

Tramadol versus Codeine and the Short-term Risk of Cardiovascular Events in Patients with Non-Cancer Pain: A Population-Based Cohort Study

Short Title: Tramadol and Cardiovascular Events

Linda B. Ou, PharmD, MSc^{1,2}, Laurent Azoulay PhD^{2,3,4}, Pauline Reynier MSc², Robert W. Platt PhD^{2,3,5}, Sarah Yoon MSc², Roland Grad MD MSc⁶, Kristian B. Filion PhD^{2,3,7}

¹Department of Pharmacy, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

²Centre of Clinical Epidemiology, Lady Davis Institute,
Jewish General Hospital, McGill University, Montreal, QC, Canada

³Department of Epidemiology, Biostatistics, and Occupational Health,
McGill University, Montreal, QC, Canada

⁴Gerald Bronfman Department of Oncology, McGill University, Montreal, QC, Canada

⁵Department of Pediatrics, McGill University, Montreal, QC, Canada

⁶Department of Family Medicine, McGill University, Montreal, QC, Canada

⁷Department of Medicine, McGill University, Montreal, QC, Canada

Abstract word count: 249

Manuscript word count: 3774; Tables: 3, Figures: 1

Keywords: Tramadol, Codeine, Opioids, Cardiovascular Safety, Myocardial Infarction, Mortality

Address for Correspondence:

Kristian B. Filion, PhD, FAHA
Associate Professor and William Dawson Scholar
Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health
McGill University
3755 Cote Ste-Catherine Road, Suite H410.1
Montreal, Quebec, Canada
Telephone: (514) 340-8222 Ext. 28394
Fax: (514) 340-7564
Email: kristian.filion@mcgill.ca

LBO and SY were Master of Science students at McGill University, Montreal, Canada at the time of this study. LBO is currently a clinical pharmacist at Sunnybrook Health Sciences Centre. SY is currently employed at IQVIA (Ottawa, Canada).

What is already known about this subject?

- Tramadol use has increased during the opioid crisis because of its perceived safety and lower risk of abuse relative to other opioids.
- Given its multimodal mechanism of action, there is a biological rationale that tramadol could increase the risk of adverse cardiovascular events.
- Little is known about tramadol's cardiovascular safety.

What this study adds?

- Tramadol was not associated with short-term increased risk of myocardial infarction, unstable angina, ischemic stroke, coronary revascularization, cardiovascular deaths, and all-cause mortality, when compared with codeine.
- This population-based cohort study provides important reassurance of the short-term cardiovascular safety of tramadol as an alternative to codeine for pain control.

ABSTRACT

Aim: The effect of tramadol on the cardiovascular system is largely unknown. There is concern that, with its multimodal mechanism of action to increase serotonin and norepinephrine levels in the body, it could increase the risk of arterial ischemia and cardiovascular events. We aimed to compare the short-term risk of cardiovascular events with the use of tramadol to that of codeine among patients with non-cancer pain.

Methods: We conducted a retrospective population-based cohort study using data from the Clinical Practice Research Datalink (CPRD) with new users of tramadol or codeine from April 1998 to March 2017. Exposure was defined using an approach analogous to an intention-to-treat, with a maximum follow-up of 30 days. The primary endpoint was myocardial infarction, and secondary endpoints were unstable angina, ischemic stroke, coronary revascularization, cardiovascular death, and all-cause mortality. Hazard ratios (HRs) were estimated using Cox proportional hazards models, adjusted for high-dimensional propensity score.

Results: The final cohort included 123,394 tramadol users and 914,333 codeine users. When tramadol was compared to codeine, the adjusted hazard ratio (HR) of myocardial infarction was 1.00 (95% CI 0.81-1.24). There was also no evidence of elevated risks of unstable angina (0.92; 95% CI 0.67-1.27), ischemic stroke (0.98; 95% CI 0.82-1.17), coronary revascularization (0.97; 95% CI 0.69-1.38), cardiovascular death (1.07; 95% CI 0.93-1.23), or all-cause mortality (1.03; 95% CI 0.94-1.14) when tramadol was compared to codeine.

Conclusions: Short-term use of tramadol, compared with codeine, was not associated with an increased risk of cardiac events among patients with non-cancer pain.

INTRODUCTION

[Tramadol](#) is a synthetic weak opioid[1] used for the treatment of moderate to moderately severe pain.[2] Its place in therapy for pain management is similar to [codeine](#). [3] Marketed as a drug with a lower risk of abuse and misuse than other opioid medications, tramadol has been preferentially prescribed over codeine in the last decade.[4] Prescriptions for tramadol increased by 65% in United States from 2007 to 2011, ranking third among all opioids prescribed.[5] In addition, it has been shown to be prescribed more often by family practice and internal medicine physicians compared to other opioids.[6] Similarly, tramadol prescriptions increased by 7-fold between 2006 and 2017 in the United Kingdom.[7] The increased rate of tramadol use may also be explained by its exclusion from the controlled and narcotic drug schedule in many countries prior to 2014.[8, 9]

Although tramadol and codeine are both weak opioids, their pharmacologic profiles differ substantially. In addition to being a [μ-opioid receptor](#) agonist, tramadol also inhibits the reuptake of [serotonin](#) and [norepinephrine](#). [10] This dual mechanism contributes to its analgesic effects, but it may also result in a different adverse effect profile than the classic opioids. Increased serotonin levels can result in autonomic hyperactivity, which can lead to numerous cardiac adverse events, such as tachycardia, hypertension, and cardiac arrhythmia.[11] High serotonin levels are associated with an increased risk of coronary artery disease.[12] In addition to the vasoconstrictive effects demonstrated by norepinephrine, both norepinephrine and serotonin can activate platelet aggregation and increase platelet production.[13-15] Furthermore, tramadol has been shown to increase blood pressure in both human and animal models, occurring minutes after administration.[10, 16] In patients who were given preoperative tramadol, postoperative troponin I level was shown to be the highest at 8 hours post-surgery.[17] Thus, the biochemical changes

from the rise of serotonin and norepinephrine are likely to occur quickly after tramadol administration. Given the potential clinical and population health consequences of these physiologic effects and the increasing use of tramadol in pain management, there is a need to evaluate the acute cardiovascular safety of tramadol. To our knowledge, there has been four observational studies that previously investigated the cardiovascular safety of tramadol in a real-world setting.[18-21] However, these studies had important methodological limitations, including the use of composite endpoints[18], voluntary reporting bias[19], confounding by indication[19-21], potential outcome misclassification[21], and conducted in highly-selected patient population that may not be reflective of routine practice [18-21]. Therefore, the objective of our population-based cohort study was to compare the short-term cardiovascular safety of tramadol to that of codeine in patients with non-cancer pain.

METHODS

Data source

We conducted a retrospective, population-based cohort study with data from the Clinical Practice Research Datalink (CPRD). The CPRD is a computerized healthcare database in the United Kingdom of general practitioner records from 700 practices and over 79 million person-years of follow-up starting in 1987. The CPRD contains detailed clinical records that include demographic data, diagnoses (based on the Read coding system), prescriptions written by the general practitioner (coded using the British National Formulary), laboratory test data, and clinical (e.g., blood pressure) and lifestyle information (e.g., smoking). CPRD data have been validated extensively and shown to be of high quality.[22, 23] We linked CPRD data to hospitalization data through Hospital Episode Statistics (HES) and vital statistics data from the Office for National Statistics (ONS).[24] HES contains information on admissions to English hospitals, with diagnoses recorded as primary or secondary diagnoses using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes and medical procedures recorded using OPCS Classification of Interventions and Procedures (OPCS-4) codes.[25] ONS includes official cause of death data (recorded using ICD-9 and ICD-10 codes) for deaths that occurred both in the community and hospital with details taken from the death certificate.[24]

The research protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC 17_212AMnA) and by the Research Ethics Board of Jewish General Hospital, Montreal, Canada.

Study population

We identified all patients aged 18 years or older who had a new prescription for tramadol or codeine between April 1st, 1998 and March 31st, 2017. New use was defined as no prescriptions for tramadol or codeine in the year before cohort entry; we restricted inclusion to new users to avoid any bias associated with the study of prevalent users.[26] Cohort entry was defined by the date of the new prescription of either tramadol or codeine. We excluded all patients with less than one year of medical history in the CPRD and those who were prescribed more than one type of opioid on the cohort entry date. We also excluded all patients with diagnosis or treatment for cancer as defined by Read codes in the CPRD (except for non-melanoma skin cancer) prior to cohort entry as certain chemotherapies and radiotherapy are known to cause cardiac-related adverse effects and distinction is often made in cancer-related pain management in research and clinical guidelines.[27] Patients were followed until an event (described below) or censoring due to death, end of registration with CPRD, diagnosis of cancer, end of study period (March 31st, 2017), or a maximum follow-up of 30 days.

Exposure assessment

Exposure was defined using an approach analogous to an intention-to-treat in which patients were classified according to their cohort entry defining opioid prescription (tramadol or codeine) and considered exposed to the opioid throughout follow-up. An intention-to-treat approach was used as these drugs are often used on an ‘as needed’ basis and prescription duration data are often missing in the CPRD. Follow-up was restricted to 30 days as we expect little changes to occur to the initial prescription during this period. We also anticipate patients would be the most

susceptible to the outcomes of interest during this initial administration period as the body adapts to the physiological changes associated with the use of these drugs.

Outcomes

The primary outcome was hospitalization or death due to myocardial infarction (ICD-10 codes: I21.x, I22.x, I23.x; ICD-9 code: 410.x) in the primary or secondary position of diagnosis. The secondary outcomes were unstable angina (ICD-10: I20.0; ICD-9: 411.1), ischemic stroke (ICD-10: I63.x, I64.x, I67.81, I67.82, I67.89, I67.9, G45.0, G45.1, G45.2, G45.3, G45.8, G45.9, G46.x; ICD-9: 433.x, 434.x, 437.1, 437.8, 437.9, 435.x), coronary revascularization, cardiovascular death, and all-cause mortality. Unstable angina and ischemic stroke were defined using hospitalization and vital statistics data.[28] Coronary revascularization was defined by OPCS-4 codes in the primary or secondary position in the hospitalization data. Deaths were defined as cardiovascular if the primary underlying cause of death was related to diseases of the cardiovascular system (ICD-10: I00 – I82.x; ICD-9: 391.x – 453.x). Finally, all-cause mortality was defined as any death that occurred during the study period irrespective of the underlying cause. The event date was defined as the date of admission for hospitalized events or the date of death for fatal events.

Potential confounders

Potential confounders included demographic and lifestyle information, blood pressure level, comorbidities, medication use, opioid indication, and measures of overall health. Demographic and lifestyle characteristics were assessed at baseline and included age, sex, body mass index [BMI] (<18.5, 18.5-24.9, 25.0-29.9, ≥ 30.0 kg/m²), and smoking (ever, never), with BMI and smoking

assessed in the 5 years before cohort entry. Systolic and diastolic blood pressure were determined using the most recent measure in the year before cohort entry. Comorbidities, measured any time prior to cohort entry, were alcohol-related disorders, anxiety, arrhythmia, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, depression, diabetes mellitus, dyslipidemia, heart failure, hypertension, liver cirrhosis, peripheral vascular disease, rheumatoid arthritis, sleep apnea, venous thromboembolism, previous myocardial infarction, and previous coronary revascularization.[29-35] Medications, prescribed in the year before cohort entry, were aspirin (also known as acetylsalicylic acid or ASA), other anti-platelet agents, anticoagulants, angiotensin-converting enzyme inhibitor, angiotensin-II receptor blockers, calcium channel blockers, beta-blockers, statins, non-ASA nonsteroidal anti-inflammatory drugs (NSAIDs), serotonin-norepinephrine reuptake inhibitors, selective-serotonin reuptake inhibitors, tricyclic antidepressant, monoamine oxidase inhibitors, loop diuretics, thiazide diuretics, potassium-sparing diuretics, strong and moderate cytochrome P450 2D6 inhibitors/inducers (**Supplementary Table 1**), and opioids other than tramadol or codeine. Indications for opioid therapy such as injury, dental, surgery, and pain related syndromes were captured in the 90 days prior to cohort entry. Comorbidities and indications for opioid therapy were defined by Read codes in the CPRD. Finally, we assessed other proxies for overall health status including number of drug classes prescribed, number of hospitalizations, and number of general practitioner visits within the year prior to cohort entry.

Statistical analyses

Descriptive statistics were used to describe baseline patient characteristics at cohort entry. Distributions of baseline characteristics of tramadol and codeine users were compared using

standardized differences, with standardized differences of 0.1 or more considered important.[36] To minimize potential confounding, we estimated high-dimensional propensity scores (HDPS) using a logistic regression model that included pre-specified covariates and up to 500 empirically-identified variables.[37] Initiation year (cohort entry year) of tramadol or codeine were also included as covariates in the HDPS model. Areas of non-overlap of the HDPS distributions were trimmed. In our primary analysis, we used a Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (CI) for myocardial infarction for tramadol versus codeine, with the outcome model including the exposure variable, indicator variables for HDPS decile, and interaction terms between HDPS decile and HDPS in its continuous form. In secondary analyses, we repeated our primary analysis for each of our secondary endpoints. Subgroup analysis was conducted in patients with or without previous history of cardiovascular disease to assess potential effect modification.

Sensitivity analyses

We performed ten sensitivity analyses to assess the robustness of our results. First, we repeated our primary analysis but matching on the logit of the HDPS (1:1 ratio using nearest neighbour matching with no caliper) to assess potential residual confounding. Second, we repeated our primary analysis with HDPS modeled using a restricted cubic spline to allow for non-linear effects. Third, we restricted follow-up duration to 14 days to identify potential misclassification from shorter or ‘as needed’ usage of tramadol or codeine for acute pain. Fourth, we used a maximum follow-up of 60 days to examine the impact of the maximum follow-up duration on our results. Fifth, as codeine and tramadol are available in many combination forms with acetaminophen, aspirin, and/or caffeine, analyses were repeated restricting exposure to

formulations containing tramadol or codeine alone. Sixth, the outcome of hospitalization for myocardial infarction was restricted to those with diagnostic code in the primary position to examine potential outcome misclassification. Seventh, we also restricted to deaths from myocardial infarction as one of the underlying causes of death in addition to hospitalization diagnostic code in the primary position. Eighth, the study period was restricted to before June 10th, 2014 as this represents the date in which tramadol was rescheduled as a controlled drug in the UK to ensure that changes to the drug scheduling did not influence prescriber's choice of therapy. Ninth, despite our relatively short duration of follow-up, death from non-cardiovascular causes represents a potential competing risk that could result in informative censoring. Thus, we repeated our analysis using inverse probability of censoring weighting to account for potential informative censoring due to non-cardiovascular death. Finally, the use of an indicator variable for missing data could lead to bias if the variable with missing data is an important confounder.[38] Therefore, we used multiple imputation using the fully conditional specification approach to impute missing data for BMI, smoking, and blood pressure for the primary endpoint of myocardial infarction. All of the potential confounders described above were included in the imputation model. We imputed 5 datasets, and results were combined using Rubin's rules.

RESULTS

Patient characteristics

We initially identified 1,286,816 patients aged 18+ years who received at least one prescription for tramadol or codeine during the study period (**Figure 1**). After the application of our inclusion criteria, 1,037,727 new users of tramadol or codeine were included in our final study cohort. The cohort included 123,394 patients who were prescribed tramadol and 914,333 patients who were prescribed codeine.

The mean age at cohort entry was 54.4 years (standard deviation: 17.7) for the tramadol group and 52.4 years (standard deviation: 19.0) for the codeine group (**Table 1**). Most baseline characteristics were similar between both groups. However, important differences were present in proxies for overall health; tramadol users appeared to visit their general practitioner more often, take more medications, and were hospitalized more frequently in the previous year. In addition, tramadol users were more likely to be prescribed non-ASA NSAIDs, other opioids, and tricyclic antidepressant medications.

Primary and secondary analyses

Table 2 describes the results of our primary and secondary analyses. Overall, there were 752 myocardial infarctions in 84,595 person-years (PYs) of follow-up during the 30-day follow-up (incidence rate per 1000 PYs [IR]: 8.9; 95% CI, 8.3-9.4). The incidence rates for the secondary endpoints ranged from 3.3 per 1000 PYs (95% CI, 2.8-3.7) for coronary revascularization to 41.1 per 1000 PYs (95% CI, 39.8-42.5) for all-cause mortality. Stratified by exposure, there were 106 myocardial infarctions in 10,051 PYs of follow-up in the tramadol group and 646 myocardial infarctions in 74,544 PYs of follow-up in the codeine group. After adjusting for HDPS, tramadol

was not associated with an increased rate of myocardial infarction compared with codeine (adjusted HR, 1.00; 95% CI, 0.81-1.24). Similarly, compared with codeine, tramadol was not associated with higher rates of unstable angina (adjusted HR, 0.92; 95% CI, 0.67-1.27), ischemic stroke (adjusted HR, 0.98; 95% CI, 0.82-1.17), coronary revascularization (adjusted HR, 0.97; 95% CI, 0.69-1.38), cardiovascular death (adjusted HR, 1.07; 95% CI, 0.93-1.23), or all-cause mortality (adjusted HR, 1.03; 95% CI, 0.94-1.14). In our subgroup analysis (**Table 3**), there was also no difference in the rate of myocardial infarction in patients with or without previous history of cardiovascular disease.

Sensitivity analyses

The sensitivity analysis that used inverse probability of censoring weighting to account for potential informative censoring due to non-cardiovascular death produced an adjusted HR of 1.22 (95% CI, 0.992-1.49). The results of the other sensitivity analysis were consistent with those of our primary analysis (**Supplementary Table 2**).

DISCUSSION

Our study was designed to examine the short-term cardiovascular safety of tramadol in patients treated for non-cancer pain. There was no evidence of an increased risk of short-term cardiovascular events with tramadol versus codeine in our population-based cohort study. Consistent results were observed for our primary and secondary endpoints and across several sensitivity analyses.

Two recent studies[39, 40] have shown that tramadol is associated with an increased risk of mortality in the adult population compared to NSAIDs or non-use. However, both study results were limited by confounding by indication as patients with multiple comorbidities such as cardiovascular, renal, or bleeding disorders, who were at higher risk of mortality, may have been prescribed tramadol due to potential contraindication to NSAIDs. When compared to codeine, tramadol was not associated with increased mortality, which is consistent with our results.[39] To our knowledge, the association between tramadol and cardiovascular events has been examined in four previous observational studies.[18-21] Soloman and colleagues[18] conducted a retrospective cohort study that compared tramadol to hydrocodone, finding no association with a composite cardiovascular outcome of myocardial infarction, stroke, heart failure, revascularization, and out-of-hospital cardiac death at 30 days (incidence rate ratio, 0.99; 95% CI, 0.71-1.39). However, the use of a composite endpoint represents an important limitation as important associations with individual endpoints may be masked or diluted by the inclusion of other components for which no association exists.[41] Our study included larger number of tramadol users, which allowed for the investigation of each outcome individually. A second study[19] relying on pharmacovigilance data showed tramadol had only 6 reported cardiac adverse drug reactions (reporting odds ratio [OR], 0.43; 95% CI, 0.18-1.11) and 16 reported vascular adverse drug reactions (reporting OR, 0.24;

95% CI, 0.14-0.42), with dextropropoxyphene as the reference group. This study was limited by the underreporting of adverse drug reactions[42] and absence of adjustment for differences in patient characteristics or cardiovascular risk factors. Such pharmacovigilance studies are also prone to reporting biases and a lack of denominator, and they should thus be considered hypothesis generating. In the third study[20], a nested case-control study (11,693 cases and 44,897 controls) found that the risk of myocardial infarction associated with current use of opioid compared to no current use was increased (OR, 1.29; 95% CI, 1.19-1.37). Specifically, tramadol use (195 cases, 593 controls) showed a trend towards an increased odds of myocardial infarction compared to non-use (OR, 1.19; 95% CI, 1.00-1.42). However, some misclassification of exposure is possible as use was defined as a single prescription in the last 2 years, which may have included a large period of non-use. In addition, non-use is not a relevant reference group clinically and can lead to confounding by indication.[43] Finally, a population based cohort study[21] found an increased risk of incident myocardial infarction among new users of tramadol compared to naproxen among patients with history of osteoarthritis (HR, 1.68; 95% CI, 1.16-2.41), but no difference compared to diclofenac or codeine. However, this study had several potential limitations. These limitations include confounding by indication, patients at higher risk of myocardial infarction may have been preferentially prescribed tramadol due to the known cardiovascular risks of NSAIDs. Outcome misclassification is also possible as events were identified using Read codes entered by general practitioners in the community as opposed to ICD codes in hospitalization data. In addition, this study was limited by small sample size with a low event rate due to restriction of the study population to people with a history of osteoarthritis, and more than half of eligible patients were excluded due to missing values and propensity score matching.

Despite plausible biological rationale for an increased risk of ischemia with the use of tramadol due to its effects on the serotonin and norepinephrine receptors, there remains no evidence that these physiologic changes result in short-term cardiovascular events. It is possible that the associated adverse effect does not occur at the doses typically used for pain management. Nevertheless, short-term tramadol use appears to be safe with respect to cardiovascular events relative to codeine for the treatment of non-cancer pain.

This study had several strengths. With a large sample size, few exclusion criteria, and the use of population-based, real-world data, the results are applicable to many individuals. Its large size also resulted in precise treatment effects. Our use of an active comparator, new-user design avoided the depletion of susceptibles that can occur when studying prevalent users. Furthermore, with our use of an active comparator (codeine) used for the same indication, we reduced potential confounding. In addition, both tramadol and codeine are metabolized by CYP2D6 to an active metabolite; they would therefore be similarly affected due to pharmacogenetic variations in the population. Finally, our study performed rigorous statistical adjustment and explored various short-term cardiovascular risks in our secondary outcomes not present in previous studies. A number of sensitivity analyses were also conducted to ensure the robustness of our results, and their results were consistent with those of our primary analysis.

Our study also had several potential limitations. First, opioids are often prescribed on an ‘as needed’ basis for pain management. Consequently, it is unclear how much of the medication the patient used. Furthermore, the CPRD records prescriptions issued by the general practitioner and not dispensing records by the pharmacy, further increasing potential exposure misclassification. This misclassification is likely non-differential and bias the effect estimates towards the null, which may partly explain the observed null results in our study. Second, we did not adjust for time-

varying confounding. However, with follow-up restricted to a maximum of 30 days, we expect changes in covariate values to be minimal. Third, with most opioids prescribed ‘as needed’ and most prescriptions missing duration values, we used an intention-to-treat approach with our follow-up period restricted to 30 days. It is possible that this period was too short or too long to observe events that occurred due to exposure to codeine or tramadol. For this reason, we conducted two separate sensitivity analyses with follow-up of 14 days and 60 days, which produced results that were consistent with those of our primary analysis. Fourth, a sensitivity analysis of our primary outcome was conducted using multiple imputation for the missing data, and our results were consistent. Nevertheless, our sensitivity analyses suggest that our analyses may be affected by informative censoring due to non-cardiovascular death; accounting for this potential limitation resulted in an adjusted HR of 1.22 (95% CI, 0.992-1.49). Finally, we were unable to account for potential confounders such as diet, substance abuse, and socioeconomic class as they were unavailable in our data. Due to the observational nature of our study, residual confounding remains possible.

CONCLUSIONS

In patients treated for acute or chronic non-cancer pain, tramadol was not associated with short-term increased risk of adverse cardiovascular events, including myocardial infarction, unstable angina, ischemic stroke, coronary revascularization, cardiovascular deaths, and all-cause mortality, compared with codeine. These results provide reassurance with respect to the short-term cardiovascular safety of tramadol compared to codeine and should be considered when assessing benefits and risks of different treatment options for non-cancer pain.

Funding

This research is funded by the Canadian Institutes of Health Research (CIHR) operating grant (Grant number PJT-152912).

Ethical Approval

The research protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC 17_212AMnA) and by the Research Ethics Board of Jewish General Hospital, Montreal, Canada.

Conflict of Interest Disclosures

Dr. Azoulay served as a consultant for Janssen and Pfizer for work unrelated to this study. Ms. Yoon was a Master of Science student at McGill University, Montreal, Canada at the time of this study. She is currently a data analyst at IQVIA (Ottawa, Canada). The work on this study was conducted prior to her employment at IQVIA.

Data Availability

The data are available in the article and in its online supplementary material. No additional data is available.

Author Contributions

LBO drafted the manuscript. KBF developed the study protocol and all authors contributed to the study design, interpretation of study results, and critically reviewed the manuscript. PR performed data management and statistical analysis. All authors approved the final versions of the manuscript. KBF is the guarantor.

Acknowledgments

Ms. Yoon was supported by a Frederick Banting and Charles Best Canada Graduate Scholarship program award from the CIHR. Drs. Filion and Azoulay are supported by salary

support awards from the *Fonds de recherche du Québec – Santé* (FRQS; Quebec Foundation for Health Research) and William Dawson Scholar awards from McGill University. Dr. Platt holds the Albert Boehringer I chair in pharmacoepidemiology at McGill University.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019 a,b).[44, 45]

REFERENCES

1. Lewis KS, Han NH. Tramadol: a new centrally acting analgesic. *Am J Health Syst Pharm* 1997; 54: 643-52.
2. McCarberg B. Tramadol extended-release in the management of chronic pain. *Therapeutics and clinical risk management* 2007; 3: 401-10.
3. World Health Organization. WHO's Cancer Pain Ladder for Adults. In.
4. Canadian Institute for Health Information. Pan-Canadian Trends in the Prescribing of Opioids, 2012-2016. In, Ottawa, ON: CIHI, 2017.
5. Manchikanti L, Helm S, 2nd, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV. Opioid epidemic in the United States. *Pain Physician* 2012; 15: Es9-38.
6. Bigal LM, Bibeau K, Dunbar S. Tramadol Prescription over a 4-Year Period in the USA. *Curr Pain Headache Rep* 2019; 23: 76.
7. Jani M, Birlie Yimer B, Sheppard T, Lunt M, Dixon WG. Time trends and prescribing patterns of opioid drugs in UK primary care patients with non-cancer pain: A retrospective cohort study. *PLOS Medicine* 2020; 17: e1003270.
8. Drug Enforcement Administration. Tramadol. In, 2014.
9. Misuse of Drugs Act 1971 (Ketamine etc.) (Amendment) Order 2014. In, 2014.
10. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004; 43: 879-923.
11. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. *Ochsner J* 2013; 13: 533-40.
12. Vikenes K, Farstad M, Nordrehaug JE. Serotonin is associated with coronary artery disease and cardiac events. *Circulation* 1999; 100: 483-9.

13. Frishman WH, Okin S, Huberfeld S. Serotonin antagonism in the treatment of systemic hypertension: the role of ketanserin. *Med Clin North Am* 1988; 72: 501-22.
14. Larsson PT, Wallen NH, Hjemdahl P. Norepinephrine-induced human platelet activation in vivo is only partly counteracted by aspirin. *Circulation* 1994; 89: 1951-7.
15. Sloan JA, Hooper M, Izzo JL, Jr. Effects of circulating norepinephrine on platelet, leukocyte and red blood cell counts by alpha 1-adrenergic stimulation. *Am J Cardiol* 1989; 63: 1140-2.
16. Itami T, Tamaru N, Kawase K, Ishizuka T, Tamura J, Miyoshi K, Umar MA, Inoue H, Yamashita K. Cardiovascular effects of tramadol in dogs anesthetized with sevoflurane. *J Vet Med Sci* 2011; 73: 1603-9.
17. Wagner R, Piler P, Bedanova H, Adamek P, Grodecka L, Freiburger T. Myocardial injury is decreased by late remote ischaemic preconditioning and aggravated by tramadol in patients undergoing cardiac surgery: a randomised controlled trial. *Interact Cardiovasc Thorac Surg* 2010; 11: 758-62.
18. Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J, Schneeweiss S. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med* 2010; 170: 1979-86.
19. Tavassoli N, Lapeyre-Mestre M, Sommet A, Montastruc JL. Reporting rate of adverse drug reactions to the French pharmacovigilance system with three step 2 analgesic drugs: dextropropoxyphene, tramadol and codeine (in combination with paracetamol). *Br J Clin Pharmacol* 2009; 68: 422-6.
20. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *J Intern Med* 2013; 273: 511-26.

21. Wei J, Wood MJ, Dubreuil M, Tomasson G, LaRoche MR, Zeng C, Lu N, Lin J, Choi HK, Lei G, Zhang Y. Association of tramadol with risk of myocardial infarction among patients with osteoarthritis. *Osteoarthritis Cartilage* 2020; 28: 137-45.
22. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010; 69: 4-14.
23. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010; 60: e128-36.
24. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International Journal of Epidemiology* 2015; 44: 827-36.
25. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *International Journal of Epidemiology* 2017; 46: 1093-93i.
26. Danaei G, Tavakkoli M, Hernán MA. Bias in Observational Studies of Prevalent Users: Lessons for Comparative Effectiveness Research From a Meta-Analysis of Statins. *American Journal of Epidemiology* 2012; 175: 250-62.
27. Bovelli D, Plataniotis G, Roila F, On behalf of the EGWG. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. *Annals of Oncology* 2010; 21: v277-v82.
28. Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. *Neurol Clin* 2008; 26: 871-95, vii.

29. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364: 937-52.
30. Rockhill B. Traditional risk factors for coronary heart disease. *JAMA* 2004; 291: 299-99.
31. Allen CL, Bayraktutan U. Risk factors for ischaemic stroke. *Int J Stroke* 2008; 3: 105-16.
32. Zegkos T, Kitas G, Dimitroulas T. Cardiovascular risk in rheumatoid arthritis: assessment, management and next steps. *Therapeutic advances in musculoskeletal disease* 2016; 8: 86-101.
33. Meisinger C, Doring A, Lowel H. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. *Eur Heart J* 2006; 27: 1245-50.
34. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091-7.
35. Sacco RL. Risk factors and outcomes for ischemic stroke. *Neurology* 1995; 45: S10-4.
36. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001; 54: 387-98.
37. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009; 20: 512-22.
38. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 1995; 142: 1255-64.

39. Zeng C, Dubreuil M, LaRoche MR, Lu N, Wei J, Choi HK, Lei G, Zhang Y. Association of Tramadol With All-Cause Mortality Among Patients With Osteoarthritis. *Jama* 2019; 321: 969-82.
40. Jeong S, Tchoe HJ, Li J, Shin JY. All-Cause Mortality Associated with Tramadol Use: A Case-Crossover Study. *Drug Saf* 2019; 42: 785-96.
41. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, Alonso-Coello P, Alonso J, Worster A, Upadhye S, Jaeschke R, Schunemann HJ, Permyer-Miralda G, Pacheco-Huergo V, Domingo-Salvany A, Wu P, Mills EJ, Guyatt GH. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *Bmj* 2007; 334: 786.
42. Begaud B, Martin K, Haramburu F, Moore N. Rates of spontaneous reporting of adverse drug reactions in France. *Jama* 2002; 288: 1588.
43. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Current epidemiology reports* 2015; 2: 221-28.
44. Alexander SP, Christopoulos A, Davenport AP, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD, Pawson AJ, Southan C, Davies JA, Abbracchio MP, Alexander W, Al-Hosaini K, Bäck M, Barnes NM, Bathgate R, Beaulieu JM, Bernstein KE, Bettler B, Birdsall NJM, Blaho V, Boulay F, Bousquet C, Bräuner-Osborne H, Burnstock G, Caló G, Castaño JP, Catt KJ, Ceruti S, Chazot P, Chiang N, Chini B, Chun J, Cianciulli A, Civelli O, Clapp LH, Couture R, Csaba Z, Dahlgren C, Dent G, Singh KD, Douglas SD, Dournaud P, Eguchi S, Escher E, Filardo EJ, Fong T, Fumagalli M, Gainetdinov RR, Gasparo M, Gerard C, Gershengorn M, Gobeil F, Goodfriend TL, Goudet C, Gregory KJ, Gundlach AL,

Hamann J, Hanson J, Hauger RL, Hay DL, Heinemann A, Hollenberg MD, Holliday ND, Horiuchi M, Hoyer D, Hunyady L, Husain A, AP IJ, Inagami T, Jacobson KA, Jensen RT, Jockers R, Jonnalagadda D, Karnik S, Kaupmann K, Kemp J, Kennedy C, Kihara Y, Kitazawa T, Koziellewicz P, Kreienkamp HJ, Kukkonen JP, Langenhan T, Leach K, Lecca D, Lee JD, Leeman SE, Leprince J, Li XX, Williams TL, Lolait SJ, Lupp A, Macrae R, Maguire J, Mazella J, McArdle CA, Melmed S, Michel MC, Miller LJ, Mitolo V, Mouillac B, Müller CE, Murphy P, Nahon JL, Ngo T, Norel X, Nyimanu D, O'Carroll AM, Offermanns S, Panaro MA, Parmentier M, Pertwee RG, Pin JP, Prossnitz ER, Quinn M, Ramachandran R, Ray M, Reinscheid RK, Rondard P, Rovati GE, Ruzza C, Sanger GJ, Schöneberg T, Schulte G, Schulz S, Segaloff DL, Serhan CN, Stoddart LA, Sugimoto Y, Summers R, Tan VP, Thal D, Thomas WW, Timmermans P, Tirupula K, Tulipano G, Unal H, Unger T, Valant C, Vanderheyden P, Vaudry D, Vaudry H, Vilardaga JP, Walker CS, Wang JM, Ward DT, Wester HJ, Willars GB, Woodruff TM, Yao C, Ye RD. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: G protein-coupled receptors. *Br J Pharmacol* 2021; 178 Suppl 1: S27-s156.

45. Alexander SP, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD, Pawson AJ, Southan C, Davies JA, Amarosi L, Anderson CMH, Beart PM, Broer S, Dawson PA, Hagenbuch B, Hammond JR, Inui KI, Kanai Y, Kemp S, Stewart G, Thwaites DT, Verri T. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Transporters. *Br J Pharmacol* 2021; 178 Suppl 1: S412-s513.

TABLE LEGEND

- Table 1.** Baseline Characteristics of Patients using Tramadol and Codeine
- Table 2.** Association Between Tramadol vs. Codeine and the Risk of Adverse Cardiovascular Events
- Table 3.** Subgroup Analysis for Myocardial Infarction in Patients with or without Previous History of Cardiovascular Disease

Table 1. Baseline Characteristics of Patients using Tramadol and Codeine

Characteristics^a	Tramadol (n=123,394)	Codeine (n=914,333)	Standardized Difference
Age, mean (SD), y	54.4 ± 17.7	52.4 ± 19.0	0.011
Male sex (%)	53,679 (43.5)	386,232 (42.2)	0.025
Cohort entry year			
1998	1,682 (1.4)	19,588 (2.1)	0.059
1999	2,613 (2.1)	27,989 (3.1)	0.059
2000	3,469 (2.8)	32,860 (3.6)	0.044
2001	4,887 (4.0)	41,521 (4.5)	0.029
2002	6,140 (5.0)	45,356 (5.0)	0.001
2003	7,564 (6.1)	51,812 (5.7)	0.02
2004	8,653 (7.0)	55,294 (6.1)	0.039
2005	9,685 (7.9)	68,848 (7.5)	0.012
2006	9,427 (7.6)	65,578 (7.2)	0.018
2007	9,557 (7.8)	65,209 (7.1)	0.023
2008	9,164 (7.4)	64,960 (7.1)	0.012
2009	9,249 (7.5)	62,617 (6.9)	0.025
2010	8,899 (7.2)	60,244 (6.6)	0.025
2011	8,279 (6.7)	56,428 (6.2)	0.022
2012	7,966 (6.5)	54,372 (6.0)	0.021
2013	6,605 (5.4)	47,774 (5.2)	0.006
2014	4,558 (3.7)	39,585 (4.3)	0.032
2015	2,767 (2.2)	29,786 (3.3)	0.062
2016	1,853 (1.5)	20,504 (2.2)	0.055
2017	377 (0.3)	4,008 (0.4)	0.022
Comorbidities			
Alcohol related disorders	7,921 (6.4)	52,985 (5.8)	0.026
Anxiety	16,264 (13.2)	111,642 (12.2)	0.029
Arrhythmia	5,834 (4.7)	38,354 (4.2)	0.026
Cerebrovascular disease	5,697 (4.6)	37,547 (4.1)	0.025
Chronic kidney disease	5,589 (4.5)	37,783 (4.1)	0.02
Coronary artery disease	11,878 (9.6)	71,473 (7.8)	0.064
Coronary revascularization	3,297 (2.7)	16,438 (1.8)	0.059
COPD	11,061 (9.0)	71,895 (7.9)	0.04
Diabetes	16,382 (13.3)	110,832(12.1)	0.035
Depression	37,254 (30.2)	241,855(26.5)	0.083
Dyslipidemia	14,489 (11.7)	93,233 (10.2)	0.049
Heart failure	3,039 (2.5)	18,452 (2.0)	0.03
Hypertension	31,396 (25.4)	212,309 (23.2)	0.05
Peripheral vascular disease	3,007 (2.4)	15,607 (1.7)	0.05
Liver cirrhosis	183 (0.2)	821 (0.1)	0.017
Sleep apnea	995 (0.8)	5,348 (0.6)	0.027
Rheumatoid arthritis	2,879 (2.3)	11,105 (1.2)	0.085

Previous myocardial infarction	4,281(3.5)	26,110 (2.9)	0.035
Previous venous thromboembolism	6,545 (5.3)	36,972 (4.0)	0.06
BMI			
<18.5 kg/m ²	1,579 (1.3)	13,533 (1.5)	0.017
18.5 – 24.9 kg/m ²	25,423 (20.6)	205,124(22.4)	0.045
25.0 – 29.9 kg/m ²	28,598 (23.2)	213,074(23.3)	0.003
≥30.0 kg/m ²	27,511 (22.3)	180,530(19.7)	0.063
Missing	40,283 (32.6)	302,072 (33.0)	0.008
Health visits in the year prior to cohort entry			
Number of general practitioner visits	3.4 ± 5.4	2.6 ± 4.6	0.158
Number of hospitalizations			
0	93,218 (75.6)	783,295 (85.7)	0.258
1	21,154 (17.1)	98,051 (10.7)	0.186
>1	9,022 (7.3)	32,987 (3.6)	0.164
Smoking			
Ever smoked	64,971 (52.6)	463,128 (50.6)	0.040
Never smoked	37,336 (30.3)	291,545 (31.9)	0.035
Missing	21,087 (17.1)	159,660 (17.5)	0.010
Blood pressure			
Systolic, mmHg	133.6 ± 18.5	132.6 ± 25.3	0.046
Diastolic, mmHg	78.6 ± 10.4	78.0 ± 10.5	0.049
Missing	50,014 (40.5)	375,883 (41.1)	0.012
Indication			
Injury	5,187 (4.2)	43,266 (4.7)	0.026
Musculoskeletal pain	16 (0.01)	101 (0.01)	0.018
Abdominal pain	10,448 (8.5)	59,831 (6.5)	0.073
Dental	838 (0.7)	6,760 (0.7)	0.072
Surgery	14,774 (12.0)	53,613 (5.9)	0.216
Headache	130 (0.1)	1,153 (0.1)	0.061
Neuralgia	106 (0.09)	336 (0.04)	0.02
Other pain	10,834 (8.8)	64,161 (7.0)	0.065
Medications			
Number of drug classes ^b	8.0 (5.7)	6.6 (4.8)	0.277
Aspirin	17,506 (14.2)	111,639 (12.2)	0.058
Other anti-platelets	3,044 (2.5)	16,571 (1.8)	0.045
Anticoagulants	4,197 (3.4)	24,005 (2.6)	0.045
ACE inhibitors	16,978 (13.8)	109,882 (12.0)	0.052
ARBs	6,675 (5.4)	39,435 (4.3)	0.051
Calcium channel blockers	14,992 (12.2)	96,591 (10.6)	0.05
Beta-blockers	15,383 (12.5)	103,615 (11.3)	0.035
Loop diuretics	9,988 (8.1)	52,718 (5.8)	0.092
Potassium-sparing diuretics	3,696 (3.0)	18,692 (2.0)	0.061
Thiazide diuretics	13,320 (10.8)	90,015 (9.8)	0.031

Statins	21,682 (17.6)	136,810 (15.0)	0.071
SNRIs	2,108 (1.7)	10,740 (1.2)	0.045
SSRIs	15,124 (12.3)	97,220 (10.6)	0.051
TCAs	15,254 (12.4)	64,690 (7.1)	0.179
MOAIs	46 (0.04)	290 (0.03)	0.003
Non-ASA NSAIDs	57,269 (46.4)	347,832 (38.0)	0.17
Opioids [other than tramadol or codeine]	34,620 (28.1)	96,401 (10.5)	0.455
CYP2D6 inducers	145 (0.1)	632 (0.1)	0.016
CYP2D6 inhibitors	10,224 (8.3)	64,993 (7.1)	0.044

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disorder; MOAI: monoamine oxidase inhibitor; NSAID: non-steroidal anti-inflammatory drugs; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

^aData are presented as n (%) or mean $\pm$ standard deviation.

^bNumber of BNF drug classes prescribed in the year prior to cohort entry

Table 2. Association Between Tramadol vs. Codeine and the Risk of Adverse Cardiovascular Events.

	No. of Events	No. of Patients ^a	No. of Person-Years	Incidence Rate (95% CI) ^b	Adjusted HR (95% CI) ^c
Myocardial infarction					
Overall	752	1,037,356	84,595	8.9 (8.3-9.5)	
Codeine	646	913,966	74,544	8.7 (8.0-9.4)	1.00 (Ref)
Tramadol	106	123,390	10,051	10.5 (8.7-12.8)	1.00 (0.81-1.24)
Unstable Angina					
Overall	307	1,037,414	84,609	3.6 (3.2-4.1)	
Codeine	259	914,025	74,557	3.5 (3.1-3.9)	1.00 (Ref)
Tramadol	48	123,389	10,052	4.8 (3.6-6.3)	0.92 (0.67-1.27)
Ischemic Stroke					
Overall	1149	1,037,509	84,593	13.6 (12.8-14.4)	
Codeine	997	914,121	74,545	13.4 (12.6-14.2)	1.00 (Ref)
Tramadol	152	123,388	10,048	15.1 (12.9-17.7)	0.98 (0.82-1.17)
Coronary Revascularization					
Overall	276	1,037,632	84,629	3.3 (2.9-3.7)	
Codeine	236	914,242	74,577	3.2 (2.8-3.6)	1.00 (Ref)
Tramadol	40	123,390	10,052	4.0 (2.9-5.4)	0.97 (0.69-1.38)
Cardiovascular Death					
Overall	1,687	1,037,415	84,622	19.9 (19.0-20.9)	
Codeine	1,439	914,025	74,569	19.3 (18.3-20.3)	1.00 (Ref)
Tramadol	248	123,390	10,054	24.7 (21.8-27.9)	1.07 (0.93-1.23)
All-cause Mortality					
Overall	3481	1,037,566	84,635	41.1 (39.8-42.5)	
Codeine	2,985	914,178	74,581	40.0 (38.6-41.5)	1.00 (Ref)
Tramadol	496	123,388	10,053	49.3 (45.2-53.9)	1.03 (0.94-1.14)

Abbreviations: CI: confidence interval; HR: hazard ratio

^a Slight variations were present in the patients included for each outcome due to HDPS trimming,^b Incidence rate are expressed as events per 1000 person-years.^c Adjusted for indicator variables for HDPS decile (measured at cohort entry), and interaction terms between HDPS decile and HDPS in its continuous form.

Table 3. Subgroup Analysis for Myocardial Infarction in Patients with or without Previous History of Cardiovascular Disease

	No. of Events	No. of Patients ^a	No. of Person-Years	Incidence Rate (95% CI) ^b	Adjusted HR (95% CI) ^c
History of Cardiovascular Disease					
Overall	423	131,418	10,651	39.7 (36.1-43.7)	
Codeine	359	113,069	9,164	39.2 (35.3-43.4)	1.00 (Ref)
Tramadol	64	18,349	1,487	43.0 (33.7-55.0)	1.06 (0.80-1.40)
No History of Cardiovascular Disease					
Overall	329	905,941	73,944	4.4 (4.0-5.0)	
Codeine	287	800,907	65,381	4.4 (3.9-4.9)	1.00 (Ref)
Tramadol	42	105,034	8,563	4.9 (3.6-6.6)	0.94 (0.67-1.32)

Abbreviations: CI: confidence interval; HR: hazard ratio

^a Slight variation were present in the patients included for each outcome due to HDPS trimming

^b Incidence rate are expressed as events per 1000 person-years.

^c Adjusted for indicator variables for HDPS decile (measured at cohort entry), and interaction terms between HDPS decile and HDPS in its continuous form.

FIGURE LEGEND

Figure 1. Flow Chart Describing Cohort Construction. Abbreviations: CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics.