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Association of Tramadol Use with Risk of Hip Fracture

Jie Wei, PhD[1,2,3], **Nancy E. Lane, MD**[4], **Marcy B. Bolster, MD**[2], **Maureen Dubreuil, MD, MSc**[5,6], **Chao Zeng, MD, PhD**[2,3,7], **Devyani Misra, MD, MS**[8], **Na Lu, MPH**[2,9], **Hyon K. Choi, MD, DrPH**[2,3], **Guanghua Lei, MD, PhD**[7,10,*], **Yuqing Zhang, DSc**[2,3,*]

[1]Health Management Center, Xiangya Hospital, Central South University, Changsha, Hunan, China

[2]Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[3]The Mongan Institute, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[4]Center for Musculoskeletal Health and Department of Medicine, University of California School of Medicine, Sacramento, California, USA

[5]Boston University School of Medicine, Boston, Massachusetts, USA

[6]VA Boston Healthcare System, Boston, Massachusetts, USA

[7]Department of Orthopaedics, Xiangya Hospital, Central South University, Changsha, Hunan, China

[8]Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

[9]Arthritis Research Canada, Richmond, British Columbia, Canada

[10]National Clinical Research Center of Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, China.

[*]**Correspondence to: Guanghua Lei**, Department of Orthopaedics, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, China, 410008, Tel: 86073184327326, lei_guanghua@csu.edu.cn; **Yuqing Zhang**, Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, Massachusetts, USA, 02114, Tel: 16176439624, yzhang108@mgh.harvard.edu.

Author Contributions

JW, NEL, MBB, MD, CZ, DM, NL, HKC, GL and YZ made substantial contributions to the conception and design of the study. All authors contributed to the writing and editing of the study protocol. JW conducted the data cleaning, and data analysis. All authors contributed to the interpretation of results. JW wrote the first draft. YZ and GL had full access to the data and take responsibility for the content and guarantee the integrity and accuracy of the work undertaken. All authors have read, provided critical feedback on intellectual content and approved the final manuscript.

Supplemental data

Appendix

Disclosures

No conflict of interest for any of the authors.

Ethical approval

This study received approval from the medical ethical committee of Xiangya Hospital (2018091077), with waiver of informed consent.

Patient Consent

Not required.

Scientific approval

The protocol of this study was approved by the THIN Scientific Review Committee (18THIN078).

Abstract

Several professional organizations have recommended tramadol as one of the first-line or second-line therapies for patients with chronic noncancer pain and its prescription has been increasing rapidly worldwide; however, the safety profile of tramadol, such as risk of fracture, remains unclear. This study aimed to examine the association of tramadol with risk of hip fracture. Among individuals age 50 years or older without a history of hip fracture, cancer, or opioid use disorder in The Health Improvement Network (THIN) database in the United Kingdom general practice (2000–2017), five sequential propensity-score matched cohort studies were assembled, i.e., participants who initiated tramadol or those who initiated one of the following medications: codeine (n=146,956) (another commonly used weak opioid), naproxen (n=115,109) or ibuprofen (n=107,438) (commonly used nonselective non-steroidal anti-inflammatory drugs [NSAIDs]), celecoxib (n=43,130) or etoricoxib (n=27,689) (cyclooxygenase-2 inhibitors). The outcome was incident hip fracture over one year. After propensity-score matching, the included participants had a mean age of 65.7 years, and 56.9% were women. During the one-year follow-up, 518 hip fracture (3.7/1000 person-years) occurred in the tramadol cohort and 401 (2.9/1000 person-years) occurred in the codeine cohort. Compared with codeine, hazard ratio (HR) of hip fracture for tramadol was 1.28 (95% confidence interval[CI]:1.13–1.46). Risk of hip fracture was also higher in the tramadol cohort than in the naproxen (2.9/1000 person-years for tramadol, 1.7/1000 person-years for naproxen; HR=1.69, 95%CI:1.41–2.03), ibuprofen (3.4/1000 person-years for tramadol, 2.0/1000 person-years for ibuprofen; HR=1.65, 95%CI:1.39–1.96), celecoxib (3.4/1000 person-years for tramadol, 1.8/1000 person-years for celecoxib; HR=1.85, 95%CI:1.40–2.44), or etoricoxib (2.9/1000 person-years for tramadol, 1.5/1000 person-years for etoricoxib; HR=1.96, 95%CI:1.34–2.87) cohort. In this population-based cohort study, the initiation of tramadol was associated with a higher risk of hip fracture than initiation of codeine and commonly used NSAIDs, suggesting a need to re-visit several guidelines on tramadol use in clinical practice.

Keywords

Tramadol; Fracture; Cohort

INTRODUCTION

In the general population aged 50 years and older, about 20% of men and 50% of women are likely to sustain at least one fracture during the remainder of their lives, which often results in increased morbidity and mortality.[1,2] The healthcare burden related to fracture is expected to double by 2025.[3–5] Polypharmacy is common among elderly patients due to multiple comorbidities, and some medications may intensify the risk of fracture, either through their effect on increasing fall risk and/or through an effect on bone metabolism.[6–9]

Tramadol, a commonly used weak opioid for the treatment of pain,[10–14] has been considered an analgesic alternative, since its perceived risk of serious cardiovascular and gastrointestinal adverse effects was lower than that of non-steroidal anti-inflammatory drugs (NSAIDs),[15,16] and its risk of addiction and respiratory depression was lower than that of traditional opioids.[17,18] As a result, tramadol use has been increasing rapidly worldwide over the past decades.[10–14] For example, data from Truven Health Analytics MarketScan in

the United States showed that prescriptions of tramadol increased by 22.8% between 2012 and 2015,[10] and tramadol dispensing rates increased in each of the provinces in Canada, with the highest in Nova Scotia increasing from 0.50/defined daily doses (DDD) in 2007 to 2.64/DDD in 2016.[11]

Nevertheless, a recently-published population-based cohort study reported a significantly higher all-cause mortality rate with tramadol use than with commonly used NSAIDs among patients with osteoarthritis;[14] however, the specific mechanisms linking tramadol use to an increased risk of mortality remains unclear. To date, several studies have reported that tramadol use might increase the risk of falls (a strong risk factor for fracture),[19–22] but only a few studies have addressed the potential relationship between tramadol use and the risk of fracture, and the results are inconclusive.[23–25] Furthermore, few, if any, studies have compared the risk of hip fracture, one that ranks among the top 10 leading causes of disability globally,[26,27] among tramadol initiators with that among initiators of other commonly used analgesics.

To fill this knowledge gap, we compared the risk of incident hip fracture among tramadol initiators with the initiators of one of the following medications: codeine (another commonly used weak opioid), naproxen or ibuprofen (commonly used nonselective NSAIDs), celecoxib or etoricoxib (cyclooxygenase-2 [COX-2] inhibitors) by conducting five propensity-score matched cohort studies.

MATERIALS AND METHODS

Data Source

This study was based on the data retrieved from The Health Improvement Network (THIN), which contains medical records of about 17 million individuals from 770 general practices in the United Kingdom (UK). In THIN, the following data was recorded for each patient: anthropometrics, socio-demographics, lifestyle habits, GP visit details, diagnoses from specialists' evaluations and hospital admissions, as well as laboratory testing results. All the diagnoses in THIN were coded by the Read classification system [28] while the medications were coded by Multilex classification system.[29] Previous studies have demonstrated that THIN data was valid for both epidemiological and clinical studies.[30]

Study Design and Cohort Definition

Included in this analysis were participants who were 50 years or older between January 2000 and December 2016 and had not been prescribed tramadol or its active comparator (i.e., codeine, naproxen, ibuprofen, celecoxib, or etoricoxib) over one year or more before entering this study. Individuals who had a history of hip fracture, cancer, or opioid use disorder prior to entry into this study cohort were excluded.

We compared the risk of incident hip fracture between participants who initiated tramadol and those who initiated one of the following pain-relief medications: codeine (another commonly used weak opioid), naproxen or ibuprofen (commonly used nonselective NSAIDs), celecoxib or etoricoxib (COX-2 inhibitors). The index date is defined as the date of initiating either tramadol or the comparator for the corresponding participants. The total

time interval from January 2000 to December 2016 was divided into 17 one-year blocks. Within each time block, we identified tramadol or the comparator initiators and calculated the propensity-score for tramadol initiation using logistic regression. Propensity score is defined as the probability of treatment assignment conditional on observed baseline characteristics,[31] which can be calculated based on the following variables: age at index date, sex, Townsend Deprivation Index[32], body mass index (BMI), alcohol drinking habits, smoking status, comorbidities and medication use before the index date, and healthcare utilization (i.e., number of hospitalization, general practice visit, and specialist referral during the past year prior to the index date (variables listed in Table 1). Within each time block tramadol initiators were matched 1:1 to the comparator initiators using the greedy-matching algorithm, i.e., for each tramadol initiator, a comparator initiator with the closest propensity score was selected[31]. Propensity score matching is used to balance many covariates in epidemiological studies and to reduce the effect of confounding by indication.[31] We adopted this method to assemble five propensity-score matched cohort studies: tramadol vs. codeine, tramadol vs. naproxen, tramadol vs. ibuprofen, tramadol vs. celecoxib, and tramadol vs. etoricoxib, respectively.

Assessment of Outcome

The incident hip fracture during a one-year follow-up period was the primary outcome of the study. Hip fracture was identified by using Read Codes as previous studies have done in THIN.[33–35]

Statistical Analysis

The baseline characteristics of the tramadol cohort were compared with that of each of the active comparison cohorts, i.e., codeine, naproxen, ibuprofen, celecoxib, or etoricoxib cohort. We adopted an “intention-to-treat” analysis method to compute the follow-up time for each participant, while person-years of follow-up for each participant were calculated as the time frame from the index date to the earliest occurrence of the following: incident hip fracture, disenrollment from a GP practice, age of ninety, death, or the end of one year follow-up. We computed the rate of incident hip fracture for each cohort and plotted cumulative incidence curves of hip fracture. We calculated the absolute rate difference (RD) in incident hip fracture between the tramadol cohort and each of the active comparison cohorts according to the following formula: RD = rate (tramadol) - rate (comparison). The hazard ratio (HR) of incident hip fracture for the tramadol initiation was obtained using cause-specific Cox proportional hazard models accounting for the competing risk of death when compared with each comparator.[36] We performed the sex-specific analyses to test whether the relation of tramadol initiation to the risk of hip fracture in men differed from that in women.

A total of seven sensitivity analyses were performed to test the robustness of findings. Firstly, we excluded the participants with a propensity-score above the 97.5th percentile of the propensity-score of the comparator cohort and below the 2.5th percentile of the propensity-score of the tramadol cohort.[37] Secondly, we restricted our analyses to the participants who were not prescribed other opioids before index date to minimize the residual confounding effect by indication. Thirdly, we performed missing data imputation

analyses and imputed five datasets in total. We calculated the effect estimates and their confidence intervals (CIs) from each imputed dataset. Then, we calculated the overall effect estimate and its confidence intervals from five imputed datasets using Rubin's rules.[38] Fourthly, we performed an "as-treated" analysis to account for non-adherence of medications under investigation throughout study period. Specifically, individuals were followed from the index date until the earliest occurrence of the following: an incident hip fracture, disenrollment from a GP practice, age of ninety, death, the end of a one-year follow-up period, drug discontinuation or change of initiated medication (e.g., swapping from tramadol to codeine or vice versa, while comparing the two). If a participant had not refilled a prescription for a period of more than 60 days,[39] the follow-up time would be censored at that time. Fifthly, we conducted quantitative sensitivity analyses to evaluate the minimum unmeasured confounding effect that would explain away an association observed in previous analyses.[40] Sixthly, we conducted a sensitivity analysis for atraumatic hip fracture. Specifically, the atraumatic hip fracture was considered as the outcome, and cause-specific Cox proportional hazard models accounting for the competing risk of death were performed when compared with each comparison cohort. Lastly, we performed a sensitivity analysis restricted to individuals aged 60 years or older.

All statistical analyses were performed on SAS V.9.4 with $P < 0.05$ as statistical significance.

RESULTS

Of 3,755,932 patients who met the inclusion criteria, 612,981 patients initiated with either tramadol (n= 337,167) or codeine (n= 275,814) treatment without prescription history of both drugs before entering this study. We excluded 102,483 patients who had a history of cancer, opioid use disorder, or hip fracture, and 138,126 patients who had missing information on BMI, smoking status, alcohol drinking, or Townsend Deprivation Index Score. Of the remaining (n=372,372), 146,956 initiators of tramadol (72.7%) were matched to the same number of initiators of codeine by propensity-score (Figure 1). The selection process for the other four propensity-score matched cohorts is illustrated in the Appendix.

The baseline characteristics of each before and after propensity-score matched cohort are presented in Table 1 and Appendix. The mean age was between 65.0 and 66.5 years in different propensity-score matched cohorts, and approximately 60% were women. Overall, the characteristics across the propensity-score matched cohorts were balanced, with all of the standardized differences < 0.1[41].

The tramadol cohort had a higher risk of incident hip fracture than did the codeine cohort (Figure 2). As shown in Table 2, a total of 518 cases of hip fracture (3.7/1000 person-years) were reported in the tramadol cohort and 401 cases (2.9/1000 person-years) were reported in the codeine cohort during the one year follow-up. The RD of incident hip fracture in the tramadol cohort vs. that in the codeine cohort was 0.8 (95% CI: 0.4 to 1.2) /1000 person-years and the corresponding HR was 1.28 (95% CI: 1.13 to 1.46) (Figure 3). Meanwhile, the tramadol cohort also exhibited a higher risk of incident hip fracture than did the codeine cohort among both the female (HR = 1.18, 95% CI: 1.02 to 1.38) and male subgroup (HR =

1.60, 95% CI: 1.24 to 2.06) (Figure 3, RDs were showed in Appendix). The results of sensitivity analyses (i.e., propensity-score trimming, restricting analyses among the participants without history of other opioids use, missing data imputation, “as-treated” approach, or restricting outcome to atraumatic hip fracture) did not change materially (Appendix). Furthermore, according to the quantitative sensitivity analyses, the observed association (i.e., HR = 1.28) might be explained by the residual confounding effect if there is an unmeasured covariate with HR≥1.88 with both tramadol use and risk of hip fracture.

The tramadol cohort also had a higher risk of incident hip fracture than did either the naproxen (Figure 4A) or the ibuprofen (Figure 4B) cohort. As shown in Table 3, a total of 313 cases of incident hip fracture (2.9/1000 person-years) were reported in the tramadol cohort and 185 (1.7/1000 person-years) cases were reported in the naproxen cohort. Relative to naproxen initiation, the HR of hip fracture for initiation of tramadol was 1.69 (95% CI: 1.41 to 2.03) (Figure 3) and the corresponding RD was 1.2 (95% CI: 0.8 to 1.6) /1000 person-years (Table 3). Similarly, the risk of incident hip fracture was also higher in the tramadol cohort (3.4/1000 person-years) than in the ibuprofen cohort (2.0/1000 person-years) (HR = 1.65, 95% CI: 1.39 to 1.96) (Table 3 and Figure 3). Results from sex subgroup analyses (Figure 3, Appendix) and several sensitivity analyses did not change materially (Appendix).

The risk of incident hip fracture was higher in the tramadol cohort than in either the celecoxib cohort (3.4/1000 person-years vs. 1.8/1000 person-years) (Figure 4C) or the etoricoxib cohort (2.9/1000 person-years vs. 1.5/1000 person-years) (Figure 4D). The RDs of incident hip fracture for the tramadol cohort were 1.6 (95% CI: 0.9 to 2.3) and 1.5 (95% CI: 0.7 to 2.3) /1000 person-years, compared with the celecoxib and the etoricoxib cohorts, respectively (Table 3). The corresponding HRs were 1.85 (95% CI: 1.40 to 2.44) and 1.96 (95% CI: 1.34 to 2.87), respectively (Figure 3). The results of sex subgroup analyses (Figure 3, Appendix) and sensitivity analyses (Appendix) remained similar.

In addition, according to the quantitative sensitivity analyses the relation (i.e., HR) of potential residual confounder(s) to both tramadol initiation and incident hip fracture need to be≥2.69 in order to completely explain away the weakest association observed in our primary analyses of comparison of tramadol initiators with NSAIDs initiators (i.e., HR = 1.65 for tramadol initiators vs. ibuprofen initiators).

DISCUSSION

This population-based cohort study, utilizing a relatively large sample, found that the initiation of tramadol involved a higher risk of incident hip fracture than did the initiation of either a commonly-used weak opioid (i.e., codeine) or commonly-used NSAIDs (i.e., naproxen, ibuprofen, celecoxib, and etoricoxib). The sensitivity analyses had similar results, indicating that the observed associations were robust and raising a concern on the potential risk of hip fracture among initiators of tramadol use.

Comparison with Previous Studies

To date, tramadol has become one of the most commonly used pain-relief medications around the world; however, to our knowledge, its safety profile, such as risk of fracture, remains unclear. Several studies have examined the association between tramadol use and the risk of fracture in various settings, but the results are conflicting.[23–25] One case-control study based on the data retrieved from the Denmark national registry reported that tramadol users had an approximately 55% higher risk of fracture at the hip, forearm, or spine than non-users; however, the corresponding association with codeine users was much weaker (odds ratio [OR] = 1.16).[23] Similarly, a study from the UK General Practice Research Database suggested that the current use of tramadol (OR = 1.25) or codeine (OR = 1.20) vs. non-use was associated with an increased risk of fracture at either hip, humerus, or wrist.[25] Unfortunately, these findings are likely to be susceptible to the potential confounding by indication because both studies used non-users as a comparison group.[23,25] In a propensity-score matched cohort study using the US Medicare database the authors claimed that the incidence of fracture at hip, pelvis, wrist, and humerus was lower in tramadol initiators (7/100 person-years) than that in codeine initiators (27/100 person-years) during the 180-day follow-up period.[24] However, the study was unable to adjust for BMI, smoking, and alcohol use due to lack of the information from the database.[24] Second, the two important demographic factors for fracture are substantially different in these two studies. In the previously published study,[24] the average age of subjects was approximately 80 years and 80% were women. In our study, the average age was 65 years and 66% were women. Furthermore, the study did not specifically evaluate the association of tramadol initiation with the risk of hip fracture, a disease that is often associated with the worse consequence, such as disability and death.[26,27] As a result, (i.e., different study population, different outcome variable), the incidence rate of fracture in their study was much higher than ours (270 per 1000 person-years vs. 2.9 per 1000 person-years in codeine cohort; 70 per 1000 person-years vs. 3.7 per 1000 person-years in tramadol cohort).[24] Our study demonstrated that the risk of hip fracture among tramadol initiators is not only higher than that among NSAIDs initiators, but also higher than that among codeine (another weak opioid) initiators. Further studies that evaluate the potential mechanisms, such as whether tramadol use increases the risk of osteoporosis or risk of fall, will help us better elaborate the association between tramadol use and the risk of hip fracture.

Possible Explanations

Previous studies have found that tramadol could activate μ opioid receptors and suppress central serotonin and norepinephrine reuptake, resulting in seizures,[18] dizziness,[42,43] and/or delirium.[44] Subsequently, such side effects may cause an increased risk of fall. In fact, several studies have reported that tramadol use was indeed associated with a higher risk of fall, which is a critical risk factors for fracture.[19–22] All these studies appear to suggest that relation of tramadol to the risk of hip fracture may be, at least partly, through its effect on fall.

Strengths and Limitations

Several characteristics of the present study deserve comment. First, using a population-based cohort study we found that the risk of incident hip fracture among tramadol initiators was not only higher than that among NSAIDs initiators, but also higher than that among codeine initiators, suggesting that the confounding by indication may not substantially account for an increased risk of hip fracture for tramadol. This was further supported by the evidence that risk factor profiles between initial prescription of tramadol and that of codeine were similar even before propensity-matching, except a few (e.g., BMI was higher among tramadol than codeine prescriptions) that may lower the risk of fracture for tramadol. Nevertheless, as in all observational studies, we can't rule out the impact of potential residual confounders when comparing the risk of hip fracture between initial prescription of tramadol and other pain-relief medications. Second, we adopted a new-user design to compare the risk of hip fracture among tramadol initiators with initiators of several commonly used pain-relief medications. This design minimizes the potential selection bias. Third, because THIN does not include bone density or any frailty measurements, these two potential confounders could not be adjusted for in our analysis. Fourth, administrative data are often lacking in information of over-the-counter medications use (e.g., NSAIDs); thus, the exposure assessment is susceptible to misclassification bias. Such bias, if occurs, would affect the observed association either towards the null (i.e., stop taking tramadol but taking the over-the-counter NSAIDs) or away the null (i.e., taking tramadol and over-the-counter NSAIDs at the same time). Since the National Health Service England provides free healthcare for most services, including medications, ordered by GPs to individuals aged 60 years or older, it is unlikely that most patients would purchase these drugs over-the-counter without a prescription. In a sensitivity analysis restricted to individuals aged 60 years or older, we found that the relation of tramadol initiation to the risk of hip fracture did not change materially when compared with other pain-relief medications (tramadol vs. codeine: HR=1.28 (95% CI: (1.12 to 1.47); tramadol vs. naproxen: HR=1.68 (95% CI: 1.39 to 2.04); tramadol vs. ibuprofen: HR=1.67 (95% CI: 1.39 to 1.99); tramadol vs. celecoxib: HR=1.75 (95% CI: 1.32 to 2.32); tramadol vs. etoricoxib: HR=1.91 (95% CI: 1.28 to 2.84)), suggesting the impact of over-the-counter NSAIDs use may not be substantial. In addition, most patients who took pain-relief medication often change their initiated treatment; thus, hip fracture could occur after subjects stopped or changed their medication. Thus, estimates would be larger from "as-treated" analysis than "intention-to-treat analysis" due to minimizing misclassification, likely to be non-differential, of exposure. Finally, the biological mechanisms accounting for the association between tramadol use and the risk of hip fracture have not been fully understood; thus, future studies are warranted to elucidate such an association.

Clinical Implications

Pain is highly prevalent among the elderly population. In parallel to the aging process of the society, both frailty and chronic diseases involving pain are likely to increase. Owing to the adverse effects of commonly used NSAIDs (i.e., their cardiovascular, gastrointestinal, or renal risks) and safety concerns of traditional opioids (i.e., dependence and increased mortality), tramadol has been considered as an alternative pain relief medication.[15–18] Several professional organizations have strongly or conditionally recommended tramadol as the first-line therapy for the treatment of osteoarthritis,[45,46] Grade A for management of

pain in patients with fibromyalgia,[47,48] or the second-line therapy for chronic low back pain patients with an inadequate response to non-pharmacologic treatments,[49] and its use has been increasing rapidly over the past decades.[12,13,50,51] Although the HR value of tramadol vs. naproxen in men (2.46) is larger than that in women (1.45), the rate difference in men (1.38/1000 person-years) is closer to that observed in women (1.05/1000 person-years). The large difference in HRs observed in men and women is likely due to relatively low risk of hip fracture in men who were initially prescribed naproxen. Considering the significant impact of hip fracture on morbidity, mortality, and healthcare cost,[52] our results point to the need to consider tramadol's associated risk of fracture in clinical practice and treatment guidelines.

CONCLUSION

In this population-based cohort study we found that the initiation of tramadol was associated with a higher risk of hip fracture than the initiation of codeine and commonly used NSAIDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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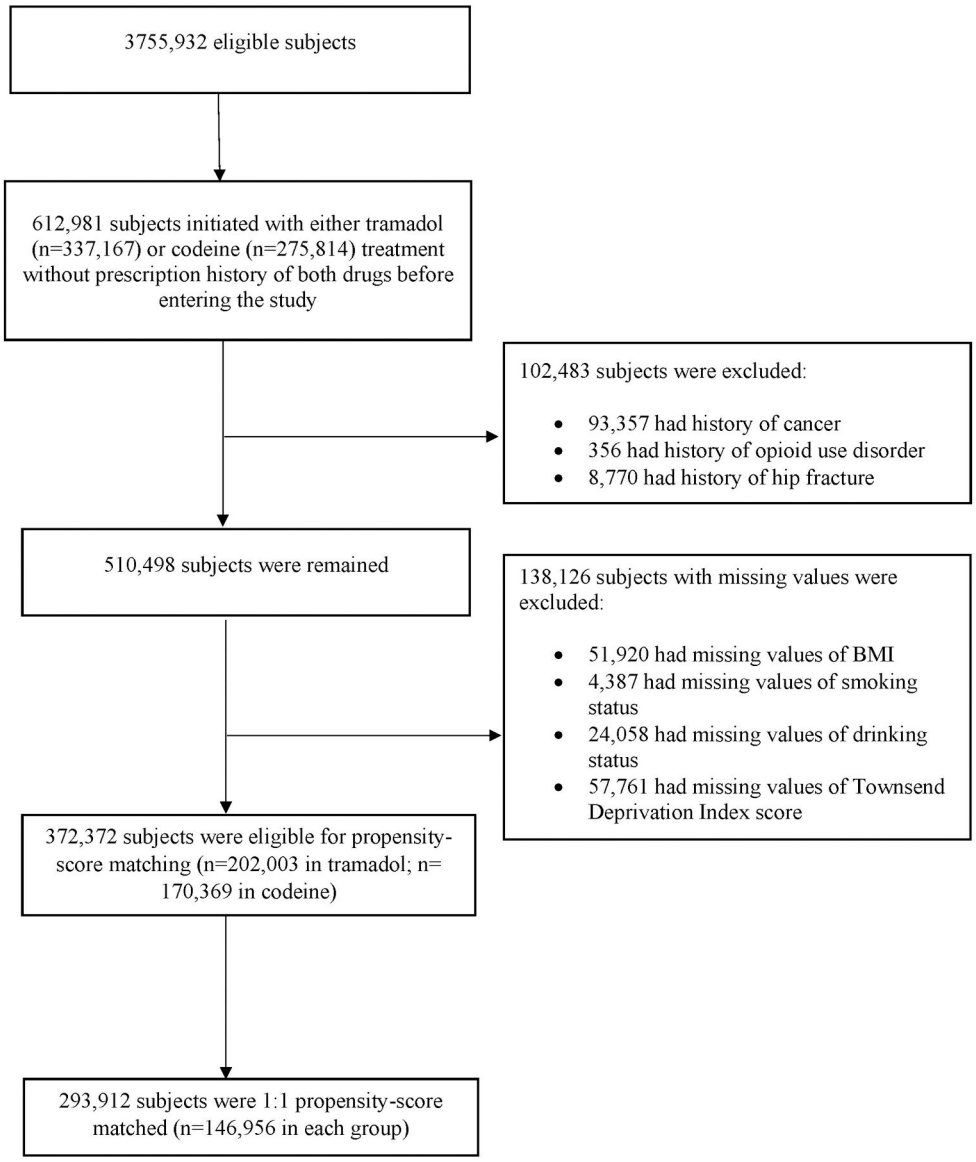


Figure 1.

Selection Process of Propensity-score Matched Cohorts of Patients with Noncancer Pain and Tramadol Initiation Comparing with Initiation of Codeine.

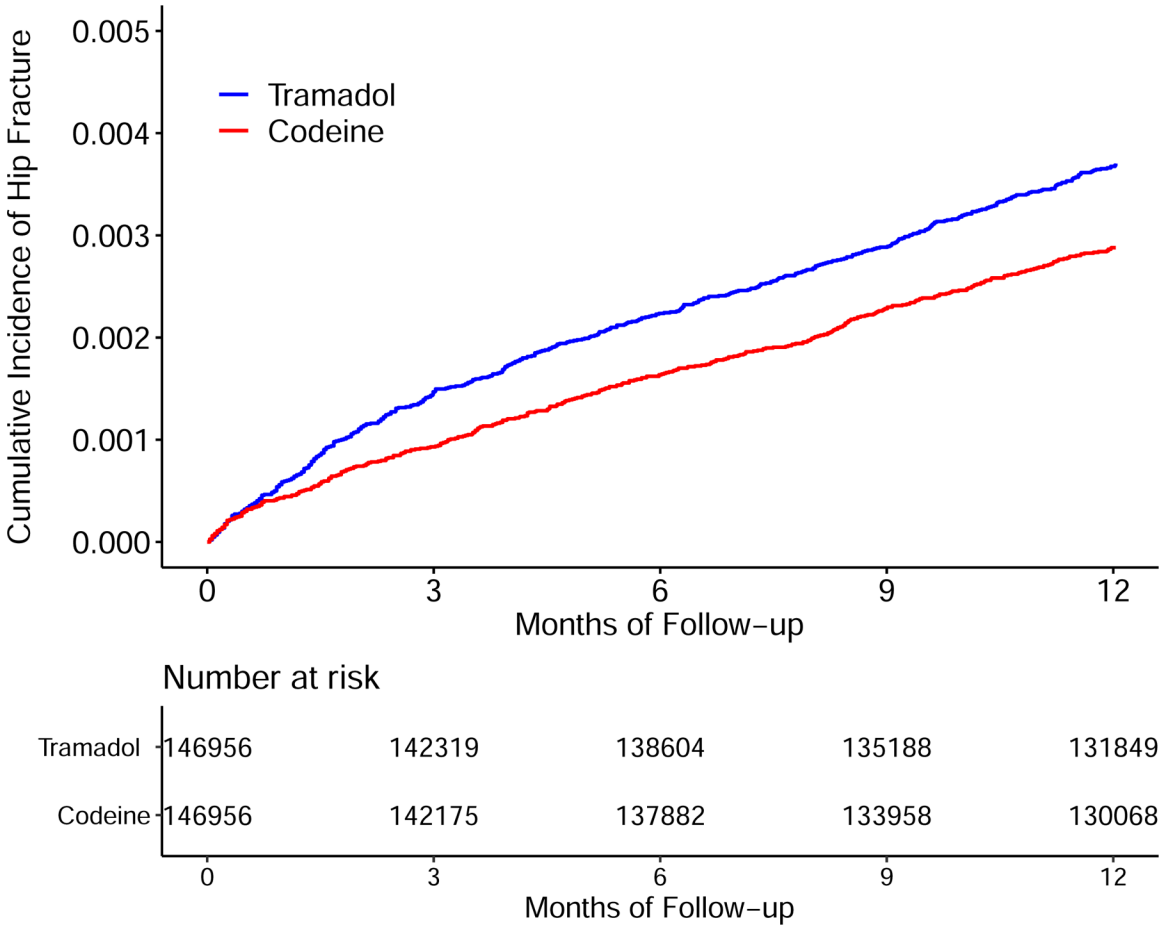


Figure 2.
Time to Incident Hip Fracture for the Propensity-score Matched Cohorts of Patients with Noncancer Pain and Tramadol Initiation Comparing with Initiation of Codeine.

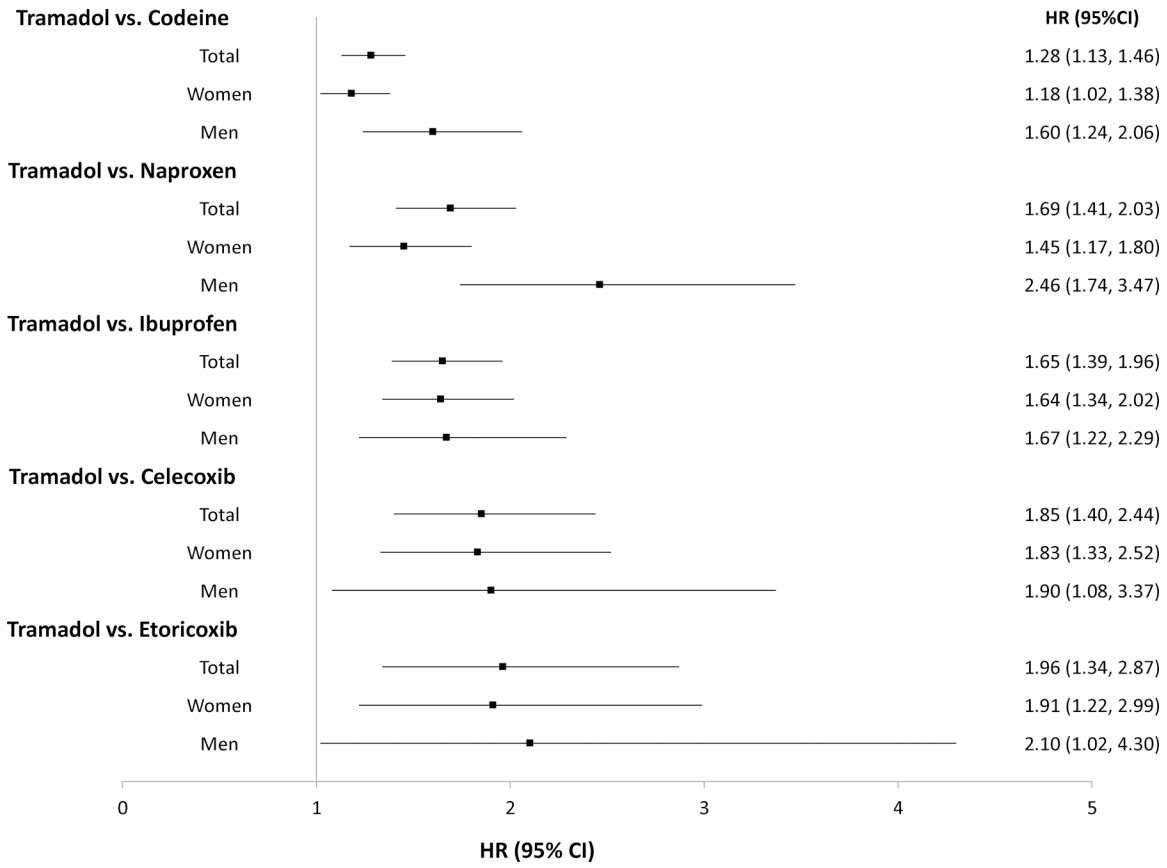
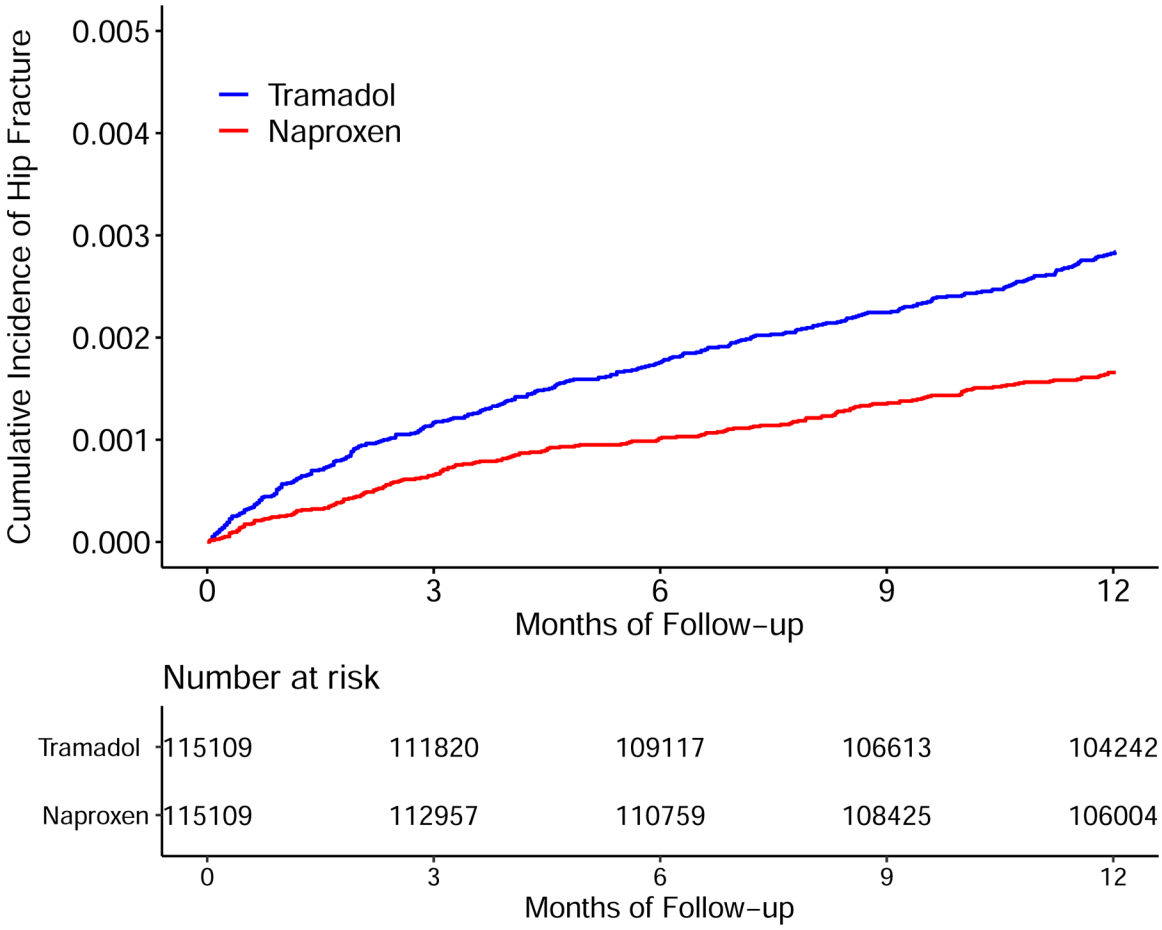
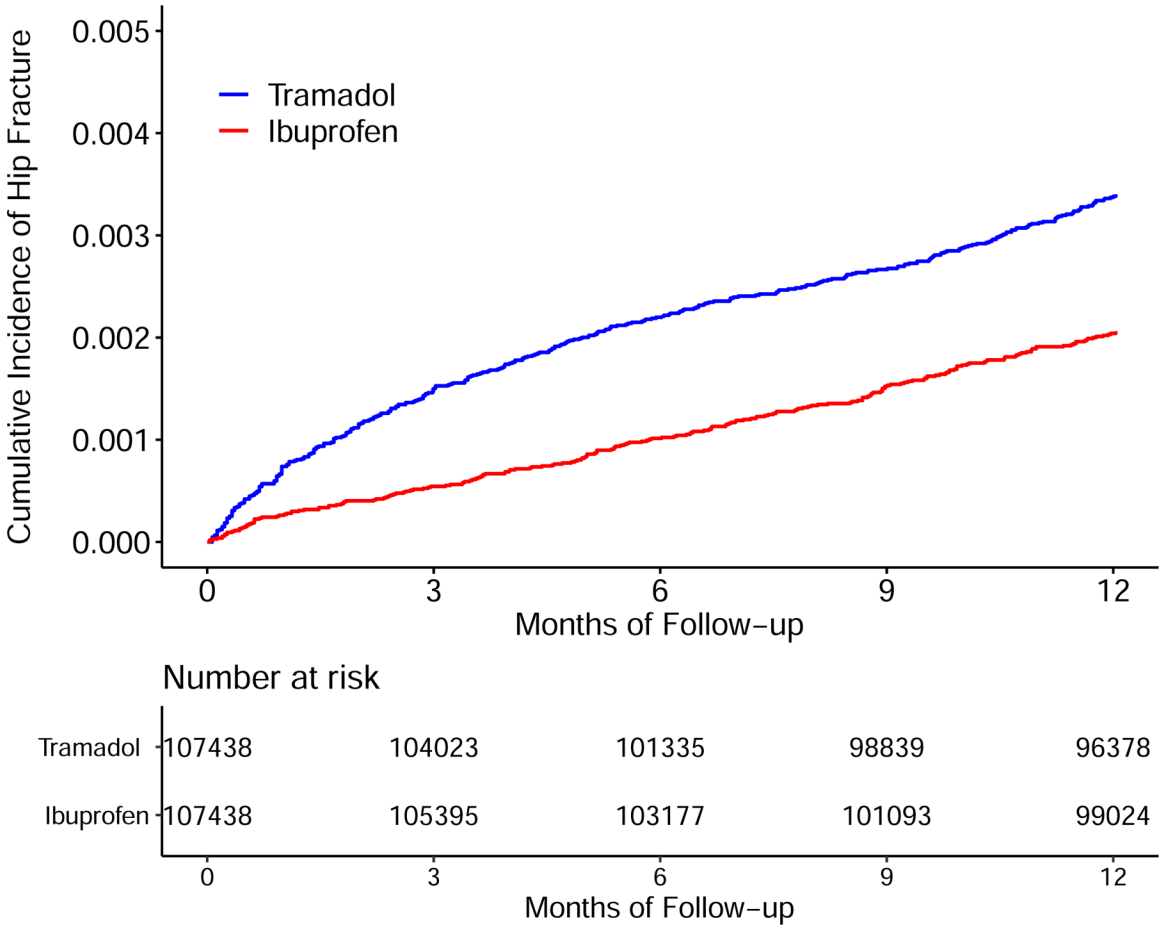
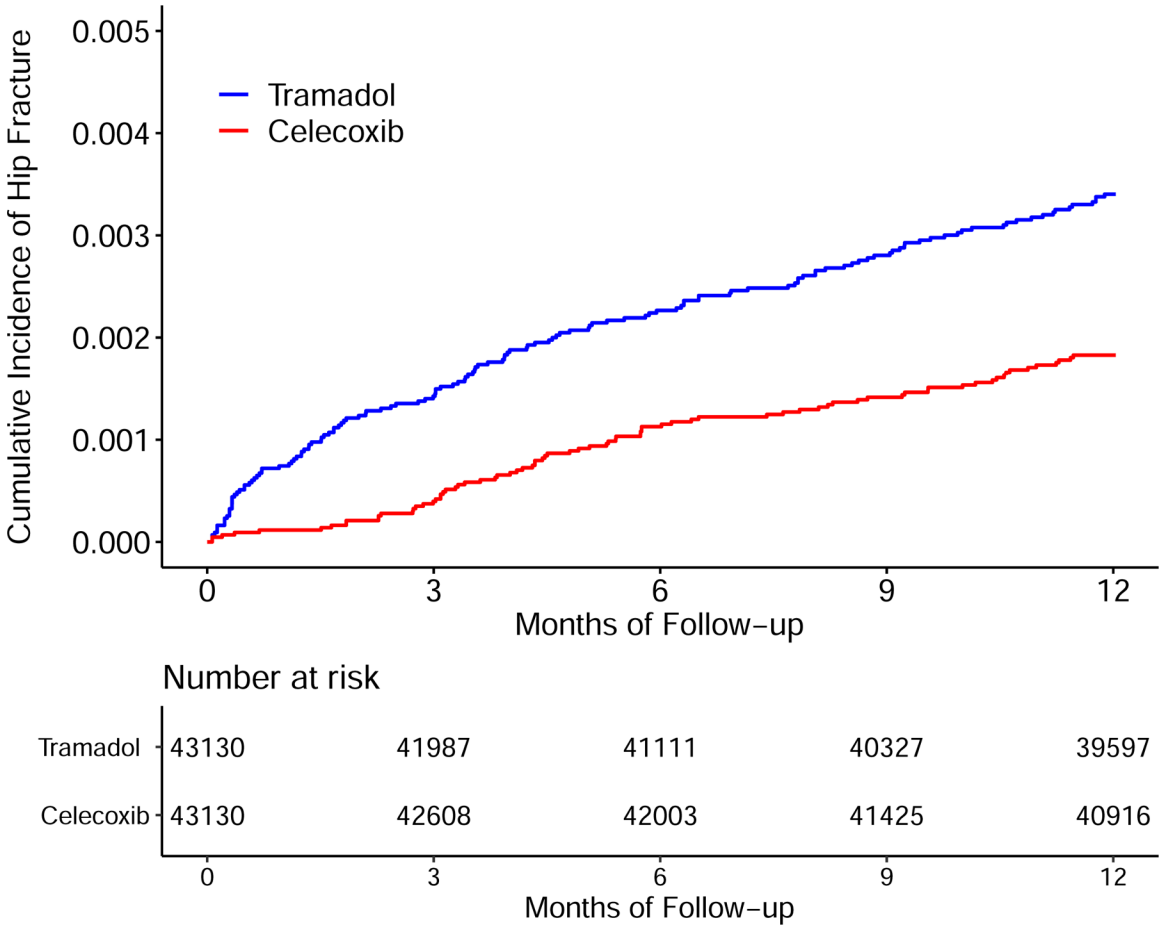


Figure 3.

Forest Plot of Hazard Ratios and Related 95% Confidence Intervals of Hip Fracture for the Propensity-score Matched Cohorts of Patients with Noncancer Pain and Tramadol Initiation Comparing with Initiation of Codeine, Naproxen, Ibuprofen, Celecoxib, or Etoricoxib.







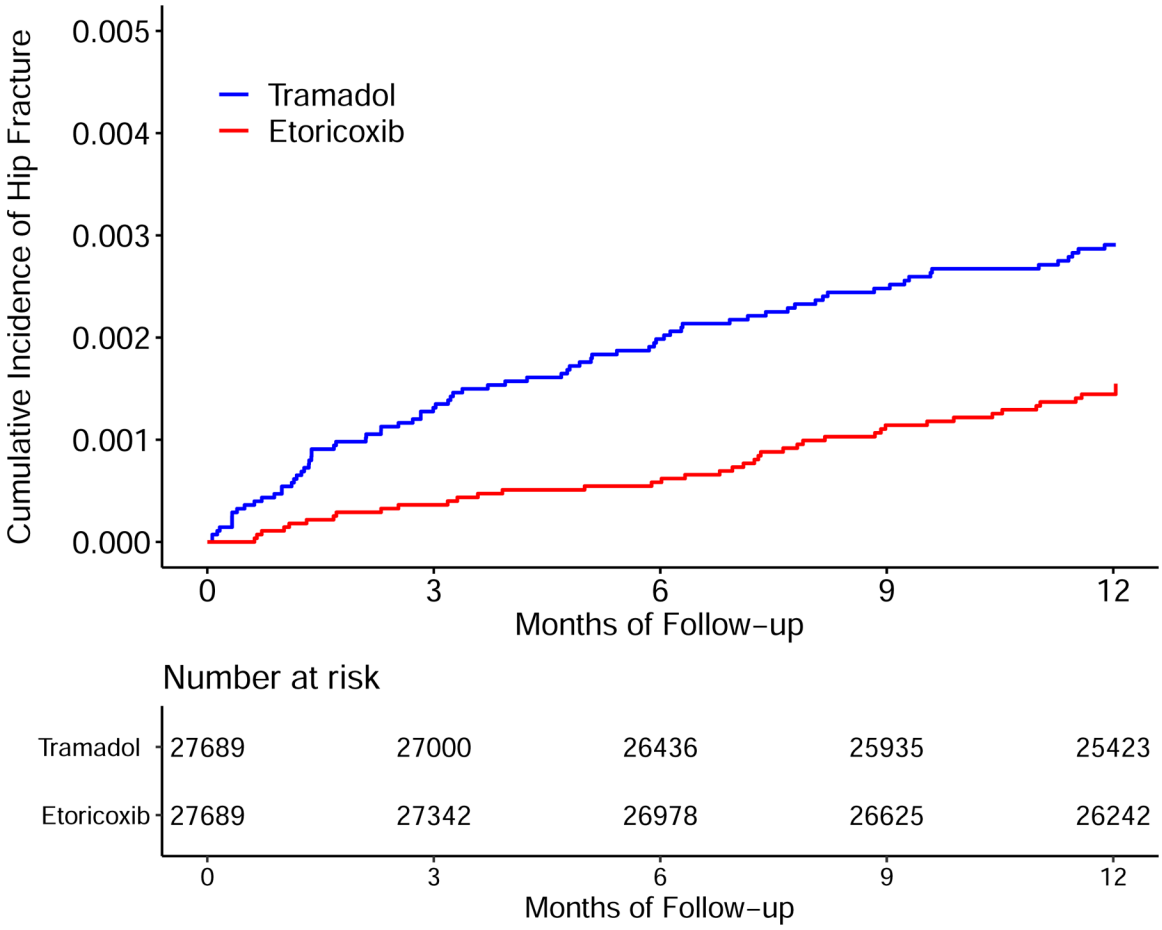


Figure 4.

Time to Incident Hip Fracture for the Propensity-score Matched Cohorts of Patients with Noncancer Pain and Tramadol Initiation Comparing with Initiation of Naproxen (A), Ibuprofen (B), Celecoxib (C), or Etoricoxib (D).

Table 1.

Basic Characteristics of Tramadol Cohort Compared with Codeine Cohort

	Before propensity-score matched			Propensity-score matched		
	Tramadol	**Codeine**	**Standard difference**	**Tramadol**	**Codeine**	**Standard difference**
Participants, n	202,003	170,369		146,956	146,956	
Demographics						
Age, mean (SD), y	65.9 (10.0)	67.1 (10.3)	0.112	66.5 (10.1)	66.5 (10.1)	0.001
Socioeconomic deprivation index, mean (SD) †	2.8 (1.4)	2.6 (1.3)	0.122	2.7 (1.3)	2.7 (1.3)	0.001
Female (%)	57.5	57.9	0.009	57.4	57.5	0.001
BMI, mean (SD), kg/m^2	28.5 (5.8)	27.8 (5.4)	0.126	28.1 (5.5)	28.1 (5.5)	0.001
Lifestyle factors						
Drinking (%)			0.030			0.002
None	21.1	19.9		20.1	20.2	
Past	3.0	2.9		2.8	2.8	
Current	75.9	77.2		77.1	77.0	
Smoking (%)			0.132			0.003
None	47.2	52.0		50.3	50.4	
Past	31.8	31.9		32.1	32.1	
Current	20.9	16.1		17.6	17.5	
Comorbidity (%)						
Other fracture#	8.3	7.7	0.022	7.9	7.8	0.001
Fall	11.2	12.6	0.044	11.9	11.8	<0.001
Osteoporosis	9.0	7.9	0.038	8.2	8.2	0.001
Seizure	0.6	0.7	0.010	0.6	0.6	0.001
Diabetes	15.2	14.9	0.009	14.8	14.8	0.001
Hypertension	45.8	46.4	0.010	46.0	46.1	0.001
Liver disease	2.5	2.5	0.001	2.5	2.5	0.001
Chronic kidney disease	8.3	9.2	0.033	8.7	8.7	0.001
Transient ischaemic attack	3.2	3.5	0.013	3.3	3.3	0.001
Ischaemic heart disease	16.6	16.0	0.018	16.1	16.0	0.002
Congestive heart failure	3.6	3.9	0.017	3.6	3.6	0.001
Myocardial infarction	6.5	6.3	0.007	6.4	6.3	0.001
Stroke	4.0	4.4	0.025	4.1	4.1	0.001
Angina	10.5	10.2	0.010	10.2	10.2	<0.001
Peripheral vascular disease	2.4	1.8	0.044	2.0	2.0	0.003
Venous thromboembolism	3.6	3.3	0.014	3.4	3.4	0.001
Pneumonia or infection	7.4	7.4	0.002	7.4	7.3	0.001
Hyperlipidaemia	15.3	14.6	0.020	14.7	14.8	0.001
Dementia	0.7	1.4	0.074	0.8	0.9	0.002
Varicose veins	10.2	10.3	0.001	10.3	10.3	0.001

	Before propensity-score matched			Propensity-score matched		
	Tramadol	Codeine	Standard difference	Tramadol	Codeine	Standard difference
Other circulatory disease	28.3	28.8	0.010	28.6	28.5	0.001
Osteoarthritis	33.9	28.5	0.116	30.4	30.5	0.001
Rheumatoid arthritis	2.8	1.9	0.057	2.2	2.1	0.004
Depression	15.1	13.0	0.062	13.5	13.5	0.001
Chronic obstructive pulmonary disease	7.2	6.0	0.046	6.4	6.3	0.003
Atrial fibrillation	5.3	6.4	0.046	5.8	5.8	<0.001
Anxiety	15.8	15.0	0.023	15.1	15.1	<0.001
Sleep disorder or sleep apnea	1.9	1.6	0.020	1.7	1.7	<0.001
Peptic ulcer	7.8	6.6	0.047	7.0	6.9	0.003
Alcohol abuse	3.6	2.6	0.058	2.8	2.8	0.002
Medication (%)						
Other opioids *	19.0	11.0	0.227	12.8	12.4	0.010
Other NSAIDs *	79.1	69.9	0.212	74.5	74.7	0.005
Aspirin	34.9	34.2	0.016	34.2	34.0	0.003
Bisphosphonates	8.1	6.7	0.052	7.1	7.0	0.004
Statin	40.6	38.2	0.050	38.8	38.8	<0.001
Glucocorticoids	23.6	21.7	0.047	22.4	22.2	0.005
Nitrates	15.4	14.4	0.028	14.6	14.5	0.003
Antihypertensive medicine	64.7	63.1	0.035	63.4	63.4	<0.001
Antidiabetic medicine	11.5	10.9	0.017	11.1	11.0	0.001
ACE inhibitors	34.3	34.8	0.010	34.5	34.5	0.001
Beta receptor inhibitors	35.2	35.3	0.001	35.1	35.1	<0.001
Calcium channel blockers	32.0	31.3	0.015	31.4	31.3	0.001
Loop diuretics	19.2	17.5	0.044	17.7	17.6	0.002
Thiazide diuretics	33.0	32.7	0.006	32.7	32.8	0.001
Potassium-sparing diuretics	8.5	7.6	0.034	7.8	7.7	0.003
Angiotensin receptor blocker	12.4	12.0	0.011	12.3	12.0	0.009
Insulin	3.4	3.0	0.019	3.1	3.1	<0.001
Anticoagulants	7.1	7.8	0.025	7.4	7.3	0.001
Benzodiazepines	41.0	32.5	0.178	35.2	35.1	0.002
SSRI	26.8	22.0	0.113	23.2	23.2	<0.001
SNRI	7.9	5.7	0.085	6.2	6.2	0.002
Antiepileptic medicine	10.7	7.5	0.112	8.3	8.2	0.004
Estrogen	19.2	18.0	0.029	18.5	18.6	0.002
PPIs	54.0	46.7	0.148	49.3	49.2	0.003
H2 blockers	24.7	21.5	0.076	22.7	22.5	0.005
Healthcare utilization, mean (SD)						
Hospitalizations ‡	0.5 (1.2)	0.4 (1.1)	0.037	0.4 (1.1)	0.4 (1.1)	0.005
General practice visits ‡	7.2 (6.6)	6.9 (6.5)	0.045	7.0 (6.6)	7.0 (6.4)	0.003

	Before propensity-score matched			Propensity-score matched		
	Tramadol	**Codeine**	**Standard difference**	**Tramadol**	**Codeine**	**Standard difference**
Specialist referrals‡	0.6 (1.1)	0.5 (1.0)	0.095	0.6 (1.0)	0.6 (1.0)	0.004

BMI, body mass index; n, number; y, years; SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin converting enzyme; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin-norepinephrine reuptake inhibitor; PPIs, proton pump inhibitor; H2 blockers, histamine-2 blockers.

†The Socio-Economic Deprivation Index (i.e., Townsend Deprivation Index) was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

#Other fracture refers to spine and wrist fracture.

*Other NSAIDs or opioids means other NSAIDs or opioids use prior to the index date.

‡Frequency during the past one year.

Table 2.

Incident Hip Fracture Within One Year Among Patients Initiating Tramadol Comparing with Initiation of another Commonly Used Weak Opioid (Codeine)

	Weak opioid	
	Tramadol vs. Codeine	
Participants (n)	146,956	146,956
Incident hip fracture (n)	518	401
Mean follow-up (years)	0.95	0.94
Rate (/1000 person-years) *	3.7	2.9
RD (/1000 person-years, 95% CI)	0.8 (0.4, 1.2)	0.0 (reference)

n, number; RD, rate difference; 95% CI, 95% confidence interval.

* Number (rate) of competing event (i.e., death) in tramadol and codeine group was 5,449 (39.2/1000 person-years) and 4,984 (36.0/1000 person-years), respectively.

Table 3.

Incident Hip Fracture Within One Year Among Patients Initiating Tramadol Comparing with Initiation of One of Two Commonly Used Nonselective NSAIDs (Naproxen, Ibuprofen) or One of Two Cyclooxygenase-2 Inhibitors (Celecoxib, Etoricoxib)

	Nonselective NSAIDs			
	Tramadol vs. Naproxen		Tramadol vs. Ibuprofen	
Participants (n)	115,109	115,109	107,438	107,438
Incident hip fracture (n)	313	185	349	212
Mean follow-up (years)	0.95	0.96	0.95	0.96
Rate (/1000 person-years) *	2.9	1.7	3.4	2.0
RD (/1000 person-years, 95% CI)	1.2 (0.8, 1.6)	0.0 (reference)	1.4 (0.9, 1.8)	0.0 (reference)
	Cyclooxygenase-2 Inhibitors			
	Tramadol vs. Celecoxib		**Tramadol vs. Etoricoxib**	
Participants (n)	43,130	43,130	27,689	27,689
Incident hip fracture (n)	142	77	78	40
Mean follow-up (years)	0.96	0.98	0.96	0.98
Rate (/1000 person-years)	3.4	1.8	2.9	1.5
RD (/1000 person-years, 95% CI)	1.6 (0.9, 2.3)	0.0 (reference)	1.5 (0.7, 2.3)	0.0 (reference)

NSAIDs, non-steroidal anti-inflammatory drugs; n, number; RD, rate difference; 95% CI, 95% confidence interval.

* Number (rate) of competing event (i.e., death) in comparison of tramadol and naproxen group was 3,418 (31.2/1000 person-years) and 1,431 (12.9/1000 person-years), in comparison of tramadol and ibuprofen group was 3,958 (38.9/1000 person-years) and 1,977 (19.1/1000 person-years), in comparison of tramadol and celecoxib group was 1,776 (43.3/1000 person-years) and 751 (17.8/1000 person-years), in comparison of tramadol and etoricoxib group was 877 (33.1/1000 person-years) and 366 (13.5/1000 person-years), respectively.