriptions. We also found that concurrent prescribing of opioids with benzodiazepines (12%) was more prevalent than concurrent prescribing of opioids with gabapentinoids (5%). In adjusted analysis, factors associated with our primary outcome of any concurrent prescribing included younger age; female gender; White race; diagnosis of cervical, lung, head/neck, or esophageal cancer; receipt of surgery or chemotherapy; increased comorbidity burden; prior diagnosis of chronic pain, anxiety, or substance use disorder; and the use of any of the medications of interest before cancer diagnosis.

Our study adds to the small evidence base concerning population-level patterns of concurrent opioid/benzodiazepine prescribing. Because concurrent opioid/benzodiazepine prescribing was much more prevalent in our sample than concurrent opioid/gabapentinoid prescribing, results derived from our secondary model focused on concurrent opioid/

benzodiazepine were generally consistent with those from our primary model focused on any concurrent prescribing.

These results confirm several findings from two previously published population-based studies of concurrent opioid/benzodiazepine prescribing two conducted among older women with breast cancer [6, 16], and one among older adults with breast, lung, colorectal, or head/neck cancer [17]. Specifically, we found race/ethnicity, receipt of chemotherapy, a prior diagnosis of anxiety, and use of either opioids or benzodiazepines at diagnosis to be associated with concurrent opioid/benzodiazepine prescribing after diagnosis.

Our analysis also provides several new insights. First, previous studies of concurrent opioid/benzodiazepine prescribing in cancer have not accounted for substance use disorder history—a known risk factor for opioid misuse and overdose [18, 19]. In the present analysis, patients with a prior substance use disorder diagnosis were more likely to experience concurrent prescribing of opioids/benzodiazepines, compounding their risk for adverse opioid-related outcomes.

There are several possible explanations for this finding. First, patients with substance use disorders often have co-occurring anxiety associated with pain [20]; when necessary, providers may opt to prescribe both opioids and benzodiazepines for co-occurring pain and anxiety with increased monitoring and/or additional risk mitigation efforts (e.g., prescribing naloxone). A second potential explanation is that providers may lack knowledge about a patient's substance use history. While the American Society of Clinical Oncology recommends that oncologists systematically assess patients' substance use disorder history to inform risk-stratified monitoring [21], based on prior research, providers frequently do not ask their patients about their substance use history [22]. A third potential explanation is that providers may know of a patient's substance use history,

Table 2 Modified Poisson model-estimated risk ratios of concurrent use in 12-month post-diagnosis

Variable	Adjusted risk ratio and 95% confidence interval		
	Any concurrent prescribing	Opioid/benzodiazepine	Opioid/gabapentinoid
Sociodemographic characteristics			
Age, categorized			
Category 1 (19–49)	1.47 (1.27, 1.70)	1.47 (1.24, 1.73)	1.33 (0.99, 1.77)
Category 2 (50–59)	1.19 (1.05, 1.34)	1.21 (1.07, 1.38)	1.13 (0.90, 1.41)
Category 3 (60–69)	0.77 (0.70, 0.86)	0.76 (0.68, 0.85)	0.82 (0.70, 0.97)
Category 4 (70–79)	0.77 (0.67, 0.89)	0.71 (0.60, 0.84)	0.76 (0.60, 0.97)
Category 5 (80 +)	(Ref)	(ref)	(ref)
Gender			
Female	1.15 (1.01, 1.31)	1.34 (1.15, 1.56)	1.00 (0.80, 1.26)
Male	(Ref)	(ref)	(ref)
Race/ethnicity			
Non-Hispanic Black	0.35 (0.15, 0.83)	0.27 (0.09, 0.84)	0.57 (0.18, 1.80)
Hispanic	0.75 (0.66, 0.84)	0.57 (0.48, 0.66)	1.04 (0.86, 1.25)
Other	0.94 (0.76, 1.17)	0.90 (0.70, 1.15)	1.10 (0.74, 1.62)
Non-Hispanic White	(Ref)	(ref)	(ref)
Rural/urban residence			
Rural	1.09 (0.99, 1.20)	1.05 (0.95, 1.16)	1.08 (0.92, 1.26)
Urban	(Ref)	(ref)	(ref)
Percentage of residents with high school education in census track of residence			
Quartile 1	1.11 (0.96, 1.28)	1.02 (0.87, 1.19)	1.49 (1.14, 1.95)
Quartile 2	1.13 (0.99, 1.29)	1.08 (0.94, 1.24)	1.44 (1.12, 1.85)
Quartile 3	1.12 (0.99, 1.26)	1.05 (0.93, 1.19)	1.54 (1.22, 1.95)
Quartile 4 (the highest education)	(Ref)	(ref)	(ref)
Median household income in census track of residence			
Quartile 2	0.97 (0.86, 1.09)	0.99 (0.87, 1.12)	0.98 (0.78, 1.23)
Quartile 3	0.99 (0.88, 1.13)	1.00 (0.87, 1.15)	0.90 (0.71, 1.14)
Quartile 4	1.08 (0.94, 1.23)	1.07 (0.92, 1.24)	1.03 (0.8, 1.33)
Table 2. Continued			
Quartile 1 (the highest income)	(Ref)	(ref)	(ref)
Insurance provider			
Medicare only	0.86 (0.77, 0.96)	0.84 (0.74, 0.95)	0.88 (0.71, 1.08)
Any BCBS	(Ref)	(ref)	(ref)
Clinical characteristics			
Cancer type			
Breast	1.08 (0.93, 1.24)	1.17 (0.99, 1.38)	0.88 (0.69, 1.13)
Cervical	1.54 (1.11, 2.14)	1.55 (1.05, 2.31)	1.72 (1.05, 2.82)
Endometrial/uterine	0.89 (0.72, 1.10)	0.87 (0.68, 1.12)	0.76 (0.52, 1.10)
Esophageal	1.17 (0.83, 1.67)	1.51 (1.04, 2.19)	0.93 (0.45, 1.90)
Head/neck	1.59 (1.27, 1.99)	1.79 (1.39, 2.30)	1.08 (0.70, 1.66)
Lung (NSCL)	1.34 (1.14, 1.57)	1.40 (1.17, 1.67)	1.34 (1.04, 1.74)
Melanoma	0.69 (0.56, 0.85)	0.69 (0.54, 0.89)	0.68 (0.49, 0.95)
Ovarian	1.20 (0.89, 1.61)	1.20 (0.85, 1.71)	1.15 (0.69, 1.94)
Prostate	0.85 (0.71, 1.01)	1.05 (0.86, 1.28)	0.55 (0.41, 0.75)
Testicular	0.64 (0.28, 1.47)	0.77 (0.30, 1.93)	0.71 (0.18, 2.86)
Colorectal	(Ref)	(ref)	(ref)
Cancer stage			
Regional	1.20 (1.10, 1.31)	1.19 (1.08, 1.32)	1.15 (0.98, 1.35)
Local	(Ref)	(ref)	(ref)

Table 2 (continued)

Variable	Adjusted risk ratio and 95% confidence interval		
	Any concurrent prescribing	Opioid/benzodiazepine	Opioid/gabapentinoid
Charlson Comorbidity Index			
1	1.18 (1.02, 1.36)	1.07 (0.91, 1.25)	1.4 (1.06, 1.86)
2+	1.12 (1.02, 1.22)	1.10 (1.00, 1.22)	1.39 (1.17, 1.64)
0	(Ref)	(ref)	(ref)
Prior diagnosis of depression and/or anxiety			
Anxiety			
Yes	1.19 (1.07, 1.32)	1.26 (1.12, 1.41)	1.02 (0.84, 1.24)
No	(Ref)	(ref)	(ref)
Depression			
Yes	1.10 (0.99, 1.21)	1.13 (1.01, 1.26)	1.01 (0.85, 1.22)
Table 2. Continued			
No	(Ref)	(ref)	(ref)
Substance use disorder			
Yes	1.27 (1.05, 1.54)	1.32 (1.08, 1.63)	1.33 (0.98, 1.82)
No	(Ref)	(ref)	(ref)
Prior diagnosis of fibromyalgia or chronic pain			
Yes	1.19 (1.06, 1.33)	1.16 (1.03, 1.32)	1.40 (1.18, 1.66)
No	(Ref)	(ref)	(ref)
Prior opioid use			
Yes	2.43 (2.21, 2.67)	2.39 (2.15, 2.66)	2.87 (2.44, 3.38)
No	(Ref)	(ref)	(ref)
Prior benzodiazepine use			
Yes	4.08 (3.72, 4.47)	5.62 (5.11, 6.19)	-
No	(Ref)	(ref)	-
Prior gabapentinoids use			
Yes	3.82 (3.32, 4.39)	-	15.43 (13.21, 18.03)
No	(Ref)	-	(ref)
Cancer treatment			
Adjuvant chemotherapy			
Yes	1.53 (1.40, 1.67)	1.51 (1.37, 1.66)	1.78 (1.52, 2.09)
No	(Ref)	(ref)	(ref)
Surgery and radiation			
Surgery			
Yes	1.19 (1.05, 1.34)	1.12 (0.99, 1.28)	1.48 (1.19, 1.84)
No	(Ref)	(ref)	(ref)
Radiation			
Yes	1.04 (0.95, 1.14)	1.07 (0.97, 1.19)	1.05 (0.89, 1.23)
No	(Ref)	(ref)	(ref)
Treatment setting			
Major medical center	1.01 (0.92, 1.11)	0.95 (0.85, 1.06)	1.02 (0.86, 1.21)
Community-based cancer center	(Ref)	(ref)	(ref)

but lack information about their concurrent medication use, particularly in cases where opioids and benzodiazepines are prescribed by different providers and/or in different health systems. Our findings highlight potential opportunities to strengthen routine assessment of substance use history and routine use of state prescription drug monitoring program (PDMP) databases in oncology. Both are included in oncology guidelines [21] as strategies to inform risk-based prescribing and monitoring.

Our study also provides new information about the association of cancer type with concurrent opioid/benzodiazepine prescribing. In our cohort, patients with cervical,

head/neck, lung, and esophageal cancers had an increased likelihood of concurrent opioid/benzodiazepine prescribing. Given behavioral factors (e.g., smoking, alcohol use) that may contribute to the development of cervical, head/neck, lung, and esophageal cancers, patients diagnosed with these cancers may experience a greater burden of substance use disorder and related mental health conditions; they may also be at increased risk for harms associated with concurrent prescribing [21].

Further, treatment for each of these cancers is often multimodal and may include surgery, radiation therapy, and chemotherapy, which can result in additional physical and psychological symptom burden from treatment-related adverse effects and, correspondingly, increased need for symptom-directed medications such as opioids and benzodiazepines. In the case of esophageal and some head/neck cancers, high morbidity and shorter median survival may also contribute to higher rates of co-prescribing. It may not be feasible or clinically beneficial to avoid overlap in opioid/benzodiazepine prescriptions for patients who require both medications to better tolerate anti-cancer treatment and/or to improve quality of life.

When both medications are required at the same time, oncology practice guidelines recommend prescription of naloxone. Research on uptake of naloxone prescribing for patients with cancer who are at increased risk of overdose is lacking; however, available data indicate that uptake is extremely limited among both oncology and palliative care providers [23]. Providing naloxone in the context of concurrent opioids/benzodiazepine prescribing seems particularly important for patients who have additional risk factors, including a history of substance use disorder. Assessing and improving uptake of targeted naloxone prescribing in cancer care represent an important area for future research.

In the context of new evidence suggesting that gabapentinoids exacerbate the risk of opioid overdose [4, 5], our population-based study also provides new information about the prevalence of and factors associated with the practice of prescribing gabapentinoids concurrently with opioids among patients diagnosed with cancer. Based on our results, it is relatively uncommon for patients with cancer to be prescribed opioids and gabapentinoids at the same time, potentially because gabapentinoids are increasingly prescribed as an alternative to opioid therapy, particularly for neuropathic pain [24].

We are aware of only one previously published study that specifically examined concurrent prescribing of opioids with gabapentinoids in the cancer care context. That study was conducted within the supportive care clinic of a comprehensive cancer center, and the authors observed a much higher prevalence of concurrent opioid/gabapentinoid prescribing than we did (49% vs. 5%) [25]. Our differential findings are likely partly explained by our different study denominators.

The previous study was restricted to patients prescribed opioids, whereas our denominator included all patients who met diagnostic and continuous insurance enrollment eligibility criteria. In addition, our focus was on non-metastatic cancer, whereas the cohort for the previous study was primarily composed of patients with metastatic cancer. Patients with metastatic cancer often have more complex pain management needs and, as a result, may require medication for both nociceptive pain (opioids) and neuropathic pain (gabapentinoids) simultaneously.

Across outcomes, we observed differences in concurrent prescribing related to demographics—specifically, age and correspondingly, insurance provider—likely reflecting increased caution in prescribing to older adults, consistent with guideline recommendations. Further, we observed racial differences in concurrent prescribing. Specifically, in our study, Black and Hispanic patients were less likely to experience concurrent prescribing. While avoiding concurrent prescribing is consistent with available evidence and guideline recommendations, it is unlikely that the racial differences we observed are reflective of higher quality care for Black and Hispanic patients. Rather, these differences may indicate under-treatment of symptoms among Black and Hispanic patients due to implicit bias and systemic racism in healthcare [26–28]. Future studies should investigate potentially modifiable factors (e.g., implicit bias, cultural competence, communication) contributing to racial disparities in pharmacological symptom management in cancer in an effort to improve equity in symptom and quality of life outcomes.

Our study has several limitations. We used claims-based measures of overlapping prescriptions, which do not necessarily indicate concurrent use (i.e., taking both prescribed drugs at the same time). Relatedly, opioids and benzodiazepines are sometimes prescribed as-needed, meaning patients may use them beyond the claims' minimum days' supply; the implication is that we may have underestimated overlapping days for some patients. In addition, estimating the prevalence of concurrent prescribing in the year following cancer diagnosis required that we exclude patients who died during that period, including those who may have died from overdose. It is also important to acknowledge that we did not assess overdose or other potential harms (e.g., falls) resulting from co-prescribing. Future research should examine the risk of overdose and other potential harms among patients with cancer.

To summarize, in our retrospective cohort study of North Carolina adults diagnosed with non-metastatic cancer, we found that 15% of patients were prescribed opioids alongside benzodiazepines or gabapentinoids during the year following diagnosis. The associations we observed between patient characteristics and risk of concurrent prescribing highlight several potential opportunities for future research, including

implementation of systematic and patient-centered assessments of prior substance use disorder, and assessing the use of state prescription drug monitoring program databases and uptake of targeted naloxone prescribing in oncology. In addition, in the context of existing evidence on racial disparities in cancer-related symptom burden, observed racial differences in concurrent prescribing may indicate inadequate symptom management or care access among Black and Hispanic patients. Understanding and addressing multilevel barriers to equitable symptom management represent an important area for future research.

Availability of data

Not applicable.

Declarations

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