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

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# Administrative details

**Study description** 

<b>EU PAS number</b> EUPAS36689		
Study ID		
45210		
DARWIN EU® study		
No		
Study countries  Spain		

Despite the growing awareness of the harms produced by chronic opioid use, tramadol is still favourably recommended by remarkable clinical guidelines, therefore we aimed to assess the incidence of adverse events among incident users of tramadol compared to codeine users among subjects ≥ 18 years old in Catalonia, Spain. We conducted a population-based cohort study using the SIDIAP database (www.sidiap.org) which is a primary care database that covers over 5 million subjects in Catalonia (Spain). We included all incident users of study drugs (tramadol/codeine) (2007-2017) with no use in the previous year and  $\geq$ 18 years old,  $\geq$ 1 year of valid data. We excluded those with combined dispensation of tramadol and codeine in the same day as well as subjects with any of the outcome events of interest 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. Our exposure were incident tramadol or codeine use (active comparator) and our outcomes, a composite cardiovascular event (cardiac arrythmia, heart failure, myocardial infarction, stroke), delirium, fractures, falls, sleep disorders, constipation, opioid dependence/abuse, all-cause mortality. Confounders: sociodemographic and socioeconomic characteristics, life style factors (alcohol and tobacco status), medical conditions and drugs, ATCs prescribed, GP visits, hospital admissions and traffic accidents. We calculated the Incidence rates, absolute rate difference, and adjusted hazard ratios with 95% confidence intervals using cause-specific Cox proportional hazards regression model accounting for competing risk of death. Propensity-score matching was used to minimize confounding.

#### **Study status**

**Finalised** 

## Research institutions and networks

## **Institutions**



# Contact details

## **Study institution contact**

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Study contact

creyes@idiapjgol.info

## **Primary lead investigator**

Carlen Reyes

**Primary lead investigator** 

# Study timelines

#### Date when funding contract was signed

Planned: 28/06/2018 Actual: 28/06/2018

## Study start date

Planned: 01/09/2020 Actual: 01/09/2020

#### **Date of final study report**

Planned: 30/09/2021 Actual: 19/10/2021

# Sources of funding

Other

# More details on funding

IDIAP Jordi Gol

# Study protocol

tramadol protocol FINAL.pdf (344.25 KB)

Tramadol protocol amended.pdf (931.92 KB)

# Regulatory

Was the study required by a regulatory body?

No

#### Is the study required by a Risk Management Plan (RMP)?

Not applicable

# Methodological aspects

# Study type

# Study type list

#### **Study topic:**

Human medicinal product

Disease /health condition

#### **Study type:**

Non-interventional study

## Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness Safety study (incl. comparative)

#### **Data collection methods:**

Secondary use of data

#### Main study objective:

To assess the incidence of adverse events among incident users of tramadol compared to codeine users among subjects  $\geq$  18 years old in Catalonia, Spain.

# Study Design

#### Non-interventional study design

Cohort

# Study drug and medical condition

#### **Anatomical Therapeutic Chemical (ATC) code**

(R05DA04) codeine

codeine

(N02AA79) codeine, combinations with psycholeptics

codeine, combinations with psycholeptics

(N02AJ06) codeine and paracetamol

codeine and paracetamol

(N02AJ07) codeine and acetylsalicylic acid

codeine and acetylsalicylic acid

(N02AJ08) codeine and ibuprofen

codeine and ibuprofen

(N02AJ09) codeine and other non-opioid analgesics

codeine and other non-opioid analgesics

(N02AJ13) tramadol and paracetamol

tramadol and paracetamol

(N02AJ14) tramadol and dexketoprofen

tramadol and dexketoprofen

(N02AJ15) tramadol and other non-opioid analgesics

tramadol and other non-opioid analgesics

(N02AX02) tramadol

tramadol

#### Medical condition to be studied

Delirium

Drug abuse

Fear of falling

Drug dependence

Death

Cardiovascular disorder

Cerebrovascular accident

Constipation

Sleep disorder

Multiple fractures

# Population studied

## Short description of the study 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.

#### Age groups

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

## **Estimated number of subjects**

1186887

# Study design details

#### Data analysis plan

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. 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.

## **Documents**

#### **Study results**

JOI210102\_annotatedproof-2-2-3.pdf (1.07 MB)

# Data management

## **ENCePP Seal**

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

#### **Conflicts of interest of investigators**

coi disclosure-CR.pdf (1.2 MB)

## Data sources

#### Data source(s)

The Information System for Research in Primary Care (SIDIAP)

#### Data source(s), other

**SIDIAP** 

#### Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

Drug dispensing/prescription data

Electronic healthcare records (EHR)

Other

#### Data sources (types), other

Prescription event monitoring

# Use of a Common Data Model (CDM)

## **CDM** mapping

No

# Data quality specifications

#### **Check conformance**

Unknown

## **Check completeness**

Unknown

# **Check stability**

Unknown

# **Check logical consistency**

Unknown

# Data characterisation

## **Data characterisation conducted**

No