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

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Abstract

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

Objective—Compare all-cause mortality for chronic noncancer pain patients 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 (HR) and risk differences (RD, difference in incidence of death between patients with long-acting opioid and control-drug therapy) were calculated for long-acting-opioid versus control-medication patients.

Results—There were 22,912 new episodes of prescribed therapy for both long-acting opioids and control medications (mean age 48, 60% women) with respective mean follow-up of 176 and 128 days and 185 and 87 deaths, respectively. The HR for total mortality was 1.64 (95% CI, 1.26–

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2.12) with an RD of 69 excess deaths (28–121) per 10,000 person-years. Increased risk was due to out-of-hospital deaths (154 long-acting opioid, 60 control deaths; HR = 1.90 [1.40–2.58], RD = 67 [30–117] 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 (1.24–2.39) with an RD of 47 excess deaths (16–91) per 10,000 person years. The HR for cardiovascular deaths (79 long-acting opioid, 36 control deaths) was 1.65 (1.10–2.46) with an RD of 29 excess deaths (5–65) per 10,000 person-years. The HR during the first 30 days of therapy (53 long-acting opioid, 13 control deaths) was 4.16 (2.27–7.63) with an RD of 200 excess deaths (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 for 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.

The pronounced increase in the prescribing of opioid analgesics for chronic noncancer pain has led to escalating concern regarding their 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 for 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, given prolonged drug levels and the link between the increase in their use and that for opioid overdose deaths.[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 regarding 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 three questions. First, did total mortality differ between the two groups? Second, what was the relative risk for deaths outside of 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 IRBs 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, palliative, or end-of-life care (Appendix Tables 1–2).[20] Thus, the cohort excluded persons 75 years of age 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 for 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) in the past 90 days. The study drugs were the *long-acting opioids* (morphine SR, oxycodone CR, transdermal fentanyl, methadone) and the *control drugs*: anticonvulsants indicated for chronic pain (gabapentin, pregabalin, carbamazepine), or low-dose cyclic antidepressants (Appendix Table 5). 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 (Appendix Tables 3–5) 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 (Appendix Table 6). 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 control drug patient was randomly selected for every opioid patient, randomly discarding opioid patients if there were too few control drug patients. 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 (Appendix Table 6).

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: one year with no filled prescription, filling of a prescription for a drug in a different class (e.g., a long-acting opioid patient or an anticonvulsant patient starts a cyclic antidepressant, regardless of dose), death, failure to meet inclusion-exclusion criteria, or end of the study. Patients who left the cohort could reenter if they subsequently became eligible. Since the episodes were non-overlapping 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 one refill interval to become known.

End points

The study end point was all deaths during study follow-up. *Hospital* deaths were those for patients hospitalized on a day of current study drug use who died 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 (Appendix Table 7). In one analysis, we examined cardiovascular mortality for the subgroups defined by specific cardiovascular diagnoses (Appendix Table 8).

Statistical Analysis

The statistical analysis compared the adjusted risk of death during follow-up for long-acting opioid patients to that for control medication patients. Relative risk was estimated with the hazard ratio (HR), calculated from Cox regression models (Appendix §6). 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 non-proportional hazards (see Allison,[26] p.172). Other time-dependent covariates were not included in the primary analysis because these might be on the causal pathway for mortality (e.g., non-fatal injury). A sensitivity analysis included a time-

dependent propensity score[27] that accounted for changes in study covariates during follow-up (Appendix §6).

The adjusted risk difference (RD), or difference in the incidence of death between patients with long-acting opioid and control-drug therapy, was estimated. The RD was calculated as I_0*(HR-1), where HR is the adjusted hazard ratio and I_0 the unadjusted incidence for control medication patients. 95% confidence intervals 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 days of prior use on the day a study drug prescription was filled. Cutpoints for low (≤ cutpoint) versus high dose (> cutpoint) were the approximate median time-dependent doses: 60 mg/day morphine equivalents, 600 mg/day gabapentin equivalents and 40 mg/day amitriptyline equivalents. The regression analysis was stratified by 20 quantiles of a time-dependent disease risk score (Appendix §6).[28–30] The disease risk score, the risk of death as a function of the study covariates given the reference exposure category, facilitates analyses for multiple exposure categories, given that propensity scores are less suited to non-binary 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 non-overdose and cardiovascular death categories to include hospital deaths.

The effect of cardiovascular death misclassification was assessed (Appendix §8) 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 done with SAS version 9.4. All p-values are two-sided, with a p-value less than .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 age of the matched patients was 48 years and 60% were female. 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 medications and psychotropic drugs, including skeletal muscle relaxants (63%), non-steroidal antiinflammatory drugs (70%), benzodiazepines (52%), and selective serotonin or serotonin and norepinephrine reuptake inhibitor antidepressants (45%).

The most commonly prescribed 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.

Long-acting opioid patients had 185 deaths during 11,070 person-years of follow-up (167 per 10,000 person-years), whereas there were 87 deaths during 8,066 person-years of follow-up for control medication patients (108 per 10,000). The adjusted HR for death from any cause during follow-up was 1.64 (1.26–2.12), and the RD was 69 (28–121) 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 [1.40–2.58], RD = 67 [30–117] per 10,000 person-years), which constituted 79% of study deaths. There was no increased risk for in-hospital deaths (HR = 1.00 [0.59–1.69], RD = 0 [−14–23] per 10,000 person-years). The HR for out-of-hospital deaths with a cause of death other than unintentional overdose was 1.72 (1.24–2.39) with an RD of 47 (16–91) per 10,000 person-years. The most frequent category of non-overdose deaths was cardiovascular deaths, with an HR of 1.65 (1.10–2.46) and an RD of 29 (5–65) per 10,000 person-years. Long-acting opioid patients had elevated cardiovascular mortality for all of the subgroups defined by specific cardiovascular diagnoses, with the exception of diabetes (Appendix Table 8).

The increased mortality for long-acting opioid patients was limited to the first 180 days of prescribed therapy (Figure). During the first 30 days of therapy, the HR was 4.16 (2.27–7.63) and the RD was 200 (80–420) per 10,000 person-years; for the remainder of the first 180 days the HR was 1.56 (1.05–2.30) and the RD was 74 (7–172) per 10,000 person-years. By contrast, once long-acting opioid patients had more than 180 days of therapy, their risk of death did not differ significantly from that of comparable control drug patients (HR = 1.03 [0.67–1.57], RD = 3 [−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 control drug patients (Figure). For low doses (≤60 mg of morphine or its equivalent) the HR was 1.54 (1.01–2.34) and the RD was 51 (1–126) per 10,000 person-years; for high doses (>60 mg morphine or its equivalent) the HR was 1.94 (1.40–2.70) and the RD was 111 (47–200) per 10,000 person-years. Similarly, long-acting opioid patients had greater mortality within groups defined by baseline short-acting opioid doses of ≤30 mg or >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 (Appendix §8) 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 (1.10–2.46) to 1.58 (1.05–2.36), although, depending on the specific adjudication criteria, the HR could have been as small as 1.36 (0.90–2.06, no longer statistically significant) or as large as 1.79 (1.21–2.66) (Appendix §8).

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 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 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 two 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 for 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 for the hospital deaths and the marked elevation in risk early in therapy argue against such confounding.

The increased risk for 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 followup 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 for cardiovascular death persisted when patients prescribed methadone, a known pro-arrhythmic 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, including both obstructive and central sleep apnea;[35–37] and 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, 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 non-selective NSAIDs.[38]

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 upon 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 and the convenience sample analysis had several other limitations (Appendix §8). Furthermore, more than two-thirds of the excess deaths for long-acting opioid patients were not coded as 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 of age 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, as 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 CDC guideline for prescribing opioids for chronic noncancer pain that “of primary importance, nonopoid 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 nonopoid

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 non-overdose 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]

Conclusion

Prescription of long-acting opioids for chronic noncancer pain, compared with anticonvulsants or cyclic antidepressants, was associated with a significantly increased risk for 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

What is the relative risk of death from any cause for patients with chronic noncancer pain and no evidence of end-of-life care who begin therapy with either long-acting opioids or analgesic anticonvulsants or cyclic antidepressants, alternative medications for moderate to severe chronic pain?

Findings

In this retrospective cohort study that included 22,912 new episodes of prescribed therapy for both long-acting opioids and alternative medications, the long-acting opioid patients had a 64% increased risk of all-cause mortality, including a 65% increased risk for cardiovascular death.

Meaning

These findings support recommendations from recent guidelines to avoid opioid therapy for chronic noncancer pain when possible.

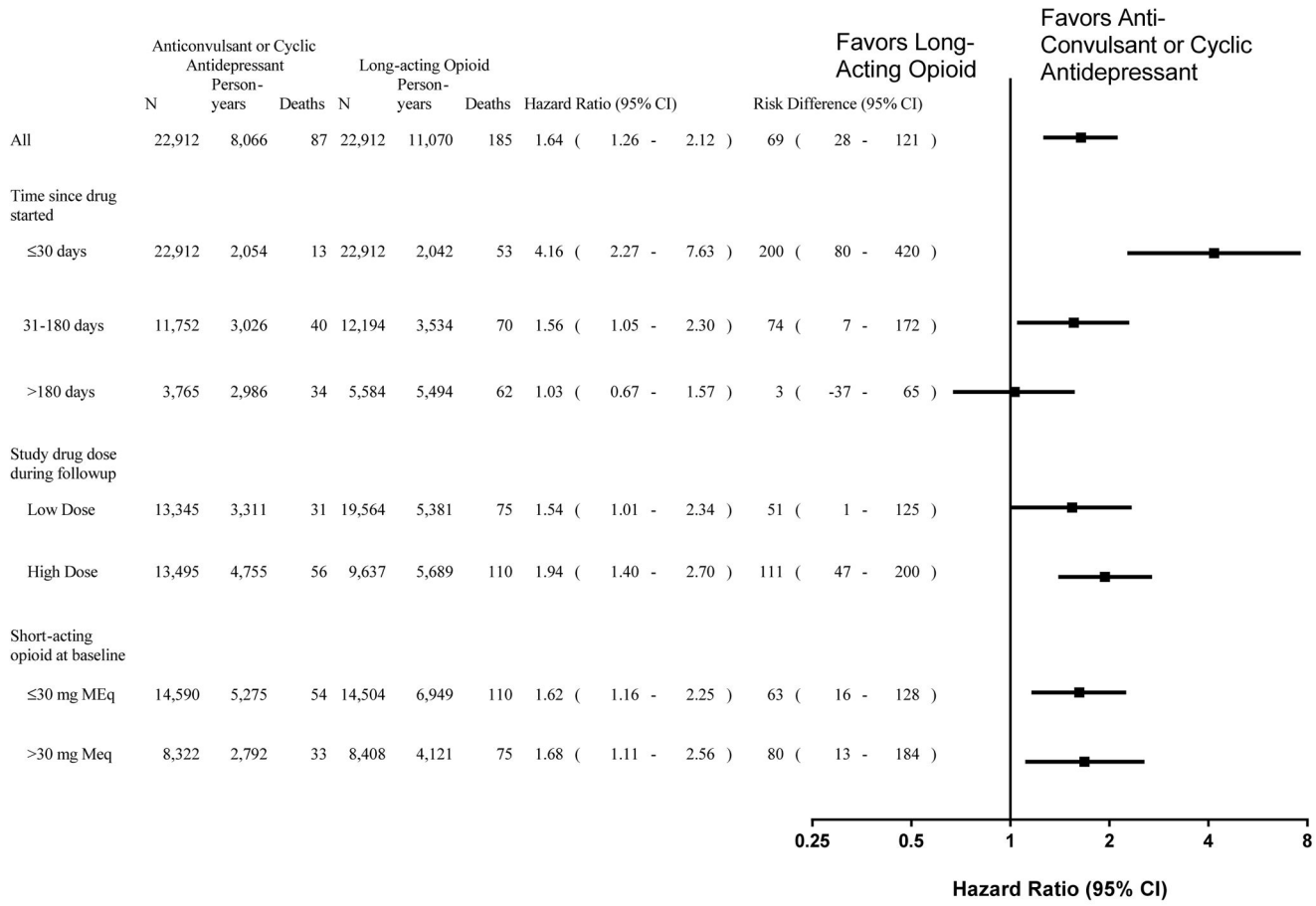

Figure. Mortality according to study drug duration, dose, and baseline use short-acting opioids

N indicates number of patients. An individual patient can be in multiple duration and dose categories during followup; thus, the numbers do not sum to the total cohort size. Adjusted hazard ratios and risk differences are shown are shown (95% confidence interval in parentheses) for current use of long-acting opioids versus 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 followup. Cutpoints for low (≤ cutpoint) versus high (> cutpoint) study drug dose were: 60 mg/day morphine equivalents, 600 mg/day gabapentin equivalents and 40 mg/day amitriptyline equivalents. For short-acting opioids, doses are in morphine equivalents.

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Table 1

Selected baseline characteristics[a] for new episodes of study drug therapy. Abbreviations: SD, standard deviation; SSRI, selective serotonin uptake inhibitor; SNRI, selective norepinephrine uptake inhibitor; COPD, chronic obstructive pulmonary disease; ED, emergency department.

	Before Matching			After Matching		
	Anticonvulsant or Cyclic Antidepressant	Long-Acting Opioid	Standardized difference, %	Anticonvulsant or Cyclic Antidepressant	Long-Acting Opioid	Standardized difference, %
N 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%
Female sex	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 days						
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%)	4,167 (18%)	5.8%	4,093 (18%)	4,108 (18%)	0.2%
Headache	29,782 (23%)	2,783 (12%)	28.4%	2,663 (12%)	2,773 (12%)	1.5%
Other neurologic pain	25,343 (19%)	3,909 (17%)	6.4%	3,736 (16%)	3,855 (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 days use past year	13,937 (11%)	6,430 (28%)	44.4%	6,025 (26%)	6,192 (27%)	1.6%
Current use	55,652 (42%)	15,733 (68%)	36.6%	15,629 (68%)	15,361 (67%)	2.5%
Current use >60 mg morphine equivalents	6,315 (5%)	3,440 (15%)	34.1%	3,012 (13%)	3,239 (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%
Non-steroidal antiinflammatory 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%)	3,046 (13%)	3.9%	2,987 (13%)	2,997 (13%)	0.1%
Other comorbidity past year						
AMI, revascularization, or angina	7,002 (5%)	1,426 (6%)	3.5%	1,398 (6%)	1,402 (6%)	0.1%
Congestive heart failure	5,219 (4%)	1,269 (5%)	7.0%	1,239 (5%)	1,237 (5%)	0.0%

	Before Matching			After Matching		
	Anticonvulsant or Cyclic Antidepressant	Long-Acting Opioid	Standardized difference, %	Anticonvulsant or Cyclic Antidepressant	Long-Acting Opioid	Standardized difference, %
Cerebrovascular disease	6,979 (5%)	1,236 (5%)	0.0%	1,239 (5%)	1,213 (5%)	0.5%
COPD	18,696 (14%)	4,751 (20%)	16.5%	4,593 (20%)	4,611 (20%)	0.2%
Asthma	14,501 (11%)	2,620 (11%)	0.8%	2,488 (11%)	2,578 (11%)	1.3%
Home oxygen	5,305 (4%)	1,416 (6%)	9.4%	1,389 (6%)	1,372 (6%)	0.3%
Hospital stay	18,740 (14%)	4,108 (18%)	9.3%	3,986 (17%)	4,025 (18%)	0.4%
Injury ED visit	37,430 (28%)	7,676 (33%)	9.9%	7,635 (33%)	7,531 (33%)	1.0%

[a]The characteristics were selected as those the authors considered to most likely to be associated with greater risk of mortality and with the decision to prescribe a long-acting opioid. Appendix Table 6 lists the distribution of all study covariates.

Table 2

Study drugs before and after matching. Abbreviations: IQR, interquartile range, SR, sustained release, CR, controlled release.

	Before Matching	After Matching
	N (%)	*N (%)*
Patients		
Long-acting opioids		
All	23,308 (100%)	22,912 (100%)
Morphine SR	12,891 (55%)	12,667 (55%)
Oxycodone CR	5,539 (24%)	5,446 (24%)
Fentanyl transdermal	3,377 (14%)	3,323 (14%)
Methadone	1,501 (6%)	1,476 (6%)
Anticonvulsant or cyclic antidepressant		
All	131,883 (100%)	22,912 (100%)
Gabapentin	53,078 (40%)	10,879 (47%)
Pregabalin	7,272 (6%)	1,403 (6%)
Carbamazepine	3,884 (3%)	579 (3%)
Amitriptyline	48,072 (36%)	6,959 (30%)
Doxepin	7,382 (6%)	1,266 (6%)
Nortriptyline	7,075 (5%)	1,071 (5%)
Other cyclic antidepressant	5,120 (4%)	755 (3%)
Dose, mg, median (IQR)	Median (IQR)	Median (IQR)
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)

Table 3

Mortality according to underlying cause of death.

	Anticonvulsant or Cyclic Antidepressant (8,066 person-years follow-up)		Long-acting Opioid (11,070 person-years follow-up)		Adjusted Hazard Ratio[a] (95% CI)	Adjusted Risk Difference[a,b] (95% CI)	p
	Deaths	Incidence/10,000 Person-Years	Deaths	Incidence/10,000 Person-Years			
All deaths	87	107.9	185	167.1	1.64 (1.26–2.12)	68.5 (28.2–120.7)	<.001
Out-of-hospital deaths	60	74.4	154	139.1	1.90 (1.40–2.58)	67.1 (30.1–117.3)	<.001
Unintentional overdose deaths[c]	7	8.7	34	30.7	3.37 (1.47–7.70)	20.6 (4.1–58.1)	0.004
Other causes of death	53	65.7	120	108.4	1.72 (1.24–2.39)	47.4 (15.7–91.4)	0.001
Cardiovascular	36	44.6	79	71.4	1.65 (1.10–2.46)	28.9 (4.6–65.3)	0.015
Respiratory	3	3.7	10	9.0	3.00 (0.81–11.09)	7.4 (−0.7–37.5)	0.100
Other Injury	11	13.6	19	17.2	1.15 (0.54–2.47)	2.1 (−6.3–20.0)	0.716
Other	3	3.7	12	10.8	3.72 (1.04–13.30)	10.1 (0.2–45.7)	0.043
Hospital Deaths	27	33.5	31	28.0	1.00 (0.59–1.69)	0.0 (−13.6–23.1)	0.996

[a] Adjusted for baseline propensity score decile and age and calendar year during followup.

[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 for overdose, overdose mortality in the study cohort is likely to be lower than that in a more general patient population.

Table 4

Sensitivity analyses. CI = confidence interval.

	Anticonvulsant (AC) or Cyclic Antidepressant (TCA)		Long-acting Opioids (LAO)		Adjusted Hazard Ratio[a] (95% CI)		Adjusted Risk Difference[a,b] (95% CI)		p
	Deaths	*Incidence/10,000 Person-Years*	*Deaths*	*Incidence/10,000 Person-Years*					
Methadone excluded (AC or TCA: 22,912 patients, 8,066 person-years; LAO: 21,436 patients, 10,255 person-years)									
All deaths	87	107.9	166	161.9	1.56	(1.20–2.04)	60.9	(21.7–111.9)	0.001
Out of hospital deaths	60	74.4	135	131.6	1.77	(1.30–2.41)	57.3	(22.2–105.1)	<.001
Not overdose death	53	65.7	106	103.4	1.62	(1.16–2.26)	40.6	(10.3–83.1)	0.005
Cardiovascular deaths	36	44.6	70	68.3	1.56	(1.04–2.35)	25.1	(1.7–60.4)	0.033
Neurologic pain diagnosis (AC or TCA: 14,316 patients, 4,923 person-years; LAO: 14,021 patients, 7,013 person-years)									
All deaths	50	101.6	101	144.0	1.54	(1.09–2.18)	54.9	(9.1–119.6)	0.015
Out of hospital deaths	35	71.1	90	128.3	1.91	(1.28–2.85)	64.8	(20.2–131.2)	0.001
Not overdose death	32	65.0	64	91.3	1.52	(0.98–2.34)	33.6	(−1.1–87.2)	0.059
Cardiovascular deaths	19	38.6	40	57.0	1.60	(0.92–2.79)	23.2	(−3.2–69.2)	0.098
Anticonvulsant-only control group (AC:20,296 patients, 7,991 person-years; LAO: 20,296 patients, 9,441 person-years)									
All deaths	84	105.1	148	156.8	1.56	(1.19–2.05)	58.8	(19.8–110.0)	0.001
Out of hospital deaths	61	76.3	126	133.5	1.79	(1.31–2.43)	60.0	(23.7–109.5)	<.001
Not overdose death	48	60.1	98	103.8	1.80	(1.27–2.55)	48.0	(16.1–93.3)	0.001
Cardiovascular deaths	29	36.3	66	69.9	1.97	(1.27–3.07)	35.3	(9.6–75.2)	0.003
Cyclic antidepressant-only control group (TCA:18,106 patients, 5,650 person-years; LAO: 18,106 patients, 8,626 person-years)									
All deaths	52	92.0	123	142.6	1.84	(1.32–2.56)	77.3	(29.7–143.7)	<.001
Out of hospital deaths	29	51.3	100	115.9	2.52	(1.65–3.83)	77.8	(33.5–145.4)	<.001
Not overdose death	26	46.0	80	92.7	2.31	(1.47–3.63)	60.4	(21.8–121.0)	<.001
Cardiovascular deaths	17	30.1	50	58.0	2.25	(1.28–3.94)	37.6	(8.5–88.5)	0.005
Cohort entry 2003 or later (AC or TCA: 15,209 patients, 5,080 person-years; LAO: 15,030 patients, 6,150 person-years)									
All deaths	49	96.5	103	167.5	1.82	(1.29–2.56)	78.8	(27.8–150.7)	<.001
Out of hospital deaths	37	72.8	88	143.1	1.98	(1.34–2.92)	71.5	(25.1–140.0)	<.001
Not overdose death	31	61.0	66	107.3	1.80	(1.17–2.77)	48.9	(10.4–108.3)	<.001
Cardiovascular deaths	19	37.4	43	69.9	1.84	(1.06–3.18)	31.3	(2.4–81.4)	0.029

	Anticonvulsant (AC) or Cyclic Antidepressant (TCA)		Long-acting Opioids (LAO)		Adjusted Hazard Ratio[a] (95% CI)		Adjusted Risk Difference[a,b] (95% CI)		p
	Deaths	*Incidence/10,000 Person-Years*	*Deaths*	*Incidence/10,000 Person-Years*					
Duration therapy <180 days (AC or TCA: 22,912 patients, 5,081 person-years; LAO: 22,912 patients, 5,576 person-years)									
All deaths	53	104.3	123	220.6	2.16	(1.56–2.98)	121.0	(58.8–206.8)	<.001
Out of hospital deaths	39	76.8	101	181.1	2.39	(1.65–3.46)	106.5	(49.8–188.6)	<.001
Not overdose death	36	70.9	77	138.1	1.98	(1.33–2.94)	69.4	(23.4–137.6)	<.001
Cardiovascular deaths	22	43.3	50	89.7	2.12	(1.28–3.50)	48.4	(12.1–108.2)	0.004
Deaths with unknown cause not considered cardiovascular deaths (AC or TCA: 22,912 patients, 8,066 person-years; LAO: 22,912 patients, 11,070 person-years)									
Not overdose death	53	65.7	120	108.4	1.72	(1.24–2.39)	47.4	(15.7–91.4)	0.001
Cardiovascular deaths	35	43.4	72	65.0	1.55	(1.03–2.34)	23.8	(1.2–58.0)	0.037
Specific death categories include hospital deaths (AC or TCA: 22,912 patients, 8,066 person-years; LAO: 22,912 patients, 11,070 person-years)									
Not overdose death	77	95.5	151	136.4	1.55	(1.17–2.05)	52.4	(16.4–100.1)	0.002
Cardiovascular deaths	51	63.2	96	86.7	1.46	(1.03–2.07)	29.2	(2.2–67.5)	0.031

[a] Adjusted for baseline propensity score decile and age and calendar year during followup.

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