Tramadol and the Risk of Adverse Cardiovascular Events for Patients with Non-Cancer Pain

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Submitted April 2019

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

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ABSTRACT

Tramadol and codeine are both weak opioids indicated for the treatment of acute and chronic moderate to moderately severe pain, though their pharmacologic profiles differ substantially. Due to the perceived low risk of abuse of tramadol compared to other opioid, prescriptions for tramadol have increased by 30% in Canada and 65% in the United States over the last decade. Aside from acting on the μ-opioid receptor, tramadol also exerts its analgesic activity through inhibiting the reuptake of serotonin and norepinephrine in the central nervous system. Excess amounts of both neurotransmitters can have pro-arrhythmic effects and can stimulate the sympathetic nervous system, resulting in vasoconstriction and blood pressure elevation. It can also cause platelet aggregation and coagulation. These physiological adverse effects, which have been demonstrated in animal and human models, could potentially result in increased risks of myocardial infarction, ischemic stroke, and arrhythmia. Evidence on the effect of tramadol and cardiovascular safety is limited and requires further investigation.

In this thesis, I conducted a retrospective, population-based cohort study to examine the rates of myocardial infarction, unstable angina, coronary revascularization, ischemic stroke, cardiovascular death, and all-cause mortality with the use of tramadol compared to those with the use of codeine among patients with non-cancer pain. Using data from the United Kingdom's Clinical Practice Research Datalink (CPRD), linked to hospitalization and vital statistics data, I identified new users of tramadol or codeine who were 18 years or older with at least one year of enrolment in the CPRD database prior to cohort entry. Cohort entry was defined by the date of new prescription of either tramadol or codeine, with exposure defined using an approach analogous to an intention-to-treat. Endpoints were defined using hospitalization and vital statistics data. Patients were followed until an event occurred or censored on death, end of

registration with CPRD, diagnosis of cancer, end of study period (March 31st, 2017), or a maximum follow-up of 30 days. Hazard ratio (HR) and corresponding 95% confidence interval (CI) comparing tramadol to codeine were estimated using Cox Proportional hazards models, adjusted for high-dimensional propensity score to minimize potential confounding.

Our final cohort included 1,037,727 new users (123,394 tramadol and 914,333 codeine) from April 1st, 1998 to March 31st, 2017. Most baseline characteristics were similar between the tramadol and codeine groups (standardized differences < 0.1). The mean age at cohort entry was 54.4±17.7 years for the tramadol group and 52.4±19.0 years for the codeine group. Compared with the use of codeine, the use of tramadol was not associated with an increased risk of myocardial infarction (adjusted HR: 1.003, 95% CI: 0.81, 1.24). There was also no evidence of increased risk of the secondary outcomes of unstable angina, ischemic stroke, coronary revascularization, cardiovascular death, and all-cause mortality.

The use of tramadol was not found to increase risk of myocardial infarction and other atherosclerotic events compared with the use of codeine. Nonetheless, prescriptions for both medications should be used judiciously based on the risks and benefits of current treatment in the presence of the ongoing opioid epidemic. Future studies are required to further investigate the association of arrhythmia and sudden cardiac death due to tramadol's effect on the QT interval and its propensity for serotonin syndrome.

RESUME

Le tramadol et la codéine sont tous deux des opioïdes faibles indiqués pour le traitement de douleurs aiguës à modérément sévères, bien que leurs profils pharmacologiques diffèrent sensiblement. En raison de la perception de faible risque d'abus d'utilisation du tramadol par rapport à ses homologues, les ordonnances pour le tramadol ont augmenté de 30% au Canada et de 65% aux États-Unis au cours de la dernière décennie. En plus d'agir sur le récepteur μ-opioïde, le tramadol exerce également son activité analgésique en inhibant le recaptage de la sérotonine et de la norépinéphrine dans le système nerveux central. Les quantités excédentaires de ces deux neurotransmetteurs peuvent avoir des effets pro-arythmiques ainsi que des effets stimulants pour le système nerveux sympathique, ce qui entraîne une vasoconstriction et une élévation de la pression artérielle. Il peut également provoquer l'agrégation de plaque et la coagulation. Ces effets indésirables, démontrés chez les modèles animaux et humains, pourraient potentiellement entraîner des risques accrus d'infarctus du myocarde, d'arrêt vasculo-cérébral (AVC) ischémique et d'arythmie. Les données probantes sur la sécurité cardiovasculaire du tramadol sont limitées et nécessitent un complément d'étude.

Pour cette thèse, j'ai mené une étude de cohorte rétrospective basée sur la population, examiné les taux d'infarctus du myocarde, d'angine instable, de revascularisation coronarienne, d'AVC ischémique, de mortalité cardiovasculaire et de mortalité de toutes causes associées à l'utilisation du tramadol en comparaison à l'utilisation de la codéine chez les patients souffrant de douleurs non-cancéreuses. Utilisant des données de la Clinical Practice Research Datalink (CPRD) au Royaume-Uni. Ces données ont également été liées aux données d'hospitalisation et aux données de statistiques démographiques. J'ai identifié de nouveaux utilisateurs du tramadol ou de la codéine âgés de 18 ans ou plus et avec au moins un an d'inscription dans la base de

données CPRD précédent la date d'entrée dans la cohorte. La date d'entrée dans la cohorte a été définie par la date de la nouvelle prescription de tramadol ou de codéine, avec une exposition définie à l'aide d'une approche analogue à une analyse de l'intention de traitement. Les issues ont été définies en utilisant les données d'hospitalisation et de statistiques démographiques. Les patients ont été suivis jusqu'à ce qu'une issue survienne, la fin de l'enregistrement avec CPRD, un diagnostic de cancer, la fin de la période d'étude (31 mars 2017), la mort, ou un suivi maximum de 30 jours. Le rapport de risque instantané et l'intervalle de confiance (IC) correspondant de 95% comparant le risque associé au tramadol et à la codéine ont été évalués à l'aide des modèles de risques proportionnels de Cox et ajustés pour le score de propension de grande dimension afin de minimiser la confusion potentielle.

Notre cohorte finale comprenait 1 037 727 utilisateurs incidents (123 394 de tramadol et 914 333 de codéine) entre le 1er avril 1998 et le 31 mars 2017. La majorité des comorbidités et de l'utilisation des médicaments mesurés à la date d'entrée dans la cohorte se sont avérées semblables entre les groupes tramadol et codéine (différences normalisées < 0,1). L'âge moyen à l'entrée de cohorte pour le groupe de tramadol était 54,4±17,7 années et 52,4±19,0 années pour le groupe de codéine. Par rapport à l'utilisation de la codéine, l'utilisation du tramadol n'a pas été associée à un risque accru d'infarctus du myocarde (rapport de risque ajusté: 1,02; 95% IC: 0,82 - 1,28). De plus, il n'y a pas de preuve d'un risque accru de conséquences secondaires d'angine instable, d'accident vasculaire cérébral ischémique, de révascularisation coronarienne, de mortalité cardiovasculaire et de mortalité toutes causes confondues.

L'utilisation du tramadol ne semble pas augmenter le risque d'infarctus du myocarde ni d'autres événements athérosclérotiques par rapport à l'utilisation de la codéine. Néanmoins, les prescriptions pour les deux médicaments devraient être utilisées judicieusement en fonction des

risques et des bénéfices du traitement, surtout en présence de l'épidémie actuelle d'opioïdes. Davantage d’études sont nécessaires pour étudier l'arythmie et la mort cardiaque soudaine due à l'effet du tramadol sur le récepteur le système nerveux.

CONTRIBUTION OF AUTHORS

Linda Ou, BScPharm

I contributed to my thesis through study design, implementation, and drafting of the manuscript and thesis. I developed or updated all variable definitions used to define both covariates and outcomes for my cohort study. I drafted an amendment of the study protocol to incorporate changes in the exposure definition, outcome definition, and addition of covariates to the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink. I also conducted some of the descriptive statistics presented in my thesis.

Kristian Filion, PhD

Dr. Filion was my thesis supervisor. He conceived the thesis topic, developed the study protocol, and acquired the data for analyses, and supervised all aspects of the study. He was instrumental in providing insight with study design and methodology as well as interpretation of the data. He reviewed all drafts of the thesis and manuscript.

Pauline Reynier, MSc

Ms. Reynier was the statistical analyst for this project. She provided important insight with respect to the statistical aspects of the study design. She performed data management and complex statistical modeling. She assisted with the interpretation of data.

Laurent Azoulay, PhD

Dr. Azoulay was my thesis committee member. He assisted with the design of the study and provided insight given previous experience investigating adverse effects of tramadol.

Roland Grad, MD, MSc

Dr. Grad was my thesis committee member. He provided clinical expertise with respect to opioids and pain treatment and contributed to the development of the study protocol.

Sarah Yoon, MSc

Ms. Yoon was a graduate student in the Department of Epidemiology, Biostatistics, and Occupational Health at McGill University. We worked closely together in developing the operational variable definitions for several of the covariates.

Robert W. Platt, PhD

Dr. Platt was a collaborator for this project where he provided important insight in statistical analyses and modeling approach used.

ACKNOWLEGEMENTS

I am thankful for everyone who has helped and provided guidance for me during the course of my MSc Epidemiology degree at McGill University. I would like to acknowledge the course instructors that instilled me the foundational knowledge of epidemiology and data analyses. Most importantly, I would like to thank my thesis supervisor, Dr. Kristian Filion, who provided me continuous support and guidance for my thesis. Despite his busy schedule, he would make time for regular meetings with me to track progress and provide opportunity for questions. His mentorship helped me grow as a researcher and will have profound impact on my career.

I would also like to thank Pauline Reynier, who is a statistical analyst in the Centre for Clinical Epidemiology of Lady Davis Institute at the Jewish General Hospital as well as the Canadian Network for Observational Drug Effect Studies (CNODES). She provided statistical support and resolved problems that we encountered during analyses. She was vital in helping me complete this thesis and always available for consultations.

I would also like to thank my thesis committee members Dr. Laurent Azoulay and Dr. Roland Grad who provided expertise and guidance with conception of the thesis study design. They were always available for consultations when needed.

I would also like to thank Dr. Robert Platt and Sarah Yoon for their important contributions to my thesis. Dr. Platt provided important insight in the statistical analyses of my thesis project and it was very much appreciated. Sarah Yoon was a colleague who I worked with very closely throughout my thesis project. We exchanged many ideas on the essential elements of the study, particularly in building the variable definition database for our covariates and outcomes.

I would like to acknowledge the administration staff at the Department of Epidemiology, Biostatistics, and Occupational Health for their constant support in the completion of this thesis. As well, I would like to thank the staff at the Centre for Clinical Epidemiology of Lady Davis Institute at the Jewish General Hospital for their administrative support.

Lastly, I would like to thank my parents (Chunhua Ou and Cuirong Zhou) for their continuous support, both emotionally and financially.

Chapter 1: Background

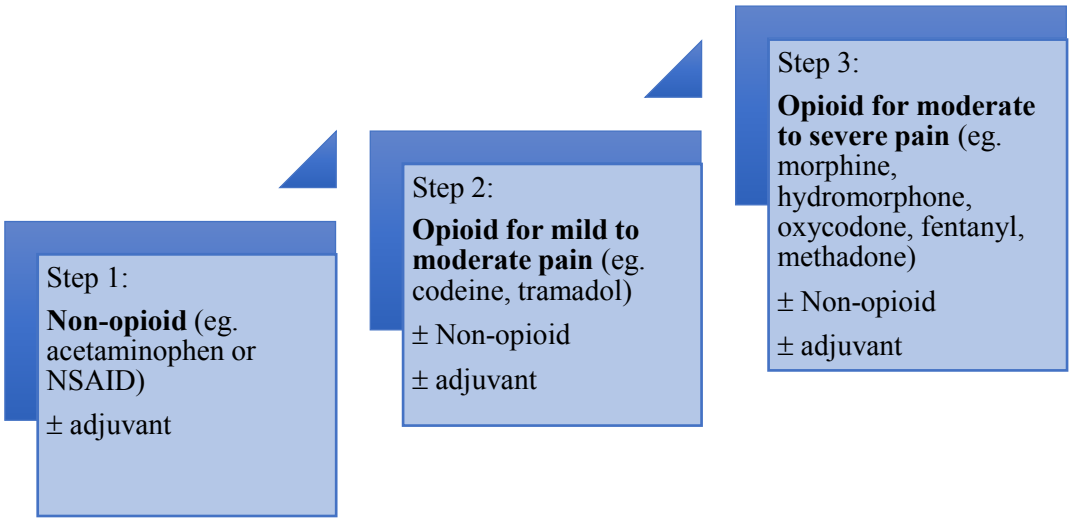
1.1 Pain Management

Pain is an unpleasant subjective sensation or experience that varies in severity, quality, and duration. It can occur through different mechanisms such as response to noxious stimulus, tissue damage, inflammation, and central or peripheral sensitization.[1] Chronic non-cancer pain is widely considered to be non-malignant pain lasting longer than three months.[2] It is a common condition affecting up to 37.3% of people in developed countries and up to 41.1% of people in developing countries, with higher prevalence in females and the elderly.[3]

Treatment algorithm

The objective of non-cancer pain management is often relief of symptomatic pain with the goal of functional improvement and increased quality of life.[4,5] It is often achieved through the use of pharmacotherapy, with the choice of medication therapy dependent upon the severity of pain and its impact on the patient. In 1986, the World Health Organization introduced a step-wise approach to cancer pain management through the application of an analgesic ladder,[6] where escalation of therapy is recommended when pain is not adequately controlled (see Figure 1.1). The initial step consists of non-opioid analgesics such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). Other medications, including anxiolytics, antidepressants, anticonvulsants, and cannabinoids, can be used adjunctively to further reduce pain or anxiety associated with pain. Subsequently, a weak opioid (codeine or tramadol) can be initiated if pain is not adequately relieved. If the desired level of pain reduction is not achieved, the weak opioid should then be switched to a strong opioid, most commonly oxycodone, morphine, or hydromorphone with fentanyl and methadone reserved as last line treatment for opioid tolerant patients.

Figure 0.1 World Health Organization Analgesic Ladder



Adapted from: *World Health Organization*

The analgesic ladder provided an important foundation for guiding the management of acute and chronic non-cancer pain, although evidence has suggested that treatment can start at any point of the ladder and move up or down with consideration of pain severity and individual patient factors.[7,8] As pain can be a chronic issue, there are no specific guidelines regarding duration of therapy. Long-term opioid therapy has not been demonstrated to be more effective compared with either non-opioid analgesic therapy or placebo due to high medication discontinuation rates, analgesic tolerance, and opioid induced hyperalgesia.[9,10] Nonetheless, opioids are often used long-term and its use have become increasingly prevalent.[11]

Opioid safety

While they are beneficial for pain management, opioids are not benign. Overdose can often occur if the opioid is not carefully given to the patient or adequately titrated from lower dose. As well, chronic administration can lead to dependence, addiction, and/or abuse due to its euphoric properties. Common adverse effects of opioids are constipation, nausea/vomiting, sedation,

dizziness, and pruritus.[12] They can also lead to severe and life threatening adverse effects such as respiratory depression, bradycardia, and hypotension, most often in overdose situations.[13] Adverse cardiovascular effects from the use of opioids have also been reported. Corrected QT (QTc) interval should be monitored with methadone treatment as it can prolong the QT interval with the potential to trigger arrhythmia or sudden cardiac death. Oxycodone has also been shown to demonstrate dose related QT interval prolongation.[14] Other opioids (morphine, hydromorphone, hydrocodone, and meperidine) can activate histamine release and lead to vasodilation, hypotension, and syncope. The use of opioid medications concomitantly with central nervous system depressants, namely benzodiazepines, can decrease stroke volume and cardiac output.[15] In addition, one study found that the risk of cardiovascular events was increased in codeine users after 180 days.[16]

Opioid epidemic

Over the last 30 years, prescription opioid use has increased drastically due to increased advocacy for treatment of pain and strategic pharmaceutical marketing of different opioid drugs and formulations.[17] Canada ranks second in the world in the prevalence of opioid use[18] and a Health Canada survey (2015) showed that at least one in eight Canadians aged 15 years and older used an opioid pain reliever in the past year.[19] In the last 10 years, the rate of hospitalizations due to opioid poisoning increased by 53%, with an average of 16 hospitalizations per day between 2016 and 2017.[20] Opioid-related deaths tripled in Ontario between 2000 and 2015, especially in teens and young adults where one in six deaths were related to opioids in Ontarians aged 25 to 34 years.[21] Belzak and colleague[22] showed that opioid crisis have affected every region in Canada, with the highest rate of hospitalizations and deaths related to opioids in western Canada (British Columbia and Alberta) and northern territories (Yukon and Northwest Territories). Similarly, in

United States, the number of opioid-related deaths increased by 345% between 2001 and 2016, from 33.3 to 130.7 deaths per million population. Among adults aged 24 to 35 years, 20.0% of deaths were due to opioids in 2016.[23] Acknowledging this alarming trend, clinicians are now opting to prescribe tramadol over codeine for moderate to moderately severe pain as tramadol was marketed as a non-narcotic medication with low rates of abuse and misuse. Tramadol prescriptions have increased by 30% in Canada from 2012 to 2016 with a corresponding decline in codeine prescriptions.[24] In the United States, prescriptions for tramadol increased by 65% from 2007 to 2011 and ranked third among all opioid prescriptions.[25] Increasing use and abuse has led to stricter prescription requirements with rescheduling of tramadol to schedule IV Controlled Drug in the United States[26] and schedule 3 Controlled Drug in the United Kingdom[27] in 2014. However, tramadol was only recently proposed to be rescheduled as a controlled and narcotic drug by Health Canada in June 2018.[28] Previously, it can be prescribed without strict requirements similar to regular prescription medications. This may have contributed to the increase in prescriptions for tramadol compared to codeine. Tramadol's adverse effect profile is believed to be safer than classic opioids, although more studies are required to further investigate its long-term adverse effects.

1.2 Overview of Tramadol

Tramadol is an opioid drug that is unique in its pharmacologic profile compared to other opioids due to its mechanism of action. In addition to acting on the μ-opioid receptor, it also exerts analgesic effects through inhibiting the reuptake of serotonin and norepinephrine.[29] Structurally, it is derived synthetically from natural opioids codeine and morphine. Both codeine and tramadol have a 3-methoxy group on the phenyl ring where O-demethylation occurs to yield active metabolites.[30]

Pharmacology

Tramadol is a weak opioid agonist that selectively binds to μ-opioid receptor. However, its affinity for this receptor is 10 times less than codeine and 6000 times less than morphine.[31] Nevertheless, tramadol is a pro-drug with an active metabolite O-desmethyltramadol (M1) that binds with 300 times higher affinity than tramadol.[32]

Racemic forms of the (+) and (-) enantiomers of tramadol act on different receptors as part of its distinct analgesic property. Affinity for the μ-opioid receptor differs for the enantiomers as the (+) enantiomer has higher affinity than tramadol and (-) enantiomer, but less than M1 and morphine. The (+) enantiomer primarily inhibits the reuptake of serotonin and the (-) enantiomer inhibits the reuptake of noradrenaline/norepinephrine.[33]

Tramadol and its (+) enantiomer also increase serotonin efflux.[34] Due to these combined analgesic properties, oral tramadol has approximately equal potency to codeine and about 20% of the potency of oral morphine.[35] Naloxone, an opioid antagonist used as a reversal agent for opioid agonists in overdose situations, can only partially reverse the effect of tramadol due to its multimodal mechanism of action.[31]

Pharmacokinetics

Bioavailability is the proportion of a medication that has been absorbed and metabolized to reach the blood stream to produce an active effect. Upon administration of the first oral dose, the bioavailability of tramadol is 68% with peak serum concentration achieved within 2 hours. Tramadol demonstrates two-compartmental elimination kinetics, where there is an initial distribution phase followed by an elimination phase.[36] Prior to achieving equilibrium in the body in order to be eliminated, there is a distribution process from the blood to peripheral tissues. This results in an accumulation of the parent compound tramadol and the M1 active metabolite after

multiple oral doses with the half-lives of tramadol being 5.1 hours and M1 metabolite being 9 hours.[30,36] After multiple oral doses, bioavailability of tramadol rises to 90 –100%, likely due to saturation of first-pass hepatic metabolism.[29] Tramadol and its metabolites are almost exclusively eliminated through the kidneys, with 30% of the dose excreted in the urine as unchanged drug and 60% as metabolites. The remaining 10% is eliminated in the feces.[37]

The mean elimination half-life is 6 hours for immediate release forms of tramadol; the recommended dosing regimen is therefore 50 – 100 mg every 4 to 6 hours as needed for acute pain, with a maximum of 400 mg per day.[38] It is also available in extended release forms for chronic pain. In these formulations, the drug is released over an extended period of time after ingestion. Once daily administration is usually sufficient with the extended release formulation, starting dose is 100 mg, of which the dose can be increased every 5 days to a maximum dose of 300 mg per day.[39]

Pharmacogenomics

Tramadol has multiple metabolites with the major active metabolite being O-desmethyltramadol (M1), which is metabolized through cytochrome P450 CYP2D6.[40] CYP2D6 is one of the phase I enzymes that is highly polymorphic, which can affect the extent of metabolism due to genetic differences. Variation in alleles produce transformations of the CYP2D6 gene, resulting in phenotypic changes in the enzyme function.[41] In approximately 10% of Caucasians, there are no active alleles present for CYP2D6, resulting in deficiency of CYP2D6 and lack of enzyme activity.[42] CYP450 polymorphism phenotypes are classified into poor metabolizers (no activity), intermediate metabolizers (diminished activity), extensive metabolizers (normal activity), and ultrarapid metabolizers (higher than normal activity).[43] Poor metabolizers of CYP2D6 are most frequently found in African American populations, whereas

ultra-rapid metabolizers are most frequently found in Middle-Eastern and Northeast African populations.[40] Pro-drugs are drugs that required to be converted or activated in the body to produce active metabolites that are pharmacologically active, as in the case of both tramadol and codeine, poor metabolizers may experience decreased efficacy and require a dose increase. Conversely, ultra-rapid metabolizers may experience increased adverse effects and toxicities. This increased susceptibility to adverse events shown in a case report of a 22-year old Caucasian female patient with the CYP2D6 ultra-rapid metabolizer phenotype who experienced repeated episodes of cardiac arrest requiring cardiopulmonary resuscitation and treatment for refractory circulatory shock in the intensive care unit after tramadol ingestion.[44] In addition, a study investigating the effect of tramadol on patients recovering from major surgery[42] demonstrated the poor metabolizer group had a higher prevalence of non-response compared to the extensive metabolizer group. Poor metabolizers also required significantly higher doses and more frequent use of rescue medications following tramadol administration. These results provide supporting evidence for the varying levels of response to tramadol based on different CYP2D6 genotype.

1.3 Safety of Tramadol

One of the most important severe adverse effects of classic opioids is respiratory depression, which can result in hypoxemia and death. Contrary to other opioids, tramadol rarely causes clinically significant respiratory depression when used alone at therapeutic doses compared to morphine, oxycodone, or pethidine/meperidine.[29,30] The most common adverse effects of tramadol, as reported in Phase IV clinical trials, are dizziness, nausea, vomiting, constipation, headache, sedation, and euphoria.[30] Other studies have shown that tramadol causes greater nausea and vomiting but less constipation than codeine. In post marketing reports, seizures have occurred in patients taking higher than recommended doses as well as in patients

with seizure risk factors or those taking agents that lower seizure threshold. The use of naloxone in tramadol overdose cases should be used with caution as it may increase the risk of seizures.[45]

Serotonin

Tramadol achieves its analgesic effects in part by increasing serotonin levels by inhibiting serotonin reuptake and increasing serotonin release. Nonetheless, excess serotonin can also result in adverse effects, including mental status changes, neuromuscular hyperactivity, and autonomic hyperactivity in severe cases.[46] Manifestation of these symptoms is known as serotonin syndrome, where clinical presentation can range from mild to life threatening. Mild serotonin syndrome can include tachycardia, shivering, diaphoresis, mydriasis, tremor or myoclonus, and hyperreflexia. Moderate clinical presentation increases the severity and can include hypertension, hyperthermia (as high as 40^{o}C), hyperactive bowel sounds, hyperreflexia and clonus, and ocular clonus. Lastly, severe serotonin syndrome can be life threatening and can include symptoms such as muscle rigidity, hypertonicity, delirium, metabolic acidosis, rhabdomyolysis, elevation of serum aminotransaminases and creatinine, seizure, and disseminated intravascular coagulopathy.[47]

Increased serotonin levels can cause autonomic hyperactivity, leading to several cardiac adverse events such as tachycardia, hypertension, and cardiac arrhythmia. In very severe cases, serotonin syndrome can lead to disseminated intravascular coagulation, resulting in thrombosis and multiple organ failure.[48,49] Common causative agents for serotonin syndrome are antidepressants (monoamine oxidase inhibitors, tricyclic antidepressants, or selective serotonin reuptake inhibitors [SSRIs]) and atypical antipsychotics.[47] However, opioids such as tramadol, fentanyl, tapentadol, oxycodone, and methadone have also been associated with serotonin syndrome.[50] A recent review of literature demonstrated that tramadol is associated with a

significantly greater occurrence of serotonin syndrome compared to other opioids.[51] Most of the serotonin syndrome cases were due to concomitant serotonergic medications and overdose intoxications, although there has been case reports of serotonin toxicity caused by tramadol alone.[52-54]

There are several receptor subtypes of serotonin (5-hydroxytryptamine [5-HT]) receptor subtypes. 5-HT_1 and 5-HT_2 receptors are of particular interest to the cardiovascular system as it mediates vasodilatory and vasoconstrictive activities. Specifically, activating 5-HT_2 receptor can lead to vasoconstriction, platelet aggregation, and synergism with other vasoconstrictors (prostaglandin $F_{2\alpha}$, norepinephrine, angiotensin II, and histamine).[55] There is also increased sensitivity and responsiveness to serotonin in diseased blood vessels of animals with pre-existing hypertension and atherosclerosis, contributing to further vasoconstriction.[56] High serotonin levels (≥1000 nmol/L) have shown to be significantly associated with coronary artery disease with an adjusted odds ratio of 3.8 compared to study participants with lower serotonin levels. This association was especially apparent in patients younger than 70 years old.[57] Elevated blood pressure and thrombosis due to serotonin can lead to myocardial infarction and ischemic stroke in addition to its pro-arrhythmic effects.

Norepinephrine

Tramadol also inhibits the reuptake of norepinephrine through blocking the norepinephrine transporter, which can lead to activation of the sympathetic nervous system. Vasoconstrictive effects by norepinephrine causes a rise in systolic blood pressure and mean arterial pressure with a decrease in heart rate.[58,59] Higher levels of plasma norepinephrine have also been shown to increase platelet production and activate platelet aggregation and coagulation, occurring at plasma levels readily produced through exercise and mental stress.[60,61] The degree of platelet

increase is highly dependent on the concentration of plasma norepinephrine as changes in platelet levels occurs quickly and corresponds to the dose of norepinephrine infusion.[62] Through norepinephrine's effects on blood pressure and platelet function, there is also increased risk of thrombosis and ischemia.

As tramadol is known to increase serotonin and norepinephrine levels in the body, and both neurotransmitters affect the circulatory system through changes in blood pressure, heart rate, and platelet function. These physiological changes could increase the risk of cardiovascular diseases such as myocardial infarction, ischemic stroke, cardiac arrhythmia, and venous thromboembolism. However, to our knowledge, little epidemiologic evidence is available regarding the association between tramadol and the risk of adverse cardiovascular events

1.4 Original thesis work

Thesis objective

This thesis will aim to compare the rate of myocardial infarction, unstable angina, ischemic stroke, coronary revascularization, cardiovascular death, and all-cause mortality with current use of tramadol to that of the current use of codeine among patients with non-cancer pain.

Thesis overview

Chapter 2 will introduce existing literature concerning the effects of tramadol on cardiovascular health in experimental and observational studies; as well as the increasing need for more evidence in this area. Chapter 3 will describe the design and implementation of a retrospective cohort study that I conducted using a population-based healthcare database. Chapter 4 will contain an original research manuscript exploring the association of tramadol with arterial ischemia, namely myocardial infarction, unstable angina, ischemic, stroke, coronary revascularization, cardiovascular death, and all-cause mortality. Chapter 5 will provide discussions of the important findings of my original research and its strengths and limitations. Finally, chapter 6 will provide the overall conclusion and describe implications of this work for future research.

Chapter 2: Literature Review

To identify the relevant literature examining tramadol and the risk of adverse cardiovascular events, I systematically searched PubMed using MeSH (Medical Subject Headings) terms and keywords related to the exposure and cardiovascular outcomes of interest (**Supplementary A. Table 1**), which were combined using Boolean logic to generate a complete list of available studies indexed in PubMed. Titles and abstracts were screened, and studies considered relevant to the research question were identified and included. Publicly available adverse drug reactions database was also searched for tramadol to identify any reported cardiovascular events associated with its use. Cardiovascular studies of medications with similar mechanism of action on the serotonin and/or norepinephrine receptors were also included to supplement existing studies on tramadol and provide further inferences regarding the association of serotonin/norepinephrine and the risk of cardiovascular events.

2.1 Experimental studies of the cardiovascular effects of tramadol

Tramadol infusion in rats has been shown to be cardioprotective in ischemia-reperfusion injury by reducing the infarct size in the myocardium, while also offering possible protection against myocardial insult after ischemia.[63,64] This hypothesis was then tested in a single-blinded randomized controlled trial[65] in patients undergoing coronary artery bypass grafting (CABG) with administration of two doses of tramadol before surgery. There were 101 patients randomized to receive either remote ischaemic preconditioning (RIPC), tramadol, or control. Contrary to previous findings from animal studies, preoperative tramadol significantly increased postoperative troponin I levels at three time intervals (8, 16, and 24 hours), indicating a greater level of myocardial damage. Troponin I was the highest after 8 hours for tramadol at 3.97μg/L from 0.02μg/L before the operation. Administration of tramadol in dogs showed a mild but

significant increase in arterial blood pressure and systemic vascular resistance.[66] Similarly, tramadol slightly increased arterial blood pressure and heart rate in anaesthetized rabbits and demonstrated dose-related positive inotropic effects in vitro.[67]

Randomized controlled trials are often unable to detect adverse drug reactions such as adverse cardiovascular events since these outcomes are relatively uncommon and trials are usually underpowered to detect such safety outcomes due to their limited sample size or duration of follow-up. This is particularly true for medications such as analgesics, where trials are typically designed to examine changes in pain, an outcome that can be usually assessed with a relatively modest sample size. Furthermore, randomized controlled trials are often conducted in a controlled environment where patients are monitored closely and participants carefully selected into the trial based on rigid inclusion criteria. Consequently, the generalizability of trial results to a real-world setting is often quite limited, particularly in patients who are typically excluded from trials such as very young or very old, pregnant patients, and patients with severe diseases such as chronic kidney disease. Thus, there exists an increasing need to investigate the association of adverse cardiovascular outcomes with tramadol through large, rigorous, and well-designed observational studies in a real-world setting.

2.2 Observational studies of the cardiovascular effects of tramadol

Case reports

Several cases of cardiovascular toxicity with tramadol have been reported, frequently following tramadol intoxication or overdose.[68-70] These cases typically presented with asystole followed by ventricular arrhythmia or cardiac arrest with refractory cardiogenic shock. Other clinical presentations included seizures and multiple organ failure. In addition, intravenous tramadol administration has been linked to Kounis syndrome, an allergic reaction involving

clinical features and findings of acute coronary syndrome triggered by the release of inflammatory cytokines and mast cell activation,[71] in patients who were previously healthy with no cardiovascular risk factors. Clinical symptoms of palpitations, chest pain, dyspnea, and hemodynamic instability occurred soon after administration, leading to the diagnosis of myocardial infarction.[72,73]

A pharmacovigilance study in France[74] compared adverse drug reaction (ADR) reports of WHO step 2 weak opioids used in combination with paracetamol from January 1st, 1987 to December 31st, 2006: dextropropoxyphene/paracetamol (14,247,943 person-years of use), tramadol/paracetamol (655,746 person-years of use), and codeine/paracetamol (4,575,058 person-years of use). There were 3,553 ADR reports with dextropropoxyphene/paracetamol, 292 with tramadol/paracetamol, and 573 with codeine/paracetamol. Tramadol had the highest rate of reported ADRs despite being a new medication with the smallest number of person-years of use. Nonetheless, tramadol had only 6 reported cardiac ADRs (reporting odds ratio [OR]: 0.43, 95% confidence interval [CI]: 0.18, 1.11) and 16 reported vascular ADRs (reporting OR: 0.24, 95% CI: 0.14, 0.42), with dextropropoxyphene as the reference group. There were several limitations from this study. Data were drawn from a voluntary reporting system where adverse drug reactions are markedly underreported with reporting rate of 5% in the French pharmacovigilance system.[75] Furthermore, the analyses did not adjust for differences in patient characteristics or cardiovascular risk factor levels. In addition, the rates of cardiac and vascular events were reported as percentage of the overall reported adverse drug reactions as opposed to the rate of adverse events in the overall population of users. Therefore, these rates can only indicate that there is a low frequency of cardiovascular events as compared to other reported adverse effects of tramadol.

VigiAccess is a database created by the World Health Organization that compiles reported adverse drug reactions from health authorities on medicinal products around the world. In January 2018, I queried the database, there were approximately 3592 reported cases cardiac disorders related to tramadol, including 337 cases of cardiac arrest, 376 cases of cardiac arrhythmia, 254 cases of myocardial ischemia/angina pectoris, and 51 cases of thrombosis.[76] As the adverse drug reaction reporting system is usually voluntary, the incidence of adverse reactions is often grossly underreported. The rate of reporting may also depend on the severity of the adverse reaction and the perception of association between the medication and the adverse event. Furthermore, with no denominator, these adverse event reporting systems are unable to provide risk estimates. Nonetheless, they are powerful tools for signal generation, and these data suggest that the cardiovascular effects of tramadol require further investigation.

Cohort studies

QT interval prolongation can lead to possible onset of arrhythmia or serious cases of torsade de pointes with potential consequences including sudden cardiac death. Keller et al.[77] assessed the effect of tramadol on the QT-interval in 115 patients who received 150-400mg/day of tramadol for an average of 4 days in a clinical setting. Due to lower baseline QTc, no patients were found to have QTc interval greater than 450 ms in males or 470 ms in females, which are typically used by clinicians as the threshold for torsades de pointes. At the end of this study, there were no cases of arrhythmia, ventricular tachycardia, torsades de pointes, or sudden cardiac death. However, tramadol administration prolonged the QTc interval >30 ms in 44% of patients and >60 ms in 20% of patients. Prolongation of QTc interval was highly correlated with the concentration of tramadol in the plasma, demonstrating a dose-response relationship. This study provides important insight regarding tramadol's potential for cardiac arrhythmia beyond its

effect on the serotonin receptor. However, its sample size and short follow-up represent important limitations, and although QTc interval prolongation is often used as a monitoring parameter for torsade de pointes/arrhythmia, it does not indicate actual occurrence. Further, methodologically rigorous epidemiological studies with clinically significant endpoints is necessary to investigate the potential association of tramadol and arrhythmic events.

A cohort study[16] conducted in the United States from 1996 to 2005 investigated the safety of opioid therapies (codeine, hydrocodone, oxycodone, propoxyphene, and tramadol) for non-malignant pain. A total of 6275 study subjects were matched on propensity score for each exposure group. Study outcomes included: fractures, cardiovascular events, gastrointestinal bleeding or bowel obstructions, hospitalization, and mortality. The cardiovascular outcome was a composite outcome of myocardial infarction, stroke, heart failure, revascularization, and out-of-hospital cardiac death. With hydrocodone used as the reference group, there were no significant differences in adverse cardiovascular events in the tramadol group at 30 days (incidence rate ratio: 0.99, 95% CI: 0.71, 1.39) and 180 days of follow-up (incidence rate ratio: 1.10, 95% CI: 0.87, 1.40). However, with the use of a composite endpoint, important increases for different cardiovascular events may have been masked or diluted by the inclusion of other, non-relevant outcomes as part of the composite endpoint.[78] Event rates for individual cardiovascular events were not presented to allow further interpretation and analysis. Furthermore, included patients were Medicare beneficiaries in the United States, restricting inclusion to patients age 65 years or older. With an average age of 78 years old, the generalizability of study results to the general public is unclear, particularly since pain conditions are prevalent among all age groups.

2.3 Studies of Medications with Similar Mechanism of Action

Previous investigations of medications with similar pharmacologic profiles may also provide some insight into the possible cardiovascular effects of tramadol. Antidepressants such as SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) inhibit the reuptake of serotonin and/or norepinephrine with a similar mechanism as tramadol, and the currently available evidence regarding SSRIs and the risk of myocardial infarction is conflicting. A case-control study[79] (653 cases of first myocardial infarction and 2990 controls) conducted in the Philadelphia metropolitan area in smokers aged 30 – 65 years old found that the current use of SSRIs was protective against a first myocardial infarction (OR: 0.35, 95% CI: 0.18, 0.68) versus non-use of antidepressants. However, this study, which only had 13 exposed cases and was originally designed to examine the association between nicotine patch and myocardial infarction, was not designed to assess this drug safety question. The use of random-digit dialing to identify controls is also prone to selection bias as it restricts inclusion to those with phones. Furthermore, with the study population restricted to smokers, the generalizability of its results is unclear. In contrast, a pooled cohort of elderly patients[80] (1,052 SSRI users and 10,856 nonantidepressant users) was found to have significantly higher odds of acute myocardial infarction in SSRI users compared to nonusers (OR: 1.85, 95% CI: 1.13, 3.04). Exposure was assessed in the year prior to the year of which the outcome occurred. In both studies, confounding by indication represents an important limitation as depression is considered to be an independent risk factor for cardiovascular disease and both used a reference category of non-use. Nevertheless, additional studies have demonstrated that current use of SSRIs may be associated with decreased risk of acute myocardial infarction.[81-84]

Venlafaxine, a SNRI antidepressant, has the closest resemblance to tramadol in its pharmacologic profile as it has high affinity for both the serotonin and norepinephrine receptors. It has been shown to significantly increase blood pressure and heart rate after one week of therapy.[85] Coupland et al.[86] compared antidepressant use and the risk of adverse outcomes in 60,746 older patients in a population-based cohort study using data from the QResearch primary care database in the United Kingdom. Venlafaxine had one of the highest rates of adverse outcomes in several categories, including stroke/transient ischemic attacks (absolute risk of 3.34% over one year). However, other observational studies have shown that venlafaxine, compared to SSRIs, is not associated with higher risk of sudden cardiac death or the composite endpoint of acute myocardial infarction, congestive heart failure, gastrointestinal hemorrhage, and death.[87,88] A nested case-control (568 cases and 14,812 controls) conducted using the General Practice Research Database with average follow-up of 3.3 years found no evidence of sudden cardiac death or near death associated with venlafaxine compared to fluoxetine (adjusted OR: 0.66, 95% CI: 0.38, 1.14) and citalopram (adjusted OR 0.89, 95% CI: 0.50, 1.60).[87] Similarly, a population-based retrospective cohort study (48,876 venlafaxine users and 41,238 sertraline users) using administrative health care databases in Ontario, Canada did not find significant difference in the composite endpoint of adverse cardiac events (hazard ratio: 0.97, 95% CI: 0.93, 1.02). With the use of composite endpoint, it is very difficult to interpret the results given the heterogeneous nature of the included endpoints. Ultimately, neither study provided meaningful data on the association of ischemic events with venlafaxine. In summary, there exists conflicting and limited evidence on the cardiovascular effects of both SSRIs and SNRIs. While these previous studies have raised some safety signals, there remains a need to

conduct a large, methodologically rigorous study examining the cardiovascular profile of tramadol.

Chapter 3: Methods

In the following chapter, I provide a more detailed description of my study methods. While some of this information is also included in the methods section of the enclosed manuscript, I have included this chapter to provide additional details and insight into the methodological process used.

3.1 Data Source

The data source was the Clinical Practice Research Datalink (CPRD) from the United Kingdom. It is a computerized healthcare database that was set up in 1987 and has been the most widely used administrative database for observational and interventional research internationally.[89] It contains an 8% representative sample of the population of the United Kingdom. As of July 2013, it contained data from 674 practices with over 79 million person-years of follow-up.[90] The vast amount of patient information and extensive longitudinal follow-up time in CPRD allows for researchers to study rare outcomes and diseases that have a longer latency period.[91] Demographic, diagnosis and prescription data are regularly recorded by the primary care general practitioners; these data are stored in an encrypted manner and anonymized to preserve confidentiality. Demographic characteristics recorded include sex, date of birth, ethnicity, region, and registration status. Diagnosis coded with read codes and prescription medications coded with product codes are actively recorded by the general practitioners through documentations in the electronic health system for each patient visit. However, this does not include medication dispensing data from the community pharmacies to indicate the medications had been obtained by the patients. The availability of certain clinical data in CPRD not typically found in administrative databases makes it unique, this includes blood pressure, laboratory test values, smoking status, alcohol intake, body mass index (BMI), and vaccination history recorded

in the general practitioner office. A systematic review which explored the validity of diagnostic coding in CPRD showed that most of the diagnosis codes were recorded correctly with good agreements in disease prevalence between CPRD and other datasets.[92] However, it does have some limitations, including a lack of information regarding medications or supplements taken over the counter, no data from specialists, and no dosing frequency for medications.[91] General practitioners serve as the gatekeepers to the healthcare system in United Kingdom, and reports from specialists are required to be sent back to the general practitioner and recorded into the CPRD.[93]

The CPRD can be linked to other National Health Service data holdings, including Hospital Episode Statistics (HES), which contains full hospitalization data, and the Office for National Statistics (ONS), which contains vital statistics. Linkage is available from 1997 to present for ~58% of CPRD patients and restricted to 75% of English patients who (1) registered at a participating English practice prior to the transfer of identifiers to the trusted third party for matching; (2) had a valid identifier for linkage (either NHS number or postcode); and (3) had not opted out or dissented from the CPRD or the linkage scheme. Inclusion was restricted to linkable practices. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnostic codes are used in HES data and ICD-9/ICD-10 codes are used to define underlying cause of death in ONS data. Medical procedures are recorded using OPCS Classification of Interventions and Procedures (OPCS-4) codes in HES.

3.2 Study Population

The study cohort included new users of tramadol or codeine between April 1st, 1998 and March 31st, 2017. Cohort entry was defined by the date of this new prescription. Patients were considered to be new users if they had not been prescribed either tramadol or codeine in the year

prior to cohort entry. The cohort was restricted to patients 18 years or older with at least one year of enrolment in the CPRD database prior to cohort entry to measure baseline characteristics and previous opioid use. We excluded patients who used either tramadol or codeine in the year prior to cohort entry to avoid bias associated with the inclusion of prevalent users.[94] Patients who were prescribed more than one type of opioid on the date of cohort entry were also excluded to allow for the assessment of the individual effects of tramadol and codeine on the cardiovascular system. Furthermore, patients with diagnosis or treatment for cancer other than non-melanoma skin cancer prior to cohort entry were excluded as certain chemotherapy and radiotherapy are known to cause cardiac-related adverse effects.[95] In addition, distinction is often made between treatment for chronic non-cancer pain and cancer-related pain in both research and clinical practice guidelines. Therefore, our study population excluded cancer patients and focused on the safety of treatment of non-cancer pain. Patients were followed until an outcome (defined below) or censoring due to death (for non-fatal endpoints only), end of registration with CPRD, diagnosis of cancer, end of study period (March 31st, 2017), or a maximum follow-up of 30 days.

3.3 Exposure

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 for an 'as needed' basis and prescription duration data are often missing in the CPRD. Only oral, transdermal, and injectable formulations of tramadol and codeine were included in our exposure definition. Lag time was not added as the outcomes of interest were deemed to be acute and biological changes were not considered to be irreversible. Follow-up was restricted to 30 days as we expect little changes to occur to the initial

prescription during that period. We also anticipate acute cardiovascular events to develop soon after exposure as biochemical changes from the rise of serotonin and norepinephrine occur quickly after tramadol administration. Patients would be the most susceptible to the outcomes of interest during this initial administration period as the body adapts to the physiological changes.

Codeine was used as the reference category for several reasons. First, the use of an active comparator greatly reduces potential confounding by indication and by other variables.[96] Second, the use of an active comparator addresses the most clinically relevant question; clinicians and other knowledge users are seeking to provide the therapy that optimizes benefits while minimizing risks and harms, and not treating pain is not a viable option. In addition to being unethical to do so, unmanaged pain can lead to several undesired health consequences; untreated or inadequately managed acute pain can lead to chronic pain, which can result in fatigue, dysphoria, myalgia, sleep disturbance, and compromised immune function.[97,98] Nonsteroidal anti-inflammatory drugs (NSAIDs) are not appropriate to use as the comparator since tramadol patients have often tried NSAIDs prior with little to no benefit and consequently required escalation of therapy. NSAIDs are also known to increase blood pressure and cardiovascular adverse effects. Oxycodone, morphine, and hydromorphone are analgesics with higher potency and usually used in patients with more severe pain who failed treatment with tramadol or codeine. In contrast, codeine is used at the same point in the treatment of pain (both are weak opioids indicated for the treatment of acute and chronic moderate to moderately severe pain). They also have the same mechanism of action on the μ-opioid receptor, and codeine is also a pro-drug metabolized through CYP2D6 and any genetic variation in CYP2D6 would affect both drugs equally. However, codeine does not affect serotonin or norepinephrine levels in the body,

allowing for the assessment of tramadol's effect on the cardiovascular system through its action on the serotonin and norepinephrine receptors.

3.4 Outcomes

The primary outcome was hospitalization or death due to myocardial infarction defined by the presence of a corresponding ICD-10 code (I21.x, I22.x, I23.x) or ICD-9 code (410.x) in HES (as a primary or secondary diagnosis) or ONS (as underlying cause of death). The secondary outcomes were hospitalization or death due to unstable angina (ICD-10 code I20.0; ICD-9 code 411.1), coronary revascularization (OPCS-4 codes K40.1 – K51.9, K55.3, K75.1 – K75.9), hospitalization or death due to ischemic stroke (ICD-10 codes 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 codes 433.x, 434.x, 437.1, 437.8, 437.9, 435.x), cardiovascular death, and all-cause mortality. Unspecified stroke was considered to be ischemic as majority of strokes are ischemic in nature.[99] Cardiovascular death was defined by ICD codes in which the primary underlying cause of death was related to the diseases of the cardiovascular system (ICD-10 codes I00 – I82.x; ICD-9 codes 391.x – 453.x). Finally, all-cause mortality was defined as all deaths that occurred during the study period irrespective of the underlying cause. The event date was defined as the date of admission for hospitalization or date of death for fatal events. Previous validation study had identified the death registry as a useful source for identification of fatal acute myocardial infarction.[100] Read codes were not used to identify non-fatal and fatal outcomes as we want to ensure only clinically important events were included in the analyses through hospitalization and mortality data; outpatient diagnoses without corresponding hospitalization or vital statistics are also more likely to be prone to misclassification.

3.5 Covariates

Demographic and lifestyle characteristics were assessed at baseline. These characteristics included age, sex, BMI, and smoking status. BMI was divided into four categories: underweight (<18.5 kg/m^2), normal weight (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), and obese (≥30.0 kg/m^2). Smoking status was classified as ever or never smoker. We also assessed average systolic and diastolic blood pressure. Blood pressure was defined as the last recorded measure in the previous year while BMI and smoking status was defined as the last recorded assessment in the last 5 years. If there was more than one blood pressure taken on the same day, the highest value was used. Number of drug classes, number of hospitalizations, and number of physician visits were measured in the year prior to cohort entry. These are important parameters to consider as they serve as a proxy for overall health status.

Potential risk factors for arterial ischemia were identified from the literature and considered as potential confounders. These variables included alcohol-related disorders, anxiety, arrhythmia, cerebrovascular disease, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, depression, dyslipidemia, heart failure, hypertension, peripheral vascular disease, liver cirrhosis, sleep apnea, rheumatoid arthritis, venous thromboembolism, previous myocardial infarction, previous coronary revascularization, and medications prescribed (aspirin, other anti-platelet agents. anticoagulants, angiotensin-converting enzyme inhibitor, angiotensin-II receptor blockers, calcium channel blockers, beta-blockers, SNRIs, SSRIs, tricyclic antidepressant, monoamine oxidase inhibitors, loop diuretics, thiazide diuretics, potassium-sparing diuretics, Cytochrome P450 2D6 inhibitors/inducers, and opioids other than tramadol or codeine).[101-107] Comorbidities were defined by the presence of a relevant Read code any time prior to cohort entry, and medications were defined by product

codes indicating a prescription in the year before cohort entry. Previous coronary revascularization was identified through OPCS-4 procedure codes recorded in HES. Finally, indication for opioid use was assessed in the 90 days prior to cohort entry and classified as injury or trauma, musculoskeletal pain, abdominal and pelvic pain, dental, surgery, headache, neuralgia, and other pain.

I created operational variable definitions by systematically searching the CPRD code browser (version 3.0.0) to identify all relevant Read codes and product codes. Diagnostic definitions were created by searching for keywords and Read codes, and drug definitions were created by searching for British National Formulary category, generic drug names, and trade names. After identifying all relevant Read codes or product codes in the code browser, I compiled them to finalize the operational variable definition. Variable definitions for outcome variables were constructed in a similar manner using ICD codes. The process of operationalizing variable definitions is an important step for pharmacoepidemiologic research as these variable definitions are used to identify the covariates and outcomes in the database. Errors in these definitions could result in the misclassification of covariates or outcomes. Some of the variable definitions for this study have been previously constructed by members of the research team, and others were created by myself (**Supplementary A. Table 2**). Therefore, to ensure accuracy of my outcome variable definition, I searched studies that have used the CPRD database with published variable definition(s). My variable definition was compared with theirs, and any discrepancies were addressed.

3.6 Data Analyses

Patient characteristics at cohort entry were described as mean ± standard deviation for continuous variables and counts (percentage) for discrete categorical variables. The distribution

of baseline characteristics among tramadol and codeine users were compared using standardized differences. Standardized differences were calculated by using the difference in means or proportions divided by the standard error. This approach is more informative than hypothesis testing (e.g. using the student t-test or Wilcoxon rank-sum test) as sample size does not influence the results,[108] which is important in a large population-based database study. Standardized differences between groups of > 0.1 (10%) were considered to be important.[108,109] Event rates and 95% CI for MI were estimated with Poisson distribution, overall and by exposure category.

The primary analysis employed high-dimensional propensity score (HDPS) models and an approach analogous to intention-to-treat. The HDPS models included the previously specified covariates and up to 500 empirically-identified covariates. In observational studies, confounding by indication and by other variables often occur as exposures were not randomly assigned as in the case of a randomized controlled trial.[110] This can result in important biases affecting the results of the study. The use of propensity score is a method implemented to mimic random allocation by assigning probability of treatment based on the observed baseline covariates.[111] Adjustment of propensity score allows comparison of groups with an equal chance of receiving either treatment in patients with similar prognostic variables, therefore reducing this bias.[112] In order to impute the propensity score, a logistic model is used to estimate the propensity (or probability) of a patient receiving a tramadol prescription versus a codeine prescription given their covariate pattern. This propensity score can then be used in designing a study through matching or stratification or be included in the analysis of results through weighting or statistical adjustment to reduce confounding. While the traditional propensity score typically includes pre-specified covariates only, the HDPS includes up to 500 empirically-identified covariates to further reduce residual confounding by accounting for proxies of unknown and unmeasured

confounders identified by the algorithm. Schneeweiss et al. have demonstrated that using the HDPS produces results that are closer to the expected findings from randomized controlled trials compared to traditional propensity scores that use pre-defined covariates only.[113] I then used a Cox proportional hazards model to estimate the hazard ratio and 95% CI for myocardial infarction with tramadol versus codeine. This outcome model included the exposure variable, indicator variables for HDPS decile (measured at cohort entry), and interaction terms between HDPS decile and HDPS in its continuous form. The interaction term was used to reduce residual confounding within each decile. The primary analysis was repeated for our secondary outcomes of unstable angina, ischemic stroke, coronary revascularization, cardiovascular death, and all-cause mortality.

Seven sensitivity analyses were conducted to assess the robustness of our results. First, to examine potential residual confounding, we matched on the logit of the HDPS in 1:1 ratio on the nearest neighbour with no caliper; we then adjusted for the HDPS using a similar approach as described in the primary analysis to minimize potential residual confounding. Second, we changed the maximum follow-up to 60 days to examine the potential impact of censoring. Third, as codeine is available in many combination forms, including acetaminophen, aspirin, and/or caffeine, the analysis was repeated to include those that contain only codeine as the reference group. Fourth, the outcome of hospitalization for MI was restricted to those with diagnostic code in the primary position to examine the potential consequence of outcome misclassification. The same analysis was repeated to include deaths for MI as one of the underlying causes of death. Sixth, the analysis was conducted with a new end date of June 10th, 2014 as this represents the date in which tramadol was rescheduled as a controlled drug in the UK. This ensured that changes to the drug scheduling did not influence prescriber's choice of therapy and hence the

results of our study. Finally, missing data for variables were included through the use of an indicator variable in our propensity score. This approach could lead to bias if the variable with missing data is an important confounder.[114] Therefore, an analysis using multiple imputation for missing data was conducted for the primary analysis to ensure the use of indicator variable did not bias our results.

Preface to Manuscript

In chapter 2, I provided a detailed description of the need for a methodologically rigorous assessment of the cardiovascular effects of tramadol and described the study methodology in detail in chapter 3. In chapter 4, I conducted a retrospective population-based cohort study using data from the CPRD comparing tramadol versus codeine for the outcomes of adverse cardiovascular events, including myocardial infarction, unstable angina, ischemic stroke, coronary revascularization, cardiovascular death, and all-cause mortality. This study incorporated: (1) new user design to avoid prevalent user bias; (2) active comparator codeine to minimize confounding by indication and by other variables; (3) outcomes defined by ICD-9/10 codes in hospitalization and vital statistics data to include clinically important events and to reduce misclassification; (4) adjustment of HDPS scores to reduce potential confounding; and (5) maximum follow-up of 30 days in the setting of acute outcomes and to avoid time-varying confounding.

Chapter 4: Original Research Article

Tramadol and the Risk of Cardiovascular Events: A Population Based Cohort Study

Short Title: Tramadol and Cardiovascular Events

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

ABSTRACT

Introduction: 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.

Objectives: To compare the rate 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 1,037,727 new users (123,394 tramadol and 914,333 codeine). The adjusted HR of myocardial infarction associated with tramadol compared to codeine was 1.003 (95% CI: 0.81, 1.24). There was also no elevated risk 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), and all-cause mortality (1.03, 95% CI: 0.94, 1.14) when tramadol was compared to codeine.

Conclusion: We found no evidence of increased risk of cardiovascular events when tramadol was compared with codeine.

Introduction

Tramadol is a synthetic weak opioid[1] used for the treatment of moderate to moderately severe pain.[2] It is part of the second step of the World Health Organization analgesic ladder along with codeine.[3] Marketed as a non-narcotic with low risk of abuse and misuse, tramadol has been preferentially prescribed over codeine in the last decade. Prescriptions for tramadol increased by 65% in United States from 2007 to 2011, ranking third among all opioids prescribed.[4] Increased use of tramadol may also be explained by its exclusion from the controlled and narcotic drug schedule in many countries prior to 2014.[5,6]

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.[7] This dual mechanism contributes to the analgesic effects of tramadol, but it also may result in a difference of adverse effect profile than the classic opioids. Increased serotonin levels can result in autonomic hyperactivity, which can lead to numerous cardiac adverse events in tachycardia, hypertension, and cardiac arrhythmia.[8] High serotonin levels are associated with an increased risk of coronary artery disease.[9] In addition to the vasoconstrictive effects demonstrated by norepinephrine, both norepinephrine and serotonin can activate platelet aggregation and increase platelet production.[10-12] Furthermore, tramadol has been shown to increase blood pressure in both human and animal models.[7,13] 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 cardiovascular safety of tramadol. To our knowledge, there has only been three observational studies that previously investigated the cardiovascular safety of tramadol in a real-world setting. However, these studies had important methodological limitations, including the use of composite endpoints, voluntary

reporting bias, confounding by indication, and low generalizability. Therefore, the objective of this population-based cohort study was to compare the 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 that contains the general practitioner records from 674 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, body mass index) not typically available in administrative databases. CPRD data have been validated extensively and shown to be of high quality.[14,15] In addition, it can be linked to other National Health Service data holdings, including hospitalization data through Hospital Episode Statistics (HES) and vital statistics data from the Office for National Statistics (ONS).[16] HES contains information on admissions to English hospitals, with diagnoses recorded using 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. 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.[16]

The research protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC 17_212A, which was made available to journal reviewers) and by the Research Ethics Board at Jewish General Hospital, Montreal, Canada.

Study population

We identified all patients aged 18 years or older who were linkable to HES and 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 to new users to avoid any bias associated with the study of prevalent users.[17] 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 observation time in the CPRD and those who were prescribed for more than one type of opioid on cohort entry date. We also excluded all patients with diagnosis or treatment for cancer (except for non-melanoma skin cancer) prior to cohort entry as certain chemotherapy and radiotherapy are known to cause cardiac-related adverse effects.[18] In addition, distinction is often made between treatment for chronic non-cancer pain and cancer-related pain in both research and clinical practice guidelines. Therefore, our study population excluded cancer patients and focused on the safety of treatment of non-cancer pain. Patients were followed until an event 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 the follow-up. An intention-to-treat approach was used as these drugs are often used for an 'as needed' basis and prescription duration data are often missing in the CPRD. Only oral, transdermal, and injectable formulations of tramadol and codeine were included in our exposure definition. Follow-up was restricted to 30

days as we expect little changes to occur to the initial prescription during that period. We also anticipate acute cardiovascular events to develop soon after exposure as biochemical changes from the rise of serotonin and norepinephrine occur quickly after tramadol administration. Patients would be the most susceptible to the outcomes of interest during this initial administration period as the body adapts to the physiological changes.

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). 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; unspecified stroke was considered to be ischemic as majority of strokes are ischemic in nature.[19] Coronary revascularization was defined by OPCS-4 codes in hospitalization data. Deaths were defined as cardiovascular if the primary underlying cause of death was related to the diseases of the cardiovascular system (ICD-10: I00 – I82.x; ICD-9: 391.x – 453.x). Finally, all-cause mortality was defined as all deaths 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, BMI

(<18.5, 18.5-24.9, 25.0-29.9, ≥ 30.0 kg/m^2), 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. Missing data for BMI, smoking, and blood pressure were included through the use of an indicator variable in our propensity score. 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.[20-26] Medications, prescribed before cohort entry, were aspirin, other anti-platelet agents. anticoagulants, angiotensin-converting enzyme inhibitor, angiotensin-II receptor blockers, calcium channel blockers, beta-blockers, serotonin-norepinephrine reuptake inhibitors, selective-serotonin reuptake inhibitors, tricyclic antidepressant, monoamine oxidase inhibitors, loop diuretics, thiazide diuretics, potassium-sparing diuretics, Cytochrome P450 2D6 inhibitors/inducers, and opioids other than tramadol or codeine. Indication for opioid medications was captured in the 90 days prior to cohort entry. Finally, other proxies for overall health status were adjusted including number of drug classes prescribed, number of hospitalizations, and number of physician visits within the year prior to cohort entry.

Statistical analyses

Descriptive statistics was used to describe baseline patient characteristics on cohort entry. Distribution of baseline characteristics of tramadol and codeine users were compared using standardized differences. Standardized differences of 0.1 or more were considered to be important.[27] Overall event rates and rates by treatment group were determined using the Poisson

distribution. To minimize potential confounding, we estimated a high-dimensional propensity score (HDPS) using a logistic regression model that included the pre-specified covariates (described above) and up to 500 empirically-identified variables.[28] 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.

Sensitivity analyses

We performed seven sensitivity analysis 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) in addition to adjusting for HDPS to examine potential residual confounding. Second, we used a maximum follow-up of 60 days to examine the impact of the maximum duration of follow-up on our results. Third, as codeine and tramadol are available in many combination forms with acetaminophen, aspirin, and/or caffeine, analyses were repeated restricting exposure to formulations only containing tramadol or codeine alone. Fourth, the outcome of hospitalization for myocardial infarction was restricted to those with diagnostic code in the primary position to examine potential outcome misclassification. Fifth, we also restricted to deaths for myocardial infarction as one of the underlying causes of death in addition to hospitalization diagnostic code in the primary position. Sixth, 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. Finally, the use of an indicator variable for missing data could lead to bias if the missing data variable is an important confounder.[29] Therefore, an analysis using multiple imputation for the missing data was conducted for the primary analysis to ensure the use of indicator variable did not bias our results.

Results

We identified 1,286,816 patients aged 18+ 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 who received tramadol and 914,333 who received codeine.

The mean age at cohort entry was 54.4 years for the tramadol group and 52.4 years 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, takes more medications per patient, 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.

Table 2 describes the results of our primary and secondary analyses. During the 30 day follow-up, there were 752 myocardial infarctions in 84,595 person-years (PYs) of 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 the 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 the rate of myocardial infarction compared with codeine (adjusted HR: 1.003, 95% CI: 0.81, 1.24). Similarly, compared with codeine, tramadol

was not associated with the 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).

Sensitivity analyses

The results of the sensitivity analysis were consistent with those of our primary analysis (**Supplementary Table 1**).

Discussion

Our study was designed to examine the cardiovascular safety of tramadol in patients treated for non-cancer pain. Using a population-based cohort, there was no evidence of an increased risk of cardiovascular events with tramadol versus codeine, a weak opioid indicated for the treatment of acute and chronic moderate to moderately severe pain. Consistent results were observed for our primary and secondary endpoints and across several sensitivity analyses.

To our knowledge, the association between tramadol and cardiovascular events has been examined in three previous observational studies.[30-32] Soloman and colleagues[30] 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.[33] Our study included larger number of tramadol users, allowing for the investigation of each outcome individually and confirmed that tramadol was not associated with these cardiovascular events. A second study[31] relied 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. Its limitations were underreporting of adverse drug reactions[34] and absence of adjustment for differences in patient characteristics or cardiovascular risk factor levels. Thus, our results would provide a more accurate estimation of the risk of cardiovascular events of tramadol. In the third study[32], a nested case control study (11,693 cases and 44,897 controls) found the risk of

myocardial infarction associated with current use of opioid compared to non-use was significantly increased (OR: 1.29, 95% CI: 1.19, 1.37). Specifically, tramadol use (195 cases, 593 controls) showed a trend towards an increase in the risk of myocardial infarction compared to non-use (OR: 1.19, 95% CI: 1.00, 1.42). This risk is diluted as use is defined as a single prescription in the last 2 years. First, non-use is not a good comparator group and can lead to confounding by indication.[35] Second, defining use as a single prescription in the last 2 years can include a large period of non-use, thus does not allow for a meaningful comparison.

Despite strong 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 cardiovascular events. It is possible that the associated adverse effect does not occur at regular doses used for pain management. Nevertheless, tramadol appears to be safe with respect to cardiovascular events relative to codeine for the treatment of non-cancer pain.

Strengths

This study had several strengths. With a large sample size, few exclusion criteria, and use of population-based, real-world data, it is generalizable. Its large size also resulted in precise treatment effects. Our use of a new-user design avoided the depletion of susceptibles that can occur when studying prevalent users. Furthermore, with our use of an active comparator for the same indication and rigorous statistical adjustment, we reduced confounding. Finally, results were consistent across several sensitivity analyses.

Limitations

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 patient characteristics 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 to observe events that occurred due to cumulative exposure to codeine or tramadol beyond 30 days. For this reason, we conducted a sensitivity analysis extending follow-up to 60 days, which produced results that were consistent with those of our primary analysis. Furthermore, current exposure is most likely the etiologically-relevant time-window given the acute nature of the endpoints examined. The missing data for BMI, smoking, and blood pressure were included through the use of an indicator variable in the propensity score. As the point estimate of the outcomes were analyzed using HDPS deciles as oppose to the individual variables, the missing data had little effect on the results since it is not missing in the model. We also conducted a sensitivity analysis on our primary outcome using multiple imputation for the missing data and our results were consistent. Finally, as is true with all observational studies, residual confounding remains possible.

Conclusion

In patients treated for acute or chronic non-cancer pain, tramadol was not associated with the 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 cardiovascular safety of tramadol and should be considered when assessing benefits and risks of different treatment options for pain.

ACKNOWLEDGEMENTS

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

DISCLOSURES

The authors have no relationships to disclose.

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Table 1. Baseline Characteristics of Patients using Tramadol and Codeine

Characteristics	Tramadol (n=123,394)	Codeine (n=914,333)	Standardized Difference
Age (years)	54.4 (17.7)	52.4 (19.0)	0.011
Male	53,679 (43.50)	386,232(42.24)	0.025
Cohort entry (year)			
1998	1,682 (1.36)	19,588 (2.14)	0.059
1999	2,613 (2.12)	27,989 (3.06)	0.059
2000	3,469 (2.81)	32,860 (3.59)	0.044
2001	4,887 (3.96)	41,521 (4.54)	0.029
2002	6,140 (4.98)	45,356 (4.96)	0.001
2003	7,564 (6.13)	51,812 (5.67)	0.02
2004	8,653 (7.01)	55,294 (6.05)	0.039
2005	9,685 (7.85)	68,848 (7.53)	0.012
2006	9,427 (7.64)	65,578 (7.17)	0.018
2007	9,557 (7.75)	65,209 (7.13)	0.023
2008	9,164 (7.43)	64,960 (7.10)	0.012
2009	9,249 (7.50)	62,617 (6.85)	0.025
2010	8,899 (7.21)	60,244 (6.59)	0.025
2011	8,279 (6.71)	56,428 (6.17)	0.022
2012	7,966 (6.46)	54,372 (5.95)	0.021
2013	6,605 (5.35)	47,774 (5.23)	0.006
2014	4,558 (3.69)	39,585 (4.33)	0.032
2015	2,767 (2.24)	29,786 (3.26)	0.062
2016	1,853 (1.50)	20,504 (2.24)	0.055
2017	377 (0.31)	4,008 (0.44)	0.022
Comorbidities			
Alcohol related disorders	7,921 (6.42)	52,985 (5.79)	0.026
Anxiety	16,264 (13.18)	111,642 (12.21)	0.029
Arrhythmia	5,834 (4.73)	38,354 (4.19)	0.026
Cerebrovascular disease	5,697 (4.62)	37,547 (4.11)	0.025
Chronic kidney disease	5,589 (4.53)	37,783 (4.13)	0.02
Coronary artery disease	11,878 (9.63)	71,473 (7.82)	0.064
Coronary revascularization	3,297 (2.67)	16,438 (1.80)	0.059
COPD	11,061 (8.96)	71,895 (7.86)	0.04
Diabetes	16,382 (13.28)	110,832(12.12)	0.035
Depression	37,254 (30.19)	241,855(26.45)	0.083
Dyslipidemia	14,489 (11.74)	93,233 (10.20)	0.049
Heart failure	3,039 (2.46)	18,452 (2.02)	0.03
Hypertension	31,396 (25.44)	212,309 (23.22)	0.05
Peripheral vascular disease	3,007 (2.44)	15,607 (1.71)	0.05
Liver cirrhosis	183 (0.15)	821 (0.09)	0.017
Sleep apnea	995 (0.81)	5,348 (0.58)	0.027
Rheumatoid arthritis	2,879 (2.33)	11,105 (1.21)	0.085

Previous myocardial infarction	4,281(3.47)	26,110 (2.86)	0.035
Previous venous thromboembolism	6,545 (5.30)	36,972 (4.04)	0.06
BMI			
Underweight: <18.5	1,579 (1.28)	13,533 (1.48)	0.022
Normal weight: 18.5 – 24.9	25,423 (20.60)	205,124(22.43)	0.062
Overweight: 25.0 – 29.9	28,598 (23.18)	213,074(23.30)	0.008
Obese: ≥30.0	27,511 (22.30)	180,530(19.74)	0.078
Missing	40,283 (32.65)	302,072 (33.04)	
Health visits in the year prior to cohort entry			
Number of physician visits	3.4 (5.4)	2.6 (4.6)	0.158
Number of hospitalizations			
0	93,218 (75.55)	783,295(85.67)	0.258
1	21,154 (17.14)	98,051 (10.72)	0.186
>1	9,022 (7.31)	32,987 (3.61)	0.164
Lifestyle			
Smoker	64,971 (52.65)	463,128(50.65)	0.044
Missing	21,087 (17.09)	159,660 (17.46)	
Average blood pressure			
Systolic	133.6 (18.5)	132.6 (25.3)	0.046
Diastolic	78.6 (10.4)	78.0 (10.5)	0.049
Missing	50,014 (40.5)	375,883 (41.1)	
Indication			
Injury	5,187 (4.20)	43,266 (4.73)	0.026
Musculoskeletal pain	16 (0.01)	101 (0.01)	0.018
Abdominal pain	10,448 (8.47)	59,831 (6.54)	0.073
Dental	838 (0.68)	6,760 (0.74)	0.072
Surgery	14,774 (11.97)	53,613 (5.86)	0.216
Headache	130 (0.11)	1,153 (0.13)	0.061
Other pain	10,834 (8.78)	64,161 (7.02)	0.065
Neuralgia	106 (0.09)	336 (0.04)	0.02
Medications			
Number of drug classes	8.0 (5.7)	6.6 (4.8)	0.277
Aspirin	17,506 (14.19)	111,639(12.21)	0.058
Other anti-platelets	3,044 (2.47)	16,571 (1.81)	0.045
Anticoagulants	4,197 (3.40)	24,005 (2.63)	0.045
ACE inhibitors	16,978 (13.76)	109,882(12.02)	0.052
ARBs	6,675 (5.41)	39,435 (4.31)	0.051
Calcium channel blockers	14,992 (12.15)	96,591 (10.56)	0.05
Beta-blockers	15,383 (12.47)	103,615(11.33)	0.035
Loop diuretics	9,988 (8.09)	52,718 (5.77)	0.092
Potassium-sparing diuretics	3,696 (3.00)	18,692 (2.04)	0.061
Thiazide diuretics	13,320 (10.79)	90,015 (9.84)	0.031
Statins	21,682 (17.57)	136,810(14.96)	0.071

SNRIs	2,108 (1.71)	10,740 (1.17)	0.045
SSRIs	15,124 (12.26)	97,220 (10.63)	0.051
TCAs	15,254 (12.36)	64,690 (7.08)	0.179
MOAIs	46 (0.04)	290 (0.03)	0.003
Non-ASA NSAIDs	57,269 (46.41)	347,832(38.04)	0.17
Opioids [other than tramadol or codeine]	34,620 (28.06)	96,401 (10.54)	0.455
CYP2D6 inducers	145 (0.12)	632 (0.07)	0.016
CYP2D6 inhibitors	10,224 (8.29)	64,993 (7.11)	0.044

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

Table 2. Primary and Secondary Analyses of Outcomes Comparing Tramadol vs. Codeine

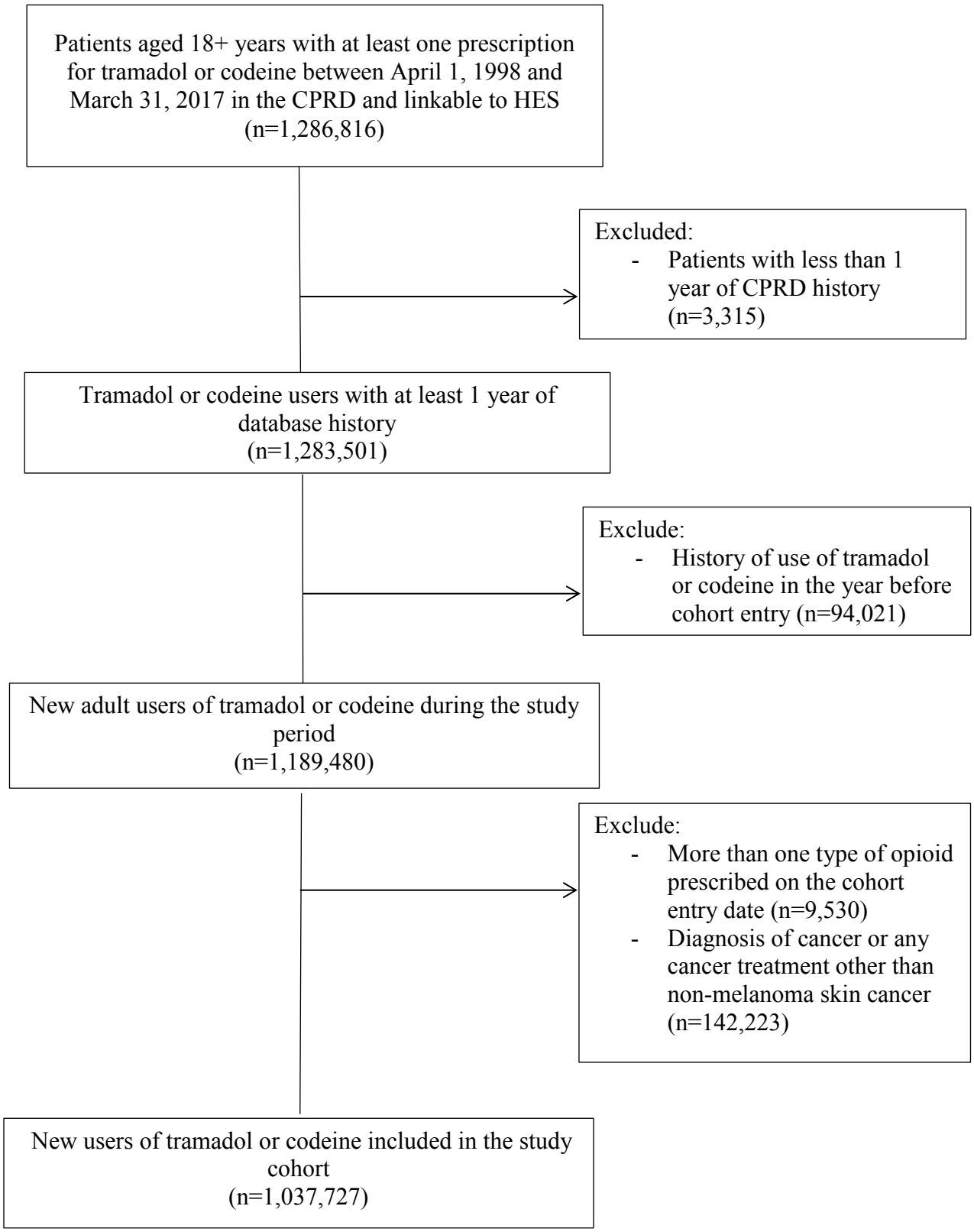
Exposure	Events	Person-Years	Incidence Rate (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)†
MI	752	84,595	8.9 (8.3, 9.5)		
Codeine	646	74,544	8.7 (8.0, 9.4)	1.00 (Ref)	1.00 (Ref)
Tramadol	106	10,051	10.5 (8.7, 12.8)	1.22 (0.991, 1.49)	1.003 (0.81, 1.24)
Unstable Angina	307	84,609	3.6 (3.2, 4.1)		
Codeine	259	74,557	3.5 (3.1, 3.9)	1.00 (Ref)	1.00 (Ref)
Tramadol	48	10,052	4.8 (3.6, 6.3)	1.38 (1.01, 1.87)	0.92 (0.67, 1.27)
Ischemic Stroke	1149	84,593	13.6 (12.8, 14.4)		
Codeine	997	74,545	13.4 (12.6, 14.2)	1.00 (Ref)	1.00 (Ref)
Tramadol	152	10,048	15.1 (12.9, 17.7)	1.13 (0.95, 1.34)	0.98 (0.82, 1.17)
Coronary Revascularization	276	84,629	3.3 (2.9, 3.7)		
Codeine	236	74,577	3.2 (2.8, 3.6)	1.00 (Ref)	1.00 (Ref)
Tramadol	40	10,052	4.0 (2.9, 5.4)	1.26 (0.90, 1.76)	0.97 (0.69, 1.38)
Cardiovascular death	1,687	84,622	19.9 (19.0, 20.9)		
Codeine	1,439	74,569	19.3 (18.3, 20.3)	1.00 (Ref)	1.00 (Ref)
Tramadol	248	10,054	24.7 (21.8, 27.9)	1.28 (1.12, 1.46)	1.07 (0.93, 1.23)
All-cause mortality	3481	84,635	41.1 (39.8, 42.5)		
Codeine	2,985	74,581	40.0 (38.6, 41.5)	1.00 (Ref)	1.00 (Ref)
Tramadol	496	10,053	49.3 (45.2, 53.9)	1.23 (1.12, 1.36)	1.03 (0.94, 1.14)

Slight variation in the patients included for each outcome due to HDPS trimming
Abbreviations: MI: myocardial infarction; HR: hazard ratio; CI: confidence interval
*Incidence rate are expressed as events per 1000 person-years.
† 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 of Patients Included and Excluded in the Cohort

Figure 1. Flow Chart of Patients Included and Excluded in the Cohort



SUPPLEMENTARY

Supplementary Table 1. Sensitivity analyses conducted to assess the risk of myocardial infarction comparing tramadol vs. codeine

Exposure	Events	Person-Years	Incidence Rate (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI) †
Matched on HDPS (N=246,780)					
MI	223	20,106	10.9 (9.7, 12.6)		
Codeine	117	10,055	11.6 (9.7, 13.9)	1.00 (Ref)	1.00 (Ref)
Tramadol	106	10,051	10.5 (8.7, 12.8)	0.91 (0.70, 1.18)	0.91 (0.70, 1.18)
Restricting follow-up to 60 days (N=1,037,496)					
MI	1,193	167,937.69	7.1 (6.7, 7.5)		
Codeine	1,010	148,000.94	6.8 (6.4, 7.3)	1.00 (Ref)	1.00 (Ref)
Tramadol	182	19,936.75	9.2 (7.9, 10.6)	1.35 (1.15, 1.57)	1.09 (0.92, 1.28)
Comparing formulations contain codeine or tramadol only (N=294,620)					
MI	258	23,988	10.8 (9.5, 12.2)		
Codeine only	153	14,321	10.7 (9.1, 12.5)	1.00 (Ref)	1.00 (Ref)
Tramadol only	105	9,668	10.9 (9.0, 13.1)	1.02 (0.79, 1.30)	0.89 (0.67, 1.17)
Hospitalization with diagnosis code in the primary position (N=1,037,457)					
MI	434	84,608	5.1 (4.7, 5.6)		
Codeine	376	74,556	5.0 (4.6, 5.6)	1.00 (Ref)	1.00 (Ref)
Tramadol	58	10,051	5.8 (4.5, 7.5)	1.14 (0.87, 1.51)	0.94 (0.70, 1.25)
Hospitalization diagnosis in the primary position and any cause of death (N=1,037,279)					
MI	652	84,593	7.7 (7.1, 8.3)		
Codeine	559	74,542	7.5 (6.9, 8.1)	1.00 (Ref)	1.00 (Ref)
Tramadol	93	10,051	9.3 (7.6, 11.3)	1.23 (0.99, 1.54)	1.04 (0.82, 1.31)
Study censor date as June 10th, 2014 (N=955,254)					
MI	703	77,841	9.0 (8.4, 9.7)		
Codeine	602	68,372	8.8 (8.1, 9.5)	1.00 (Ref)	1.00 (Ref)
Tramadol	101	9,469	10.7 (8.8, 13.0)	1.21 (0.98, 1.50)	0.99 (0.79, 1.23)
Primary analysis using multiple imputation for missing data (N=1,037,264)					
MI	752	84,587	8.9 (8.3, 9.5)		
Codeine	646	74,537	8.7 (8.0, 9.4)	1.00 (Ref)	1.00 (Ref)
Tramadol	106	10,050	10.5 (8.7, 12.8)	1.22 (0.99, 1.49)	1.004 (0.81, 1.24)

Abbreviations: MI: myocardial infarction; HR: hazard ratio; CI: confidence interval
*Incidence rate are expressed as events per 1000 person-years.
† Adjusted for indicator variables for HDPS decile (measured at cohort entry), and interaction terms between HDPS decile and HDPS in its continuous form

Chapter 5: Discussion

Study results

With a strong biological mechanism supporting a potential association between tramadol and adverse cardiovascular events, I conducted a retrospective cohort study using the CPRD database to explore the association of cardiovascular events in patients treated with tramadol as compared to codeine in non-cancer pain. I found 106 myocardial infarction events in 10,051 person-years (PYs) of follow-up in the tramadol group (crude incidence rate per 1000 person-years [IR]:10.5, 95% CI: 8.7, 12.8) and 646 myocardial infarction events in 74,544 PYs of follow-up in the codeine group (IR: 8.7, 95% CI: 8.0, 9.4). After adjusting for HDPS, there was no evidence of increased risk of myocardial infarction when tramadol was compared to codeine (HR: 1.003, 95% CI: 0.81, 1.24). Similar results were observed for the secondary endpoints of unstable angina, ischemic stroke, coronary revascularization, cardiovascular death, and all-cause mortality. The seven sensitivity analyses also produced results that were consistent with those of the primary analysis, suggesting robustness and reliability of my results.

Confounding

Several strategies were used to minimize potential confounding. First, we used codeine as an active comparator to reduce potential confounding by indication and by other unknown variables.[96] It provides a fair comparison with equipotent analgesic profile in the types of patients who will require treatment for acute and chronic moderate to moderately severe pain. Second, we adjusted for HDPS, which included an extensive list of pre-specified potential confounders and 500 empirically identified covariates. Furthermore, we included interaction terms between HDPS decile and HDPS in its continuous form, reducing residual confounding within the deciles, and matched for HDPS in sensitivity analyses. Time-varying confounding was

not considered as our follow-up period was defined to be maximum of 30 days, and it is unlikely that patient characteristics will change much over such a short duration. Despite our best efforts, residual confounding remains possible given the observational nature of this study.

Selection

We established selection criteria to critically assess the individual effects of tramadol and codeine on cardiovascular safety in a very focused manner. However, these criteria were minimal, which include restricting to patients who had sufficient amount of data (1 year of up-to-standard CPRD history) to asses for baseline characteristics, new users of tramadol or codeine to avoid depletion of susceptibles, and treatment of non-cancer pain. Due to our limited exclusion criteria, our study results are highly generalizable. The start of follow-up is determined by the date of new prescription for either tramadol or codeine, eliminating immortal time bias. As our follow-up period was maximum of 30 days, patients were censored at 30 days even if they took the medication for longer. It is possible that patients who take longer to develop the event were selected out of the study, however, this should be minimal as physiologic changes to norepinephrine and serotonin levels occur quickly and acute cardiovascular outcomes were assessed.

Classification of exposure

Classification of exposure in our study was largely dependent on how the CPRD structure their data capture. Exposures were identified with pre-specified product codes in the CPRD, but their measurement requires the general practitioner to accurately record it in the system and for patients to take the medication when prescribed. As there is no linkage to the pharmacy dispensing data, it is unknown whether prescriptions were filled after it was prescribed by the general practitioner. In addition, both tramadol and codeine are often used as needed for pain

where administration is largely patient dependent. Due to wide range of dosing regimens, it is possible that patients could have taken more than the intended dose or little to none of the pain medication. As prescription data from specialists are not recorded in the CPRD, we would not be able to capture users who received their initial prescription from the specialists, thus missing the etiologically-relevant time-window and the possibility of classifying prevalent users as new users when the prescriptions were continued by their general practitioners. These scenarios discussed above would result in non-differential misclassification of the exposure as they would affect both codeine and tramadol equally. As a result, this would bias the effect towards the null, which is a possible explanation of the observed null results.

Combination products containing low doses of codeine are available over the counter in United Kingdom, whereas all combination products containing tramadol requires a prescription. Exposure to these formulations would not be recorded in the CPRD and new users of codeine may have had previous exposure to codeine over the counter, thus result in differential misclassification of exposure. This would bias the effect estimates away from the null. In our sensitivity analyses, we excluded any prescription combination products containing tramadol or codeine to ensure the effect shown is not due to any other components of the medication. This decreased the sample size significantly to 294,628 but the results were consistent with those of the main analysis. Finally, the follow-up period was extended to 60 days to ensure outcomes were not missed if the cardiovascular effect was due to cumulative exposure to tramadol or codeine.

Measurement of outcome

Several steps were taken to ensure the measurement of outcomes were appropriate and accurate. Variable definitions of outcomes were extensively searched and compared to ensure the

ICD codes were comprehensive and accurate. Furthermore, the outcomes of the study were defined by hospitalization or death to ensure only clinically important outcomes were identified. In addition, we preformed several sensitivity analyses to assess outcome misclassification. First, outcome of hospitalization was restricted to diagnostic code in the primary position. Second, inclusion of ONS data with underlying cause of death was added to hospitalization with diagnostic code in the primary position. The results of all the sensitivity analyses agreed with the primary analysis demonstrating no difference in the risk of MI when comparing the use of tramadol to codeine.

Bias due to missing data

Data were missing in 33% of patients for BMI, 17% of patients for smoking, and 41% of patients for blood pressure. Missing data for these variables were included through the use of an indicator variable in our propensity score. As point estimate of the outcomes were analyzed using the HDPS deciles as oppose to the individual variables, the missing data had little effect on the results as it is not missing in the model. We also conducted a sensitivity analysis using multiple imputation for missing data for our primary outcome of myocardial infarction, which showed our results to be consistent.

Implications of this study

This study was particularly important in the presence of increased use of tramadol globally due to its perceived low risk of misuse and abuse. We were able to demonstrate its null effect on atherosclerosis and arterial ischemia of the cardiovascular system compared to codeine. It provides reassurance that tramadol can be used safely with no concern for arterial ischemia despite its effect on the serotonin and norepinephrine receptors. Thus, it remains an option for the management of acute and chronic moderate to moderately severe pain in patients seeking

additional pain relief after trials of acetaminophen and NSAIDs. Tramadol may also be effective for patients who received inadequate analgesia from codeine due to its multimodal mechanism to relieve pain. There is less cases of respiratory depression for tramadol at normal doses compared to other opioids,[115-117] making it a better alternative in patients with breathing difficulties such as chronic obstructive pulmonary disease. All opioids possess high risk of adverse effects as described previously. Benefits and risks of opioid therapy must be weighed carefully before initiation.

The major limitation of this study is that we are unsure of the amount of medications the included patients actually took, as is the case for majority of studies conducted using administrative databases. This is also difficult as both tramadol and codeine can be taken on an 'as needed' basis for pain where dosing may fluctuate day to day. The uncertainty may have contributed to our null finding as non-differential misclassification bias the effect estimates towards the null. Future studies that could monitor actual intake of tramadol and codeine could be helpful to confirm our study findings. It is also not known how tramadol's multimodal mechanism of action on serotonin and norepinephrine receptors would affect the heart rhythm. Further research is required to explore the association of arrhythmia (atrial fibrillation and ventricular arrhythmia) and sudden cardiac death due to tramadol's QT-prolonging effect and risk of serotonin syndrome. This will be part of our future investigation to fill in this gap in knowledge.

Chapter 6: Conclusions

The objective of this thesis was to compare the rate of adverse cardiovascular events with use of tramadol to that of codeine among patients with acute or chronic non-cancer pain. This was achieved through a retrospective population-based cohort study using data from the CPRD. Despite strong biological plausibility, I found no evidence of an association between tramadol use and risk of adverse cardiovascular events, including myocardial infarction, unstable angina, ischemic stroke, coronary revascularization, cardiovascular death, and all-cause mortality when compared to codeine. These results provide important reassurance regarding the cardiovascular safety of tramadol. Nonetheless, prescriptions for both medications should be used judiciously based on the risks and benefits of current treatment in the presence of the ongoing opioid epidemic.

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Supplementary A. Additional Tables

Table 1. Search strategy of tramadol and cardiovascular events conducted in PubMed

Search Number	Search Terms
1	"tramadol"[Mesh] OR tramadol[tw]
2	"Myocardial Infarction"[Mesh] OR myocardial infarction[tw] OR heart attack[tw] OR "Coronary Thrombosis"[Mesh] OR "Coronary Occlusion"[Mesh] OR "Acute Coronary Syndrome"[Mesh]
3	"Angina, Unstable"[Mesh] OR unstable angina[tw] OR angina at rest[tw]
4	"Percutaneous Coronary Intervention"[Mesh] OR percutaneous coronary intervention[tw] OR coronary revascularization[tw]
5	"Stroke"[Mesh] OR ischemic stroke[tw] OR cerebrovascular accident[tw] or cerebral embolism[tw]
6	"Venous Thromboembolism"[Mesh] OR "Venous Thrombosis"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Thromboembolism"[Mesh] OR "Thrombosis"[Mesh] OR "Upper Extremity Deep Vein Thrombosis"[Mesh] OR deep vein thrombosis[tw] OR pulmonary embolism[tw] OR venous thromboembolism[tw]
7	"Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR atrial fibrillation[tw] OR atrial flutter[tw] OR supraventricular arrhythmia[tw] OR atrial arrhythmia[tw]
8	"Arrhythmias, Cardiac"[Mesh] OR cardiac arrhythmias[tw] OR cardiac dysrhythmia[tw] OR ventricular arrhythmia[tw] OR asystole[tw]
9	"Ventricular Fibrillation"[Mesh] OR ventricular fibrillation[tw] OR "Torsades de Pointes"[Mesh] OR torsades de pointes[tw] OR "Ventricular Flutter"[Mesh] OR ventricular flutter[tw] OR "Tachycardia, Ventricular"[Mesh] or ventricular tachycardia[tw]
10	"Out-of-Hospital Cardiac Arrest"[Mesh] OR out of hospital cardiac arrest[tw] OR "Heart Arrest"[Mesh] OR heart arrest[tw] OR cardiac arrest[tw] OR circulatory arrest[tw]
11	"Death, Sudden, Cardiac"[Mesh] OR sudden cardiac death[tw] OR sudden death[tw] OR cardiac death[tw] OR cardiovascular death[tw]
12	Search #2 OR Search #3 OR ….. Search #11
13	Search #1 AND Search #12

Table 2. Variable definitions for exposure, outcome, and covariates

Variable	Previously defined	Newly defined
Exposure		
Tramadol	X	
Codeine	X	
Outcome		
MI		X
Unstable angina		X
Ischemic stroke		X
Coronary revascularization		X
Cardiovascular death		X
All-cause mortality	X	
Censoring		
Cancer or cancer treatment	X	
Covariates		
Alcohol related disorders	X	
Anxiety		X
Coronary artery disease	X	
Chronic kidney disease		X
COPD	X	
Diabetes	X	
Depression	X	
Dyslipidemia		X
Heart failure	X	
Hypertension	X	
Peripheral vascular disease	X	
Liver cirrhosis	X	
Sleep apnea	X	
Rheumatoid arthritis		X
History of myocardial infarction		X
History of arrhythmia		X
History of cerebrovascular disease	X	
History of venous thromboembolism		X
History of coronary revascularization		X
BMI	X	
Smoker	X	
Indication for opioid	X	
Medications		
Aspirin	X	
Other anti-platelets	X	
Anticoagulants		X
ACE inhibitors	X	
ARBs	X	
Calcium channel blockers	X	

Beta-blockers	X	
Loop diuretics	X	
Potassium-sparing diuretics	X	
Thiazide diuretics	X	
Statins	X	
SNRIs		X
SSRIs		X
TCAs		X
MOAIs		X
Non-ASA NSAIDs	X	
Opioids [other than tramadol or codeine]	X	
CYP2D6 inducers		X
CYP2D6 inhibitors		X

Supplementary B. Ethics approval

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CENTRE DE RÉADAPTATION CONSTANCE-LETHBRIDGE REHABILITATION CENTRE
CENTRE DE RÉADAPTATION MAB-MACKAY REHABILITATION CENTRE
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CLSC MÉTRO
CLSC DE PARC-EXTENSION
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October 24, 2017

Dr. Samy Suissa
Centre for Clinical Epidemiology
Jewish General Hospital
Contact: Marisa Mancini

SUBJECT: **Ethics Protocol: CODIM-MBM 17-161**
Title: "The adverse effects of tramadol"

Dear Dr. Suissa,

Thank you for submitting the following documents pertaining to the above-mentioned study to the Research Review Office:

- Protocol (August 8, 2016)
- ISAC Evaluation of Protocols for Research Involving CPRD Data-Approval, 11/10/2017

The Research Ethics Committees of the West-Central Montreal Health (Federalwide Assurance Number: 0796) are designated by the province (MSSS) and follows the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), the membership requirements for Research Ethics Boards defined in Part C Division 5 of the Food and Drugs Regulations; acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

As this study involves no more than minimal risk in accordance with TCPS 2 article 6.12, this protocol received a delegated research ethics review. We are pleased to inform you that the above-mentioned documents are granted Delegated Approval for the period of one year.

For quality assurance purposes, you must use the "Research Ethics Approval" stamped consent

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Montreal*

form when obtaining consent by making copies of the enclosed one. For your information, the above-mentioned protocol will be presented for corroborative approval at the next meeting of the **MBM** Research Ethics Committee to be held on November 10, 2017.

Please note that it is the Investigator's responsibility to ensure that all necessary final approval letters (Feasibility) are granted before the study can be initiated at our site.

Delegated Approval Date:	**October 24, 2017**
Expiration date of Delegated Approval:	**October 23, 2018**

Your "Continuing Review Application" must be received by the Research Review Office one month before the expiration date above in order to ensure timely review. Otherwise, the study will be terminated.

Respectfully,

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Medical/Biomedical Research Ethics Committee

Resource for this project:
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