Original Investigation

Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain

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IMPORTANCE Long-acting opioids increase the risk of unintentional overdose deaths but also may increase mortality from cardiorespiratory and other causes.

OBJECTIVE To compare all-cause mortality for patients with chronic noncancer pain who were prescribed either long-acting opioids or alternative medications for moderate to severe chronic pain.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study between 1999 and 2012 of Tennessee Medicaid patients with chronic noncancer pain and no evidence of palliative or end-of-life care.

EXPOSURES Propensity score–matched new episodes of prescribed therapy for long-acting opioids or either analgesic anticonvulsants or low-dose cyclic antidepressants (control medications).

MAIN OUTCOMES AND MEASURES Total and cause-specific mortality as determined from death certificates. Adjusted hazard ratios (HRs) and risk differences (difference in incidence of death) were calculated for long-acting opioid therapy vs control medication.

RESULTS There were 22 912 new episodes of prescribed therapy for both long-acting opioids and control medications (mean [SD] age, 48 [11] years; 60% women). The long-acting opioid group was followed up for a mean 176 days and had 185 deaths and the control treatment group was followed up for a mean 128 days and had 87 deaths. The HR for total mortality was 1.64 (95% CI, 1.26-2.12) with a risk difference of 68.5 excess deaths (95% CI, 28.2-120.7) per 10 000 person-years. Increased risk was due to out-of-hospital deaths (154 long-acting opioid, 60 control deaths; HR, 1.90; 95% CI, 1.40-2.58; risk difference, 67.1; 95% CI, 30.1-117.3) excess deaths per 10 000 person-years. For out-of-hospital deaths other than unintentional overdose (120 long-acting opioid, 53 control deaths), the HR was 1.72 (95% CI, 1.24-2.39) with a risk difference of 47.4 excess deaths (95% CI, 15.7-91.4) per 10 000 person-years. The HR for cardiovascular deaths (79 long-acting opioid, 36 control deaths) was 1.65 (95% CI, 1.10-2.46) with a risk difference of 28.9 excess deaths (95% CI, 4.6-65.3) per 10 000 person-years. The HR during the first 30 days of therapy (53 long-acting opioid, 13 control deaths) was 4.16 (95% CI, 2.27-7.63) with a risk difference of 200 excess deaths (95% CI, 80-420) per 10 000 person-years.

CONCLUSIONS AND RELEVANCE Prescription of long-acting opioids for chronic noncancer pain, compared with anticonvulsants or cyclic antidepressants, was associated with a significantly increased risk of all-cause mortality, including deaths from causes other than overdose, with a modest absolute risk difference. These findings should be considered when evaluating harms and benefits of treatment.

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The pronounced increase in prescribing opioid analgesics for chronic noncancer pain has led to escalating concern about potential harms.[1] The increase in opioid prescribing is paralleled by an increase in overdose deaths,[1-3] and there is a dose-related elevation in the risk of overdose hospitalization or death.[4,5] However, the focus on drug overdose may underestimate the harms of opioid analgesics. Opioids can cause or exacerbate sleep-disordered breathing,[6] potentially increasing the risk of adverse cardiovascular events.[7] Opioids also have adverse psychomotor,[8] endocrine,[8] gastrointestinal,[9] and immunologic[10] effects. Long-acting opioids, included in chronic pain guidelines and recommended for patients with frequent or constant pain,[11] are of particular concern because the prolonged drug levels might increase toxicity. Their more frequent use has been associated with an increase in deaths from opioid overdose.[1,3]Thus, comparative studies of the safety of long-acting opioids relative to other therapy for chronic noncancer pain are needed. Common alternative medications for moderate to severe chronic pain include analgesic anticonvulsants[12,13] and low-dose cyclic antidepressants.[14] Although these drugs are thought to be relatively safe, they do have potentially serious adverse effects.[12,15] However, there are limited data from population-based studies about the comparative safety of long-acting opioids.

This study compared the risk of death among patients initiating long-acting opioid therapy for chronic noncancer pain with that for matched patients initiating therapy with either an analgesic anticonvulsant or a low-dose cyclic antidepressant. There were 3 questions. First, did total mortality differ between the 2 groups? Second, what was the relative risk of deaths outside the hospital, which are less likely to be due to existing conditions and most plausibly related to opioid adverse effects?[16] Third, were there differences in the risk of deaths other than those from unintentional medication overdose?

Methods

Cohort

This retrospective cohort study included Tennessee Medicaid enrollees initiating therapy with a study drug from 1999 through 2012. The Medicaid files provided an efficient source of data for identifying the cohort, determining periods of probable exposure to medications, and ascertaining deaths.[17,18] The Medicaid data included enrollment, pharmacy, hospital, outpatient, and nursing home files, augmented with linkage to death certificates[17,19] and a statewide hospital discharge database. The study was reviewed and approved by the institutional review boards of Vanderbilt University and the State of Tennessee Health Department, which waived informed consent.

To improve study capacity to identify medication-related deaths, thus reducing the potential for confounding, the cohort was limited to patients without evidence of cancer, or palliative, or end-of-life care (eTables 1 and 2 in the Supplement).[20] Thus, the cohort excluded persons aged 75 years or older; patients with cancer, other life-threatening diseases, or evidence of hospice or other terminal care; and nursing home residents. Hospitalized patients could not enter the cohort until 30 days after discharge, because deaths during this period may have been related to the reasons for the hospitalization. Persons with recorded evidence of drug abuse were excluded, given the increased risk of abuse-related medication overdose.

The cohort consisted of qualifying patients initiating therapy[21] with the study drugs who had a diagnosis of chronic pain (back, other musculoskeletal, abdominal, headache, other neurologic pain) in the past 90 days. The study drugs were the long-acting opioids (sustained release [SR] morphine, controlled release [CR] oxycodone, transdermal fentanyl, and methadone). The control drugs were either anticonvulsants indicated for chronic pain (gabapentin, pregabalin, carbamazepine) or low-dose cyclic antidepressants (eTable 5 in the Supplement). Patients had a new episode of therapy when they filled a study drug prescription with no prior fill for a drug in that class for the previous year (except for the past 30 days, permitting inclusion of persons starting drug after hospitalization). They could not have had a prescription filled in the prior year for any of the other study drugs. Patients were excluded if the starting daily dose (eTables 3-5 in the Supplement) was not recommended for chronic pain (cyclic antidepressants >150-mg amitriptyline equivalents) or was unusually high (long-acting opioids >180-mg morphine equivalents,[22] or anticonvulsants >1800-mg gabapentin equivalents).

Matching

To reduce potential confounding, new episodes of therapy for long-acting opioids were matched to new episodes of therapy for the control drugs according to propensity score, the probability of long-acting opioid use, given the study covariates on cohort entry. These were factors with a plausible direct or indirect relation to both study drug use and mortality (eTable 6 in the Supplement). The 122 covariates included demographic characteristics, diagnoses related to chronic pain, use of short-acting opioids and other medications for pain, benzodiazepines and other psychotropic medications linked with risk of overdose death,[23] psychiatric diagnoses, cardiovascular conditions, respiratory diseases, other illnesses, and medical care utilization.

The frequency matching was performed by dividing the cohort into centiles (1%) according to the long-acting opioid propensity score distribution. Within each centile, one patient prescribed the control drug was randomly selected for every patient prescribed an opioid, randomly discarding patients receiving opioids if there were too few patients receiving the control drug. The random frequency matching increased the likelihood that all matches were of equal quality and permitted an unmatched analysis. The final cohort consisted of 1:1 frequency-matched new episodes of therapy with the long-acting opioids and the control drugs (eTable 6 in the Supplement).

Follow-up

Patients entered the cohort on the date of the filling of the first study drug prescription. They left the cohort on the earliest

of completing 1 year without filling a study drug prescription, filling a prescription for a drug in a different class (eg, when a patients who had been prescribed a long-acting opioid or an anticonvulsant started a cyclic antidepressant, regardless of dose), dying, not meeting inclusion-exclusion criteria, or coming to the end of the study. Patients who left the cohort could reenter if they subsequently became eligible. Because the episodes were nonoverlapping and the end point occurred only once, statistical independence assumptions were satisfied.[24]

Follow-up was further restricted to the dispensed days of medication therapy included in each study prescription, the time during which patients were most likely to be taking the drug. This period was defined as the interval between the filling of the prescription and the earliest of the end of the days of supply, filling of a subsequent prescription for a drug in the same class, or end of study follow-up. Person-time from the day after hospital admission through the 30 days following discharge was not considered active medication therapy because in-hospital medication data were unavailable and post-discharge medication changes could take up to 1 refill interval to become known.

End Points

The end point was all deaths that occurred during the study follow-up. Hospital death was defined as occurring if patients were admitted to the hospital on a day during which they had used one of the study drugs and died either while in the hospital or within 30 days of admission. All other deaths were considered out-of-hospital deaths (including patients who died in the emergency department) and were further classified as unintentional medication overdose or other deaths. The latter included cardiovascular, respiratory, other injury, or other deaths (eTable 7 in the Supplement). In 1 analysis, we examined cardiovascular mortality for the subgroups defined by specific cardiovascular diagnoses (eTable 8 in the Supplement).

Statistical Analysis

The statistical analysis compared the adjusted risk of death during follow-up for patients in the long-acting opioid group with those in the control medication group. Relative risk was estimated with the hazard ratio (HR), calculated from Cox regression models (Statistical Analysis section in the Supplement). To adjust for residual confounding, regression models were stratified according to deciles of the baseline propensity score.[25] The primary models included age, calendar year, and study medication as time-dependent covariates, estimated via a counting process formulation that accommodates nonproportional hazards.[26(p172)] Other time-dependent covariates were not included in the primary analysis because these might be on the causal pathway for mortality (eg, nonfatal injury). A sensitivity analysis included a time-dependent propensity score[27] that accounted for changes in study covariates during follow-up (Statistical Analysis section in the Supplement).

The adjusted risk difference, or difference in the incidence of death between patients in both groups, was estimated. The risk difference was calculated as $I_0 \times (HR - 1)$, for which HR is the adjusted HR and I_0 the unadjusted incidence for patients in the control medication group. The 95% CIs were calculated analogously.

The analysis included a time-dependent analysis of the relation of duration of study drug therapy and dose during follow-up to total study mortality. Duration was defined as cumulative dispensed days of therapy on the day a study drug prescription was filled. Cut points for low (≤cut point) vs high dose (>cut point) were the approximate median time-dependent doses: 60-mg/d morphine equivalents, 600-mg/d gabapentin equivalents, and 40-mg/d amitriptyline equivalents. The regression analysis was stratified by 20 quantiles of a time-dependent disease risk score (Statistical Analysis section in the Supplement).[28-30] The disease risk score, the risk of death as a function of the study covariates estimated for the reference exposure category, facilitates analyses for multiple exposure categories, given that propensity scores are less suited to nonbinary comparisons.[28-30]

Sensitivity analyses that assessed populations of particular interest or tested study assumptions were performed. These included exclusion of patients prescribed methadone, restriction of the cohort to patients with a diagnosis of neurologic pain, use of control groups consisting exclusively of propensity-score matched anticonvulsant or cyclic antidepressant patients, exclusion of patients entering the cohort before 2003, restriction of analysis to the first 180 days of therapy, exclusion of deaths with unknown cause from the cardiovascular death category, and expansion of the nonoverdose and cardiovascular death categories to include hospital deaths.

The effect of cardiovascular death misclassification was assessed (Sensitivity Analysis in the Supplement) by adjudication of a convenience sample of 50 deaths from a previous study of long-acting opioids for which medical records had been reviewed.[16] The analysis made the conservative assumption that control medication deaths were not misclassified.

All analyses were performed with SAS version 9.4 (SAS Institute Inc). All *P* values were 2-sided, with a *P* value <.05 indicating statistical significance.

Results

There were 23 308 new episodes of prescriptions for long-acting opioids and 131 883 new episodes of prescriptions for control medications (**Table 1**). These groups differed with regard to baseline characteristics, with standardized differences exceeding 10% for most study covariates (Table 1). After matching, the cohort included 22 912 long-acting opioid episodes and an equal number of control medication episodes. The matched long-acting opioid and control medication groups were more comparable, with no standardized difference exceeding 3% and the majority less than 1%. The mean (SD) age of the matched patients was 48 (11) years and 60% were women. The most common chronic pain diagnoses were back pain (75%), other musculoskeletal pain (63%), and abdominal pain (18%). More than 96% of study patients had filled a prescription for a short-acting opioid in the prior year, and 68% had a current prescription for these drugs at the beginning of follow-up. Patients frequently filled prescriptions for other pain

Table 1. Selected Baseline Characteristics for New Episodes of Prescribed Study Drug Therapy[a]

	No. (%) of Patients					
	Before Matching			After Matching		
	Anticonvulsant or Cyclic Antidepressant	Long-Acting Opioid	Standardized Difference, %	Anticonvulsant or Cyclic Antidepressant	Long-Acting Opioid	Standardized Difference, %
No. in cohort	131 883	23 308		22 912	22 912	
Demographics						
Age, mean (SD), y	46.7 (11.0)	47.9 (10.5)	11.2	47.9 (10.7)	47.9 (10.5)	0.0
Women	96 163 (73)	13 878 (60)	28.6	13 696 (60)	13 738 (60)	0.4
Medicaid disability enrollment	61 948 (47)	13 701 (59)	23.8	13 421 (59)	13 385 (58)	0.3
Chronic pain past 90 d						
Back pain	65 880 (50)	17 462 (75)	53.4	17 333 (76)	17 071 (75)	2.6
Other musculoskeletal pain	75 103 (57)	14 796 (63)	13.4	14 601 (64)	14 512 (63)	0.8
Abdominal pain	26 577 (20)	4167 (18)	5.8	4093 (18)	4108 (18)	0.2
Headache	29 782 (23)	2783 (12)	28.4	2663 (12)	2773 (12)	1.5
Other neurologic pain	25 343 (19)	3909 (17)	6.4	3736 (16)	3855 (17)	1.4
Short-acting opioid use						
Any use past year	110 487 (84)	22 468 (96)	43.2	22 203 (97)	22 072 (96)	3.2
>270 d use past year	13 937 (11)	6430 (28)	44.4	6025 (26)	6192 (27)	1.6
Current use	55 652 (42)	15 733 (68)	36.6	15 629 (68)	15 361 (67)	2.5
Current use of >60 mg morphine equivalents	6315 (5)	3440 (15)	34.1	3012 (13)	3239 (14)	2.9
Other analgesic or psychotropic drug past year						
Skeletal muscle relaxant	67 544 (51)	14 659 (63)	23.8	14 378 (63)	14 361 (63)	0.2
Nonsteroidal anti-inflammatory drug	95 366 (72)	16 099 (69)	7.1	16 008 (70)	15 886 (69)	1.2
Benzodiazepine	46 613 (35)	12 338 (53)	36.0	11 774 (51)	11 986 (52)	1.9
SSRI or SNRI	52 751 (40)	10 641 (46)	11.4	10 360 (45)	10 436 (46)	0.7
Trazodone	15 529 (12)	3046 (13)	3.9	2987 (13)	2997 (13)	0.1
Other comorbidity past year						
AMI, revascularization, or angina	7002 (5)	1426 (6)	3.5	1398 (6)	1402 (6)	0.1
Congestive heart failure	5219 (4)	1269 (5)	7.0	1239 (5)	1237 (5)	0.0
Cerebrovascular disease	6979 (5)	1236 (5)	0.0	1239 (5)	1213 (5)	0.5
COPD	18 696 (14)	4751 (20)	16.5	4593 (20)	4611 (20)	0.2
Asthma	14 501 (11)	2620 (11)	0.8	2488 (11)	2578 (11)	1.3
Home oxygen	5305 (4)	1416 (6)	9.4	1389 (6)	1372 (6)	0.3
Hospital stay	18 740 (14)	4108 (18)	9.3	3986 (17)	4025 (18)	0.4
Injury ED visit	37 430 (28)	7676 (33)	9.9	7635 (33)	7531 (33)	1.0

Abbreviations: AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; ED, emergency department; SNRI, selective norepinephrine uptake inhibitor; SSRI, selective serotonin uptake inhibitor.

[a] The characteristics were selected that were considered to most likely to be associated with greater risk of mortality and with the decision to prescribe a long-acting opioid. eTable 6 (in the Supplement) lists the distribution of all study covariates.

medications and psychotropic drugs, including skeletal muscle relaxants (63%), nonsteroidal anti-inflammatory drugs (70%), benzodiazepines (52%), and selective serotonin or serotonin and norepinephrine reuptake inhibitor antidepressants (45%).

The most commonly prescribed study medications in the cohort were morphine SR, gabapentin, and amitriptyline (**Table 2**). The median doses at the time of cohort entry were 50-mg morphine equivalents for the long-acting opioids, 600-mg gabapentin equivalents for the analgesic anticonvulsants, and 25-mg amitriptyline equivalents for the cyclic antidepressants.

Patients in the long-acting opioid group had 185 deaths during 11 070 person-years of follow-up (167.1 per 10 000 person-years), whereas patients in the control medication group had 87 deaths during 8066 person-years of follow-up (107.9 per 10 000). The adjusted HR for death from any cause during follow-up was 1.64 (95% CI, 1.26-2.12), and the risk difference was 68.5 (95% CI, 28.2-120.7) excess deaths per 10 000 person-years (**Table 3**). The elevated risk of death for long-acting opioids was confined to the out-of-hospital deaths (HR, 1.90; 95% CI, 1.40-2.58; risk difference, 67.1; 95% CI, 30.1-117.3 per 10 000 person-years), which constituted 79% of the study deaths. There was no increased risk of in-hospital deaths (HR, 1.00; 95% CI, 0.59-1.69; risk difference, 0; 95% CI −13.6 to 23.1 per 10 000 person-years). The HR for out-of-hospital deaths with a cause of death other than unintentional overdose was 1.72 (95% CI, 1.24-2.39) with a risk difference of 47.4 (95% CI, 15.7-91.4) per 10 000 person-years. The most frequent category of

nonoverdose deaths was cardiovascular deaths, with an HR of 1.65 (95% CI, 1.10-2.46) and a risk difference of 28.9 (95% CI, 4.6-65.3) per 10 000 person-years. Patients in the long-acting opioid group had elevated cardiovascular mortality for all of the subgroups defined by specific cardiovascular diagnoses, with the exception of diabetes (eTable 8 in the Supplement).

The increased mortality for the long-acting opioid group was limited to the first 180 days of prescribed therapy (**Figure**). During the first 30 days of therapy, the HR was 4.16 (95% CI, 2.27-7.63) and the risk difference was 200 (95% CI, 80-420) per 10 000 person-years; for the remainder of the first 180 days the HR was 1.56 (95% CI, 1.05-2.30) and the risk difference was 74 (95% CI, 7-172) per 10 000 person-years. By contrast, once patients in the long-acting opioid group had more than 180 days of therapy, their risk of death did not differ significantly from that of the control drug group (HR, 1.03; 95% CI, 0.67-1.57; risk difference, 3; 95% CI, −37-65 per 10 000 person-years).

For both low and high doses of study drugs, total mortality for long-acting opioid patients was greater than that for comparable patients in the control medication group (Figure). For low doses (≤60 mg of morphine or its equivalent) the HR was 1.54 (95% CI, 1.01-2.34) and the risk difference was 51 (95% CI, 1-126) per 10 000 person-years; for high doses (>60 mg morphine or its equivalent) the HR was 1.94 (95% CI, 1.40-2.70) and the risk difference was 111 (95% CI, 47-200) per 10 000 person-years. Similarly, patients in the long-acting opioid group had greater mortality within categories defined by baseline short-acting opioid doses of 30 mg or less or more than 30 mg morphine equivalents.

Sensitivity analyses that assessed populations of particular interest or tested study assumptions were performed (**Table 4**). In each case, findings were similar to those from the primary analysis.

The medical records–based cardiovascular death misclassification analysis (Sensitivity Analysis section in the Supplement) found that 44% of total out-of-hospital deaths in the convenience sample met the criteria for cardiovascular death, slightly lower than the 46% based on the death certificate underlying cause of death. This degree of misclassification would decrease the observed HR for cardiovascular deaths from 1.65 (95% CI, 1.10-2.46) to 1.58 (95% CI, 1.05-2.36), although, depending on the specific adjudication criteria, the HR could have

Table 2. Prescribed Study Drugs Before and After Matching

	Before Matching	After Matching
Patients		
Long-acting opioids, No. (%)		
All	23 308 (100)	22 912 (100)
Morphine SR	12 891 (55)	12 667 (55)
Oxycodone CR	5539 (24)	5446 (24)
Fentanyl transdermal	3377 (14)	3323 (14)
Methadone	1501 (6)	1476 (6)
Anticonvulsant or cyclic antidepressant, No. (%)		
All	131 883 (100)	22 912 (100)
Gabapentin	53 078 (40)	10 879 (47)
Pregabalin	7272 (6)	1403 (6)
Carbamazepine	3884 (3)	579 (3)
Amitriptyline	48 072 (36)	6959 (30)
Doxepin	7382 (6)	1266 (6)
Nortriptyline	7075 (5)	1071 (5)
Other cyclic antidepressant	5120 (4)	755 (3)
Dose, median (IQR), mg		
Long-acting opioids, morphine equivalents	50 (30-60)	50 (30-60)
Analgesic anticonvulsants, gabapentin equivalents	600 (300-900)	600 (300-900)
Cyclic antidepressants, amitriptyline equivalents	25 (25-50)	25 (25-50)

Abbreviations: CR, controlled release; IQR, interquartile range; SR, sustained release.

Table 3. Mortality According to Underlying Cause of Death

	Anticonvulsant or Cyclic Antidepressant (Person-Years of Follow-up = 8066)		Long-Acting Opioid (Person-Years of Follow-up = 11 070)				
Deaths	Deaths	Incidence per 10 000 Person-Years	Deaths	Incidence per 10 000 Person-Years	Adjusted Hazard Ratio (95% CI)[a]	Adjusted Risk Difference (95% CI)[a,b]	*P* Value
All	87	107.9	185	167.1	1.64 (1.26 to 2.12)	68.5 (28.2 to 120.7)	<.001
Out-of-hospital	60	74.4	154	139.1	1.90 (1.40 to 2.58)	67.1 (30.1 to 117.3)	<.001
Unintentional overdose[c]	7	8.7	34	30.7	3.37 (1.47 to 7.70)	20.6 (4.1 to 58.1)	.004
Other causes	53	65.7	120	108.4	1.72 (1.24 to 2.39)	47.4 (15.7 to 91.4)	.001
Cardiovascular	36	44.6	79	71.4	1.65 (1.10 to 2.46)	28.9 (4.6 to 65.3)	.02
Respiratory	3	3.7	10	9.0	3.00 (0.81 to 11.09)	7.4 (−0.7 to 37.5)	.10
Other injury	11	13.6	19	17.2	1.15 (0.54 to 2.47)	2.1 (−6.3 to 20.0)	.72
Other	3	3.7	12	10.8	3.72 (1.04 to 13.30)	10.1 (0.2 to 45.7)	.04
Hospital	27	33.5	31	28.0	1.00 (0.59 to 1.69)	0 (−13.6 to 23.1)	>.99

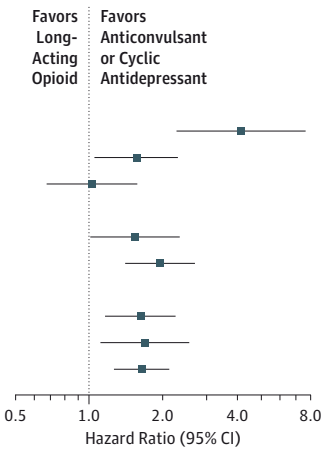
[a] Adjusted for baseline propensity score decile, age, and calendar year during follow-up.

[b] Risk differences for the specific causes of death do not sum because the regression model parameters are estimated separately for each cause.

[c] The cohort excluded patients with a diagnosis of or procedure for treatment of substance abuse other than nicotine or alcohol as well as those prescribed buprenorphine. Because such patients would plausibly have increased risk of overdose, overdose mortality in the study cohort is likely to be lower than that in a more general patient population.

Figure. Mortality According to Study Drug Duration, Dose, and Baseline Use of Short-Acting Opioids

	Anticonvulsant or Cyclic Antidepressant			Long-acting Opioid				
	No. of Patients	Person-Years	No. of Deaths	No. of Patients	Person-Years	No. of Deaths	Risk Difference (95% CI)	Hazard Ratio (95% CI)
Time since drug started, d								
≤30	22912	2054	13	22912	2042	53	200 (80 to 420)	4.16 (2.27-7.63)
31-180	11752	3026	40	12194	3534	70	74 (7 to 172)	1.56 (1.05-2.30)
>180	3765	2986	34	5584	5494	62	3 (-37 to 65)	1.03 (0.67-1.57)
Study drug dose during follow-up								
Low	13345	3311	31	19564	5381	75	51 (1 to 125)	1.54 (1.01-2.34)
High	13495	4755	56	9637	5689	110	111 (47 to 200)	1.94 (1.40-2.70)
Short-acting opioid at baseline, mg								
≤30	14590	5275	54	14504	6949	110	63 (16 to 128)	1.62 (1.16-2.25)
>30	8322	2792	33	8408	4121	75	80 (13 to 184)	1.68 (1.11-2.56)
All	22912	8066	87	22912	11070	185	69 (28 to 121)	1.64 (1.26-2.12)



An individual patient can be in multiple duration and dose categories during follow-up; thus, the numbers do not sum to the total cohort size. Adjusted hazard ratios and risk differences are shown for current use of long-acting opioids vs current use of analgesic anticonvulsants or cyclic antidepressants. The estimates according to duration of use and study drug dose during follow-up are adjusted for a time-dependent disease risk score; those for baseline use of short-acting opioids are adjusted for baseline propensity score and age and calendar year during follow-up. Cut points for low (≤cut point) vs high (>cut point) study drug dose were 60-mg/d morphine equivalents, 600-mg/d gabapentin equivalents, and 40-mg/d amitriptyline equivalents. For short-acting opioids, doses are in morphine equivalents.

been as small as 1.36 (95% CI, 0.90-2.06, no longer statistically significant) or as large as 1.79 (95% CI, 1.21-2.66) (Sensitivity Analysis section in the Supplement).

Discussion

Although long-acting opioids increase the risk of unintentional overdose,[1-3,5] their overall safety relative to other medications commonly prescribed to treat noncancer pain has not been previously well quantified. This study found that patients prescribed therapy for a long-acting opioid had a risk of all-cause mortality that was 1.64 times greater than that for matched patients starting an analgesic anticonvulsant or a low-dose cyclic antidepressant, corresponding to 69 excess deaths per 10 000 person-years of therapy. This difference was explained by a 1.90 times greater risk of out-of-hospital deaths. More than two-thirds of the excess deaths were due to causes other than unintentional overdose; of these, more than one-half were cardiovascular deaths. The increased risk was confined to the first 180 days of prescribed therapy but was present for long-acting opioid doses of 60 mg or less of morphine-equivalents.

The study was designed to reduce confounding by factors associated with starting a long-acting opioid. The cohort excluded patients with evidence of palliative or end-of-life care. It was restricted to those initiating therapy with study medications, managing the bias inherent in study of those who survive a high-risk early exposure period.[21] Patients in the 2 study groups were tightly matched according to potential confounders, including chronic pain diagnoses, patterns of prior use of short-acting opioids and other analgesics, use of benzodiazepines and other psychotropic drugs associated with increased risk of overdose deaths,[23] and cardiovascular, respiratory, and other somatic comorbidity.

It is important to consider whether the elevated risk of long-acting opioids is due to confounding by indication. Long-acting opioids have been widely recommended for chronic noncancer pain.[11,22] Gabapentin and pregabalin are indicated for neuropathic pain and fibromyalgia,[12,31,32] and low-dose cyclic antidepressants for chronic back pain, neuropathic pain, and fibromyalgia.[14,32,33] In clinical practice all are widely prescribed for chronic back and other musculoskeletal pain,[13,14,32,34] by far the most common recorded diagnosis in the study cohort. Thus, material confounding by indication seems unlikely, a conclusion supported by the essentially unchanged findings for control groups restricted to patients with a diagnosis of neurologic pain or consisting exclusively of patients prescribed either anticonvulsants or cyclic antidepressants alone. Patients starting a long-acting opioid may have had other unmeasured factors that increased risk of death; however, the absence of increased risk of the hospital deaths and the marked elevation in risk early in therapy argue against such confounding.

The increased risk of long-acting opioids was not confined to deaths identified as due to unintentional overdose. Thus, of the estimated 69 excess deaths per 10 000 person-years of follow-up among long-acting opioid patients, 47 had an underlying cause of death other than unintentional overdose and 29 had a cardiovascular cause of death. The increased risk of cardiovascular death persisted when patients prescribed methadone, a known proarrhythmic drug,[16] were excluded from the cohort.

The increased risk of cardiovascular death could be related to adverse respiratory effects of long-acting opioids. Opioids can cause or exacerbate sleep-disordered breathing,

Table 4. Sensitivity Analyses

	Anticonvulsant or Cyclic Antidepressant		Long-Acting Opioids		Adjusted (95% CI)		
Deaths	Deaths	Incidence per 10 000 Person-Years	Deaths	Incidence per 10 000 Person-Years	Hazard Ratio[a]	Risk Difference[a,b]	*P* Value
Methadone Excluded	**22 912 Patients, 8066 Person-Years**		**21 436 Patients, 10 255 Person-Years**				
All	87	107.9	166	161.9	1.56 (1.20 to 2.04)	60.9 (21.7 to 111.9)	.001
Out of hospital	60	74.4	135	131.6	1.77 (1.30 to 2.41)	57.3 (22.2 to 105.1)	<.001
Not overdose death	53	65.7	106	103.4	1.62 (1.16 to 2.26)	40.6 (10.3 to 83.1)	.005
Cardiovascular	36	44.6	70	68.3	1.56 (1.04 to 2.35)	25.1 (1.7 to 60.4)	.03
Neurologic Pain Diagnosis	**14 316 Patients, 4923 Person-Years**		**14 021 Patients, 7013 Person-Years**				
All	50	101.6	101	144.0	1.54 (1.09 to 2.18)	54.9 (9.1 to 119.6)	.02
Out of hospital	35	71.1	90	128.3	1.91 (1.28 to 2.85)	64.8 (20.2 to 131.2)	.001
Not overdose death	32	65.0	64	91.3	1.52 (0.98 to 2.34)	33.6 (−1.1 to 87.2)	.06
Cardiovascular	19	38.6	40	57.0	1.60 (0.92 to 2.79)	23.2 (−3.2 to 69.2)	.10
Anticonvulsant-Only Control Group	**20 296 Patients, 7991 Person-Years**		**20 296 Patients, 9441 Person-Years**				
All	84	105.1	148	156.8	1.56 (1.19 to 2.05)	58.8 (19.8 to 110.0)	.001
Out of hospital	61	76.3	126	133.5	1.79 (1.31 to 2.43)	60.0 (23.7 to 109.5)	<.001
Not overdose death	48	60.1	98	103.8	1.80 (1.27 to 2.55)	48.0 (16.1 to 93.3)	.001
Cardiovascular	29	36.3	66	69.9	1.97 (1.27 to 3.07)	35.3 (9.6 to 75.2)	.003
Cyclic Antidepressant-Only Control Group	**18 106 Patients, 5650 Person-Years**		**18 106 Patients, 8626 Person-Years**				
All	52	92.0	123	142.6	1.84 (1.32 to 2.56)	77.3 (29.7 to 143.7)	<.001
Out of hospital	29	51.3	100	115.9	2.52 (1.65 to 3.83)	77.8 (33.5 to 145.4)	<.001
Not overdose death	26	46.0	80	92.7	2.31 (1.47 to 3.63)	60.4 (21.8 to 121.0)	<.001
Cardiovascular	17	30.1	50	58.0	2.25 (1.28 to 3.94)	37.6 (8.5 to 88.5)	.005
Cohort Entry 2003 or Later	**15 209 Patients, 5080 Person-Years**		**15 030 Patients, 6150 Person-Years**				
All	49	96.5	103	167.5	1.82 (1.29 to 2.56)	78.8 (27.8 to 150.7)	<.001
Out of hospital	37	72.8	88	143.1	1.98 (1.34 to 2.92)	71.5 (25.1 to 140.0)	<.001
Not overdose death	31	61.0	66	107.3	1.80 (1.17 to 2.77)	48.9 (10.4 to 108.3)	<.001
Cardiovascular	19	37.4	43	69.9	1.84 (1.06 to 3.18)	31.3 (2.4 to 81.4)	.03
Duration Therapy <180 d	**22 912 Patients, 5081 Person-Years**		**22 912 Patients, 5576 Person-Years**				
All	53	104.3	123	220.6	2.16 (1.56 to 2.98)	121.0 (58.8 to 206.8)	<.001
Out of hospital	39	76.8	101	181.1	2.39 (1.65 to 3.46)	106.5 (49.8 to 188.6)	<.001
Not overdose death	36	70.9	77	138.1	1.98 (1.33 to 2.94)	69.4 (23.4 to 137.6)	<.001
Cardiovascular	22	43.3	50	89.7	2.12 (1.28 to 3.50)	48.4 (12.1 to 108.2)	.004
Deaths With Unknown Cause Not Considered Cardiovascular Deaths	**22 912 Patients, 8066 Person-Years**		**22 912 Patients, 11 070 Person-Years**				
Not overdose death	53	65.7	120	108.4	1.72 (1.24 to 2.39)	47.4 (15.7 to 91.4)	.001
Cardiovascular	35	43.4	72	65.0	1.55 (1.03 to 2.34)	23.8 (1.2 to 58.0)	.04
Specific Death Categories Include Hospital Deaths	**22 912 Patients, 8066 Person-Years**		**22 912 Patients, 11 070 Person-Years**				
Not overdose death	77	95.5	151	136.4	1.55 (1.17 to 2.05)	52.4 (16.4 to 100.1)	.002
Cardiovascular	51	63.2	96	86.7	1.46 (1.03 to 2.07)	29.2 (2.2 to 67.5)	.03

[a] Adjusted for baseline propensity score decile and age and calendar year during follow-up.

[b] Risk differences for the specific causes of death do not sum because the regression model parameters are estimated separately for each cause.

including both obstructive and central sleep apnea.[35-37] Patients with sleep-disordered breathing have increased incidence of nocturnal arrhythmias, myocardial ischemia or infarction, and sudden death.[7] Study findings are consistent with those of Solomon and colleagues,[38] who found that older adults with arthritis prescribed opioids (predominantly short-acting) had nearly twice the risk of out-of-hospital cardiac death as did comparable patients prescribed nonselective NSAIDs.

A study limitation was reliance on the death certificate to classify the cause of death, thus raising the possibility that the cardiovascular death finding was due to misclassification. A sensitivity analysis based on a convenience sample of deaths for which medical records were reviewed provided evidence that misclassification was unlikely to explain the elevated cardiovascular death risk, although under a worst-case scenario the cardiovascular death HR was no longer statistically significant. The convenience sample analysis had several other limitations (Sensitivity Analysis section in the Supplement). Furthermore, more than two-thirds of the excess deaths for patients in the long-acting opioid group were not coded as being due to unintentional overdose. If there is this degree of misclassification, then previous research on opioid mortality, most of which has focused on overdose deaths identified from death certificates,[2,3,5] has substantially underestimated the true risks of opioids.

The study cohort differed from other populations of patients taking long-acting opioids. To improve study capacity to detect adverse effects of long-acting opioids, the cohort consisted of patients for whom illness-related deaths should be relatively infrequent. Thus, it excluded persons 75 years or older; patients with cancer; other life-threatening diseases, or evidence of palliative or end-of-life care; and nursing home residents. These restrictions were likely to reduce study cohort mortality because the excluded patients would have higher baseline risk and could be more susceptible to adverse medication effects. The cohort also excluded patients with any recorded evidence of drug abuse, thus underestimating the potential for overdose. Conversely, the cohort consisted of Medicaid enrollees, who are likely to have had greater mortality than the population at large.[39]

The study findings reinforce the conclusion of the recent Centers for Disease Control and Prevention's (CDC's) guideline for prescribing opioids for chronic noncancer pain that "of primary importance, nonopioid therapy is preferred for treatment of chronic pain."[20] Although this study did not consider medication efficacy, the CDC's synthesis of the available evidence suggests the efficacy of nonopioid pharmacotherapy for many chronic conditions is at least equal to that of opioids. The study finding that prescription of long-acting opioids was associated with increased cardiovascular and other nonoverdose mortality adds to the already considerable known harms of the opioids and thus should be considered when assessing the benefits and harms of medications for chronic pain. Nevertheless, for some individual patients, the therapeutic benefits from long-acting opioid therapy may outweigh the modest increase in mortality risk. As the CDC guideline indicates, all prescribing decisions must be based on an evaluation of the source and severity of the patient's pain and a discussion of the "known risks and realistic benefits of opioid therapy."[20]

Conclusions

Prescription of long-acting opioids for chronic noncancer pain, compared with anticonvulsants or cyclic antidepressants, was associated with a significantly increased risk of all-cause mortality, including deaths from causes other than overdose, with a modest absolute risk difference. These findings should be considered when evaluating harms and benefits of treatment.

ARTICLE INFORMATION

Author Contributions: Dr Ray had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ray, Chung, Murray, Stein.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ray.
Critical revision of the manuscript for important intellectual content: Ray, Chung, Murray, Hall, Stein.
Obtained funding: Ray.
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Study supervision: Ray, Chung.

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