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Long-term opioid therapy trajectories and overdose in patients with and without cancer

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ABSTRACT

Objective Pain is experienced by most patients with cancer and opioids are a cornerstone of management. Our objectives were (1) to identify patterns or trajectories of long-term opioid therapy (LTOT) and their correlates among patients with and without cancer and (2) to assess the association between trajectories and risk for opioid overdose, considering the potential moderating role of cancer.

Methods and analysis We conducted a retrospective cohort study among individuals in the US Veterans Health Administration database with incident LTOT with and without cancer (N=44 351; N=285 772, respectively) between 2010 and 2017. We investigated the relationship between LTOT trajectory and all International Classification of Diseases (ICD)-9-defined and ICD-10-defined accidental and intentional opioid-related overdoses.

Results Trajectories of opioid receipt observed in patients without cancer and replicated in patients with cancer were: low-dose/stable trend, low-dose/de-escalating trend, moderate-dose/stable trend, moderate-dose/escalating with quadratic downturn trend and high-dose/escalating with quadratic downturn trend. Time to first overdose was significantly predicted by higher-dose and escalating trajectories; the two low-dose trajectories conferred similar, lower risk. Conditional HRs (99% CI) for the moderate-dose, moderate-dose/escalating with quadratic downturn and high-dose/escalating with quadratic downturn trends were 1.84 (1.18 to 2.85), 2.56 (1.54 to 4.25) and 2.41 (1.37 to 4.26), respectively. Effects of trajectories on time to overdose did not differ by presence of cancer; inferences were replicated when restricting to patients with stage 3/4 cancer.

Conclusion Patients with cancer face opioid overdose risks such as patients without cancer. Future studies should seek to expand and address our knowledge about opioid risk in patients with cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ US cancer pain guidelines assume that the benefits of treating pain in patients with cancer with opioids nearly always outweigh potential harms. However, patients with active or prior cancer have been routinely excluded from studies of long-term opioid therapy harms.

⇒ Recently, there has been an increasing awareness that opioid dose is not static and that the opioid dose pattern or trajectory plays an important role in harms.

WHAT THIS STUDY ADDS

⇒ This study found five distinct opioid dose trajectories, and these findings are similar to prior studies that also found multiple stable, escalating and de-escalating trajectories and found correlations between high-dose/persistent and high-dose escalating trajectories and serious outcomes (eg, hospitalisation, overdose, mortality).

⇒ This study differed from prior studies in that we did not find a stable high dose, a high-dose de-escalating trajectory or a rapidly escalating trajectory.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that patients with cancer could benefit from receipt of the same types of education, naloxone kits, and informed consent about LTOT afforded to other patients and that clinicians who prescribe to patients with cancer should receive the same training about risk-mitigation strategies as other treating clinicians.

INTRODUCTION

Long-term opioid therapy (LTOT) for pain in patients with cancer is a critical yet understudied area. Pain is experienced by most patients with cancer[1] and per recent guidelines,[2] opioids remain a cornerstone of pain management in this population.[3] Opioid prescribing rates in patients with cancer reflect this approach: a recent study using data from the National Survey on Drug Use and Health found that about half of patients with a cancer diagnosis in the past year were prescribed an opioid during that year (54.3%, 95% CI 50.2% to 58.4%).[4]

A prevalent belief in the field, reflected in prominent US cancer pain guidelines,[5 6] has been that the benefits of treating pain in

patients with cancer with opioids nearly always outweigh potential harms. While there are certainly situations in which the potential for benefit more clearly outweighs potential harms (eg, severe pain and very short prognosis), the data supporting this belief more broadly are limited, as patients with active or prior cancer have been routinely excluded from studies of LTOT harms. This is particularly true of overdose—the leading cause of accidental death in US adults.[6] Research in populations with 'non-cancer' pain indicates that the risk of overdose is dose dependent, with markedly increased risk among those receiving high-dose LTOT (defined as >90 mg morphine equivalent daily dose (MEDD)[7–11]). Recently, there has been an increasing awareness that opioid dose is not static and that the opioid dose pattern or trajectory plays an important role in harms.[12] Specifically, LTOT with significant dose variability[13] or escalating dose trajectories[14 15] has been found to confer higher risk. The few studies of opioid-related harms among patients with cancer generally support that serious harms including overdose occur, but these studies have significant methodologic limitations. As a result, one group has described the evidence base about opioid harms as 'one of the scarcest bodies of the literature in cancer'.[16–18]

A common approach to evaluating harms related to medications is to conduct a randomised trial. However, despite a limited evidence base, opioids are considered to be standard of care for the treatment of pain in individuals with cancer. Therefore, the ethics of conducting a randomised trial in which standard of care is withheld would be questionable, and recruitment barriers might be prohibitive. Additionally, many serious opioid-related outcomes, such as overdose and death, are relatively rare, limiting prospective approaches. These challenges underscore the importance of large databases to answer important questions about opioids in patients with cancer. U.S. Department of Veterans Affairs (VA) data offer many advantages in observational work including a universal, nation-wide electronic medical record that integrates diagnostic, laboratory and pharmacy data and a population that once in care tends to remain in the VA system.

Therefore, we aimed to (1) identify trajectories of LTOT and their correlates among patients with and without cancer and (2) assess the association between trajectories and risk for opioid overdose, considering the potential moderating role of cancer. To do this, we conducted a retrospective, cross-sectional study (including repeating measures) examining overdose risk among individuals with and without cancer in a large, national, contemporary US Veterans Health Administration (VHA) sample. We hypothesised that (1) LTOT trajectories characterised by higher and/or variable dose would pose greater risk for opioid overdose and (2) the risk for overdose associated with LTOT trajectories would not differ by cancer status.

METHODS

Study design and data sources

The study was conducted under a Data Use Agreement with VHA and US Centers for Medicare & Medicaid Services (CMS). Using data from the VHA Corporate Data Warehouse (CDW) and CMS, we identified a retrospective cohort of patients with incident LTOT from 2010 to 2017. Individuals with prior intermittent opioid exposure were included, so long as they were experiencing their first LTOT event. Patients in the cohort (1) were ≥18 years of age at the time of incident LTOT, (2) were engaged in VHA care, defined as ≥2 outpatient visits or ≥1 inpatient admissions within the year prior to cohort entry and (3) received LTOT, defined as 90 consecutive days' opioid prescription receipt (allowing for a 30-day gap between fills).[19] Opioids were levorphanol, meperidine, tapentadol, tramadol, codeine, hydrocodone, oxycodone, morphine, fentanyl, hydromorphone, oxymorphone, propoxyphene and pentazocine. Methadone in pill form was included, but liquid methadone and sublingual buprenorphine formulations were excluded as in the USA they are primarily used to treat substance use disorder. Patients were excluded if they died or entered hospice care (indicating end-of-life prognosis) within the 90-day interval of cohort entry and were right censored when they entered hospice care after the first 90-day interval.

Variable definitions and determinations

Cancer status group

Cancer status was determined by recorded diagnosis in the US Veterans Affairs Central Cancer Registry, including all stages of cancer but excluding non-melanoma skin cancer, and was defined as a time-invariant grouping variable. Patients with a cancer diagnosis any time between 2004 and the end of the study period were grouped as patients with cancer. We chose this inclusive approach to defining cancer diagnosis to not miss participants with cancer that could have been associated with pain leading to LTOT during the study period. This approach is also inclusive of the entire cancer care continuum, from diagnosis to cure and long-term survivorship; LTOT for pain is used across this continuum. In subsequent sensitivity analyses, we restricted the subset of patients with cancer to those whose cancer stage was 3 or 4 at cohort entry, to increase the likelihood that pain and resulting LTOT was related to the participant's cancer diagnosis.

LTOT and opioid dose

Opioid receipt was determined by CDW data and quantified for each 30-day period during and following the index LTOT period as the mean non-zero MEDD, using standardised conversions to MEDD and accounting for overlapping prescriptions.[20 21] For 30-day periods showing no prescription, 0 mg was recorded if patients were actively engaged in VHA care. If VHA care was not present and/or the patient received non-VA-based palliative or hospice care, the interval was treated as missing

to avoid risk of bias by assuming no prescription. Data were then aggregated by 90-day period as the unweighted mean MEDD of each non-zero component 30-day period under the assumption of underlying continuous prescriptions with gaps in refill (consistent with the LTOT definition). 90-day periods with all three 30-day components having no opioid prescription data were interpreted as no opioid prescription if patients were actively engaged in VHA care for all 30-day intervals; in these cases, 0 mg MEDD was recorded. Given sparse MEDD values of >100 mg resulting in failure of trajectory models to estimate plausible solutions, models truncated mean MEDD at 100 mg, corresponding to the 95th percentile of mean MEDD values for patients without cancer and the 94th percentile for patients with cancer.

Overdose

All accidental and intentional opioid-related overdose events were identified within CDW by International Classification of Diseases (ICD)-9 and ICD-10 codes following US Centers for Disease Control and Prevention recommendations.[22] Any overdose within each 90-day period was represented by a dichotomous indicator.[14] Although fatal and non-fatal overdose events were not differentiated, we identified patients with an overdose who died within the same or the next 90-day period. Time in 90-day increments from LTOT initiation to first overdose event was modelled in survival analysis.

Other variables

Covariates measured prior to entry into the cohort included demographic characteristics and indicators of chronic medical conditions determined by ICD-9 and ICD-10 codes (chronic obstructive pulmonary disease, cirrhosis, congestive heart failure, coronary artery disease, diabetes, hepatitis C and renal insufficiency, musculoskeletal disorder defined as chronic back or neck pain, osteoarthritis, fibromyalgia and the Charlson Comorbidity Index, a weighted composite of 19 conditions).[23] Covariates recorded in the data set as time-varying were included as indicators of any occurrence during the analysis period prior to the overdose event. These included mental health disorder comprising psychosis, depression, bipolar disorder and post-traumatic stress disorder[24–27]; opioid use disorder (OUD); substance use disorder comprising all non-opioid 'abuse' or 'dependence' including alcohol and nicotine; and benzodiazepine co-prescription determined by pharmacy data (online supplemental table 1). To account for an increase in initiatives targeting opioid safety,[28] including mandatory training for prescribers and availability of non-pharmacologic pain treatment options such as chiropracty, cognitive–behavioural therapy and acupuncture, we included a marker of LTOT after 2015.

Statistical analysis

Analyses proceeded in three stages. We first sought to identify trajectories of prescribed daily opioid dose exemplifying the treatment received by all patients with and without cancer in the cohort. We then assessed factors associated with these trajectories. Finally, we assessed whether trajectory membership conferred differential risk for opioid overdose, accounting for factors associated with trajectories that might confound results.

Latent growth mixture modelling

Applying methods used by Rentsch *et al* in a distinct population and time period, we used the TRAJ procedure[16] within SAS software (Enterprise Guide V.8.2 update[4]) to conduct latent growth mixture modelling (LGMM) to assess patterns or trajectories of opioid receipt among VA patients nationally over time.[14] LGMM is a powerful method to determine differences in trajectories of opioid dosing within a sample. The model estimates the probability that individuals have 'membership' in a particular trajectory versus other trajectories; distinct trajectories suggest the presence of subgroups within the sample. The TRAJ procedure uses likelihood-based estimation to derive unbiased model estimates using all available data, allowing for unequally spaced observations due to missing data under the assumption of missing at random. Trajectories of LTOT dose receipt over sixteen 90-day intervals (ie, 4 years) from the time of incident LTOT were estimated. See online supplemental methods for additional details. Final trajectories were labelled as 'high', 'moderate' or 'low' dose if their starting values were >90 mg MEDD, 30–90 mg MEDD or<30 mg MEDD, respectively, and were labelled as 'escalating', 'de-escalating' or 'stable' given positive, negative or zero linear change in dose, respectively.[16] The two escalating trajectories were further labelled 'with quadratic downturn' to signify their non-linear shape.

Patients were assigned to the trajectory consistent with their highest probability of membership. To assess correlates of trajectory membership, we conducted individual chi-square tests to determine: (1) the association between cancer status and trajectory membership and (2) within each cancer status group, the association between each categorical covariate and trajectory membership. The association between age, Charlson Comorbidity Index and trajectory membership within group was assessed by general linear modelling. All tests of statistical significance were evaluated using alpha=0.01.

Time to event modelling

Using Cox proportional hazards regression modelling via the PHREG procedure within SAS software,[4] stratifying on cancer status, time to first opioid overdose within 16 90-day intervals following the index LTOT was modelled as a function of trajectory to which the patient was assigned, controlling for trajectory-associated and cancer-associated covariates. Stratification on cancer group status allowed these groups to differ in terms of baseline risk of overdose and the assessment of differences in covariate effects by group. Death was specified as a competing outcome. The hypothesised safest trajectory based on the lowest intercept and stable slope was specified as the

reference group. Using likelihood ratio testing, the effects of trajectory and each covariate was tested for moderation by cancer status by comparing overall model fit with and without interactions with the cancer-group indicator. In a sensitivity analysis, we re-estimated the final survival model using the Firth penalised partial likelihood estimation to correct for potential estimation bias due to the rare outcome.[29] The sensitivity analysis specified death as a censoring variable rather than competing risk given that Firth correction is not available in SAS for competing risk models and essentially identical model estimates (ie, identical estimates of effect and 99% CI limits identical within 0.1) when specifying death as a censoring variable versus competing risk without the Firth correction.

Patient and public involvement

In our efforts to design a study involving patients with cancer treated with LTOT, we identified a retrospective cohort from VA CDW and CMS that would fulfil our research needs. As previously stated, patients with active or prior cancer have been routinely excluded from studies of potential LTOT harms. Identification of problems with LTOT for patients with cancer, therefore, was identified as a priority for study by the authors. As this research studied a retrospective cohort, no current patients on LTOT took part in the study's design. However, we performed a companion qualitative study to gain a deeper understanding of patient and provider perspectives on the positive and negative aspects of LTOT among patients with cancer[30]; findings from that study strongly influenced the present one. Also, the authors' ongoing direct work with individuals with cancer prescribed LTOT informed this research at every step, and will continue to inform the dissemination of this study's results.

RESULTS

Among 332 319 patients with incident LTOT, 330 123 (99.3%) who remained in VHA care for the first 90-day period of meeting LTOT criteria were included in analyses (online supplemental figure 1). Of those, a total of 44 351 (13.4%) had a cancer diagnosis. Stage of earliest recorded cancer ranged from 0 (4.10%) to 4 (20.83%), with 21.31% of diagnoses indicating stage was 'NA' or unknown. As summarised in table 1, those with cancer were more likely to be male, black and older. Patients with cancer were less likely to have a mental health disorder, OUD, musculoskeletal disorder or fibromyalgia but were more likely to have a non-opioid substance use disorder and each of the other medical conditions considered in analyses with the exception of osteoarthritis for which there was no group difference. Patients with cancer were more likely than patients without cancer to have experienced hospice or non-VA palliative care; however, mean rates of missing mg MEDD data not associated with hospice entry were similar across groups (12% (SD=25%)

Table 1 Patient characteristics and latent trajectory by cancer group*

	With cancer N=44 351	Without cancer N=285 772	Total N=330 123
Female, n (%)	1600 (3.61)	19 937 (6.98)	21 537 (6.52)
Black, n (%)	8265 (18.64)	43 000 (15.05)	51 265 (15.53)
Hispanic or latino, n (%)	1404 (3.17)	11 498 (4.02)	12 902 (3.91)
Age in years (mean, SD)	69.83 (9.19)	64.04 (14.09)	64.81 (13.68)
Initiated LTOT after 2015, n (%)	2719 (6.13)	13 509 (4.73)	16 228 (4.92)
Benzodiazepine, n (%)	19 814 (44.68)	126 639 (44.31)	146 453 (44.36)
Opioid use disorder, n (%)	2173 (4.90)	20 403 (7.14)	22 576 (6.84)
Substance use disorder, n (%)	22 014 (49.64)	128 645 (45.02)	150 659 (45.64)
Mental health disorder, n (%)	23 503 (52.99)	172 378 (60.32)	195 881 (59.34)
COPD, n (%)	12 150 (27.40)	46 148 (16.15)	58 298 (17.66)
Cirrhosis, n (%)	1396 (3.15)	3122 (1.09)	4518 (1.37)
CHF, n (%)	3823 (8.62)	16 637 (5.82)	20 460 (6.20)
Diabetes, n (%)	13 179 (29.72)	78 355 (27.42)	91 534 (27.73)
Hepatitis C, n (%)	3806 (8.58)	14 072 (4.92)	17 878 (5.42)
Coronary artery disease, n (%)	9287 (20.94)	49 102 (17.18)	58 389 (17.69)
Renal insufficiency, n (%)	2693 (6.07)	9346 (3.27)	12 039 (3.64)
Charlson Comorbidity Index (mean, SD)	3.22 (2.98)	1.23 (1.72)	1.50 (2.05)
Musculoskeletal disorder, n (%)	17 487 (39.43)	135 201 (47.31)	152 688 (46.25)
Fibromyalgia, n (%)	687 (1.55)	6559 (2.30)	7246 (2.19)
Osteoarthritis, n (%)	9743 (21.97)	64 004 (22.40)	73 747 (22.34)

*All associations statistically significant at p<0.001 except benzodiazepine coprescription (p=0.15) and osteoarthritis (p=0.04).
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LTOT, long-term opioid therapy.

for patients with cancer; 11% (SD=20%) for patients without cancer).

Observed rates of overdose

Patients with and without cancer were equally likely to have experienced an overdose event while in VHA care within the 4year analysis period (prevalence=0.10% for both; p=0.82) (table 2). A total of 19 of 317 patients with an overdose died within the same or the next 90-day period.

Latent growth mixture modelling

Results of this analysis are presented in table 2 and figure 1A,B. The mean probability of membership for each trajectory was ≥0.90 for patients without cancer and ≥0.78 for patients with cancer, indicating good discrimination between classes for both groups.[30]

Patients with cancer were more likely to have received moderate-dose, moderate-dose/escalating with quadratic downturn and high-dose/escalating with quadratic downturn trajectories of LTOT and were less likely to have received low-dose and low-dose/de-escalating trajectories. Conversely, patients *without* cancer were more likely to have received low-dose and low-dose/de-escalating trajectories of LTOT and less likely to have received the three higher-dose trajectories.

Time to event

The unconditional risk of overdose as assessed by baseline cumulative incidence functions did not differ significantly by cancer group status. Within cancer and non-cancer groups, the unconditional risk for overdose differed by trajectory. Figure 2 illustrates differences in baseline risk by each trajectory. Controlling for covariates in the survival model stratified on cancer group status, patients in three of the four trajectories—high-dose/escalating with quadratic downturn trend, moderate-dose/escalating with quadratic downturn trend and moderate-dose—were at significantly greater risk for overdose, relative to the reference (low-dose) trajectory (table 3). The conditional effect of the low-dose/de-escalating trajectory did not differ from the reference (low-dose) trajectory. Cancer group did not significantly moderate the effects of trajectories or covariates; thus, the single set of coefficients reported in table 3 represents the covariate effects for both groups. Estimates of trajectory effects for the cancer group are shown in online supplemental table 2.

Sensitivity analysis

In sensitivity analyses, restricting modelling of patients with cancer to those whose cancer stage was 3 or 4 at the time of entry into the cohort (N=11 174; 25.19% of patients with cancer), inferences of the LGMM and survival analysis did not change; trajectories were largely replicated although intercepts (representing trajectory starting MEDD values) and linear increases in the two escalating trajectories were higher, and larger proportions of patients received the high-dose and moderate-dose/escalating trajectories (online supplemental figure 2). In the full survival model, each trajectory that was significant in the more inclusive analysis remained statistically significant and positively associated with risk for overdose (online supplemental table 3). Inferences about covariate effects were also replicated, and effects were not moderated by cancer status. Using Firth-corrected estimates with the full sample resulted in minor differences in point estimates and identical model inferences to the model with competing risks without bias correction (online supplemental table 4).

DISCUSSION

Statement of principal findings

In a large retrospective, cross-sectional study (including repeated measures) of patients on LTOT with and without cancer, we identified 319 opioid overdoses. While overdose is a rare outcome, it is typically thought of as the 'tip of the iceberg' of more serious morbidity related to opioid use, including opioid misuse and use disorder. We identified similar trajectories of opioid receipt and risk of overdose among individuals with and without cancer. Perhaps this study's most important finding is we found no evidence of moderation for risks by cancer status. This is particularly noteworthy because currently, cancer pain guidelines do not explicitly acknowledge risk of overdose as an important consideration in titration of opioids for pain. This has been reflected in companion qualitative interviews, where we observed oncology-based clinicians express an inclination to prescribe opioids even in the case of risk of OUD relapse because the suffering from cancer pain was perceived to outweigh that risk.[31]

Strengths, including relative to other studies

While others have found that variability in opioid dosing per se is associated with opioid overdose,[13] a strength of our study is that we are one of many groups taking a newer approach that relates opioid dose trajectory to a serious outcome such as opioid overdose. This approach represents a shift in thinking about opioid risk, from a dyadic to a dynamic variable.

Our study found five distinct opioid dose trajectories. Our findings are similar to prior studies that also found multiple stable, escalating and de-escalating trajectories and found correlations between high-dose/persistent and high-dose escalating trajectories and serious outcomes (eg, hospitalisation, overdose, mortality).[11 14 15 32] However, our study differed from prior studies in that we did not find a stable high dose, a high-dose de-escalating trajectory, or a rapidly escalating trajectory.[14 15] Differences may be explained by different practice settings (eg, non-VA health systems, Medicare), different study periods (ie, studies that started and ended earlier may have seen higher doses and escalation due to changes in overall opioid prescribing patterns during this period), and different methods (eg, other studies used log-transformation of dose, more liberal trajectory extraction

Table 2 Distribution of overdose and covariates by latent trajectory and cancer status*

	With cancer (N=44 351)					Without cancer (N=285 772)				
Trajectory	**Low dose**	**Low dose/de-esc**	**Mod/stable**	**Mod/esc**	**High/esc**	**Low-dose**	**Low-dose/de-esc**	**Mod/stable**	**Mod/esc**	**High/esc**
Trajectory membership, n (%)	N=13 705 (30.90)	N=9355 (21.09)	N=11 308 (25.50)	N=5068 (11.43)	N=4915 (11.08)	N=102 871 (36.00)	N=79 877 (27.95)	N=66 820 (23.38)	N=22 649 (7.93)	N=13 555 (4.74)
Overdose event†, n (%)	11 (0.08)	6 (0.06)	14 (0.12)	7 (0.14)	6 (0.12)	47 (0.05)	76 (0.10)	72 (0.11)	48 (0.21)	30 (0.22)
Female, n (%)	538 (3.93)	378 (4.04)	373 (3.30)	165 (3.26)	146 (2.97)	7456 (7.25)	6408 (8.02)	4014 (6.01)	1341 (5.92)	718 (5.30)
Black, n (%)	2542 (18.55)	1903 (20.34)	2043 (18.07)	887 (17.50)	890 (18.11)	15679 (15.24)	13 829 (17.31)	9498 (14.21)	2736 (12.08)	1258 (9.28)
Age (mean, SD)	71.36 (9.58)	69.71 (9.55)	69.81 (8.83)	68.39 (8.37)	67.26 (8.11)	65.21 (14.23)	62.36 (15.00)	64.42 (13.32)	63.61 (13.00)	63.79 (11.82)
Initiated LTOT after 2015, n (%)	676 (4.93)	663 (7.09)	615 (5.44)	339 (6.69)	426 (8.67)	5243 (5.10)	4717 (5.91)	2313 (3.46)	706 (3.12)	530 (3.91)
Benzodiazepine, n (%)	5557 (40.55)	3567 (38.13)	5354 (49.35)	2721 (53.69)	2615 (53.20)	41277 (40.13)	31 640 (39.61)	32 461 (48.58)	13066 (57.69)	8195 (60.46)
Opioid use disorder, n (%)	501 (3.66)	392 (4.19)	550 (4.86)	372 (7.34)	358 (7.28)	4874 (4.74)	5797 (7.26)	4900 (7.33)	2752 (12.15)	2080 (15.34)
Substance use disorder, n (%)	6379 (46.55)	4607 (49.25)	5810 (51.38)	2726 (53.79)	2492 (50.70)	42728 (41.54)	37 144 (46.50)	31 116 (46.57)	11 196 (49.43)	6461 (47.67)
Mental health disorder, n (%)	7050 (51.44)	5089 (54.40)	6099 (53.94)	2811 (55.47)	2454 (49.93)	58229 (56.60)	50 094 (62.71)	40 357 (60.40)	14 830 (65.48)	8868 (65.42)
COPD, n (%)	3732 (27.23)	23.15 (24.75)	3345 (29.58)	1417 (27.96)	1341 (27.28)	17013 (16.54)	11 876 (14.87)	11443 (17.13)	3715 (16.40)	2101 (15.50)
Cirrhosis, n (%)	389 (2.84)	2.12 (2.27)	387 (3.42)	207 (4.08)	201 (4.09)	992 (0.96)	877 (1.10)	766 (1.15)	299 (1.32)	188 (1.39)
CHF, n (%)	1370 (10.00)	724 (7.74)	1014 (8.97)	387 (7.64)	328 (6.67)	6468 (6.29)	4186 (5.24)	4089 (6.12)	1224 (5.40)	670 (4.94)
Diabetes, n (%)	4481 (32.70)	2827 (30.22)	3363 (29.74)	1369 (27.01)	1139 (23.17)	29423 (28.60)	21 793 (27.28)	18307 (27.40)	5758 (25.42)	3074 (22.68)
Hepatitis C, n (%)	971 (7.09)	721 (7.71)	1019 (9.01)	547 (10.79)	548 (11.15)	4353 (4.23)	4068 (5.09)	3458 (5.18)	1282 (5.66)	911 (6.72)
Coronary artery disease, n (%)	3102 (22.63)	1971 (21.07)	2454 (21.70)	998 (19.69)	762 (15.50)	18781 (18.26)	12 802 (16.03)	11886 (17.79)	3674 (16.22)	1959 (14.45)
Renal insufficiency, n (%)	897 (6.55)	522 (5.58)	709 (6.27)	291 (5.74)	274 (5.57)	3548 (3.45)	2607 (3.26)	2144 (3.21)	699 (3.09)	348 (2.57)
Charlson Index, n (%)	2.97 (2.78)	3.01 (2.70)	3.31 (3.05)	3.51 (3.23)	3.82 (3.43)	1.25 (1.71)	1.20 (1.69)	1.24 (1.73)	1.23 (1.76)	1.26 (1.90)
Musculoskeletal disorder	5744 (41.91)	3631 (38.81)	4592 (40.61)	1935 (38.18)	1585 (32.25)	47454 (46.13)	37 312 (46.71)	32 813 (49.11)	11 360 (50.16)	6262 (46.20)
Fibromyalgia	224 (1.63)	147 (1.57)	173 (1.53)	76 (1.50)	67 (1.36)	2291 (2.23)	1774 (2.22)	1534 (2.30)	588 (2.60)	372 (2.74)
Osteoarthritis	3548 (25.89)	2138 (22.85)	2507 (22.17)	873 (17.23)	677 (13.77)	24136 (23.46)	18026 (22.57)	15198 (22.74)	4465 (19.71)	2179 (16.08)

*All associations statistically significant at p<0.001 except overdose event rate (p=0.31), fibromyalgia (p=0.75) and renal insufficiency (p=0.01), all among patients with cancer.
†Overdose events occurring during U.S. Department of Veterans Affairs care within 16 quarters following cohort entry.
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; High/esc, high-dose/escalating with quadratic downturn trend; Low-dose, low-dose/stable trend; Low-dose/de-esc, low-dose/de-escalating trend; LTOT, long-term opioid therapy; Mod/esc, moderate-dose/escalating with quadratic downturn trend; Mod/stable, moderate-dose/stable trend.

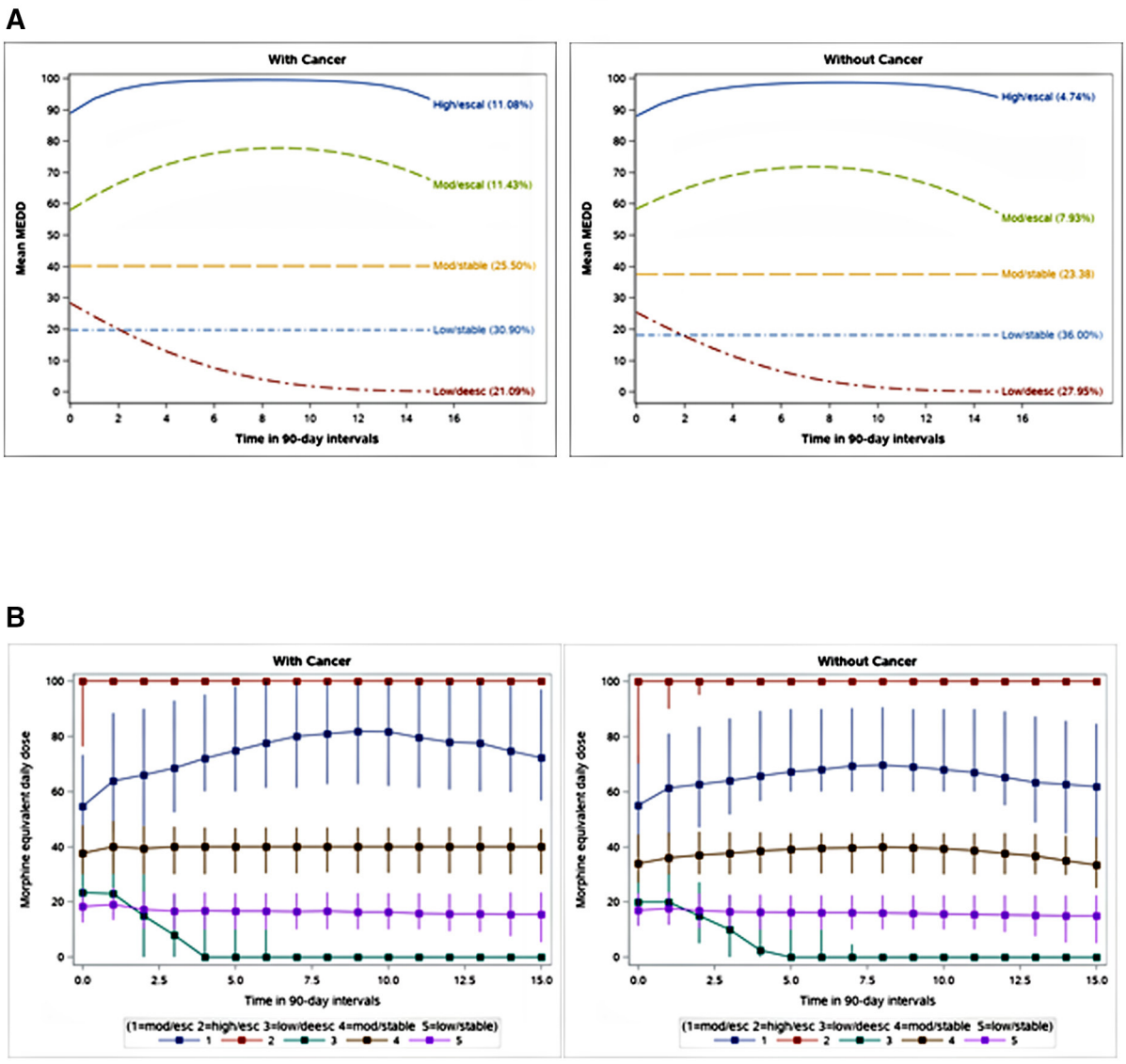

Figure 1 (A) Opioid dosing trajectories with percent-of-sample membership by cancer group. Note: Trajectory intercepts represent mg morphine equivalent daily dose (MEDD) start values and slope estimates represent mean linear and quadratic change in mg MEDD per 90-day interval. Intercepts (SE) and slopes (SE) for each trajectory for patients with and without cancer, respectively: low-dose/stable trend (intercept=16.74 (0.10); 15.97 (0.03)); (2) moderate-dose/stable trend (intercept=39.81 (0.14); 37.33 (0.03)); (3) low-dose/de-escalating trend (intercept=27.05 (0.16); 24.44 (0.05), linear slope= −5.00 (0.03); −4.45 (0.01)); (4) moderate-dose/escalating with quadratic downturn trend (intercept=58.29 (0.32); 58.50 (0.11), linear slope=5.05 (0.11); 3.81 (0.03), quadratic slope =−0.29 (0.01); −0.26 (0.00)); high dose/escalating with quadratic downturn trend (intercept=96.09 (0.40); 92.47 (0.16), linear slope=10.26 (0.19); 6.86 (0.05), quadratic slope =−0.64 (0.01); −0.41 (0.00)). (B) Median, IQR of opioid dose by time and latent trajectory.

criteria). Divergent approaches to aggregating dose across days within intervals (such as averaging in days of 0 mg vs averaging only non-0 mg days) could result in different trajectory shapes from comparable data. Necessary truncation at 100 mg MEDD to achieve model convergence precluded our observing trajectories exceeding this maximum that were described in other studies.

Our study was consistent with others in identifying greater risk for an opioid-related outcome (ie, overdose) among patients receiving higher or escalating versus lower or de-escalating doses. This commonality across many studies, robust to differences in population, context and measurement methods, underscores the stability of this conclusion.

While similar trajectories occurred in both groups in this study, patients with cancer were disproportionately represented in the higher-dose trajectories, consistent with prior literature[31 33] and the escalating quadratic trajectories. This is not surprising, as cancer pain treatment guidelines advise dose escalation in response to poorly controlled pain.[34] Also notable among these results, patients without cancer in the higher-risk trajectories were more likely to have additional risk factors for overdose, including mental

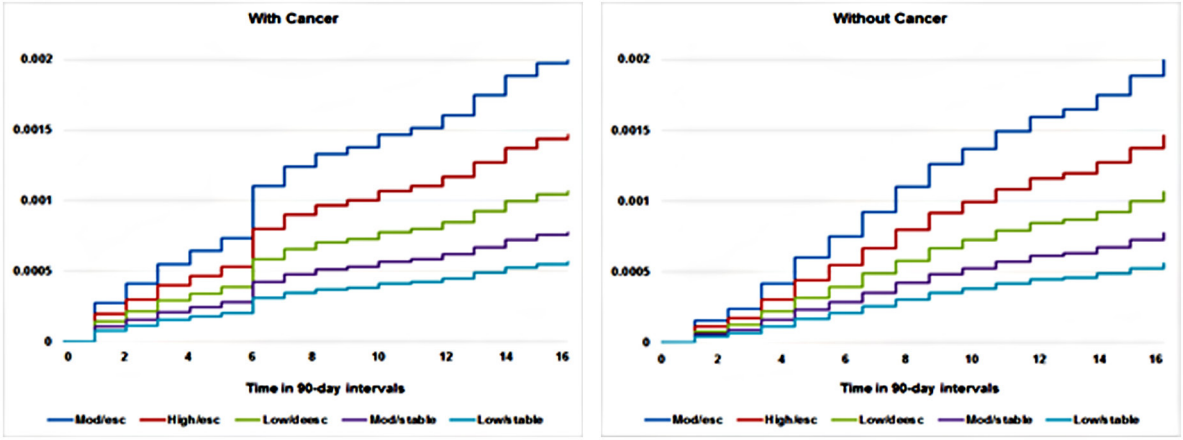

Figure 2 Baseline cumulative incidence functions for opioid overdose by opioid dosing trajectory. Note: High-dose/escalating with quadratic downturn and moderate-dose/escalating with quadratic downturn trend trajectories have the steepest unconditional incidence functions for opioid overdose.

health disorders and OUD. With these factors considered in the model, the effects of trajectories remained statistically significant.

There is inconsistency in other relevant studies' findings with respect to the relative risk to patients with cancer. As with the present study, a recent study using Surveillance, Epidemiology and End Results-Medicare data found no difference in a composite outcome of OUD and non-fatal overdose between patients with and without cancer.[34] Likewise, three studies have found that patients with metastatic cancer[35–37] prescribed an opioid have reduced survival, an association heavily confounded by indication.[35] Finally, a recent large observational study suggested that cancer

Table 3 Cox stratified proportional hazards regression model estimates

Predictor	Unadjusted HR	99% CI	Adjusted HR	99% CI
High-dose/escalating with quadratic downturn trend	**3.97**	2.28 to 6.93	**2.41**	1.37 to 4.26
Moderate-dose/escalating with quadratic downturn trend	**4.01**	2.46 to 6.54	**2.56**	1.54 to 4.25
Moderate-dose/stable trend	**2.22**	1.43 to 3.44	**1.84**	1.18 to 2.85
Low-dose/de-escalating trend	**1.85**	1.19 to 2.87	1.44	0.92 to 2.25
Low-dose/stable trend (reference)	NA	NA	NA	NA
Female			0.75	0.40 to 1.41
Black			0.90	0.60 to 1.34
Initiated LTOT after 2015			0.40	0.12 to 1.31
Benzodiazepine			0.89	0.66 to 1.21
Age			**0.99**	0.97 to 1.00
Opioid use disorder			**8.46**	6.22 to 11.52
Substance use disorder			1.26	0.91 to 1.74
Mental health disorder			**1.68**	1.13 to 2.51
COPD			1.12	0.75 to 1.67
Cirrhosis			0.66	0.22 to 1.96
CHF			1.74	0.94 to 3.22
Diabetes			0.83	0.56 to 1.25
Hepatitis C			**1.61**	1.05 to 2.47
Coronary artery disease			0.79	0.49 to 1.28
Renal insufficiency			**3.39**	1.96 to 5.86
Charlson Index			0.97	0.88 to 1.06
Musculoskeletal disorder			1.32	0.97 to 1.78
Fibromyalgia			0.95	0.38 to 2.41
Osteoarthritis			1.00	0.69 to 1.45

Boldface=p<0.01.
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LTOT, long-term opioid therapy.

survivors have 10 times lower rates of opioid-related deaths than patients without cancer.[38] However, this study relied on notoriously inaccurate 'cause of death' ICD fields, in which only comorbidities that directly led to the cause of death (opioid overdose in this case), rather than comorbidities in general, are listed.[39] Therefore, our study represents a major methodologic step forward in that, while also from a large single-payer database, it uses a more reliable ICD-based overdose outcome.

Weaknesses, including in relation to other studies

This study has limitations. Since our study was conducted in the US VHA, generalisability to other settings may be limited.[40] Our study lacked data on out-of-VA opioid use but the largest source of opioids that would be different across groups—hospice care—was a censoring criterion in the study. Greater rates of hospice and palliative care created higher rates of missing prescription data for patients with cancer. Relatedly, because VHA electronic health records do not record 'no opioid prescription', per se, we made informed assumptions about the meaning of missing prescription values following cohort entry. There are alternative methods to calculate morphine milligram equivalents by interval in the absence of prescription data, each with limitations. We modelled the mean of days prescribed to reflect the average dose when taken. This approach is commonly used in substance use research describing the amount of use *on use days* (eg, number of drinks on drinking days). We determined *a priori* that modelling the dose prescribed, when prescribed, within an interval was more reflective of prescriber behaviour (our research question) than modelling average dose across days prescribed and not prescribed. Assuming no prescription in the temporal context (eg, within the same 90-day interval) of active prescription raises potential for bias toward zero, a risk of an alternative approach. Variation across studies in methods to define trajectories should be considered when comparing conclusions about trajectory-associated risks. Overdose events were rare in both groups, which limited power to detect a trajectory-by-cancer status interaction; however, a strength of the study is the use of a specific, clinically important outcome and a diverse national sample of patients. Importantly, sensitivity analysis correcting for potential bias due to rare events did not change model inferences. The retrospective cohort design may have led to unmeasured confounders; prospective studies are needed to address this limitation, and the findings may not apply to other opioid-related harms. Because trajectory was used as a predictor (rather than time-updated dose) the temporal relationship between particular dose or acute change in dose and overdose was not modelled. Since we limited our investigation to overdose, the findings may not apply to other important opioid-related harms. We assumed presence of cancer and LTOT meant the latter's indication was cancer pain; however, even clinically, these distinctions are challenging to make. Nonetheless, if LTOT is prescribed for another condition in a patient with cancer, understanding LTOT's impact in the context of cancer is still critical. More broadly, the taxonomy of pain in patients with cancer (eg, pain due to the cancer itself or to treatment, chronic pain exacerbated by cancer) has been poorly defined in the literature.[41] Also, we were not able to determine whether an overdose was accidental or intentional, and misclassification of overdose in individuals with cancer is an important challenge to the field.[42] We were only able to include overdoses for which people received care within VHA. Finally, we treated cancer as a grouping variable; additional research is needed to understand the role of cancer attributes such as stage on the relationship between LTOT and overdose.

Implications for clinical care and policy

Importantly, our findings suggest that (1) patients with cancer could benefit from receipt of the same types of education, and informed consent about LTOT afforded to other patients and (2) clinicians who prescribe to patients with cancer should receive the same training about risk-mitigation strategies as other treating clinicians. Although overdose is rare, these strategies are likely important for preventing other adverse opioid-related events beneath this 'tip of the iceberg' such as opioid misuse and OUD.

Future directions

This study highlights the need to build the evidence base about opioid-related risks and benefits in this patient population—including how to mitigate these risks and, when they turn into actual harms, what to do to prevent even more serious harms like overdose. This evidence base should be used to inform patient-centred shared decision-making about opioid prescribing in cancer.

CONCLUSION

While guidelines endorse the use of opioids for cancer pain, patients with cancer—such as patients without cancer—face opioid overdose risks. Clinicians and researchers should consider this when counselling patients with cancer about the risks of opioids. Additionally, these findings have relevance when developing inclusion criteria for studies of LTOT. Future studies should seek to expand our knowledge about opioid risk in patients with cancer and how to address it.

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