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Association of Tramadol vs Codeine Prescription Dispensation With Mortality and Other Adverse Clinical Outcomes

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IMPORTANCE Although tramadol is increasingly used to manage chronic noncancer pain, few safety studies have compared it with other opioids.

OBJECTIVE To assess the associations of tramadol, compared with codeine, with mortality and other adverse clinical outcomes as used in outpatient settings.

DESIGN, SETTING, AND PARTICIPANTS Retrospective, population-based, propensity score–matched cohort study using a primary care database with routinely collected medical records and pharmacy dispensations covering more than 80% of the population of Catalonia, Spain (≈6 million people). Patients 18 years or older with 1 or more year of available data and dispensation of tramadol or codeine (2007-2017) were included and followed up to December 31, 2017.

EXPOSURES New prescription dispensation of tramadol or codeine (no dispensation in the previous year).

MAIN OUTCOMES AND MEASURES Outcomes studied were all-cause mortality, cardiovascular events, fractures, constipation, delirium, falls, opioid abuse/dependence, and sleep disorders within 1 year after the first dispensation. Absolute rate differences (ARDs) and hazard ratios (HRs) with 95% confidence intervals were calculated using cause-specific Cox models.

RESULTS Of the 1 093 064 patients with a tramadol or codeine dispensation during the study period (326 921 for tramadol, 762 492 for codeine, 3651 for both drugs concomitantly), a total of 368 960 patients (184 480 propensity score–matched pairs) were included after study exclusions and propensity score matching (mean age, 53.1 [SD, 16.1] years; 57.3% women). Compared with codeine, tramadol dispensation was significantly associated with a higher risk of all-cause mortality (incidence, 13.00 vs 5.61 per 1000 person-years; HR, 2.31 [95% CI, 2.08-2.56]; ARD, 7.37 [95% CI, 6.09-8.78] per 1000 person-years), cardiovascular events (incidence, 10.03 vs 8.67 per 1000 person-years; HR, 1.15 [95% CI, 1.05-1.27]; ARD, 1.36 [95% CI, 0.45-2.36] per 1000 person-years), and fractures (incidence, 12.26 vs 8.13 per 1000 person-years; HR, 1.50 [95% CI, 1.37-1.65]; ARD, 4.10 [95% CI, 3.02-5.29] per 1000 person-years). No significant difference was observed for the risk of falls, delirium, constipation, opioid abuse/dependence, or sleep disorders.

CONCLUSIONS AND RELEVANCE In this population-based cohort study, a new prescription dispensation of tramadol, compared with codeine, was significantly associated with a higher risk of subsequent all-cause mortality, cardiovascular events, and fractures, but there was no significant difference in the risk of constipation, delirium, falls, opioid abuse/dependence, or sleep disorders. The findings should be interpreted cautiously, given the potential for residual confounding.

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Supplemental content

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Opioids are used in the pharmaceutical treatment of moderate to severe cancer pain and are commonly prescribed for chronic noncancer pain when alternative therapies no longer provide sufficient relief.[1,2] Tramadol was considered to be a relatively safe opioid[3-5] and in 2013 was strongly recommended by the American Academy of Orthopaedic Surgeons for patients with symptomatic knee osteoarthritis.[6] Data from opioid utilization studies conducted in 2019-2020 found that tramadol was the most prescribed opioid in the UK,[7] The Netherlands,[8] and Spain.[9] In the US, the age-adjusted rate of drug overdose deaths involving synthetic opioids (mostly fentanyl but also tramadol) increased from 1.0 per 100 000 in 2013 to 11.4 in 2019.[10]

Tramadol's common non-life-threatening adverse effects (eg, headache, itching, and nausea) are well-established. However, evidence regarding serious adverse events compared with other opioids is still scarce.[11-13] An observational study found that tramadol initiation was associated with increased risk of all-cause mortality in patients with osteoarthritis.[14]

Given the widespread use of tramadol to manage a broad spectrum of painful conditions, its safety profile should be comparatively assessed and its beneficial effects weighed against potential harms. This population-based cohort study compared risks of all-cause mortality, cardiovascular events, fractures, constipation, delirium, falls, opioid abuse/dependence, and sleep disorders between patients who received prescription dispensations for tramadol vs codeine. It also investigated whether the relative risk was consistent across different pain indications in adults.

Key Points

Question Is tramadol compared with codeine prescription dispensation associated with differences in the risk of mortality and other clinical outcomes?

Findings In this retrospective cohort study that used propensity score matching and included 368 960 participants, a new prescription dispensation of tramadol, compared with codeine, was significantly associated with a higher risk of all-cause mortality (HR, 2.31), cardiovascular events (HR, 1.15), and fractures (HR, 1.50), but there was no significant difference in the risk of constipation, delirium, falls, opioid abuse/dependence, or sleep disorders.

Meaning New prescription dispensation of tramadol, compared with codeine, was significantly associated with a higher risk of mortality, cardiovascular events, and fractures, although the findings should be interpreted cautiously, given the potential for residual confounding.

Methods

Data Sources

This retrospective cohort study used data from the System for the Development of Research in Primary Care (SIDIAP), which comprises routinely collected anonymized electronic primary-care records (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] codes) and sociodemographic data for a representative sample (>80%) of Catalonia, Spain. This database links with the national pharmacy claims for community pharmacy dispensations (Anatomical Therapeutic Chemical code, dispensation date, and number of packages). Previous studies have demonstrated the database's validity and quality for research.[15-17]

The local ethics committee (Comité Ético de Investigación of the Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina) approved this study (registration number P18/085). Informed consent was not required. The study protocol was registered in the European Union Post-Authorisation Studies register (EUPAS36689).

Study Design and Cohort Definition

We conducted a retrospective cohort study to compare the risks associated with new prescription dispensations of tramadol vs codeine. Codeine was used as the active comparator to mitigate confounding by indication,[18] as both tramadol and codeine are weak opioids with similar indication coverage and are frequently prescribed in Spain.[19] "New dispensation" was defined by applying a fixed 12-month look-back period in which the patient had continuous data coverage but did not have any opioid dispensation. If a patient had multiple new dispensation episodes, only the first one was used.

All patients who were dispensed tramadol, codeine, or both between January 1, 2007, and December 31, 2017, were identified and categorized in the tramadol or codeine cohort according to the first redeemed drug. Patients with both drugs dispensed on the same day were excluded.

Cohorts were constructed by including patients who were 18 years or older, had at least 1 year of database enrollment before the first drug dispensation (index date), and had not been dispensed any opioids in the 12 months before or on entering the study. Those with a history of burn injuries, traffic crashes, major surgical procedures (amputation and joint replacement surgery), or any of the studied outcomes on or before the index date were excluded.

Baseline Characteristics

The study population was characterized at the index date considering the following potential confounders: sociodemographic factors (age, sex, residence region, and socioeconomic deprivation), medical conditions, Charlson Comorbidity Index, concomitant medication use (psychotropics, nonsteroidal anti-inflammatory drugs [NSAIDs], and other analgesics), and health care utilization. Socioeconomic deprivation was measured with the MEDEA (Mortalidad en áreas pequeñas Españolas y Desigualdades Socioeconómicas y Ambientales) index, which describes socioeconomic and environmental inequalities among 175 small areas of Spain. This index is divided into equal-sized quintiles, with the first quintile representing the least-deprived and last quintile representing the most socioeconomically deprived.[20] Health care utilization was quantified by frequency of general practice visits and hospital admissions in the past 12 months.

Health conditions expected to be linked to the opioid prescription dispensation or to be associated with any of the study outcomes were identified and included common opioid indications (cancer, back pain, neck/shoulder pain, osteoarthritis, cough, migraine), musculoskeletal diseases, chronic obstructive pulmonary disease, fibromyalgia, dyspnea, peripheral vascular disease, angina, transient ischemic attack, osteoporosis, diarrhea, rheumatoid arthritis, malabsorption disorders, pulmonary edema, diabetes, chronic liver disease, chronic kidney disease, Alzheimer disease, and Parkinson disease. eFigure 1 in the Supplement shows the study design and covariate assessment schema.[21]

Controlling for Confounding

Potential confounding by indication was reduced by using propensity score matching.[22] For each inclusion year, propensity scores for tramadol vs codeine dispensation were calculated using a logistic regression model that included all baseline characteristics shown in the **Table**.

Patients with a new tramadol dispensation were matched 1:1 to those with a new codeine dispensation using caliper matching within a caliper of 0.2 times the standard error of the logit propensity score and an exact matching of inclusion year. Individuals not matched with another patient were excluded.

Study Outcomes

The study outcomes were all-cause mortality, cardiovascular events (stroke, cardiac arrhythmia, myocardial infarction, and heart failure), fracture (hip, vertebral, and other), falls, delirium, constipation, sleep disorders, and opioid abuse ("abuse" is the term used in the *ICD* coding)/dependence within 1 year. The *ICD-10* codes for the identification of study outcomes were provided in the eAppendix 2 in the Supplement.

Statistical Analyses

Baseline characteristics of the tramadol and codeine cohort participants before and after matching were compared. Missing values for living area and socioeconomic deprivation were imputed with a single data set using binary and polytomous logistic regression models, respectively. Covariate balance was assessed using the absolute standardized mean difference (ASMD). Acceptable matching was indicated by an ASMD less than 0.1.[23]

For each individual, person-years of follow-up for each outcome from the index date to the first of database disenrollment, 1 year after indexing, end of the study period (December 31, 2017), or outcome occurrence was calculated. One-year cumulative incidences were computed using the Kaplan-Meier method and survival curves were plotted. Hazard ratios (HRs) were estimated using cause-specific Cox proportional hazards regression accounting for competing risk of death.[24] The proportional hazards assumption was tested for exposure with respect to each study outcome using the Kolmogorov supremum test and HR was reported at 3, 6, and 9 months if the assumption was violated.[25] Absolute rate differences (ARDs) were calculated as $I_0 \times (HR - 1)$, where I_0 is the incidence in the control group (codeine). To ensure that the overall confidence level for multiple tests is 0.95, Bonferroni-corrected confidence intervals in the main analyses are reported, which for 8 primary outcomes is [1 - (0.05/8)]*100 = 99.375%. All estimates from subgroup or sensitivity analyses are provided with regular 95% CIs.

Prespecified Subgroup and Sensitivity Analyses

All subsequent analyses were only conducted for outcomes that had an incidence rate higher than 10.0 per 1000 person-years or had a statistically significant difference in the main analysis. Prespecified subgroup analyses on the matched cohort with further adjustment of propensity scores in the Cox model, categorizing by age (18-39, 40-59, and ≥60 years), sex (female and male), common pain indications (cancer, cough, neurologic diseases, back pain, neck/shoulder pain, and osteoarthritis), Charlson Comorbidity Index (0, 1-2, and ≥3), and concomitant psychotropic and NSAID prescription dispensation (yes and no) were performed. The likelihood ratio test was used to examine significant multiplicative interaction effects in the Cox model. The exploratory dose-dependent analysis was described in eFigure 3 in the Supplement.

Eight sensitivity analyses were conducted. First, a multivariable Cox-proportional hazard model to estimate the HRs of study outcomes in the entire cohort.[26] Second, a "stratified Cox model" to control for matching structure in the matched cohort. Third, a complete-case analysis, excluding participants with missing baseline characteristic values. Fourth, to better identify new tramadol and codeine dispensations, the look-back period was extended from 1 to 3 years. Fifth, to increase drug specificity, the analysis was limited to single-formulation tramadol, excluding combinations with another nonnarcotic chemical. Sixth, tramadol may have been prescribed to relieve pain caused by an undiagnosed disease under study, such as fractures. A 3-month lag window, excluding patients with outcomes that occurred within 3 months after the index date was introduced.[27] Seventh, a Fine-Gray subdistribution hazard, an alternative approach to account for the competing risk of death, was used.[24] Eighth, a comparison of the risks during the "on-treatment" period that began with the initial prescription date and ended 30 days after the last fill would have run out was carried out. A gap of 90 days or more without a fill terminated the on-treatment period (see eFigure 2 in the Supplement for the details).

All analyses were conducted using R version 3.6.2 (R Foundation for Statistical Computing). *P* values were 2-sided, and $P < .05$ was considered significant. eAppendix 1 and 2 in the Supplement list the Anatomical Therapeutic Chemical and *ICD-10* codes used.

Results

Study Population and Baseline Characteristics

Of the 1 093 064 patients with a tramadol or codeine dispensation between January 1, 2007, and December 31, 2017, a total of 326 921 were first dispensed tramadol, 762 492 were first dispensed codeine, and 3651 were first dispensed both

Table. Baseline Characteristics of New Tramadol and Codeine Users Before and After Propensity-Score Matching

	Before matching			After matching		
	No. (%)			No. (%)		
	Tramadol	Codeine	ASMD	Tramadol	Codeine	ASMD
No. of participants	240 261	599 228		184 480	184 480	
Calendar year						
2007	22 545 (9.4)	108 010 (18.0)	0.25	21 631 (11.7)	21 631 (11.7)	<0.01
2008	22 887 (9.5)	92 706 (15.5)	0.18	21 446 (11.6)	21 446 (11.6)	<0.01
2009	21 339 (8.9)	87 784 (14.6)	0.18	19 810 (10.7)	19 810 (10.7)	<0.01
2010	21 345 (8.9)	61 408 (10.2)	0.04	18 645 (10.1)	18 645 (10.1)	<0.01
2011	20 423 (8.5)	60 337 (10.1)	0.05	17 414 (9.4)	17 414 (9.4)	<0.01
2012	18 659 (7.8)	42 382 (7.1)	0.02	14 940 (8.1)	14 940 (8.1)	<0.01
2013	19 250 (8.0)	26 778 (4.5)	0.14	12 477 (6.8)	12 477 (6.8)	<0.01
2014	21 073 (8.8)	28 438 (4.7)	0.16	13 289 (7.2)	13 289 (7.2)	<0.01
2015	22 550 (9.4)	31 725 (5.3)	0.15	14 648 (7.9)	14 648 (7.9)	<0.01
2016	24 070 (10.0)	30 047 (5.0)	0.19	14 515 (7.9)	14 515 (7.9)	<0.01
2017	26 120 (10.9)	29 613 (4.9)	0.22	15 665 (8.5)	15 665 (8.5)	<0.01
Age, mean (SD), y	54.1 (16.2)	45.3 (16.3)	0.54	52.7 (16.2)	53.5 (16.1)	0.04
Sex						
Male	102 280 (42.6)	271 274 (45.3)	0.05	78 703 (42.7)	78 713 (42.7)	<0.01
Female	137 981 (57.4)	327 954 (54.7)	0.05	105 777 (57.3)	105 767 (57.3)	<0.01
Socioeconomic deprivation[a]						
U1 (least deprived)	40 231 (16.7)	95 500 (15.9)	0.02	30 942 (16.8)	31 080 (16.8)	<0.01
U2	47 841 (19.9)	118 451 (19.8)	<0.01	36 695 (19.9)	36 645 (19.9)	<0.01
U3	50 517 (21.0)	128 510 (21.4)	0.01	38 944 (21.1)	38 943 (21.1)	<0.01
U4	52 901 (22.0)	131 550 (22.0)	<0.01	40 425 (21.9)	40 497 (22.0)	<0.01
U5 (most deprived)	48 771 (20.3)	125 217 (20.9)	0.01	37 474 (20.3)	37 315 (20.2)	<0.01
Rural residence	44 060 (18.3)	115 718 (19.3)	0.02	33 562 (18.2)	33 649 (18.2)	<0.01
Common opioid indications						
Back pain	129 471 (53.9)	184 539 (30.8)	0.48	87 606 (47.5)	89 710 (48.6)	0.02
Neck/shoulder pain	79 040 (32.9)	111 010 (18.5)	0.33	52 851 (28.6)	54 489 (29.5)	0.02
Osteoarthritis	45 476 (18.9)	40 877 (6.8)	0.36	28 206 (15.3)	28 433 (15.4)	<0.01
Cough	14 472 (6.0)	54 295 (9.1)	0.11	11 602 (6.3)	11 189 (6.1)	<0.01
Migraine	10 712 (4.5)	22 071 (3.7)	0.03	7895 (4.3)	8084 (4.4)	<0.01
Cancer	10 168 (4.2)	8515 (1.4)	0.17	5963 (3.2)	6115 (3.3)	<0.01
Other comorbidities						
Diabetes	26 232 (10.9)	37 168 (6.2)	0.16	17 958 (9.7)	18 599 (10.1)	0.01
Other musculoskeletal disorders	13 309 (5.5)	15 861 (2.6)	0.14	8496 (4.6)	8677 (4.7)	<0.01
COPD	6811 (2.8)	8771 (1.5)	0.09	4511 (2.4)	4646 (2.5)	<0.01
Chronic kidney disease	6306 (2.6)	4710 (0.8)	0.14	3468 (1.9)	3497 (1.9)	<0.01
Fibromyalgia	4461 (1.9)	1631 (0.3)	0.15	1984 (1.1)	1555 (0.8)	0.02
Dyspnea	3863 (1.6)	5030 (0.8)	0.07	2407 (1.3)	2500 (1.4)	<0.01
Peripheral vascular disease	2597 (1.1)	2018 (0.3)	0.08	1420 (0.8)	1420 (0.8)	<0.01
Angina	2249 (0.9)	2692 (0.4)	0.05	1515 (0.8)	1554 (0.8)	<0.01
TIA	1242 (0.5)	1290 (0.2)	0.05	754 (0.4)	806 (0.4)	<0.01
Osteoporosis	845 (0.4)	488 (0.1)	0.05	440 (0.2)	395 (0.2)	<0.01
Parkinson disease	892 (0.4)	759 (0.1)	0.04	534 (0.3)	539 (0.3)	<0.01
Alzheimer disease	953 (0.4)	1104 (0.2)	0.03	702 (0.4)	725 (0.4)	<0.01
Chronic liver disease	680 (0.3)	710 (0.1)	0.03	424 (0.2)	428 (0.2)	<0.01
Diarrhea	747 (0.3)	1720 (0.3)	<0.01	554 (0.3)	540 (0.3)	<0.01
Rheumatoid arthritis	445 (0.2)	372 (0.1)	0.03	227 (0.1)	236 (0.1)	<0.01
Malabsorption disorders	465 (0.2)	969 (0.2)	<0.01	333 (0.2)	336 (0.2)	<0.01
Pulmonary edema	64 (<0.1)	67 (<0.1)	0.01	32 (<0.1)	37 (<0.1)	<0.01

(continued)

Table. Baseline Characteristics of New Tramadol and Codeine Users Before and After Propensity-Score Matching (continued)

	Before matching			After matching		
	No. (%)			No. (%)		
	Tramadol	Codeine	ASMD	Tramadol	Codeine	ASMD
Charlson Comorbidity Index[b]						
0	176 076 (73.3)	502 922 (83.9)	0.26	140 794 (76.3)	139 713 (75.7)	0.01
1-2	55 479 (23.1)	89 439 (14.9)	0.20	38 885 (21.1)	39 961 (21.7)	0.01
≥3	8706 (3.6)	6867 (1.1)	0.16	4801 (2.6)	4806 (2.6)	<0.01
Concomitant medication in the year prior to the index visit						
Psychotropics						
Benzodiazepines	71 881 (29.9)	99 437 (16.6)	0.31	48 709 (26.4)	49 543 (26.9)	0.01
Anticonvulsant	32 153 (13.4)	18 590 (3.1)	0.38	16 321 (8.8)	14 400 (7.8)	0.03
SSRIs	26 972 (11.2)	48 296 (8.1)	0.10	20 252 (11.0)	20 461 (11.1)	<0.01
Hypnotics	15 147 (6.3)	20 045 (3.3)	0.13	10 653 (5.8)	10 618 (5.8)	<0.01
NSAIDs						
Ibuprofen	80 916 (33.7)	207 684 (34.7)	0.02	63 472 (34.4)	63 381 (34.4)	<0.01
Diclofenac	54 571 (22.7)	56 862 (9.5)	0.36	36 215 (19.6)	35 353 (19.2)	0.01
Other NSAIDs[c]	46 642 (19.4)	34 885 (5.8)	0.41	27 197 (14.7)	25 653 (13.9)	0.02
Naproxen	29 280 (12.2)	29 194 (4.9)	0.26	16 630 (9.0)	17 042 (9.2)	<0.01
Celecoxib	5832 (2.4)	2569 (0.4)	0.16	2903 (1.6)	2320 (1.3)	0.02
Other analgesics						
Paracetamol/acetaminophen	97 358 (40.5)	191 456 (32.0)	0.17	68 365 (37.1)	68 032 (36.9)	<0.01
Metamizole	53 545 (22.3)	38 815 (6.5)	0.46	29 202 (15.8)	27 668 (15.0)	0.02
Health care utilization in the year prior to the index visit, mean (SD)						
General practitioner visits	7.1 (5.3)	5.3 (4.4)	0.35	6.6 (5.1)	6.6 (5.0)	<0.01
Hospital admissions	3.3 (5.6)	2.0 (3.8)	0.27	2.9 (4.9)	2.9 (5.1)	<0.01

Abbreviations: ASMD, absolute standardized mean difference; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack.

[a] As assessed using the MEDEA index (http://www.proyectomedea.org/eng/indice-de-privacion.html); "U" indicates "urban."

[b] Charlson Comorbidity Index was calculated using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* coding algorithm based on the R *comorbidity* package (R Foundation for Statistical Computing).

[c] All other NSAIDs included are listed in eAppendix 1 in the Supplement.

drugs concomitantly and were excluded. A total of 839 489 tramadol or codeine initiators were identified by excluding 86 660 patients who were dispensed tramadol and 163 264 patients who were dispensed codeine and did not meet eligibility criteria. After propensity score matching, the matched cohort included 368 960 participants: 184 480 in the tramadol cohort and 184 480 in the codeine cohort. **Figure 1** shows the participant selection process.

The Table reports the participants' baseline characteristics before and after propensity score matching. After matching, the 2 cohorts of new users were comparable for all observed features, with no ASMD exceeding 0.1 and most not exceeding 0.01. The mean age of patients was 52.7 (SD, 16.2) years in the tramadol cohort and 53.5 (SD, 16.1) years in the codeine cohort. The prevalence of cancer was 3.2% and 3.3%, respectively, in the tramadol and codeine cohorts. The most common diagnoses were back pain (47.5% vs 48.5%), neck/shoulder pain (28.6% vs 29.5%), and osteoarthritis (15.3% vs 15.5%). The drugs most frequently dispensed were ibuprofen (34.4% vs 34.3%) and paracetamol/acetaminophen (37.1% vs 36.8%).

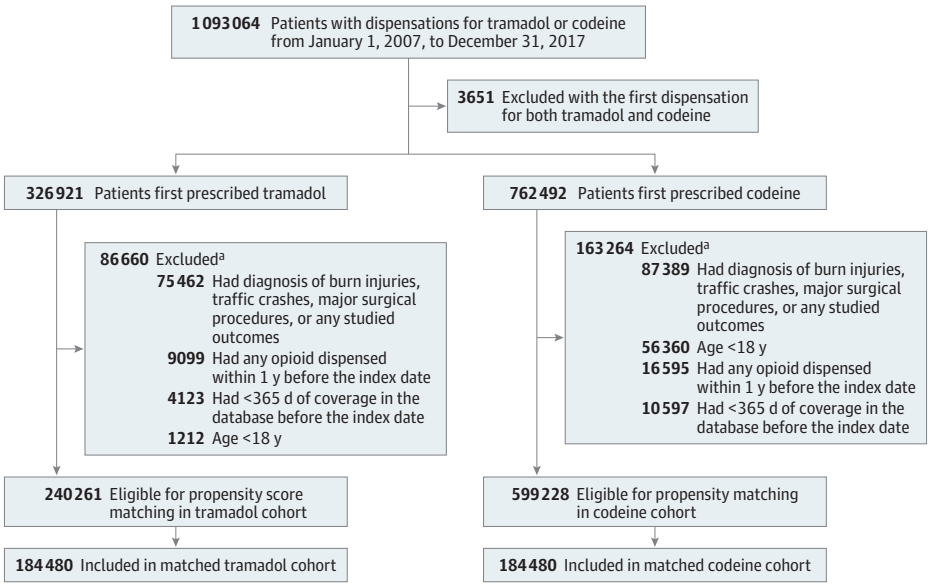
The proportions of residential area and socioeconomic deprivation index data missing across the entire data set were 0.04% and 27.04%, respectively.

Figure 2 shows Kaplan-Meier plots in the matched cohorts. During 1-year follow-up, participants with a prescription dispensation of tramadol had a significantly higher risk of all-cause mortality, cardiovascular disease, and fractures (1-year cumulative incidence of all-cause mortality, 12.86 [95% CI, 12.34 to 13.38] per 1000 participants in the tramadol cohort vs 5.59 [95% CI 5.25 to 5.94] per 1000 in the codeine cohort; cardiovascular disease, 9.97 [95% CI, 9.50 to 10.43] per 1000 participants in the tramadol cohort vs 8.62 [95% CI, 8.19 to 9.05] per 1000 in the codeine cohort; and fractures, 12.07 [95% CI, 11.56 to 12.57] per 1000 participants in the tramadol cohort vs 8.08 [95% CI, 7.67 to 8.50] per 1000 in the codeine cohort). Kaplan-Meier plots for the unmatched cohorts are provided in eFigure 4 in the Supplement.

Association of Drug Dispensation With Adverse Outcomes

Compared with codeine, tramadol prescription dispensation was significantly associated with a higher risk of mortality

Figure 1. Selection Process of Participants for the Study



[a] Patients could be excluded for more than 1 reason.

(13.00 vs 5.61 per 1000 person-years; HR, 2.31 [95% CI, 2.08 to 2.56]; ARD, 7.37 [95% CI, 6.09 to 8.78] per 1000 person-years), cardiovascular events (10.03 vs 8.67 per 1000 person-years; HR, 1.15 [95% CI, 1.05 to 1.27]; ARD, 1.36 [95% CI, 0.45 to 2.36] per 1000 person-years), and fractures (12.26 vs 8.13 per 1000 person-years; HR, 1.50 [95% CI, 1.37 to 1.65]; ARD, 4.10 [95% CI, 3.02 to 5.29] per 1000 person-years).

For tramadol compared with codeine prescription dispensation, there was no significant difference in the risk of constipation (6.98 vs 6.41 per 1000 person-years; HR, 1.08 [95% CI, 0.97 to 1.21]; ARD, 0.56 [95% CI, −0.17 to 1.39] per 1000 person-years), delirium (0.21 vs 0.20 per 1000 person-years; HR, 1.02 [95% CI, 0.54 to 1.93]; ARD, 0.00 [95% CI, −0.06 to 0.18] per 1000 person-years), falls (2.75 vs 2.32 per 1000 person-years; HR, 1.18 [95% CI, 0.98 to 1.42]; ARD, 0.43 [95% CI, −0.02 to 0.98] per 1000 person-years), opioid abuse/dependence (0.12 vs 0.06 per 1000 person-years; HR, 1.91 [95% CI, 0.72 to 5.08]; ARD, 0.05 [95% CI, −0.01 to 0.24] per 1000 person-years), and sleep disorders (2.22 vs 2.08 per 1000 person-years; HR, 1.06 [95% CI, 0.87 to 1.29]; ARD, 0.13 [95% CI, −0.26 to 0.62] per 1000 person-years) (**Figure 3**).

Because the proportional hazards assumption was violated for the mortality ($P < .001$) and fractures ($P < .001$) outcomes, the follow-up period was shortened to 3 or less, 6, and 9 months. The HR decreased gradually as time after tramadol dispensation increased (eTable 1 in the Supplement).

Subgroup and Sensitivity Analyses

The increased mortality risk associated with tramadol was significantly greater among younger compared with older adults (HR, 3.14 [95% CI, 1.82 to 5.41] vs HR, 2.39 [95% CI, 2.20 to 2.60]; $P < .001$ for interaction) (**Figure 4**). Women had a significantly greater risk of cardiovascular events than men (HR, 1.32 [95% CI, 1.19 to 1.46] vs 1.03 [95% CI, 0.93 to 1.13]; $P < .001$ for interaction) (**Figure 5**). Participants with the most-prevalent comorbidities compared with the least-prevalent comorbidities had a significantly higher fracture risk (HR, 2.20 [95% CI, 1.57 to 3.09] vs 1.47 [95% CI, 1.35 to 1.59]; $P = .004$ for interaction) (**Figure 6**). Subgroup ARDs varied depending on their baseline risk for each outcome.

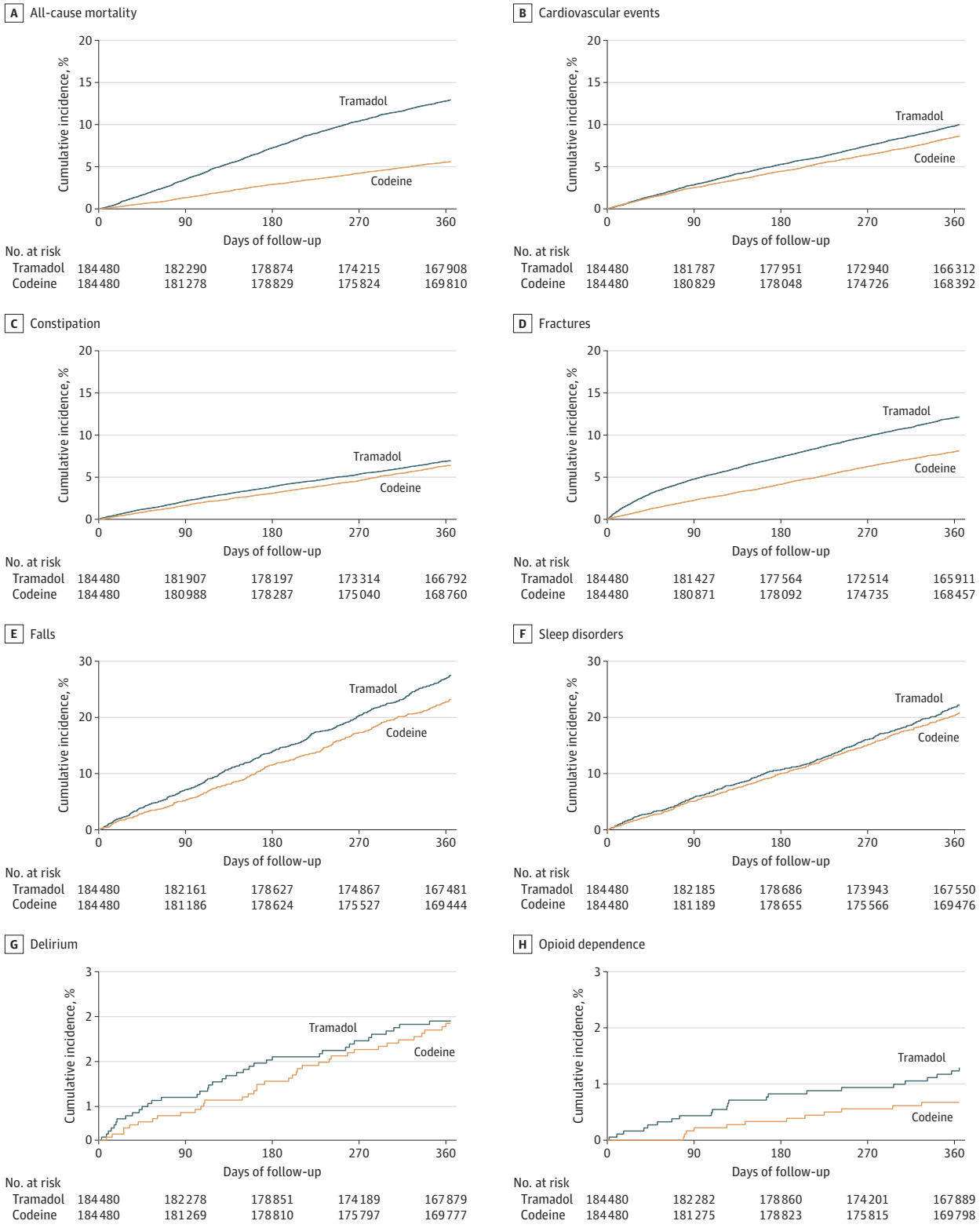
The sensitivity analyses (eTable 2 in the Supplement) consistently indicated that patients in the tramadol cohort experienced significantly higher risks of mortality, cardiovascular events, and fractures than patients in the codeine cohort.

Discussion

In this retrospective population-based cohort study, the prescription dispensation of tramadol was significantly associated with greater risks of mortality, cardiovascular events, and fractures than the prescription dispensation of codeine. No significant difference was found in the risks of constipation, delirium, falls, opioid abuse/dependence, or sleep disorders in the year after treatment initiation. The results remained consistent and robust across subgroup and sensitivity analyses.

Musich et al[28] recently reported 59% increased risk of cardiovascular hospitalizations, 41% increased risk of falls/fractures, and 21% increased risk of mortality among patients with osteoarthritis 65 years or older starting tramadol, compared with nonusers. However, this comparison has limited clinical relevance, as individuals prescribed an opioid are likely to be unhealthier than those who are not. Two recent studies using the UK's Health Improvement Network database found patients with osteoarthritis who used tramadol had a greater risk of hip fracture (HR, 1.28 [95% CI, 1.13 to 1.46])[29] and myocardial infarction (HR, 1.23 [95% CI, 0.95 to 1.60])[30] than those who used codeine. Comparing tramadol with codeine is clinically relevant, as they are both

Figure 2. Kaplan-Meier Cumulative Incidence Plots for All Study Outcomes Within 1 Year in the Matched Cohort



Most patients in each group were observed for the whole year. There were no primary or secondary outcomes; all study outcomes were prespecified and treated equally. Cumulative incidence (95% CI) per 1000 participants, tramadol vs codeine: A, 12.86 (12.34-13.38) vs 5.59 (5.25-5.94). B, 9.97 (9.50-10.43) vs 8.62 (8.19-9.05). C, 6.92 (6.54-7.31) vs 6.39 (6.02-6.76). D, 12.07 (11.56-12.57) vs 8.08 (7.67-8.50). E, 2.75 (2.50-2.99) vs 2.32 (2.09-2.54). F, 2.22 (2.00-2.44) vs 2.08 (1.87-2.29). G, 0.21 (0.14-0.2) vs 0.20% (0.14-0.27). H, 0.12 (0.07-0.18) vs 0.06 (0.02-0.10).

Figure 3. Event Counts, Incidence Rates, Absolute Rate Differences, and Adjusted Hazard Ratios for 8 Study Outcomes Within 1 Year in the Matched Cohort

Outcome	Tramadol (n = 184 480) No. of Events	Tramadol (n = 184 480) Incidence rate per 1000 person-years	Codeine (n = 184 480) No. of Events	Codeine (n = 184 480) Incidence rate per 1000 person-years	Rate difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)
All-cause mortality	2307	13.00	999	5.61	7.37 (6.09 to 8.78)	2.31 (2.08 to 2.56)
Cardiovascular events	1772	10.03	1536	8.67	1.36 (0.45 to 2.36)	1.15 (1.05 to 1.27)
Constipation	1234	6.98	1137	6.41	0.56 (-0.17 to 1.39)	1.08 (0.97 to 1.21)
Delirium	38	0.21	37	0.20	0.00 (-0.09 to 0.18)	1.02 (0.54 to 1.93)
Fractures	2160	12.26	1442	8.13	4.10 (3.02 to 5.29)	1.50 (1.37 to 1.65)
Falls	488	2.75	413	2.32	0.43 (-0.02 to 0.98)	1.18 (0.98 to 1.42)
Opioid abuse/dependence	23	0.12	12	0.06	0.05 (-0.01 to 0.24)	1.91 (0.72 to 5.08)
Sleep disorders	394	2.22	371	2.08	0.13 (-0.26 to 0.62)	1.06 (0.87 to 1.29)

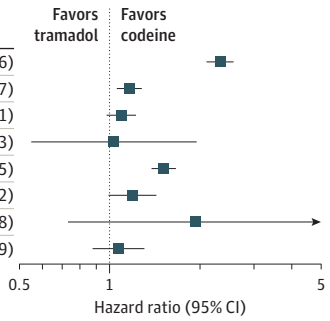
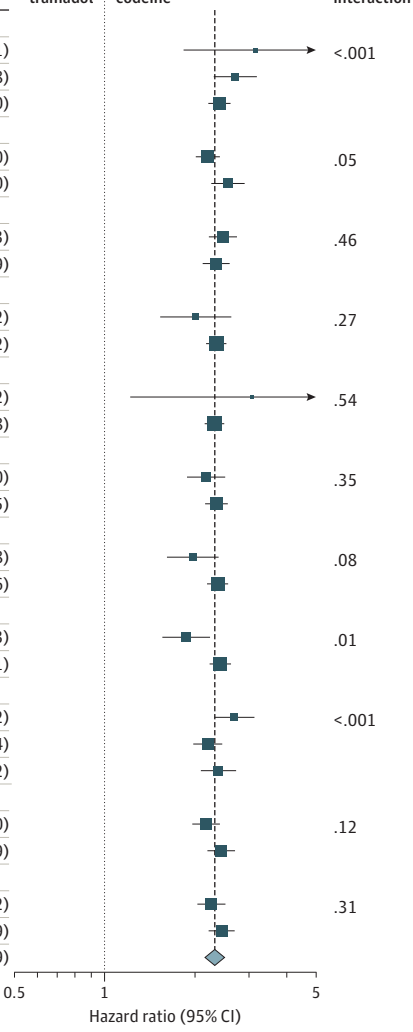


Figure 4. Subgroup-Specific Associations of Tramadol vs Codeine With All-Cause Mortality

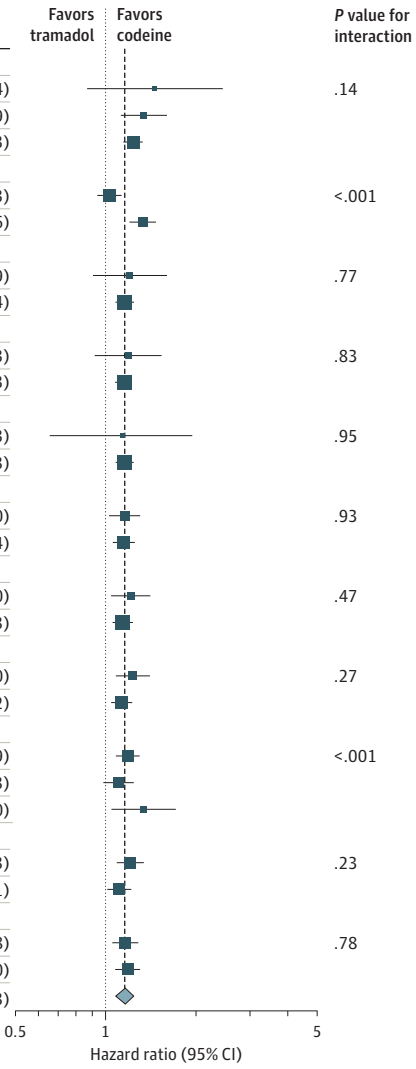
Subgroup	No. of participants, % Tramadol	No. of participants, % Codeine	Incidence rate per 1000 person-years Tramadol	Incidence rate per 1000 person-years Codeine	Rate difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)	*P* value for interaction
Age, y							
18-39	44 269 (23.9)	42 974 (23.2)	1.2	0.4	0.85 (0.33-1.76)	3.14 (1.82-5.41)	<.001
40-59	78 881 (42.7)	73 168 (39.6)	7.3	2.7	4.60 (3.49-5.90)	2.70 (2.29-3.18)	
≥60	61 330 (33.2)	68 338 (37.0)	28.6	11.9	16.62 (14.31-19.14)	2.39 (2.20-2.60)	
Sex							
Men	78 703 (42.6)	78 713 (42.6)	19.3	8.8	10.51 (8.82-12.36)	2.19 (2.00-2.40)	.05
Women	105 777 (57.3)	105 767 (57.3)	8.2	3.2	4.98 (4.00-6.09)	2.55 (2.25-2.90)	
Cancer							
Yes	5963 (3.2)	6115 (3.3)	213.2	85.9	125.44 (103.89-149.44)	2.46 (2.20-2.73)	.46
No	178 517 (96.7)	178 365 (96.6)	7.0	3.0	4.01 (3.33-4.77)	2.33 (2.11-2.59)	
Cough							
Yes	11 602 (6.2)	11 189 (6.0)	15.2	7.5	7.51 (3.96-12.18)	2.00 (1.52-2.62)	.27
No	172 878 (93.7)	173 291 (93.9)	12.8	5.4	7.23 (6.29-8.24)	2.33 (2.16-2.52)	
Migraine							
Yes	7895 (4.2)	8084 (4.3)	2.3	0.7	1.44 (0.15-4.70)	3.06 (1.21-7.72)	.54
No	176 585 (95.7)	176 396 (95.6)	13.4	5.8	7.58 (6.62-8.62)	2.30 (2.14-2.48)	
Back pain							
Yes	87 606 (47.4)	89 710 (48.6)	6.7	3.1	3.61 (2.70-4.66)	2.16 (1.87-2.50)	.35
No	96 874 (52.5)	94 770 (51.3)	18.5	7.9	10.61 (9.08-12.28)	2.34 (2.14-2.55)	
Neck/shoulder pain							
Yes	52 851 (28.6)	54 489 (29.5)	5.7	2.9	2.77 (1.76-4.00)	1.95 (1.60-2.38)	.08
No	131 629 (71.3)	129 991 (70.4)	15.8	6.7	9.13 (7.91-10.45)	2.36 (2.18-2.56)	
Osteoarthritis							
Yes	28 206 (15.2)	28 433 (15.4)	12.1	6.5	5.60 (3.59-8.00)	1.86 (1.55-2.23)	.01
No	156 274 (84.7)	156 047 (84.5)	13.1	5.4	7.63 (6.61-8.73)	2.41 (2.22-2.61)	
CCI score							
0	140 794 (76.3)	139 713 (75.7)	4.5	1.6	2.69 (2.09-3.40)	2.68 (2.30-3.12)	<.001
1-2	38 885 (21.0)	39 961 (21.6)	26.7	12.2	14.56 (11.77-17.68)	2.19 (1.96-2.44)	
≥3	4801 (2.6)	4806 (2.6)	167.5	69.8	96.33 (75.49-120.16)	2.38 (2.08-2.72)	
Psychotropics							
Yes	70 020 (37.9)	67 271 (36.4)	16.7	7.7	8.97 (7.31-10.82)	2.16 (1.95-2.40)	.12
No	114 460 (62.0)	117 209 (63.5)	10.6	4.3	6.14 (5.10-7.30)	2.43 (2.18-2.69)	
NSAIDs							
Yes	109 645 (59.4)	104 263 (56.5)	9.6	4.2	5.28 (4.27-6.41)	2.25 (2.01-2.52)	.31
No	74 835 (40.5)	80 217 (43.4)	17.9	7.3	10.49 (8.81-12.35)	2.43 (2.20-2.69)	
Overall	184 480	184 480	13.0	5.6	7.35 (6.43-8.35)	2.31 (2.14-2.49)	



Sizes of data markers reflect the sample size in each subanalysis. CCI indicates Charlson Comorbidity Index; NSAID, nonsteroidal anti-inflammatory drug.

Figure 5. Subgroup-Specific Associations of Tramadol vs Codeine With Cardiovascular Events

Subgroup	No. of participants, %		Incidence rate per 1000 person-years		Rate difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)	P value for interaction
	Tramadol	Codeine	Tramadol	Codeine			
Age, y							
18-39	44 269 (23.9)	42 974 (23.2)	0.8	0.5	0.22 (-0.06 to 0.72)	1.45 (0.86 to 2.44)	.14
40-59	78 881 (42.7)	73 168 (39.6)	4.0	3.0	1.01 (0.37 to 1.79)	1.33 (1.12 to 1.59)	
≥60	61 330 (33.2)	68 338 (37.0)	24.5	19.8	4.65 (2.88 to 6.56)	1.23 (1.14 to 1.33)	
Sex							
Men	78 703 (42.6)	78 713 (42.6)	12.0	11.6	0.34 (-0.71 to 1.51)	1.03 (0.93 to 1.13)	<.001
Women	105 777 (57.3)	105 767 (57.3)	8.5	6.4	2.09 (1.27 to 2.99)	1.32 (1.19 to 1.46)	
Cancer							
Yes	5963 (3.2)	6115 (3.3)	20.1	16.6	3.39 (-1.51 to 9.91)	1.20 (0.90 to 1.59)	.77
No	178 517 (96.7)	178 365 (96.6)	9.7	8.4	1.32 (0.66 to 2.03)	1.15 (1.07 to 1.24)	
Cough							
Yes	11 602 (6.2)	11 189 (6.0)	12.5	10.5	1.97 (-0.82 to 5.58)	1.18 (0.92 to 1.53)	.83
No	172 878 (93.7)	173 291 (93.9)	9.8	8.5	1.31 (0.64 to 2.03)	1.15 (1.07 to 1.23)	
Migraine							
Yes	7895 (4.2)	8084 (4.3)	3.8	3.3	0.46 (-1.08 to 3.08)	1.14 (0.67 to 1.93)	.95
No	176 585 (95.7)	176 396 (95.6)	10.3	8.9	1.39 (0.71 to 2.13)	1.15 (1.08 to 1.23)	
Back pain							
Yes	87 606 (47.4)	89 710 (48.6)	6.9	6.0	0.93 (0.16 to 1.81)	1.15 (1.02 to 1.30)	.93
No	96 874 (52.5)	94 770 (51.3)	12.7	11.1	1.65 (0.63 to 2.76)	1.14 (1.05 to 1.24)	
Neck/shoulder pain							
Yes	52 851 (28.6)	54 489 (29.5)	7.5	6.2	1.31 (0.27 to 2.52)	1.21 (1.04 to 1.40)	.47
No	131 629 (71.3)	129 991 (70.4)	11.0	9.6	1.34 (0.53 to 2.21)	1.13 (1.05 to 1.23)	
Osteoarthritis							
Yes	28 206 (15.2)	28 433 (15.4)	18.6	15.1	3.49 (1.23 to 6.07)	1.23 (1.08 to 1.40)	.27
No	156 274 (84.7)	156 047 (84.5)	8.4	7.4	0.96 (0.32 to 1.66)	1.13 (1.04 to 1.22)	
CCI score							
0	140 794 (76.3)	139 713 (75.7)	7.6	6.4	1.18 (0.52 to 1.89)	1.18 (1.08 to 1.29)	<.001
1-2	38 885 (21.0)	39 961 (21.6)	16.2	14.7	1.52 (−0.24 to 3.51)	1.10 (0.98 to 1.23)	
≥3	4801 (2.6)	4806 (2.6)	35.3	26.2	8.83 (1.21 to 18.55)	1.33 (1.04 to 1.70)	
Psychotropics							
Yes	70 020 (37.9)	67 271 (36.4)	12.0	10.0	2.07 (0.89 to 3.38)	1.20 (1.08 to 1.33)	.23
No	114 460 (62.0)	117 209 (63.5)	8.7	7.8	0.86 (0.10 to 1.69)	1.11 (1.01 to 1.21)	
NSAIDs							
Yes	109 645 (59.4)	104 263 (56.5)	8.2	7.0	1.13 (0.36 to 1.98)	1.16 (1.05 to 1.28)	.78
No	74 835 (40.5)	80 217 (43.4)	12.7	10.7	1.96 (0.82 to 3.22)	1.18 (1.07 to 1.30)	
Overall	184 480	184 480	10.0	8.6	1.35 (0.69 to 2.05)	1.15 (1.08 to 1.23)	



Sizes of data markers reflect the sample size in each subanalysis. CCI indicates Charlson Comorbidity Index; NSAID, nonsteroidal anti-inflammatory drug.

"weak" opioids (lower morphine equivalent dose) used for the second step of the World Health Organization pain ladder, such as moderate noncancer pain.

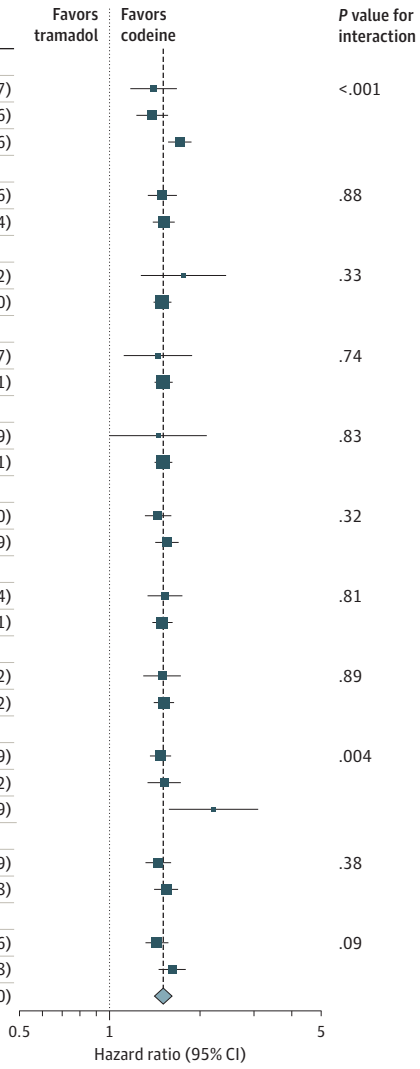
This study expanded on previous studies by comparing tramadol with codeine for various indications in all adult age groups and found that, compared with codeine, tramadol prescription dispensation was significantly associated with a higher risk of mortality, cardiovascular events, and fractures in all age groups, independent of previous comorbid conditions.

Two studies have shown results that differ from the results of the present study. Solomon et al[31] compared 5 opioids commonly prescribed in the US in 31 375 Medicare patients. They found that codeine users had higher incidence rates of mortality compared with tramadol users (70 vs 40 per 1000 person-years), cardiovascular events (170 vs 110 per 1000 person-years), and fractures (270 vs 70 per 1000 person-years) during 180 days of follow-up. However, this study may have been subject to selection bias, because codeine users also had greater risks of these outcomes than users of oxycodone, propoxyphene, and hydrocodone, which contradicts what might be expected from physicians' experience and the morphine milligram equivalents of the 5 drugs.

Zeng et al[14] conducted a head-to-head comparison of mortality risk between tramadol, codeine, and several NSAIDs and found that tramadol initiation was associated with an increased risk of mortality compared with NSAIDs but not codeine (HR, 0.94 [95% CI, 0.83 to 1.05]). However, they used a UK-based sample of 16 922 older patients with osteoarthritis (mean age, 71 years), who differed substantially from the general population in terms of comorbidities and polypharmacy. This sample was possibly subject to depletion of susceptibility bias, in which early increased risk of acute adverse events is attenuated after a long drug exposure. The study relied on general practice prescriptions, which are more susceptible to

Figure 6. Subgroup-Specific Associations of Tramadol vs Codeine With Fractures

Subgroup	No. of participants, %		Incidence rate per 1000 person-years		Rate difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)	*P* value for interaction
	Tramadol	Codeine	Tramadol	Codeine			
Age, y							
18-39	44 269 (23.9)	42 974 (23.2)	6.9	4.9	1.95 (0.83-3.29)	1.39 (1.17-1.67)	<.001
40-59	78 881 (42.7)	73 168 (39.6)	8.5	6.1	2.35 (1.38-3.44)	1.38 (1.22-1.56)	
≥60	61 330 (33.2)	68 338 (37.0)	20.9	12.2	8.62 (6.84-10.56)	1.70 (1.56-1.86)	
Sex							
Men	78 703 (42.6)	78 713 (42.6)	10.4	6.9	3.41 (2.33-4.62)	1.49 (1.33-1.66)	.88
Women	105 777 (57.3)	105 767 (57.3)	13.6	9.0	4.59 (3.50-5.78)	1.51 (1.38-1.64)	
Cancer							
Yes	5963 (3.2)	6115 (3.3)	18.9	10.6	8.00 (2.85-15.13)	1.75 (1.26-2.42)	.33
No	178 517 (96.7)	178 365 (96.6)	12.0	8.0	3.96 (3.18-4.81)	1.49 (1.39-1.60)	
Cough							
Yes	11 602 (6.2)	11 189 (6.0)	13.4	9.2	4.09 (1.05-8.04)	1.44 (1.11-1.87)	.74
No	172 878 (93.7)	173 291 (93.9)	12.1	8.0	4.07 (3.26-4.93)	1.50 (1.40-1.61)	
Migraine							
Yes	7895 (4.2)	8084 (4.3)	9.0	6.2	2.78 (0.00-6.79)	1.44 (1.00-2.09)	.83
No	176 585 (95.7)	176 396 (95.6)	12.4	8.2	4.15 (3.34-5.02)	1.50 (1.40-1.61)	
Back pain							
Yes	87 606 (47.4)	89 710 (48.6)	11.0	7.6	3.40 (2.34-4.56)	1.44 (1.30-1.60)	.32
No	96 874 (52.5)	94 770 (51.3)	13.3	8.6	4.71 (3.57-5.95)	1.54 (1.41-1.69)	
Neck/shoulder pain							
Yes	52 851 (28.6)	54 489 (29.5)	10.8	7.1	3.72 (2.38-5.26)	1.52 (1.33-1.74)	.81
No	131 629 (71.3)	129 991 (70.4)	12.8	8.5	4.21 (3.27-5.23)	1.49 (1.38-1.61)	
Osteoarthritis							
Yes	28 206 (15.2)	28 433 (15.4)	17.1	11.4	5.60 (3.33-8.21)	1.49 (1.29-1.72)	.89
No	156 274 (84.7)	156 047 (84.5)	11.3	7.5	3.82 (2.99-4.70)	1.50 (1.39-1.62)	
CCI score							
0	140 794 (76.3)	139 713 (75.7)	10.8	7.3	3.46 (2.62-4.36)	1.47 (1.35-1.59)	.004
1-2	38 885 (21.0)	39 961 (21.6)	16.1	10.6	5.46 (3.55-7.63)	1.51 (1.33-1.72)	
≥3	4801 (2.6)	4806 (2.6)	25.0	11.2	13.51 (6.39-23.50)	2.20 (1.57-3.09)	
Psychotropics							
Yes	70 020 (37.9)	67 271 (36.4)	15.0	10.3	4.62 (3.23-6.15)	1.44 (1.31-1.59)	.38
No	114 460 (62.0)	117 209 (63.5)	10.5	6.8	3.65 (2.74-4.65)	1.53 (1.40-1.68)	
NSAIDs							
Yes	109 645 (59.4)	104 263 (56.5)	11.9	8.3	3.60 (2.61-4.69)	1.43 (1.31-1.56)	.09
No	74 835 (40.5)	80 217 (43.4)	12.7	7.8	4.76 (3.53-6.13)	1.61 (1.45-1.78)	
Overall	184 480	184 480	12.2	8.1	4.09 (3.30-4.93)	1.50 (1.40-1.60)	



Sizes of data markers reflect the sample size in each subanalysis. CCI indicates Charlson Comorbidity Index; NSAID, nonsteroidal anti-inflammatory drug.

exposure misclassification than drug dispensation records because nonadherence to opioid medications is common.[32] The participants were also unlikely to truly be new users, as weak opioids used to be available over the counter in the UK.[33]

Limitations

This study has several limitations. First, although tramadol and codeine have been widely indicated for managing moderate to severe pain, confounding by indication could have affected the study findings. For example, codeine is often prescribed to control coughs, and a higher prevalence of cough has been observed among patients with codeine prescription dispensation (9.1%) than among patients with tramadol prescription dispensation (6.0%) before matching. However, the results remained almost unchanged when restricting the analysis to patients with or without a prior cough diagnosis, suggesting this residual indication bias is unlikely to have had a great effect. Also, tramadol may be expected to be prescribed for patients with severe illness because of a perception that it has a relatively safe profile, which could explain part of the observed associations.

Second, despite that the propensity score matching balanced the observed baseline characteristics between the 2 groups and that the subgroup analyses produced results that were highly consistent with those from the main analysis, unmeasured confounders may have nonetheless biased the estimates.

Third, the magnitude of associations between the packages of tramadol dispensation and the adverse outcomes should be interpreted cautiously. Dispensed packages of tramadol is a crude proxy for assessing dose and could instead be a reflection of anticipated pain levels, which might explain the observed association.

Fourth, this study did not include the cause of death. Given the difficulty of disentangling how much of the mortality risk

was specifically related to the actual dispensation of tramadol, this estimate may be falsely elevated.

Fifth, some of the study outcomes, especially delirium and sleep disorders, may have been underestimated in routine clinical practice. Also, tramadol or codeine prescription dispensation does not necessarily indicate exposure to either drug, as the adherence is largely unknown. However, any underestimation and nonadherence are likely to have been the same in both groups, either not affecting the between-group comparison or distorting the associations toward the null.

Conclusions

In this population-based cohort study, a new prescription dispensation of tramadol, compared with codeine, was significantly associated with a higher risk of subsequent all-cause mortality, cardiovascular events, and fractures, but there was no significant difference in the risk of constipation, delirium, falls, opioid abuse/dependence, or sleep disorders. The findings should be interpreted cautiously, given the potential for residual confounding.

ARTICLE INFORMATION

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