"Comparative safety study of tramadol and codeine users: a population-based cohort study."

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ABSTRACT

Background: Despite the growing awareness of the harms produced by chronic opioid use, tramadol is still favorably recommended by remarkable clinical guidelines even as a first line therapy in certain subgroup of patients such as those with high cardiovascular risk. Objectives1. To assess the incidence of adverse events among incident users of tramadol compared to codeine users among subjects ≥ 18 years old in Catalonia, Spain 2. To investigate the association between tramadol used with currently prescribed dosages and one year risk of cardiovascular diseases, fractures and mortality Methods: population-based cohort study (SIDIAP database). Inclusion criteria: all incident users of study drugs (tramadol/codeine) (2007-2017) with no use in the previous year and ≥18 years old, ≥1 year of valid data. Exclusions: Combined dispensation of tramadol and codeine in the same day. Subjects with any of the outcome events of interest (ICD-10 in annex) at the index date. Follow-up: (latest of) start of the study period or 1-year of valid data until (earliest of) end of enrolment, date of last capturing data, event of interest or end of follow-up. We used a new-user cohort design, in with

patients were followed from the first tramadol prescription (study entry) up to one year after the initiation and a case-control design nested in the new user's cohort. We classified the one-year cumulative tramadol doses (nDDD) into seven categories. Patients with the outcome (cases) were 1:5 matched to those without the outcome (controls) using Propensity Score derived from their baseline characteristics.

Exposures: Incident tramadol or codeine (active comparator). Outcomes: Composite cardiovascular events (cardiac arrythmia, heart failure, myocardial infarction, stroke), delirium, fractures (hip, pelvis, wrist, humerus), falls, sleep disorders (sleep apnea, somnolence), constipation, opioid dependence/abuse, all-cause mortality. Confounders: Age, sex, geographic region, BMI (WHO classification), socioeconomic status (MEDEA), life style factors (alcohol and tobacco status); Medical conditions: Charlson comorbidity index (CCI), cancer, pulmonary oedema, peripheral vascular disease, diabetes (type 1 and 2), diarrhea, malabsorption disorders, COPD, chronic cough, neurologic pathologies (migraine), burn injuries, chronic musculoskeletal pain disorders, rheumatologic disorders, cardiovascular events (angina, TIA), Alzheimer and Parkinson disease, chronic liver and chronic kidney disease, major surgeries; medications (ATC codes): hypnotics, benzodiazepines, aspirin, SSRI, anticonvulsant. ATCs prescribed, GP visits, hospital admissions and traffic accidents.

Statistics: Incidence rates (IR), absolute rate difference (RDs), and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using cause-specific Cox proportional hazards regression model accounting for competing risk of death. Propensity-score (PS) matching was used to minimize confounding. The logistic regression was used to compute odd ratios in the nested case control study.

KEY WORDS: tramadol, adverse events, primary care

BACKGROUND

Opioids act as pain relievers through the interaction with the opioid receptor on nerve cells in the brain and nervous system. Traditionally these drugs were used to relieve pain in cancer patients, however, in the late 90s', concerns on the lack of pain relief on certain non-cancer patients broadened the prescription of these drugs for the treatment of acute, end-of life and non-cancer pain. This led to a fourfold increase in the sales of opioids in the United States from 1999 to 2010 [1], with 6.9% of the adults in 2011-2012 reporting use of opioids in the last 30 days [2]. The increase in the use of these drugs also affected Spain; the Spanish Agency of Drugs and Health Products (AEMPs) reported that between 2008 and 2015 the use of opioids increased an 83.5% [3] and more recent reports reflect an increase of weak opioids, such as tramadol [4].

Despite the growing awareness of the harms produced by chronic opioid use [5], tramadol is still favorably recommended by remarkable clinical guidelines [6-8] even as a first line therapy in certain subgroup of patients such as those with high cardiovascular risk [9]. As a result, tramadol prescriptions have seen a substantial surge around the world. For example, tramadol is the top utilized opioid in the UK [10], the Netherlands [11], Denmark, Sweden and Norway [12]. In the United States, though not used as commonly as in European countries, prescriptions of tramadol had continuously increased by 22.8% between 2012 and 2015[13].

Serious adverse events related to tramadol overdose is well established, but current evidence regarding potential harms attributed to the standard tramadol use is inconclusive [14-15], which in fact may lead to more safety issues than its overdose or abuse from the population level. A few case studies have reported that tramadol can possibly cause or exacerbate fatal acute cardiovascular events [16-17]. Concerns for tramadol safety have been recently raised by two large observational studies suggesting

tramadol therapy was associated with increased risks of all-cause mortality [18] compared to NSAIDs and prolonged opioid use compared to even strong opioids [19]. Considering the growing and favorable use of tramadol to treat a wide range of pain conditions, especially escalating chronic non-cancer pains. It is crucial to comprehensively assess the safety profile of tramadol to help re-weight its beneficial analgesic effects against potential harms. The objectives of this large population-based cohort study was to 1) examine whether use of tramadol is associated with comparable or elevated risks of previously reported adverse events than codeine, another weak potency opioid 2) investigate whether the risks were consistent across various pain conditions in adults and 3) investigate the association between tramadol used with the current doses and one-year risks of CVD, fractures and mortality.

HYPOTHESIS:

Adverse events are more frequently diagnosed among tramadol users compared to codeine users.

Adverse events are more frequently diagnosed among those who take higher doses of tramadol.

OBJECTIVES:

1-To assess the incidence of adverse events among incident users of tramadol compared to codeine users among subjects ≥ 18 years old in Catalonia, Spain.

2-To investigated the association between tramadol used with presently recommended doses and one-year risks of CVDs, fractures and mortality.

The objective 1 will be addressed for the overall population but also after stratification by indication (muscle-skeletal diagnosis vs others), sex and age (≥18 to <44, ≥44 to <64, ≥ 64 and over)

METHODS:

Study design:

We will use a population-based cohort study which will encompass first two cohorts:

1-Incident tramadol users

2- incident codeine users (active comparator)

For the assessment of adverse event with the currently prescribed tramadol doses, a cohort of new-tramadol users will be created and followed for 1 year and a nested cases-control study will be carried out in this new-tramadol users' cohort. Cases will be those with the outcome (CVD, fractures or mortality) and controls those without the outcome matched by Propensity score based on their baseline characteristics.

In the new-user cohort design, patients will be followed from the first tramadol prescription (study entry) up to one year after the initiation, and a case-control design nested in the new-user cohort.

We will classify the one-year cumulative tramadol doses (expressed as the number of defined daily dose (nDDD)) into seven categories, including (0, 2.5], (2.5, 5], (5, 10], (10, 20], (20, 30], (30, 60], and >60.

Setting:

We will use data from the SIDIAP database. SIDIAP comprises electronic medical records of patients registered in any of the 274-participating primary health care practices in Catalonia, covering a population of 5.8 million patients (75 % of the Catalonian population in 2006) and with a total of 3414 participating general practitioners. SIDIAP encompasses the clinical and referral events registered in primary care medical records, comprehensive demographic information, prescriptions, referrals and laboratory test results and has recently been validated for OA. Health professionals gather this information using

International Statistical Classification of Diseases and Related Health Problems (ICD) 10 codes for symptoms and co-morbidities and structured spreadsheets designed for the collection of clinical and administrative variables, including country of origin, gender, age, BMI, smoking status and drinking status. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. SIDIAP is fully linked to the official pharmacy invoice database, which will be the source of data on drug utilization for the current study.

Source population:

All subjects registered for at least 1 year in the SIDIAP database during the study period.

The source population includes all users of any of the study drugs (tramadol/codeine) during the study period, aged 18 years or older at the time of therapy initiation.

Study period:

from 1st January 2007 to the 31st December 2017 (future updating of the results will be carried out when data is available)

Study population:

The study population for the drug safety study will include all incident users (with no use in the previous one year) of any of the study drugs (tramadol/codeine) during the study period aged 18 years or older at the time of therapy initiation.

For a detailed list of study drugs see annex 1

Inclusion/exclusion criteria:

Inclusion criteria:

Continuous enrolment in the database for at least 1 year previous to the inclusion in the cohort (start date).

Age 18 years or older at start date.

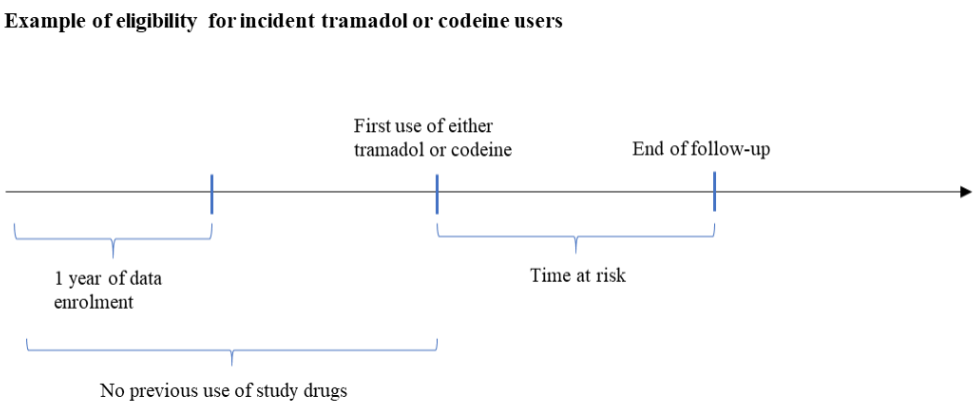
No use of both index and comparator drug (tramadol/ codeine) in the previous 1 year

Cohort construction:

COHORT 1: At least 1 pharmacy dispensations of tramadol (with no previous use of codeine either in separate dispensation or combined) dispensed (as per pharmacy invoice records) during the study period (1st January 2007 to 31st December 2017).

COHORT 2: At least 1 pharmacy dispensations of codeine (with no previous use of tramadol either in separate dispensation or combined) dispensed (as per pharmacy invoice records) during the study period (1st January 2007 to 31st December 2017).

Events will be identified through the medical records (ICD-10 Codes). Only the adverse events occurring during the exposure period will be considered (see Variable section, Outcome WP2 page 10)



Nested case control study

For the case control study nested in the new-tramadol users' cohort, cases will be those defined

as having the outcome (CVD, Fracture, mortality) and controls will be those without. They will be matched 1:5.

Exclusion criteria:

Combined dispensation of tramadol and codeine in the same day

Subjects with any of the outcome events of interest (ICD-10 in annex) at the index date

Follow-up:

Patients will be followed from the date of the incident dispensation of tramadol or codeine (index date), which follows the latest of the following dates (start date):

- Start of the study period
- One year of valid data in database

Until the earliest of:

- End of enrolment in the database (due to moving out or death)
- Date of last data capturing in the database (31st December 2019)
- Event of interest.
- End of follow-up (one year after index date or end of continuous drug use depending on the definition of time at-risk)

Variables:

Exposures (ATC in the Annex):

The main drugs of interest will tramadol and codeine (active comparator).

Patients will hence be categorized into at least one of these two exposure cohorts:

1. tramadol

2. codeine (active comparator)

If multiple new use episodes are identified for a person, we will restrict our analyses only to the first one as it is more likely to be the first-ever use episode in contrast to subsequent ones.

Exposure categorization

Incidence rates of each of the study events will be calculated during the period at-risk (One-year range after index date or continuous drug use period). In order to define periods of continuous use of study drugs, any two dispensations of the same drug will be concatenated if the gap between the end of the first of the two prescriptions and the start of the second of the two prescriptions was less than 90 days apart, a carry-over period of 30 days will be added after last prescription to account for lack of compliance and carryover effects.

Outcomes (ICD-10 in the annex):

The following outcomes will be analyzed

1. Composite cardiovascular events (cardiac arrythmia, heart failure, myocardial infarction, stroke)
2. Delirium
3. Fractures (hip, pelvis, wrist, humerus)
4. Falls
5. Sleep disorders (sleep apnea, somnolence)
6. Constipation
7. Opioid dependence/abuse
8. All-cause mortality

Events will be identified through the medical records (ICD-10 Codes in annex 3). Only the adverse events occurring during the exposure period will be considered within 1

year following the initial prescription of tramadol or its comparator codeine

Potential confounders (to be assessed in the year before index):

All potential confounders will be identified from medical records through ICD-10 codes (See table in annex 4).

General confounders:

Age

Sex

Geographic region

BMI (WHO classification)

Socioeconomic status (MEDEA)

Life style factors (alcohol and tobacco status)

Medical conditions:

Charlson comorbidity index (CCI)

Cancer (all cancers will be considered except skin cancer without metastasis) on or before cohort entry

Pulmonary oedema at cohort entry

Peripheral vascular disease on or before cohort entry

Diabetes (type 1 and 2) on or before cohort entry

Diarrhea at cohort entry

Malabsorption disorders at cohort entry

COPD on or before cohort entry

Chronic cough at cohort entry

Neurologic pathologies (migraine) at cohort entry

Burn injuries at cohort entry

Chronic musculoskeletal pain disorders (see ICD codes annex) on or before cohort entry

Rheumatologic disorders (see ICD-10 codes annex) on or before cohort entry,

Cardiovascular events (angina, TIA) at cohort entry

Alzheimer and Parkinson disease on or before cohort entry,

Chronic liver and chronic kidney disease on or before cohort entry

Charlson Comorbidity Index

Procedures: major surgeries at cohort entry

Drugs: use of specific medications at cohort entry assessed through ATC codes

(Hypnotics (ATC N05C), benzodiazepines (ATC N05B), aspirin (ATC B01AC06),

SSRI (ATC N06AB), anticonvulsant (ATC N03))

Number of different ATCs prescribed at cohort entry

Other:

Number of GP visits during the drug exposure period

Number of hospital admissions, assessed through linkage with CMBD database, during the drug exposure period

Traffic accidents assessed through ICD-10 codes, during the drug exposure period

Statistical analysis:

Unadjusted incidence rates (and 95%CIs) of each of the events of interest stratified by drug exposure cohort will be calculated. We will use both a propensity score-matched and multivariable survival analysis to compare time to first adverse event amongst new tramadol users or codeine users. Propensity score and multivariable adjustment methods will be used to address the issue of non-randomization of different opioid users with accounting for potential confounders. The propensity score represents the probability of the use of target drug, conditional on the values of observed confounding variables. We will calculate the propensity score by fitting multivariable logistic regression models

(Including potentially confounding factors). On propensity score, target drug users will be matched to active comparison drug users, using a caliper width of 0.2 SD. Any confounders with remaining imbalance between target and comparison groups even after propensity score matching will be included in the survival model. Both "intention to treatment" and "on treatment" analyses approaches will be adopted. Cox proportional hazard regression models will be used to estimate relative risk. Competing survival will be considered for the competing risk of death.

For the new users cohort study and nested case-control, time-varying Cox model will be applied to compute hazard ratios, adjusting for pre-specified covariates for the new user cohort. Whereas in the case-control design, patients with the outcome (cases) were 1:5 matched for those without outcome (control) using propensity scores derived from their baseline characteristics (see illustration below). The logistic regression model was then used to compute odds ratios.

Sample size

All subjects registered in the SIDIAP database, aged at least 18 years old who fulfil the inclusion criteria will be included in the study. In a previous feasibility study carried out to explore the expected population to be included, out of 7,251,277 subjects with data available in the SIDIAP database, 1,186,887 subjects were aged at least 18 years old and were prescribed an opioid pain killer during the period of study (2007-2016).

Missing information:

Since the underlying data represent attended medical care, we assume that absence of information of clinical events means absence of that condition. Variables with missingness will treated as categorical with a missing category.

LIMITATIONS OF THE STUDY:

Information collected from population databases such as the SIDIAP database that

nourishes itself from the information of the computerized medical records of primary care health centers have one main difference with the traditional cohort studies; there can be an under-registration of the events of interest. This classification bias is random and it could underestimate the association between the adverse events analyzed and the drug used, leading to conclusions that do not represent reality.

The information gathered from the pharmacy invoices reflects the dispensation of the medications analyzed but we are not going to be able to fully determine if the patient takes the treatment or not. However, we are only including repeated dispensations (at least 2) to overcome this limitation. At last, hospital information is only available for a subgroup of hospitals, those pertaining to the ICS ("Institut Catala de la Salut") which might lead to an underestimation of the adverse events, however, the SIDIAP database covers >80% of the primary health care centers and it is likely that subjects suffering an adverse event in an no ICS hospital will afterwards report to their general practitioner in the primary health care center and therefore the adverse events missed will be recaptured then minimizing the underestimation bias described above.

ETHICAL CONSIDERATIONS:

This study has been approved by the Ethics Committee of reference from the IDIAP Jordi Gol the 30/05/2018 with the code P18/085.

WORK PLAN:

APRIL-MAY 2018: protocol elaboration and submission to the ethical committee of reference (CR, DPA)

SEPTEMBER 2019-DECEMBER 2019: Data extraction and data management (SIDIAP team)

JANUARY-APRIL 2021- Data analysis and Drug safety study results (WP1) (JX, CR,

DPA)

MAY-JUNE 2021: 1. Analysis and internal discussion of the results (JX, CR, DPA)

JULY-SEPTEMBER: Interim report of results and writing of manuscripts for high impact journal (JX, CR, DPA, DML, CC, ADP, XNS, AT, ME)

EXPERIENCE OF THE TEAM:

The PI Carlen Reyes, has actively participated in several research projects since 2007 with different research centers (Biomedical institute San Pau (IIB Sant Pau)-Eap Sardenya and IDIAP Jordi Gol). In 2014 she obtained her thesis with 2 studies, the first a case-control multi-centric study aimed to determine the association between the proton-pump inhibitors and the incidence of fragility fracture (Bone 2013 Feb;52(2):557-61) and the second analyzing the association between the charlson comorbidity index and the hip fracture in men using the SIDIAP database (Osteoporosis International 2014. June;25(6);1751-8). From January to March 2014, she did a short-fellowship in the Nuffield Orthopedic Hospital (Oxford University) supervised by Daniel Prieto Alhambra, where she continued her epidemiological studies with the SIDIAP database with several published manuscript as a result. Since 2015, the PI works for the IDIAP Jordi Gol research institute under the supervision of Dr. Daniel Prieto Alhambra as post-doctoral researcher with whom she has collaborated and published 7 studies in high impact journals as the first author.

Junqing Xie is a DPhil student who studied preventive medicine at Shandong University (2015) and completed an MSc in Epidemiology and Biostatistics at Peking University (2018) in China. Actually, is working with Dr Prieto Alhambra in the Nuffield Department of Orthopedics, Rheumatology and Musculoskeletal Sciences (NDORMS) in Oxford. Before joining the NDORMS, he was awarded a Statistical Programming

Training Fellowship (2018-2019) in the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) based on the Big Data Institute of the University of Oxford. His DPhil research focuses on using pharmacoepidemiologic and pharmacogenomic approaches to study opioid safety.

Overall, the research team counts with more than 30 manuscripts published in high impact journals and has received several national grants for research; three grants from Barcelona city for research in primary care (2008, 2009 and 2012) and two grants from the Spanish Society of Bone Mineral Metabolism (SEIOMM) among others. Furthermore, many of the researchers pertaining to the team have received awards related to their research: Award of the Hispanic Foundation of Osteoporosis and Metabolic Illnesses (FHOEMO) in 2011 "Prevalencia de hipovitaminosis D en una población con fractura osteoporótica atendida en la Atención Primaria de Salud"), 2014 ("Factores de riesgo previos a una fractura por fragilidad y abordaje de los mismos desde la Atención Primaria de Salud") and 2016 ("Persistencia a dos años entre usuarias de distintos fármacos anti-osteoporóticos: estudio de cohortes de base poblacional"). They were also awarded with the Italofármaco award to the best communication in the SEIOMM Congress 2012("Los estadios previos al diagnóstico de la diabetes tipo 2 no afectan al riesgo de fractura: estudio de base poblacional DIAFOS"), 2015 ("Tratamiento con insulina y riesgo de fracturas óseas en pacientes con diabetes mellitus tipo 2: estudio de cohortes poblacionales apareadas por propensity score") and 2016 ("Uso de fármacos anti-osteoporosis en pacientes con DM2: estudio de cohortes de base poblacional"). Finally, two ESCEO-Health Care Provider Scholarships in 2014 and 2015, granted by the International Osteoporosis Foundation for the research works on the risk of hip fracture among type 2 diabetic patients and mortality predictors after the vertebral fracture.

FUNDING

There is no funding for this project given that it is an internal project already agreed with the technical committee. Neither the PI nor the other members of the research team have conflict of interest for this study.

APPLICABILITY AND RELEVANCE OF THE FINDINGS:

There has been an increase in the opioid prescription reported worldwide which has led to an increase in the severe adverse events secondary to the use, abuse and dependence of such drugs. There is scarcity of data regarding real incidence of adverse events linked to the use of tramadol in the Spanish population and given that these medications are mostly prescribed as pain-killers, which is a frequent consequence in many age-related chronic diseases, it is important to analyze the incidence of the most frequent adverse events in our setting using real world data. Given that there are other medications that could be prescribed as pain-killers it is also important to compare the safety of tramadol use with another weak opioid such as the codeine. The results of this study will help to better assess the real incidence of adverse events associated to the use of tramadol an codeine in our population.

RESOURCES TO CARRY OUT THE STUDY

The data for this study will be provided thanks to an internal agreement between Dr Daniel Prieto Alhambra and the IDIAP Jordi Gol foundation. The PI, Dr Carlen Reyes is nowadays working 20h/week for the IDIAP Jordi Gol, which enables her to carry out this study. Furthermore, this study is part of the DPhil research of Junqing Xie carried out actually in the NDORMS in Oxford. The other members of the research team have also agreed to collaborate to carry out this study.

REFERENCES:

1-CDC. Vital signs: Overdoses of prescription opioid pain relievers. United States, 1999–2008. MMWR 2011;60:1487–92.

2- Frenk SM, Porter KS, Paulozzi LJ. Prescription opioid analgesic use among adults: United States, 1999-2012. NCHS Data Brief 2015:1–8.

3- Departamento de medicamentos de uso humano. Utilización de medicamentos opioids en España durante el periodo 2008-2015 [document on internet]. Agencia Española de Medicamentos y Productos Sanitarios. Ministerio de Sanidad, Servicio Sociales e Igualdad. 21/02/2017. URL:https://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/opioides-2008-2015.pdf

4- Area del medicament. Informe d'utilització de medicaments opioids a Catalunya (2012-2016). Barcelona: Servei Català de la Salut. Departament de Salut. Generalitat de Catalunya; 2017

5-Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016;315(15):1624-1645. doi:10.1001/jama.2016.1464.

6-Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis & rheumatology (Hoboken, N.J.). 2020;72(2):220-233. doi:10.1002/art.41142.

7-Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017;166(7):514-530. doi:10.7326/M16-2367.

8-National Institute for Health and Care Excellence. Neuropathic pain in adults:

pharmacological management in non-specialist settings. https://www.nice.org.uk/guidance/cg173/resources/neuropathic-pain-in-adults-pharmacological-management-in-nonspecialist-settings-pdf-35109750554053. Accessed July 8, 2020.

9-destrada. guia_atencion_pacientes_dolor_opioides_mat_metodologico_aquas2018. http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2018/guia_atencion_pacientes_dolor_opioides_mat_metodologico_aquas2018.pdf. Accessed July 8, 2020.

10-Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B. Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. The Lancet Psychiatry. 2019;6(2):140-150. doi:10.1016/S2215-0366(18)30471-1.

11-Kalkman GA, Kramers C, van Dongen RT, van den Brink W, Schellekens A. Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study. The Lancet Public Health. 2019;4(10):e498-e505. doi:10.1016/S2468-2667(19)30128-8.

12- Jarlbaek L. Opioid prescribing habits differ between Denmark, Sweden and Norway - and they change over time. Scand J Pain. 2019;19(3):491-499. doi:10.1515/sjpain-2018-0342.

13- Bigal LM, Bibeau K, Dunbar S. Tramadol Prescription over a 4-Year Period in the USA. Curr Pain Headache Rep. 2019;23(10):76. doi:10.1007/s11916-019-0777-x.

14-Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4):276-286. doi:10.7326/M14-2559.

15- Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane

Reviews. Cochrane Database Syst Rev. 2017;10:CD012509.
doi:10.1002/14651858.CD012509.pub2.

16-Garrett PM. Tramadol Overdose and Serotonin Syndrome Manifesting as Acute Right Heart Dysfunction. 2004.

17-K. Michaud*, M. Augsburger, N. Romain, C. Giroud, P. Mangin ´´ Medecine Le. Fatal overdose of tramadol and alprazolam. 1999.

18-Zeng C, Dubreuil M, LaRochelle MR, et al. Association of Tramadol With All-Cause Mortality Among Patients With Osteoarthritis. JAMA. 2019;321(10):969-982. doi:10.1001/jama.2019.1347.

19-Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. BMJ. 2019;365:l1849.

ANNEXES:

1- ATC opioid codes:

ATC code	Name
N02AA59	codeine, combinations excl. psycholeptics
N02AA79	codeine, combinations with psycholeptics
N02AJ06	codeine and paracetamol
N02AJ07	codeine and acetylsalicylic acid
N02AJ08	codeine andibuprofen

N02AJ09	codeine and other non-opioid analgesics
N02AJ13	tramadol and paracetamol
N02AJ14	tramadol and dexketoprofen
N02AJ15	tramadol and other non-opioidanalgesics
N02AX02	tramadol
R05DA04	codeine

2- ICD-10 Codes for chronic musculoskeletal disorders:

Musculoskeletal medical condition	**ICD-10 code**
Osteoarthritis polyarticular	M15
Hand OA	M18 M15.2
Hip OA	M16
Knee OA	M17
Spine OA	M47.8 M47.9
Unspecific OA	M19
Rheumatoid arthritis	M06.9
Osteoporosis unspecified	M80.9

Postmenopausal osteoporosis	M80.0

Other osteoporosis	M80.8
Osteoporosis of disuse	M80.2
Idiopathic osteoporosis	M80.5
Drug-induced osteoporosis	M80.4
Postoophorectomy osteoporosis	M80.1
Fybromialgia	M79.7

3- ICD-10 Codes for adverse events:

Delirium		F05, F050, F051, F058, F059, F114, F194
Falls		V00-Y99
Opioid abuse		F11.1
Opioid dependence		F11.2
All-cause mortality		A00-Y89
Composite cardiovascular events		
Atrial fibrilation		A52.06, I48.91, I49.8
Flutter		I48.92, I49.8, I49.02
Arrytmia		I49.9
Bradiarrytmia		I49.8
Cardiac insufficiency /heart failure	Heart failure	I50*
	Heart failure, unspecified	I50.9
	Congestive heart failure	I50.0
	Congestive heart disease	I50.9
	Left ventricular failure	I50.1

	Hypertensive heart diseasewith (congestive) heart failure	I11.0

	Hypertensive heart and renal disease with (congestive) heart failure	I13.0
	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2
Myocardialinfarction	Cardiac infarction	I22*
	Cardiac infarction	I21*
	Acute myocardial infarction	I21*
	Acute myocardial infarction, unspecified	I21.9
	Myocardial infarction (acute) NOS	I21.3
	Old myocardial infarction#	I25.2
	Subsequent/recurrent myocardial infarction	I22
	Subsequent myocardial infarction of unspecified site	I22.9
	Subsequent myocardial infarction of other sites	I22.8

	Subsequent myocardial infarction of anterior wall	I22.0
	Subsequent myocardial infarction of inferior wall	I22.1
	Subsequent acute sub endocardial myocardial infarction	I22.2
	Subsequent non transmural myocardial infarction NOS	I22.2
	Subsequent myocardial infarction (acute) NOS	I22.9

	Acute sub endocardial myocardial infarction	I21.4
	Non transmural myocardial infarction	I21.4
	Acute transmural myocardial infarction of unspecified site	I21.3
	Acute transmural myocardial infarction of anterior wall	I21.0122.0
	Acute transmural myocardial infarction ofinferior wall	I21.1 I21.19122.1

	Acute transmural myocardial infarction ofother sites	I21.2 I21.29122.8
	Non-Q wave myocardial infarction NOS	I21.4 122.2
	Non-ST elevation (NSTEMI) myocardial infarction	I21.4122.2
Stroke	Stroke, not specified as hemorrhage or	I64
	Stroke NOS	I63.9
	Intracerebral haemorrhage	I61*
	Non-traumatic subarachnoidal bleeding	I60*
	Sequelae of stroke, not specified as hemorrhage or infarction	I69*
	Brain stem stroke syndrome	G46.3
	Cerebellar stroke syndrome	G46.4

	Other and unspecified intracranial haemorrhage	I62*
	Cerebral infarction	I63*
	Sequelae of stroke NOS	I69.3

Constipation	K59.00, K59.02, K59.09
Sleep disorders	
Sleep apnea	G47.30
Somnolence	R40.0
Fractures:	
Osteoporosis with pathological fracture	M80
Fracture of clavicle	S42.0
Fracture of scapula	S42.1
FRACTURE OF humerus	S42.2-S42.4
Fracture of forearm	S52
Fracture of hand	S62.0-S62.4
Fracture of thoracic vertebra	S22.0
Multiple fractures of thoracic spine	S22.1
Fracture of lumbar vertebra	S32.0
Multiple fractures of lumbar spine and pelvis	S32.7
Fracture of other part of pelvis	S32.8
Fracture of spine, level unspecified	T08
Fracture of sternum	S22.2
Fracture of rib	S22.3
Fractures of two or more ribs	S22.4
Flail chest	S22.5
Fracture of sacrum	S32.1
Fracture of coccyx	S32.2
Fracture of ilium	S32.3
Fracture of acetabulum	S32.4

Fracture of pubis	S32.5

Fracture of head and neck of femur	S72.0
Fracture femur	S72.1-S72.4
Multiple fractures of femur	S72.7
Other fractures of femur	S72.8
Fracture of femur, part unspecified	S72.9
Fracture of patella	S82.0
Fracture of tibia	S82.1-S82.8
Fracture of calcaneus	S92.0
Fracture of talus	S92.1
Fracture of other and unspecified tarsal bone(s)	S92.3

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4- ICD-10 Codes for confounders

Variable		**ICD-10 code**
Cancer		C02.4-C26.9, C30-C97
Pulmonary oedema		J81
Peripheral vascular disease		I73.9
Diabetes (Type 1 and 2)	Diabetes	E11*,E12*, E13*, E14*
	Type 1 Diabetes mellitus	E10*
Diarrhoea		K59.1
Malabsorption disorder	Intestinal malabsorption	K90*
	Intestinal malabsorption	K90.9

	unspecified	
COPD	Chronic obstructive pulmonary disease, unspecified	J44.9
	Other chronic obstructive pulmonary disease	J44
	Other specified chronic obstructive pulmonary disease	J44.8

	Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1
	Chronic obstructive pulmonary disease with acute lower respiratory infection	J44.0
Cough		R05
Dyspnea		R06.0
Neurologic pathologies (Migrane)		G43*
Burn injuries		T30.0
Angina	Angina pectoris	I20*

	Angina pectoris, unspecified	I20.9
	Angina of effort	I20.8
	Anginal syndrome	I20.9
	Cardiac angina	I20.9
	Ischemic chest pain	I20.9
	Unstable angina	I20.0
	Intermediate coronary syndrome Acute coronary syndrome	I20.0
	Angina pectoris with documented spasm	I20.1
	Other forms of angina pectoris	I20.8
TIA	Transient cerebralischemic attack, unspecified	G45.9

	TIA - Transient ischemic attack	G45.0, -G45.3
	Other transient cerebral ischemic attacks and related syndromes	G45.8
Alzheimer disease	Alzheimer disease	F00*,G30*

	Alzheimer disease unspecified	G30.9
Parkinson disease		G20, G21, G21.1, G21.2, G21.3, G21.8, G21.9, G22
Chronic Liver disease	Chronic hepatitis	K73.9
	Hepatic cirrhosis	K74.60
Chronic kidney disease	Chronic kidney disease	N18*
	Chronic kidney disease unspecified	N18.9
Traffic accidents	Traffic accident	V87.9
	With Collision	V87.7
	Without collision	V87.8

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