Title

Opioid tapering in older cancer survivors does not increase psychiatric or drug hospitalization rates.

Journal

Journal of the National Cancer Institute, 116(4)

Authors

Riviere, Paul

Morgan, Kylie

Deshler, Leah

et al.

Publication Date

2024-04-05

DOI

10.1093/jnci/djad241

Peer reviewed

OXFORD

JNCI: Journal of the National Cancer Institute, 2024, **116(4),** 606–612

https://doi.org/10.1093/jnci/djad241
Advance Access Publication Date: November 16, 2023
Article

Opioid tapering in older cancer survivors does not increase psychiatric or drug hospitalization rates

Paul Riviere, MD,[1,2,*] Kylie M. Morgan, BS,[1,2] Leah N. Deshler, MS,[1,2] Xinyi Huang, MS,[1,3] Carla Marienfeld, MD,[4] Christopher J. Coyne, MD, MPH,[1,5] Brent S. Rose, MD,[2] James D. Murphy, MD, MS[1,2]

[1]Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA, USA
[2]Center for Health Equity and Education Research, University of California San Diego, La Jolla, CA, USA
[3]Division of Biostatistics and Bioinformatics, Herbert Wertheim School of Public Health and Human Longevity Science, University of California San Diego, La Jolla, CA, USA
[4]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
[5]Department of Emergency Medicine, University of California San Diego, La Jolla, CA, USA

*Correspondence to: Paul Riviere, MD, Department of Radiation Medicine and Applied Sciences, 3855 Health Sciences Dr, Mail Code 0843, La Jolla, CA 92093, USA (e-mail: p2riviere@health.ucsd.edu).

Abstract

Background: Opioid tapering in the general population is linked to increases in hospitalizations or emergency department visits related to psychiatric or drug-related diagnoses. Cancer survivors represent a unique population with different opioid indications, prescription patterns, and more frequent follow-up care. This study sought to describe patterns of opioid tapering among older cancer survivors and to test the hypothesis of whether older cancer survivors face increased risks of adverse events with opioid tapering.

Methods: Using the Surveillance, Epidemiology and End Results Medicare–linked database, we identified 15 002 Medicare-beneficiary cancer survivors diagnosed between 2010 and 2017 prescribed opioids consistently for at least 6 months after their cancer diagnosis. Tapering was defined as a binary time-varying event occurring with any monthly oral morphine equivalent reduction of 15% or more from the previous month. Primary diagnostic billing codes associated with emergency room or hospital admissions were used for the composite endpoint of psychiatric- or drug-related event(s).

Results: There were 3.86 events per 100 patient-months, with 97.8% events being mental health emergencies, 1.91% events being overdose emergencies, and 0.25% involving both. Using a generalized estimating equation for repeated measure time-based analysis, opioid tapering was not statistically associated with acute events in the 3-month posttaper period (odds ratio [OR] = 1.02; $P = .62$) or at any point in the future (OR = 0.96; $P = .46$).

Conclusions: Opioid tapering in older cancer survivors does not appear to be linked to a higher risk of acute psychiatric- or drug-related events, in contrast to prior research in the general population.

The population of cancer survivors and people living with cancer in the United States is expected to continue to grow in the coming decades as the population ages and survival improves (1,2). This will require increased system-wide management of cancer survivorship issues including cancer and cancer treatment–related pain. Cancer survivors, a broad term including patients cured of their cancers, patients who have completed treatment for cancer and are still in a close surveillance period, and patients living with cancer, commonly suffer from long-term cancer-related pain and cancer treatment–related pain (3,4). Opioids are recognized as the mainstay in the medical management of moderate to severe cancer and cancer treatment–related pain (5). Undertreatment of cancer pain can worsen patient quality of life (6-8), and it is challenging for oncologists to weigh the risks and benefits of opioid therapy in cancer patients (9). However, there are no data to guide opioid tapering in cancer survivors prescribed opioids chronically, as acknowledged by the American Society for Clinical Oncology guidelines (10).

Recent studies in the general population have implicated the period following opioid tapering as being higher risk of acute psychiatric or drug overdose hospitalizations or emergency department visits in cohorts of patients without cancer diagnoses (11,12). Research has not evaluated the impact of opioid tapering among cancer survivors specifically. In contrast to individuals in prior opioid tapering studies, cancer survivors tend to be older (13), use lower doses of opioids chronically (11,14), have closer multidisciplinary follow-up, and have different indications (15) for long-term opioid therapy. These different characteristics among cancer survivors could potentially influence risks of opioid tapering. This retrospective cohort study seeks to define patterns of opioid tapering and test among older cancer survivors and test the hypothesis of whether opioid tapering is associated with acute psychiatric or drug overdose events.

Methods

Study data and cohort

This retrospective cohort study used the Surveillance, Epidemiology and End Results (SEER) Medicare–linked database.

Received: September 22, 2023. **Revised:** November 6, 2023. **Accepted:** November 13, 2023

SEER is a nationwide cancer registry that also collects clinical, demographic, and cause of death information for individuals diagnosed with cancer; it is linked with claims data for Medicare beneficiaries including outpatient claims, national carrier history claims, and pharmacy claims. The cohort included Medicare-enrolled patients diagnosed with cancer of the following primary sites: bladder, breast, colon and rectum, head and neck, kidney, lung, and prostate. To ascertain comorbidities and opioid prescriptions prior to cancer diagnosis, patients had to have at least 1 year of continuous Medicare enrollment prior to cancer diagnosis. Additionally, for inclusion, patients had to have a first cancer diagnosis between 2010 and 2017 as well as complete demographic data, biopsy-proven malignancy, and no other cancer diagnoses and had to have been diagnosed while alive (ie, no cancer diagnoses at time of autopsy). The final cohort was defined by excluding cancer survivors who were never prescribed opioids, were not consistently prescribed opioids for a 6-month period (and thus never establish a baseline opioid requirement) (11), or who had missing or no follow-up data following the baseline period (*see* Figure 1). Patient-level individual opioid prescriptions (16) were tabulated, specifically excluding opioids commonly prescribed for nonanalgesic purposes including buprenorphine, butorphanol tartrate, guaifenesin, nalbuphine, and belladonna. Methadone for opioid use disorder is prescribed outpatient in opioid treatment programs not reimbursed by Medicare part D, so this was presumed to be prescribed for pain indications in this cohort.

Opioid calculations

Individual patient opioid prescriptions were converted into oral morphine equivalents (17), grouped by month, and then tabulated longitudinally. The opioid baseline period was defined as having at least 6 months that varied by no more than 10% above or below the previous monthly oral morphine equivalents (11). Tapering status was defined as a binary time-varying event occurring with any monthly oral morphine equivalents dose reduction greater than or equal to 15% between a month and the previous month (11). All other months were labeled "non-tapering," and patients could undergo multiple tapering periods (11).

Outcome variables

A composite endpoint of overdose events and acute mental health events as primary hospital or emergency room admission was identified through Medicare claims files using the International Classification of Diseases, Clinical Modification codes, as has been previously described (11). An event was considered to be opioid taper–related if it occurred within 3 months of tapering.

Covariables and comorbidity variables

As a measure of prior acute mental health or drug-related events, we also tabulated these events occurring during the baseline period; in analyses, this was treated as a binary whether or not patients had 1 or more prior event(s). High-risk psychiatric diagnosis was defined as prior diagnosis of attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, or schizophrenia, as previously described in the Opioid Risk Tool (18).

Statistical analysis

Descriptive statistics reported 2-sided *P* values with an alpha less than .05 considered statistically significant; this included χ^2 or Kruskall–Wallis rank sum testing as appropriate (19). For the primary endpoint analysis (emergency room visit or hospitalization because of overdose or acute mental health) with relation to tapering vs nontapering periods, we used a generalized estimating equation with an autoregressive correlation structure, binomial distribution, and logit link function to account for within-patient correlation and longitudinal repeated measure data (20,21).

Analysis was performed using R version 4.3.1 (22) with generalized estimating equation using the geepack version 1.3.9 statistical package (23).

Results

Patient population

We identified 585 702 patients diagnosed within the SEER-Medicare database with Medicare enrollment. We then eliminated patients who never filled opioid prescriptions through Medicare part D (thus eliminating patients without Medicare part D enrollment as well), patients without characterized cancer-directed therapy start dates, and patients who were prescribed opioids intermittently without a 6-month stable period to establish a baseline; of patients who were prescribed opioids, only 7.7% received these medications long enough to establish a baseline (Figure 1). Eliminating patients who had no follow-up after establishment of a baseline resulted in a final cohort of 15 002 patients. The median baseline daily oral morphine equivalents was 30 mg (interquartile range [IQR] = 15-44) with a right-skewed distribution (Figure 2). Cohort demographics are shown in Table 1. From time of baseline completion, median follow-up time was 23 months (IQR = 10-35 months).

Opioid tapering

Overall, of the 15 002 patients in the cohort of patients with at least a 6-month period of baseline opioid prescriptions, 8311 underwent a taper at some point in the observation period, and 6691 patients never initiated an opioid taper. Patients who never underwent opioid taper were relatively older, had lower baseline opioid use, were less likely to have any opioid use predating their cancer diagnosis, and were less likely to have a prior high-risk psychiatric diagnosis (all $P < .05$; Table 1) (18). In multivariable logistic regression (Table 2), the likelihood of initiating an opioid taper decreased with age but increased with female patients, those with prior opioid use, and patients with a higher opioid baseline (measured by monthly prescribed oral morphine equivalents). Psychiatric or overdose events did not affect the odds of initiating an opioid taper.

Mental health emergency or drug overdose hospitalizations and emergency room visits

A total of 11 206 hospitalization or emergency room visits for mental health crisis or overdose (denoted as "events") were identified, among 978 unique patients, representing 6.5% of the study population. Overall, this summed up to approximately 3.86 events per 100 patient-months, with 97.8% of events being mental health emergencies, 1.91% of events being overdose emergencies, and 0.25% involving both.

Initiation of an opioid taper was not found to have a statistically significant effect on acute events in the 3-month posttapering period: the univariable odds ratio [OR] was 1.02 (95% confidence interval [CI] = 0.96 to 1.08; $P = .62$) and multivariable was 1.01 (95% CI = 0.95 to 1.08; $P = .68$; Table 3). Prior events in the baseline period resulted in an odds ratio of 9.49 (95% CI = 8.37 to 10.77; $P < .001$), and the presence of high-risk psychiatric diagnoses conferred an odds ratio of 2.35 (95% CI = 2.01 to 2.74; $P < .001$) but having opioid prescriptions prior to cancer diagnosis did not have a statistically significant effect ($P = .191$) (Table 3).

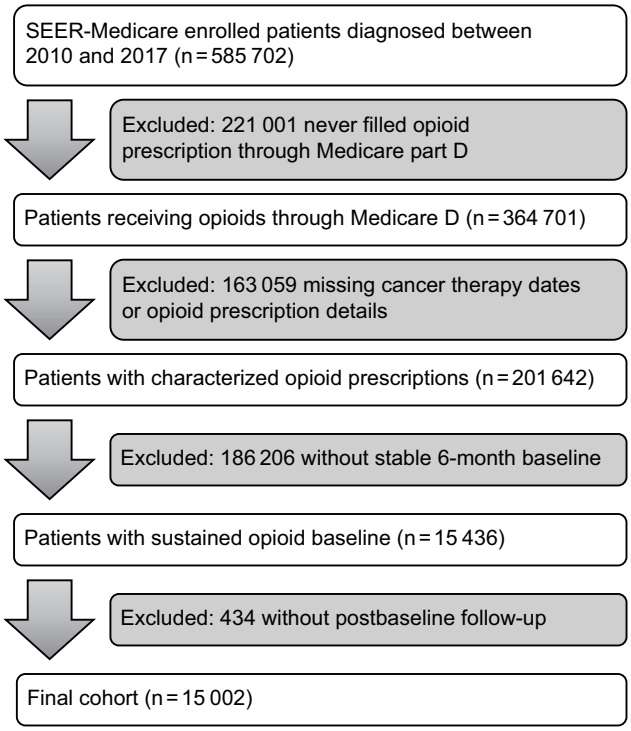

Figure 1. Flow diagram detailing incremental cohort selection based on inclusion and exclusion criteria. SEER = Surveillance, Epidemiology and End Results.

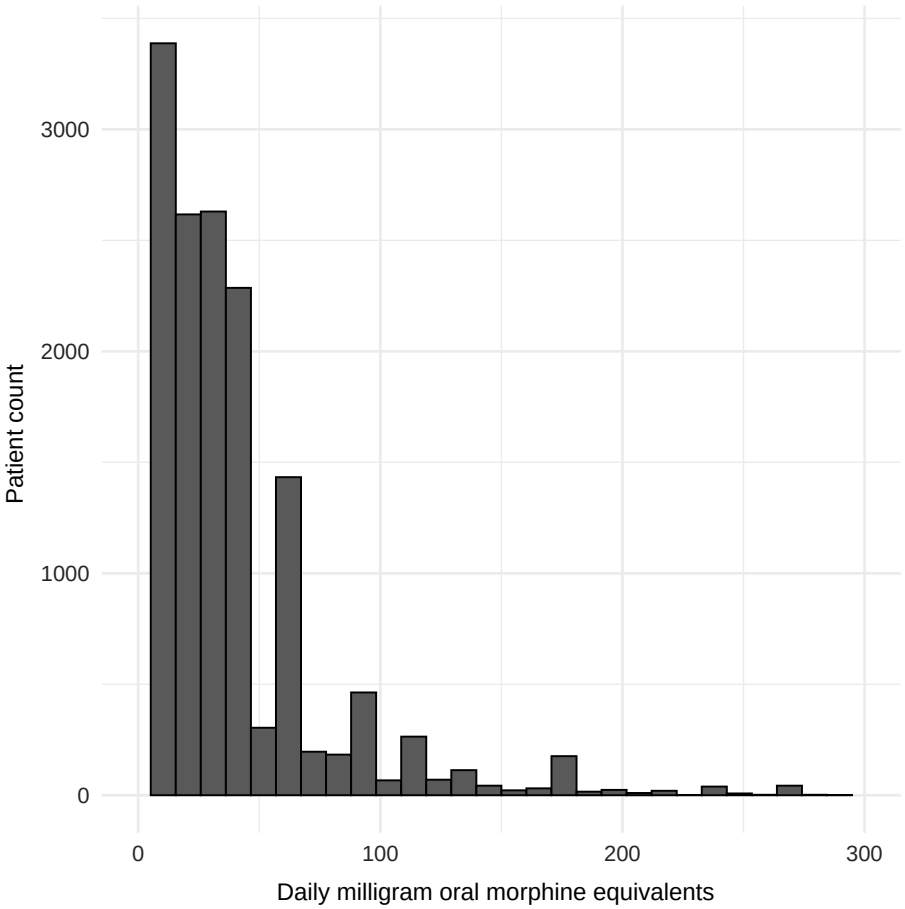

Figure 2. Histogram of daily oral milligram morphine equivalents in the baseline period.

Table 1. Demographics[a]

Variable	Never tapered No. (%)	Ever tapered No. (%)	P
Total No.	6691	8311	—
Sex			
Male	2906 (43.4)	3494 (42)	.09
Female	3785 (56.6)	4817 (58)	
Primary tumor site			
Bladder	575 (8.6)	753 (9.1)	.003
Breast	1857 (27.8)	2390 (28.8)	
Colorectal	1067 (15.9)	1259 (15.1)	
Head and neck	312 (4.7)	435 (5.2)	
Kidney	337 (5)	484 (5.8)	
Lung	1425 (21.3)	1581 (19)	
Prostate	1118 (16.7)	1409 (17)	
Age, year			
66-70	2360 (35.3)	3353 (40.3)	<.001
71-75	1850 (27.6)	2341 (28.2)	
76-85	1951 (29.2)	2193 (26.4)	
85 and older	530 (7.9)	424 (5.1)	
Race			
Black	676 (10.1)	874 (10.5)	
Other	142 (2.1)	176 (2.1)	
Unknown	38 (0.6)	48 (0.6)	
White	5835 (87.2)	7213 (86.8)	.875
Baseline median monthly milligram oral morphine equivalent (IQR)	675 (450-1200)	900 (600-1800)	<.001
Precancer opioid prescription(s)			
No	2111 (31.5)	1922 (23.1)	<.001
Yes	4580 (68.5)	6389 (76.9)	
Any events prior to baseline period			
No	6186 (92.5)	7646 (92)	.317
Yes	505 (7.5)	665 (8.0)	
Charlson comorbidity index			
0	2268 (33.9)	2883 (34.7)	.223
1	1685 (25.2)	2143 (25.8)	
≥2	2738 (40.9)	3285 (39.5)	
High-risk psychiatric diagnosis			
No	6243 (93.3)	7662 (92.2)	.010
Yes	448 (6.7)	649 (7.8)	
Area poverty rate			
<5%	828 (12.4)	1120 (13.5)	<.001
5% to <10%	1305 (19.5)	1694 (20.4)	
10% to <20%	1848 (27.6)	2389 (28.7)	
20% to 100%	1634 (24.4)	2097 (25.2)	
Unknown	1076 (16.1)	1011 (12.2)	

[a] IQR = interquartile range.

We performed several sensitivity analyses for this endpoint. First, we repeated this analysis removing the 3-month time restriction, finding that opioid tapering was not associated with a higher risk of events at any time in the future period of more than 3 months after tapering (OR = 0.96, 95% CI = 0.87 to 1.07; $P = .46$). Subsequently, we repeated the 3-month posttapering analysis in specific subgroups, finding that tapering still remained unassociated with acute events in patients with high-risk psychiatric diagnoses or prior opioid tapering events during the baseline period ($P = .95$), the youngest group of patients aged 66-70 years ($P = .54$), or in patients with more favorable cancer subtypes (breast and prostate) ($P = .50$). Finally, we repeated the analyses using tapering thresholds of 10%, 20%, and 50%, finding no effect of these tapering thresholds on risk of subsequent events (Supplementary Tables 1-3, available online, respectively).

Discussion

Our study suggests that in contrast to the general adult population previously studied and reported on, older cancer survivors do not appear to be at a higher risk of drug overdose or psychiatric-related complications requiring emergency room visits or inpatient hospitalization following opioid tapering. Indeed, only 7.7% of the patients prescribed opioids for cancer pain needed them for sufficient time to establish a baseline chronic opioid requirement. The majority of patients who were prescribed opioids long term following cancer-directed therapies had been prescribed opioids in the prior year leading to their diagnosis suggesting that long-term cancer-related pain may not be the predominant determinant of opioid use in this group of cancer survivors. However, among patients who were consistently prescribed opioids following cancer-directed therapy, only 45% attempted to taper at any point in the following 2 years.

Our findings highlight differences in the older cancer population, in contrast to 2 recent studies of opioid tapering in the noncancer population, among whom approximately three-quarters were aged 65 years and younger (11,12) and most of whom were prescribed lower daily oral morphine equivalents than what was observed in our cohort. In those studies, the overdose event rate was approximately fivefold higher than in our study, while the psychiatric event rate was almost five- to tenfold lower. Without having data on the distribution of these events, it is unclear if this is driven by a higher number of affected patients rather than a difference in event-rate among a subset of patients. Separately,

Table 2. Opioid tapering logistic regression[a]

Variable	Value	OR (95% CI)	P
Race (referent: White)	Black	1.00 (0.97 to 1.03)	.996
	Other	1.01 (0.96 to 1.07)	.758
	Unknown	1.01 (0.91 to 1.12)	.806
Charlson comorbidity index (referent: 0)	1	0.99 (0.97 to 1.01)	.476
	≥2	0.98 (0.96 to 1.00)	.014
Any events prior to baseline period		0.99 (0.97 to 1.02)	.688
Sex (referent: male)	Female	1.03 (1.01 to 1.05)	<.001
Age, y (referent 66-70)	71-75	0.99 (0.97 to 1.00)	.122
	76-85	0.97 (0.95 to 0.99)	.006
	Older than 85	0.91 (0.88 to 0.94)	<.001
High-risk psychiatric diagnosis		1.03 (1.00 to 1.06)	.049
Precancer opioid prescription(s)		1.09 (1.07 to 1.11)	<.001
Baseline opioid use quartile (referent: First)	Second	1.10 (1.08 to 1.13)	<.001
	Third	1.18 (1.15 to 1.22)	<.001
	Fourth	1.25 (1.22 to 1.28)	<.001
Area poverty rate (referent <5%)	5% to <10%	0.99 (0.96 to 1.01)	.28
	10% to <20%	0.98 (0.96 to 1.01)	.212
	20% to 100%	0.98 (0.95 to 1.00)	.098
	Unknown	0.90 (0.88 to 0.93)	<.001

[a] Logistic regression calculating odds of a patient undergoing an opioid taper at any point during the study period. CI = confidence interval; OR = odds ratio.

Table 3. Acute psychiatric or overdose hospitalizations[a]

Variable	Value	OR (95% CI)	P
Opioid tapering in past 3 months		1.01 (0.95 to 1.079)	.677
Race (referent: White)	Black	0.85 (0.69 to 1.04)	.113
	Other	0.93 (0.55 to 1.578)	.791
	Unknown	0.87 (0.42 to 1.84)	.723
Months elapsed, scaled		1.21 (1.16 to 1.271)	<.001
Any events prior to baseline period		9.53 (8.4 to 10.816)	<.001
Sex (referent: male)	Female	1.27 (1.13 to 1.421)	<.001
Charlson comorbidity index (referent: 0)	1	1.03 (0.89 to 1.189)	.684
	≥2	1.23 (1.08 to 1.4)	.002
Age, y (referent: 66-70)	71-75	1.00 (0.88 to 1.138)	.976
	76-85	1.09 (0.95 to 1.255)	.198
	Older than 85	1.19 (0.93 to 1.515)	.168
High-risk psychiatric diagnosis		2.33 (2.00 to 2.725)	<.001
Precancer opioid prescription(s)		0.92 (0.81 to 1.055)	.243
Patient baseline oral morphine equivalents		1.00 (1.00 to 1.00)	.348
Area poverty rate (referent <5%)	5% to <10%	0.81 (0.67 to 0.97)	.023
	10% to <20%	0.74 (0.62 to 0.884)	<.001
	20% to 100%	0.74 (0.61 to 0.897)	.002
	Unknown	0.75 (0.61 to 0.92)	.006

[a] Results of generalized estimating equation of odds of an acute psychiatric or overdose hospitalization. CI = confidence interval; OR = odds ratio.

a study of US veterans, which had an age and daily oral morphine equivalents distribution that was more similar to our study, found that opioid cessation was associated with a short-term increased risk of death from overdose or suicide. However, without an age-stratified analysis studying patients aged older than 65 years and with both a different exposure and endpoint, it is difficult to put these findings in comparison to the current study. This invites further investigation of younger cancer patients and other possible complications of opioid tapering. Overall, our findings suggest that older cancer survivors do not follow the patterns of mostly younger patients without cancer diagnoses who are prescribed opioids for sustained time periods. Whether this is a cancer-specific factor or a result of age and patterns of opioid prescription (ie, relatively short chronic prescription period of 6 months and low average oral morphine equivalents) should be further elucidated. In sensitivity analyses within our cohort—patients more closely resembling those patients from the prior studies (ie, among breast or prostate cancer patients who on aggregate have a favorable prognosis or among relatively younger patients in our cohort)—we did not find any signal to indicate a link between opioid tapering and acute psychiatric- or opioid-related hospitalizations or emergency room visits.

We found that cancer survivors who are prescribed opioids for a sustained period during or after their cancer-directed treatment largely remain on a stable or increasing dose indefinitely. This is in the larger context of findings that physicians nationwide are underdiagnosing opioid use disorder in cancer survivors given the consistently low rate of these diagnoses even in patients chronically prescribed opioids long after achieving cure (14,24) and the rising rates of opioid-related adverse events in the United States (25,26). Our findings of a relatively low rate of opioid tapering, let alone discontinuation among cancer survivors prescribed opioids long term, suggest that these patients are likely to continue being prescribed these medications in a pattern

analogous to the general population (27). Interestingly, these patients with prior opioid use were slightly more likely to initiate a taper as compared with patients who initiated long-term opioids following cancer treatment.

An important limitation of the SEER-Medicare dataset is the age restriction to patients aged older than 65 years; data from SEER would suggest that this accounts for approximately half of cancer patients in the United States (13). Given that opioid use disorder is most prevalent in those aged 35-44 years (28), it is important that the findings of this study not be applied to younger cancer patients, and future work will need to explore opioid-related outcomes in the posttapering period in a younger cohort of cancer survivors. Additionally, this analysis would likely miss patients who died from opioid overdose who were not brought to a hospital or emergency room. Finally, because of the requirements of a baseline opioid prescription period, many patients were eliminated from the cohort; however, this also demonstrates that many patients prescribed opioids for treatment of cancer-related pain likely use these medications only transiently.

Overall, we found that psychiatric- and drug overdose–related events are rare in older cancer survivors and are driven by a small subset of patients often with a prior history of such events. In contrast to the general population of patients prescribed opioids chronically, the posttapering period is not associated with a higher risk of these events, even in patients with higher-risk psychiatric and other medical comorbidities. We conclude that concerns of future psychiatric or overdose complications necessitating emergent care or hospitalization associated with opioid tapering should not be a major consideration when determining whether to initiate opioids for the management of cancer or cancer treatment–related acute pain in older patients. Physicians concerned about the risk of drug or psychiatric events in their patients should be aware of any such prior events in the past or the presence of psychiatric comorbid conditions that were found to be associated with decreased likelihood of initiating an opioid taper in the future.

Data availability

This project was conducted with data from the Surveillance, Epidemiology, and End Results (SEER) Medicare–linked database. These data are available with permission from SEER-Medicare to investigators for the study of specific research questions but, due to the risk of patient re-identification, are not accessible for public use.

Author contributions

Paul Riviere, MD (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing), Kylie M Morgan, BS (Conceptualization; Data curation; Formal analysis; Methodology; Visualization; Writing—original draft; Writing—review & editing), Leah N Deshler, MS (Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing—original draft; Writing—review & editing), Xinyi Huang, MS (Conceptualization; Formal analysis; Investigation; Methodology; Writing—review & editing), Carla Marienfeld, MD (Conceptualization; Methodology; Validation; Writing—original draft; Writing—review & editing), Christopher J Coyne, MD, MPH (Conceptualization; Funding acquisition; Supervision; Writing—original draft; Writing—review & editing), Brent S Rose, MD (Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Writing—original draft; Writing—review & editing), and James D Murphy, MD, MS (Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—original draft; Writing—review & editing).

Funding

Research reported in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Number R03DA053541.

Conflicts of interest

The authors declare no conflicts of interest with regards to this work.

Acknowledgements

The funder had not role in the study design; the collection, analysis, or interpretation of the data; the writing of the manuscript or decision to submit it for publication.
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016;25(7):1029-1036. doi:10.1158/1055-9965.EPI-16-0133
2. Gallicchio L, Devasia TP, Tonorezos E, Mollica MA, Mariotto A. Estimation of the number of individuals living with metastatic cancer in the United States. *J Natl Cancer Inst*. 2022;114(11):1476-1483. doi:10.1093/jnci/djac158
3. Filipponi C, Masiero M, Pizzoli SFM, et al. A comprehensive analysis of the cancer chronic pain experience: a narrative review. *Cancer Manag Res*. 2022;14:2173-2184. doi:10.2147/CMAR.S355653
4. Bennett MI, Kaasa S, Barke A, et al.; IASP Taskforce for the Classification of Chronic Pain The IASP classification of chronic pain for ICD-11: Chronic cancer-related pain. *Pain*. 2019;160(1):38-44. doi:10.1097/j.pain.0000000000001363
5. Paice JA, Lacchetti C, Bruera E. Management of chronic pain in survivors of adult cancers: ASCO clinical practice guideline summary. *JOP*. 2016;12(8):757-762.
6. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. a review of published literature. *Ann Oncol*. 2008;19(12):1985-1991. doi:10.1093/annonc/mdn419
7. Fisch MJ, Lee J-W, Weiss M, et al. Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. *J Clin Oncol*. 2012;30(16):1980-1988. doi:10.1200/JClinOncol.2011.39.2381
8. Shen W-C, Chen J-S, Shao Y-Y, et al. Impact of undertreatment of cancer pain with analgesic drugs on patient outcomes: a nationwide survey of outpatient cancer patient care in Taiwan.

J Pain Symptom Manage. 2017;54(1):55-65 e51. doi:10.1016/j.jpainsymman.2017.02.018
9. Vitzthum LK, Riviere P, Murphy JD. Managing cancer pain during the opioid epidemic-balancing caution and compassion. *JAMA Oncol*. 2020;6(7):1103-1104. doi:10.1001/jamaoncol.2020.0779.
10. Paice JA, Bohlke K, Barton D, et al. Use of opioids for adults with pain from cancer or cancer treatment: ASCO guideline. *J Clin Oncol*. 2023;41(4):914-930. doi:10.1200/JClinOncol.22.02198
11. Agnoli A, Xing G, Tancredi DJ, et al. Association of dose tapering with overdose or mental health crisis among patients prescribed long-term opioids. *JAMA*. 2021;326(5):411-419. doi:10.1001/jama.2021.11013
12. Fenton JJ, Magnan E, Tseregounis IE, et al. Long-term risk of overdose or mental health crisis after opioid dose tapering. *JAMA Netw Open*. 2022;5(6):e2216726. doi:10.1001/jamanetworkopen.2022.16726
13. *National Cancer Institute. Age and Cancer Risk*. 2021. https://www.cancer.gov/about-cancer/causes-prevention/risk/age. Accessed November 19, 2022.
14. Vitzthum LK, Riviere P, Sheridan P, et al. Predicting persistent opioid use, abuse and toxicity among cancer survivors. *J Natl Cancer Inst*. 2020;112(7):720-727. doi:10.1093/jnci/djz200
15. Mikosz CA, Zhang K, Haegerich T, et al. Indication-specific opioid prescribing for US patients with medicaid or private insurance, 2017. *JAMA Netw Open*. 2020;3(5):e204514. doi:10.1001/jamanetworkopen.2020.4514
16. Salz T, Lavery JA, Lipitz-Snyderman AN, et al. Trends in opioid use among older survivors of colorectal, lung, and breast cancers. *J Clin Oncol*. 2019;37(12):1001-1011. doi:10.1200/JClinOncol.18.00938
17. U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS). *Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors Table for Prescription Drug Coverage*. https://www.hhs.gov/guidance/document/opioid-oral-morphine-milligram-equivalent-mme-conversion-factors-0
18. Webster LR. Risk factors for opioid-use disorder and overdose. *Anesth Analg*. 2017;125(5):1741-1748. doi:10.1213/ANE.0000000000002496
19. Vittinghoff E. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. New York, NY: Springer; 2005.
20. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis*. 2nd ed. Hoboken, NJ: Wiley; 2011.
21. Weiss RE. *Modeling Longitudinal Data*. New York, NY: Springer; 2005.
22. R: A Language and Environment for Statistical Computing V. 4.3.1. Vienna, Austria: R Foundation for Statistical Computing, 2021.
23. Halekoh U, Hojsgaard S, Yan J. The R Package geepack for Generalized Estimating Equations. *J Stat Softw*. 2006;15(2):1-11. doi:DOI 10.18637/jss.v015.i02
24. Lee JS-J, Hu HM, Edelman AL, et al. New persistent opioid use among patients with cancer after curative-intent surgery. *J Clin Oncol*. 2017;35(36):4042-4049. doi:10.1200/JClinOncol.2017.74.1363
25. Chua IS, Leiter RE, Brizzi KT, et al. US national trends in opioid-related hospitalizations among patients with cancer. *JAMA Oncol*. 2019;5(5):734-735. doi:10.1001/jamaoncol.2019.0042
26. Jairam V, Yang DX, Yu JB, Park HS. Emergency department visits for opioid overdoses among patients with cancer. *J Natl Cancer Inst*. 2020;112(9):938-943., doi:10.1093/jnci/djz233
27. Chou R, Ballantyne J, Lembke A. Rethinking opioid dose tapering, prescription opioid dependence, and indications for buprenorphine. *Ann Intern Med*. 2019;171(6):427-429. doi:10.7326/M19-1488
28. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *Lancet*. 2019;393(10182):1760-1772. doi:10.1016/S0140-6736(18)33078-2