Study Report C1-002

27/03/2023

Version 2.1

TABLE OF CONTENTS

Document History

Version	Date	Description
V1.0	17/01/2023	**Final Version for EMA review**
V2.0	01/02/2023	**Revised Version of study report**
V2.1	27/03/2023	**Link to Shiny App updated**

Study Title	Drug utilisation of valproate-containing medicinal products in women of childbearing potential
Study Report Version identifier	V2.1
Dates Study Report updates	27/03/2023
EU PAS register number	EUPAS50789
Active substance	**Drug of interest** N03AG01 Valproic acid N03AG01 Sodium valproate N03AG01 Magnesium valproate N03AG01 Valproate semisodium N03AG02 Valpromide **Alternative treatments** N03AF01 Carbamazepine N03AA02 Phenobarbital N03AB02 Phenytoin N03AA03 Primidone N05BA09 Clobazam N03AE01 Clonazepam N03AF04 Eslicarbazepine acetate N03AX09 Lamotrigine N03AF02 Oxcarbazepine N03AX22 Perampanel N03AF03 Rufinamide N03AX11 Topiramate N03AX15 Zonisamide N03AX23 Brivaracetam N03AD01 Ethosuximide N03AX12 Gabapentin N03AX18 Lacosamide N03AX14 Levetiracetam N03AX16 Pregabalin N03AG06 Tiagabine N03AG04 Vigabatrin N05AN01 Lithium N05AH04 Quetiapine N05AH03 Olanzapine N03AX09 Lamotrigine C07AA05 Propranolol C07AB02 Metoprolol

	C07AB03 Atenolol C07AA12 Nadolol C07AA06 Timolol C07AB07 Bisprolol N03AX11 Topiramate N06AA09 Amitriptyline N07CA03 Flunarizine N02CX01 Pizotifen N02CX02 Clonidine
Medicinal product	NA
Research question and objectives	Study Objectives: 1. To characterise the prevalence and incidence of use of valproate, valproate containing medicines, and alternative antiepileptic therapies among women aged 12 to 55 years of age, stratified by calendar year and age 2. To characterise the use of valproic acid or valproate containing medicines among women aged 12 to 55 years of age, stratified by indication, calendar year and age
Country(-ies) of study	The study included data sources from the Netherlands, Spain, Finland, Belgium, Germany and United Kingdom
Author(s)	Dr. Annika Jödicke Dr. Albert Prats-Uribe

1. DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Principal Investigators	Dr. Annika Jödicke Dr. Albert Prats-Uribe	University of Oxford
Data Scientists	Dr. Martí Català Sabaté Dr. Edward Burn	University of Oxford
Epidemiologists	Dr. Albert Prats-Uribe Dr. Annika Jödicke	University of Oxford
Clinical Domain Experts	Prof. Daniel Prieto-Alhambra Ass. Prof. Katia Verhamme	University of Oxford Erasmus MC
Statistician	Dr. Maria de Ridder	Erasmus MC
Data Partner*	**Names**	**Organisation**
Data Partner(s)	Ass. Prof. Talita Duarte Salles	IDIAP Jordi Gol Erasmus MC
	Dr. Eeva Kronqvist Tommi Taneli Kauko	Auria Clinical Informatics, Hospital District of Southwest Finland
	James Brash	IQVIA

*Data partners' role is only to execute code at their data source, and they don't have an investigator role.

2. DATA SOURCES

This study was conducted using routinely collected data from 6 databases in 6 European countries (5 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland (ACI Varha, [former HDSF]), Finland
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

Note: From January 1st, 2023, the HDSF data has been included to Varha, which is responsible for organizing social and health services in Southwest Finland. HDSF has therefore been renamed and is referred to as ACI Varha in this report.

Detailed information on data source is described below.

Country	Name of Database	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Calendar period covered by each data source.	Contributing to Population-level DUS and/or patient-level DUS?
NL	IPCI	Primary care	EHR	1.39 million	01/01/2022	Both
ES	SIDIAP	Primary care	EHR	5.8 million	06/2022	Both
BE	IQVIA LPD Belgium	outpatient specialist care	EHR	435,200	30/06/2022	Both
DE	IQVIA DA Germany	outpatient specialist care	EHR	8.5 million	30/06/2022	Both
FI	ACI VARHA [former HDSF]	In- and outpatient special care	EHR	765,000	07/11/2022	Population-level DUS
UK	CPRD GOLD	Primary care	EHR	3 million	06/2020	Both

NL = The Netherlands, ES = Spain, BE = Belgium, DE = Germany, FI = Finland, UK = United Kingdom, IPCI = Integrated Primary Care Information Project; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, ACI VARHA = Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland, CPRD GOLD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record. Exposure is based on prescription data.

3. ABSTRACT

Title

Drug utilisation of valproate-containing medicinal products in women of childbearing potential.

Rationale and Background

Vaproic acid/valproate-containing medicines (VPA) are first-line treatment for generalised tonic-clonic seizures (epilepsy) and adjunctive therapies in other types of seizures. They are also used as second-line treatments or adjuncts for the treatment of bipolar disorder, and for migraine prevention. Valproic acid is a teratogen, with prenatal exposure carrying a substantial risk of neurodevelopmental impairment and congenital malformations in the child. Therefore, its use in women of childbearing age is restricted to prevent valproate exposure during conception and pregnancy.

The European Medicines Agency (EMA) has issued risk minimisation measures in 2014 and 2018 including a compulsory pregnancy prevention program. Timely information on the use of VPA in young women across Europe is important.

Research question and Objectives

The objectives of this study were

1. To characterise the prevalence and incidence of use of valproate, valproate containing medicines, and alternative therapies among women aged 12 to 55 years of age, stratified by calendar year and age
2. To characterise the use of valproic acid or valproate containing medicines among women aged 12 to 55 years of age, stratified by indication, calendar year and age.

Research Methods

Study design

- Population level cohort study (Objective 1, Population-level VPA utilisation)
- New user cohort study (Objective 2, Patient-level VPA utilisation)

Population

Population-level utilisation of VPA and alternative treatments: All women aged between 12 years and ≤55 years between 01/01/2010 and 31/12/2021 (or latest date available), with at least 365 days of prior history before the day they become eligible for study inclusion. For the calculation of incidence, anyone with prior use of VPA will be excluded from the analysis.

Patient-level VPA utilisation: New users of VPA in the period between 01/01/2010 and 31/12/2021 (or latest date available), with at least 365 days of visibility prior to the date of their first VPA prescription, and no used VPA in the previous 365 days.

Variables

Drug of interest ("VPA"): Valproic acid, Sodium valproate, Magnesium valproate, Valproate semisodium and Valpromide

Alternative treatments: Carbamazepine, Phenobarbital, Phenytoin, Primidone, Clobazam, Clonazepam, Eslicarbazepine acetate, Lamotrigine, Oxcarbazepine, Perampanel, Rufinamide, Topiramate, Zonisamide,

Brivaracetam, Ethosuximide, Gabapentin, Lacosamide, Levetiracetam, Pregabalin, Tiagabine, Vigabatrin [alternative antiepileptics], Lithium, Quetiapine, Olanzapine, Lamotrigine [alternatives for treatment of bipolar disorder], Propranolol, Metoprolol, Atenolol, Nadolol, Timolol, Bisprolol, Topiramate, Amitriptyline, Flunarizine, Pizotifen, Clonidine [alternatives for migraine prevention].

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland (ACI VARHA [former HDSF]), Finland
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

ACI Varha only contributed to Objective 1.

Sample size

No sample size has been calculated. Prior to study initiation, feasibility counts were generated in the general population in each database.

Data analyses

For all analyses a minimum cell count of 5 were used when reporting results, with any smaller counts suppred.

Population-level VPA utilisation: Annual period prevalence of VPA use and alternative treatments were estimated, as were annual incidence rates per 100,000 person years, stratified for age groups and calendar time.

Patient-level VPA utilisation: Large-scale patient-level characterisation was conducted. Index date was the date of the first VPA prescription for each person. Medical history was assessed for anytime - 366 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. Medication use was reported for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. The frequency of indication, namely epilepsy, bipolar disorder and migraine at index date was assessed. Initial dose/strength and treatment duration were estimated and the 25th percentile (p25), median, mean, p75 were provided. Analyses were stratified for age groups, calendar year and indication (where possible).

Results

Population-level utilisation of VPA and alternative treatments:

The incidence of new use of VPA amongst women 12 to 55 years decreased over the period 2010-2021 for all analysed datasets: ACI VARHA, CPRD GOLD, IPCI, SIDIAP, IQVIA Belgium LTD, and IQVIA Germany DA, from a maximum of 250 new users per 100,000 person years in 2010 to less than 89 in 2021.

The prevalence of use of VPA in women aged 12-55 decreased between 2010 and 2021 for most analysed datasets. In CPRD GOLD, the prevalence of use of VPA decreased steadily, going from an initial prevalence of 0.361% (0.352% to 0.369%) in 2010 to 0.243% (0.234% to 0.253%) in 2019. IQVIA Belgium LTD and IQVIA GERMANY DA also showed decreasing prevalence: from 0.158% (0.136% to 0.184%) in 2014 to 0.051% (0.038% to 0.069%) in 2022 for Belgium and from 0.037% (0.035% to 0.041%) in 2010 to 0.027% (0.025% to

0.031%) in Germany. In SIDIAP the prevalence grew from 2010 until it peaked in 2015 at 0.372% (0.363% to 0.381%), to then decrease substantially. In IPCI the incidence was stable for the period 2010-2015 at around 0.23% and then decreased in 2015-2021. By 2021, the prevalence of use of valproate in this same population was of 0.271% (0.263% to 0.279%) in SIDIAP and 0.164% (0.152% to 0.178%) in IPCI.

In all datasets the prevalence of use of VPA increased with age. The older age groups (>= 45 or more – 55 years old) had prevalences of use between 0.4% and 0.5% and remained stable or increased during the study period. Conversely, younger age groups (<45) had a lower prevalence, and which decreased over time, halving the initial prevalence at the end of the study for most databases. Incidence of use of VPA showed a decreasing pattern for all age groups in all databases.

As for alternative antiepileptics, the most prevalent treatments were pregabalin and/or gabapentin, and their prevalence increased during the study period for all databases. Prevalence of lamotrigine, lithium, olanzapine and quetiapine increased from 2010 to 2021 in all databases, with quetiapine consistently more prevalent. Amongst medicines for migraine prevention, beta blockers and amitriptyline were the most prescribed. Beta blockers use remained stable or increased during the study period for all databases except for IPCI. Incidence of amitriptyline use remained stable in all databases or decreased, but the prevalence of use increased.

Patient-level VPA utilisation:

6416, 1241,10,398, 945 and 4,002 eligible women initiated VPA within the study period in CPRD GOLD, IPCI,SIDIAP, IQVIA Belgium LPD and IQVIA Germany DA, respectively. The median age in these cohorts of women ranged between 40 and 43 years.. Healthcare utilisation was high with the median number of visits ranging between 5 in IQVIA Germany DA and 29 in CPRD. Anxiety and depressive disorders were frequent comorbidities, with 20%-39% and 16%-44% having a history of these before treatment start. The level of prescription of contraceptives was highest in CPRD GOLD, followed by IQVIA Belgium LPD, IPCI and lowest in SIDIAP and IQVIA Germany DA. Use of hormonal contraception varied greatly across age groups, with highest levels of prescriptions being observed in women between 15-39 compared to lower rates in the >50 and 12-14 year age groups.

At the date of their first VPA prescription, most women (ranging between 66% and 95% in the different databases) had no record of a diagnosis for epilepsy, bipolar disorder or migraine (except for IQVIA Belgium LPD with 27%).. Among those with a specific diagnosis recorded, migraine was the most common indication in CPRD GOLD (5.7%), whereas epilepsy was the most common indication in all other databases Notably, VPA was uncommon for migraine in SIDIAP (0.3%) and bipolar disorder in IPCI (0.7%).

Across databases, initial daily doses/strength for VPA ranged between a median 500mg/day and 875mg/day. Average treatment duration varied substantially between databases, with a median of 50 days in IQVIA Belgium LPD, 82 days, 98 days, and 100 days in CPRD GOLD, IPCI and IQVIA Germany DA, respectively, and 1 year in SIDIAP. Although initial dose did not change over the course of the study in all databases, cumulative annual use decreased in SIDIAP (from 2012 onwards) and IQVIA Germany DA (from 2019 onwards), but remained stable for CPRD GOLD, IPCI and IQVIA Belgium LPD.

Discussion

At the population level, the prevalence of use of VPA among women of childbearing age has declined since 2015 in all data sources. Incidence declined over the same period in all six databases. Conversely, alternative antiepileptics have increased in uptake in the same period, with gabapentinoids showing a more obvious increasing trend. Similarly, lamotrigine, lithium, olanzapine, quetiapine on one hand, and beta blockers and

amitriptyline on another also increased in use as alternatives for bipolar disorder treatment and migraine prevention respectively.

Our patient-level analyses showed that the indication of use of VPA is not well documented in medical records. Where recorded, migraine and epilepsy were the most common indications. Levels of prescriptions of hormonal contraceptives were low, and varied greatly across age groups and between databases, with differences between the latter potentially due to country-specific reimbursement strategies and completeness of contraception prescription recordings. Although initial dose did not change over time, cumulative annual use decreased in SIDIAP compared to the beginning of the study period and IQVIA Germany DA after 2019.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
ACI VARHA	Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland
IPCI	Integrated Primary Care Information Project
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PRAC	Pharmacovigilance Risk Assessment Committee
RMM	Risk minimisation measures
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
VPA	Valproic acid/valproate-containing medicine

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
NA				

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Final Study Protocol	01/09/2022	01/09/2022
Creation of Analytical code	09/2022-12/2022	
Execution of Analytical Code on the data	01/2023	
Interim Study Report (if applicable)	NA	NA
Final Study Report	17/01/2023	17/01/2023
Revised study report		01/02/2023
Draft Manuscript (if agreed on)		
Final Manuscript (if agreed on)		

7. RATIONALE AND BACKGROUND

Valproic acid/valproate salts are gamma-amino butyric acid (GABA) agonists, which have been used as a potent anti-epileptic agent since the mid-1960s[1 2]. Valproic acid/valproate-containing medicines (VPA) are currently recommended as first-line treatment for generalised tonic-clonic seizures, and as an adjunctive therapy for other types of seizures. In the late 2000s, their indication was extended to include treatment of manic episodes in bipolar disorder, and in some countries, they are also used for migraine prevention[1 3].

VPA are serious (dose-dependent) teratogens, with prenatal exposure carrying a substantially increased risk of neurodevelopmental impairment and congenital malformations in the child[4-8]. Therefore, their use during pregnancy is contraindicated with few exceptions, and pregnancy prevention measures were implemented for young women to reduce the risk of VPA exposed pregnancies.

In 2014, the European Medicines Agency (EMA) reinforced warnings on VPA use among women of childbearing age, stating that VPA and its derivatives should not be prescribed, except in case of intolerance or ineffectiveness of alternatives[9]. Subsequently, several studies assessed the incidence of VPA use among young women with epilepsy following the issue of risk minimization measures (RMM): While prevalence of VPA use in women of childbearing age decreased in France, there were still young women being started on VPA[9]. A multinational, European study assessing the effectiveness of the RMM measures in France, Germany, Spain, Sweden and UK using routinely-collected outpatient data, reports an increase in the proportion of VPA initiated as second-line therapy in incident users in Sweden and UK[10], while it remained unchanged in Germany and Spain[11] and decreased in France[12]. These results suggested that the effectiveness of the RMM on VPA use was limited. However, the incidence rate of VPA exposed pregnancies in Spain and UK was successfully reduced[10 11]. In Ireland, no changes in monthly prevalence in VPA use was seen among women aged 16–44 years before and after the RMM implementation, but a significant decreasing trend of use in younger women aged 16-24 was reported[13].

In 2018, again, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) issued new restrictions on the use of valproate-containing medication and presented a new pregnancy prevention program to minimise valproate exposure during pregnancy and conception[5]: PRAC emphasised that valproate must not be used in pregnancy for bipolar disorder and migraine. While it should also be avoided in epilepsy, valproate may be

the most effective medication for some people with specific epilepsies[4]. Hence, for some women it may not be possible to stop valproate and they may need to continue treatment under specialist care during pregnancy to avoid uncontrolled seizures. For female patients in child-bearing age, valproate must not be used unless the conditions of the new pregnancy prevention programme are met, which includes effective contraception, pregnancy tests, counselling patients about the risk of valproate treatment, annual treatment review by a specialist and completing a risk acknowledgement form[5]. Surveys among neurologists in Sweden and Norway, however, revealed limited implementation and use of the new pregnancy prevention program, with 44% having prescribed VPA to women of childbearing age in the last 2019/2020 years, with only a small minority using patient information brochures or the risk acknowledgement form[14]. A similar survey among Italian experts in epilepsy showed that while people were aware of the new recommendation and VPA was less prescribed for first-line treatments, 64% reported to have difficulties to implement the recommendations for their female patients[15].

Little information is currently available on the prevalence and incidence of VPA use across Europe in women of childbearing-age before and after the new RMM recommendation in 2018. A recent study observed no declining trend of incidence after the 2018 intervention compared to the time prior[16]. Additionally, more insight into the characteristics of recent new users including their indication for treatment is needed. The EMA therefore requested a combined population-level and patient-level VPA utilisation study through the DARWIN EU initiative.

8. RESEARCH QUESTION AND OBJECTIVES

This study will address the following objectives:

1. To characterise the prevalence and incidence of use of VPA and alternative antiepileptic therapies among women aged 12 to 55 years of age. Analyses will be stratified by calendar year and age.
2. To characterise the use of VPA among women aged 12 to 55 years of age. Analyses will be stratified by indication (i.e. epilepsy, bipolar disorder and migraine prevention), calendar year and age.

Table 8.1: Primary research question and objective

Objectives:	1.To characterise the prevalence and incidence of use of VPA and alternative antiepileptic therapies among women aged 12 to 55 years of age. Analyses will be stratified by calendar year and age. 2.To characterise the use of VPA among women aged 12 to 55 years of age. Analyses will be stratified by indication (i.e. epilepsy, bipolar disorder and migraine prevention), calendar year and age.
Hypothesis:	NA
Population *(mention key inclusion-exclusion criteria):*	All women present in the databases and aged between ≥12 years and ≤55 years on 1st of January of each year in the period 01/01/2010-31/12/2021 (or the latest available), with at least 365 days of data availability before the day they become eligible for study inclusion.
Exposure:	Valproic acid, valproate and valpromide (“VPA”)
Comparator:	Alternative antiepileptic therapies

Outcome:	NA
Time *(when follow up begins and ends):*	Follow-up will start on a pre-specified calendar time point e.g. 1st of January for each calendar year between 01/01/2010-31/12/2021 for the calculation of annual incidence/prevalence rates. End of follow-up will be defined as the earliest of loss to follow-up, end of data availablility, or death
Setting:	Electronic Health Care Record Databases across Europe namely IPCI, SIDIAP, IQVIA LPD Belgium, IQVIA DA Germany, ACI VARHA [former HDSF] and CPRD GOLD
Main measure of effect:	Incidence and Prevalence, Patient-level drug utilisation

9. RESEARCH METHODS

9.1 Study Type and Study Design

Retrospective cohort studies will be conducted using routinely-collected health data from 4 databases. The study will comprise two consecutive parts:

1. A population-based cohort study will be conducted to address objective 1, assessing the prevalence and incidence of VPA and alternative treatments.
2. A new drug user cohort will be used to characterise patient-level VPA utilisation.

9.2 Study Setting and Data Sources

This study will be conducted using routinely collected data from 6 databases in 6 European countries (5 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland (ACI VARHA [former HDSF]), Finland
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

ACI Varha only contributed to Objective 1.

Detailed information on data sources is described in **Table 9.1**.

Table 9.1. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Data lock for the last update
NL	IPCI	Database covers primary care setting where valproate prescriptions are issued.	Primary care	EHR	1.39M	01/01/2022
ES	SIDIAP		Primary care	EHR	5.8 million	30/06/2022
BE	IQVIA LPD Belgium		outpatient specialist care	EHR	435,200	30/06/2022
DE	IQVIA DA Germany		outpatient specialist care	EHR	8.5 million	30/06/2022
FI	ACI VARHA [former HDSF]		in-and outpatient specialist care	EHR	765,000	07/11/2022
UK	CPRD GOLD		Primary care	EHR	3 million	06/2020

NL = The Netherlands, ES = Spain, FI = Finland, UK = United Kingdom, IPCI = Integrated Primary Care Information Project; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, LPD = Longitudinal Patient Database, DA = Disease Analyzer, ACI VARHA [FORMER HDSF] = Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland, CPRD GOLD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record. Exposure is based on prescription data.

Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[17] The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996[17]. The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval for this study was obtained from the Governance Board[17].

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[18]. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Approval for this study was granted by both SIDIAP's Scientific and Ethics Committee.

Longitudinal Patient Database (LPD) Belgium, Belgium (IQVIA)

LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers time from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Disease Analyser (DA) Germany, Germany (IQVIA)

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings[19]. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. 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. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland (ACI VARHA [former HDSF])

The data covers the patient register at the Hospital District of Southwest Finland (ACI VARHA [FORMER HDSF]), containing Turku University Hospital, which is one of the five university hospitals in Finland. It covers the public specialist health care and most emergency health care in the area of Southwest Finland (Varsinais-Suomi) for all demographic groups (765K persons). The data is utilized for scientific research from the data lake in the ACI VARHA [former HDSF] under the Finnish legislation (The Act on Secondary Use of Health and Social Data). The most relevant data domains are patients, visits, inpatient episodes, diagnoses, laboratory results, procedures, medication, pathology, radiology, radiotherapy and chemotherapy. Approval for this study was granted.

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD[20] comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients. Approval for this study was granted via the Research Data Governance Process.

9.3 Study Period

The study period started on 1st January 2010 until the latest data available as provided in Table 9.1

9.4 Follow-up

9.4.1 Population-level Utilization of VPA and alternative treatments

Both incidence and prevalence require an appropriate denominator population and their contributed observation time to first be identified. 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 (1st January 2010), 2) date at which they have a year of prior history recorded, 3) date at which they reach a minimum age (12 years old for the overall population or the lower age limit of a strata when stratifying by age). Participants will stop contributing person time at the earliest date of the following: 1) study end date (end of available data in each of the data sources), 2) date at which their observation period ends, 3) the last day in which they have the maximum age (55 years old for the overall population or the upper age limit of a strata when stratifying by age).

An example of entry and exit into the denominator population is shown in **Figure 9.1**. In this example person IDs 1 and 3 enter the study on the day they reach the minimum age and exits at the study end date. Person ID 2 enters the study on the study start date and exits at the maximum age. Person ID 4 enters the study on the day they reach the minimum age and leaves when they exit the database (the end of their observation period). Person ID 5 enters the study on the day they have sufficient prior history and exits at the study end date. Lastly, person ID 6 has two observation periods in the database. For the first they enter and contribute

time until their exit, for the second they start contributing time again once they have sufficient prior history and exit at the maximum age.

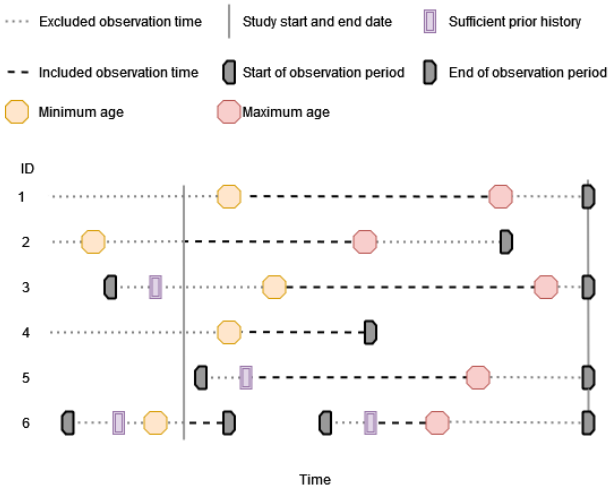


Figure 9.1. Included observation time for the denominator population

9.4.2 Patient-level Utilisation of VPA

Participants were followed up from the day of therapy initiation, i.e. the date of the first prescription of valproic acid/valproate-containing medication (index date), until the earliest of loss to follow-up, end of data availablility, death, or end of continuous exposure.

9.5 Study Population with in and exclusion criteria

9.5.1 Population-level Utilisation of VPA and alternative treatments

The study cohort comprised all women aged between ≥12 years and ≤55 years on 1st of January of each year in the period 2010-2022 (or the latest available), with at least 365 days of data availability before the day they became eligible for study inclusion.

Additional eligibility criteria were applied for the calculation of incidence rates: The observation time of users of the drug of interest was excluded during use and 365 days afterwards. For this study, incident VPA users were not excluded if they had alternative anti-epileptic treatments in the past and started VPA as second-line therapy of add-on.

9.5.2 Patient-level Utilisation of VPA

New users of VPA in the period between 01/01/2010 and 31/12/2021 (or latest date available), with at least 365 days of visibility prior to the date of their first VPA prescription, and not used VPA in the previous 365 days.

Table 9.2. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
all women aged between ≥12 years and ≤55 years on 1st of January of each year in the period 2010-2022 (or the latest available)	See under inclusion criterion	After	N/A	Primary care and combination of primary and secondary care for IQVIA Germany and Finland (ACI VARHA [former HDSF])	N/A	N/A	All women within the selected databases	N/A	N/A
Prior database history of 1 year	Study participants were required to have a year of prior history observed before contributing observation time	After	1 year	Primary care and combination of primary and secondary care for IQVIA Germany and Finland (ACI VARHA [former HDSF])	N/A	N/A	All women within the selected databases	N/A	N/A

* After as first possible study entry date is selected and then it is checked whether patient has one year of database history. In a sensitivity analysis, this rule will be removed. In another sensitivity analysis, required history will be increased to 3 years

9.6 Variables

9.6.1. Exposure/s

Concept lists for drug exposure are included in Appendix I.

9.6.1.1 Primary exposure of interest:

ATC	Name
N03AG01 N03AG02	valproic acid, sodium valproate, magnesium valproate, valproate semisodium, valpromide

9.6.1.2 Secondary drugs of interest, i.e. alternative treatments for the same indications (Population-level Utilisation study only)

Therapeutic drug class: N03A

1) Other anti-epileptic drugs:

ATC	Name
N03AF01	Carbamazepine
N03AA02	Phenobarbital
N03AB02	Phenytoin
N03AA03	Primidone
N05BA09	Clobazam
N03AE01	Clonazepam
N03AF04	Eslicarbazepine acetate
N03AX09	Lamotrigine
N03AF02	Oxcarbazepine
N03AX22	Perampanel
N03AF03	Rufinamide
N03AX11	Topiramate
N03AX15	Zonisamide
N03AX23	Brivaracetam
N03AD01	Ethosuximide
N03AX12	Gabapentin
N03AX18	Lacosamide
N03AX14	Levetiracetam
N03AX16	Pregabalin
N03AG06	Tiagabine
N03AG04	Vigabatrin

2) Other drugs for bipolar disorder treatment (maintenance):

ATC	Name
N05AN01	Lithium
N05AH04	Quetiapine
N05AH03	Olanzapine
N03AX09	Lamotrigine

3) Alternatives for migraine prophylaxis:

ATC	Name
C07AA05	Propranolol
C07AB02	Metoprolol
C07AB03	Atenolol
C07AA12	Nadolol
C07AA06	Timolol
C07AB07	Bisoprolol
N03AX11	Topiramate
N06AA09	Amitriptyline
N07CA03	Flunarizine
N02CX01	Pizotifen
N02CX02	Clonidine

9.6.2. Outcome/s

N/A

9.6.3. Other covariates, including confounders, effect modifiers and other variables

9.6.3.1 Covariates for stratification in population-level drug utilisation study:

- Age: 5-year age bands (apart from 12-14, and 55 band) were used: 12-14, 15-19, 20-24, … , 50-54, 55.
- Calendar year

9.6.3.2 Covariates for patient-level drug utilisation study:

- Age: 5-year age bands were used: 12-14, 15-19, 20-24, … , 50-54, 55.
- The following conditions were of interest (indication):
    - Epilepsy
    - Bipolar disorder
    - Migraine (indication: migraine prevention)
- Co-morbidities and co-medication for large-scale patient characterisation

Table 9.3. Exposure details

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations :	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
VPA	Code lists provided in Appendix I	365days for new users	Calendar year	Primary and secondary care	RxNorm	N/A	Women aged 12-55 in the respective databases	Previous VPA use	N/A	N/A
Alternative treatments for epilepsy, bipolar disorder and migraine preventsion	Code lists provided in Appendix I	365days for new users	Calendar year	Primary and secondary care	RxNorm	N/A	Women aged 12-55 in the respective databases	Previous use of the same ingredient	N/A	N/A

Table 9.4. Operational definition of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study population	Measurement characteristics/validation	Source for algorithm
Indication of Use	Check for conditions of interest related to use of VPA (epilepsy, bipolar disorder, migraine, "other"*)	Counts	At index date and in a window of 7, 30 days and anytime as sensitivity analysis	Primary care and combination of primary and secondary care for Finland (ACI VARHA [former HDSF])	SNOMED	N/A	Women aged 12-55 in the respective databases	N/A	N/A
Comorbidity (see 8.8.4)	Large-scale patient-level characterisation with regard to underlying comorbidity	Counts	At index date (ID), for 30 to 1 day before ID, for 365 to 31 days before ID and at any time before ID	Primary care and combination of primary and secondary care for Finland (ACI VARHA [former HDSF])	SNOMED	N/A	N/A	N/A	N/A
Concomitant medication (see 8.8.4)	Large-scale patient-level characterisation with regard to use of concomitant drugs	Counts	At index date (ID), for 30 to 1 day before ID and for 365 to 31 days before ID	Primary care and combination of primary and secondary care for Finland (ACI VARHA [former HDSF])	RxNorm	N/A	N/A	N/A	N/A

*If none of the specific indications was recorded during the assessment window, but there was a record for any other conditions the person will be included to the "other" indication group

9.7 Sample size

No sample size was calculated for this study. Prior to the development of the study protocol, feasibility counts were generated for this drug utilisation study in the general population of the respective databases.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were performed. After all the tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results.

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

9.9 Statistical Methods

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.2 Complete Catalogue of Standard Analyses which describes the type of analysis in function of the study type.

Table 9.5. Description of Study Types and Type of analysis

STUDY TYPE	TYPE OF ANALYSIS
Population Level DUS	- Population-based incidence rates - Population-based prevalence
Patient Level DUS	- Characterisation of patient-level features for new VPA users - Frequency and % of indication/s - Estimation of minimum, 25th percentile (p25), median, 75th percentile (p75), and maximum initially prescribed or dispensed dose/strength of VPA - Estimation of minimum, 25th percentile (p25), median, 75th percentile (p75), and maximum treatment duration VPA

9.9.1 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts < 5 were suppressed.

9.9.2 Statistical model specification and assumptions of the analytical approach considered

R-packages

We used the R package "DrugUtilizationCharacteristics" for the patient-level drug utilisation analyses including patient-level characterisation, and "IncidencePrevalence" package for the population-level

estimation of drug utilisation. The study package is available via https://github.com/darwin-eu-studies/C1-002-ValproatePopulationDUS

Drug exposure calculations

Drug eras were defined as follows: Exposure started at the date of the first prescription, e.g. the index date the person entered the cohort. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications.

Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 30 days. The time between the two joined eras was considered as exposed by the first era as show in **Figure 9.2**.

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	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

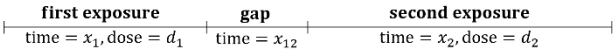


Figure 9.2. Gap era joint mode

If two eras overlapped, the overlap time was considered exposed by the first era (**Figure 9.3**). No time was 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"		$\max(d_1, d_2)$

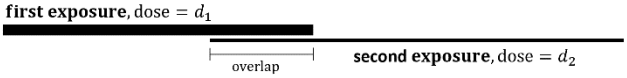


Figure 9.3. Gap era overlap mode

If two eras started at the same date, the overlapping period was considered exposed by both. We did not consider repetitive exposure.

New user cohorts

New users were 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 was

required prior to that prescription. New users were required to not have been exposed to the drug of interest for at least 365 days prior the current prescription. If the index day did not fulfil the exposure washout criteria the whole exposure was eliminated.

9.9.3 Methods to derive parameters of interest

Calendar time

Calendar time was based on the calendar year of the index prescription.

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups were used for stratification: 12-14, 15-19, 20-24, 25-29,30-34, 35-39, 40-44, 45-49, 50-54, 55.

Indication

Indication was determined based on recordings of 3 pre-defined conditions, namely epilepsy, bipolar disorder and migraine, at the date of the first prescription of the respective drug (= index date)[primary definition] or during assessment windows [sensitivity analyses]. If none of the specific indications was recorded on the index date or during the assessment window, but there was a record for any other conditions, the person was considered having an "other" indication.

Characterisation of patient-level features

Large-scale patient-level characterisation was conducted. Co-variates were extracted for the following time intervals: Concepts in the "condition" domain were assessed for anytime - 366 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. Concepts in the "drug" domain were reported for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date.

Co-variates to be presented in a summary baseline characteristics table were pre-defined, comprising medical history and medication use.

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

Population-level drug utilisation study

Prevalence and incidence calculations were conducted separately for VPA and each alternative treatment.

Prevalence calculations

Prevalence was calculated as annual period prevalence which summarised the total number of individuals who used the drug of interest during a given year divided by the population at risk of getting exposed during that year. Therefore, period prevalence gave the proportion of individuals exposed at any time during a specified interval. An illustration of the calculation of period prevalence is shown below in **Figure 9.4**. Between time t+2 and t+3, two of the five study participants are VPA users giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the year with one of the five study participants VPA users giving a prevalence of 20%. 95% confidence intervals were calculated using the Wilson Score method for binomial distribution.

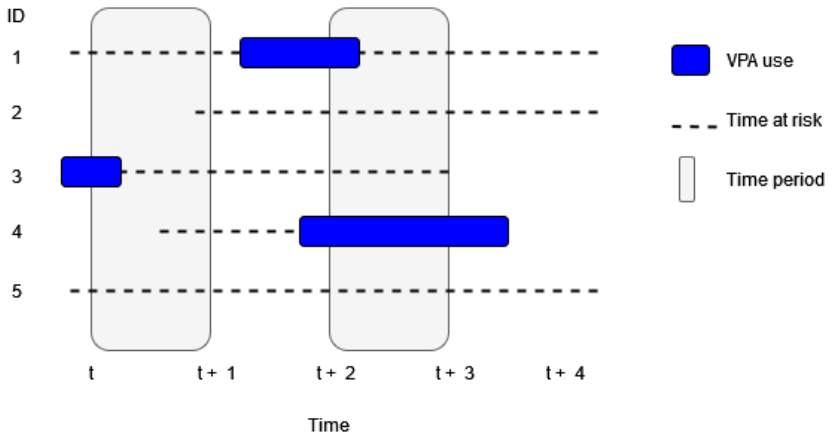


Figure 9.4. Period prevalence example for VPA use

Incidence calculations

Annual incidence rates for VPA and alternative treatments were estimated as the number of **new users** divided by the accumulated person-time of the population at risk of getting exposed during the period for each calendar year, and the result provided as number of new users per 100,000 person-years. 95% confidence intervals were calculated using the "exact" method for Poisson distribution. 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) were excluded. Those study participants who entered the denominator population then contributed time at risk up to their first prescription (e.g. VPA use) during the study period. If they did not have a drug exposure, they contributed time at risk as described above (until study end, end of observation period, or the last day of maximum age).

An illustration of the calculation of incidence of VPA use is shown below in **Figure 9.5**. Person ID 1 and 4 contribute time at risk up to the point at which they become incident users of VPA. Person ID 2 and 5 are not seen to use VPA and so contribute time at risk but no incident outcomes. Meanwhile, Person ID 3 is excluded from the analysis as they are seen to have had the outcome before the study start date.

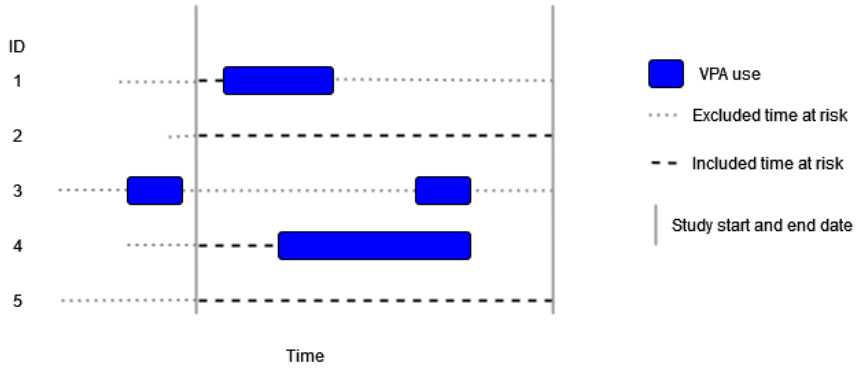


Figure 9.5. Incidence example for VPA use

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 and percentage (N, %) with a record within the pre-specified time windows was provided.

Indication

The number of persons and percentage (N, %) with a record of the respective indication (specific: epilepsy, bipolar disorder, migraine prevention; "other") was provided. If a person had a record of more than one specific indication, that person was included in both specific indication groups separately.

Initially prescribed or dispensed dose/strength

For each prescription at index date, the prescribed dose/strength was retrieved from the drug_exposure and drug_strength tables, where the amount quantity and units were available.

The quality of recording of drug dose and drug strengths might be of varying quality for different databases. Therefore, data quality checks were conducted to evaluate the quality of the recording of units, dosage and strength (OMOP drug_exposure and drug_strength tables) for VPA in the databases this study were conducted in.

From this, the initial dose/strength in the cohort was characterised by the minimum dose/strength, p25, median, p75, and maximum dose/strength.

Note: VPA is typically used in different doses for different indications: While dose recommendations might vary between countries, valproate for epilepsy in adults is typically initiated with 600 mg daily in 2–4 divided doses. For treatment of manic episodes associated with bipolar disorder the initial dose of valproic acid is 750 mg daily given in 2–3 divided doses. For migraine, prophylaxis is initiated at 250 mg twice daily in adults (https://bnf.nice.org.uk/drugs/valproic-acid/).

Therefore, in databases where no dosage information was available but only the strength of the product (e.g. CPRD), strength might not display the actual daily dose taken by the person.

Treatment duration

Treatment duration was calculated as the duration of the first continuous exposure episode. Estimations of treatment duration were summarized providing the minimum, 25th percentile (p25), median, 75th percentile (p75), and maximum treatment duration. For databases, where duration could not be calculated due to e.g. missing information on quantity or dosing, treatment duration was not provided.

9.9.5 Methods to control for potential sources of bias

NA

9.9.6 Methods to deal with missing data

For the drug utilisation studies we assumed that the absence of prescription records meant that the person did not receive the respective drug. For indications, we assumed that the missingness of a record of the respective condition meant that that condition was not the indication for the drug prescription.

9.9.7 Description of sensitivity analyses

- Indication gap: In addition to indication recorded at the index date, pre-defined conditions (potential indications) were also assessed in the 7 days, 30 days and any time before index date.

9.9.8 Evidence synthesis

Results from analyses described are presented separately for each database and no meta-analysis of results was conducted.

9.10 Deviations from the protocol

Included databases and analyses:

Patient-level drug utilisation analyses were provided for CPRD GOLD, IPCI, IQVIA Germany, IQVIA Belgium and SIDIAP. For ACI VARHA [FORMER HDSF], only population-level analyses were included due to missing patient-level data on drug use.

Statistical analyses:

For prescribed dose/strength and treatment duration in addition to median, mean and standard deviation were provided.

Planned sensitivity analyses not conducted:

Population-level drug utilisation analyses stratified for indication for VPA, and incidence and prevalence of alternative treatments have not been conducted in a subgroup of patients with epilepsy, bipolar disorder and migraine as planned, due to small numbers of people with the respective indications.

Indication of bipolar disorder: only a broad definition for bipolar disorder including unspecified and manic episodes, was used. This was decided during phenotyping as recordings of the condition were used as a proxy for indication, hence a broad definition is more inclusive.

Additional stratified analysis:

Tables of baseline characteristics of new drug users, as well as descriptive measures of initial dose/strength, and treatment duration were stratified for indication in addition.

10. DATA MANAGEMENT

10.1. Data management

All databases have previously mapped their data to the OMOP common data model. This enabled 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 was 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 was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated

data. The results from each of the contributing data sites were then be combined in tables and figures for this study report.

10.2. Data storage and protection

For this study, participants from various EU member states and from the UK processed personal data from individuals which was 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 were 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 were run, which generated non-identifiable aggregate summary results. All and any results with n<5 participants were suppressed using cell suppression to minimise risk of reidentification.

The output files were stored in the DARWIN EU Data transfer zone. These output files did not contain any data that allow identification of subjects included in the study. The DTZ implemented 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.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it was expected that data partners would have run the OHDSI Data Quality **Dashboard** tool (https://github.com/OHDSI/DataQualityDashboard). This tool provided numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focused on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality was solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories had one or more subcategories and were evaluated in two contexts: validation and verification. Validation related to how well data aligned with external benchmarks with expectations derived from known true standards, while verification related to how well data conformed to local knowledge, metadata descriptions, and system assumptions. Additionally, two more tools were used to control the quality of data during the onboarding. **Achilles** for database characterisation, running 293 analyses against the data. This output is not shared with the DARWIN-EU® CC as it reveals granular information of the data. It is expected that the data partners review the Achilles output internally. Secondly, **CdmOnboarding** generates a Word report with the most important database characteristics, providing insight in the readiness of the database to use for network studies. The output is shared with and inspected by the DARWIN-EU® CC.

Study specific quality control

When defining drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level. For drugs that are often prescribed in fixed combinations, e.g. beta-blockers, 2 sets of code lists were provided including (1) all products containing the drug of interest, and (2)

excluding fixed combinations (referred to as "mono"). A pharmacist reviewed the codes for VPA and alternative treatments.

When defining cohorts for indications, a systematic search of potential codes for inclusion was conducted using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) was run to assess the use of different codes for diagnoses and conditions across the databases contributing to the study and identify any codes potentially omitted in error.

The study code was based on two R packages being developed to (1) estimate Incidence and Prevalence and (2) characterise drug utilisation using the OMOP common data model. These packages include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing.

The study protocol was registered in the EUPAS Registry (EUPAS50798)

12. RESULTS

All results are available in a web-application ("shiny app") at https://data-dev.darwin-eu.org/EUPAS50789/

12.1. Population-level DUS

12.1.1. Participants

Table 12.1.1 describes the number of people included and excluded by each criterion. The whole cohorts amount to 15,662,217 people in CPRD, 2,647,547 in IPCI, 8,265,343 in SIDIAP, 801,405 in ACI VARHA, 1,134,075 in IQVIA Belgium LPD, and 40,243,608 in IQVIA GERMANY DA. Of those, 2,948,860; 718,835; 2,494,052; 157,361; 218,250; and 5,152,752 respectively were women aged 12-55 during the study period and had been in the database for at least 1 year. Further 30,393 women in CPRD GOLD, 23,316 women in IPCI, 30,632 women in SIDIAP, 1,925 in ACI VARHA, and 5,273 in IQVIA Belgium LPD were excluded from the prevalence calculations due to not being observed at least a full calendar year (Jan to Dec) during the study period. No woman was excluded in IQVIA GERMANY DA due to this. For the incidence estimation, 3,728 women in CPRD GOLD, 569 in IPCI, 2,183 in SIDIAP, 42 in ACI VARHA, 104 in IQVIA Belgium LPD, and 748 in IQVIA GERMANY DA were excluded due to having a previous prescription of VPA. We further excluded 30,357 women in CPRD GOLD, 23,286 in IPCI, 30,635 in SIDIAP, 1,931 in ACI VARHA, 5299 in IQVIA Belgium LPD, and none in IQVIA GERMANY DA due to not being observed at least a full calendar year.

In ACI VARHA, CPRD, IPCI, IQVIA Belgium LPD, IQVIA GERMANY DA all women were prescribed valproate or valproic acid, whereas in SIDIAP 3.5% people had valpromide at index date. For SIDIAP, results are presented combining valproate, valproic acid and valpromide.

Table 12.1.1 Number of participants, the total number of VPA users in each source population during the study period overall

		CPRD GOLD		IPCI		SIDIAP	
step	**reason**	**current_n**	**excluded**	**current_n**	**excluded**	**current_n**	**excluded**
General	Starting population	15662217		2674547		8265343	
General	Missing year of birth	15662217	0	2674547	0	8265343	0
General	Missing sex	15662217	0	2674547	0	8265343	0
General	Cannot satisfy age criteria during the study period based on year of birth	11049843	4612374	1878595	795952	5740927	2524416
General	No observation time available during study period	7396634	3653209	1851114	27481	5550189	190738
General	Doesn't satisfy age criteria during the study period	7396634	0	1851114	0	5550189	0
General	Prior history requirement not fulfilled during study period	6658801	737833	1641385	209729	5349648	200541
General	Not Female	3319618	3339183	831377	810008	2601069	2748579
General	No observation time available after applying age and prior history criteria	2979253	340365	742151	89226	2524684	76385
Prevalence	Starting analysis population	2979253		742151		2524684	
Prevalence	Not observed during the complete database interval	2948860	30393	718835	23316	2494052	30632
Incidence	Starting analysis population	2979253		742151		2524684	
Incidence	Excluded due to prior event (do not pass outcome washout during study period)	2975525	3728	741582	569	2522501	2183
Incidence	Not observed during the complete database interval	2945168	30357	718296	23286	2491866	30635

		ACI VARHA		IQVIA BELGIUM LPD		IQVIA GERMANY DA	
step	**reason**	**current_n**	**excluded**	**current_n**	**excluded**	**current_n**	**excluded**
General	Starting population	801405		1134075		40243608	
General	Missing year of birth	801405	0	1134075	0	40243608	0
General	Missing sex	801397	8	1134075	0	40215065	28543
General	Cannot satisfy age criteria during the study period based on year of birth	489668	311729	801623	332452	27307664	12907401
General	No observation time available during study period	426358	63310	801623	0	23772471	3535193
General	Doesn't satisfy age criteria during the study period	426358	0	801623	0	23772471	0
General	Prior history requirement not fulfilled during study period	322989	103369	478202	323421	10005998	13766473
General	Not Female	168944	154045	254481	223721	5806799	4199199
General	No observation time available after applying age and prior history criteria	159286	9658	223523	30958	5152752	654047
Prevalence	Starting analysis population	157361		223523		5152752	
Prevalence	Not observed during the complete database interval	157361	1925	218250	5273	5152752	0
Incidence	Starting analysis population	159286		223523		5152752	
Incidence	Excluded due to prior event (do not pass outcome washout during study period)	159244	42	223419	104	5152004	748
Incidence	Not observed during the complete database interval	157313	1931	218120	5299	5152004	0

12.1.2. Descriptive Data

Descriptive data on participants is provided in the patient level analyses section (12.2.2).

12.1.3. Outcome Data

Outcome data is provided in the patient level analyses section (12.2.3).

12.1.4. Main Results

Incidence rates of VPA over time

Figure 1.1 shows new prescriptions of valproate from 2010 to 2021 in women aged 12 to 55 for each database. Detailed data on number of events, population and person-years can be found in Table 12.1.2. The incidence of valproate use decreased over the decade for all analysed datasets. In CPRD GOLD, it decreased steadily, going from an initial incidence of 287 95%CI(279 to 295) new users per 100,000 person-years in 2010 to 37 95%CI(33 to 42) in 2019. In IPCI and SIDIAP the incidence remained stable since the start of the study, 148 95%CI(126 to 172) in IPCI and 94 95%CI(90 to 99) for SIDIAP, until 2014, 139 95%CI(124 to 156) in IPCI and 88 95%CI(84 to 93) for SIDIAP, with a sustained decrease after that. By 2021 the incidence of use of valproate in women aged 12 to 55 was of 38 95%CI(31 to 45) new users per 100,000 person-years in IPCI and 34 95%CI(31 to 37) in SIDIAP. In ACI VARHA, the incidence of use decreased from 2010, with an incidence of 249 95%CI(218 to 284), to 73 95%CI(57 to 92) in 2016, and kept relatively stable until 2021, with an incidence of 89 95%CI(68 to 113). In IQVIA Belgium LPD the incidence also decreased steadily for the available time period (2014-2022) from an incidence of 115 users per 100,000 person-years 95%CI(94 to 139) to 75 95%CI(48 to 112) in 2022. IQVIA Germany had a much lower incidence than the other databases, with also a decrease in incidence, from 16 95%CI(14 to 19) in 2010 to 10 95%CI(9 to 12) in 2021.

Figure 12.1.1 - Incidence rates of VPA use in women 12 to 55 annually between 2010 and 2021

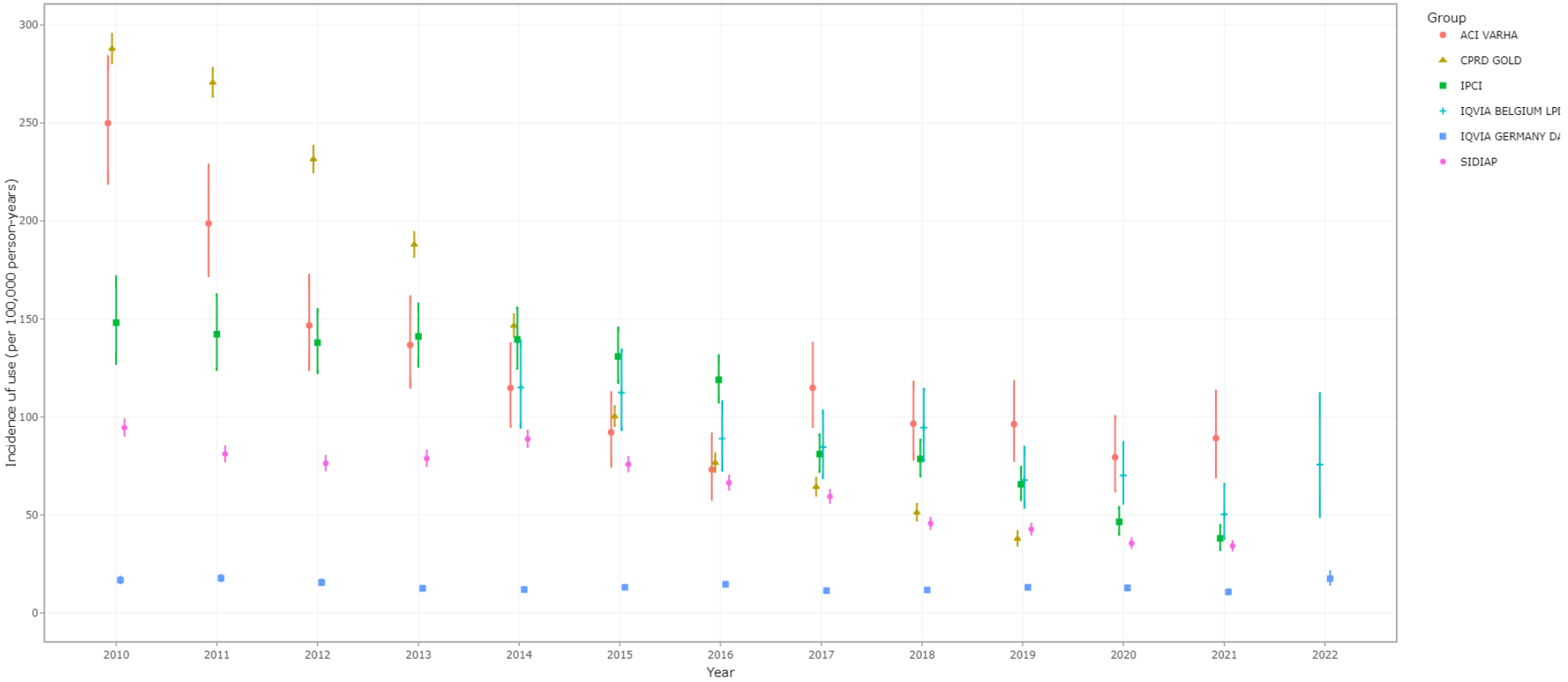


Table 12.1.2 - Incidence rates of VPA use in women 12 to 55 annually between 2010 and 2021

Data Partner	Year	N	Person-Years	Events	Incidence per 100,000 pys (95%CI)
CPRD GOLD	2010	1,887,065	1,750,138	5,038	287 (279 to 295)
CPRD GOLD	2011	1,846,790	1,706,530	4,618	270 (262 to 278)
CPRD GOLD	2012	1,806,026	1,679,658	3,888	231 (224 to 238)
CPRD GOLD	2013	1,765,607	1,601,125	3,009	187 (181 to 194)
CPRD GOLD	2014	1,650,314	1,467,642	2,151	146 (140 to 152)
CPRD GOLD	2015	1,487,218	1,304,912	1,309	100 (94 to 105)
CPRD GOLD	2016	1,242,267	1,105,986	847	76 (71 to 81)
CPRD GOLD	2017	1,106,383	987,138	635	64 (59 to 69)
CPRD GOLD	2018	1,013,803	920,973	472	51 (46 to 56)
CPRD GOLD	2019	961,853	865,772	328	37 (33 to 42)
IPCI	2010	134,949	113,424	168	148 (126 to 172)
IPCI	2011	168,269	146,235	208	142 (123 to 162)
IPCI	2012	243,916	195,016	269	137 (121 to 155)
IPCI	2013	248,764	202,701	286	141 (125 to 158)
IPCI	2014	248,561	215,020	300	139 (124 to 156)
IPCI	2015	286,518	242,958	318	130 (116 to 146)
IPCI	2016	337,927	295,885	352	118 (106 to 132)
IPCI	2017	350,716	321,944	261	81 (71 to 91)
IPCI	2018	351,522	321,846	253	78 (69 to 88)
IPCI	2019	354,310	324,506	213	65 (57 to 75)
IPCI	2020	370,090	326,872	152	46 (39 to 54)
IPCI	2021	372,213	320,539	122	38 (31 to 45)
SIDIAP	2010	1,775,300	1,728,241	1,634	94 (90 to 99)
SIDIAP	2011	1,802,834	1,729,825	1,403	81 (76 to 85)
SIDIAP	2012	1,791,938	1,713,352	1,308	76 (72 to 80)
SIDIAP	2013	1,749,308	1,690,795	1,332	78 (74 to 83)
SIDIAP	2014	1,734,575	1,673,654	1,486	88 (84 to 93)
SIDIAP	2015	1,710,561	1,649,153	1,251	75 (71 to 80)
SIDIAP	2016	1,703,605	1,641,606	1,090	66 (62 to 70)
SIDIAP	2017	1,699,105	1,634,888	971	59 (55 to 63)
SIDIAP	2018	1,702,472	1,633,113	746	45 (42 to 49)
SIDIAP	2019	1,708,451	1,635,494	698	42 (39 to 45)
SIDIAP	2020	1,722,401	1,651,105	587	35 (32 to 38)
SIDIAP	2021	1,714,037	1,645,420	563	34 (31 to 37)
ACI VARHA	2010	95,492	91,229	228	249 (218 to 284)
ACI VARHA	2011	100,077	94,584	188	198 (171 to 229)
ACI VARHA	2012	101,608	96,127	141	146 (123 to 172)
ACI VARHA	2013	103,218	97,273	133	136 (114 to 162)
ACI VARHA	2014	104,382	98,420	113	114 (94 to 138)
ACI VARHA	2015	104,716	98,748	91	92 (74 to 113)

Data Partner	Year	N	Person-Years	Events	Incidence per 100,000 pys (95%CI)
ACI VARHA	2016	104,491	98,374	72	73 (57 to 92)
ACI VARHA	2017	103,075	96,651	111	114 (94 to 138)
ACI VARHA	2018	101,017	94,229	91	96 (77 to 118)
ACI VARHA	2019	97,480	90,353	87	96 (77 to 118)
ACI VARHA	2020	92,232	84,311	67	79 (61 to 100)
ACI VARHA	2021	83,435	71,749	64	89 (68 to 113)
IQVIA BELGIUM LPD	2014	108,426	90,365	104	115 (94 to 139)
IQVIA BELGIUM LPD	2015	116,726	103,179	116	112 (92 to 134)
IQVIA BELGIUM LPD	2016	120,648	109,087	97	88 (72 to 108)
IQVIA BELGIUM LPD	2017	121,985	109,864	93	84 (68 to 103)
IQVIA BELGIUM LPD	2018	121,071	107,848	102	94 (77 to 114)
IQVIA BELGIUM LPD	2019	120,258	107,617	73	67 (53 to 85)
IQVIA BELGIUM LPD	2020	119,459	108,338	76	70 (55 to 87)
IQVIA BELGIUM LPD	2021	115,325	99,380	50	50 (37 to 66)
IQVIA BELGIUM LPD	2022	81,861	31,702	24	75 (48 to 112)
IQVIA GERMANY DA	2010	1,591,800	1,404,315	235	16 (14 to 19)
IQVIA GERMANY DA	2011	1,744,011	1,548,487	275	17 (15 to 19)
IQVIA GERMANY DA	2012	1,910,807	1,694,740	264	15 (13 to 17)
IQVIA GERMANY DA	2013	2,066,857	1,828,618	230	12 (11 to 14)
IQVIA GERMANY DA	2014	2,195,897	1,958,787	235	11 (10 to 13)
IQVIA GERMANY DA	2015	2,287,625	2,035,903	266	13 (11 to 14)
IQVIA GERMANY DA	2016	2,345,401	2,099,959	308	14 (13 to 16)
IQVIA GERMANY DA	2017	2,426,822	2,116,475	242	11 (10 to 12)
IQVIA GERMANY DA	2018	2,440,495	2,146,529	252	11 (10 to 13)
IQVIA GERMANY DA	2019	2,338,059	2,046,151	267	13 (11 to 14)
IQVIA GERMANY DA	2020	2,203,267	1,875,326	240	12 (11 to 14)
IQVIA GERMANY DA	2021	1,939,065	1,540,232	166	10 (9 to 12)
IQVIA GERMANY DA	2022	1,240,501	472,875	83	17 (13 to 21)

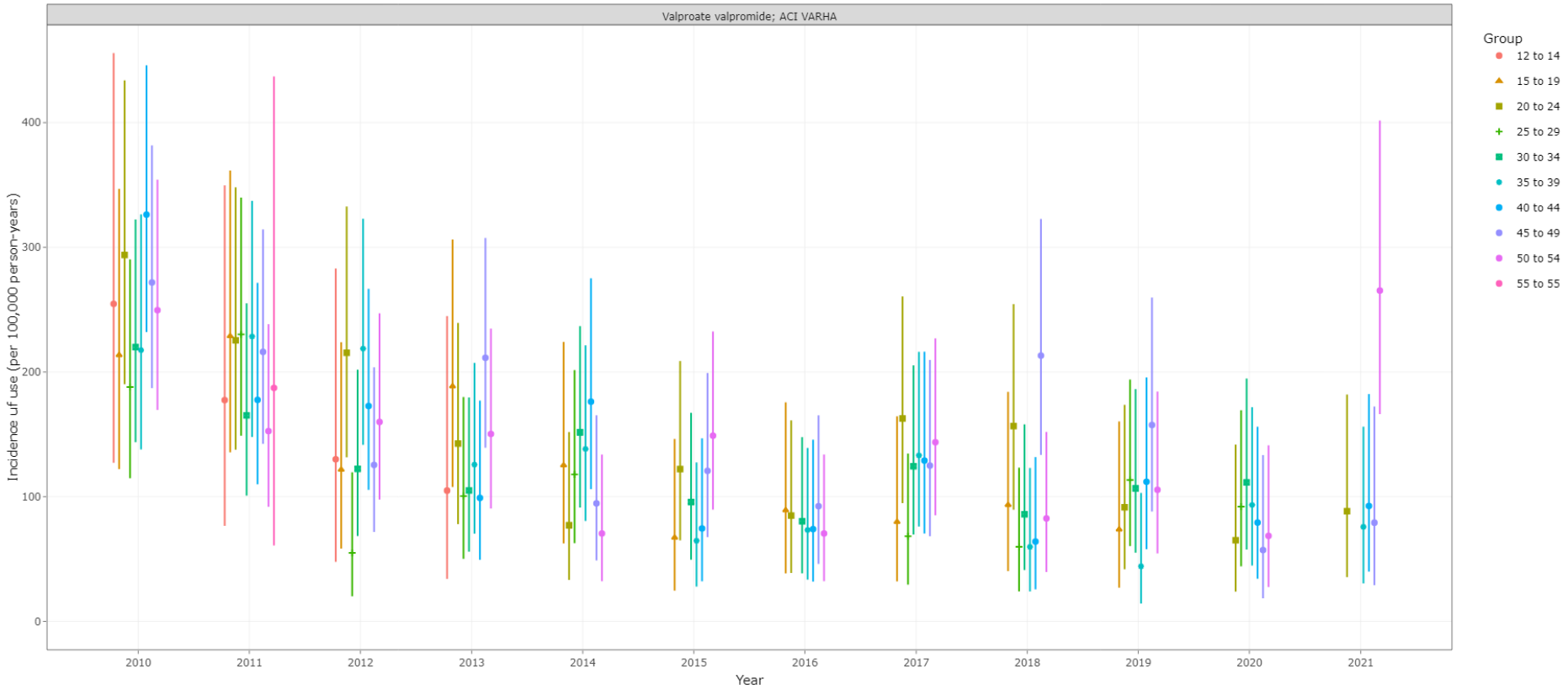
N: number of people, pys: person-years

Incidence rates of VPA over time by age

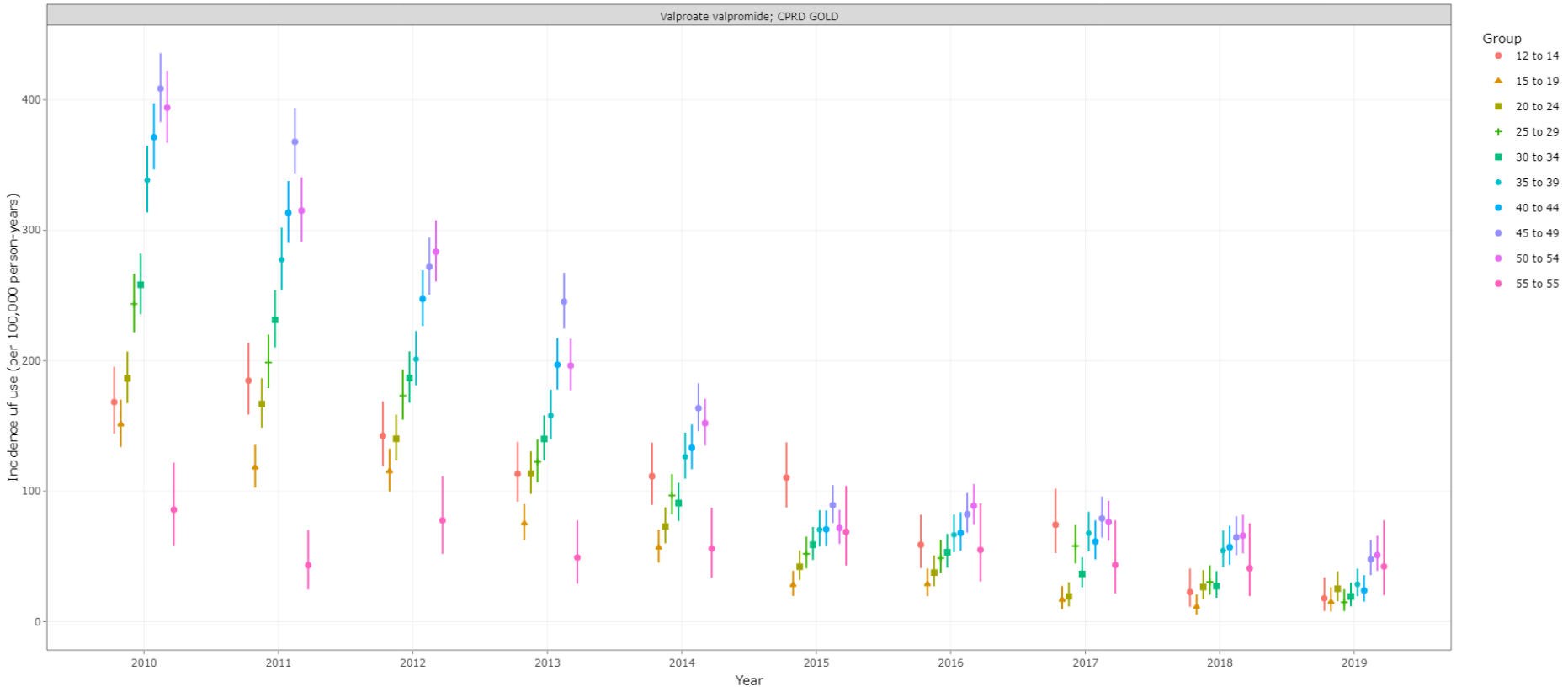
Figure 12.1.2 shows new prescriptions of valproate from 2010 to 2021 in women by age group for each database. The number of events, population and person-years for each calendar year, age group and database can be found in the shiny app (https://data-dev.darwin-eu.org/EUPAS50789/). The incident use of VPA decreased during the study period for all age groups. In ACI VARHA, IPCI, IQVIA Belgium, and IQVIA Germany all age groups show a decrease in incidence of VPA, specially in the younger age groups, however the sample size is too small to observe any meaningful differences in patterns by age. In CPRD GOLD, the incidence is higher in the older age at the start of the study period, namely of 151 (133 to 170) new prescriptions per 100,000 person-years in the 15-19 age group and 393 (367 to 422) new prescriptions per 100,000 person-years in the 50-54 age group. In 2019, the last year available for CPRD, the relative difference between age groups is maintained, but all groups have a decrease in incidence: 15 (7 to 26) for the 15-19 age group and 51 (38 to 65) for the 50-54 age group. In SIDIAP, the reduction is much more pronounced for the 12 to 14 age group, that in 2010 has an incidence of 185 (156 to 218), much higher than the rest of age groups and it ends in 2021 with an incidence of 19 (11 to 30). The rest of the age groups have a similar fall in incidence, from around 100 new users of VPA per 100,000 person years in 2010 to around 40 per 100,000 in 2019.

Figure 12.1.2 - Incidence rates of VPA over time (annually) and stratified by age

ACI VARHA



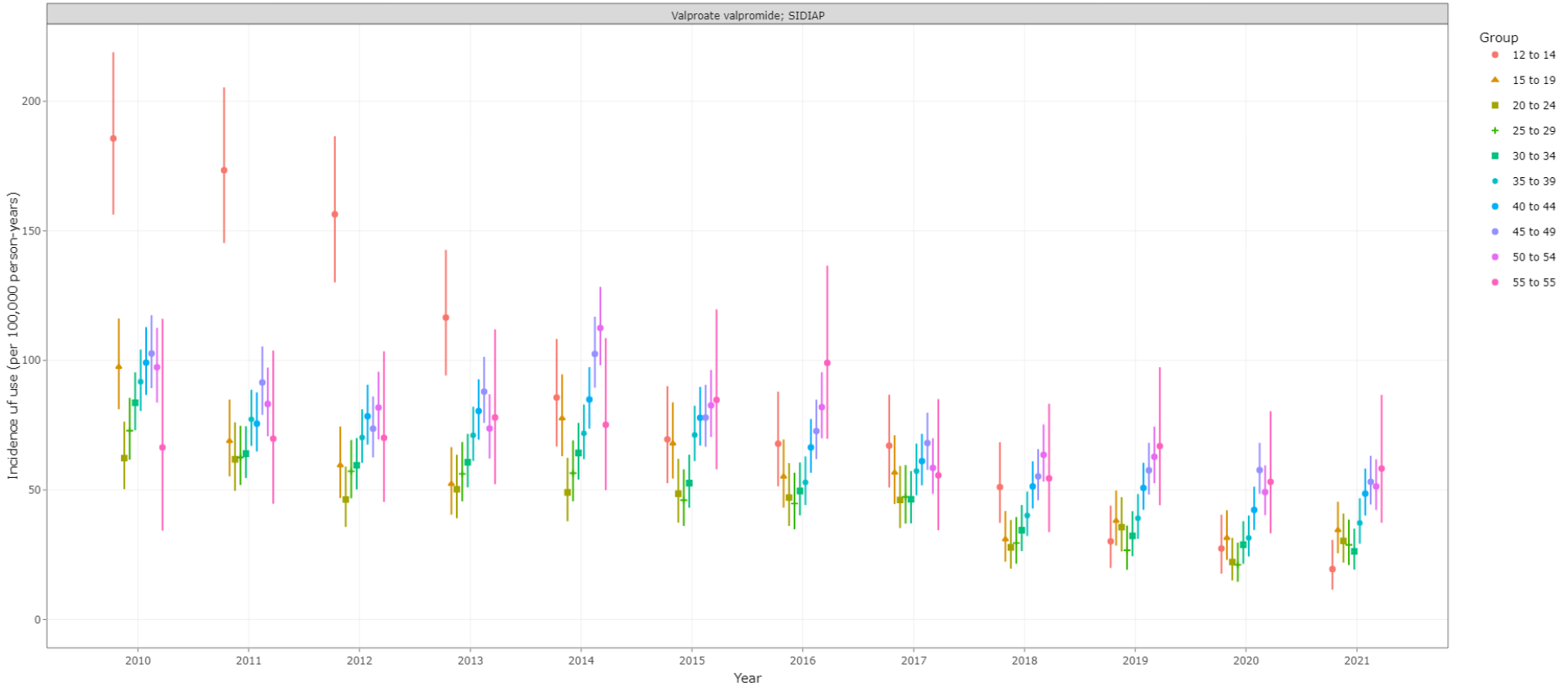
CPRD


Valproate valpromide; CPRD GOLD
Incidence of use (per 100,000 person-years)
0
100
200
300
400
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Year
Group
12 to 14
15 to 19
20 to 24
25 to 29
30 to 34
35 to 39
40 to 44
45 to 49
50 to 54
55 to 55

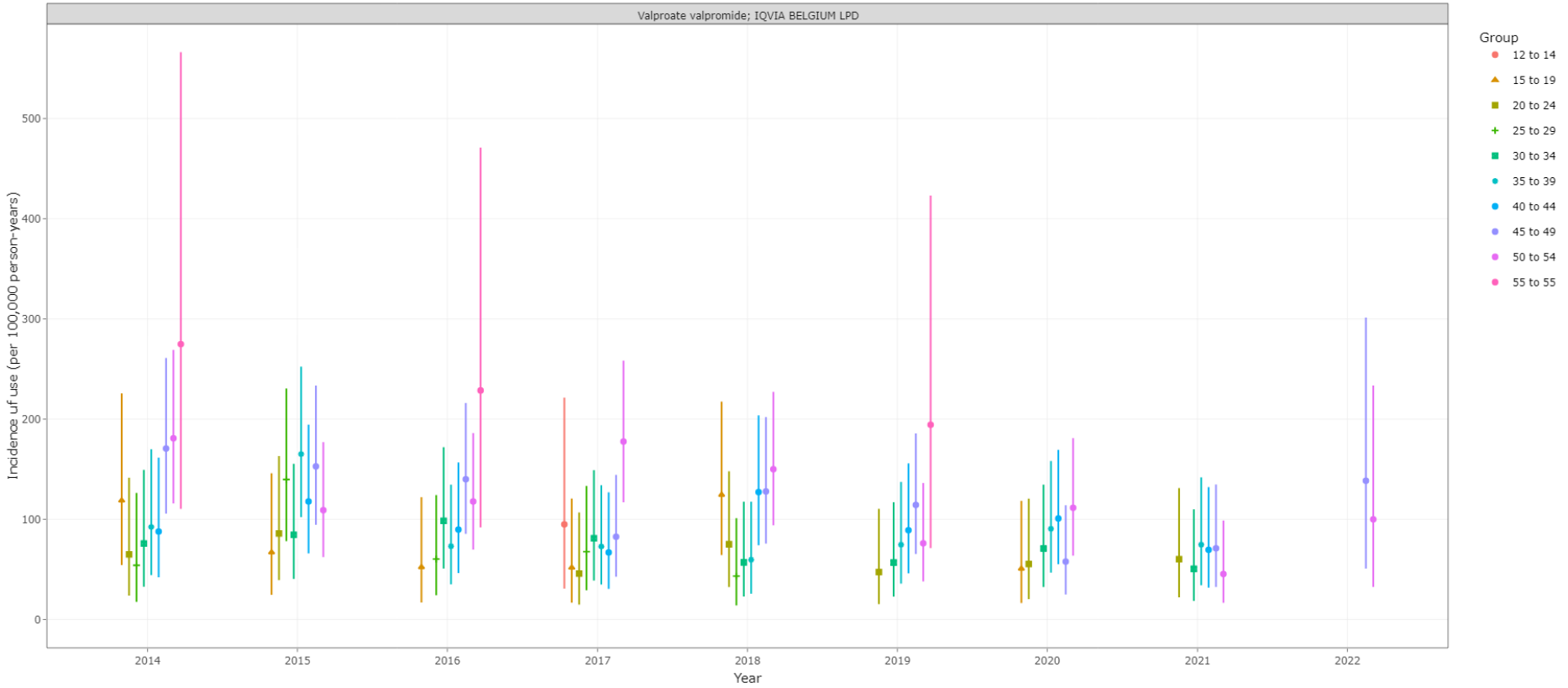
IPCI


Valproate valpromide; IPCI
Incidence uf use (per 100,000 person-years)
300
250
200
150
100
50
0
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year
Group
12 to 14
15 to 19
20 to 24
25 to 29
30 to 34
35 to 39
40 to 44
45 to 49
50 to 54
55 to 55

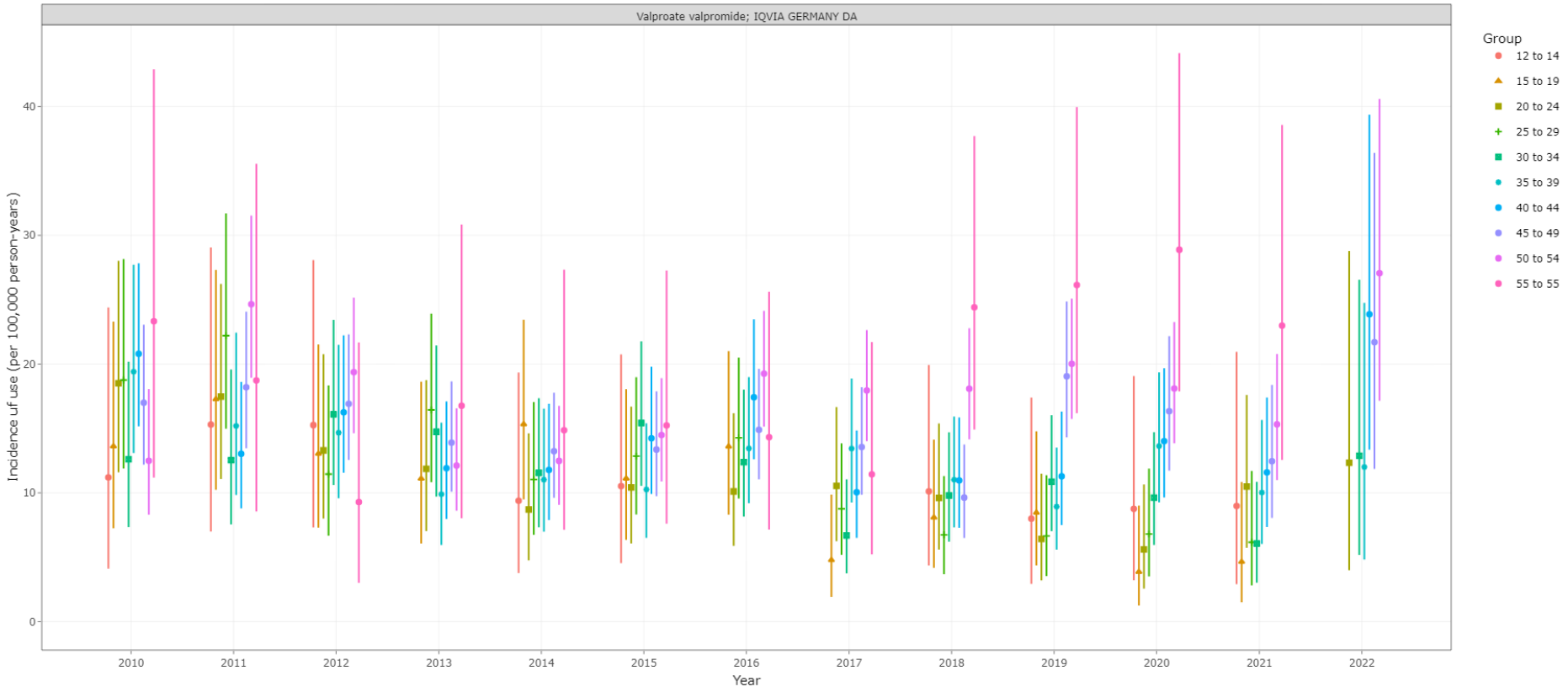
SIDIAP


Valproate valpromide; SIDIAP
Incidence uf use (per 100,000 person-years)
0
50
100
150
200
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year
Group
12 to 14
15 to 19
20 to 24
25 to 29
30 to 34
35 to 39
40 to 44
45 to 49
50 to 54
55 to 55

IQVIA BELGIUM LPD



IQVIA GERMANY DA



Prevalence of VPA over time

Figure 1.3 shows prevalent use of VPA from 2010 to 2021 in women aged 12 to 55 for each database. Detailed data on number of events, population and person-years can be found in Table 1.3.

Similarly to the incidence of valproate use, the prevalence of VPA decreased over the decade for most analysed datasets, except for ACI VARHA, where after a steady increase 2010-2102, the prevalence remained stable at around 0.37% for 2013-2019 and decreased for the last 2 years, with a prevalence of 0.301% 95%CI(0.266% to 0.340%) in 2021 . In CPRD GOLD, the prevalence of use of VPA decreased steadily, going from an initial prevalence of 0.361% 95%CI(0.352% to 0.369%) in 2010 to 0.243% 95%CI(0.234% to 0.253%) in 2019. In SIDIAP the prevalence grew since the start of the study, 0.316% 95%CI(0.308% to 0.325%), until 2015, 0.372% 95%CI(0.363% to 0.381%), with a sustained decrease after that. In IPCI the prevalence was stable for the same period (2010-2015) around 0.23% and also decreased between 2015 to 2021. By 2021, the prevalence of use of valproate in women aged 12 to 55 was of 0.164% 95%CI(0.152% to 0.178%) in IPCI and of 0.271% 95%CI(0.263% to 0.279%) in SIDIAP. As for IQVIA Belgium, the prevalence decreased steadily for the study period, from 0.158% 95%CI(0.136% to 0.184%) in 2014 to 0.051% 95%CI(0.038% to 0.069%). In IQVIA Germany, the prevalence decreased from 0.037% 95%CI(0.035% to 0.041%) in 2010 to 0.026% 95%CI(0.024 to 0.028%) in 2014 and remained stable until 2021.

Figure 12.1.3 - Period prevalence of VPA over time (annually) overall

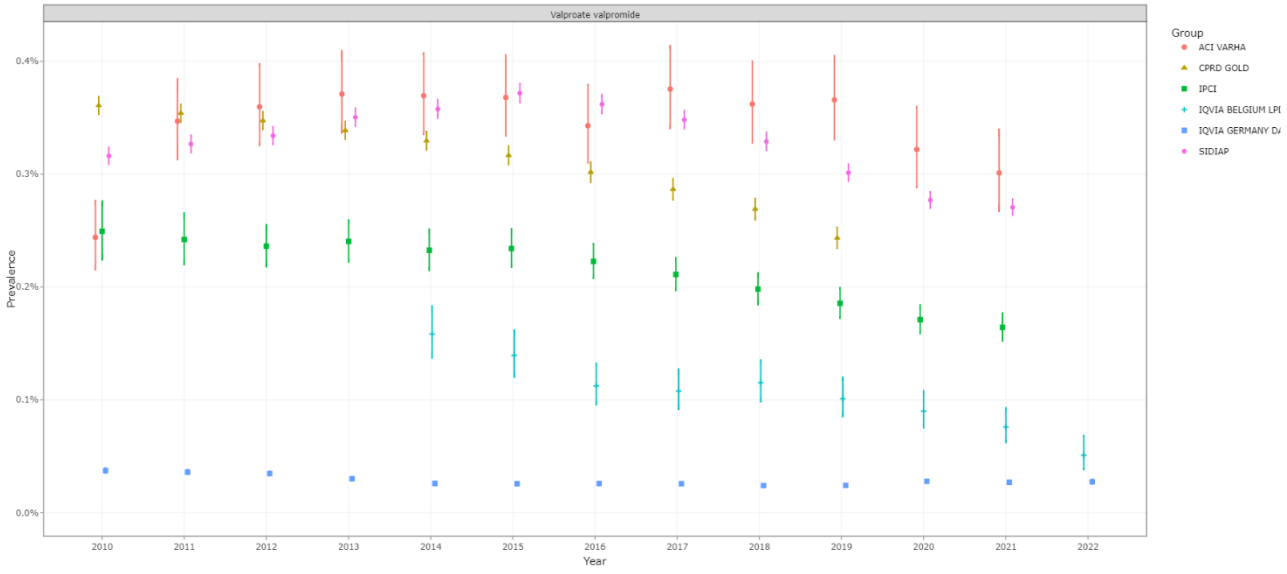


Table 12.1.3 - Period prevalences of VPA over time (annually)

Data Partner	Year	N	Events	Prevalence
CPRD GOLD	2010	1,889,901	6819	0.361% (0.352% to 0.369%)
CPRD GOLD	2011	1,849,811	6548	0.354% (0.345% to 0.363%)
CPRD GOLD	2012	1,809,753	6287	0.347% (0.339% to 0.356%)
CPRD GOLD	2013	1,770,124	5996	0.339% (0.330% to 0.347%)
CPRD GOLD	2014	1,655,338	5455	0.330% (0.321% to 0.338%)
CPRD GOLD	2015	1,492,367	4726	0.317% (0.308% to 0.326%)
CPRD GOLD	2016	1,247,006	3763	0.302% (0.292% to 0.311%)
CPRD GOLD	2017	1,110,710	3183	0.287% (0.277% to 0.297%)
CPRD GOLD	2018	1,017,890	2738	0.269% (0.259% to 0.279%)
CPRD GOLD	2019	965,732	2351	0.243% (0.234% to 0.253%)
IPCI	2010	135,110	337	0.249% (0.224% to 0.277%)
IPCI	2011	168,477	408	0.242% (0.219% to 0.266%)
IPCI	2012	244,295	577	0.236% (0.217% to 0.256%)
IPCI	2013	249,165	599	0.240% (0.222% to 0.260%)
IPCI	2014	248,942	579	0.233% (0.214% to 0.252%)
IPCI	2015	286,996	672	0.234% (0.217% to 0.252%)
IPCI	2016	338,515	754	0.223% (0.207% to 0.239%)
IPCI	2017	351,392	742	0.211% (0.196% to 0.227%)
IPCI	2018	352,212	698	0.198% (0.184% to 0.213%)
IPCI	2019	355,054	659	0.186% (0.172% to 0.200%)
IPCI	2020	370,936	635	0.171% (0.158% to 0.185%)
IPCI	2021	373,083	613	0.164% (0.152% to 0.178%)
SIDIAP	2010	1,778,468	5623	0.316% (0.308% to 0.325%)
SIDIAP	2011	1,806,593	5902	0.327% (0.318% to 0.335%)
SIDIAP	2012	1,796,244	6000	0.334% (0.326% to 0.343%)
SIDIAP	2013	1,754,204	6145	0.350% (0.342% to 0.359%)
SIDIAP	2014	1,739,993	6223	0.358% (0.349% to 0.367%)
SIDIAP	2015	1,717,003	6382	0.372% (0.363% to 0.381%)
SIDIAP	2016	1,710,850	6192	0.362% (0.353% to 0.371%)
SIDIAP	2017	1,706,988	5943	0.348% (0.339% to 0.357%)
SIDIAP	2018	1,710,907	5627	0.329% (0.320% to 0.338%)
SIDIAP	2019	1,717,146	5173	0.301% (0.293% to 0.310%)
SIDIAP	2020	1,731,308	4796	0.277% (0.269% to 0.285%)
SIDIAP	2021	1,723,004	4664	0.271% (0.263% to 0.279%)
ACI VARHA	2010	95,498	233	0.244% (0.215% to 0.277%)
ACI VARHA	2011	100,321	348	0.347% (0.312% to 0.385%)
ACI VARHA	2012	102,036	367	0.360% (0.325% to 0.398%)
ACI VARHA	2013	103,764	385	0.371% (0.336% to 0.410%)
ACI VARHA	2014	105,028	388	0.369% (0.335% to 0.408%)
ACI VARHA	2015	105,452	388	0.368% (0.333% to 0.406%)

Data Partner	Year	N	Events	Prevalence
ACI VARHA	2016	105,277	361	0.343% (0.309% to 0.380%)
ACI VARHA	2017	103,896	390	0.375% (0.340% to 0.414%)
ACI VARHA	2018	101,908	369	0.362% (0.327% to 0.401%)
ACI VARHA	2019	98,408	360	0.366% (0.330% to 0.406%)
ACI VARHA	2020	93,182	300	0.322% (0.288% to 0.360%)
ACI VARHA	2021	84,349	254	0.301% (0.266% to 0.340%)
IQVIA BELGIUM LPD	2014	108,551	172	0.158% (0.136% to 0.184%)
IQVIA BELGIUM LPD	2015	116,895	163	0.139% (0.120% to 0.163%)
IQVIA BELGIUM LPD	2016	120,905	136	0.112% (0.095% to 0.133%)
IQVIA BELGIUM LPD	2017	122,310	132	0.108% (0.091% to 0.128%)
IQVIA BELGIUM LPD	2018	121,443	140	0.115% (0.098% to 0.136%)
IQVIA BELGIUM LPD	2019	120,676	122	0.101% (0.085% to 0.121%)
IQVIA BELGIUM LPD	2020	119,876	108	0.090% (0.075% to 0.109%)
IQVIA BELGIUM LPD	2021	115,756	88	0.076% (0.062% to 0.094%)
IQVIA BELGIUM LPD	2022	82,222	42	0.051% (0.038% to 0.069%)
IQVIA GERMANY DA	2010	1,592,294	596	0.037% (0.035% to 0.041%)
IQVIA GERMANY DA	2011	1,744,606	631	0.036% (0.033% to 0.039%)
IQVIA GERMANY DA	2012	1,911,601	666	0.035% (0.032% to 0.038%)
IQVIA GERMANY DA	2013	2,067,804	626	0.030% (0.028% to 0.033%)
IQVIA GERMANY DA	2014	2,196,933	571	0.026% (0.024% to 0.028%)
IQVIA GERMANY DA	2015	2,288,734	589	0.026% (0.024% to 0.028%)
IQVIA GERMANY DA	2016	2,346,579	608	0.026% (0.024% to 0.028%)
IQVIA GERMANY DA	2017	2,428,241	626	0.026% (0.024% to 0.028%)
IQVIA GERMANY DA	2018	2,441,929	589	0.024% (0.022% to 0.026%)
IQVIA GERMANY DA	2019	2,339,499	569	0.024% (0.022% to 0.026%)
IQVIA GERMANY DA	2020	2,204,846	616	0.028% (0.026% to 0.030%)
IQVIA GERMANY DA	2021	1,940,597	523	0.027% (0.025% to 0.029%)
IQVIA GERMANY DA	2022	1,241,846	341	0.027% (0.025% to 0.031%)

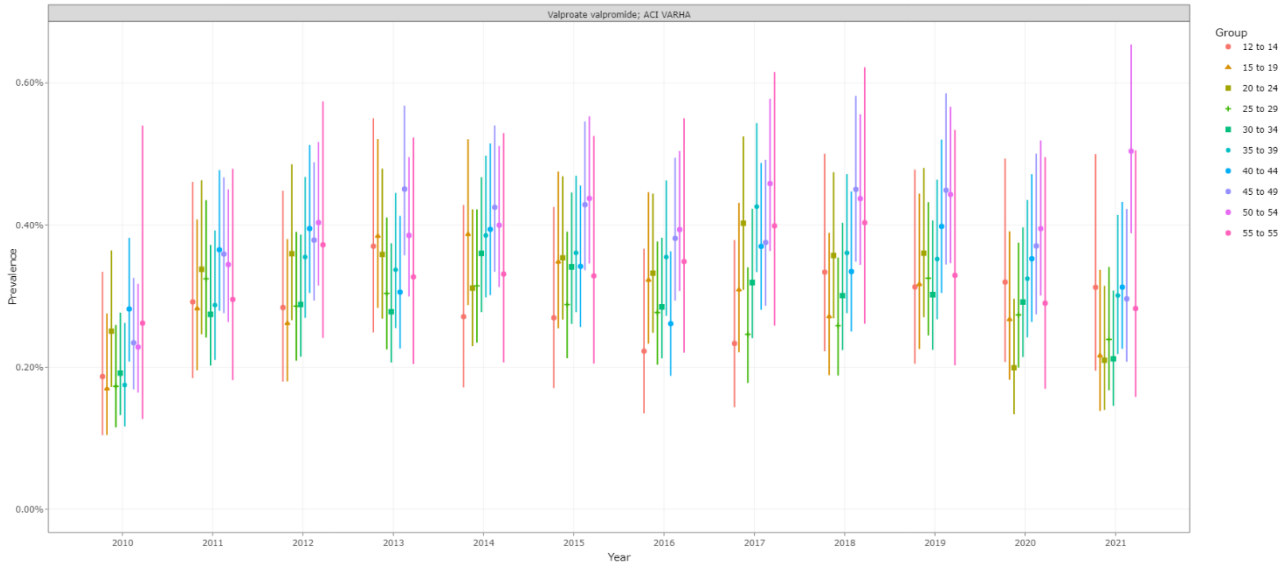
Prevalence of VPA over time by age

Figure 12.1.4 shows prevalence of use of valproate from 2010 to 2021 in women by age group for each database. The number of events, population and person-years for each calendar year, age group and database can be found in the shiny app (https://data-dev.darwin-eu.org/EUPAS50789/)

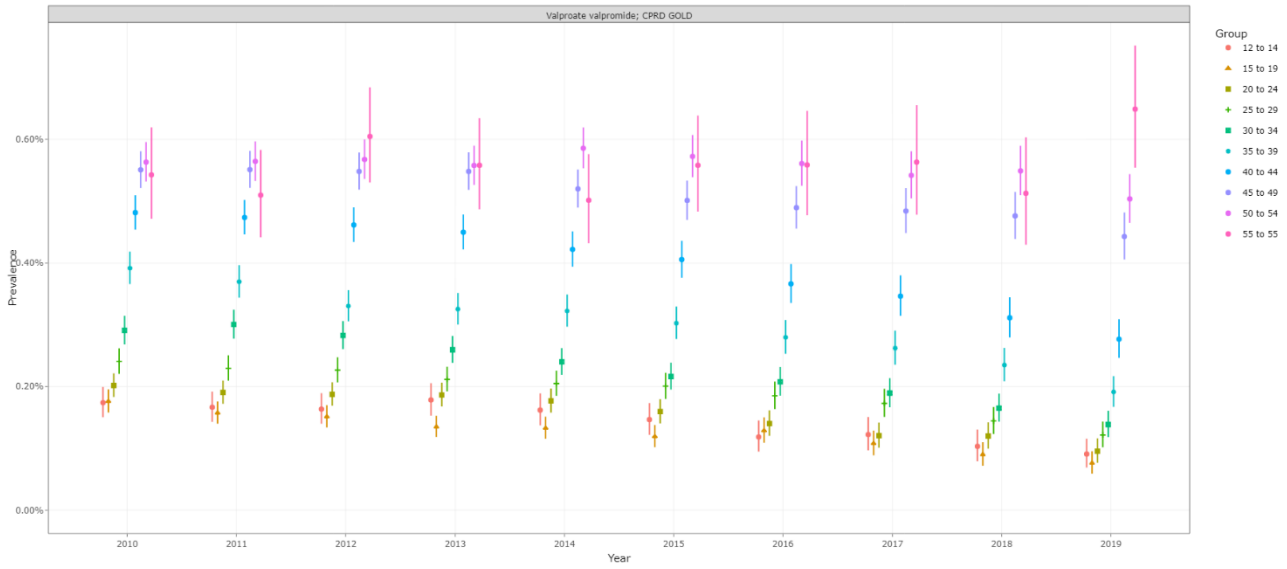
Although the prevalence of use of VPA decreased during the study period for most databases, the reduction was not equal for all age groups, with the younger age groups having a more pronounced decrease after 2015. In CPRD GOLD, the prevalence increased with age, with 0.091% (0.069% to 0.116%) in the 12 to 14 age group to 0.504% (0.465% to 0.544%) in the 50 to 54 age group in 2019. In terms of trends, the use for the 45 to 49 and the 50 to 54 age groups remained relatively stable during the whole period with a prevalence around 0.5%. The age groups younger than 45, however, experienced a decrease in prevalence. Similar trends can be seen in SIDIAP, where in the groups >45 years old prevalence increases or remains stable throughout the study period and it decreases in those <45. In IPCI, there is a decrease of prevalence in all the age groups, with the younger age groups having a lower prevalence that in the older ones. In ACI VARHA the prevalence of VPA use remains stable, however the sample size is too small to observe any meaningful differences in trends by age. In IQVIA Belgium, older age groups' prevalence decreased from 2014 to 2021, and younger age groups remained stable in a low prevalence (around 0.05%).

Figure 12.1.4 - Period prevalences of VPA over time stratified by age

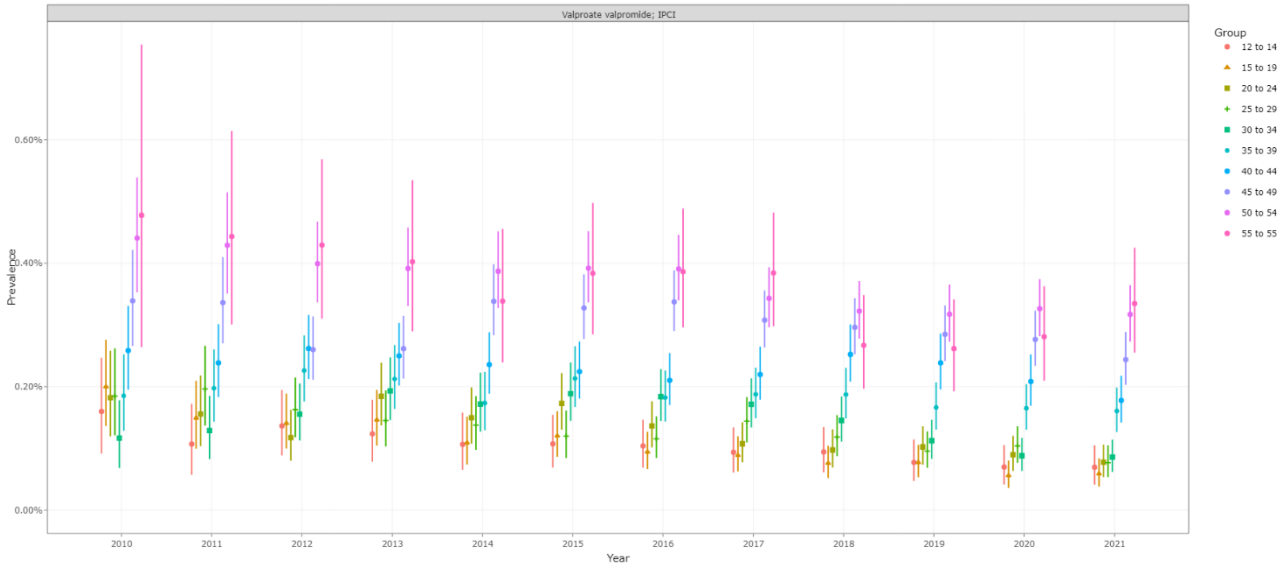
ACI VARHA



CPRD GOLD



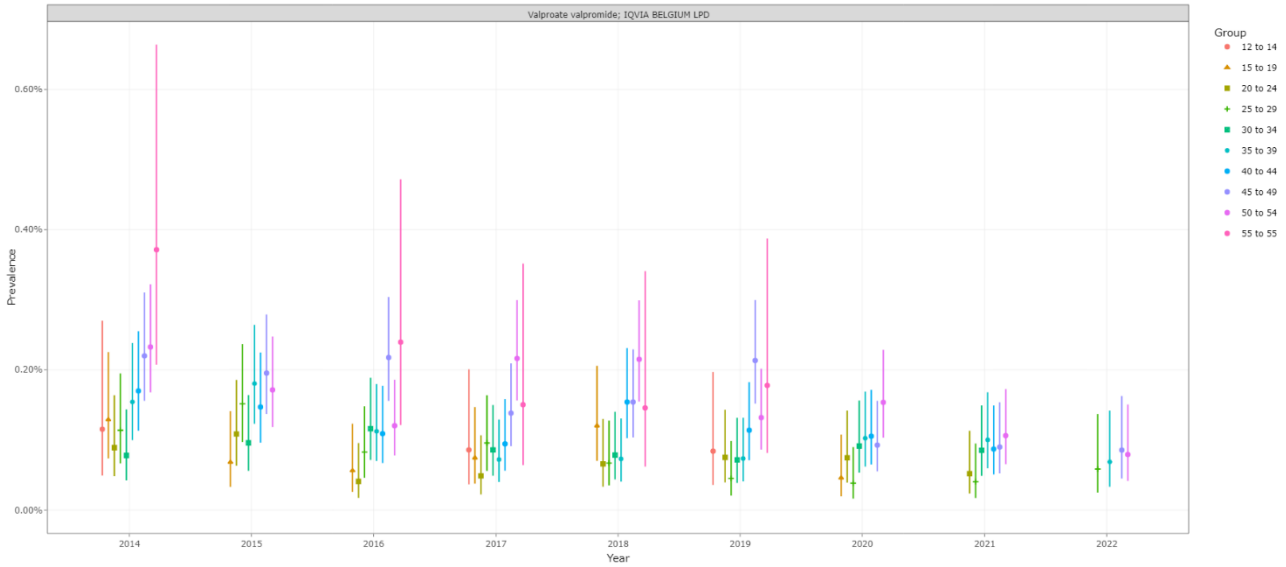
IPCI


Valproate valpromide; IPCI
Prevalence
0.60%
0.40%
0.20%
0.00%
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year
Group
12 to 14
15 to 19
20 to 24
25 to 29
30 to 34
35 to 39
40 to 44
45 to 49
50 to 54
55 to 55

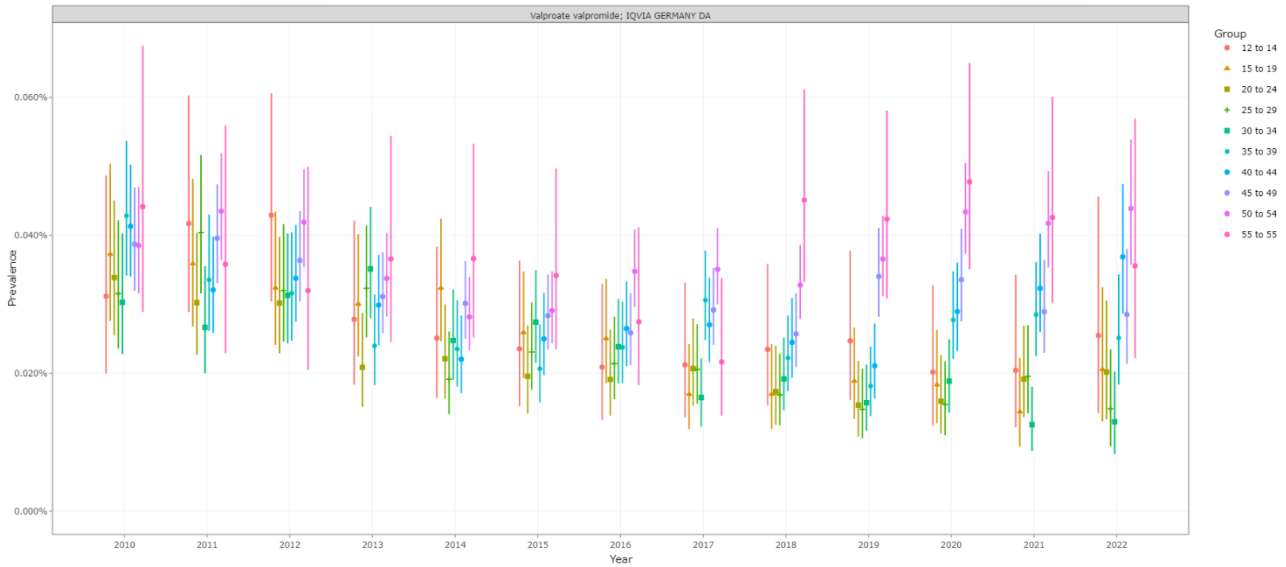
SIDIAP


Valproate valpromide; SIDIAP
Prevalence
0.50%
0.40%
0.30%
0.20%
0.10%
0.00%
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Year
Group
12 to 14
15 to 19
20 to 24
25 to 29
30 to 34
35 to 39
40 to 44
45 to 49
50 to 54
55 to 55

IQVIA BELGIUM LPD



IQVIA GERMANY DA



Incidence and Prevalence of alternative treatments

The incidence and prevalence of alternative drugs to VPA is shown in Figures 12.1.5 and 12.1.6 respectively by indication and ATC class. The denominator for both measures is the total population of women 12 to 55.

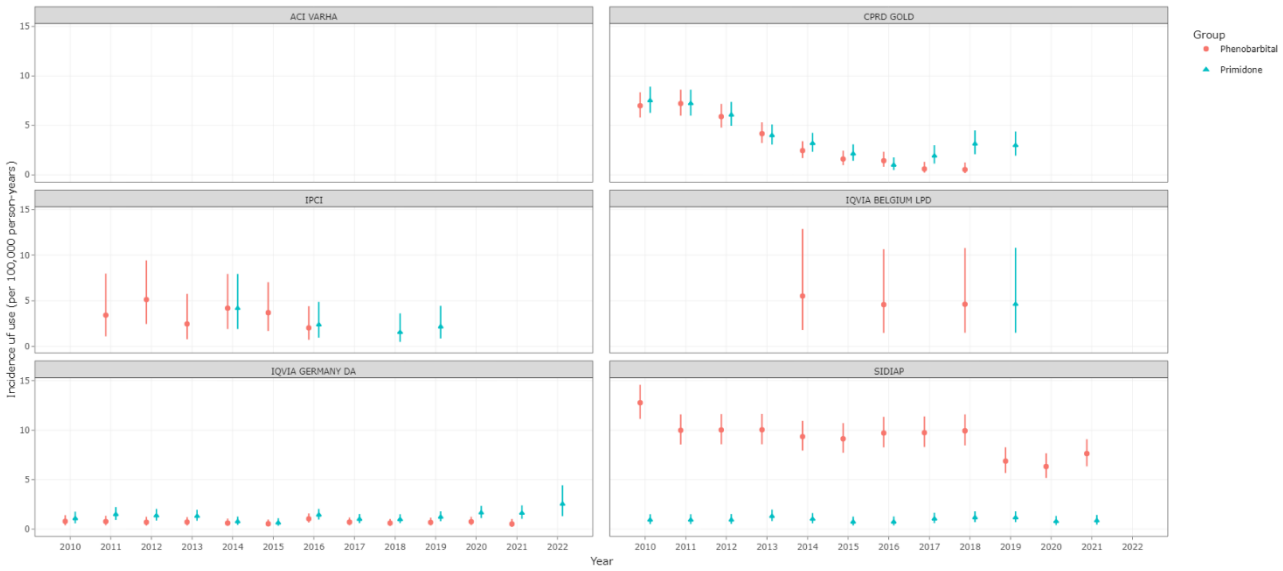
Regarding other antiepileptics, the most prevalent treatments are pregabalin and gabapentin (except in IPCI and IQVIA Belgium LPD where gabapentin has a lower prevalence) and its prevalence has increased through all the study time for all databases. The incident use of these two drugs also increases in all databases, except in CPRD, where it increases until 2014 to decrease thereafter. In addition, in SIDIAP and IQVIA Belgium, a third antiepileptic, clonazepam, shows a high prevalence and incidence also with an increasing trend.

As for the studied treatments for bipolar disorder, lamotrigine, lithium, olanzapine and quetiapine; their prevalence increases from 2010 to 2021 in all databases, with Quetiapine consistently more prescribed and more used throughout. Amongst the studied medicines for migraine prevention, beta blockers and amitriptyline are the most prescribed. Use of beta blockers remains stable or increases during the study period for all databases except for IPCI. New users of amitriptyline remain stable in all databases or decrease, but the prevalence of use increases.

Figure 12.1.5 - Incidence rates of alternative treatments over time (annually) overall

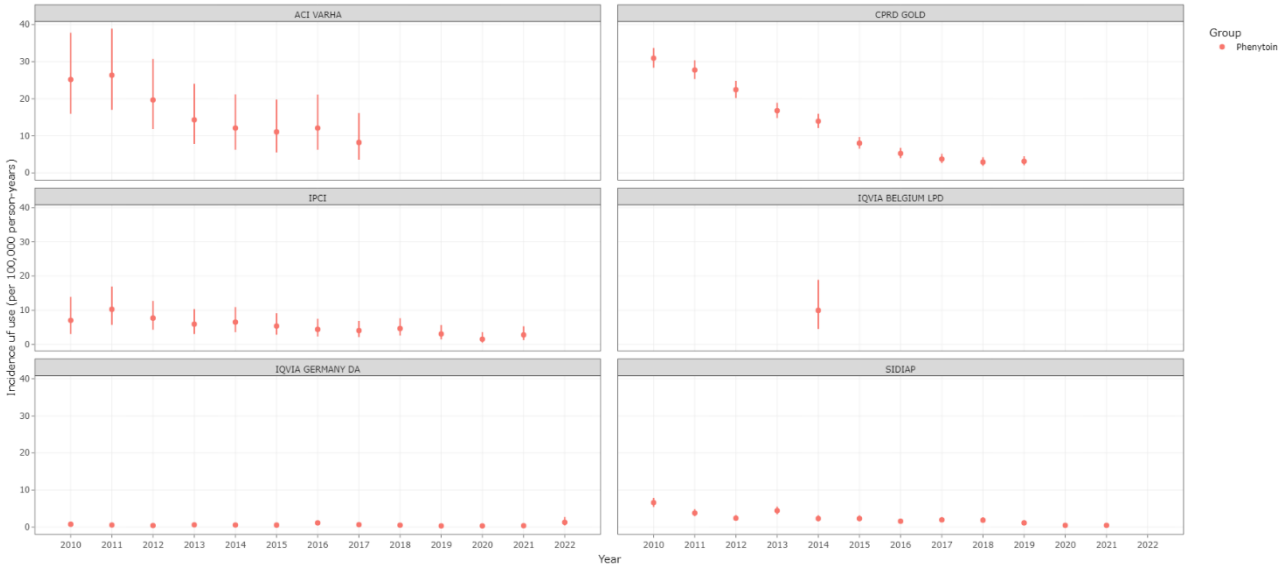
Antiepileptics

N03AA Barbiturates and derivatives

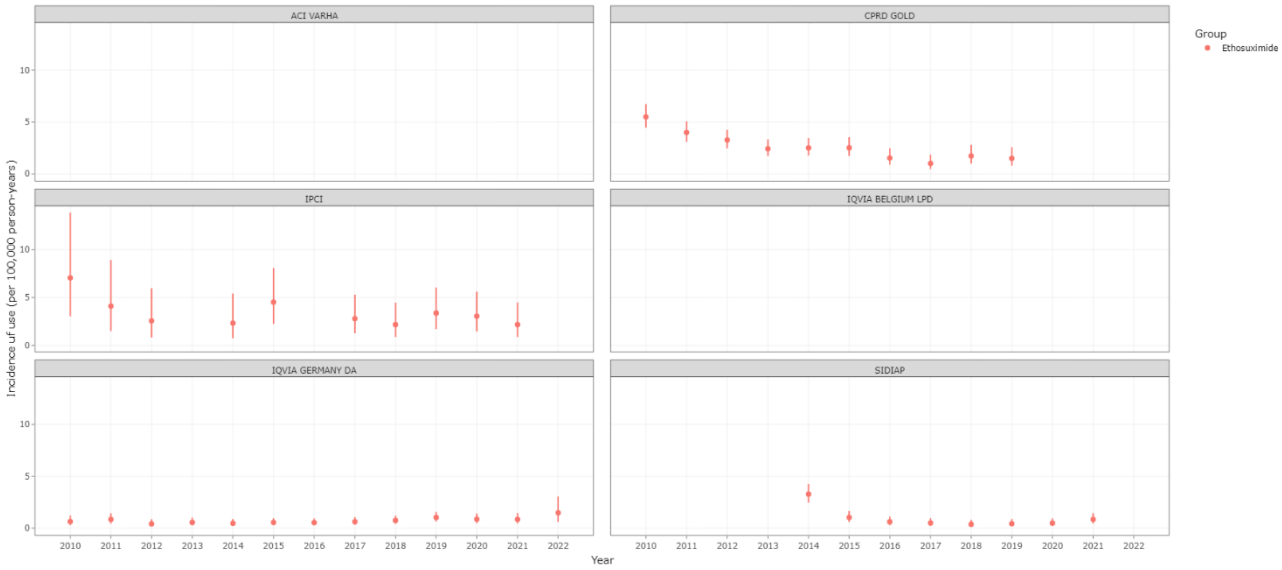


Incidence not shown if number of users <5 per time period

N03AB Hydantoin derivatives

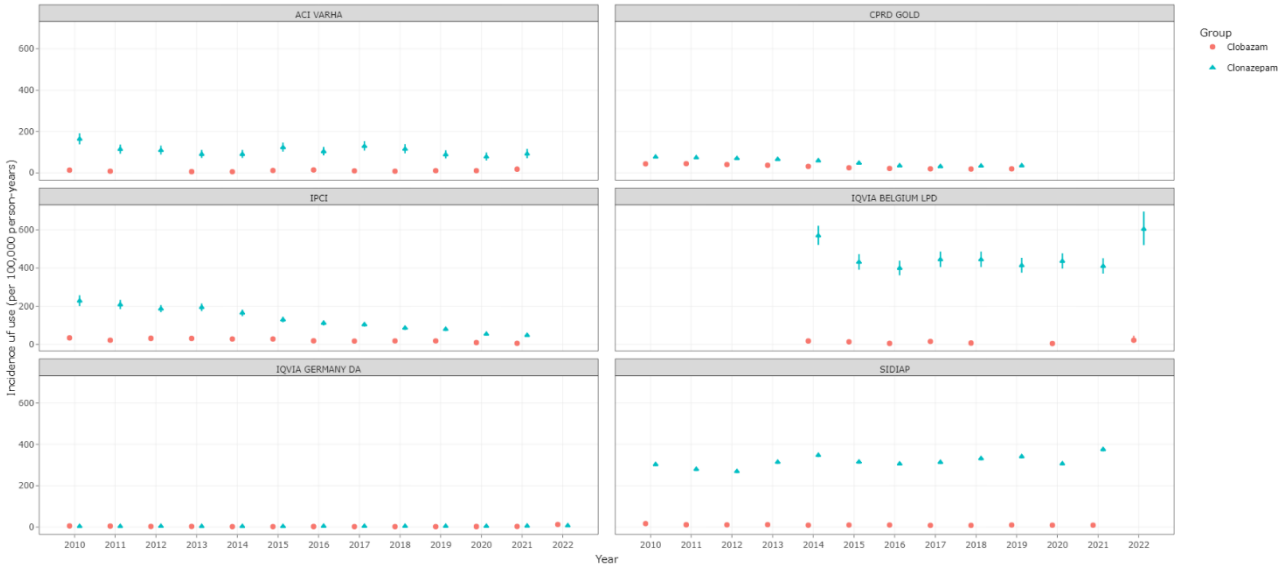


N03AD Succinimide derivatives

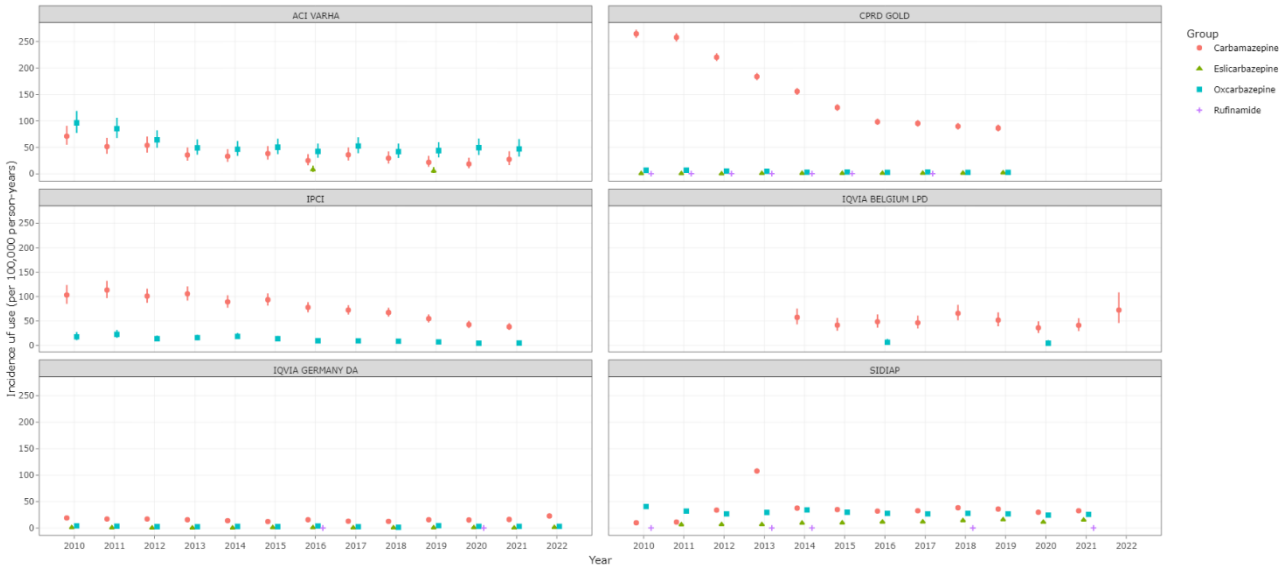


Incidence not shown if number of users <5 per time period

N03AE & N05BA Benzodiazepine derivatives

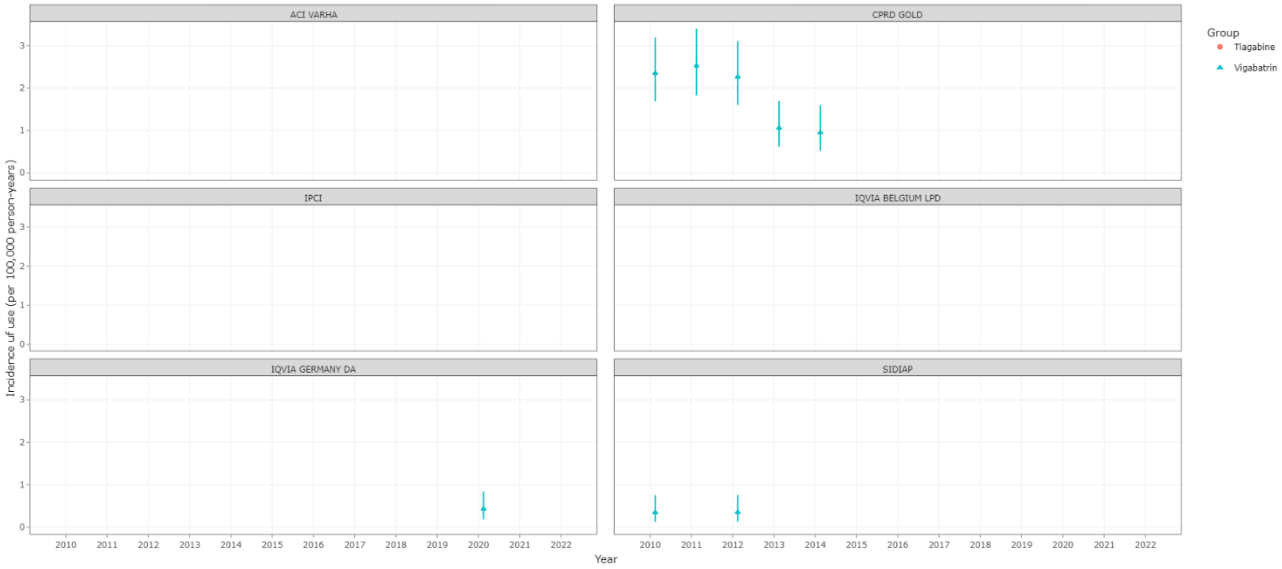


N03AF Carboxamide derivatives



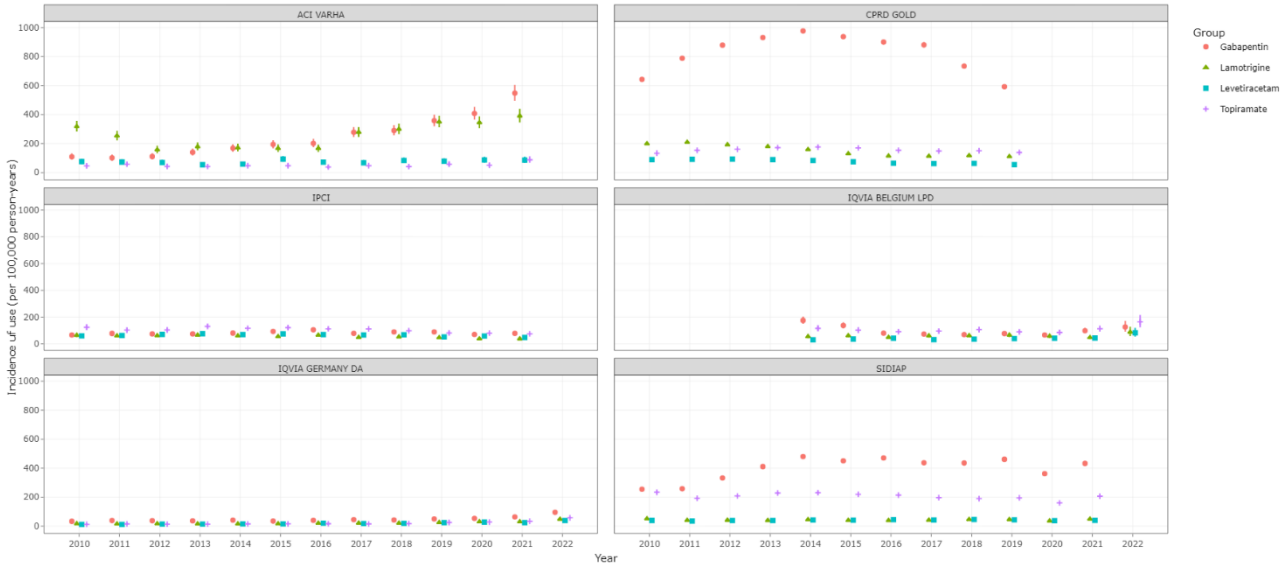
Incidence not shown if number of users <5 per time period

N03AG Fatty acid derivatives



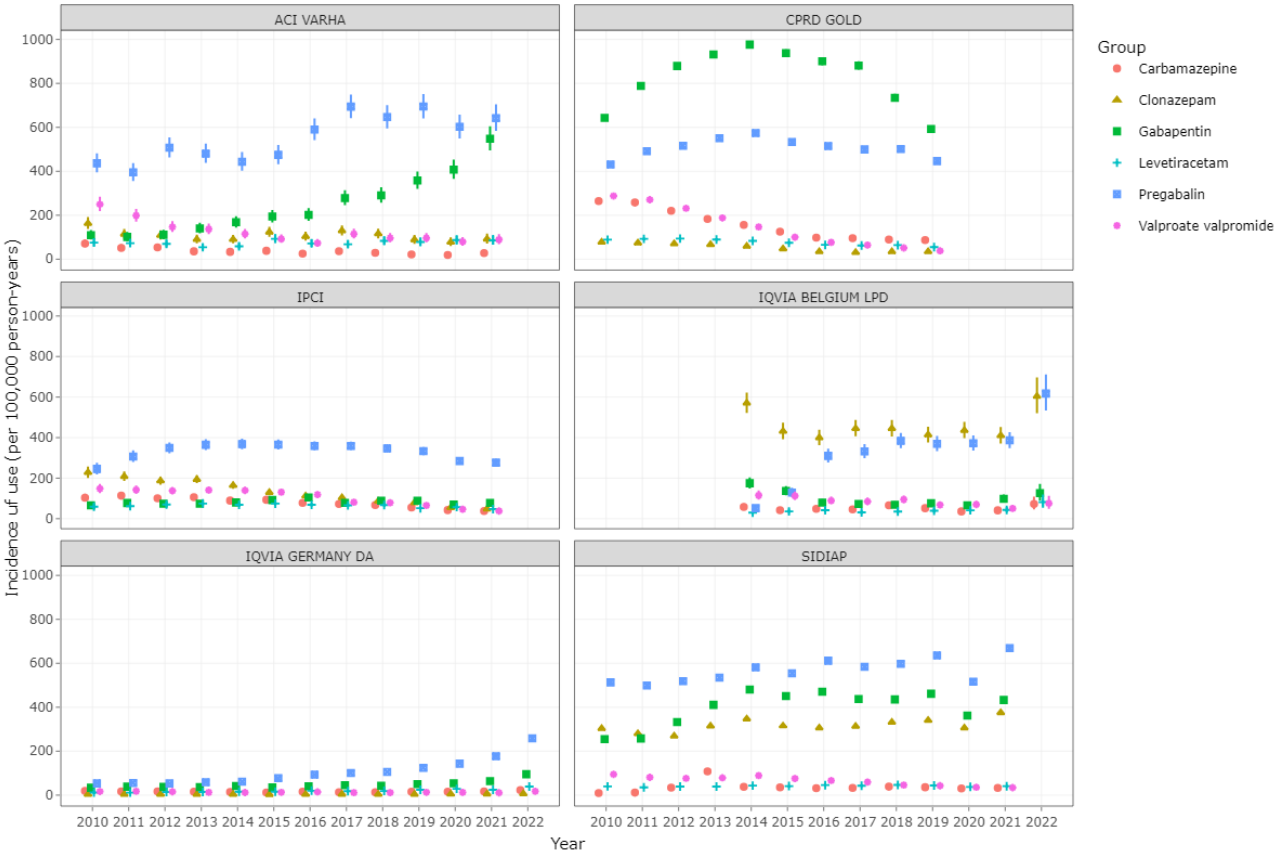
Incidence not shown if number of users <5 per time period

N03AX Other antiepileptics

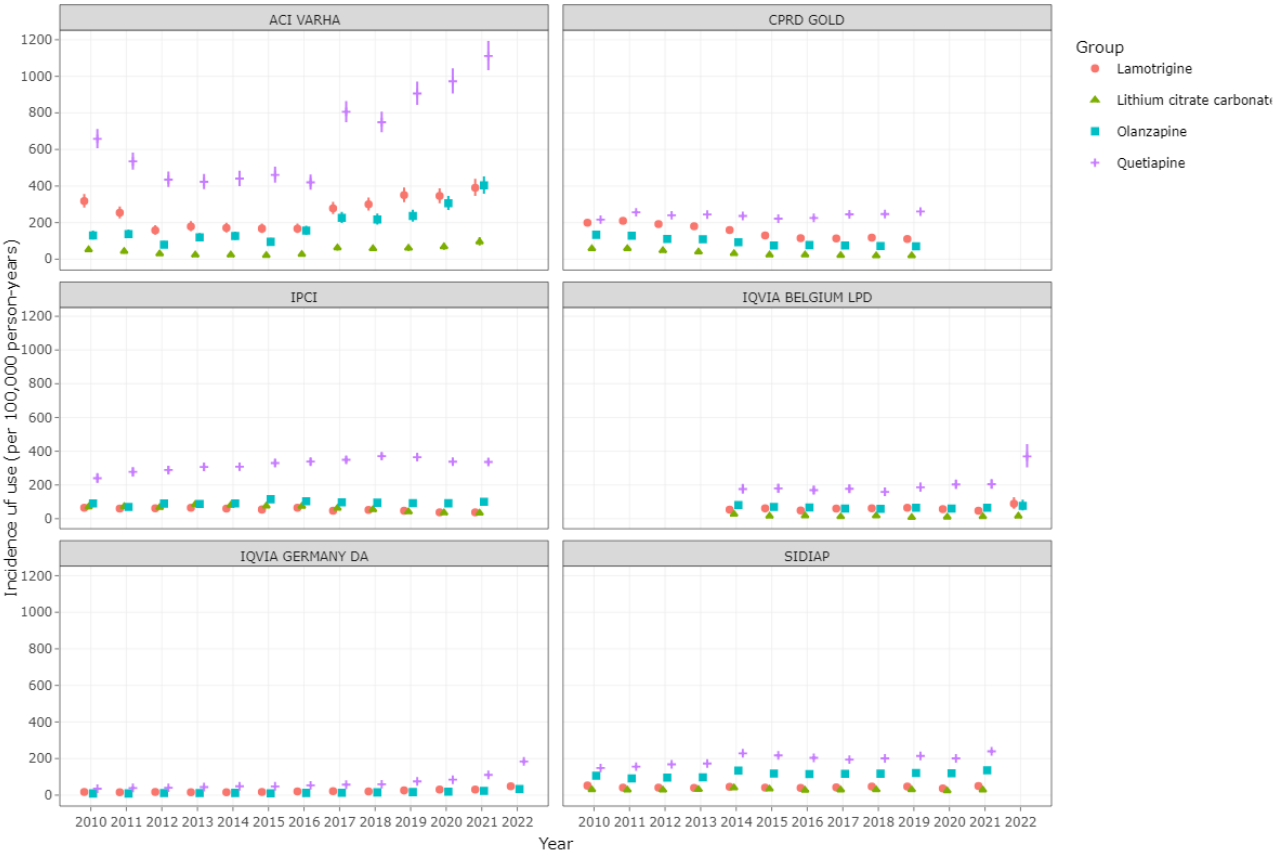


Incidence not shown if number of users <5 per time period

Top 5 Antiepileptics + VPA

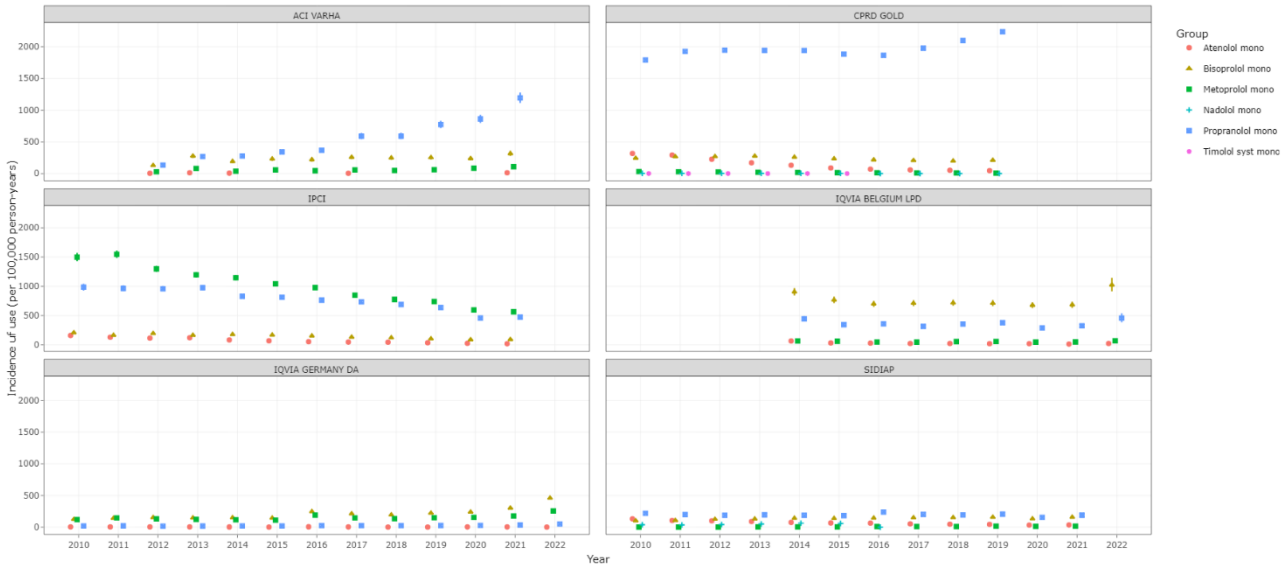


Bipolar disorder treatments



Migraine prevention treatments

C07A Beta blocking agents



Others

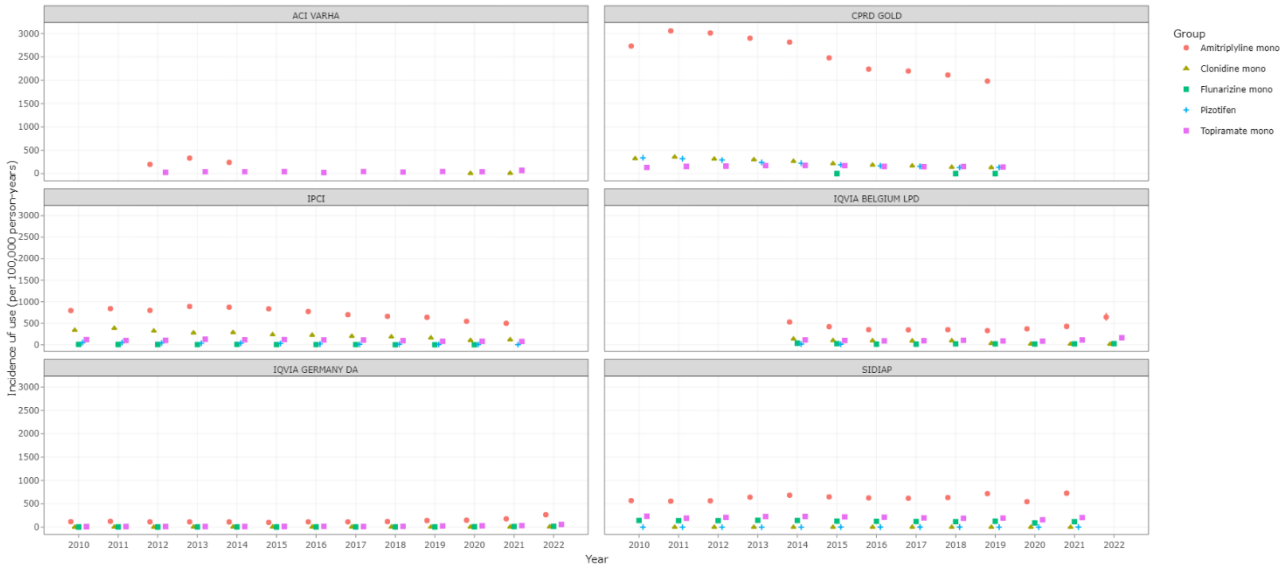
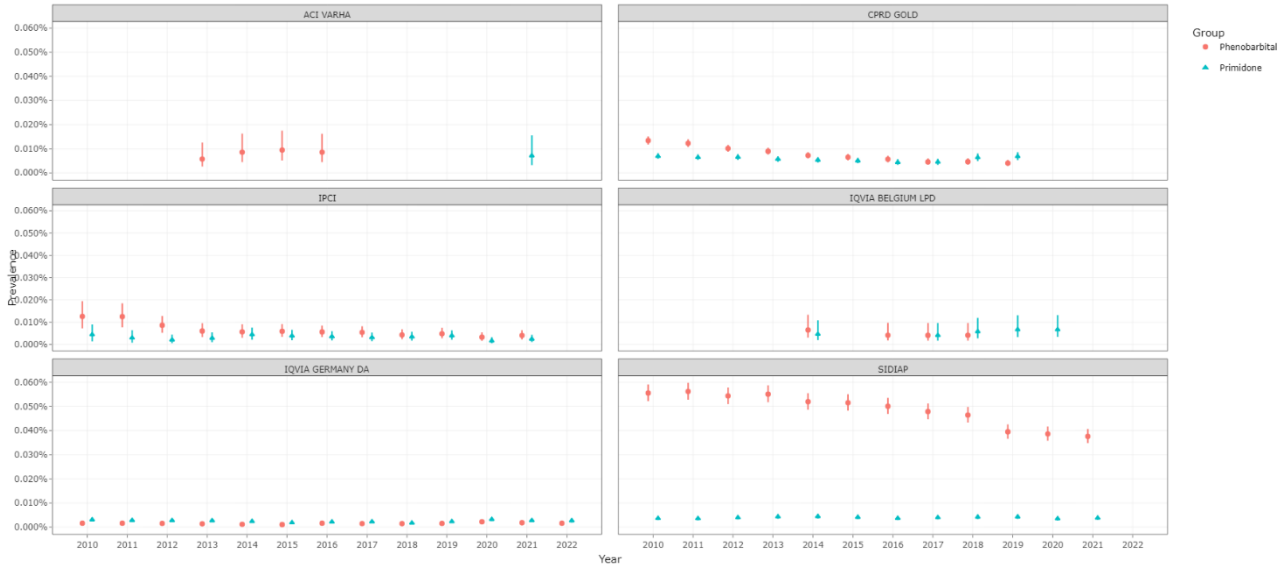


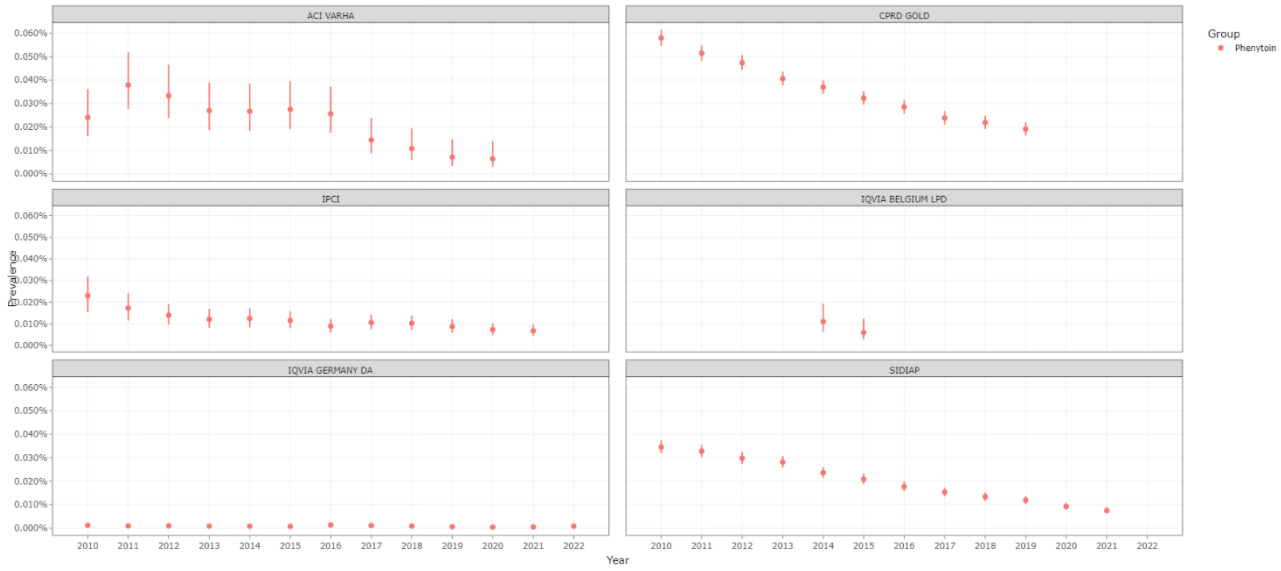
Figure 12.1.6 – Period prevalence of alternative treatments over time (annually) overall

Antiepileptics

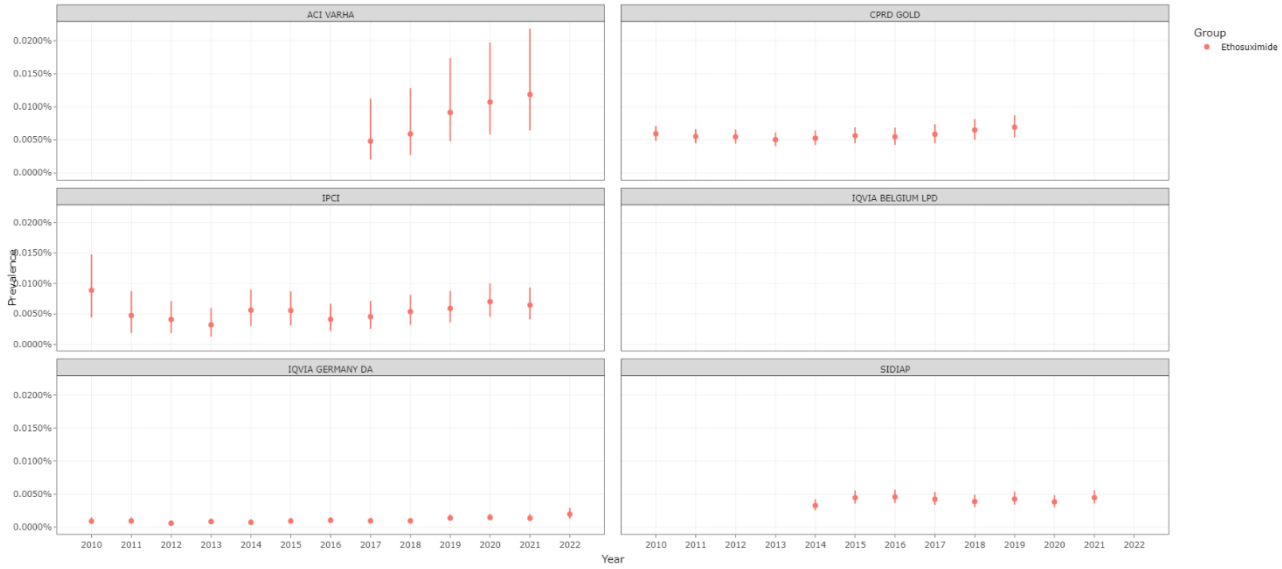
N03AA Barbiturates and derivatives



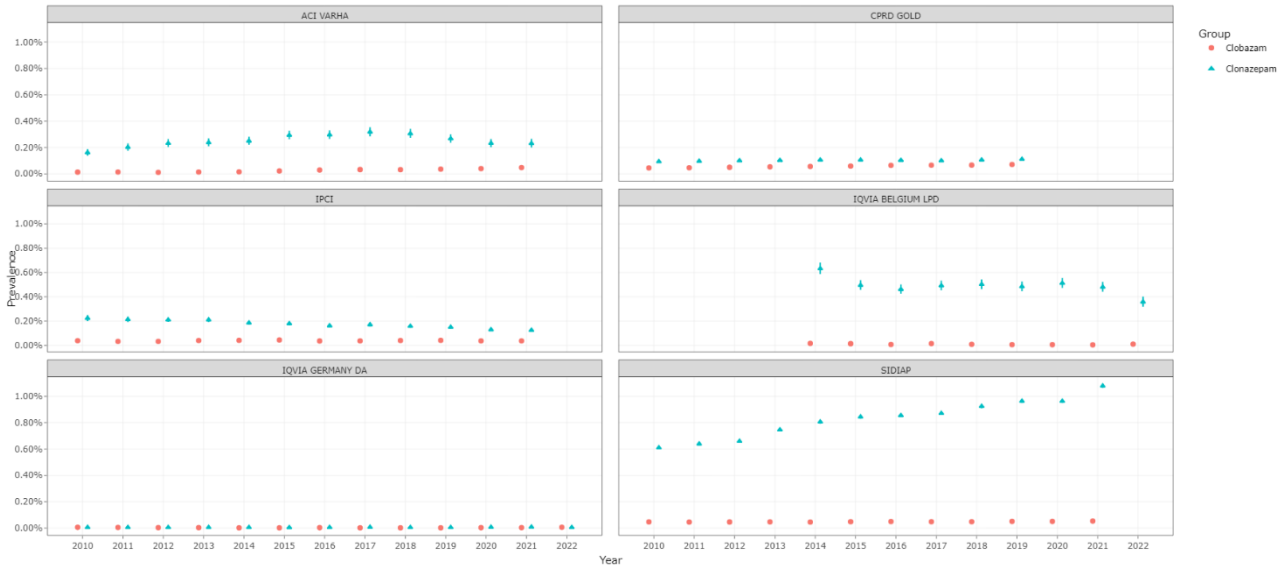
N03AB Hydantoin derivatives



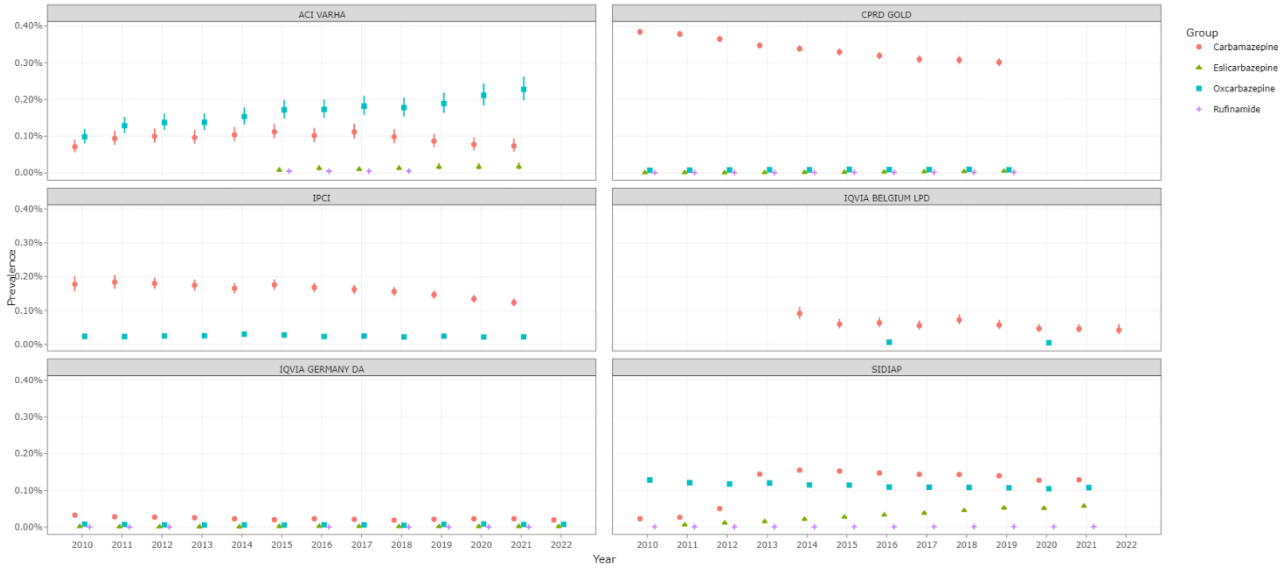
N03AD Succinimide derivatives



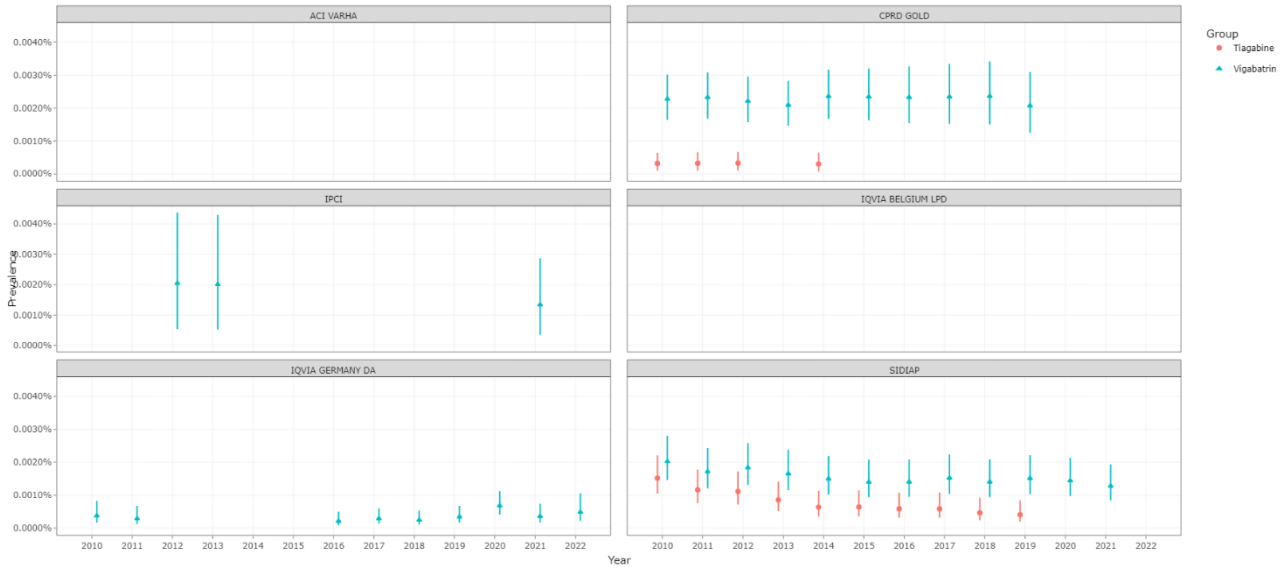
N03AE & N05BA Benzodiazepine derivatives



N03AF Carboxamide derivatives

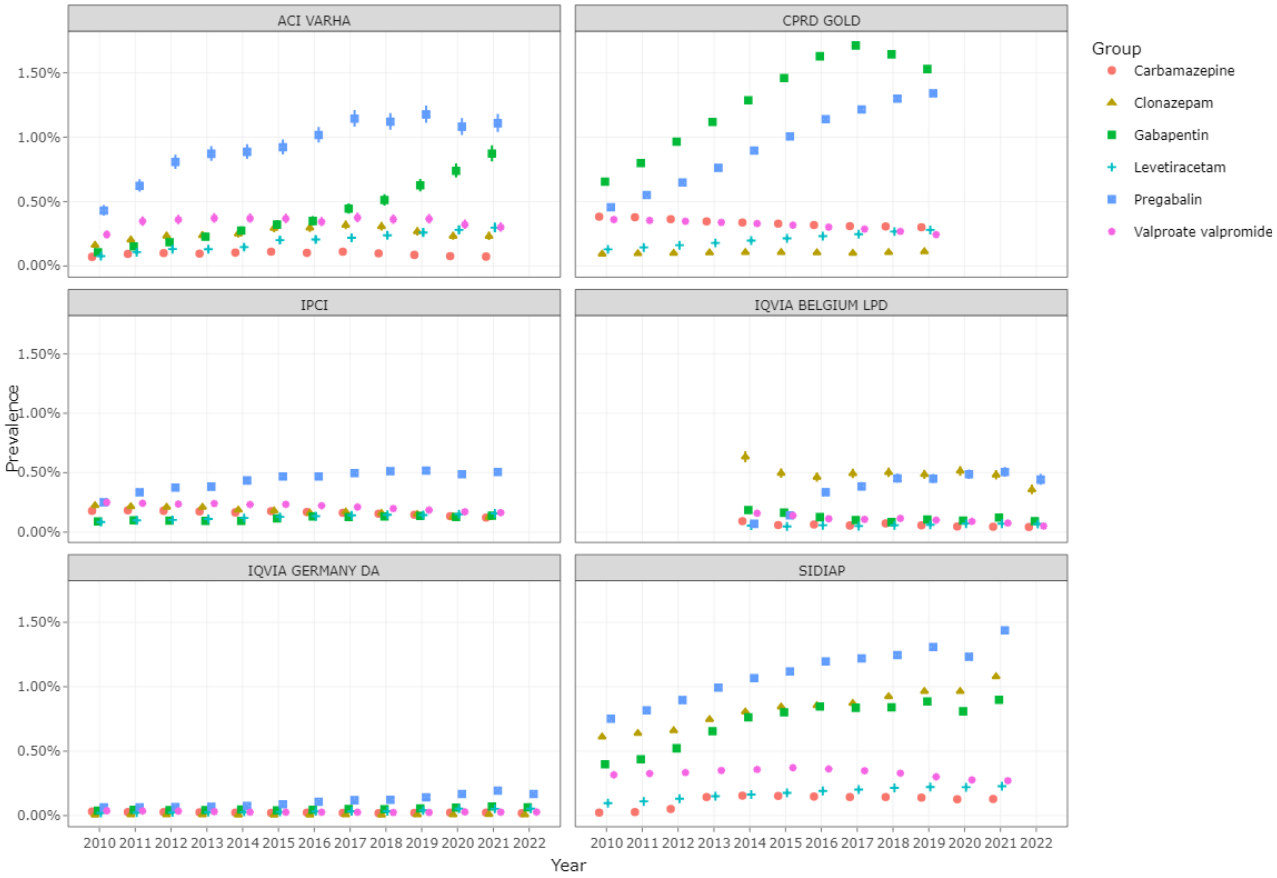


N03AG Fatty acid derivatives

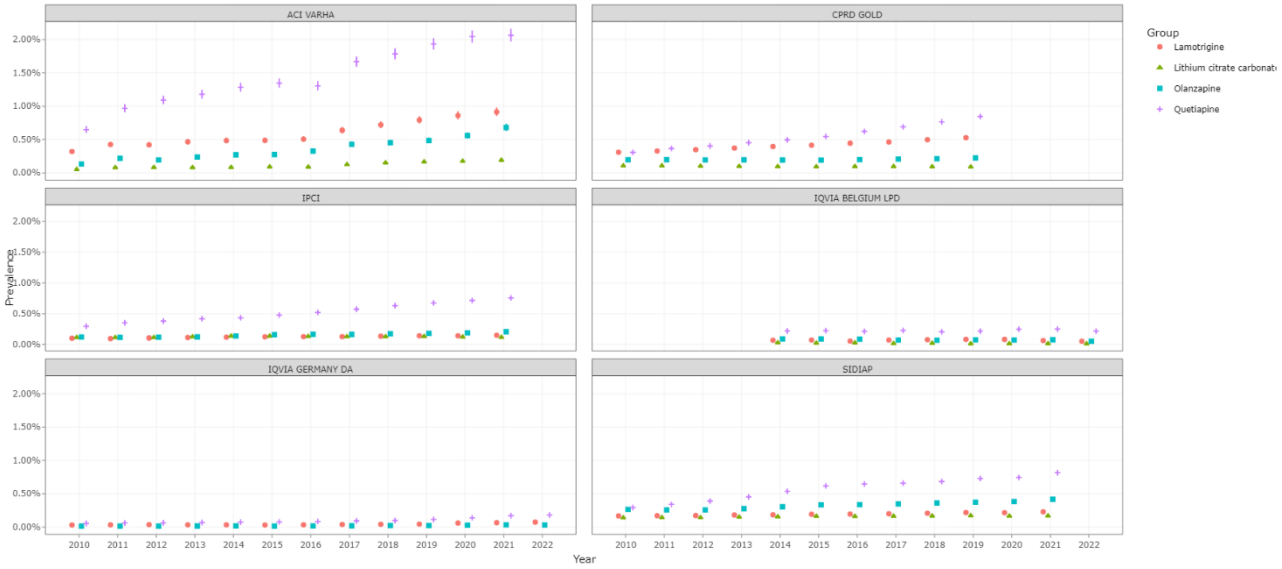


N03AX Other antiepileptics

Top 5 Antiepileptics + VPA

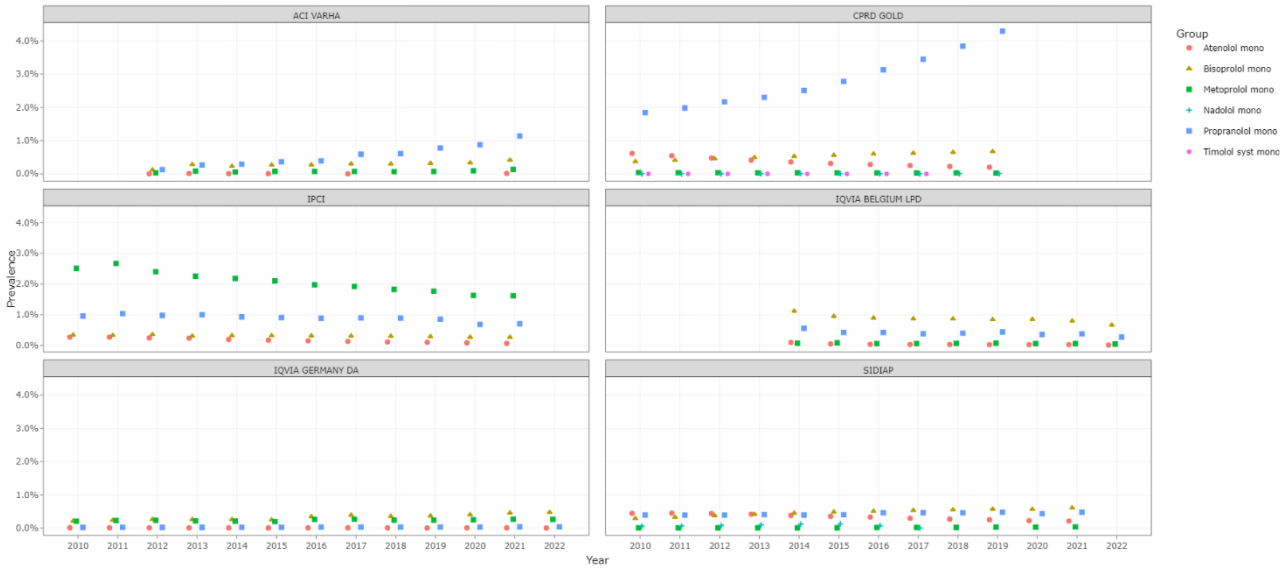


Bipolar disorder treatments

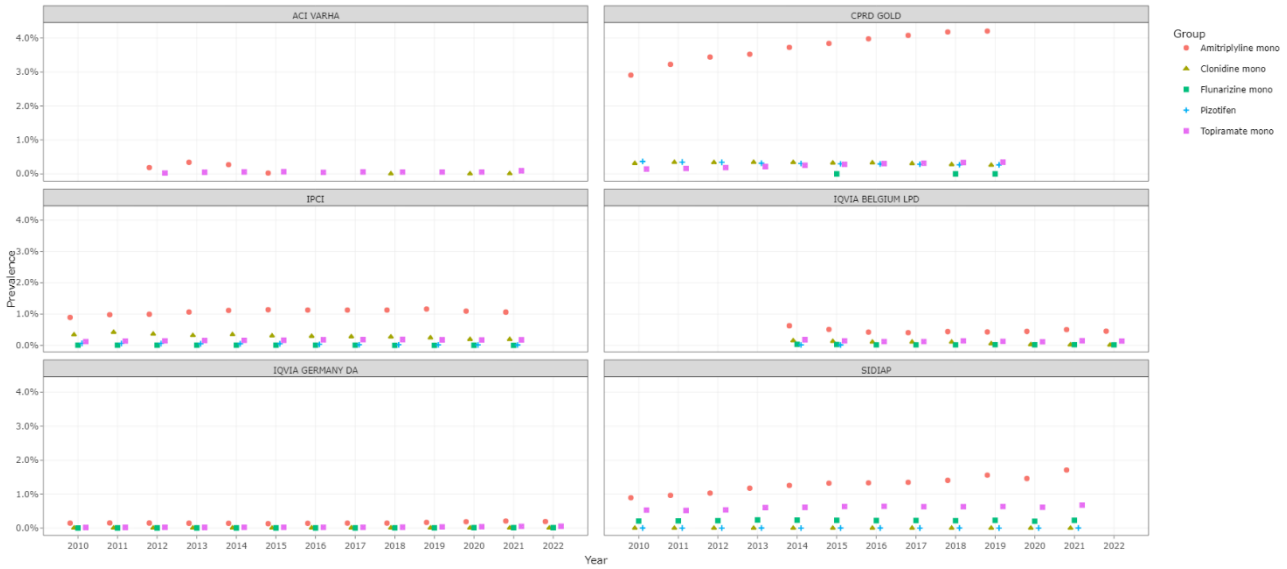


Migraine prevention treatments

C07A Beta blocking agents



Others



12.1.5 Other Analysis

Results from combinations of the presented stratifications, age groups, database, product, and year are available in the shiny app at https://data-dev.darwin-eu.org/EUPAS50789/

12.2. Patient-level DUS

Results from patient-level DUS for VPA (incl. valpromide) are provided for CPRD GOLD, IPCI, SIDIAP, IQVIA Belgium LPD and IQVIA Germany DA. In CPRD, IPCI, IQVIA Belgium LPD and IQVIA Germany DA, all women were prescribed valproate or valproic acid, whereas in SIDIAP 3.5% people had valpromide at index date. For SIDIAP, results are presented combining valproate, valproic acid and valpromide.

12.2.1. Participants

New users of VPA in the period between 01/01/2010 and 31/12/2021 (or latest date available), with at least 365 days of visibility prior to the date of their first VPA prescription, who did not use VPA in the previous 365 days were selected using the following approach:

For all people with VPA use in the respective database (N(subjects) =129,442 in CPRD GOLD, N = 19,149 in IPCI, N = 64,157 in SIDIAP, N = 6,239 in IQVIA Belgium LPD and N= 51,170 in IQVIA Germany DA), the first prescription of VPA within the study period, with 365 days of VPA-free observation time, was identified (N = 25,790 in CPRD GOLD, N = 4,644 in IPCI, N = 37,753 in SIDIAP, N = 3,211 IQVIA Belgium LPD and N = 19,162 in IQVIA Germany DA). Among those, all women meeting the criteria for study inclusion were selected (N = 6,416 in CPRD GOLD, N = 1,241 in IPCI, N = 10,398 in SIDIAP, N = 945 in IQVIA Belgium LPD and N = 4,002 in IQVIA Germany DA).

12.2.2. Descriptive Data

Summary of Baseline Characteristics

6416, 1241, 10,398, 945 and 4,002 women were eligible for study inclusion and had a first prescription of VPA within the study period in CPRD GOLD, IPCI, SIDIAP, IQVIA Belgium LPD and IQVIA Germany DA, respectively. The median age in these cohorts of women ranged between 40 and 43 years. Healthcare utilisation was high with the median number of visits ranging between 5 in IQVIA Germany DA and 29 in CPRD. Anxiety and depressive disorder were frequent comorbidities, with 20%-39% and 16%-44% having a recording of the respective diagnoses any time before treatment start. Results are summarised in Table 12.2.1 below.

Results stratified by age group presented separately in Tables 12.2.2a-e for each database. Use of hormonal contraception varied greatly between databases and across age groups, with some 40% of women between 20-29 using hormonal contraceptives in CPRD, compared to >5% of people aged 50+. The level of prescription of contraceptives was highest in CPRD GOLD, followed by IQVIA Belgium LPD, IPCI and lowest in SIDIAP and IQVIA Germany DA

Baseline characteristics stratified by calendar year and/or indication are available in the Shiny web-application.

Table 12.2.1- Baseline characteristics of new drug users at the time of therapy initiation *for all age groups, whole study period*

Database	CPRD GOLD	IPCI	SIDIAP	IQVIA Belgium LPD	IQVIA Germany DA
Number subjects	**6416**	**1241**	**10398**	**945**	**4002**
Sex, N (%)					
Female	6416 (100%)	1241 (100%)	10398 (100%)	945 (100%)	4002 (100%)
Age					
mean (std)	37.9 (11.5)	39.8 (11.6)	38 (11.7)	39.2 (11.7)	39.7 (11.9)
median [p75 - p75]	40 [29 - 47]	43 [32 - 49]	40 [30 - 48]	41 [31 - 49]	43 [31 - 50]
Age groups, N (%)					
12 to 14	155 (2.4%)	28 (2.3%)	336 (3.2%)	18 (1.9%)	97 (2.4%)
15 to 19	358 (5.6%)	66 (5.3%)	775 (7.5%)	60 (6.3%)	208 (5.2%)
20 to 24	530 (8.3%)	91 (7.3%)	637 (6.1%)	68 (7.2%)	264 (6.6%)
25 to 29	612 (9.5%)	86 (6.9%)	740 (7.1%)	67 (7.1%)	356 (8.9%)
30 to 34	700 (10.9%)	95 (7.7%)	1079 (10.4%)	89 (9.4%)	371 (9.3%)
35 to 39	816 (12.7%)	137 (11%)	1441 (13.9%)	120 (12.7%)	417 (10.4%)
40 to 44	988 (15.4%)	197 (15.9%)	1707 (16.4%)	132 (14%)	518 (12.9%)
45 to 49	1107 (17.3%)	241 (19.4%)	1747 (16.8%)	169 (17.9%)	702 (17.5%)
50 to 54	977 (15.2%)	251 (20.2%)	1651 (15.9%)	186 (19.7%)	884 (22.1%)
55	173 (2.7%)	49 (3.9%)	285 (2.7%)	36 (3.8%)	185 (4.6%)
Prior history, days					
mean (std)	3565.9 (2024)	1493.6 (877.5)	3223.6 (1301.5)	1334 (763.6)	2329 (1787.2)
median [p75 - p75]	3519 [1936 - 4827]	1309 [794 - 1991]	3112 [2173 - 4130.75]	1156 [698 - 1814]	1817 [938 - 3206.75]
Visit occurrence (prior year)					
mean (std)	32.9 (22.7)	9 (8.4)	18.2 (18.5)	7 (6.9)	7 (9.3)
median [p75 - p75]	29 [17 - 44]	7 [4 - 12]	14 [7 - 24]	6 [3 - 10]	5 [2 - 11]
General conditions (any time prior)					
Anxiety	2260 (35.2%)	392 (31.6%)	4099 (39.4%)	307 (32.5%)	806 (20.1%)
Asthma	1017 (15.9%)	102 (8.2%)	545 (5.2%)	143 (15.1%)	234 (5.8%)
Chronic Kidney Disease	146 (2.3%)	<5	128 (1.2%)	<5	63 (1.6%)

Database	CPRD GOLD	IPCI	SIDIAP	IQVIA Belgium LPD	IQVIA Germany DA
Chronic Liver Disease	20 (0.3%)	<5	103 (1%)	NA	16 (0.4%)
COPD	82 (1.3%)	21 (1.7%)	96 (0.9%)	113 (12%)	135 (3.4%)
Dementia	23 (0.4%)	<5	37 (0.4%)	<5	64 (1.6%)
Depressive disorder	2460 (38.3%)	194 (15.6%)	2610 (25.1%)	414 (43.8%)	1420 (35.5%)
Diabetes	252 (3.9%)	57 (4.6%)	366 (3.5%)	59 (6.2%)	208 (5.2%)
GERD	174 (2.7%)	19 (1.5%)	262 (2.5%)	172 (18.2%)	84 (2.1%)
Heart failure	13 (0.2%)	6 (0.5%)	18 (0.2%)	<5	43 (1.1%)
HIV	6 (0.1%)	NA	53 (0.5%)	<5	5 (0.1%)
Hypertension	333 (5.2%)	96 (7.7%)	601 (5.8%)	166 (17.6%)	431 (10.8%)
Hypothyroidism	366 (5.7%)	56 (4.5%)	896 (8.6%)	104 (11%)	313 (7.8%)
Infertility	63 (1%)	NA	144 (1.4%)	<5	<5
Inflammatory Bowel Disease	40 (0.6%)	6 (0.5%)	36 (0.3%)	7 (0.7%)	30 (0.7%)
Malignant neoplastic disease	199 (3.1%)	59 (4.8%)	332 (3.2%)	27 (2.9%)	137 (3.4%)
Myocardial Infarction	10 (0.2%)	<5	16 (0.2%)	<5	13 (0.3%)
Osteoporosis	44 (0.7%)	7 (0.6%)	84 (0.8%)	22 (2.3%)	32 (0.8%)
Pneumonia	89 (1.4%)	51 (4.1%)	369 (3.5%)	29 (3.1%)	115 (2.9%)
Rheumatoid Arthritis	25 (0.4%)	9 (0.7%)	24 (0.2%)	5 (0.5%)	32 (0.8%)
Stroke	81 (1.3%)	37 (3%)	142 (1.4%)	14 (1.5%)	81 (2%)
Venous Thromboembolism	88 (1.4%)	25 (2%)	59 (0.6%)	28 (3%)	65 (1.6%)
Medications (prior year)					
Agents acting on Renin Angiotensin System	366 (5.7%)	132 (10.6%)	618 (5.9%)	59 (6.2%)	228 (5.7%)
Antibacterials (systemic)	3043 (47.4%)	395 (31.8%)	3668 (35.3%)	308 (32.6%)	441 (11%)
Antidepressants	3774 (58.8%)	381 (30.7%)	6243 (60%)	365 (38.6%)	1102 (27.5%)
Antiepileptics	6416 (100%)	1241 (100%)	10398 (100%)	945 (100%)*	4002 (100%)
Antiinflammatory and Antirheumatic Agents	2233 (34.8%)	460 (37.1%)	5357 (51.5%)	368 (38.9%)	627 (15.7%)
Antineoplastic agents	<5	18 (1.5%)	100 (1%)	11 (1.2%)	18 (0.4%)

Database	CPRD GOLD	IPCI	SIDIAP	IQVIA Belgium LPD	IQVIA Germany DA
Antithrombotics	448 (7%)	78 (6.3%)	263 (2.5%)	27 (2.9%)	101 (2.5%)
Beta Blocking Agents	1079 (16.8%)	242 (19.5%)	695 (6.7%)	167 (17.7%)	270 (6.7%)
Calcium Channel Blockers	220 (3.4%)	50 (4%)	219 (2.1%)	30 (3.2%)	86 (2.1%)
Diuretics	314 (4.9%)	56 (4.5%)	348 (3.3%)	30 (3.2%)	172 (4.3%)
Drugs for Acid related disorder	1861 (29%)	382 (30.8%)	3519 (33.8%)	258 (27.3%)	507 (12.7%)
Drugs for obstructive airway diseases	1242 (19.4%)	315 (25.4%)	1858 (17.9%)	207 (21.9%)	197 (4.9%)
Drugs used in diabetes	262 (4.1%)	45 (3.6%)	283 (2.7%)	47 (5%)	102 (2.5%)
Hormonal contraceptives (systemic)	1291 (20.1%)	136 (11%)	415 (4%)	150 (15.9%)	59 (1.5%)
Immunosuppressants	48 (0.7%)	12 (1%)	76 (0.7%)	<5	18 (0.4%)
Lipid modifying agents	414 (6.5%)	82 (6.6%)	736 (7.1%)	63 (6.7%)	97 (2.4%)
Opioids	2149 (33.5%)	180 (14.5%)	1289 (12.4%)	206 (21.8%)	183 (4.6%)
Psycholeptics	3484 (54.3%)	626 (50.4%)	8030 (77.2%)	432 (45.7%)	1453 (36.3%)
Psychostimulants	26 (0.4%)	36 (2.9%)	429 (4.1%)	6 (0.6%)	37 (0.9%)

COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, std: standard deviation: *Rounded based on large scale characterisation

Table 12.2.2a- Baseline characteristics of new drug users at the time of therapy initiation, stratified by age group

CPRD GOLD, whole study period

Age group	**12 to 14**	**15 to 19**	**20 to 24**	**25 to 29**	**30 to 34**	**35 to 39**	**40 to 44**	**45 to 49**	**50 to 54**	**55**
Number subjects	155	358	530	612	700	816	988	1107	977	173
Sex, N (%)										
Female	155 (100%)	358 (100%)	530 (100%)	612 (100%)	700 (100%)	816 (100%)	988 (100%)	1107 (100%)	977 (100%)	173 (100%)
Age										
mean (std)	12.8 (0.8)	17.3 (1.4)	22.1 (1.4)	27.1 (1.4)	32.1 (1.4)	37 (1.4)	42.1 (1.4)	47 (1.4)	51.9 (1.4)	55 (0)
median [p75 - p75]	13 [12 - 13]	18 [16 - 18.75]	22 [21 - 23]	27 [26 - 28]	32 [31 - 33]	37 [36 - 38]	42 [41 - 43]	47 [46 - 48]	52 [51 - 53]	55 [55 - 55]
Prior history, days										
mean (std)	3226.7 (1245.2)	3617.4 (1804.4)	3427.1 (2101.1)	3293.3 (2193.2)	3129.3 (2006.9)	3196.8 (1866.9)	3538.9 (1859.6)	3893.4 (2000.9)	4042.5 (2145.7)	4029.1 (2307.7)
median [p75 - p75]	3543 [2459 - 4223]	3757 [2145 - 5043.25]	3392 [1492.75 - 4889]	3110 [1304.5 - 4574.25]	2899.5 [1470 - 4364.5]	3122.5 [1656 - 4358]	3500 [2171.25 - 4704.25]	3902 [2475.5 - 5125.5]	3945 [2491 - 5314]	4267 [2091 - 5549]
Visit occurrence (prior year)										
mean (std)	18.4 (15.4)	24.9 (15.9)	28.1 (21.7)	29.6 (19.5)	33.6 (24)	31.6 (22)	34.4 (23)	36 (22.8)	37.8 (25.4)	36.7 (19.5)
median [p75 - p75]	14 [9 - 24]	22 [14 - 32]	24 [13 - 35]	26 [15 - 39.25]	29 [17 - 45]	27 [16 - 41]	30 [18 - 46]	32 [19 - 48]	33 [22 - 48]	36 [23 - 47]
General conditions (any time prior)										
Anxiety	19 (12.3%)	70 (19.6%)	161 (30.4%)	204 (33.3%)	273 (39%)	295 (36.2%)	405 (41%)	417 (37.7%)	354 (36.2%)	62 (35.8%)
Asthma	23 (14.8%)	57 (15.9%)	91 (17.2%)	106 (17.3%)	106 (15.1%)	115 (14.1%)	167 (16.9%)	171 (15.4%)	152 (15.6%)	29 (16.8%)
Chronic Kidney Disease	0	<5	<5	<5	7 (1%)	10 (1.2%)	20 (2%)	42 (3.8%)	46 (4.7%)	13 (7.5%)
Chronic Liver Disease	0	0	0	<5	<5	<5	<5	5 (0.5%)	7 (0.7%)	0
COPD	0	<5	0	0	<5	<5	8 (0.8%)	18 (1.6%)	40 (4.1%)	9 (5.2%)
Dementia	0	<5	0	0	0	0	<5	7 (0.6%)	10 (1%)	<5
Depressive disorder	0	43 (12%)	156 (29.4%)	250 (40.8%)	306 (43.7%)	339 (41.5%)	435 (44%)	461 (41.6%)	403 (41.2%)	67 (38.7%)

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Diabetes	0	6 (1.7%)	6 (1.1%)	6 (1%)	18 (2.6%)	35 (4.3%)	46 (4.7%)	57 (5.1%)	64 (6.6%)	14 (8.1%)
GERD	<5	<5	8 (1.5%)	14 (2.3%)	12 (1.7%)	17 (2.1%)	29 (2.9%)	44 (4%)	37 (3.8%)	6 (3.5%)
Heart failure	0	0	0	0	0	<5	<5	7 (0.6%)	<5	0
HIV	0	0	0	0	0	<5	<5	<5	0	0
Hypertension	0	0	<5	<5	14 (2%)	33 (4%)	64 (6.5%)	75 (6.8%)	121 (12.4%)	22 (12.7%)
Hypothyroidism	0	<5	9 (1.7%)	14 (2.3%)	20 (2.9%)	45 (5.5%)	68 (6.9%)	98 (8.9%)	86 (8.8%)	22 (12.7%)
Infertility	0	0	<5	7 (1.1%)	10 (1.4%)	13 (1.6%)	11 (1.1%)	8 (0.7%)	10 (1%)	<5
Inflammatory Bowel Disease	0	<5	0	6 (1%)	<5	5 (0.6%)	<5	11 (1%)	11 (1.1%)	<5
Malignant neoplastic disease	<5	<5	6 (1.1%)	<5	7 (1%)	11 (1.3%)	25 (2.5%)	48 (4.3%)	77 (7.9%)	18 (10.4%)
Myocardial Infarction	0	<5	0	0	0	<5	<5	<5	<5	<5
Osteoporosis	0	<5	<5	<5	<5	<5	7 (0.7%)	8 (0.7%)	18 (1.8%)	<5
Pneumonia	<5	<5	7 (1.3%)	5 (0.8%)	8 (1.1%)	5 (0.6%)	23 (2.3%)	11 (1%)	19 (1.9%)	5 (2.9%)
Rheumatoid Arthritis	0	<5	0	0	<5	5 (0.6%)	<5	7 (0.6%)	7 (0.7%)	<5
Stroke	0	<5	0	<5	<5	5 (0.6%)	14 (1.4%)	26 (2.3%)	26 (2.7%)	5 (2.9%)
Venous Thromboembolism	0	<5	<5	8 (1.3%)	6 (0.9%)	9 (1.1%)	21 (2.1%)	18 (1.6%)	16 (1.6%)	5 (2.9%)
Medications (prior year)										
Agents acting on RAAS System	0	<5	7 (1.3%)	<5	12 (1.7%)	30 (3.7%)	65 (6.6%)	89 (8%)	129 (13.2%)	30 (17.3%)
Antibacterials (systemic)	54 (34.8%)	164 (45.8%)	240 (45.3%)	294 (48%)	356 (50.9%)	385 (47.2%)	492 (49.8%)	516 (46.6%)	471 (48.2%)	71 (41%)
Antidepressants	<5	100 (27.9%)	269 (50.8%)	353 (57.7%)	449 (64.1%)	520 (63.7%)	651 (65.9%)	715 (64.6%)	605 (61.9%)	109 (63%)
Antiepileptics	155 (100%)	358 (100%)	530 (100%)	612 (100%)	700 (100%)	816 (100%)	988 (100%)	1107 (100%)	977 (100%)	173 (100%)
Antiinflammatory/ Antirheumatic Agents	18 (11.6%)	73 (20.4%)	142 (26.8%)	194 (31.7%)	238 (34%)	299 (36.6%)	390 (39.5%)	431 (38.9%)	380 (38.9%)	68 (39.3%)

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Antineoplastic agents	0	0	<5	0	0	0	0	<5	0	0
Antithrombotics	0	8 (2.2%)	24 (4.5%)	25 (4.1%)	26 (3.7%)	38 (4.7%)	73 (7.4%)	112 (10.1%)	120 (12.3%)	22 (12.7%)
Beta Blocking Agents	<5	48 (13.4%)	83 (15.7%)	77 (12.6%)	120 (17.1%)	136 (16.7%)	184 (18.6%)	199 (18%)	199 (20.4%)	32 (18.5%)
Calcium Channel Blockers	0	<5	<5	8 (1.3%)	13 (1.9%)	17 (2.1%)	31 (3.1%)	53 (4.8%)	80 (8.2%)	13 (7.5%)
Diuretics	0	0	<5	0	12 (1.7%)	28 (3.4%)	50 (5.1%)	82 (7.4%)	118 (12.1%)	22 (12.7%)
Drugs for acid related disorder	10 (6.5%)	36 (10.1%)	97 (18.3%)	120 (19.6%)	155 (22.1%)	216 (26.5%)	349 (35.3%)	414 (37.4%)	387 (39.6%)	77 (44.5%)
Drugs for obstructive airway diseases	21 (13.5%)	50 (14%)	84 (15.8%)	111 (18.1%)	137 (19.6%)	141 (17.3%)	224 (22.7%)	234 (21.1%)	200 (20.5%)	40 (23.1%)
Drugs used in diabetes	<5	10 (2.8%)	10 (1.9%)	9 (1.5%)	19 (2.7%)	33 (4%)	43 (4.4%)	55 (5%)	67 (6.9%)	15 (8.7%)
Hormonal contraceptives (syst.)	<5	103 (28.8%)	227 (42.8%)	239 (39.1%)	227 (32.4%)	223 (27.3%)	146 (14.8%)	80 (7.2%)	41 (4.2%)	<5
Immunosuppressants	0	<5	5 (0.9%)	<5	<5	5 (0.6%)	6 (0.6%)	10 (0.9%)	13 (1.3%)	<5
Lipid modifying agents	0	<5	0	<5	13 (1.9%)	30 (3.7%)	64 (6.5%)	111 (10%)	160 (16.4%)	32 (18.5%)
Opioids	<5	46 (12.8%)	126 (23.8%)	193 (31.5%)	231 (33%)	298 (36.5%)	393 (39.8%)	423 (38.2%)	376 (38.5%)	59 (34.1%)
Psycholeptics	30 (19.4%)	116 (32.4%)	238 (44.9%)	316 (51.6%)	409 (58.4%)	465 (57%)	586 (59.3%)	635 (57.4%)	583 (59.7%)	106 (61.3%)
Psychostimulants	6 (3.9%)	<5	6 (1.1%)	<5	<5	<5	<5	<5	0	0

COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, std: standard deviation

Table 12.2.2b- Baseline characteristics of new drug users at the time of therapy initiation, stratified by age group

IPCI, whole study period

Age group	**12 to 14**	**15 to 19**	**20 to 24**	**25 to 29**	**30 to 34**	**35 to 39**	**40 to 44**	**45 to 49**	**50 to 54**	**55**
Number subjects	**28**	**66**	**91**	**86**	**95**	**137**	**197**	**241**	**251**	**49**
Sex, N (%)										
Female	28 (100%)	66 (100%)	91 (100%)	86 (100%)	95 (100%)	137 (100%)	197 (100%)	241 (100%)	251 (100%)	49 (100%)
Age										
mean (std)	12.7 (0.8)	17.5 (1.4)	22.1 (1.3)	27.1 (1.4)	32.2 (1.3)	37.2 (1.5)	42.2 (1.4)	47.2 (1.4)	52.1 (1.4)	55 (0)
median [p75 - p75]	12.5 [12 - 13]	18 [16 - 19]	22 [21 - 23]	27 [26 - 28]	32 [31 - 33]	37 [36 - 39]	42 [41 - 43]	47 [46 - 48]	52 [51 - 53]	55 [55 - 55]
Prior history, days										
mean (std)	1378.5 (712.7)	1487.9 (771.2)	1365.6 (715)	1419.8 (967.9)	1372 (918.6)	1425.7 (736.5)	1457.6 (826.6)	1564.1 (934.3)	1599.7 (954.6)	1614.1 (946.8)
median [p75 - p75]	1415 [749.5 - 1960.75]	1444 [837.25 - 2133.5]	1162 [805 - 2008]	1188.5 [734.75 - 1742]	1159 [668.5 - 1753.5]	1288 [890 - 1881]	1279 [816 - 1889]	1339 [806 - 2023]	1379 [826.5 - 2270.5]	1327 [867 - 2131]
Visit occurrence (prior year)										
mean (std)	5.4 (9.7)	6 (5)	8 (10.4)	7.9 (7.5)	8.1 (6.9)	8.6 (7.1)	8.6 (7)	9.3 (7.8)	10.6 (9.1)	13.3 (14.5)
median [p75 - p75]	3 [2 - 5.25]	4 [3 - 7]	6 [3 - 8]	6 [3.5 - 10]	7 [4 - 10]	7 [4 - 11]	7 [3 - 13]	7 [4 - 12.75]	8 [4 - 14]	9 [4 - 18.25]
General conditions (any time prior)										
Anxiety	<5	7 (10.6%)	30 (33%)	25 (29.1%)	41 (43.2%)	53 (38.7%)	68 (34.5%)	68 (28.2%)	78 (31.1%)	19 (38.8%)
Asthma	0	5 (7.6%)	6 (6.6%)	12 (14%)	<5	13 (9.5%)	19 (9.6%)	12 (5%)	27 (10.8%)	6 (12.2%)
Chronic Kidney Disease	0	0	0	0	0	0	0	0	<5	0
Chronic Liver Disease	0	0	0	0	0	<5	0	0	<5	0
COPD	0	0	0	0	0	0	0	<5	15 (6%)	<5
Dementia	0	0	0	0	0	0	0	<5	<5	<5
Depressive disorder	0	<5	6 (6.6%)	18 (20.9%)	21 (22.1%)	16 (11.7%)	38 (19.3%)	37 (15.4%)	47 (18.7%)	9 (18.4%)
Diabetes	0	0	<5	<5	<5	9 (6.6%)	5 (2.5%)	12 (5%)	18 (7.2%)	5 (10.2%)

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
GERD	0	0	0	<5	0	<5	<5	8 (3.3%)	5 (2%)	<5
Heart failure	<5	0	0	0	0	0	<5	<5	0	<5
HIV	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hypertension	0	0	0	<5	0	5 (3.6%)	9 (4.6%)	30 (12.4%)	42 (16.7%)	9 (18.4%)
Hypothyroidism	0	<5	<5	<5	<5	5 (3.6%)	9 (4.6%)	15 (6.2%)	17 (6.8%)	<5
Infertility	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Inflammatory Bowel Disease	0	0	<5	0	<5	0	<5	<5	<5	0
Malignant neoplastic disease	0	0	<5	<5	0	<5	7 (3.6%)	16 (6.6%)	27 (10.8%)	<5
Myocardial Infarction	0	0	0	0	0	0	0	<5	<5	0
Osteoporosis	0	0	0	0	0	0	0	0	5 (2%)	<5
Pneumonia	<5	<5	<5	<5	0	7 (5.1%)	<5	9 (3.7%)	16 (6.4%)	5 (10.2%)
Rheumatoid Arthritis	0	0	0	0	0	0	<5	5 (2.1%)	<5	0
Stroke	0	<5	0	<5	<5	<5	0	11 (4.6%)	18 (7.2%)	<5
Venous Thromboembolism	0	<5	0	<5	<5	<5	<5	7 (2.9%)	6 (2.4%)	<5
Medications (prior year)										
Agents acting on RAAS System	<5	<5	<5	<5	5 (5.3%)	14 (10.2%)	18 (9.1%)	33 (13.7%)	43 (17.1%)	10 (20.4%)
Antibacterials (systemic)	5 (17.9%)	19 (28.8%)	26 (28.6%)	26 (30.2%)	34 (35.8%)	40 (29.2%)	78 (39.6%)	83 (34.4%)	70 (27.9%)	14 (28.6%)
Antidepressants	0	<5	19 (20.9%)	31 (36%)	32 (33.7%)	47 (34.3%)	68 (34.5%)	78 (32.4%)	88 (35.1%)	15 (30.6%)
Antiepileptics	28 (100%)	66 (100%)	91 (100%)	86 (100%)	95 (100%)	137 (100%)	197 (100%)	241 (100%)	251 (100%)	49 (100%)
Antiinflammatory/ Antirheumatic Agents	0	15 (22.7%)	23 (25.3%)	24 (27.9%)	31 (32.6%)	53 (38.7%)	81 (41.1%)	105 (43.6%)	108 (43%)	20 (40.8%)
Antineoplastic agents	0	0	<5	0	0	<5	<5	6 (2.5%)	6 (2.4%)	0

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Antithrombotics	<5	<5	<5	<5	<5	<5	<5	23 (9.5%)	37 (14.7%)	<5
Beta Blocking Agents	<5	5 (7.6%)	11 (12.1%)	11 (12.8%)	13 (13.7%)	19 (13.9%)	51 (25.9%)	58 (24.1%)	63 (25.1%)	9 (18.4%)
Calcium Channel Blockers	0	0	<5	<5	<5	<5	7 (3.6%)	13 (5.4%)	23 (9.2%)	<5
Diuretics	<5	0	<5	0	0	<5	<5	21 (8.7%)	23 (9.2%)	<5
Drugs for acid related disorder	<5	5 (7.6%)	18 (19.8%)	21 (24.4%)	26 (27.4%)	33 (24.1%)	63 (32%)	91 (37.8%)	103 (41%)	21 (42.9%)
Drugs for obstructive airway diseases	6 (21.4%)	6 (9.1%)	18 (19.8%)	22 (25.6%)	22 (23.2%)	30 (21.9%)	58 (29.4%)	63 (26.1%)	77 (30.7%)	13 (26.5%)
Drugs used in diabetes	0	0	<5	<5	0	<5	<5	11 (4.6%)	19 (7.6%)	5 (10.2%)
Hormonal contraceptives (syst.)	<5	7 (10.6%)	14 (15.4%)	14 (16.3%)	11 (11.6%)	23 (16.8%)	21 (10.7%)	28 (11.6%)	16 (6.4%)	<5
Immunosuppressants	0	0	<5	<5	0	<5	<5	<5	<5	0
Lipid modifying agents	0	0	0	0	<5	<5	5 (2.5%)	24 (10%)	42 (16.7%)	7 (14.3%)
Opioids	0	<5	5 (5.5%)	5 (5.8%)	12 (12.6%)	18 (13.1%)	35 (17.8%)	42 (17.4%)	50 (19.9%)	10 (20.4%)
Psycholeptics	11 (39.3%)	26 (39.4%)	39 (42.9%)	38 (44.2%)	57 (60%)	74 (54%)	100 (50.8%)	114 (47.3%)	139 (55.4%)	28 (57.1%)
Psychostimulants	<5	<5	0	6 (7%)	<5	<5	6 (3%)	8 (3.3%)	5 (2%)	<5

Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, std: standard deviation

Table 12.2.2c- Baseline characteristics of new drug users at the time of therapy initiation, stratified by age group

SIDIAP, whole study period

Age group	**12 to 14**	**15 to 19**	**20 to 24**	**25 to 29**	**30 to 34**	**35 to 39**	**40 to 44**	**45 to 49**	**50 to 54**	**55**
Number subjects	**336**	**775**	**637**	**740**	**1079**	**1441**	**1707**	**1747**	**1651**	**285**
Sex, N (%)										
Female	336 (100%)	775 (100%)	637 (100%)	740 (100%)	1079 (100%)	1441 (100%)	1707 (100%)	1747 (100%)	1651 (100%)	285 (100%)
Age										
mean (std)	13.1 (0.8)	17 (1.4)	22 (1.4)	27.2 (1.4)	32.1 (1.4)	37.1 (1.4)	42 (1.4)	47 (1.4)	51.9 (1.4)	55 (0)
median [p75 - p75]	13 [12 - 14]	17 [16 - 18]	22 [21 - 23]	27 [26 - 28]	32 [31 - 33]	37 [36 - 38]	42 [41 - 43]	47 [46 - 48]	52 [51 - 53]	55 [55 - 55]
Prior history, days										
mean (std)	2979.9 (1164.8)	3218.2 (1327.9)	3161.5 (1424.5)	2881.9 (1326.1)	2929.5 (1261.8)	3031.6 (1200.8)	3323 (1280.4)	3415.1 (1304.8)	3458 (1275.1)	3507.1 (1337.6)
median [p75 - p75]	2985 [2074 - 3993]	3211 [2141.5 - 4163.5]	3022 [1999 - 4154]	2726.5 [1899.5 - 3681]	2756 [1944.5 - 3734.5]	2938 [2059 - 3796]	3208 [2284.5 - 4223]	3272 [2369 - 4404.5]	3350 [2437.5 - 4418]	3396 [2346 - 4547]
Visit occurrence (prior year)										
mean (std)	14 (10.5)	13.3 (11.1)	16.1 (13.2)	16.9 (15.3)	17.6 (17.1)	18.4 (15.9)	19.3 (18.8)	19.6 (22)	19.9 (22.9)	20.9 (19.5)
median [p75 - p75]	11 [7 - 19]	10 [6 - 18]	13 [7 - 21.75]	13 [6 - 22]	14 [7 - 23]	15 [8 - 24]	15 [7 - 26]	15 [7 - 25]	15 [8 - 26]	17 [9 - 29]
General conditions (any time prior)										
Anxiety	35 (10.4%)	159 (20.5%)	221 (34.7%)	306 (41.4%)	511 (47.4%)	642 (44.6%)	748 (43.8%)	740 (42.4%)	635 (38.5%)	102 (35.8%)
Asthma	17 (5.1%)	53 (6.8%)	23 (3.6%)	41 (5.5%)	61 (5.7%)	87 (6%)	90 (5.3%)	87 (5%)	73 (4.4%)	13 (4.6%)
Chronic Kidney Disease	0	0	<5	<5	7 (0.6%)	12 (0.8%)	16 (0.9%)	36 (2.1%)	48 (2.9%)	7 (2.5%)
Chronic Liver Disease	<5	0	<5	<5	11 (1%)	13 (0.9%)	20 (1.2%)	27 (1.5%)	22 (1.3%)	<5
COPD	0	0	0	<5	<5	8 (0.6%)	9 (0.5%)	24 (1.4%)	48 (2.9%)	<5
Dementia	<5	0	0	0	<5	<5	<5	13 (0.7%)	16 (1%)	<5

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Depressive disorder	11 (3.3%)	85 (11%)	92 (14.4%)	125 (16.9%)	246 (22.8%)	388 (26.9%)	505 (29.6%)	545 (31.2%)	525 (31.8%)	88 (30.9%)
Diabetes	<5	6 (0.8%)	<5	7 (0.9%)	24 (2.2%)	55 (3.8%)	80 (4.7%)	79 (4.5%)	87 (5.3%)	20 (7%)
GERD	<5	8 (1%)	8 (1.3%)	8 (1.1%)	19 (1.8%)	27 (1.9%)	38 (2.2%)	64 (3.7%)	71 (4.3%)	16 (5.6%)
Heart failure	0	0	0	<5	<5	<5	<5	7 (0.4%)	<5	0
HIV	0	<5	0	<5	<5	<5	13 (0.8%)	10 (0.6%)	15 (0.9%)	<5
Hypertension	<5	<5	<5	8 (1.1%)	21 (1.9%)	39 (2.7%)	88 (5.2%)	153 (8.8%)	236 (14.3%)	46 (16.1%)
Hypothyroidism	7 (2.1%)	22 (2.8%)	32 (5%)	54 (7.3%)	78 (7.2%)	104 (7.2%)	157 (9.2%)	204 (11.7%)	199 (12.1%)	39 (13.7%)
Infertility	0	0	6 (0.9%)	10 (1.4%)	20 (1.9%)	35 (2.4%)	39 (2.3%)	22 (1.3%)	11 (0.7%)	<5
Inflammatory Bowel Disease	0	0	<5	<5	<5	6 (0.4%)	8 (0.5%)	5 (0.3%)	9 (0.5%)	<5
Malignant neoplastic disease	<5	8 (1%)	<5	8 (1.1%)	21 (1.9%)	31 (2.2%)	57 (3.3%)	76 (4.4%)	101 (6.1%)	25 (8.8%)
Myocardial Infarction	0	0	<5	0	<5	0	<5	6 (0.3%)	<5	<5
Osteoporosis	0	0	<5	<5	<5	6 (0.4%)	<5	17 (1%)	46 (2.8%)	8 (2.8%)
Pneumonia	36 (10.7%)	38 (4.9%)	14 (2.2%)	16 (2.2%)	20 (1.9%)	36 (2.5%)	69 (4%)	66 (3.8%)	59 (3.6%)	15 (5.3%)
Rheumatoid Arthritis	0	0	0	0	<5	<5	7 (0.4%)	<5	8 (0.5%)	0
Stroke	<5	<5	<5	5 (0.7%)	9 (0.8%)	17 (1.2%)	17 (1%)	35 (2%)	45 (2.7%)	5 (1.8%)
Venous Thromboembolism	0	0	<5	<5	<5	14 (1%)	13 (0.8%)	16 (0.9%)	9 (0.5%)	<5
Medications (prior year)										
Agents acting on RAAS System	0	<5	<5	9 (1.2%)	17 (1.6%)	37 (2.6%)	88 (5.2%)	168 (9.6%)	244 (14.8%)	52 (18.2%)
Antibacterials (systemic)	89 (26.5%)	279 (36%)	235 (36.9%)	266 (35.9%)	374 (34.7%)	516 (35.8%)	618 (36.2%)	614 (35.1%)	578 (35%)	99 (34.7%)
Antidepressants	40 (11.9%)	314 (40.5%)	302 (47.4%)	424 (57.3%)	612 (56.7%)	881 (61.1%)	1128 (66.1%)	1170 (67%)	1160 (70.3%)	212 (74.4%)
Antiepileptics	336 (100%)	775 (100%)	637 (100%)	740 (100%)	1079 (100%)	1441 (100%)	1707 (100%)	1747 (100%)	1651 (100%)	285 (100%)

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Antiinflammatory/ Antirheumatic Agents	157 (46.7%)	353 (45.5%)	302 (47.4%)	343 (46.4%)	521 (48.3%)	761 (52.8%)	910 (53.3%)	948 (54.3%)	905 (54.8%)	157 (55.1%)
Antineoplastic agents	<5	<5	<5	<5	<5	7 (0.5%)	26 (1.5%)	16 (0.9%)	34 (2.1%)	5 (1.8%)
Antithrombotics	<5	<5	<5	6 (0.8%)	23 (2.1%)	36 (2.5%)	61 (3.6%)	58 (3.3%)	62 (3.8%)	10 (3.5%)
Beta Blocking Agents	<5	19 (2.5%)	18 (2.8%)	33 (4.5%)	51 (4.7%)	89 (6.2%)	126 (7.4%)	158 (9%)	170 (10.3%)	30 (10.5%)
Calcium Channel Blockers	0	<5	0	<5	13 (1.2%)	14 (1%)	39 (2.3%)	54 (3.1%)	79 (4.8%)	14 (4.9%)
Diuretics	<5	<5	0	<5	18 (1.7%)	27 (1.9%)	50 (2.9%)	84 (4.8%)	140 (8.5%)	23 (8.1%)
Drugs for acid related Disorder	27 (8%)	96 (12.4%)	129 (20.3%)	180 (24.3%)	319 (29.6%)	453 (31.4%)	631 (37%)	765 (43.8%)	775 (46.9%)	144 (50.5%)
Drugs for obstructive airway diseases	48 (14.3%)	104 (13.4%)	83 (13%)	114 (15.4%)	171 (15.8%)	273 (18.9%)	320 (18.7%)	345 (19.7%)	329 (19.9%)	71 (24.9%)
Drugs used in diabetes	6 (1.8%)	11 (1.4%)	<5	7 (0.9%)	13 (1.2%)	33 (2.3%)	34 (2%)	74 (4.2%)	84 (5.1%)	18 (6.3%)
Hormonal contraceptives (syst.)	<5	42 (5.4%)	65 (10.2%)	42 (5.7%)	73 (6.8%)	66 (4.6%)	69 (4%)	35 (2%)	18 (1.1%)	<5
Immunosuppressants	<5	<5	<5	<5	7 (0.6%)	<5	24 (1.4%)	12 (0.7%)	19 (1.2%)	<5
Lipid modifying agents	0	<5	5 (0.8%)	9 (1.2%)	14 (1.3%)	54 (3.7%)	81 (4.7%)	219 (12.5%)	284 (17.2%)	66 (23.2%)
Opioids	10 (3%)	31 (4%)	50 (7.8%)	46 (6.2%)	98 (9.1%)	159 (11%)	228 (13.4%)	296 (16.9%)	312 (18.9%)	59 (20.7%)
Psycholeptics	124 (36.9%)	478 (61.7%)	452 (71%)	537 (72.6%)	815 (75.5%)	1133 (78.6%)	1393 (81.6%)	1453 (83.2%)	1400 (84.8%)	245 (86%)
Psychostimulants	39 (11.6%)	82 (10.6%)	26 (4.1%)	17 (2.3%)	40 (3.7%)	50 (3.5%)	67 (3.9%)	52 (3%)	50 (3%)	6 (2.1%)

COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, std: standard deviation

Table 12.2.2d- Baseline characteristics of new drug users at the time of therapy initiation, stratified by age group

IQVIA Belgium LPD, whole study period

Age group	**12 to 14**	**15 to 19**	**20 to 24**	**25 to 29**	**30 to 34**	**35 to 39**	**40 to 44**	**45 to 49**	**50 to 54**	**55**
Number subjects	18	60	68	67	89	120	132	169	186	36
Sex, N (%)										
Female	18 (100%)	60 (100%)	68 (100%)	67 (100%)	89 (100%)	120 (100%)	132 (100%)	169 (100%)	186 (100%)	36 (100%)
Age										
mean (std)	13.3 (0.8)	17.1 (1.4)	22 (1.4)	27 (1.4)	31.9 (1.4)	37.1 (1.4)	42 (1.3)	47.2 (1.4)	52 (1.4)	55 (0)
median [p75 - p75]	13.5 [13 - 14]	17 [16 - 18]	22 [21 - 23]	27 [26 - 28]	32 [31 - 33]	37 [36 - 38]	42 [41 - 43]	47 [46 - 48]	52 [51 - 53]	55 [55 - 55]
Prior history, days										
mean (std)	1150 (500.2)	1421 (807.2)	1266 (746)	1126 (787.6)	1257 (698.8)	1328 (792.7)	1470 (783.8)	1376 (773.1)	1319 (737.5)	1406 (801.2)
median [p75 - p75]	1109.5 [725 - 1530.5]	1197 [731.75 - 1985.75]	1040.5 [663 - 1782.5]	953 [521.5 - 1388.5]	1132 [665 - 1615]	1092.5 [733.75 - 1706.5]	1309 [802.75 - 2076]	1196 [743 - 1856]	1192.5 [670.5 - 1845.25]	1209.5 [702.25 - 2004]
Visit occurrence (prior year)										
mean (std)	3 (2.4)	5 (5.1)	5 (4)	7 (6.5)	6 (5.6)	7 (6.1)	8 (8.1)	8 (8.2)	8 (7.7)	5 (4.8)
median [p75 - p75]	2.5 [2 - 4.75]	4 [2 - 7.25]	4 [3 - 8.25]	5 [3 - 9]	5 [3 - 9]	6.5 [3 - 10]	6 [4 - 11]	6 [3 - 9]	6 [3 - 12]	5 [2 - 7]
General conditions (any time prior)										
Anxiety	0	8 (13.3%)	13 (19.1%)	21 (31.3%)	30 (33.7%)	48 (40%)	48 (36.4%)	63 (37.3%)	62 (33.3%)	14 (38.9%)
Asthma	<5	11 (18.3%)	5 (7.4%)	10 (14.9%)	16 (18%)	13 (10.8%)	27 (20.5%)	33 (19.5%)	20 (10.8%)	5 (13.9%)
Chronic Kidney Disease	0	0	0	0	0	0	0	<5	<5	0
Chronic Liver Disease	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COPD	0	5 (8.3%)	<5	<5	7 (7.9%)	16 (13.3%)	20 (15.2%)	29 (17.2%)	28 (15.1%)	5 (13.9%)
Dementia	0	0	0	0	<5	0	0	0	<5	0
Depressive disorder	0	7 (11.7%)	14 (20.6%)	26 (38.8%)	33 (37.1%)	65 (54.2%)	61 (46.2%)	88 (52.1%)	97 (52.2%)	23 (63.9%)
Diabetes	0	0	<5	<5	<5	<5	10 (7.6%)	18 (10.7%)	15 (8.1%)	6 (16.7%)
GERD	<5	8 (13.3%)	10 (14.7%)	<5	15 (16.9%)	24 (20%)	27 (20.5%)	35 (20.7%)	44 (23.7%)	<5

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Heart failure	0	0	0	0	0	0	0	<5	0	0
HIV	0	0	0	0	0	<5	0	0	<5	0
Hypertension	0	<5	<5	6 (9%)	<5	12 (10%)	22 (16.7%)	51 (30.2%)	55 (29.6%)	11 (30.6%)
Hypothyroidism	0	<5	9 (13.2%)	7 (10.4%)	8 (9%)	13 (10.8%)	20 (15.2%)	18 (10.7%)	25 (13.4%)	<5
Infertility	0	0	0	0	<5	0	<5	0	0	0
Inflammatory Bowel Disease	0	0	0	0	0	<5	<5	<5	<5	0
Malignant neoplastic disease	0	0	0	0	<5	<5	<5	<5	12 (6.5%)	<5
Myocardial Infarction	0	0	0	0	0	0	0	0	<5	0
Osteoporosis	0	<5	0	<5	<5	<5	<5	6 (3.6%)	8 (4.3%)	<5
Pneumonia	0	0	0	<5	<5	<5	7 (5.3%)	7 (4.1%)	8 (4.3%)	<5
Rheumatoid Arthritis	0	0	0	0	0	0	<5	<5	<5	<5
Stroke	0	0	0	0	0	0	<5	5 (3%)	7 (3.8%)	<5
Venous Thromboembolism	0	<5	<5	0	<5	<5	8 (6.1%)	5 (3%)	6 (3.2%)	<5
Medications (prior year)										
Agents acting on RAAS System	0	<5	0	0	5 (5.6%)	<5	8 (6.1%)	20 (11.8%)	19 (10.2%)	5 (13.9%)
Antibacterials (systemic)	7 (38.9%)	19 (31.7%)	21 (30.9%)	21 (31.3%)	29 (32.6%)	41 (34.2%)	53 (40.2%)	46 (27.2%)	57 (30.6%)	14 (38.9%)
Antidepressants	0	7 (11.7%)	14 (20.6%)	24 (35.8%)	33 (37.1%)	56 (46.7%)	51 (38.6%)	82 (48.5%)	85 (45.7%)	13 (36.1%)
Antiepileptics*	18 (100%)	60 (100%)	68 (100%)	67 (100%)	89 (100%)	120 (100%)	132 (100%)	169 (100%)	186 (100%)	36 (100%)
Antiinflammatory/ Antirheumatic Agents	<5	18 (30%)	20 (29.4%)	26 (38.8%)	34 (38.2%)	51 (42.5%)	56 (42.4%)	80 (47.3%)	68 (36.6%)	12 (33.3%)
Antineoplastic agents	0	0	0	0	0	<5	<5	<5	5 (2.7%)	0
Antithrombotics	0	0	0	0	<5	<5	<5	6 (3.6%)	13 (7%)	0
Beta Blocking Agents	0	<5	7 (10.3%)	13 (19.4%)	8 (9%)	20 (16.7%)	17 (12.9%)	45 (26.6%)	48 (25.8%)	7 (19.4%)

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Calcium Channel Blockers	0	<5	0	<5	<5	<5	5 (3.8%)	6 (3.6%)	10 (5.4%)	<5
Diuretics	0	0	0	0	0	<5	8 (6.1%)	6 (3.6%)	10 (5.4%)	<5
Drugs for acid related Disorder	0	9 (15%)	13 (19.1%)	16 (23.9%)	16 (18%)	35 (29.2%)	36 (27.3%)	60 (35.5%)	66 (35.5%)	7 (19.4%)
Drugs for obstructive airway diseases	<5	12 (20%)	6 (8.8%)	16 (23.9%)	19 (21.3%)	22 (18.3%)	41 (31.1%)	40 (23.7%)	38 (20.4%)	10 (27.8%)
Drugs used in diabetes	0	0	<5	<5	<5	<5	10 (7.6%)	13 (7.7%)	12 (6.5%)	<5
Hormonal contraceptives (syst.)	0	10 (16.7%)	19 (27.9%)	13 (19.4%)	26 (29.2%)	20 (16.7%)	24 (18.2%)	29 (17.2%)	8 (4.3%)	<5
Immunosuppressants	0	0	0	0	0	0	<5	<5	<5	0
Lipid modifying agents	0	<5	<5	<5	<5	<5	5 (3.8%)	14 (8.3%)	23 (12.4%)	9 (25%)
Opioids	0	6 (10%)	10 (14.7%)	7 (10.4%)	18 (20.2%)	33 (27.5%)	38 (28.8%)	40 (23.7%)	50 (26.9%)	<5
Psycholeptics	<5	9 (15%)	19 (27.9%)	29 (43.3%)	38 (42.7%)	59 (49.2%)	58 (43.9%)	95 (56.2%)	99 (53.2%)	23 (63.9%)
Psychostimulants	0	0	<5	<5	0	0	0	<5	<5	0

COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, std: standard deviation, *Rounded based on large scale characterisation

Table 12.2.2e- Baseline characteristics of new drug users at the time of therapy initiation, stratified by age group

IQVIA Germany DA, whole study period

Age group	**12 to 14**	**15 to 19**	**20 to 24**	**25 to 29**	**30 to 34**	**35 to 39**	**40 to 44**	**45 to 49**	**50 to 54**	**55**
Number subjects	97	208	264	356	371	417	518	702	884	185
Sex, N (%)										
Female	97 (100%)	208 (100%)	264 (100%)	356 (100%)	371 (100%)	417 (100%)	518 (100%)	702 (100%)	884 (100%)	185 (100%)
Age										
mean (std)	12.8 (0.8)	17.1 (1.4)	22.2 (1.4)	27.1 (1.4)	32 (1.4)	37.1 (1.5)	42.2 (1.4)	47.1 (1.4)	52 (1.4)	55 (0)
median [p75 - p75]	13 [12 - 13]	17 [16 - 18]	22 [21 - 24]	27 [26 - 28]	32 [31 - 33]	37 [36 - 38]	42 [41 - 43]	47 [46 - 48]	52 [51 - 53]	55 [55 - 55]
Prior history, days										
mean (std)	2239 (1334.7)	2177 (1560.3)	1603 (1512.9)	1890 (1469.8)	2070 (1484.3)	2210 (1714.6)	2369 (1755.6)	2524 (1857.4)	2639 (1981.1)	2873 (2095.3)
median [p75 - p75]	2058 [1168 – 3139]	1880 [868.5 – 3090]	1063 [672.75 – 1849.5]	1500 [838.5 – 2382.5]	1644 [921.5 - 2812.5]	1698 [854 - 3131]	1874 [1031.5 - 3277.75]	2046.5 [1043.5 - 3411.75]	2157.5 [1047.75 - 3736.25]	2346 [1207 - 4297]
Visit occurrence (prior year)										
mean (std)	9 (9.5)	7 (9.3)	7 (8.3)	6 (7.6)	6 (8.2)	7 (9.4)	7 (8.4)	7 (9.2)	8 (10.4)	9 (11.2)
median [p75 - p75]	6 [2 - 11]	5 [2 - 10]	4 [2 - 9]	4 [1 - 8]	3 [1 - 9]	4 [1 - 10]	4 [1.25 - 9]	5 [2 - 11]	5 [2 - 12]	7 [2 - 13]
General conditions (any time prior)										
Anxiety	<5	15 (7.2%)	42 (15.9%)	63 (17.7%)	72 (19.4%)	89 (21.3%)	122 (23.6%)	179 (25.5%)	179 (20.2%)	42 (22.7%)
Asthma	6 (6.2%)	18 (8.7%)	12 (4.5%)	13 (3.7%)	14 (3.8%)	28 (6.7%)	32 (6.2%)	48 (6.8%)	51 (5.8%)	12 (6.5%)
Chronic Kidney Disease	<5	0	<5	<5	5 (1.3%)	<5	11 (2.1%)	11 (1.6%)	24 (2.7%)	<5
Chronic Liver Disease	0	0	0	0	<5	<5	<5	<5	5 (0.6%)	<5
COPD	8 (8.2%)	13 (6.2%)	<5	6 (1.7%)	9 (2.4%)	7 (1.7%)	19 (3.7%)	25 (3.6%)	36 (4.1%)	9 (4.9%)
Dementia	0	<5	<5	5 (1.4%)	<5	<5	7 (1.4%)	11 (1.6%)	30 (3.4%)	5 (2.7%)
Depressive disorder	<5	21 (10.1%)	58 (22%)	98 (27.5%)	112 (30.2%)	152 (36.5%)	195 (37.6%)	299 (42.6%)	401 (45.4%)	82 (44.3%)
Diabetes	<5	<5	5 (1.9%)	<5	9 (2.4%)	22 (5.3%)	27 (5.2%)	36 (5.1%)	83 (9.4%)	18 (9.7%)

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
GERD	<5	9 (4.3%)	<5	<5	5 (1.3%)	9 (2.2%)	13 (2.5%)	20 (2.8%)	14 (1.6%)	5 (2.7%)
Heart failure	0	0	<5	<5	<5	<5	<5	7 (1%)	19 (2.1%)	8 (4.3%)
HIV	0	0	0	<5	0	<5	<5	<5	<5	0
Hypertension	0	<5	9 (3.4%)	11 (3.1%)	25 (6.7%)	27 (6.5%)	58 (11.2%)	95 (13.5%)	169 (19.1%)	34 (18.4%)
Hypothyroidism	7 (7.2%)	15 (7.2%)	14 (5.3%)	29 (8.1%)	20 (5.4%)	33 (7.9%)	42 (8.1%)	50 (7.1%)	90 (10.2%)	13 (7%)
Infertility	0	0	0	0	0	0	0	0	<5	0
Inflammatory Bowel Disease	0	0	<5	5 (1.4%)	0	<5	6 (1.2%)	<5	8 (0.9%)	<5
Malignant neoplastic disease	<5	<5	<5	<5	9 (2.4%)	7 (1.7%)	16 (3.1%)	25 (3.6%)	57 (6.4%)	11 (5.9%)
Myocardial Infarction	0	0	0	0	0	0	<5	<5	8 (0.9%)	<5
Osteoporosis	<5	<5	<5	0	0	0	<5	5 (0.7%)	17 (1.9%)	6 (3.2%)
Pneumonia	10 (10.3%)	16 (7.7%)	8 (3%)	6 (1.7%)	7 (1.9%)	11 (2.6%)	11 (2.1%)	19 (2.7%)	19 (2.1%)	8 (4.3%)
Rheumatoid Arthritis	0	0	<5	0	<5	<5	5 (1%)	9 (1.3%)	12 (1.4%)	<5
Stroke	<5	<5	<5	<5	<5	5 (1.2%)	6 (1.2%)	19 (2.7%)	29 (3.3%)	10 (5.4%)
Venous Thromboembolism	0	<5	<5	<5	<5	7 (1.7%)	8 (1.5%)	19 (2.7%)	17 (1.9%)	5 (2.7%)
Medications (prior year)										
Agents acting on RAAS System	0	0	<5	<5	6 (1.6%)	15 (3.6%)	33 (6.4%)	54 (7.7%)	93 (10.5%)	19 (10.3%)
Antibacterials (systemic)	10 (10.3%)	37 (17.8%)	28 (10.6%)	38 (10.7%)	34 (9.2%)	42 (10.1%)	59 (11.4%)	75 (10.7%)	100 (11.3%)	18 (9.7%)
Antidepressants	0	17 (8.2%)	55 (20.8%)	81 (22.8%)	93 (25.1%)	104 (24.9%)	157 (30.3%)	225 (32.1%)	298 (33.7%)	72 (38.9%)
Antiepileptics	97 (100%)	208 (100%)	264 (100%)	356 (100%)	371 (100%)	417 (100%)	518 (100%)	702 (100%)	884 (100%)	185 (100%)
Antiinflammatory/ Antirheumatic Agents	15 (15.5%)	31 (14.9%)	31 (11.7%)	39 (11%)	52 (14%)	54 (12.9%)	86 (16.6%)	126 (17.9%)	155 (17.5%)	38 (20.5%)
Antineoplastic agents	<5	<5	<5	0	0	<5	<5	<5	7 (0.8%)	<5

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Antithrombotics	<5	0	<5	<5	8 (2.2%)	6 (1.4%)	13 (2.5%)	21 (3%)	42 (4.8%)	7 (3.8%)
Beta Blocking Agents	0	<5	12 (4.5%)	12 (3.4%)	18 (4.9%)	22 (5.3%)	36 (6.9%)	55 (7.8%)	96 (10.9%)	18 (9.7%)
Calcium Channel Blockers	0	0	<5	<5	<5	<5	13 (2.5%)	19 (2.7%)	34 (3.8%)	10 (5.4%)
Diuretics	0	0	<5	<5	7 (1.9%)	14 (3.4%)	26 (5%)	39 (5.6%)	68 (7.7%)	15 (8.1%)
Drugs for acid related Disorder	<5	14 (6.7%)	15 (5.7%)	33 (9.3%)	40 (10.8%)	47 (11.3%)	72 (13.9%)	87 (12.4%)	161 (18.2%)	34 (18.4%)
Drugs for obstructive airway diseases	7 (7.2%)	14 (6.7%)	11 (4.2%)	12 (3.4%)	12 (3.2%)	16 (3.8%)	30 (5.8%)	30 (4.3%)	54 (6.1%)	11 (5.9%)
Drugs used in diabetes	0	<5	<5	<5	7 (1.9%)	10 (2.4%)	14 (2.7%)	23 (3.3%)	36 (4.1%)	6 (3.2%)
Hormonal contraceptives (syst.)	0	<5	10 (3.8%)	10 (2.8%)	<5	7 (1.7%)	<5	14 (2%)	7 (0.8%)	<5
Immunosuppressants	0	0	0	<5	<5	<5	<5	5 (0.7%)	8 (0.9%)	<5
Lipid modifying agents	0	0	<5	<5	<5	7 (1.7%)	11 (2.1%)	16 (2.3%)	41 (4.6%)	16 (8.6%)
Opioids	<5	5 (2.4%)	5 (1.9%)	<5	12 (3.2%)	22 (5.3%)	24 (4.6%)	39 (5.6%)	59 (6.7%)	11 (5.9%)
Psycholeptics	31 (32%)	48 (23.1%)	96 (36.4%)	110 (30.9%)	136 (36.7%)	155 (37.2%)	185 (35.7%)	254 (36.2%)	352 (39.8%)	86 (46.5%)
Psychostimulants	<5	5 (2.4%)	7 (2.7%)	<5	<5	<5	<5	6 (0.9%)	<5	<5

COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, std: standard deviation

Large Scale Characterisation

Results from large-scale characterisation of participants with all extracted co-variates are available in the shiny app (https://data-dev.darwin-eu.org/EUPAS50789/).

12.2.3. Outcome Data

NA

12.2.4. Main Results

Indication

On the date of VPA therapy initiation, most subjects had no record of any of the three pre-specified conditions of interest (proxy for indication) in all databases except for IQVIA Belgium LPD. Among those with a specific diagnosis recorded, migraine was the most common indication in CPRD GOLD, whereas epilepsy was most common in all other databases. Notably, VPA for migraine was uncommon in SIDIAP. Results are presented in Table 12.2.3 below.

Stratification for age groups (Table 12.2.4) showed that for those women aged 12-19 with a pre-specified condition recorded at the time of the first prescription, epilepsy was the predominant diagnosis recorded across all databases.However, in older age groups, VPA was prescribed for both epilepsy and migraine prevention in CPRD, IPCI, and IQVIA Belgium LPD, and both bipolar disorder and epilepsy in SIDIAP. Epilepsy remained the predominant indication across age groups in IQVIA Germany.

Sensitivity analyses assessing indications within 7days, 30days or anytime prior index date are summarised in Table 12.2.5. Epilepsy was the most common indication of interest, with 7.3%, 10.4% and 29.3% of people in CPRD GOLD, 9.3%, 11.4% and 22.2% in IPCI and 3.1%, 3.7% and 13.5% in SIDIAP having a recording at the respective assessment windows. However, for SIDIAP bipolar disorder was the most common indication assessed anytime in patient history (14.7%). For IQVIA Belgium LPD epilepsy was recorded for 40.1%, 40.4% and 44.4%, and 25.7%, 26.9% and 55.3% in IQVIA Germany DA in the respective time windows.

Results summarising indication stratified for calendar year are available in the shiny web-application.

Table 12.2.3- Pre-specified indications at prescription date *for all age groups during the whole study period*

Database	CPRD GOLD	IPCI	SIDIAP	IQVIA BELGIUM LPD	IQVIA GERMANY DA
Number of subjects	**6416**	**1241**	**10398**	**945**	**4002**
Indication					
No indication*	1961 (30.6%)	802 (64.6%)	8207 (78.9%)	28 (3%)	1472 (36.8%)
Unknown indication**	3661 (57.1%)	239 (19.3%)	1699 (16.3%)	227 (24%)	1192 (29.8%)
Bipolar disorder	82 (1.3%)	9 (0.7%)	189 (1.8%)	68 (7.2%)	184 (4.6%)
Epilepsy	350 (5.5%)	101 (8.1%)	270 (2.6%)	382 (40.4%)	1006 (25.1%)
Migraine	363 (5.7%)	90 (7.3%)	34 (0.3%)	286 (30.3%)	174 (4.3%)

*No indication: At index date, the person did not have a record of any condition/diagnosis.**Unknown indication: None of the specific indications was recorded on index date, but there was a record for any other condition/diagnosis

Table 12.2.4- Pre-specified indications at prescription date stratified by age

Age group	Indication	CPRD GOLD	IPCI	SIDIAP	IQVIA BELGIUM LPD	IQVIA GERMANY DA
12 to 14	**Number of subjects**	**155**	**28**	**336**	**18**	**97**
	Indication					
	No indication*	64 (41.3%)	22 (78.6%)	230 (68.5%)	0	38 (39.2%)
	Unknown indication**	72 (46.5%)	0	63 (18.8%)	<5	15 (15.5%)
	Bipolar disorder	0	0	0	0	0
	Epilepsy	18 (11.6%)	6 (21.4%)	43 (12.8%)	14 (77.8%)	44 (45.4%)
	Migraine	<5	0	0	<5	0
15 to 19	**Number of subjects**	**358**	**66**	**775**	**60**	**208**
	Indication					
	No indication*	113 (31.6%)	43 (65.2%)	580 (74.8%)	<5	77 (37%)
	Unknown indication**	194 (54.2%)	6 (9.1%)	141 (18.2%)	7 (11.7%)	50 (24%)
	Bipolar disorder	<5	<5	5 (0.6%)	<5	<5
	Epilepsy	36 (10.1%)	13 (19.7%)	47 (6.1%)	31 (51.7%)	76 (36.5%)
	Migraine	12 (3.4%)	<5	<5	22 (36.7%)	<5
20 to 24	**Number of subjects**	**530**	**91**	**637**	**68**	**264**

	Indication					
	No indication*	133 (25.1%)	64 (70.3%)	483 (75.8%)	<5	90 (34.1%)
	Unknown indication**	313 (59.1%)	12 (13.2%)	115 (18.1%)	11 (16.2%)	76 (28.8%)
	Bipolar disorder	9 (1.7%)	0	14 (2.2%)	<5	<5
	Epilepsy	34 (6.4%)	10 (11%)	20 (3.1%)	27 (39.7%)	87 (33%)
	Migraine	41 (7.7%)	5 (5.5%)	5 (0.8%)	26 (38.2%)	11 (4.2%)
25 to 29	**Number of subjects**	**612**	**86**	**740**	**67**	**356**
	Indication					
	No indication*	171 (27.9%)	58 (67.4%)	576 (77.8%)	<5	131 (36.8%)
	Unknown indication**	372 (60.8%)	18 (20.9%)	135 (18.2%)	14 (20.9%)	90 (25.3%)
	Bipolar disorder	8 (1.3%)	<5	14 (1.9%)	8 (11.9%)	16 (4.5%)
	Epilepsy	32 (5.2%)	5 (5.8%)	15 (2%)	17 (25.4%)	111 (31.2%)
	Migraine	29 (4.7%)	<5	0	29 (43.3%)	9 (2.5%)
30 to 34	**Number of subjects**	**700**	**95**	**1079**	**89**	**371**
	Indication					
	No indication*	209 (29.9%)	56 (58.9%)	816 (75.6%)	<5	123 (33.2%)
	Unknown indication**	407 (58.1%)	20 (21.1%)	201 (18.6%)	22 (24.7%)	113 (30.5%)
	Bipolar disorder	8 (1.1%)	0	25 (2.3%)	<5	17 (4.6%)
	Epilepsy	35 (5%)	12 (12.6%)	29 (2.7%)	30 (33.7%)	108 (29.1%)
	Migraine	42 (6%)	7 (7.4%)	8 (0.7%)	32 (36%)	10 (2.7%)
35 to 39	**Number of subjects**	**816**	**137**	**1441**	**120**	**417**
	Indication					
	No indication*	259 (31.7%)	90 (65.7%)	1156 (80.2%)	<5	153 (36.7%)
	Unknown indication**	464 (56.9%)	28 (20.4%)	226 (15.7%)	37 (30.8%)	123 (29.5%)
	Bipolar disorder	15 (1.8%)	<5	25 (1.7%)	12 (10%)	15 (3.6%)
	Epilepsy	43 (5.3%)	12 (8.8%)	28 (1.9%)	44 (36.7%)	111 (26.6%)
	Migraine	35 (4.3%)	6 (4.4%)	6 (0.4%)	30 (25%)	17 (4.1%)
40 to 44	**Number of subjects**	**988**	**197**	**1707**	**132**	**518**
	Indication					
	No indication*	309 (31.3%)	122 (61.9%)	1364 (79.9%)	6 (4.5%)	186 (35.9%)
	Unknown indication**	549 (55.6%)	37 (18.8%)	268 (15.7%)	34 (25.8%)	157 (30.3%)
	Bipolar disorder	13 (1.3%)	<5	43 (2.5%)	<5	31 (6%)

	Epilepsy	46 (4.7%)	16 (8.1%)	30 (1.8%)	55 (41.7%)	115 (22.2%)
	Migraine	71 (7.2%)	21 (10.7%)	<5	42 (31.8%)	32 (6.2%)
45 to 49	**Number of subjects**	**1107**	**241**	**1747**	**169**	**702**
	Indication					
	No indication*	340 (30.7%)	158 (65.6%)	1413 (80.9%)	<5	245 (34.9%)
	Unknown indication**	636 (57.5%)	51 (21.2%)	284 (16.3%)	49 (29%)	226 (32.2%)
	Bipolar disorder	10 (0.9%)	<5	27 (1.5%)	12 (7.1%)	48 (6.8%)
	Epilepsy	57 (5.1%)	8 (3.3%)	18 (1%)	66 (39.1%)	149 (21.2%)
	Migraine	64 (5.8%)	23 (9.5%)	5 (0.3%)	49 (29%)	41 (5.8%)
50 to 54	**Number of subjects**	**977**	**251**	**1651**	**186**	**884**
	Indication					
	No indication*	305 (31.2%)	159 (63.3%)	1347 (81.6%)	6 (3.2%)	360 (40.7%)
	Unknown indication**	555 (56.8%)	55 (21.9%)	233 (14.1%)	44 (23.7%)	276 (31.2%)
	Bipolar disorder	15 (1.5%)	<5	29 (1.8%)	21 (11.3%)	43 (4.9%)
	Epilepsy	44 (4.5%)	13 (5.2%)	37 (2.2%)	81 (43.5%)	168 (19%)
	Migraine	58 (5.9%)	20 (8%)	5 (0.3%)	43 (23.1%)	45 (5.1%)
55	**Number of subjects**	**173**	**49**	**285**	**36**	**185**
	Indication					
	No indication*	58 (33.5%)	30 (61.2%)	242 (84.9%)		69 (37.3%)
	Unknown indication**	99 (57.2%)	12 (24.5%)	33 (11.6%)	7 (19.4%)	66 (35.7%)
	Bipolar disorder	<5	0	7 (2.5%)	<5	9 (4.9%)
	Epilepsy	5 (2.9%)	6 (12.2%)	<5	17 (47.2%)	37 (20%)
	Migraine	10 (5.8%)	<5	0	11 (30.6%)	6 (3.2%)

*No indication: At index date, the person did not have a record of any condition/diagnosis.**Unknown indication: None of the specific indications was recorded on index date, but there was a record for any other condition/diagnosis

Table 12.2.5. - Pre-specified indications during assessment windows for all age groups during whole study period.

Assessment window	Indication	CPRD GOLD	IPCI	SIDIAP	IQVIA BELGIUM LPD	IQVIA GERMANY DA
7 days	**Number of subjects**	**6416**	**1241**	**10398**	**945**	**4002**
	Indication					
	No indication*	935 (14.6%)	683 (55%)	7520 (72.3%)	28 (3%)	1360 (34%)
	Unknown indication**	4481 (69.8%)	325 (26.2%)	2286 (22%)	226 (23.9%)	1273 (31.8%)
	Bipolar disorder	141 (2.2%)	11 (0.9%)	224 (2.2%)	71 (7.5%)	186 (4.6%)
	Epilepsy	467 (7.3%)	115 (9.3%)	322 (3.1%)	382 (40.4%)	1027 (25.7%)
	Migraine	394 (6.1%)	107 (8.6%)	47 (0.5%)	286 (30.3%)	183 (4.6%)
30 days	**Indication**					
	No indication*	280 (4.4%)	509 (41%)	5966 (57.4%)	27 (2.9%)	1142 (28.5%)
	Unknown indication**	4764 (74.3%)	445 (35.9%)	3629 (34.9%)	221 (23.4%)	1420 (35.5%)
	Bipolar disorder	233 (3.6%)	14 (1.1%)	328 (3.2%)	73 (7.7%)	197 (4.9%)
	Epilepsy	666 (10.4%)	142 (11.4%)	389 (3.7%)	382 (40.4%)	1077 (26.9%)
	Migraine	477 (7.4%)	132 (10.6%)	87 (0.8%)	291 (30.8%)	200 (5%)
Anytime prior to index date	**Indication**					
	No indication*	0	<5	0	<5	10 (0.2%)
	Unknown indication**	2281 (35.6%)	565 (45.5%)	6567 (63.2%)	167 (17.7%)	1080 (27%)
	Bipolar disorder	941 (14.7%)	57 (4.6%)	1531 (14.7%)	109 (11.5%)	416 (10.4%)
	Epilepsy	1877 (29.3%)	276 (22.2%)	1399 (13.5%)	420 (44.4%)	2214 (55.3%)
	Migraine	1660 (25.9%)	371 (29.9%)	1120 (10.8%)	382 (40.4%)	553 (13.8%)

*No indication: At index date, the person did not have a record of any condition/diagnosis.
**Unknown indication: None of the specific indications was recorded on index date, but there was a record for any other condition/diagnosis

Sensitivity analyses stratified for age and calendar time are available from the shiny app (https://data-dev.darwin-eu.org/EUPAS50789/)

Drug utilisation: Dose and Treatment duration

Across databases, initial daily doses/strength for VPA ranged between a median dose of 500mg/day and 875 mg/day. Average treatment duration varied substantially between databases, with median of 50 days in IQVIA Belgium LPD, 82 days, 98 days and 100 days in CPRD GOLD, IPCI, IQVIA Germany DA and 1 year in SIDIAP.

Although initial dose did not change over the course of the study in all databases, cumulative annual use decreased in SIDIAP and IQVIA Germany DA (from 2019 onwards), but remained stable at the same level for CPRD GOLD, IPCI and IQVIA Belgium LPD over time (Fig. 12.2.1).

Treatment duration were similar across age groups in all databases, with slightly longer duration in the youngest women aged 12-14 years in CPRD and IPCI. Median initial doses/strengths were fairly stable across age groups in CPRD GOLD, SIDIAP and IQVIA Belgium LPD, and slightly increased from 600mg/day in younger age groups to 900-100mg/day in women aged >50years.

Drug utilisation varied by indication: Lower initial dose/strength and shorter treatment duration for VPA when used for migraine compared to bipolar disorder and epilepsy in CPRD GOLD, IPCI and SIDIAP.

Results are summarised in Table 12.2.6, 12.2.7a-c (stratified for age groups) and 12.2.8a-b (stratified for indication).

Table 12.2.6- Descriptive measures of initial dose/strength and treatment duration, *all age groups during whole study period*

Database name	CPRD GOLD	IPCI	SIDIAP	IQVIA BELGIUM LPD	IQVIA GERMANY DA
Treatment duration, days					
median [IQR]	82 [30 - 257.2]	98 [31 - 271.5]	364 [113 - 961]	50 [50 - 115]	100 [50 - 196]
mean (std)	264.6 (456.2)	259.9 (436.9)	773.7 (1012.9)	101.3 (119.4)	206.7 (350.3)
Number of prescriptions					
median [IQR]	1 [1 - 4]	2 [1 - 6]	2 [1 - 5]	1 [1 - 2]	1 [1 - 3]
mean (std)	9.3 (47.3)	10.5 (38.8)	3.9 (4.5)	2 (2.5)	3.4 (6.7)
Initial daily dose/strength, mg					
median [IQR]	666.7 [428.6 - 1000]	875 [500 - 1000]	597.1 [398.9 - 991]	500 [500 - 1000]	600 [600 - 1000]
mean (std)	1063.1 (1681.1)	1181 (6932.5)	757.5 (2796.5)	2104.2 (12697.2)	1323.2 (4263.1)
Cumulative dose, mg					
median [IQR]	66.464.3 [22500 - 250714.3]	85142.9 [25800 - 221625]	235062 [59423.4 - 763495.2]	40000 [25000 - 75000]	60000 [30000 - 145074.6]
mean (std)	295440.4 (644631.9)	252657.9 (522488)	701922.7 (1447723.2)	71045.2 (121933.9)	164260.8 (362340.5)
Number of drug eras					
median [IQR]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
mean (std)	1 (0)	1 (0)	1 (0.1)	1 (0)	1 (0.1)

IQR: Interquartile range, with p25 and p75 provided, std: standard deviation, mg: milligram

Table 12.2.7a- Descriptive measures of initial dose/strength and treatment duration, over the whole study period, stratified by age

CPRD GOLD

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Treatment duration, days										
median [IQR]	176 [60.5 - 406]	79.5 [28.5 - 247]	65 [28 - 169]	71 [28 - 189.2]	73 [28 - 232.5]	81 [30 - 273.2]	91 [30 - 321.5]	85 [30 - 276.5]	84 [30 - 282]	80 [30 - 328]
mean (std)	343.3 (443.7)	241.5 (427.4)	185.2 (347.9)	193.1 (341.2)	239.1 (420.3)	266.6 (444.6)	297.4 (491.8)	279.2 (463.4)	314.7 (554.2)	270.1 (430.2)
Number of prescriptions										
median [IQR]	1 [1 - 5]	1 [1 - 4]	1 [1 - 3]	1 [1 - 4]	1 [1 - 3]	1 [1 - 4]	1 [1 - 5]	1 [1 - 6]	1 [1 - 6]	1 [1 - 4]
mean (std)	6.9 (15.6)	5.9 (13.5)	4.5 (11)	7.6 (50.8)	6.9 (21.2)	7.4 (19.6)	14.7 (98.5)	10 (32.9)	11.2 (31.9)	11.4 (33.3)
Initial daily dose/strength, mg										
median [IQR]	666.7 [428.6 - 1200]	710.7 [400 - 1053.6]	666.7 [428.6 - 1071.4]	666.7 [487.5 - 1017.9]	750 [500 - 1200]	707.1 [500 - 1000]	666.7 [428.6 - 1000]	666.7 [428.6 - 1000]	666.7 [428.6 - 1000]	666.7 [500 - 1285.7]
mean (std)	980.1 (1342.1)	1183 (2522.2)	1046.6 (1880.4)	1133 (2530.2)	1140.6 (1260.9)	1087.1 (1537.3)	1019 (1172.5)	1030 (1508.1)	961.1 (1016.7)	1304.8 (3272.6)
Cumulative dose, mg										
median [IQR]	146100 [48285.7 - 422450]	60350 [22400 - 247860.7]	49900 [21000 - 164625]	56200 [21000 - 170262.5]	63100 [22500 - 239535.7]	67650 [22500 - 265950]	73750 [22500 - 305000]	67000 [22400 - 268700]	68000 [22500 - 250714.3]	88000 [22500 - 280000]
mean (std)	336316.3 (471671.9)	254101.3 (447169.3)	192672.7 (446522.3)	215121.2 (469757.5)	272085.1 (567345.9)	303571.9 (656260.8)	378627.1 (915514.3)	311654.9 (631266.3)	320728 (652837.4)	277841.9 (489254.2)
Number of drug eras										
median [IQR]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
mean (std)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)

IQR: Interquartile range, with p25 and p75 provided, std: standard deviation, mg: milligram

Table 12.2.7b- Descriptive measures of initial dose/strength and treatment duration, over the whole study period, stratified by age

IPCI

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Treatment duration, days										
median [IQR]	186 [70.5 - 490.5]	98.5 [45.8 - 249]	90 [30 - 184]	76.5 [30 - 171.8]	90 [32.5 - 285]	96.5 [45 - 245.5]	96 [30 - 303]	121 [50 - 285]	90 [30 - 284.5]	90 [30 - 216]
mean (std)	332.6 (388.4)	177.2 (184.8)	167.5 (248.6)	221.6 (491.2)	232.2 (366.2)	280.6 (441.2)	316.4 (541.2)	261.3 (366.3)	279.6 (512.8)	230.1 (392.3)
Number of prescriptions										
median [IQR]	3 [1 - 5.5]	2.5 [1 - 4]	2 [1 - 4]	2 [1 - 4]	2 [1 - 6]	2 [1 - 5]	2 [1 - 8]	3 [1 - 6.5]	2 [1 - 6.5]	2 [1 - 5]
mean (std)	6 (7.7)	3.4 (3.4)	6.3 (24.1)	10.4 (57.7)	19.6 (71.9)	12.2 (39.3)	9.4 (24)	8.5 (21.2)	12.6 (45.1)	10.6 (42.1)
Initial daily dose/strength, mg										
median [IQR]	600 [250 - 1000]	600 [300 - 1000]	642.9 [500 - 1000]	825 [350 - 1000]	600 [450 - 1000]	900 [500 - 1000]	750 [500 - 1000]	875 [500 - 1000]	1000 [500 - 1000]	1000 [600 - 1300]
mean (std)	654.8 (625.4)	729.1 (503.9)	804.8 (598.3)	781.8 (476.1)	792.6 (536.8)	2222.7 (16130.3)	852.6 (520.9)	1062.3 (3666.2)	1620.2 (9089.9)	1011.3 (686.9)
Cumulative dose, mg										
median [IQR]	93000 [15750 - 259150]	84918.8 [27750 - 174675]	60000 [15000 - 133000]	57000 [18000 - 138000]	64800 [15000 - 236419.5]	81700 [30000 - 238223.1]	90000 [22500 - 295200]	101375 [45000 - 245850]	90000 [23600 - 250650]	70650 [30000 - 216000]
mean (std)	180585.7 (219192.1)	137182.8 (170821.7)	125128.8 (260898.4)	209427.4 (613615.2)	246791.4 (554738)	287553.3 (544653.6)	300278.4 (570299.9)	249582.7 (434696)	294248.3 (615558.7)	283834.4 (645718.1)
Number of drug eras										
median [IQR]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
mean (std)	1 (0.2)	1 (0)	1 (0)	1 (0.1)	1 (0)	1 (0)	1 (0)	1 (0.1)	1 (0)	1 (0)

IQR: Interquartile range, with p25 and p75 provided, std: standard deviation, mg: milligram

Table 12.2.7c- Descriptive measures of initial dose/strength and treatment duration, over the whole study period, stratified by age

SIDIAP

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Treatment duration, days										
median [IQR]	353 [118.2 - 903.2]	362 [104 - 810]	342 [106 - 714]	321 [101 - 750]	366 [116.5 - 923]	352.5 [106 - 854.8]	366 [119 - 1049]	367.5 [124 - 1193.5]	364 [106 - 1104.8]	408 [125.5 - 1136.5]
mean (std)	704.5 (904.2)	639.8 (813.1)	610.6 (828.2)	675.1 (959.2)	763.5 (991.1)	741.4 (995.1)	815.5 (1059.8)	862 (1073.1)	838 (1086.4)	887.1 (1102.5)
Number of prescriptions										
median [IQR]	2 [1 - 5]	2 [1 - 5]	2 [1 - 4]	2 [1 - 4]	2 [1 - 5]	2 [1 - 4]	2 [1 - 5]	2 [1 - 5]	2 [1 - 5]	2 [1 - 5]
mean (std)	4.1 (4.2)	3.7 (4)	3.3 (3.7)	3.5 (4.3)	3.9 (4.5)	3.8 (4.6)	4.1 (4.7)	4.3 (4.9)	4 (4.6)	4.2 (4.9)
Initial daily dose/strength, mg										
median [IQR]	784.3 [469.6 - 991.4]	596.8 [398 - 968.5]	596.7 [454.2 - 989]	697.8 [489.5 - 989.1]	598 [400 - 993.6]	598.6 [476.2 - 996.1]	593.7 [395.3 - 992.1]	596.3 [397.6 - 990.7]	596.4 [398.8 - 990.2]	592.2 [388.2 - 991.1]
mean (std)	759.4 (434.8)	1080.9 (8217.9)	724.3 (658.6)	859.1 (3443.1)	722.1 (475.9)	738.7 (428.9)	792.1 (3764)	705.1 (443.9)	698.2 (418.1)	691.2 (432.3)
Cumulative dose, mg										
median [IQR]	238800 [62985.3 - 738797.9]	218700 [59152.9 - 588618.8]	222000 [54883 - 528265.9]	205650 [60000 - 619719.7]	239963.6 [61109.6 - 728123.6]	246503.2 [61992.2 - 709650]	238624.2 [62650 - 821430.3]	241604.2 [62689.3 - 867934]	225245.3 [55525 - 870810.6]	288669.3 [68145.5 - 938194.9]
mean (std)	591435.5 (902849.2)	578929.1 (1639121.4)	535461.1 (936903)	752812.7 (2933716.4)	726807.7 (2063418.9)	666024.3 (1078021.1)	720192.2 (1145830)	739820.7 (1146526.4)	728018 (1120431.5)	849164.3 (1335724.6)
Number of drug eras										
median [IQR]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
mean (std)	1 (0.1)	1 (0.1)	1 (0)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0)	1 (0.1)

IQR: Interquartile range, with p75 and p75 provided, std: standard deviation, mg: milligram

Table 12.2.7d- Descriptive measures of initial dose/strength and treatment duration, over the whole study period, stratified by age

IQVIA Belgium LPD

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Treatment duration, days										
median [IQR]	50 [37.5 - 187.5]	50 [41.8 - 100]	50 [50 - 105]	50 [50 - 104.5]	50 [50 - 113]	50 [50 - 145]	50 [50 - 115]	50 [50 - 101.8]	50 [50 - 126.5]	50 [50 - 100]
mean (std)	147.8 (168.7)	76.7 (56.5)	83.5 (63.2)	88.8 (95.2)	95.3 (92.5)	106.2 (98.1)	109.3 (126.9)	101.8 (134.2)	111.2 (151.9)	93.8 (119.5)
Number of prescriptions										
median [IQR]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]
mean (std)	1.6 (1.2)	1.6 (1)	1.5 (1)	1.9 (1.8)	1.8 (1.8)	2.1 (2.3)	2.3 (2.5)	2.1 (2.6)	2.1 (3.5)	2.1 (3.6)
Initial daily dose/strength, mg										
median [IQR]	500 [300 - 768.8]	600 [500 - 1000]	500 [500 - 1000]	500 [300 - 1000]	500 [300 - 1000]	550 [500 - 1000]	600 [500 - 1000]	500 [500 - 1000]	500 [500 - 1000]	500 [500 - 1000]
mean (std)	548.9 (295.8)	955.6 (1127.8)	1277.2 (3556.7)	1293.6 (3781.8)	2073.9 (11065.2)	966 (2294.8)	1631.8 (6930)	4979.7 (26827.3)	1697 (5753.1)	1507 (4323.4)
Cumulative dose, mg										
median [IQR]	46875 [25000 - 76250]	30000 [25000 - 79250]	30000 [25000 - 64700]	30000 [25000 - 50250]	50000 [15000 - 79500]	50000 [25000 - 93000]	47700 [25000 - 88800]	36900 [25000 - 75000]	45500 [25000 - 75000]	25000 [25000 - 67375]
mean (std)	60591.7 (52550.5)	53727.8 (45457.6)	59381 (87331.7)	61523.2 (84279.1)	86281.5 (191716)	70800.9 (84762.7)	79214.4 (120386.6)	66389.4 (95915.5)	79242.7 (166370.9)	53237.5 (54506.1)
Number of drug eras										
median [IQR]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
mean (std)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0.1)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)

IQR: Interquartile range, with p75 and p75 provided, std: standard deviation, mg: milligram

Table 12.2.7e- Descriptive measures of initial dose/strength and treatment duration, over the whole study period, stratified by age

IQVIA Belgium LPD

Age group	12 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55
Treatment duration, days										
median [IQR]	100 [50 - 263.8]	100 [50 - 207.2]	100 [50 - 221.8]	100 [50 - 200]	100 [50 - 168]	100 [50 - 173.5]	100 [50 - 199]	100 [50 - 187]	100 [50 - 191.8]	100 [50 - 204.5]
mean (std)	268.2 (409.6)	208.5 (318.1)	180.6 (207.7)	200 (331.8)	215.8 (394.5)	194 (328.9)	215.4 (374.2)	210.6 (386.7)	198.6 (319.3)	227.1 (431.2)
Number of prescriptions										
median [IQR]	2 [1 - 5.2]	2 [1 - 3]	1 [1 - 3]	1 [1 - 3]	1 [1 - 2]	1 [1 - 2]	1 [1 - 3]	1 [1 - 2]	1 [1 - 3]	1 [1 - 3]
mean (std)	5.6 (8.8)	3.5 (5)	3 (4.2)	3.4 (9)	3.4 (8.6)	3.2 (6.8)	3.5 (6.8)	3.2 (5.8)	3.1 (5)	3.8 (9.1)
Initial daily dose/strength, mg										
median [IQR]	600 [300 - 600]	600 [300 - 900]	600 [300 - 1000]	600 [600 - 1000]	600 [600 - 1000]	600 [600 - 1000]	600 [600 - 1000]	600 [600 - 1000]	895.5 [600 - 1200]	895.5 [600 - 1000]
mean (std)	1160.8 (3906.3)	1403.6 (4230)	1014.7 (2222.5)	1191 (3036.1)	883.1 (1255.8)	1457 (5138)	1295.9 (6128.8)	1397.8 (3960.8)	1559.9 (4665.6)	1296.7 (3185.7)
Cumulative dose, mg										
median [IQR]	60000 [17685 - 138450]	60000 [30000 - 133650]	60000 [30000 - 142825]	60000 [30600 - 153356.2]	60000 [30000 - 120000]	60000 [30000 - 135000]	60000 [30000 - 152550]	60000 [30000 - 135800]	74400 [34575 - 163150]	90000 [30000 - 160000]
mean (std)	162085 (280093.2)	140379.5 (264338.7)	120570.2 (156626.2)	177467.1 (704250.6)	159099.4 (325573.6)	161773.3 (307289.2)	177642.7 (356871.5)	158247 (291949.1)	172199.5 (299839.8)	198029.8 (443772)
Number of drug eras										
median [IQR]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
mean (std)	1 (0)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)

IQR: Interquartile range, with p25 and p75 provided, std: standard deviation, mg: milligram

Table 12.2.8a- Descriptive measures of initial dose/strength and treatment duration stratified by pre-specified indication at prescription date, *all age groups over the whole study period* **CPRD GOLD, IPCI, SIDIAP**

Database name	**CPRD GOLD**			**IPCI**			**SIDIAP**		
Indication group	**Bipolar disorder**	**Epilepsy**	**Migraine**	**Bipolar disorder**	**Epilepsy**	**Migraine**	**Bipolar disorder**	**Epilepsy**	**Migraine**
Treatment duration, days									
median [IQR]	82.5 [30 - 251]	104 [30 - 315]	30 [28 - 84.5]	75 [30 - 90]	90 [30 - 180]	80 [20 - 160]	439 [181 - 1436.5]	525 [144 - 1544]	151 [86 - 241]
mean (std)	235.3 (376.9)	269.3 (434.1)	120.5 (255.5)	98.4 (95.9)	159.1 (237.3)	162.8 (269.1)	1029.8 (1173.2)	1014.4 (1176.3)	193.8 (175.1)
Number of prescriptions									
median [IQR]	2 [1 - 7.5]	1 [1 - 5]	1 [1 - 2]	1 [1 - 1]	1 [1 - 3]	2 [1 - 5]	3 [1 - 7]	2 [1 - 5]	1 [1 - 2]
mean (std)	9 (16.7)	6.9 (16.9)	2.8 (6.6)	2.9 (5)	2.9 (4.2)	3.4 (4)	4.7 (5)	3.4 (3.2)	1.8 (1)
Initial daily dose/strength, mg									
median [IQR]	1000 [750 - 1946.4]	714.3 [508.9 - 1150]	600 [400 - 666.7]	900 [600 - 1000]	1000 [600 - 1000]	600 [500 - 1000]	899.3 [528.6 - 996.6]	980 [499.7 - 1198.5]	490.7 [320 - 596.7]
mean (std)	1665.5 (1587.2)	1182.6 (2440.9)	871.6 (3042.5)	840.7 (446)	905.9 (573.6)	750.9 (390.9)	807.6 (387.9)	928.5 (473.4)	520 (289.8)
Cumulative dose, mg									
median [IQR]	83857.1 [41250 - 232312.5]	92400 [30000 - 306117]	24800 [16800 - 58000]	54000 [15000 - 67500]	72000 [11200 - 148500]	54000 [15000 - 135000]	368233.3 [119987.5 - 1218670.3]	438395 [135000 - 1391191.9]	78600 [40481.5 - 135000]
mean (std)	285599.3 (557774.3)	258772.8 (488730.2)	84119.7 (274074.6)	88622.2 (110065.2)	142823.3 (291431)	126483.1 (232107.3)	928297.1 (1171169.8)	1006413.6 (1332281.3)	121262.8 (192897.8)
Number of drug eras									
median [IQR]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
mean (std)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0.1)	1 (0)	1 (0)

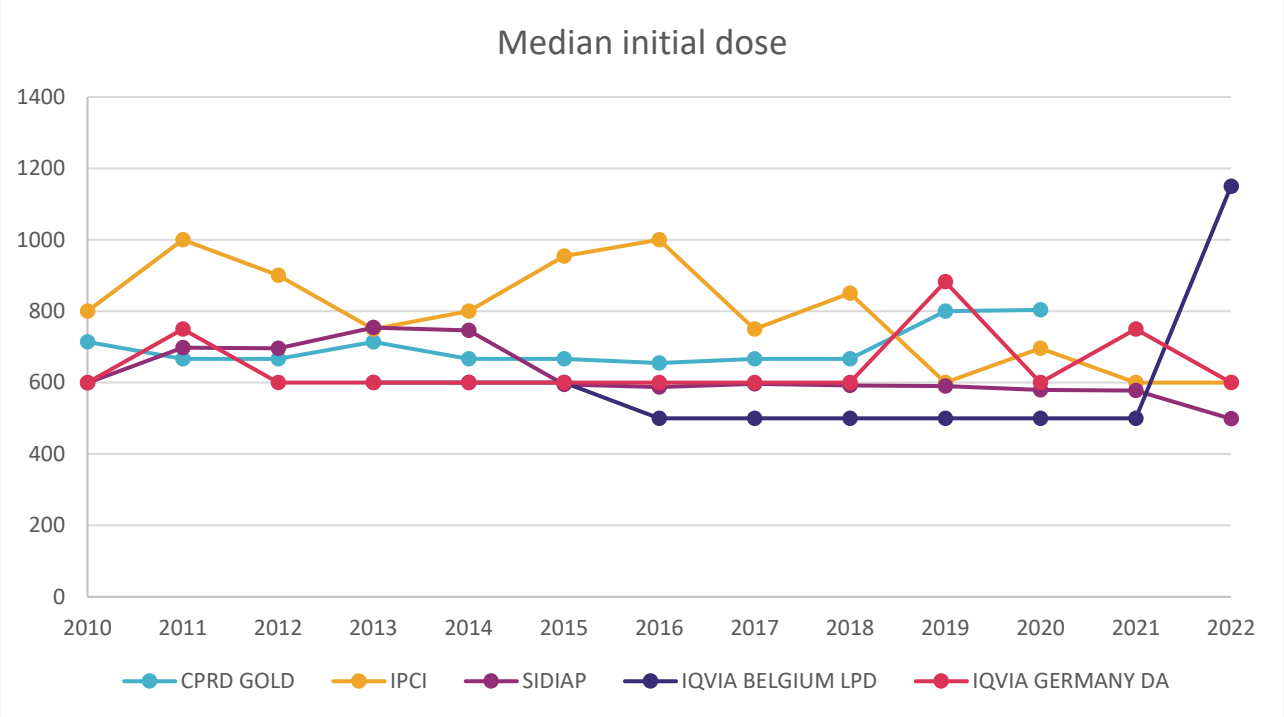
IQR: Interquartile range, with p25 and p75 provided, std: standard deviation, mg: milligram

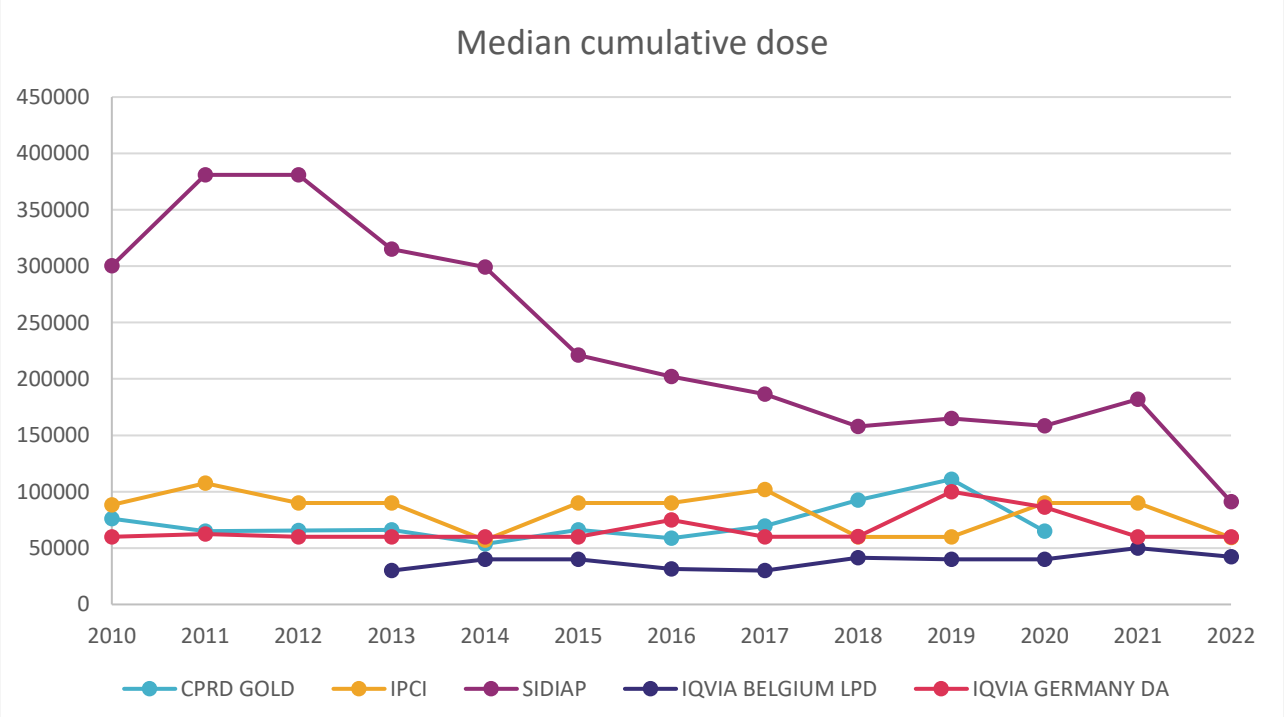
Table 12.2.8b- Descriptive measures of initial dose/strength and treatment duration stratified by pre-specified indication at prescription date, *all age groups over the whole study period* **IQVIA Belgium LPD, IQVIA Germany DA**

Database name	**IQVIA BELGIUM LPD**			**IQVIA GERMANY DA**		
Indication group	**Bipolar disorder**	**Epilepsy**	**Migraine**	**Bipolar disorder**	**Epilepsy**	**Migraine**
Treatment duration, days						
median [IQR]	50 [50 - 98]	64 [50 - 148]	50 [50 - 100]	100 [50 - 177.2]	100 [50 - 174]	50 [50 - 125.8]
mean (std)	93.4 (160.7)	114.6 (134.1)	82.9 (84.6)	153.3 (196.5)	178.1 (276.1)	115.3 (159)
Number of prescriptions						
median [IQR]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]	1 [1 - 2]
mean (std)	2.2 (4.7)	2.2 (2.5)	1.7 (1.6)	2.5 (3.1)	2.7 (4.7)	1.8 (2.5)
Initial daily dose/strength, mg						
median [IQR]	500 [500 - 1000]	600 [500 - 1000]	500 [300 - 1000]	600 [600 - 1000]	600 [600 - 1000]	600 [300 - 600]
mean (std)	1211 (3099.8)	2305.4 (13161.1)	799 (1637.4)	842.7 (456.7)	1067.2 (2137.6)	620.5 (444.3)
Cumulative dose, mg						
median [IQR]	25000 [25000 - 50000]	50000 [25000 - 1e+05]	26700 [25000 - 50000]	60000 [30000 - 143818.7]	73500 [30000 - 142500]	32100 [15000 - 60000]
mean (std)	63021 (102603.6)	90100.8 (158784.2)	47024.5 (55039.1)	125786 (183732.2)	137958.5 (240402.6)	72843.5 (108322.2)
Number of drug eras						
median [IQR]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]	1 [1 - 1]
mean (std)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0.1)	1 (0)

IQR: Interquartile range, with p25 and p75 provided, std: standard deviation, mg: milligram

Figure 12.2.1 Median initial dose and median cumulative dose yearly by database





12.2.5 Other Analysis

Results from sensitivity and additional stratifications for calendar year are available in the Shiny Web-application.

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the new guideline on good pharmacovigilance practice (EMA/873138/2011), there was no requirement for expedited reporting of adverse drug reactions as only secondary data was used.

14 DISCUSSION

14.1 Key Results

Population level DUS

The proportion of women 12 to 55 years old that initiate VPA decreased over the period 2010-2021 for all analysed datasets, ACI VARHA, CPRD GOLD, IPCI, SIDIAP, IQVIA Belgium LTD, and IQVIA Germany DA. Prevalence increased between 2010 and 2015 for IPCI and SIDIAP with a subsequent decreasing trend after that. ACI VARHA had a stable prevalence until 2019, when it started to decrease. IQVIA Belgium LTD had a decrease in prevalence of use for the visible period (2014-2022). CPRD GOLD and IQVIA GERMANY DA had a consistent decrease in prevalent use of VPA throughout. This decrease in use seen in all databases was not distributed evenly between age groups.

Younger age groups namely those <45 years old, saw a more pronounced decrease in prevalence after 2015 and amongst women 45 years old or more, the prevalence remained stable or decreased less noticeably. Prevalence throughout the study period was 2 to 3x higher for the older age groups compared to the youngest. Incidence rates of use stayed stable or decreased similarly across age groups.

The prevalence of use of other antiepileptics increased or remained stable, with the most used being pregabalin and gabapentin. As for drugs for other indications, there was an increase of use of quetiapine, beta blockers and amitriptyline.

Patient-level DUS

6416, 1241 10,398, 945 and 4,002 women initiated VPA within the study period in CPRD GOLD, IPCI, SIDIAP, IQVIA Belgium LPD and IQVIA Germany DA, respectively. The median age in these cohorts of women ranged between 40 and 43 years. Healthcare utilisation was high with the median number of visits ranging between 5 in IQVIA Germany DA and 29 in CPRD GOLD. Anxiety and depressive disorder were frequent comorbidities, with 20%-39% and 16%-44% having a recording of the respective diagnoses any time before treatment start. The level of prescription of contraceptives was highest in CPRD GOLD, followed by IQVIA Belgium LPD, IPCI and lowest in SIDIAP and IQVIA Germany DA, with differences potentially due to country-specific reimbursement strategies and completeness of recordings of contraceptives in the different databases. Use of hormonal contraception varied greatly across age groups, with highest levels of prescriptions being observed in women between 15-39 compared to lower rates in the >50 and 12-14 year age groups.

At the date of their first VPA prescription, most women had no record of a diagnosis for epilepsy, bipolar disorder or migraine (except for IQVIA Belgium LPD). Among those with a specific diagnosis recorded, migraine was the most common indication in CPRD GOLD (5.7%), whereas epilepsy was the most common indication in all other databases. Notably, VPA was uncommon for migraine in SIDIAP (0.3%) and bipolar disorder in IPCI (0.5%).

Across databases, initial daily doses/strength for VPA ranged between a median 500mg/day and 875mg/day. Average treatment duration varied substantially between databases, with a median of 50 days in IQVIA Belgium LPD, 82 days, 98 days, and 100 days in CPRD GOLD, IPCI and IQVIA Germany DA, respectively, and 1 year in SIDIAP. Although initial dose did not change over the course of the study in all databases, cumulative annual use decreased in SIDIAP (from 2012 onwards) and IQVIA Germany DA (from 2019 onwards), but remained stable at the same level for CPRD GOLD, IPCI and IQVIA Belgium LPD over time.

14.2 Limitations of the research methods

General limitations:

This study was informed by routinely collected health care data and so data quality issues had to be considered.

Drug prescriptions: A recording of a prescription did not mean that the person took the drug. Therefore, assumption of actual use and the duration of drug use were made. For databases where no dose information was available but only the strength of the product (e.g. CPRD) was recorded, strength did not display the actual dose taken by the person.

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

Database-specific limitations:

ACI VARHA [former HDSF], Finland:

- Background population: For the calculation of incidence and prevalence, all women who met the eligibility criteria in the whole database were included as denominator population. ACI Varha comprises both inpatient and outpatient specialist care, hence all people who attended any of the outpatient clinics or who were admitted to the hospital are included in the database. The denominator is only comprised of women who had a contact with secondary care, not including those who only attended primary care or had no healthcare contact at all. Furthermore, people from the catchment area who attended private specialist care are not included. However, most people attending secondary care are expected to use healthcare offered by the public sector.
- Major organisational changes happened at the beginning of 2013. EHR prescriptions were started to be recorded from 2010 onwards, but only fully collected from 2013/2014 onwards.
- For in-patient drug prescriptions, the recorded end date often may not reflect the real treatment duration as it might not be stopped after the patient is discharged. Therefore, the period of drug use recorded in the database might be much longer than the actual use, which can increase the prevalence and bias results upwards.
- In Finland, the Social Insurance Institution reimburses anti-epileptic drugs other than valproate only if the person was first prescribed valproate. In clinical practice, a valproate prescription is therefore issued

in many cases only to bypass this rule. Therefore, many patients never actually start valproate, but move on to the next treatment right away. This prescription practice increases incidence rates and bias results upwards.

Information on drug dose and duration were not available for inpatient records, that amount to >70% of prescriptions so we deemed it to be not sufficient for DUS.

14.3 Results in context

Population-level incidence and prevalence:

A previous study assessing population-level incidence and prevalence of VPA use in women of childbearing age in Europe was commissioned by the EMA: Klungel et al[16]. calculated monthly incidence and prevalence of VPA including 69,533 valproate users among a total of 9.7 million young women between 2010 and 2020 using data from Denmark, Italy, the Netherlands, Spain and the UK. Monthly incidence rates of valproate ranged between 12-564 per 100,000 persons year, and prevalence rate ranged between 1.2-7.7 per 1000 female subjects.

Our study report incidence rates of 10-287/100.000py and period prevalence between 0.3 per 1000 and 3.7 per 1000, which are comparable to the previous study.

Patient-level characterisation:

Differences between databases were seen for use of systemic hormonal contraceptives, potentially due to differences in reimbursement strategies in the different countries: Hormonal contraceptives are reimbursed by the NHS in the UK but not in Catalonia, Spain.

Drug utilisation

Recommendations for initial valproate/valproic acid doses in adults range from 600mg/day p.o. for epilepsy, 750mg/day for manic episodes associated with bipolar disorder, to 400-500mg p.o for migraine prophylaxis. Maintenance doses typically require 1-2g/day for epilepsy and mania and 1.2-1.5g/day for migraine prophylaxis.[21,22] Median initial doses seen across databases are in line with the dosing recommendations for the respective indications.

14.4 Generalisability

The study included women of childbearing age from data sources in 6 different European countries and healthcare systems (primary care in IPCI, SIDIAP, and CPRD and secondary care in ACI VARHA, IQVIA Germany DA and IQVIA Belgium LPD). While we consider results representative for the study population in the respective countries, results should not be generalised to the larger population, e.g. men and different age groups, as recommendation to avoid the use of VPA, which largely impact their use in this population, are specific for women of childbearing age.

14.5 Other information

NA

15 CONCLUSION

Incident use of VPA women of childbearing age decreased throughout the study period, with prevalence declined during the first years of the study period and remaining largely stable at a lower level afterwards. The decrease in use was generally more accentuated in younger age groups. Levels of prescriptions of hormonal contraceptives were low, and varied greatly across age groups and between databases, with differences between the latter potentially due to country-specific reimbursement strategies and completeness of contraception prescription recordings. Although initial dose did not change over time, cumulative annual use decreased in SIDIAP compared to the beginning of the study period and in IQVIA Germany DA after 2019.

16 REFERENCES

1. European Medicines Agency. Valproate 19/12/2009 [Available from: https://www.ema.europa.eu/en/medicines/human/referrals/valproateaccessed 05/08/2022.
2. Angus-Leppan H, Liu RSN. Weighing the risks of valproate in women who could become pregnant. *BMJ* 2018;361:k1596. doi: 10.1136/bmj.k1596 [published Online First: 2018/04/20]
3. Vatzaki E, Straus S, Dogne JM, et al. Latest clinical recommendations on valproate use for migraine prophylaxis in women of childbearing age: overview from European Medicines Agency and European Headache Federation. *J Headache Pain* 2018;19(1):68. doi: 10.1186/s10194-018-0898-3 [published Online First: 2018/08/16]
4. Bromley R, Weston J, Adab N, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database Syst Rev* 2014(10):CD010236. doi: 10.1002/14651858.CD010236.pub2 [published Online First: 2014/10/31]
5. European Medicines Agency. PRAC recommends new measures to avoid valproate exposure in pregnancy 09/02/2018 [Available from: https://www.ema.europa.eu/en/documents/press-release/prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdfaccessed 04/08/2022.
6. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013;309(16):1696-703. doi: 10.1001/jama.2013.2270 [published Online First: 2013/04/25]
7. Meador K, Reynolds MW, Crean S, et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res* 2008;81(1):1-13. doi: 10.1016/j.eplepsyres.2008.04.022 [published Online First: 2008/06/21]
8. Tanoshima M, Kobayashi T, Tanoshima R, et al. Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis. *Clin Pharmacol Ther* 2015;98(4):417-41. doi: 10.1002/cpt.158 [published Online First: 2015/06/06]
9. Degremont A, Polard E, Kerbrat S, et al. Impact of recommendations on sodium valproate prescription among women with epilepsy: An interrupted time-series study. *Epilepsy Behav* 2021;125:108449. doi: 10.1016/j.yebeh.2021.108449 [published Online First: 2021/11/29]
10. Ehlken B, Nishikawa C, Kaplan S, et al. Effectiveness of risk minimization measures for valproate: a drug utilization study based on implementation of a risk minimization programme in Europe, analysis of data from the UK. *Curr Med Res Opin* 2022;38(3):461-68. doi: 10.1080/03007995.2021.1997286 [published Online First: 2021/12/22]
11. Ehlken B, Stevanovic I, Kaplan S, et al. Effectiveness of risk minimisation measures for valproate: a drug utilisation study in Europe, analysis of data from Spain. *Rev Neurol* 2021;73(11):373-82. doi: 10.33588/rn.7311.2021247 [published Online First: 2021/11/27]
12. Toussi M, Shlaen M, Coste F, et al. Effectiveness of risk minimisation measures for valproate: A drug utilisation study in Europe. *Pharmacoepidemiol Drug Saf* 2021;30(3):292-303. doi: 10.1002/pds.5166 [published Online First: 2020/10/28]
13. Hughes JE, Buckley N, Looney Y, et al. Valproate utilisation trends among women of childbearing potential in Ireland between 2014 and 2019: A drug utilisation study using interrupted time series. *Pharmacoepidemiol Drug Saf* 2022;31(6):661-69. doi: 10.1002/pds.5427 [published Online First: 2022/03/15]
14. Zelano J, Sveberg L, Tauboll E, et al. Valproate Restrictions in Sweden and Norway: Online survey suggests implementation deficit. *Acta Neurol Scand* 2022;145(5):551-56. doi: 10.1111/ane.13581 [published Online First: 2022/01/08]

15. Giuliano L, La Neve A, Galimberti CA, et al. Valproate and female patients: Prescribing attitudes of Italian epileptologists. *Epilepsy Behav* 2019;97:182-86. doi: 10.1016/j.yebeh.2019.05.024 [published Online First: 2019/06/30]
16. Klungel O, Sturkenboom M, Abtahi S. Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends 2022 [Available from:
17. Vlug A, van der Lei J, Mosseveld B, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods of information in medicine* 1999;38:339-44.
18. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). *Informatics in primary care* 2011;19(3):135-45.
19. Rathmann W, Bongaerts B, Carius H, et al. Basic characteristics and representativeness of the German Disease Analyzer database. *Int J Clin Pharmacol Ther* 2018;56(10):459-66.
20. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44(3):827-36. doi: 10.1093/ije/dyv098 [published Online First: 2015/06/08]
21. British National Formulary: Sodium valproate. [Available from: https://bnf.nice.org.uk/drugs/sodium-valproate/, accessed 13/01/2023]
21. British National Formulary: Valproic acid. [Available from: https://bnf.nice.org.uk/drugs/valproic-acid/, accessed 13/01/2023]

17 ANNEXES

Appendix I: List of Stand-Alone documents

Appendix I: List of Stand-alone Documents

Document title	Version	Date	
Medication code list	V1	17/01/2023	

Medication concept sets

Drugs of interest

Drug cohort	Concept Id	Name	Excluded?	Include descendants?	Include mapped?
Valproate, valpromide	745466	Valproate	FALSE	TRUE	FALSE
	36878958	Valpromide	FALSE	TRUE	FALSE
	19018610	Calcium valproate	TRUE	TRUE	FALSE

Alternative treatments

Drug cohort	Concept Id	Name	Excluded?	Include descendants?	Include mapped?
Amitriplyline	710062	Amitriptyline	FALSE	TRUE	FALSE
Amitriplyline (mono)	43144132	Amitriptyline delayed release oral tablet	FALSE	TRUE	FALSE
	40008920	Amitriptyline Extended Release Oral Capsule	FALSE	TRUE	FALSE
	36886569	Amitriptyline extended release oral tablet	FALSE	TRUE	FALSE
	40008924	Amitriptyline Injectable Solution	FALSE	TRUE	FALSE
	40008927	Amitriptyline Oral Capsule	FALSE	TRUE	FALSE
	40008928	Amitriptyline Oral Solution	FALSE	TRUE	FALSE
	40008929	Amitriptyline Oral Suspension	FALSE	TRUE	FALSE
	40008931	Amitriptyline Oral Tablet	FALSE	TRUE	FALSE
	36891495	Amitriptyline prefilled syringe	FALSE	TRUE	FALSE
Atenolol	1314002	Atenolol	FALSE	TRUE	FALSE
Atenolol (mono)	43162296	Atenolol delayed release oral tablet	FALSE	TRUE	FALSE
	43639707	Atenolol extended release oral capsule	FALSE	TRUE	FALSE
	40010619	Atenolol Injectable Solution	FALSE	TRUE	FALSE
	40010621	Atenolol Oral Capsule	FALSE	TRUE	FALSE
	40145389	Atenolol Oral Solution	FALSE	TRUE	FALSE
	42480741	Atenolol oral suspension	FALSE	TRUE	FALSE

	40010622	Atenolol Oral Tablet	FALSE	TRUE	FALSE
	35160786	Atenolol Powder for Oral Suspension	FALSE	TRUE	FALSE
	42480742	Atenolol prefilled syringe	FALSE	TRUE	FALSE
Bisoprolol (mono)	43174403	Bisoprolol delayed release oral tablet	FALSE	TRUE	FALSE
	36784871	Bisoprolol extended release oral tablet	FALSE	TRUE	FALSE
	40862036	Bisoprolol injectable solution	FALSE	TRUE	FALSE
	36259258	Bisoprolol oral capsule	FALSE	TRUE	FALSE
	21040420	Bisoprolol oral solution	FALSE	TRUE	FALSE
	21128647	Bisoprolol oral suspension	FALSE	TRUE	FALSE
	40015379	Bisoprolol Oral Tablet	FALSE	TRUE	FALSE
	41049024	Bisoprolol rectal suppository	FALSE	TRUE	FALSE
Brivaracetam	35604901	Brivaracetam	FALSE	TRUE	FALSE
Carbamazepine	740275	Carbamazepine	FALSE	TRUE	FALSE
Clobazam	19050832	Clobazam	FALSE	TRUE	FALSE
Clonazepam	798874	Clonazepam	FALSE	TRUE	FALSE
Clonidine	1398937	Clonidine	FALSE	TRUE	FALSE
Clonidine (mono)	40026177	Clonidine Extended Release Oral Capsule	FALSE	TRUE	FALSE
	40168646	Clonidine Extended Release Oral Tablet	FALSE	TRUE	FALSE
	40168645	Clonidine Extended Release Suspension	FALSE	TRUE	FALSE
	40026180	Clonidine Injectable Solution	FALSE	TRUE	FALSE
	35606031	Clonidine Injection	FALSE	TRUE	FALSE
	40026183	Clonidine Oral Capsule	FALSE	TRUE	FALSE
	21140541	Clonidine oral solution	FALSE	TRUE	FALSE
	21081645	Clonidine oral suspension	FALSE	TRUE	FALSE
	40026184	Clonidine Oral Tablet	FALSE	TRUE	FALSE
	43782105	Clonidine prefilled applicator	FALSE	TRUE	FALSE
	42483270	Clonidine prefilled syringe	FALSE	TRUE	FALSE

	40221147	Clonidine Transdermal System	FALSE	TRUE	FALSE
Eslicarbazepine	44507780	Eslicarbazepine	FALSE	TRUE	FALSE
Ethosuximide	750119	Ethosuximide	FALSE	TRUE	FALSE
Ethosuximide_mono	750119	Ethosuximide	FALSE	TRUE	FALSE
	41050593	Ethosuximide / quinacrine oral capsule [acrisuxin]	TRUE	TRUE	FALSE
	36213608	Ethosuximide / quinacrine Oral Product	TRUE	TRUE	FALSE
	36213609	Ethosuximide / quinacrine Pill	TRUE	TRUE	FALSE
	41141562	Ethosuximide 150 mg / quinacrine 7.5 mg [acrisuxin]	TRUE	TRUE	FALSE
	19103505	Ethosuximide 150 MG / quinacrine 7.5 MG Oral Capsule	TRUE	TRUE	FALSE
	41127302	Ethosuximide 150 mg / quinacrine 7.5 mg oral capsule [acrisuxin]	TRUE	TRUE	FALSE
	41282985	Ethosuximide 150 MG / Quinacrine 7.5 MG Oral Capsule [Acrisuxin] Box of 100	TRUE	TRUE	FALSE
	41252089	Ethosuximide 150 MG / Quinacrine 7.5 MG Oral Capsule [Acrisuxin] Box of 1000	TRUE	TRUE	FALSE
	41148717	Ethosuximide 150 MG / Quinacrine 7.5 MG Oral Capsule Box of 100	TRUE	TRUE	FALSE
	41054425	Ethosuximide 150 MG / Quinacrine 7.5 MG Oral Capsule Box of 1000	TRUE	TRUE	FALSE
Flunarizine	19055183	Flunarizine	FALSE	TRUE	FALSE
Flunarizine (mono)	40041098	Flunarizine Extended Release Oral Capsule	FALSE	TRUE	FALSE
	40041099	Flunarizine Oral Capsule	FALSE	TRUE	FALSE
	40041100	Flunarizine Oral Solution	FALSE	TRUE	FALSE
	40041101	Flunarizine Oral Tablet	FALSE	TRUE	FALSE
Gabapentin	797399	Gabapentin	FALSE	TRUE	FALSE
	40708359	1000 MG gabapentin 0.06 MG/MG Topical Cream	TRUE	TRUE	FALSE
	36808731	1000 MG gabapentin 0.06 MG/MG Topical Gel	TRUE	TRUE	FALSE
	21077063	1000 MG gabapentin 0.06 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	36808712	1000 MG gabapentin 0.1 MG/MG Topical Gel	TRUE	TRUE	FALSE
	40708358	1000 MG gabapentin 0.1 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	36808661	100000 MG gabapentin 0.06 MG/MG Topical Gel	TRUE	TRUE	FALSE

	21078924	100000 MG gabapentin 0.06 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	40707861	1010 MG gabapentin 0.06 MG/MG Topical Cream	TRUE	TRUE	FALSE
	35790469	1010 MG gabapentin 0.06 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	40707860	1010 MG gabapentin 0.1 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	35797951	101000 MG gabapentin 0.06 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	36809803	45000 MG gabapentin 0.06 MG/MG Topical Gel	TRUE	TRUE	FALSE
	40705050	45000 MG gabapentin 0.06 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	36809805	45000 MG gabapentin 0.1 MG/MG Topical Gel	TRUE	TRUE	FALSE
	40705049	45000 MG gabapentin 0.1 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	36809854	50000 MG gabapentin 0.06 MG/MG Topical Gel	TRUE	TRUE	FALSE
	21088347	50000 MG gabapentin 0.06 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	35796916	99300 MG gabapentin 0.06 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	40743919	Gabapentin 0.06 MG/MG Topical Cream	TRUE	TRUE	FALSE
	36813253	Gabapentin 0.06 MG/MG Topical Gel	TRUE	TRUE	FALSE
	21160833	Gabapentin 0.06 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	36811608	Gabapentin 0.1 MG/MG Topical Gel	TRUE	TRUE	FALSE
	40743891	Gabapentin 0.1 MG/MG Vaginal Gel	TRUE	TRUE	FALSE
	40743966	Gabapentin Topical Cream	TRUE	TRUE	FALSE
	36813442	Gabapentin Topical Gel	TRUE	TRUE	FALSE
	21150880	Gabapentin Vaginal Gel	TRUE	TRUE	FALSE
Lacosamide	19087394	Lacosamide	FALSE	TRUE	FALSE
Lamotrigine	705103	Lamotrigine	FALSE	TRUE	FALSE
Levetiracetam	711584	Levetiracetam	FALSE	TRUE	FALSE
Lithium citrate/carbonate	751246	Lithium carbonate	FALSE	TRUE	FALSE
	767410	Lithium citrate	FALSE	TRUE	FALSE
Metoprolol	1307046	Metoprolol	FALSE	TRUE	FALSE
Metoprolol (mono)	35605509	Metoprolol Injection	FALSE	TRUE	FALSE

	21105879	Metoprolol oral solution	FALSE	TRUE	FALSE
	35603513	Metoprolol Cartridge	FALSE	TRUE	FALSE
	43141322	Metoprolol delayed release oral tablet	FALSE	TRUE	FALSE
	963906	Metoprolol Extended Release Oral Capsule	FALSE	TRUE	FALSE
	40061829	Metoprolol Extended Release Oral Tablet	FALSE	TRUE	FALSE
	40061831	Metoprolol Injectable Solution	FALSE	TRUE	FALSE
	21076502	Metoprolol oral capsule	FALSE	TRUE	FALSE
	21076501	Metoprolol oral suspension	FALSE	TRUE	FALSE
	40061834	Metoprolol Oral Tablet	FALSE	TRUE	FALSE
	42479694	Metoprolol prefilled syringe	FALSE	TRUE	FALSE
Nadolol	1313200	Nadolol	FALSE	TRUE	FALSE
Nadolol (mono)	21064596	Nadolol oral solution	FALSE	TRUE	FALSE
	21152967	Nadolol oral suspension	FALSE	TRUE	FALSE
	40062739	Nadolol Oral Tablet	FALSE	TRUE	FALSE
Olanzapine	785788	Olanzapine	FALSE	TRUE	FALSE
Oxcarbazepine	718122	Oxcarbazepine	FALSE	TRUE	FALSE
Perampanel	42904177	Perampanel	FALSE	TRUE	FALSE
Phenobarbital	734275	Phenobarbital	FALSE	TRUE	FALSE
Phenobarbital (mono)	40077423	Phenobarbital Injectable Solution	FALSE	TRUE	FALSE
	44120360	Phenobarbital intramuscular solution	FALSE	TRUE	FALSE
	40077427	Phenobarbital Oral Solution	FALSE	TRUE	FALSE
	42483299	Phenobarbital oral suspension	FALSE	TRUE	FALSE
	40077428	Phenobarbital Oral Tablet	FALSE	TRUE	FALSE
Phenytoin	740910	Phenytoin	FALSE	TRUE	FALSE
Pizotifen	21604384	Pizotifen; oral	FALSE	TRUE	FALSE
Pregabalin	734354	Pregabalin	FALSE	TRUE	FALSE
Primidone	751347	Primidone	FALSE	TRUE	FALSE

Propranolol	1353766	Propranolol	FALSE	TRUE	FALSE
Propranolol (mono)	40077340	Propranolol Extended Release Oral Capsule	FALSE	TRUE	FALSE
	40077365	Propranolol Oral Solution	FALSE	TRUE	FALSE
	42482725	Propranolol oral suspension	FALSE	TRUE	FALSE
	40077366	Propranolol Oral Tablet	FALSE	TRUE	FALSE
	42629333	Propranolol Injection	FALSE	TRUE	FALSE
	40077363	Propranolol Oral Capsule	FALSE	TRUE	FALSE
	42479808	Propranolol prefilled syringe	FALSE	TRUE	FALSE
	36266895	Propranolol delayed release oral capsule	FALSE	TRUE	FALSE
	43034562	Propranolol delayed release oral tablet	FALSE	TRUE	FALSE
	40077359	Propranolol Extended Release Oral Tablet	FALSE	TRUE	FALSE
	36885579	Propranolol injectable solution	FALSE	TRUE	FALSE
Quetiapine	766814	Quetiapine	FALSE	TRUE	FALSE
Rufinamide	19006586	Rufinamide	FALSE	TRUE	FALSE
Tiagabine	715458	Tiagabine	FALSE	TRUE	FALSE
Timolol (syst, mono)	43639715	Timolol oral solution	FALSE	TRUE	FALSE
	40087917	Timolol Oral Tablet	FALSE	TRUE	FALSE
Topiramate	742267	Topiramate	FALSE	TRUE	FALSE
Topiramate (mono)	41111275	Topiramate Delayed Release Oral Capsule	FALSE	TRUE	FALSE
	43189984	Topiramate Delayed Release Oral Tablet	FALSE	TRUE	FALSE
	43560771	Topiramate Extended Release Oral Capsule	FALSE	TRUE	FALSE
	40099157	Topiramate Oral Capsule	FALSE	TRUE	FALSE
	35157496	Topiramate Oral Granules	FALSE	TRUE	FALSE
	21062513	Topiramate Oral Solution	FALSE	TRUE	FALSE
	21033004	Topiramate Oral Suspension	FALSE	TRUE	FALSE
	40099159	Topiramate Oral Tablet	FALSE	TRUE	FALSE
Vigabatrin	19020002	Vigabatrin	FALSE	TRUE	FALSE

Zonisamide	744798	Zonisamide	FALSE	TRUE	FALSE