# Secular Trends in the Use of Valproate-Containing Medicines in Women of Childbearing Age in Europe: A Multinational DARWIN EU Network Study

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With respect to the content of the following presentation I have no actual or potential conflicts of interest or have any financial relationships to disclose.

# Background

- Valproate-containing medicine (VPA) are indicated for **epilepsy, bipolar disorder and migraine prevention.**
- Teratogen – risk of neurodevelopmental impairment and congenital malformations. **Contraindicated in pregnant women.**
- Restrictions of its use **in women of childbearing age**: EMA issued risk minimisation measures in 2014 and 2018
- Recent **restrictions in men (2023)**

# Objectives

The objectives of this study are

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.

# Methods: Data Partners

## UK

**Clinical Practice Research Datalink (CPRD GOLD)**

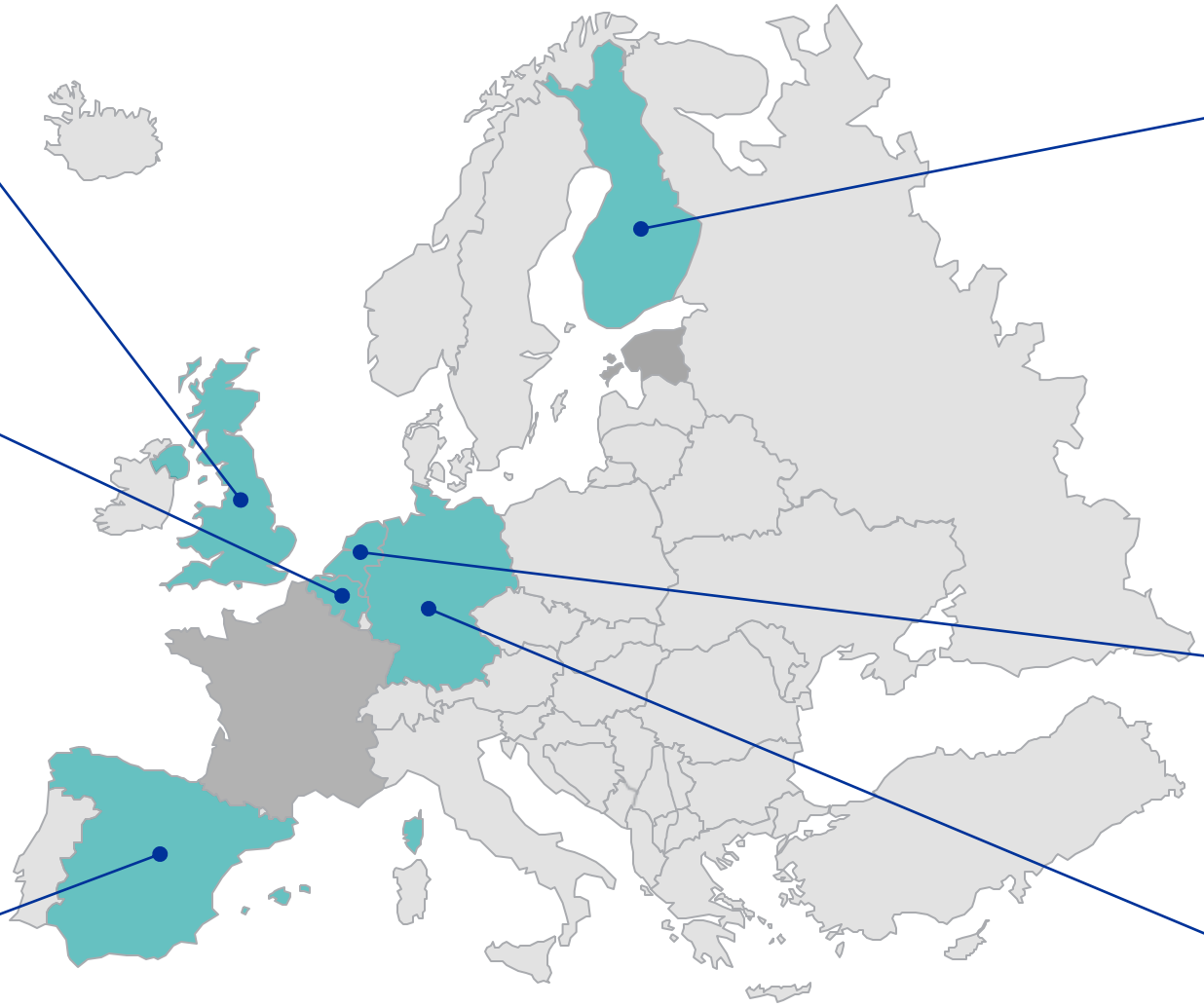
## Belgium

**IQVIA Belgium Longitudinal Patient Data**

## Spain

**IDIAPJGol**

Parc Salut Mar Barcelona, Hospital del Mar (IMIM)



## Finland

**Auria Clinical Informatics at Hospital District of Southwest Finland (HDSF)**

## Netherlands

**Integrated Primary Care Information**

Netherlands Comprehensive Cancer Organisation

## Germany

**IQVIA Germany Disease Analyser**

# Methods: Study Desing and Study Population

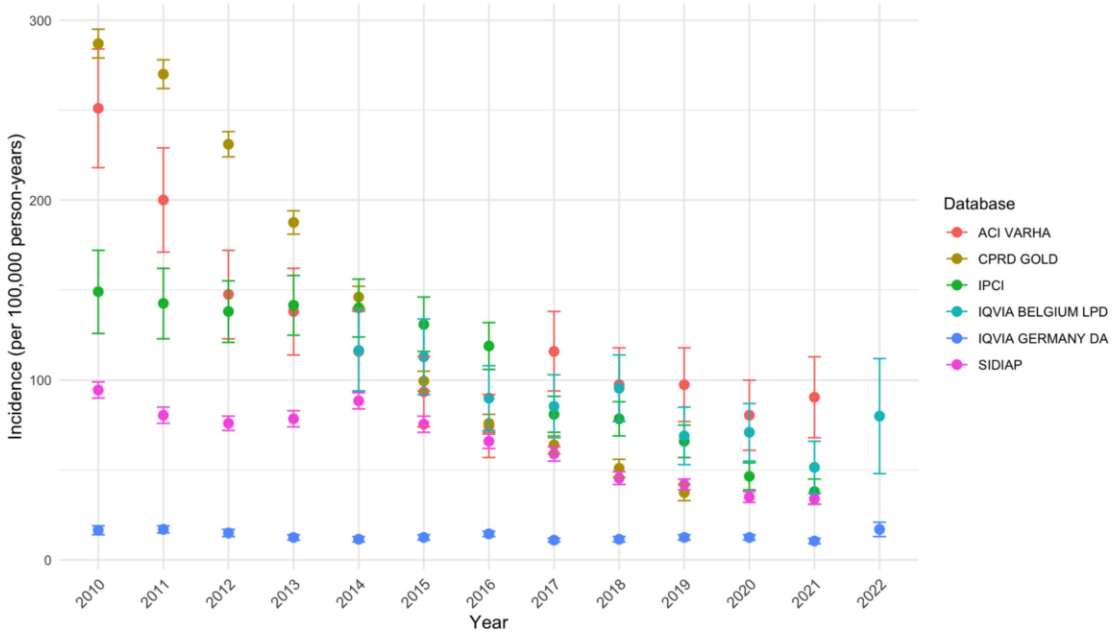
- **Drug Utilisation Study**: Population and patient level
- Included population: women between ≥12 years and ≤55 years of age (2010–2022)
- Prevalence:
  - Women contributed to the **denominator** cohort from the study start date, the date they had at least recorded 1 year of medical history or the date they reach the minimum age
  - Calculated as **annual period prevalence.**
- Incidence:
  - 365 days of **washout** for denominator calculations from the last prescription
  - Result was provided as the number of new users per 100,000

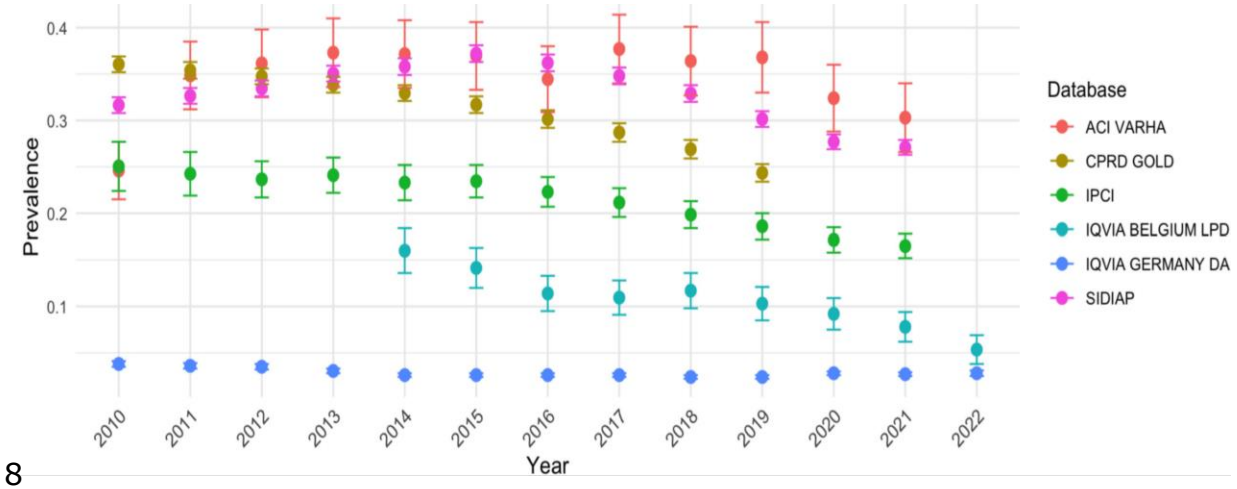
# Methods: Variables

- Exposure/s - **Drug of interest:**
  - **VPA:** Valproic acid, Sodium valproate, Magnesium valproate, Valproate semisodium and Valpromide
  - **Alternative treatments**
- Covariates for stratification in population-level drug utilisation study: **Age**: 5-year age bands were used
- Covariates for patient-level drug utilisation study:
  - **Indication**: Epilepsy, bipolar disorder, migraine
  - Co-morbidities and co-medication for **large-scale patient characterisation**

# Results Population Level

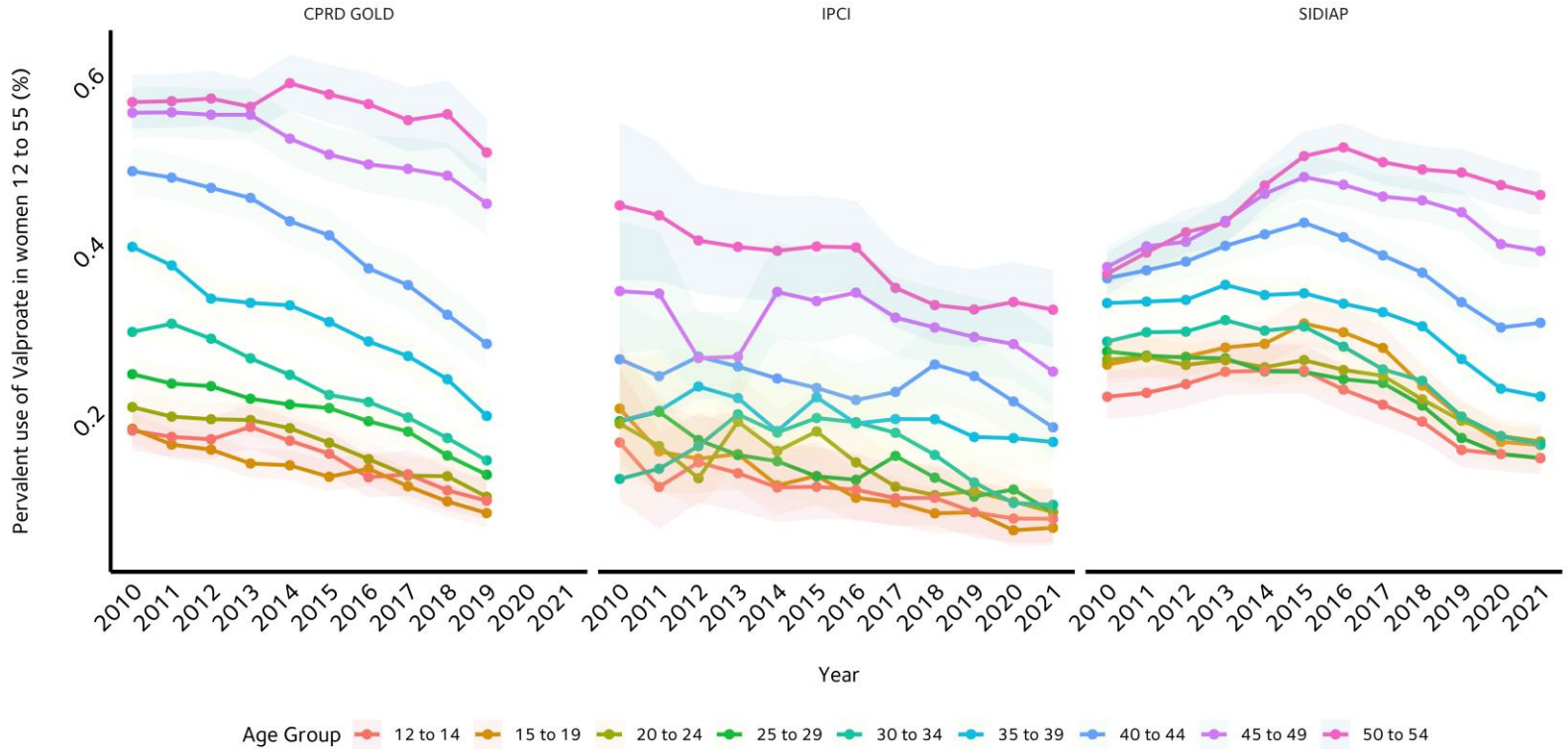
- The **incidence** of new use and **prevalence** of VPA amongst women 12 to 55 years **decreased** over the period 2010-2021
- Incidence remained **stable** for **IQVIA Germany**, sharpest **decrease in CPRD**
- Prevalence: Less pronounced decrease for ACI VARHA and IQVIA DA



# Results Population Level

- **Younger** age groups (<45) had a **lower prevalence,** which decreased over time. Incidence of use of VPA showed a decreasing pattern for all age groups in all databases.
- The prevalence of **the use of pregabalin and gabapentin** clearly **increased** during the study period, while the others followed different trends across the participating databases.



# Results Patient Level

| Database | CPRD GOLD | IPCI | SIDIAP | IQVIA Belgium LPD | IQVIA Germany DA |
|---|---|---|---|---|---|
| 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%) |
| 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%) |

# Results Patient Level

| Database | CPRD GOLD | IPCI | SIDIAP | IQVIA Belgium LPD | IQVIA Germany DA |
|---|---|---|---|---|---|
| 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%) |
| 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%) |
| 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%) |

# Conclusion

- The **incidence and prevalence of use of VPA among women of childbearing age have declined** in BE, DE, ES, NL, and the UK. Specially in younger women.
- The **prevalence of medication** use across six databases from 2010 to 2022 shows significant **differences in trends** between drugs and regions.
- Our findings, consistent with other studies, highlight **substantial regional variability in valproate use and comorbidities**—likely driven by data-source and population differences.
- This fact underscores the importance of multidatabase studies using CDMs, facilitating the **identification of regional differences** in drug utilization, comorbidities, and **prescribing practices.**

## Paper

## Shiny App

## Report