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

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Study Finalised

Administrative details

EU PAS number

EUPAS36689

Study ID

45210

DARWIN EU® study

No

Study countries

☐ Spain

Study description

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 ≥18 years old, ≥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

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

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Institution | **Educational Institution** | **Laboratory/Research/Testing facility** | **Not-for-profit** | **ENCePP partner**

Contact details

Study institution contact

Carlen Reyes creyes@idiapjgol.info

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 ≥ 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