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Long-term opioid therapy and risk of opioid overdose by derived clinical indication in North Carolina, 2006–2018

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Abstract

Purpose: Long-term opioid therapy (LTOT) has been shown to be associated with opioid overdose, but the definition of LTOT varies widely across studies. We use a rigorous LTOT definition to examine risk of opioid overdose by duration of treatment.

Methods: Data were from a large private health insurance provider in North Carolina linked to mortality records from 2006–2018. Eligible patients were adults (18–64) newly initiating opioid therapy after a pain diagnosis or surgery. We defined LTOT as ≥ 1 opioid prescription per month totaling ≥ 60 days' supply within 90 days. We used inverse probability- (IP) weighted cumulative incidence functions to estimate three-year risk of opioid overdose and IP-weighted Fine-Gray models to estimate subdistribution hazard ratios, comparing LTOT to short- to medium-term opioid therapy (SMTOT). We also examined modification by derived indication of acute pain or surgery versus chronic pain.

Results: We identified 491,369 patients, and 1.7% were exposed to LTOT. The three-year risk of opioid overdose was 0.3 percentage points ($RD_w = 0.003$, 95% CI: 0.001, 0.005) higher in LTOT patients compared to patients with SMTOT. The weighted hazard of opioid overdose was 4.4 times as high ($HR_w 4.42$, 95% CI 2.41, 8.11) among patients exposed to LTOT versus SMTOT. We did not find meaningful modification by clinical indication for opioid therapy.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to disclose.

ETHICS STATEMENT

This analysis was approved by the Institutional Review Board (IRB), Office of Human Research Ethics, the University of North Carolina at Chapel Hill. The requirement for informed consent was waived since there was no direct patient contact and all data analyzed was pre-existing.

Conclusions: Exposure to LTOT was associated with increased risk of opioid overdose in this population of privately insured patients using a rigorous definition of LTOT. These findings confirm the importance of guidelines to minimize duration of opioid therapy whenever possible.

Keywords

opioid analgesics; opioid-related disorders; opioid overdose; chronic pain; postoperative pain; acute pain; opioid epidemic

INTRODUCTION

The United States (US) drug epidemic has caused staggering levels of morbidity and mortality since the turn of the century. Opioid overdoses account for more than two-thirds of drug-related deaths^{1,2} – over 440,000 from 1999 through 2018¹ – and one-third of overdose-related emergency department (ED) visits,³ with >300,000 ED visits in 2017 alone.³ More recently, heroin and synthetic opioids have been the main drivers of the epidemic.⁴ However, prescription opioids remain a significant contributor to opioid-related morbidity and mortality.⁴ Long-term use of prescription opioids is known to be associated with opioid use disorder (OUD) and opioid overdose,^{5–7} and prescription opioid use often precedes initiation of heroin and synthetic opioids.^{8–15}

Despite known risks, opioids can have an important role in pain management.¹⁶ Millions in the US suffer from pain—55% of US adults report recent pain,¹⁷ and Centers for Disease Control and Prevention (CDC) estimates >20% experience chronic pain.¹⁸ Many of these individuals receive prescription opioids for pain management; 15% of Americans filled ≥1 opioid prescription in 2018.¹⁹ Long-term opioid therapy (LTOT) often begins with treatment of acute^{20–23} and postsurgical pain^{20,24–26} that then extends past the window of normal healing.^{23,27} In 2016, CDC released opioid prescribing guidelines recommending providers minimize duration of opioid therapy for pain patients.²⁸ Updated guidelines from 2022 more explicitly addressed acute pain, again emphasizing the importance of shorter initial durations of opioid therapy or prescribing non-opioid therapy.^{29,30}

While there is a multitude of research on incidence and risk factors for LTOT and the association between LTOT and opioid-related harms, the LTOT definition used in the literature varies widely,^{31–33} with many studies not accounting for consistent long-term use.^{32,33} Further, most research is conducted in one of three main contexts: (1) postsurgical, (2) chronic non-cancer pain (CNCP), or (3) any opioid prescription regardless of indication. Few studies have examined the relationship between opioid therapy duration and opioid overdose according to initial pain indication.³⁴ Patients with CNCP may initiate opioid therapy with a clinical goal of long-term pain management, restoring functional status, or quality of life,²⁹ and treatment recommendations differ for CNCP patients compared to acute or postsurgical pain patients.²⁸

We aimed to apply a rigorous definition of LTOT to analyze the association between LTOT and short- and long-term incidence of opioid overdose. We further sought to characterize whether this relationship is modified by the derived pain indication for the initial opioid prescription.

METHODS

Data Source

We used de-identified claims data from a large private health insurance provider in North Carolina (NC). This data source included all pharmaceutical claims for outpatient prescriptions, medical claims for inpatient and outpatient visits, and membership files for individuals aged 18–64 with at least one of: an outpatient claim for opioids, pain diagnosis, or surgical procedure from January 1, 2006 to September 30, 2018.³⁵ To identify deaths in this population, claims data were then linked to mortality records from the NC Department of Health and Human Services (DHHS) using a hierarchical matching algorithm (eFigure 1).

Study Population

We identified adults aged 18–64 initiating outpatient prescription opioids (eTable 1) between July 1, 2006 and July 1, 2018 with ≥ 180 days of continuous enrollment (washout period) before their index date. Included patients had a derived indication of pain management, defined as invasive surgery (i.e., postsurgical pain) using Current Procedural Terminology (CPT) codes,³⁶ or diagnosed acute or chronic pain^{25,37–39} using *International Classification of Diseases, 9th* (ICD-9-CM) and *10th Revision* (ICD-10-CM), *Clinical Modification* codes (eTable 2). The index date for surgical patients was the (1) opioid claim date if the first claim was ≤ 14 days after the surgery end date, or (2) outpatient surgery date or final day of an inpatient stay if the first opioid claim was ≤ 14 days before the surgery start date (eFigure 2A-2B). For nonsurgical patients, the index date was the date of the first opioid claim ≤ 14 days after a pain diagnosis (eFigure 2B). We assigned clinical indication for opioid therapy hierarchically: (1) postsurgical pain, (2) acute pain (without invasive surgery), and (3) chronic pain (without acute pain or invasive surgery).

We implemented a new-user design,⁴⁰ excluding patients with opioid claims during the 180-day washout or evidence of opioid overdose or OUD (eTable 3) using all-available lookback.^{41,42} Patients were also excluded if they had a history of malignant cancer (all-available lookback) or surgery ≤ 180 days before index, due to the potentially complex nature of their pain and treatment regimens. Patients were followed forward 90 days from the index date for exposure classification and were excluded if they experienced any of (1) opioid overdose, (2) death, (3) disenrollment, (4) invasive surgery, or (5) cancer diagnosis in that period (eFigure 2C).

Exposure

We defined long-term opioid therapy (LTOT) as consistent opioid use for ≥ 90 days,⁴³ using the date of fill and days' supply (eMethods) to calculate the total days' supply of prescribed opioids received and the timing of receipt. Our definition of LTOT required ≥ 1 opioid prescription in each of the 30-day periods within the 90-day exposure classification window after the index date,⁴⁴ with cumulative days' supply totaling ≥ 60 days (eFigure 3). A prescription was determined to occur in a 30-day period if it was dispensed in that period, or if the date of fill plus days' supply fell within that 30-day period. We defined short- to medium-term opioid therapy (SMTOT) as < 60 cumulative days' supply and/or < 1

opioid prescription per 30-day period. On day 90 (anchoring date) patients were classified as exposed to LTOT or SMTOT (eFigure 2C, 3).

Outcomes & Follow-up

The outcome of interest was incident nonfatal or fatal opioid overdose within three years. In inpatient, outpatient, and ED claims, clinically recognized opioid overdose was defined using ICD-9-CM and ICD-10-CM diagnosis codes (eTable 3).^{45,46} For ICD-10-CM codes, we included codes for any type of opioid-related poisoning, limited to initial encounters. In death records, fatal opioid overdose was defined using ICD-10 codes³⁷ for underlying and contributing causes (eTable 4).

We followed patients forward from the anchoring date until first of (1) opioid overdose (outcome), (2) cancer diagnosis or death not due to opioid overdose (competing risks^{47,48}), or (3) disenrollment or administrative censoring at three years of follow-up or September 30, 2018 (censoring event).

Patient Characteristics

We identified clinical and demographic characteristics *a priori* as potential confounders using a directed acyclic graph (eFigure 4). Characteristics identified at the index date included derived clinical indication (surgery, acute pain, or chronic pain), initial opioid dose (<20, 20–49, 50–89, 90+) in morphine milligram equivalents (MMEs) (eMethods), opioid duration of action (e.g., extended-release), sex, age (modeled using restricted cubic spline with 3 knots), and year (categorical: 2006–2009, 2010–2016, 2017–2018). Additional clinical characteristics included prescriptions for benzodiazepines, other anxiolytics, selective serotonin reuptake inhibitors (SSRI), other antidepressants, gabapentin, diagnosed depression, anxiety or post-traumatic stress disorder (PTSD), non-opioid substance use disorders (SUD), chronic obstructive pulmonary disease (COPD), acute or chronic back/neck pain, neuropathic pain, or arthritis pain ≤ 180 days before the index date. Finally, we identified inpatient or ED visits ≤ 30 days before the index date.

Statistical analyses

Our primary aim was to examine the association between LTOT and three-year risk of opioid overdose. We used stabilized inverse probability (IP) of treatment weights (IPTW), derived from propensity scores estimated using conditional logistic regression (eMethods) to account for measured confounding (described above). To account for informative censoring from disenrollment, we estimated time-varying stabilized IP censoring weights (IPCW) using pooled logistic regression, accounting for exposure status and baseline covariates described above in *Patient Characteristics*. We multiplied IPTW by IPCW to obtain total IP weights (IPW), and truncated IPW at the upper and lower 0.02%. We assessed covariate balance after weighting using standardized mean differences (eFigure 5). We used the cumulative incidence function accounting for competing risks^{47–49} (see Outcomes & Follow-up, above) to calculate weighted risk differences (RD_w) at six, 12, 24, and 36 months, using robust variance estimators to obtain conservative 95% confidence intervals (CI). Additionally, we used Fine-Gray⁴⁹ models to estimate weighted sub-distribution

hazard ratios (HR_w) with robust standard errors. We used the Efron method⁵⁰ for tied event times and Schoenfeld's residuals to evaluate the proportional hazards assumption.

Our secondary aim was to examine modification of the association between LTOT and opioid overdose by derived clinical indication (chronic pain versus acute pain or surgery). We examined the magnitude of stratum-specific estimates and CI overlap for evidence of meaningful modification.

We conducted two sensitivity analyses examining the robustness of our findings to varying LTOT definitions. First, we relaxed the LTOT definition to ≥ 1 prescription per 30-days without a days' supply requirement, re-estimated IPW and repeated primary analyses. Second, we categorized patients as exposed to short-term (without ≥ 1 prescription per 30-days or < 30 days' supply), medium-term (≥ 1 prescription per 30-days, 30–59 days' supply), and long-term (≥ 1 prescription per 30-days, ≥ 60 days' supply) opioid therapy. We re-estimated IPTW using multinomial logistic regression and repeated primary analyses.

Finally, we investigated the threat of survivor bias due to exclusion of overdoses occurring in the 90-day exposure window ($n=74$), described in eMethods.

Data management was completed in SAS 9.4 (Cary, NC) and analyses in R v3.6.0 (eTable 5).^{51,52}

RESULTS

We identified 491,369 patients initiating opioids for a pain indication between July 1, 2006 and July 1, 2018 (eFigure 6). Of these, 8,268 patients (1.7%) went on to receive LTOT (Table 1). Patients with LTOT were more likely to be aged 45–64 and were majority male. Most (77%) with LTOT had a clinical indication of chronic pain, versus 32% with SMTOT. Counter-intuitively, patients with LTOT were less likely to receive an initial dose of 50–89 MMEs (LTOT: 11%, SMTOT: 21%) or ≥ 90 MMEs (8%, 10%) but were more likely to receive longer initial days' supply. Patients with LTOT were more likely to have had recent prescriptions for benzodiazepines (26%, 12%), SSRIs (17%, 12%), other antidepressants (19%, 9%), or gabapentin (13%, 3%). LTOT patients also had higher prevalence of comorbidities.

Median follow-up was 793 (interquartile range [IQR]: 319–1095) days. Patients with LTOT contributed less follow-up (median 643 days [IQR: 268–1095]) than patients with SMTOT (796 days [320–1095]), due to the distribution of patient outcomes by exposure (eTable 6). We identified 347 incident opioid overdoses within three years of follow-up, 17% ($n=60$) of which were fatal. The proportion of overdoses that were fatal was higher among patients with LTOT (24% vs. 17%). The crude overall three-year risk of opioid overdose was 0.10% (95% CI: 0.09, 0.11), and cumulative incidence was consistently higher in patients with LTOT compared to SMTOT (eFigure 7).

In weighted analyses, cumulative incidence of opioid overdose among patients with LTOT was consistently higher than patients with SMTOT after the first five months of follow-up (Figure 1). The three-year risk of opioid overdose was 0.3 percentage points ($RD_w = 0.003$,

95% CI: 0.001, 0.005) higher among patients exposed to LTOT compared to SMTOT (Figure 3, eTable 7). The weighted hazard of opioid overdose was 4.4 times as high ($HR_w = 4.42$, 95% CI 2.41, 8.11) among patients with LTOT compared to SMTOT (Figure 4, eTable 8).

In stratified analyses, patients with a chronic pain indication who were exposed to LTOT had higher risk of opioid overdose after the first five months of follow-up than patients with SMTOT (eFigure 8). Patients with an acute pain or surgery indication and exposed to LTOT also had higher three-year risk of opioid overdose than patients with SMTOT, although with considerable CI overlap. Stratified estimates did not differ significantly from each other at any point during follow-up, so we cannot infer meaningful modification by initial clinical indication (Figure 2). Stratified results are imprecise at later points of follow-up due to small case counts and should be interpreted with caution.

Sensitivity Analyses

In the first sensitivity analysis, 25,076 patients (5.1%) had LTOT. The trend in the relationship between LTOT and opioid overdose was similar to the primary analysis, but estimates were attenuated towards the null (Figure 3, eTable 7). The weighted hazard of opioid overdose was 3.1 times as high ($HR_w = 3.12$, 95% CI 2.10, 4.66) among patients with LTOT compared to SMTOT (Figure 4, eTable 8).

In our second sensitivity analysis (categorical exposure), 473,255 patients (96.3%) received short-term, 9,846 (2.0%) had medium-term, and 8,268 (1.7%) received long-term opioid therapy. The absolute RDs comparing patients exposed to LTOT to patients with short-term opioid therapy were comparable to the primary analysis (Figure 3, eTable 7). Further, cumulative incidence of opioid overdose among patients with medium-term opioid therapy was consistently higher than among patients with short-term therapy through three years. However, the magnitude of the association was smaller than estimates comparing LTOT to short-term therapy after the first year of follow-up. These results suggest a possible dose-response relationship between duration of opioid therapy and subsequent overdose risk, particularly as time since initiation increases.

Finally, we examined outcomes occurring <90 versus ≥90 days after the index date (eMethods). In summary, an ED visit ≤30 days before the index date was the only significant difference, suggesting there was likely not strong measurable selective pressure leading to survivor bias in primary analyses.

DISCUSSION

In this cohort of patients initiating prescription opioids for pain or surgery, cumulative incidence of opioid overdose was notably higher among patients with LTOT compared to SMTOT. Further, our results were robust to varying exposure definitions for duration of opioid therapy. Less conservative definitions still demonstrated increased risk of opioid overdose among patients exposed to LTOT, as well as a possible dose-response relationship between duration of opioid therapy and subsequent overdose risk when using a categorical

exposure definition. We did not observe meaningful modification of the relationship between duration of opioid therapy and risk of opioid overdose by derived clinical indication.

In our study, 1.7% of patients initiating opioids went on to have LTOT. This is lower than many,^{32,33,53} but not all,^{32,33,54} previous estimates of LTOT incidence after surgery or for chronic pain management among opioid-naïve patients. There is no consistent definition of LTOT used in the literature,^{32,33} and our LTOT definition is more conservative than in many previous studies,^{32,33,53} requiring monthly exposure to prescription opioids with ≥ 60 total days' supply within 90 days following opioid initiation. This conservative definition focuses on consistent exposure to opioid therapy compared to definitions that only account for whether the patient receives a prescription at some point in the future, which may lead to classification of a later separate prescription of possibly different etiology as related to the initial opioid therapy episode despite a gap in treatment. Our approach minimized the likelihood that we were evaluating patients exposed to repeated short-term episodes of opioid therapy, instead measuring overdose risk in patients continuously exposed to opioid therapy. Relaxing our LTOT definition to monthly exposure with no days' supply requirement resulted in 5.1% of patients exposed to LTOT in our population, consistent with the range of previous estimates using less conservative LTOT definitions among opioid-naïve patients.^{32,55,56}

Our findings are consistent with existing evidence that LTOT is associated with higher risk of adverse outcomes, including OUD and overdose,^{5,55} and reinforce the importance of CDC prescribing guidelines that emphasize minimizing initial duration of opioid therapy whenever possible.^{28,29} While prescription opioids have an important role in pain management, the clinical benefit of LTOT compared to treatment with non-opioid analgesics has been called into question.^{28–30}

Presumably unintended long-term use has been noted as an adverse outcome of postsurgical and acute pain management, where opioid therapy continues past the expected window of healing.^{20,25,26,53,55–57} Several challenges in managing CNCP that can increase risk of OUD and opioid overdose have been noted in previous research, including dose escalations and hyperalgesia,^{58,59} tapering or stoppage of opioids,^{28,35,60} and use of long-acting versus short-acting opioids in pain management.^{29,61,62} However, we did not find strong evidence of modification by derived clinical indication.

Consistent with previous work, patients with LTOT in our study had higher prevalence of baseline characteristics that are known risk factors for opioid overdose, including benzodiazepines, extended-release opioids,⁶¹ SUD, depression and anxiety, and COPD.^{26,32,56,63,64} These findings suggest that patients initiating opioids who transition to LTOT have several clinical comorbidities that not only are known to increase risk of LTOT but also opioid-related morbidity and mortality. We controlled for these factors using IPTW and still observed increased risk of opioid overdose among patients exposed to LTOT. Despite our methodologically rigorous approach, our results may be subject to residual or unmeasured confounding common with insurance claims, which may under-measure important confounders such as SUDs and mental health conditions.

Our study makes use of a large population of privately insured patients in NC during the height of the prescription opioid epidemic. While many previous studies have examined prescription opioid use in specific surgical or chronic pain cohorts, we used a broad population of patients initiating opioids for a derived postsurgical or nonsurgical pain indication. However, our results in this privately insured NC population may not generalize to the larger US population. Our study population was also restricted to patients without a history of cancer; therefore, our results may not generalize to patients prescribed opioids for cancer-related pain. Additionally, we excluded patients with a history of OUD and overdose to obtain a study population of patients without a history of opioid use, thus our results do not generalize to patients with a history of OUD who might be at increased risk of opioid overdose after starting opioids for pain management.

There are several additional limitations worth noting. First, pharmaceutical claims only capture prescriptions that were filled and billed to insurance, not medications paid for out of pocket or what was consumed. However, we believe our LTOT definition more adequately captures true consistent long-term use than prior definitions. Second, claims data under-measure opioid overdoses, with studies demonstrating low sensitivity but high specificity and acceptable positive predictive values.^{45,46} Fatal opioid overdoses are also under-measured in death records,⁶⁵ but we used linked death records to identify fatal events that may be missed in claims data. Additionally, we do not expect differential outcome classification by duration of therapy so do not expect this under-measurement to be a significant source of bias. Further, because diagnostic codes for opioid overdose have high specificity, clinically recognized opioid overdoses are likely true opioid overdoses. Finally, to measure long-term risk of opioid overdose by duration of opioid therapy we restricted our study population to patients with ≥ 90 days of follow-up after their index date, excluding acute outcomes occurring within 90 days. Results from sensitivity analyses suggested that there was likely not a strong measurable selective pressure leading to survivor bias. We further addressed selection bias from missed outcomes >90 days using IPCW to account for informative censoring.

CONCLUSIONS

While a small minority of patients initiating opioid therapy had LTOT, they had notably higher risk of opioid overdose. Further, we found evidence of a potential dose-response relationship between duration of opioid therapy and risk of opioid overdose. The literature lacks a standard LTOT definition, and this analysis utilized a more conservative LTOT definition than many previous studies. Future work should examine this definition in other patient populations. While opioid therapy has an important role in pain management, these findings reinforce the importance of CDC guidelines to minimize the duration of opioid therapy whenever possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Long-term opioid therapy (LTOT) is known to be associated with opioid overdose, but the LTOT definition varies widely across studies, with many not accounting for consistent long-term use.
- We aimed to build upon prior research by applying a rigorous LTOT definition to analyze the association between LTOT and opioid overdose and examine whether this relationship is modified by initial pain indication.
- LTOT was associated with increased risk of opioid overdose using a rigorous exposure definition. There was not strong evidence of modification by initial indication.
- Our findings confirm the importance of CDC guidelines to minimize duration of opioid therapy.

PLAIN LANGUAGE SUMMARY

Long-term opioid therapy (LTOT) is known to be associated with opioid overdose, but the LTOT definition varies widely across studies. Many studies use LTOT definitions that do not fully account for consistent long-term prescription opioid use. We sought to add to the literature on risks associated with LTOT by using a rigorous definition of LTOT that more appropriately considers consistent prescription opioid use. We also sought to examine whether risk of opioid overdose by duration of opioid therapy differs by the original pain indication associated with prescription opioid initiation (modification). Among a cohort of privately insured adult patients (18–64 years) in North Carolina who were newly initiating prescription opioids after a diagnosis of acute pain or chronic pain or after surgery, we found that LTOT was associated with increased risk of opioid overdose over three years using a rigorous exposure definition and that this relationship held when we relaxed our LTOT definition in sensitivity analyses. However, there was not strong evidence of modification by the initial pain indication. Our findings confirm the importance of CDC guidelines to minimize duration of opioid therapy or prioritize non-opioid therapy, particularly for acute pain.

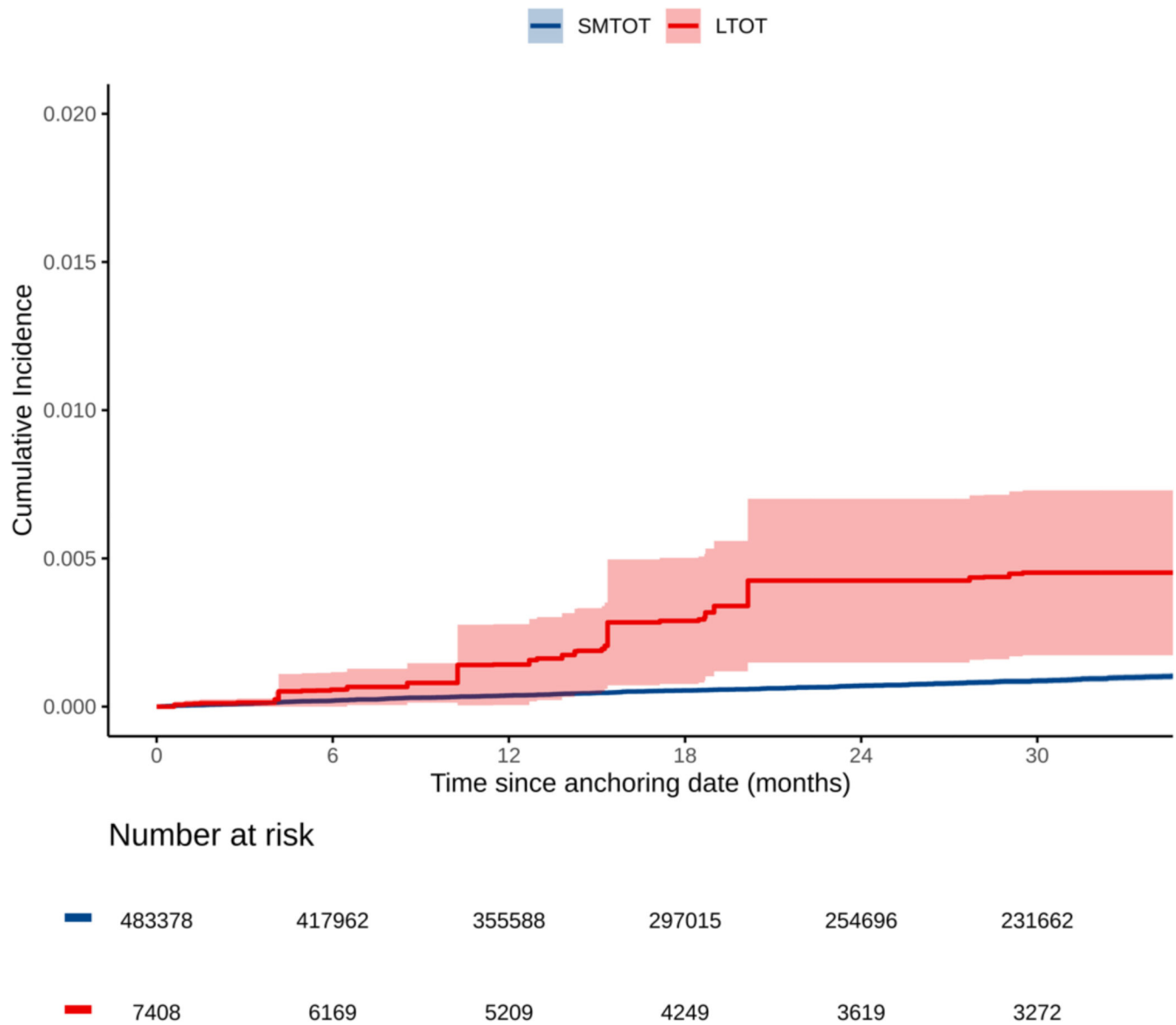


Figure 1. Weighted cumulative incidence of opioid overdose by duration of opioid therapy. Among 491,369 initiating opioid therapy following a pain diagnosis or surgery in North Carolina from 2006 to 2018. Abbreviations: SMTOT, short-to-medium-term opioid therapy; LTOT, long-term opioid therapy

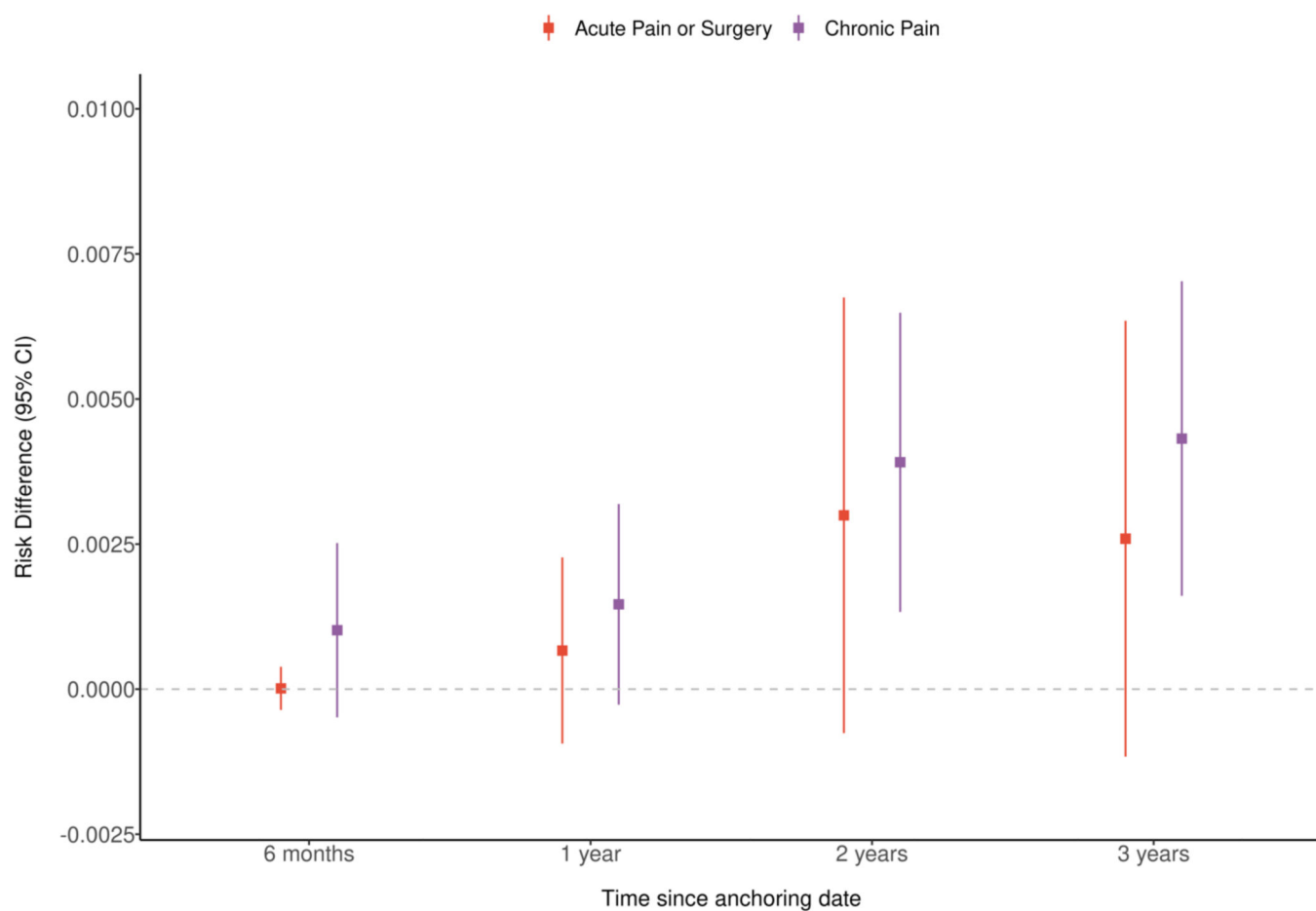


Figure 2. Weighted risk differences comparing LTOT to SMTOT, stratified by clinical indication of acute pain or surgery versus chronic pain.

Among 491,369 initiating opioid therapy following a pain diagnosis or surgery in North Carolina from 2006 to 2018. Abbreviations: SMTOT, short-to-medium-term opioid therapy; LTOT, long-term opioid therapy; CI, confidence interval

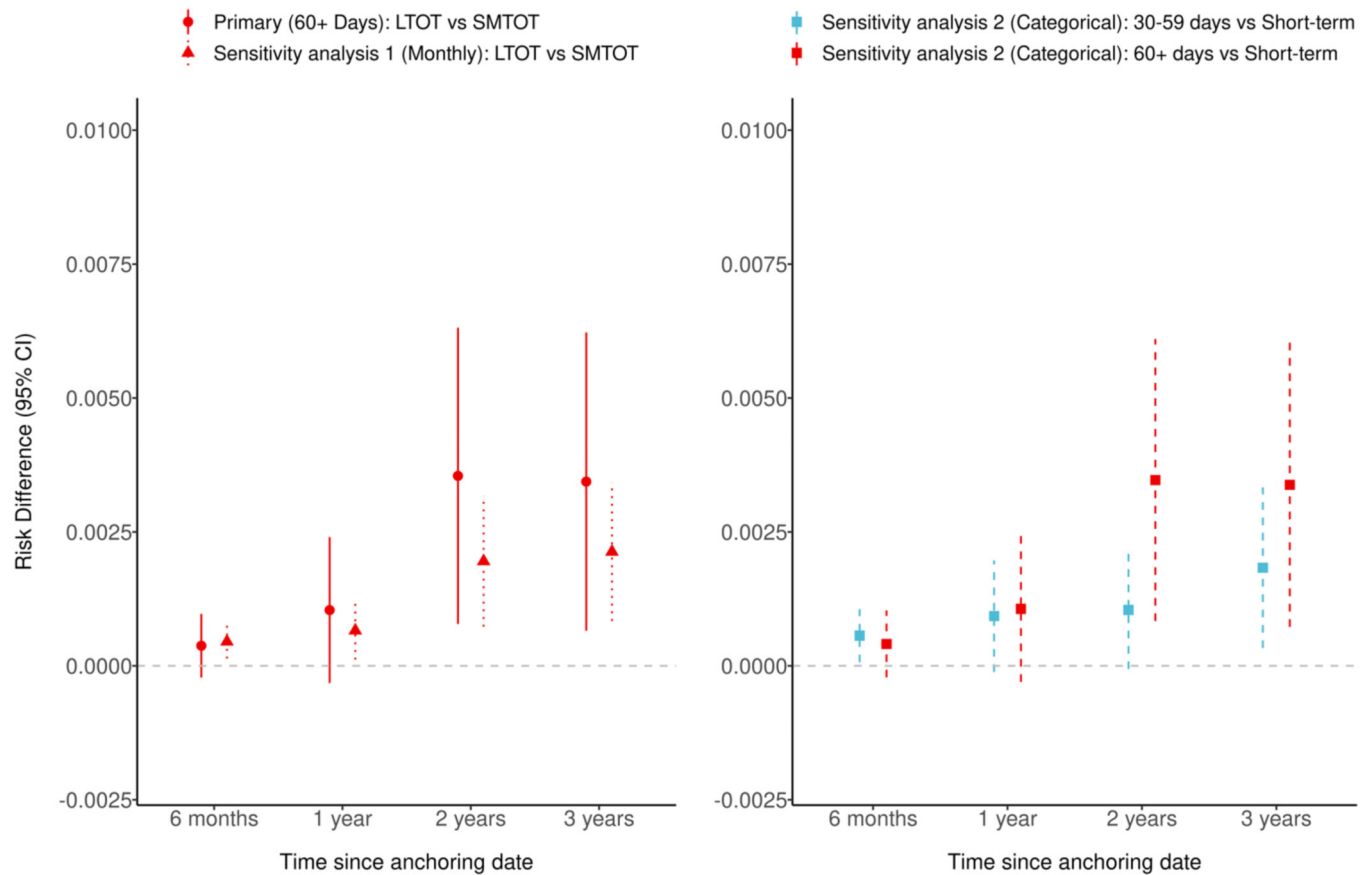


Figure 3. Weighted risk difference of opioid overdose comparing longer duration of opioid therapy to short-term opioid therapy through three years of follow-up, using varying exposure definitions.

Among 491,369 initiating opioid therapy following a pain diagnosis or surgery in North Carolina from 2006 to 2018. Abbreviations: SMTOT, short-to-medium-term opioid therapy; LTOT, long-term opioid therapy; CI, confidence interval

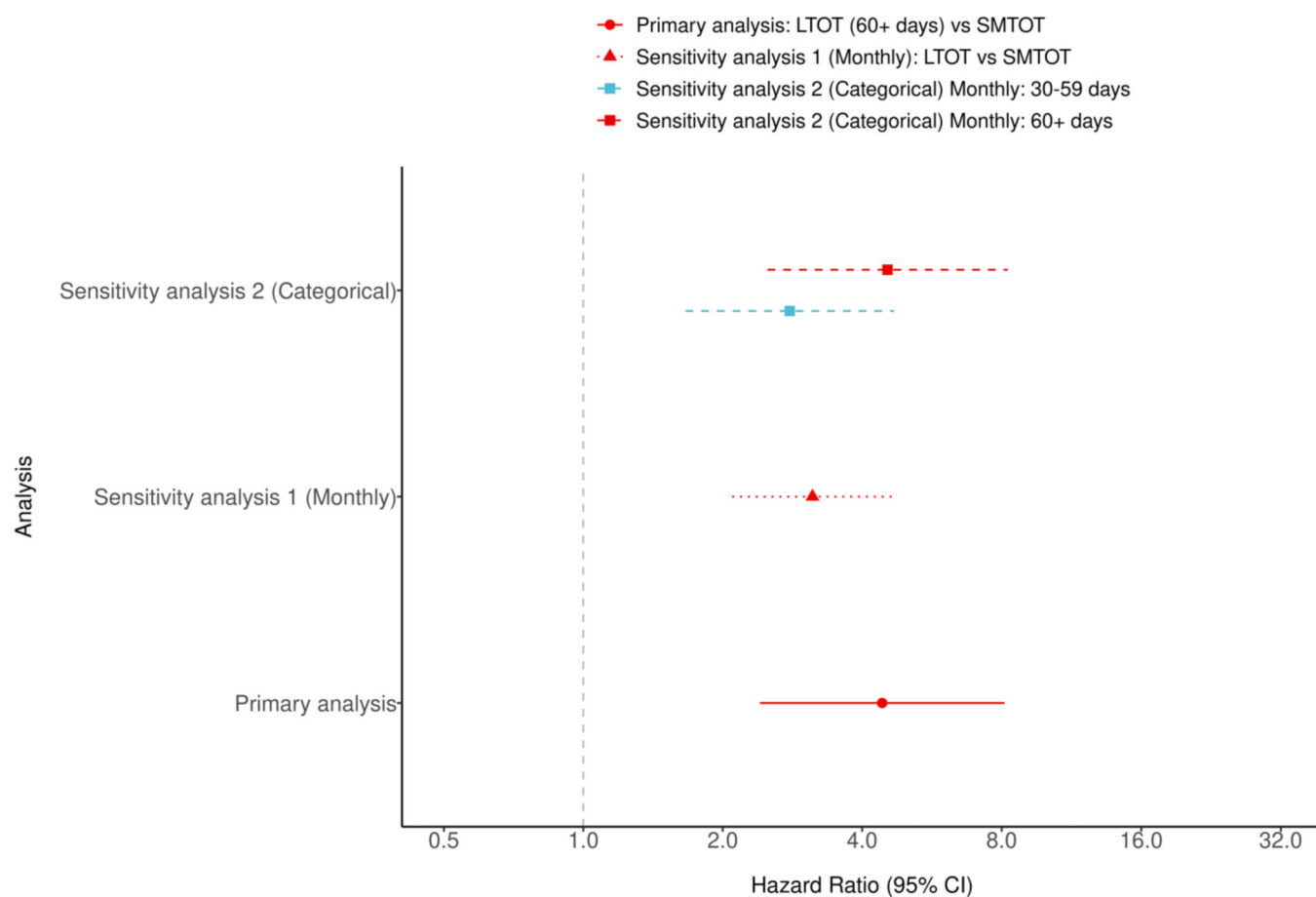


Figure 4. Weighted hazard ratios comparing longer duration of opioid therapy to short-term opioid therapy, using varying exposure definitions.

Among 491,369 initiating opioid therapy following a pain diagnosis or surgery in North Carolina from 2006 to 2018. Abbreviations: SMTOT, short-to-medium-term opioid therapy; LTOT, long-term opioid therapy; CI, confidence interval

Table 1.

Baseline demographic and clinical characteristics of patients initiating opioid analgesics following a pain diagnosis or surgery in North Carolina, 2006–2018

	Overall (n= 491369)	SMTOT (n= 483101)	LTOT (n= 8268)
Derived clinical indication (%)			
Surgery	173837 (35.4)	172946 (35.8)	891 (10.8)
Acute pain	156372 (31.8)	155345 (32.2)	1027 (12.4)
Chronic pain	161160 (32.8)	154810 (32.0)	6350 (76.8)
Age category (%)			
18–24	43426 (8.8)	43189 (8.9)	237 (2.9)
25–34	93560 (19.0)	92424 (19.1)	1136 (13.7)
35–44	119714 (24.4)	117913 (24.4)	1801 (21.8)
45–54	130805 (26.6)	128069 (26.5)	2736 (33.1)
55–64	103864 (21.1)	101506 (21.0)	2358 (28.5)
Sex: Female (%)	246910 (50.2)	243249 (50.4)	3661 (44.3)
Year (%)			
2006	30332 (6.2)	29868 (6.2)	464 (5.6)
2007	58959 (12.0)	58026 (12.0)	933 (11.3)
2008	53498 (10.9)	52669 (10.9)	829 (10.0)
2009	49863 (10.1)	49025 (10.1)	838 (10.1)
2010	44402 (9.0)	43705 (9.0)	697 (8.4)
2011	38899 (7.9)	38248 (7.9)	651 (7.9)
2012	35432 (7.2)	34838 (7.2)	594 (7.2)
2013	34321 (7.0)	33677 (7.0)	644 (7.8)
2014	36084 (7.3)	35346 (7.3)	738 (8.9)
2015	37612 (7.7)	36834 (7.6)	778 (9.4)
2016	30108 (6.1)	29581 (6.1)	527 (6.4)
2017	29255 (6.0)	28810 (6.0)	445 (5.4)
2018	12604 (2.6)	12474 (2.6)	130 (1.6)
Pain Diagnoses:			
Back or neck (%)	155516 (31.6)	150894 (31.2)	4622 (55.9)
Arthritis (%)	41535 (8.5)	39985 (8.3)	1550 (18.7)
Neuropathic (%)	39377 (8.0)	37866 (7.8)	1511 (18.3)
Benzodiazepines (%)	61734 (12.6)	59594 (12.3)	2140 (25.9)
Anxiolytics (%)	8898 (1.8)	8636 (1.8)	262 (3.2)
SSRI (%)	57934 (11.8)	56494 (11.7)	1440 (17.4)
Other antidepressants (%)	45154 (9.2)	43569 (9.0)	1585 (19.2)
Gabapentin (%)	13152 (2.7)	12095 (2.5)	1057 (12.8)
Depression (%)	35250 (7.2)	34165 (7.1)	1085 (13.1)
Anxiety or PTSD (%)	40171 (8.2)	38962 (8.1)	1209 (14.6)
Substance Use Disorder (%)	5868 (1.2)	5629 (1.2)	239 (2.9)
COPD (%)	11561 (2.4)	11179 (2.3)	382 (4.6)

	Overall (n= 491369)	SMTOT (n= 483101)	LTOT (n= 8268)
Initial dose (MME) (%)			
<20MMEs	62219 (12.7)	59101 (12.2)	3118 (37.7)
20-<50MMEs	276833 (56.3)	273173 (56.5)	3660 (44.3)
50-<90MMEs	103735 (21.1)	102868 (21.3)	867 (10.5)
90+MMEs	48582 (9.9)	47959 (9.9)	623 (7.5)
Initial days' supply (%)			
0–3 Days' Supply	160209 (32.6)	159716 (33.1)	493 (6.0)
4–7 Days' Supply	223186 (45.4)	222006 (46.0)	1180 (14.3)
8–14 Days' Supply	65575 (13.3)	64595 (13.4)	980 (11.9)
15–30 Days' Supply	41671 (8.5)	36347 (7.5)	5324 (64.4)
>30 Days' Supply	728 (0.1)	437 (0.1)	291 (3.5)
Emergency department visit (%)	132414 (26.9)	131196 (27.2)	1218 (14.7)
Inpatient visit (%)	52768 (10.7)	52022 (10.8)	746 (9.0)
Extended-release opioid (%)	3314 (0.7)	2805 (0.6)	509 (6.2)

Abbreviations: SMTOT, short-to-medium-term opioid therapy; LTOT, long-term opioid therapy; SSRI, selective serotonin reuptake inhibitor; PTSD, post-traumatic stress disorder; COPD, chronic obstructive pulmonary disease; MME, morphine milligram equivalents