Detection of therapeutic cascades associated with gabapentinoids and benzodiazepines in adults over 65 years old in Spain using BIFAP through prescription sequence symmetry analysis (GABALOOP)

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Study Planned

Administrative details

EU PAS number

EUPAS1000000241

Study ID

1000000241

DARWIN EU® study

No

Study countries

☐ Spain

Study description

Introduction: Increasing awareness of certain therapeutic cascades among healthcare professionals through evidence derived from research is crucial for their prevention. Benzodiazepines and gabapentinoids may be related to two of these cascades, and their prescription is on the rise.

Objective: The main objective is to estimate the rates of sequential drug prescription combinations in the Spanish population aged over 65 with polypharmacy, compared to the rest of the population. Secondary objectives include studying individual factors associated with these combinations.

Material and Methods: The study design is longitudinal and retrospective, using Symmetrical Sequential Prescription Analysis (SSPA). Data from the BIFAP database, which includes primary care information in Spain, will be utilized.

Variables: Prescription times of the drugs considered exposure and event, as well as clinical and sociodemographic variables related to that prescription, will be collected.

Statistical Analysis: The main characteristics of patients with cascades will be described. Sequence ratios will be calculated to identify asymmetry in prescriptions. A multilevel model will be adjusted to analyze individual factors associated with therapeutic cascades.

Discussion: Trends in prescriptions over time and the variety of indications for the studied drugs may limit some of the results. In summary, the protocol focuses on investigating the prevalence and factors associated with therapeutic cascades and polypharmacy in older adults in Spain, using BIFAP data and a symmetrical sequential prescription analysis approach.

Study status

Planned

Research institutions and networks

Institutions

Gerencia Asistencial de Atención Primaria

First published: 01/02/2024

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Institution | Hospital/Clinic/Other health care facility

Universidad Rey Juan Carlos (URJC)

Spain

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Institution | Educational Institution | Laboratory/Research/Testing facility

Networks

Las Redes de Investigación Cooperativa Orientadas a Resultados en Salud (RICORS)

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Network

RICAPP

Contact details

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Study timelines

Date when funding contract was signed

Planned: 30/04/2023

Actual: 30/08/2023

Study start date
Planned: 30/11/2023

Date of final study report
Planned: 31/12/2025

Sources of funding

- No external funding

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:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Disease epidemiology

Drug utilisation

Safety study (incl. comparative)

Study design:

A retrospective, multicenter, longitudinal study using Symmetrical Prescription Sequence Analysis (ASSP).

Main study objective:

The objective of this study is to estimate the crude and adjusted rates of sequential prescription combinations of diuretics after gabapentinoids (GABA-DA) and antivertiginous drugs after benzodiazepines (BZD-AV) in the Spanish population over 65 years old with polypharmacy, compared to the rest of the population included in BIFAP.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

PREGABALIN

Study drug International non-proprietary name (INN) or common name

PREGABALIN

Anatomical Therapeutic Chemical (ATC) code

(C03AA) Thiazides, plain

Thiazides, plain

(C03BA) Sulfonamides, plain

Sulfonamides, plain

(C03DA) Aldosterone antagonists

Aldosterone antagonists

(C03EA) Low-ceiling diuretics and potassium-sparing agents

Low-ceiling diuretics and potassium-sparing agents

(N02BF02) pregabalin

pregabalin

(N03A) ANTIEPILEPTICS

ANTIEPILEPTICS

(N05A) ANTIPSYCHOTICS

ANTIPSYCHOTICS

(N05AX) Other antipsychotics

Other antipsychotics

(N05B) ANXIOLYTICS

ANXIOLYTICS

(N05C) HYPNOTICS AND SEDATIVES

HYPNOTICS AND SEDATIVES

(N07CA) Antivertigo preparations

Antivertigo preparations

Population studied

Age groups

- Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Estimated number of subjects

20000

Study design details

Setting

All patients with more than 360 days of continuous inclusion in the BIFAP registry prior to the first prescription date of the drug classified as exposure (Appendix I) will be included. This date will determine the cohort entry date, and patients must have at least 180 days of follow-up after this date and remain in the database from the cohort entry date. A drug-free period of 180 days prior to the cohort entry date will be required. The result/event drug will be accepted if initiated within 90 days before or after the cohort entry date. Patients prescribed both the exposure and result drugs simultaneously on the same day will be excluded.

Comparators

Benzodiaceipnes-Antivertiginous drugs

Outcomes

Prescription Cascade

Data analysis plan

The sociodemographic and clinical characteristics of the patients will be described using the mean and standard deviation for normal distributions (or median and range if skewed or non-normal) and by frequency and percentage for categorical variables.

For the symmetrical prescription sequence analysis (ASSP), the sequence ratio, which measures the asymmetry of two specific sequences, will be calculated. This requires identifying new users of both drugs. This analysis was introduced by Petri in 1998 as a rapid cohort crossover method to detect drug-related safety events. It will be calculated by dividing the number of people for whom the event drug was initiated after the exposure drug by the number of people for whom the exposure drug was prescribed after the event drug. Calculated weekly throughout the year, a symmetrical pattern in the distribution of event drug initiation before and after the start of an exposure drug would be expected in the absence of an association. If the event is a very small proportion, the association may be attenuated; therefore, the entire accessible Spanish population is also studied. To minimize the effect of a trend change in the prescription of any of the drugs (gabapentinoids and benzodiazepines, which have increased in recent years), a null effect sequence ratio will be calculated for the background prescription rate of the medications, and adjusted rates will be compared with the population over 65 years old, where a higher risk of diuretic prescription compared to the rest has been observed in other studies (polypharmacy patients <65 years old and non-polypharmacy patients of any age).

To study the factors associated with presenting a therapeutic cascade , a mixed-effects multilevel logistic regression model will be adjusted, using the anonymized physician as a random effect, assuming the physician as the main prescriber, and adjusted for the rest of the first-level variables as fixed effects (independent variables).

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.

Data sources

Data source(s)

Hospitalizations database (Spain)

BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)

Data sources (types)

Drug dispensing/prescription data

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after creation of study variables