Study Protocol

P3-C1-012

DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics

16/12/2024

Version 4.0

Contents

Study Title	DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics
Protocol version	V4.0
Date	16/12/2024
EU PAS number	EUPAS1000000330
Active substance	**Drug of interest** Common antipsychotics (ATC: N05A) Substances included: • Sulpiride • Quetiapine • Risperidone • Olanzapine • Haloperidol • Aripiprazole • Piamperone • Prothipendyl • Prochlorperazine • Chlorprothixene • Promazine • Paliperidone • Zuclopenthixol • Clozapine • Fluspirilene • Amisulpride • Fluphenazine • Perphenazine • Pimozide • Ziprasidone
Medicinal product	Not applicable
Research question and objectives	Study Objectives: 1. To characterise individuals in the general population with first use of common antipsychotic initiation in terms of age, gender, indication and comorbidities. 2. To measure trends in the incidence of antipsychotic prescribing in individuals overall, by typical/atypical grouping and by 20 most common individual drug substances. Results will be stratified by

	database, calendar year, age group (<65, 65-74, 75-84, ≥85) and sex. 3. To characterise first use of antipsychotic drug therapy in individuals after initiation by drug substance (in terms of dose and duration). Results will be stratified by drug route, age and sex. 4. To measure overall survival in the general population with first use of antipsychotic overall, for typical/atypical grouping and for the top 20 most common drug substances.
Countries of study	Spain, Netherlands, Denmark, Germany, Belgium, Croatia
Authors	W.Wang, M.Pineda-Moncusí

LIST OF ABBREVIATIONS

Acronyms/terms	Description
BPSD	Behavioural and Psychological Symptoms of Dementia
CHI	Catalan Health Institute
CDM	Common Data Model
DA	Disease Analyzer
DARWIN EU	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
ID	Index Date
IPCI	Integrated Primary Care Information Project
IQR	Interquartile Range
LPD	Longitudinal Patient Database
NAJS	Croatian National Public Health Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

1. TITLE

DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Marta Pineda Moncusí Edward Burn	University of Oxford
Data Scientist	Mike Du Edward Burn	University of Oxford
Epidemiologist	Wanning Wang Daniel Prieto Alhambra	University of Oxford University of Oxford/Erasmus MC University
Clinical Domain Expert	Danielle Newby	University of Oxford
Data Analyst	Mike Du	University of Oxford
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Talita Duarte	SIDIAP
	Anna Palomar	
	Irene López Sánchez	
	Agustina Giuliodori	
	Katia Verhamme	IPCI
	Claus Møldrup Elvira Bräuner Susanne Bruun	DK-DHR
	Dina Vojinovic	IQVIA DA Germany, IQVIA LPD Belgium
	Isabella Kaczmarczyk	
	James Brash	
	Gargi Jadhav	
	Akram Mendez	
	Hanne van Ballegooijen	
	Pero Ivanko	NAJS
	Marko Čavlina	
	Antea Jezidžić	
	Emanuel Brađašević	
	Lucija Raič	

*Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

3. ABSTRACT

Title

DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics

Rationale and background

Antipsychotic drugs have been associated with several adverse drug reactions, particularly in the elderly. Somnolence, hypotension, extrapyramidal side effects and gait abnormalities are well-recognised side effects that may in turn contribute to the risk of falls and fracture in elderly persons (1). Similarly, cardiovascular adverse effects, falls and injuries may increase mortality.

Antipsychotic drugs are indicated for the management of schizophrenia and bipolar disorder. Antipsychotics are also used to manage behavioural and psychological symptoms of dementia (BPSD) and recommendations over their use suggest they should be discontinued after BPSD symptoms resolve. Safety concerns have previously led to regulatory warnings and risk communications over their use (2,3).

Antipsychotic drugs can be classified into typical and atypical antipsychotics with different recommendations for their use. For example, guidelines recommend the preferential use of atypical antipsychotics when required for the management of BPSD (4).

The rationale of the study is to provide an overview of common antipsychotic prescribing in Europe, and to describe the characteristics of patients initiating antipsychotics. This may help to contextualize information contained in future antipsychotic periodic safety update reports.

Research question and objectives

1. To characterise individuals in the general population with first use of common antipsychotic initiation in terms of age, gender, indication and comorbidities.
2. To measure trends in the incidence of antipsychotic prescribing in individuals overall, by typical/atypical grouping and by 20 most common individual drug substances. Results will be stratified by database, calendar year, age group (<65, 65-74, 75-84, ≥85) and sex.
3. To characterise first use of antipsychotic drug therapy in individuals after initiation by drug substance (in terms of dose and duration). Results will be stratified by drug route, age and sex.
4. To measure overall survival in the general population with first use of antipsychotic overall, for typical/atypical grouping and for top 20 most common drug substances.

Methods

Study design

- New user cohort study (Objective 1 and 4, Patient-level antipsychotic utilisation)
- Population level cohort study (Objective 2, Population-level antipsychotic drug utilisation)
- New user cohort study (Objective 3, Patient-level characterisation)

Population

Population-level antipsychotic utilisation: all individuals between 01/01/2013 and 31/12/2023, with at least 365 days of prior history before the day they become eligible for study inclusion. For incidence, anyone with prior use of antipsychotic/s of interest will be excluded from the analysis.

Patient-level antipsychotic drug utilisation and patient-level characterisation: New users of antipsychotic drugs in the period between 01/01/2013 and 31/12/2023 (or latest date available), with at least 365 days

of visibility prior to the date of their first antipsychotic prescription and no prior use of the respective antipsychotic drug/s.

Variables

Drugs of interest: Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone

Data sources

- SIDIAP (Spain, Primary Care Database) [Objective 1 to 4]
- IPCI (Netherlands, Primary Care Database) [Objective 1 to 4]
- DK-DHR (Denmark, National Registry) [Objective 1 to 4]
- IQVIA DA Germany (Primary and Secondary care database) [Objective 1 to 3]
- IQVIA LPD Belgium (Primary and Secondary care database) [Objective 1 to 3]
- NAJS Croatia (Croatia, National Registry) [Objective 1 and 2]

Statistical analysis

Population-level antipsychotic utilisation, patient-level antipsychotic drug utilisation, and patient-level characterisation will be conducted in databases based on data availability.

Population-level antipsychotic utilisation: annual antipsychotic use incidence rates per 100,000 person years will be estimated overall, by typical/atypical grouping and by top 20 individual drug substances. Results will be stratified by database, calendar year, age and sex.

Patient-level antipsychotic drug utilisation: patient-level characterisation of new antipsychotic users will be conducted at index date (date of first prescription of the antipsychotic of interest), including patient demographics. Records of dementia, schizophrenia, bipolar disorder, depression and insomnia in the week/month or any time before antipsychotic initiation will be used as a proxy for indication and will be reported as proportions.

Initial and cumulative dose and treatment duration will be estimated for the first treatment era and the median [IQR] will be provided. Results will be stratified by drug route (restricting to antipsychotic with systemic routes).

Survival analyses using Kaplan-Meier curves for 1 year mortality will be conducted to estimate the probability of overall survival in new users of antipsychotic drugs overall, by typical/atypical grouping and by top 20 individual drug substances.

For all analyses a minimum cell counts of 5 will be used when reporting results, with any smaller counts will be noted as <5.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverables	Timelines
Draft Study Protocol	26/08/2024
Final Study Protocol	September 2024
Creation of Analytical code	October 2024
Execution of Analytical Code on the data	October 2024
Draft Study Report	November
Final Study Report	End of November 2024

6. RATIONALE AND BACKGROUND

Antipsychotic drugs have been associated with several adverse drug reactions, particularly in the elderly. Somnolence, hypotension, extrapyramidal side effects and gait abnormalities are well-recognised side effects that may in turn contribute to the risk of falls and fracture in elderly persons (1). Similarly, cardiovascular adverse effects, falls and injuries may increase mortality.

Antipsychotic drugs are indicated for the management of schizophrenia and bipolar disorder. Antipsychotics are also used to manage behavioural and psychological symptoms of dementia (BPSD) and recommendations over their use suggest they should be discontinued after BPSD symptoms resolve. Safety concerns have previously led to regulatory warnings and risk communications over their use (2,3).

Antipsychotic drugs can be classified into typical and atypical antipsychotics with different recommendations for their use. For example, guidelines recommend the preferential use of atypical antipsychotics when required for the management of BPSD (4).

The rationale of the study is to provide an overview of common antipsychotic prescribing in Europe, and to describe the characteristics of patients initiating antipsychotics. This may help to contextualize information contained in future antipsychotic periodic safety update reports.

7. RESEARCH QUESTION AND OBJECTIVES

Description of the proposed objectives to be achieved in the study (**Table 1**).

Table 1. Research questions and objectives.

A. Objective 1.

Objective:	To characterise individuals in the general population with first use of common antipsychotic initiation in terms of age, gender, indication and comorbidities.
Hypothesis:	Not applicable
Population:	New users will be defined as having prescription of an antipsychotic (overall or typical/atypical antipsychotic use) in the period between 1/1/2013 and 31/12/2023 with 1 year of prior data availability and no prior use of the respective antipsychotic drug/s.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone)
Comparator:	None
Outcome:	None
Time:	Follow-up will start on the date of incident antipsychotic prescription and/or dispensation (index date). End of follow-up will be defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2023).
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark], NAJS [Croatia]
Main measure of effect:	We will describe demographic characteristics including age, sex, comorbidities, and assess the proportion of new users with a record of dementia, schizophrenia, bipolar disorder, depression and insomnia in the week, month or any time before index date as a proxy for indication.

B. Objective 2.

Objective:	To measure trends in the incidence of antipsychotic prescribing in individuals overall, by typical/atypical grouping and by 20 most common individual drug substances. Results will be stratified by

	database, calendar year, age group (<65, 65-74, 75-84, ≥85) and sex
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 1/1/2013 and 31/12/2023), with at least 1 year of data availability, and no prior use of the respective antipsychotic drug/s, will be included for incidence rate calculations.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on a pre-specified calendar time point, namely 1st of January for each calendar year between 2013-2023 for the calculation of annual incidence rates. End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (e.g. 31st December 2023).
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark], NAJS[Croatia]
Main measure of effect:	Incidence of antipsychotic drug use

C. Objective 3.

Objective:	To characterise first use of antipsychotic drug therapy in individuals after initiation by drug substance (in terms of dose and duration). Results will be stratified by drug route, age and sex.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 1/1/2013 and 31/12/2023 with at least 1 year of data availability, and no prior use of the respective antipsychotic drug/s, will be included.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone)

Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on the date of incident antipsychotic prescription and/or dispensation (index date). End of follow-up will be defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2023).
Setting:	Inpatient and outpatient setting using data from the following 5 data sources: IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark]
Main measure of effect:	Duration of antipsychotic use (first treatment era) expressed as median [IQR] Antipsychotics dose (cumulative and initial) expressed as median [IQR]

D. Objective 4.

Objective:	To measure overall survival in the general population with first use of antipsychotic overall, for typical/atypical grouping and for the top 20 most common drug substances.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of antipsychotics in the period between 1/1/2013 and 31/12/2023 (or latest date available, whatever comes first), with at least 1 year of data availability, and no prior use of the respective antipsychotic drug/s, will be included.
Exposure:	Common antipsychotics (Sulpiride, Quetiapine, Risperidone, Olanzapine, Haloperidol, Aripiprazole, Piamperone, Prothipendyl, Prochlorperazine, Chlorprothixene, Promazine, Paliperidone, Zuclopenthixol, Clozapine, Fluspirilene, Amisulpride, Fluphenazine, Perphenazine, Pimozide, and Ziprasidone)
Comparator:	None
Outcome:	Death
Time *(when follow up begins and ends):*	Follow-up will start on the date of incident antipsychotic prescription and/or dispensation (index date). End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2023).

Setting:	Inpatient and outpatient setting using data from the following 3 data sources: SIDIAP [Spain], IPCI [The Netherlands], DK-DHR [Denmark]
Main measure of effect:	Kaplan Meier curves to estimate 1 year probability of overall survival

8. RESEARCH METHODS

8.1 Study type and study design

Retrospective cohort studies will be conducted using routinely collected health data from 6 databases. **Table 2** describes the study types and related study designs. The study will comprise of four consecutive parts:

1. A new user cohort study will be conducted to characterise patient-level antipsychotic utilisation.

2. A population level cohort study will be used to assess incidence rates of antipsychotic use.

3. A new users cohort analyses will be used to describe patient level characterisation of antipsychotic use

4. A new users cohort study will be used to assess overall survival.

Table 2. Description of potential study types and related study designs.

Study type	Study design	Study classification
Population Level DUS	Population Level Cohort	Off the shelf
Patient Level DUS	New drug/s user cohort	Off the shelf
Patient-level characterisation	Cohort analysis	Off the shelf

8.2 Study setting and data sources

This study will be conducted using routinely collected data from 6 databases from 6 European countries. All databases were previously mapped to the OMOP CDM.

1. SIDIAP (Spain, Primary Care Database) [Objective 1 to 4]
2. IPCI (Netherlands, Primary Care Database) [Objective 1 to 4]
3. DK-DHR (Denmark, National Registry) [Objective 1 to 4]
4. IQVIA DA Germany (Primary Care database) [Objective 1 to 3]
5. IQVIA LPD Belgium (Primary Care database) [Objective 1 to 3]
6. NAJS (Croatia, National Registry) [Objective 1 and 2]

Data sources will contribute to objectives based on the available requisite data. IQVIA DA Germany, IQVIA LPD Belgium and NAJS (Croatia) will not contribute to Objective 4 (Survival analyses) as death records are not captured in these databases. Additionally, NAJS (Croatia) does not have drug utilisation details such as duration and amount/dose/strength reliably recorded and will not contribute to Objective 3.

Data sources were chosen for their wide geographical coverage as each database represents a different country. Since antipsychotics are commonly prescribed in both the inpatient and outpatient settings, the databases we chose reflect the broad prescription patterns for antipsychotics. The DK-DHR and NAJS are national registries that contain records on both in-patient hospital visits as well as primary care visits. IQVIA Germany DA contains data from primary care and specialists practicing in ambulatory care settings, whilst SIDIAP, IPCI and IQVIA LPD Belgium are primary care databases that covers wide geographic region of Europe.

Information on data source(s) planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in **Table 3**.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure (range for top 5 most commonly prescribed antipsychotics)	Data lock for the last update
Spain	SIDIAP	Database covers primary care setting where antipsychotics prescriptions are issued.	Primary Care	EHR	5.8 million	136,700 to 472,220 records	30/06/2023
Netherlands	IPCI	Database covers primary care setting where antipsychotics prescriptions are issued.	Primary Care	EHR	2.9 million	5,400 to 30,500 people	30/04/2024
Denmark	DK-DHR	Database covers primary and hospital in-patient care settings where antipsychotics prescriptions are issued.	Secondary Care and Hospital in-patient care	EHR, registries	5.8 million	146,200 to 1,163,500 records	21/5/2024
Germany	IQVIA Germany	Database covers primary and secondary care settings where antipsychotics	Primary & Secondary Care	EHR	43.1 million	38,700 to 149,100 people	30/09/2023

		prescriptions are issued.					
Belgium	IQVIA Belgium	Database covers primary care setting where antipsychotics prescriptions are issued.	Primary Care	EHR	8.5 million	3,000 to 10,800 people	31/12/2023
Croatia	NAJS	Database covers primary and hospital in-patient care settings where antipsychotics prescriptions are issued.	Primary, Secondary Care and Hospital in-patient care	Registry	3 million	48,200 to 114,400 people	17/11/2023

1) Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP] (Spain, Primary Care Database)

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymised patient records in Catalonia, Spain. The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymized patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

2) Integrated Primary Care Information [IPCI] (Netherlands, Primary Care Database)

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data from computer-based patient records of a selected group of GPs throughout the Netherlands (N=723). IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam with the objective to enable better post marketing surveillance of drugs. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardized to the Observational Medical Outcomes Partnership common data model (OMOP CDM),

enabling collaborative research in a large network of databases within the Observational Health Data Sciences and Informatics (OHDSI) community. The primary goal of IPCI is to enable medical research. In addition, reports are generated to inform GPs and their organizations about the provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation. The IPCI database is registered on the European Medicines Agency (EMA) ENCePP resources database (http://www.encepp.eu).

3) Danish Data Health Registries [DK-DHR] (Denmark, National Registry)

Danish health data is collected, stored and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so we have data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use.

In the present data base, we have access to the following registries for the entire Danish population of 5.9 million persons from 1.1.1995: The central Person Registry, The National Patient Registry, The Register of Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, The Clinical Laboratory Information Register, COVID-19 test and vaccination Registries, The complete Vaccination registry. All data registered from 1.1.1995 will be included.

4) IQVIA Disease Analyzer Germany [IQVIA DA Germany] (Primary Care database)

Germany DA is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes 39.6 M cumulative person. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilization studies.

5) IQVIA Longitudinal Patient Database Belgium [IQIVIA LPD Belgium] (Primary Care Database)

Belgium Longitudinal patient data (LPD) is collected from GP prescribing systems and contains patient records on all signs and symptoms, diagnoses and prescribed medications. The information recorded allows patients and doctors to be monitored longitudinally. Data are recorded directly in the LPD from doctors' surgeries in real-time during patient consultations via a practice management software system. It is used in studies to provide various market insights such as treatment trends, patient pathway analysis and treatment compliance. The panel of contributing physicians (a stable 300 GPs) is maintained as a representative sample of the primary care physician population in Belgium according to three criteria known to influence prescribing: age, sex and geographical distribution. Currently, the database is covering 1.1 M cumulative patients and covers from 2012 through to the present. The panel consists of a stable 300 GPs that are geographically well spread. The total number of active GPs in Belgium is 15.602. The regional geographical spread of physicians in the LPD data is also representative of the distribution across the country: 57% GPs in the North (compared to 54% nationally), 31% in the South (33% nationally) and 12% in Brussels (13%). The provider of the data has more than 2.250 GPs under contract so in case of a drop out a

replacement is easily found. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilization studies.

6) Croatian National Public Health Information System [NAJS] (Croatia, Registry)

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by Croatian Institute of Public Health. NAJS enables data collecting, processing, recording, managing and storing of health-related data from health care providers as well as production and management of health information. NAJS contains medical and public health data collected and stored in health registries and other health data collections including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others.

8.3 Study period

The study period will be from the 1st of January 2013 until the earliest of either 31st December 2023 or the latest date of data availability of the respective databases. For the population-level analyses for incidence, individuals will contribute person-time from the date they have reached at least 365 days of data availability.

8.4 Follow-up

For patient-level antipsychotic drug utilisation, follow up will start with first prescription of the antipsychotic of interest, and patients will be followed until loss to follow up, lack of data availability, death or end of study period, whichever comes first. The operational definition of follow-up is reported in **Table 4.**

For survival analyses, first time users who have 365 days of prior history will be followed from the first prescription of antipsychotics until the earliest of death, lack of data availability, 1 year follow up has been reached or end of the study period occurs.

To estimate the incidence rates, we require the appropriate population and their contributed observation time to first be identified. Thus, follow-up will start from the date they have reached at least 365 days of data availability. Study participants in the denominator population will begin contributing person time on the respective date of the latest of the following: 1) study start date, 2) date at which the observation period starts, 3) date at which the observation period has reached sufficient prior history. Participants will stop contributing person time at the earliest date of the following: 1) end of available data in each of the data sources or 2) date at which the observation period of the specific person ends.

An example of entry and exit into the denominator population for incidence rates is shown in **Figure 1**. In this example, person ID 1, and 3 are included as denominators after the study start date as all are being observed in the database from a prior date. Person ID 2 and 4 enter the study after the study start date, when they have reached sufficient prior history of 365 days. Person ID 1, 2 and 4 will be followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again on the date of their second observation period start and exits at study end date.

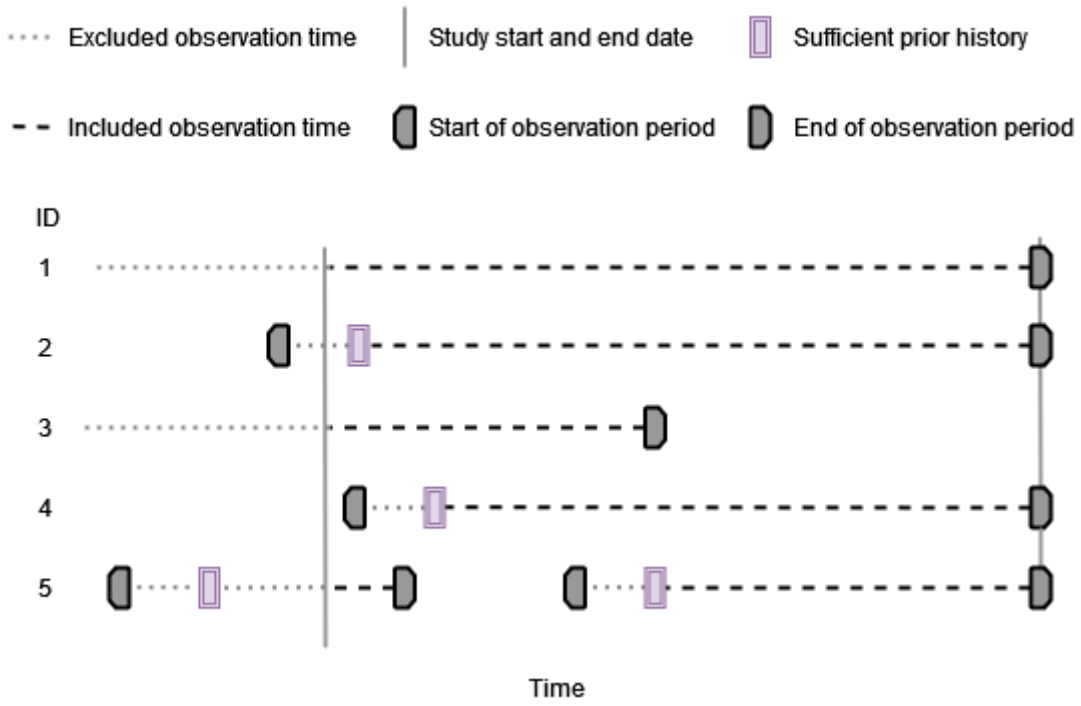

Figure 1. Included observation time for denominator population of incidence calculations .

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting	Code Type	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
All patients with incident use of medicines of interest	Patient present in the database during the study period (2013-2023) and with at least 365 days of valid database history.	Multiple	incident	[-Inf, -1]	PC, SC	n/a	n/a	Specific medicine of interest	n/a	n/a
Survival of patients with incident use of medicines of interest	Patient present in the database during the study period (2013-2023)	Multiple	incident	None	PC, SC	n/a	Death	Specific medicine of interest	n/a	n/a

PC = Primary Care, SC = Secondary Care, n/a = not applicable

8.5 Study population with inclusion and exclusion criteria

Population included in objectives 1 to 4:

The study cohort will comprise all individuals on 1st of January of each year in the period 2013-2023 (or the latest available), with at least 365 days of data availability before the day they become eligible for study inclusion. Additional eligibility criteria will be applied for the identification of new users:

When overall, no prior use of any of the common antipsychotics will be required. In other words, users with prior use of any of the antipsychotics of interest will be excluded from the analysis.

When stratified by specific antipsychotic drug, no prior use of the specific antipsychotic will be required. In other words, users with prior use of the same antipsychotic will be excluded from the analysis. The operational definitions of the inclusion criteria are presented in **Table 5**.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
All individuals on the 1st of January of each year in the period between 2013 and 2023	See under inclusion criterion	After	N/A	PC, SC	N/A	N/A	All adults within selected databases	N/A	N/A
Prior database history of 365 days	Study participants will be required to have a year of prior history observed before contributing observation time in incidence calculations, and for characterisation of new users	After	[-365, -1]	PC, SC	N/A	N/A	New users of the drugs of interest within selected databases	N/A	N/A
Washout period	New users will be required to not have used antipsychotics/the specific antipsychotic before	After	[-Inf, -1]	PC, SC	N/A	N/A	New users of the drugs of interest	N/A	N/A

[1] PC = Primary Care, SC = Secondary Care

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

n/a = not applicable

8.6 Variables

8.6.1 Exposure/s

The exposure of interest for this study is common antipsychotics (**Table 6**). Substances are included at ingredient level including combinations of the respective ingredient. The list of 20 substances accounts for around 95% of antipsychotic use across the data sources. Details of exposure are described in **Table 7**. Only the top 5 substances for each database will be included in report, the rest will be presented in the Shiny App.

For Objective 1 (Summary characterisation of new users), new users will be grouped by use of:

1) Overall use of antipsychotics
2) Typical/atypical antipsychotics

For Objective 2 (annual incidence rates) and Objective 4 (Survival analyses), exposure will be grouped by:

1) Overall use of antipsychotics
2) Typical/atypical antipsychotics
3) 20 most common individual substances per database (only the top 5 substances for each database will be included in report)

For Objective 3 (drug utilisation studies) will be by the top 20 prescribed antipsychotics (only the top 5 substances for each database will be included in report).

Table 6. List of common antipsychotics included in the study and their categorisation and use in database.

Substance Name	Typical/Atypical
Sulpiride	Atypical
Quetiapine	Atypical
Risperidone	Atypical
Olanzapine	Atypical
Haloperidol	Typical
Aripiprazole	Atypical
Pipamperone	Typical
Prothipendyl	Typical
Prochlorperazine	Typical
Chlorprothixene	Typical
Promazine	Typical
Paliperidone	Atypical
Zuclopenthixol	Typical
Clozapine	Atypical
Fluspirilene	Typical
Amisulpride	Atypical
Fluphenazine	Typical
Perphenazine	Typical
Pimozide	Typical
Ziprasidone	Atypical

*DK-DHR and NAJS not included in feasibility assessment measure. The top 5 most common antipsychotics for these databases will be determined during the analysis.

Table 7. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Common Antipsychotics	Preliminary code lists provided in Appendix 1	[-Inf, -1]	Calendar Year	PC, SC	RxNorm	N/A	All individuals who have had a prescription of the medicine of interest present in the respective databases during the study period (2013-2023)	Previous antipsychotic use	N/A	N/A

[1] PC = Primary Care, SC = Secondary Care

n/a = not applicable

8.6.2 Outcome/s

The survival analyses reporting Kaplan-Meier curves will utilise death as an outcome to evaluate 1 year survival probabilities for new users of antipsychotic drugs. Patients will be censored if they are lost to follow up, lack data availability, or the study period has ended. The operational definition of the outcomes is presented in the **Table 8**.

Table 8. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Death	1 year mortality, Kaplan-Meier curves	Yes	Time-to-event	N/A	Primary and secondary care	n/a	n/a	New users of antipsychotics	n/a	n/a

n/a = not applicable

8.6.3 Other covariates, including confounders, effect modifiers and other variables

8.6.3.1 Objective 1:

Demographic characteristics (among new users, and by typical/atypical antipsychotics) will include:

- Age
- Sex
- Indication of use: Proportion of new users with record of dementia, schizophrenia, bipolar disorder, depression and insomnia in the week/month or any time before antipsychotic-treatment initiation
- Comorbidities: chronic kidney disease, heart failure, hypertension, myocardial infarction, stroke, type 2 diabetes, obesity

8.6.3.2 Objective 2:

Incidence rates will be stratified by calendar year. Additionally, they will be stratified by:

- Age group (<65, 65-74, 75-84, ≥85 years old)
- Sex
- Typical/atypical antipsychotics
- 20 most common individual substances

8.6.3.3 Objective 3:

Drug utilisation analysis from new users of antipsychotics will include:

- Initial and cumulative dose
- Duration of use of first continuous treatment era (gap of ≤30 days between repeated prescriptions)

These will be stratified by:

- Systemic drug routes: parenteral (including "injectable" and “implant”), oral.
- Age groups: <65 years, ≥65 years
- Sex

8.6.3.4 Objective 4:

Survival analyses among new users of antipsychotics will be analysed overall and then stratified:

- Overall
- Typical/atypical antipsychotics
- Top 20 most common individual substances
- Age groups: <65 years, ≥65 years
- Sex

8.7 Study size

No sample size has been calculated. Incidence of antipsychotic use among the study population will be estimated as part of Objective 2.

8.8 Analysis

This section will describe the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data Analysis which describes the type of analysis in function of the study type. Description of type of analysis based on study type is provided in **Table 9**.

Table 9. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Population-based incidence rates
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features for new users of antipsychotic users - Frequency and % of indication/s - Estimation of median [IQR], initially prescribed or dispensed initial and cumulative dose of antipsychotics - Estimation of median [IQR] treatment duration for new users of antipsychotics
Patient-level characterisation	Off-the-shelf	- Patient-level characteristics - Survival analyses (time-to-death)

8.8.1 Federated network analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment and the Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.8.3 Patient privacy protection

Cell suppression will be applied as required by databases to protect people's privacy. Cell counts <5 will be masked.

8.8.4 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "DrugUtilization" for the patient-level drug utilisation analyses including patient-level characterisation, "IncidencePrevalence" package for the population-level estimation of drug utilisation and "CohortSurvival" for survival analyses.

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g. the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications. Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras will be considered as exposed by the first era as show in in **Figure 2.**

Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

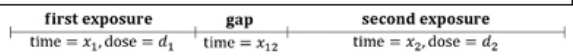

Figure 2. Gap era joint mode.

If two eras overlap, the overlap time will be considered exposed by the first era (**Figure 3**). No time will be added at the end of the combined drug era to account for the overlap.

Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

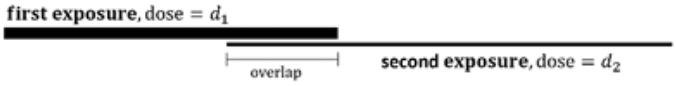

Figure 3. Gap era overlap mode.

New user cohorts

New users will be selected based on their first prescription of the respective drug of interest after the start of the study and/or in a pre-defined time window. For each patient, at least 365 days of data visibility will be required prior to that prescription. New users will be required to not have been exposed to the drug of interest any time prior the current prescription. If the index day does not fulfil the exposure washout criteria the whole exposure is eliminated.

8.8.5 Methods to derive parameters of interest

Calendar time

Calendar time will be based on the calendar year of the index prescription.

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups will be used for stratification: <65 , 65-74, 75-84, ≥85, years of age.

Indications

Indications will be determined based on recordings of 5 pre-defined conditions, namely dementia, schizophrenia, bipolar disorder, depression and insomnia, one week/month or any time before the first prescription of the respective drug (index date).

Characterisation of patient-level features (comorbidities)

Patient-level characterisation will be conducted. Covariates will be extracted for the following time intervals 30 days before index date and any time prior to index date.

Survival Analyses

To obtain Kaplan-Meier plots, patients will be followed for 1 year from their initial antipsychotic prescription to evaluate probability of survival. Deaths will be obtained from the relevant databases using OMOP CDM codes. Patients will be censored if before reaching 1 year of follow up, they were lost to follow up, lacked data availability or the study period ended.

8.8.6 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

Population-level drug utilisation study

Incidence rates will be calculated for antipsychotic treatment overall, by typical/atypical and by the 5 most common drug substances for each database.

Annual incidence rates for antipsychotic use will be calculated as the of number of new users per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) will be excluded. Those study participants who enter the denominator population will then contribute time at risk up to their first prescription (e.g. antipsychotic use) during the study period. Or if they do not have a drug exposure, they will contribute time at risk, as described above in section 8.4 (study end, end of observation period, or the last day of maximum age). An illustration of the calculation of incidence of antipsychotic use is shown below in **Figure 4**.

Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of antipsychotics. Patient ID 2 and 5 are not seen to use antipsychotics and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 is excluded from the analysis as they are seen to have had the outcome before the study start date.

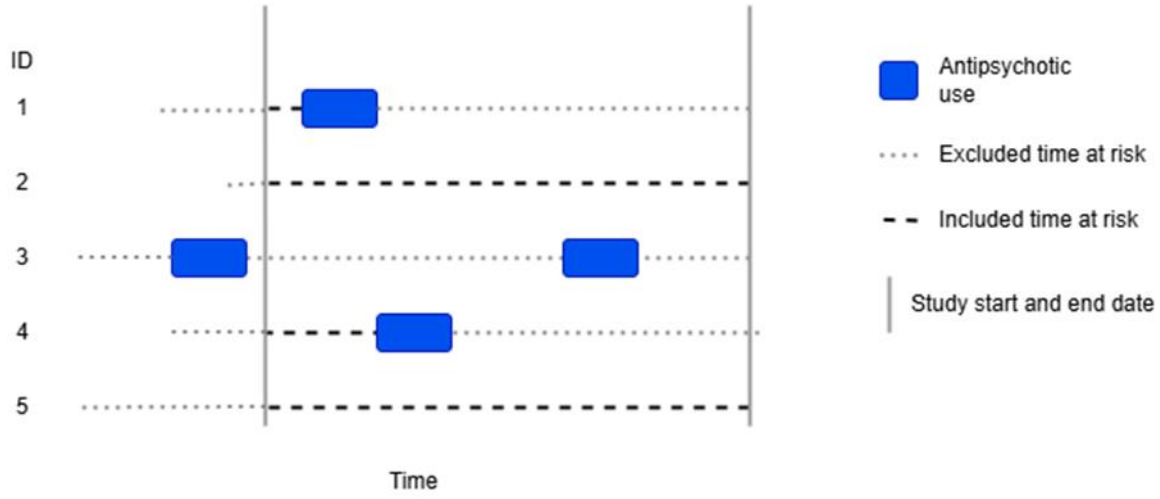

Figure 4. Incidence calculations.

Patient-level drug utilisation study

New drug user patient-level characteristics on/before index date

For each concept extracted before/at index date, the number of persons (N, %) with a record within the pre-specified time windows will be provided.

Indications and comorbidities

The number of persons (N, %) with a record of the respective indication (i.e. dementia, schizophrenia, bipolar disorder, depression and insomnia) and comorbidities will be provided. If a person has a record of more than one specific indication/comorbidity, that person will be included in both specific indication groups separately.

Initially prescribed or dispensed dose

For each prescription at index date, the prescribed dose will be retrieved from the drug_exposure tables, where the amount quantity and units are available.

The quality of recording of drug dose might be of varying quality for different databases. Therefore, data quality checks will be conducted to evaluate the quality of the recording of units, dosage (OMOP drug_exposure tables) for antipsychotics in the databases this study will be conducted in.

From this, the initial dose in the cohort will be characterised by median [IQR].

Treatment duration

Treatment duration will be calculated as the duration of the first continuous exposure episode, with less than a 30-day gap between prescriptions. Estimations of treatment duration will be summarized providing the median [IQR] treatment duration. For databases, where duration cannot be calculated due to e.g. missing information on quantity or dosing, treatment duration will not be provided.

Survival Analyses

Kaplan-Meier curves for 1-year all-cause mortality will be calculated for any new antipsychotic users, and then stratified by typical/atypical antipsychotics and the 5 most common substances per database. Kaplan-Meier curves will be used to estimate the probability of 1-year survival starting from day of treatment initiation.

8.8.7 Methods to control for potential sources of bias

None.

8.8.8 Methods to deal with missing data

None.

8.9 Evidence synthesis

Results from analyses described in Section 8.8 will be presented separately for each database and no meta-analysis of results will be conducted.

9. DATA MANAGEMENT

9.1 Data management

All databases will have been mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

This analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.2 Data storage and protection

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy. All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results. The output files are stored in the DARWIN Remote Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The RRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

10. QUALITY CONTROL

Description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of the statistical programming performed to generate the results.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected health care data and so data quality issues must be considered. In particular, a recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions around the duration of drug use will be unavoidable.

The actual reason for prescription of the drug is not recorded in any of the databases. We will assess indication via a proxy based on pre-defined conditions recorded on the date of therapy initiation. Therefore, recording of potential indication may be incomplete. In addition, the completeness of recordings of co-morbidities used for patient characterisation may vary across databases.

Additionally, prescriber speciality may also not be available in the selected databases. We will include it in the analysis when possible.

Database-specific limitations:

In IQVIA LPD Belgium and IQVIA DA Germany, the observation period of the patients in these databases is calculated based on the last visit, observation or interaction of the patient with the health care system. This methodology impacts the individuals considered “at risk” for the different drugs of interest of the study (i.e., the individuals included in the denominator populations) during the latest months of available data from the latest data lock, where healthy and/or non-frequent users of the health care system will not be

considered active. Consequently, the denominators that will be used to calculate the incident use of drugs in the population may present an artefactual decrease whilst the incident users will remain, incrementing the incidence ratios. The presence of these artefacts will be considered when interpreting the results.

In addition, IQVIA LPD Belgium, IQVIA DA Germany and NAJS Croatia databases do not report mortality, so they will be excluded from the survival analyses. Croatia NAJS does not report dose and will not be included in drug utilisation calculations. Due to the limited availability of data from these databases, we cannot produce estimates for objective 4 in case of IQVIA LPD Belgium and IQVIA DA Germany; and for objectives 3 and 4 in case of NAJS Croatia.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

13. GOVERNANCE BOARD ASPECTS

SIDIAP, IPCI,DK-DHR and NAJS will undergo their respective ethical approvals.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study Report

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the pdf report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

15. OTHER ASPECTS

None.

16. REFERENCES

1. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. The Lancet. 2019 Sep 14;394(10202):939–51.

2. Sultana J, Leal I, de Ridder M, Sturkenboom M, Trifiró G. Antipsychotic use in dementia patients in a general practice setting: a Dutch population-based study. Epidemiol Psychiatr Sci. 2016 Mar 18;25(4):403–6.

3. Guthrie B, Clark SA, Reynish EL, McCowan C, Morales DR. Differential Impact of Two Risk Communications on Antipsychotic Prescribing to People with Dementia in Scotland: Segmented Regression Time Series Analysis 2001–2011. PLOS ONE. 2013 Jul 17;8(7):e68976.

4. Frederiksen KS, Cooper C, Frisoni GB, Frölich L, Georges J, Kramberger MG, et al. A European Academy of Neurology guideline on medical management issues in dementia. Eur J Neurol. 2020;27(10):1805–20.

17. ANNEXES

Appendix I: List of Stand-Alone documents (e.g. lists with concept definitions (conditions & drugs), validation procedures, questionnaires etc.)

Appendix II: ENCePP checklist for study protocols

Appendix I: Concept List for Antipsychotic substances.

ATC Code	Substance Name	Typical/Atypical	ConceptID Ingredient
N05AL01	Sulpiride	Atypical	19136626
N05AH04	Quetiapine	Atypical	766814
N05AX08	Risperidone	Atypical	735979
N05AH03	Olanzapine	Atypical	785788
N05AD01	Haloperidol	Typical	766529
N05AX12	Aripiprazole	Atypical	757688
N05AD05	Pipamperone	Typical	19093225
N05AX07	Prothipendyl	Typical	19115044
N05AB04	Prochlorperazine	Typical	752061
N05AF03	Chlorprothixene	Typical	19095002
N05AA03	Promazine	Typical	19052903
N05AX13	Paliperidone	Atypical	703244
N05AF05	Zuclopenthixol	Typical	19010886
N05AH02	Clozapine	Atypical	800878
N05AG01	Fluspirilene	Typical	19056465
N05AL05	Amisulpride	Atypical	19057607
N05AB02	Fluphenazine	Typical	756018
N05AB03	Perphenazine	Typical	733008
N05AG02	Pimozide	Typical	745790
N05AE04	Ziprasidone	Atypical	712615

Appendix II: ENCePP checklist for study protocols.

ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title:
DARWIN EU® - Antipsychotic prescribing in the general population in Europe: a descriptive analysis of trends and patient characteristics

EU PAS Register® number: TBC
Study reference number (if applicable): P3-C1-012

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for 1.1.1 Start of data collection[1]	☒	☐	☐	5- milestones

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7 – Research questions and objectives
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
	2.1.2 The objective(s) of the study?	☒	☐	☐	
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8.5
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

[2] Date from which the analytical dataset is completely available.

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				8.3, 8.4, 8.5
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	8.6.1
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.2

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.6.2
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.6.1
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.6.2
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Appendix I
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6.2
	9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	8.7 and Appendix I
10.3	Are descriptive analyses included?	☒	☐	☐	8.8
10.4	Are stratified analyses included?	☒	☐	☐	8.8.4
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8	Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9
11.2	Are methods of quality assurance described?	☒	☐	☐	10
11.3	Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				11
	12.1.1 Selection bias?	☒	☐	☐	
	12.1.2 Information bias?	☒	☐	☐	
	12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Section 13: Ethical/data protection issues		**Yes**	**No**	**N/A**	**Section Number**
13.1	Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	13
13.2	Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	13
13.3	Have data protection requirements been described?	☒	☐	☐	13

Comments:

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Section Number**
14.1	Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☐	☒	☐	

Comments:

Name of the main author of the protocol: Wanning Wang

Date: 22/August/2024

Signature: WW