Impact of 2018 EU risk minimisation measures and revised pregnancy prevention programme on utilisation and prescribing trends of medicinal products containing valproate: an interrupted time series study

Submitted to Drug Safety

AUTHORS:

Shahab Abtahi[1], Romin Pajouheshnia[1], Carlos E. Durán[2], Judit Riera-Arnau[2,3], Magdalena Gamba[1], Ema Alsina[2], Vjola Hoxhaj[2], Morten Andersen[4], Claudia Bartolini[5], Sarah Brøgger Kristiansen[4], Jeremy Brown[6], Christine Erikstrup Hallgreen[7], Patricia Garcia-Poza[8], Helga Gardarsdottir[1,9], Rosa Gini[5], Anna Girardi[5], Emily Holthuis[10], Consuelo Huerta[11], Luisa Ibánez[3], Giorgio Limoncella[5], Mar Martín-Pérez[8], Olga Paoletti[5], Giuseppe Roberto[5], Patrick Souverein[1], Karin M.A. Swart[10], Kevin Wing[6], Miriam Sturkenboom[2], Olaf Klungel[1†].

AFFILIATIONS:

1 Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University (UU), Utrecht, the Netherlands.

2 Julius Global Health, University Medical Center Utrecht (UMCU), Utrecht, the Netherlands.

3 Clinical Pharmacology department, Hospital Universitari de la Vall d'Hebron, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.

4 Pharmacovigilance Research Center, Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences University of Copenhagen, Denmark.

5 Agenzia Regionale di Sanità della Toscana (ARS), Italy.

6 London School of Hygiene & Tropical Medicine (LSHTM), UK.

7 Copenhagen Centre for Regulatory Science, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

8 Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS), Madrid, Spain.

9 Department of Clinical Pharmacy, UMCU, Utrecht, the Netherlands.

10 PHARMO Institute for Drug Outcomes Research, Utrecht, the Netherlands.

11 Department of Public Health, Maternal and Child Health, Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain.

† Universiteit Utrecht, David de Wiedgebouw, Universiteitsweg 99, 3584 CG Utrecht, the Netherlands, email: o.h.klungel@uu.nl

Supplementary information S.1.

a) Description of the data sources used in the study

Table S.1.a-1 Overview of databases used in this study.

Characteristic	**DNR***	**ARS Tuscany**	**PHARMO Nationally representative**	**BIFAP Multi-regional**	**CPRD (HES-linked) Nationally representative**
Handling partner	UCPH	ARS	PHARMO	AEMPS	LSHTM
Country (population size, millions)	Denmark (5.8)	Italy (59.8)	Netherlands (17.1)	Spain (46.5)	UK (66)
Type of database	ADM	ADM	EMR	EMR	EMR
No. active patients in database, millions	5.8	3.6	4.2 (prior to linkage)	9	10.0
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Updates	Annual	Monthly	Annual	Annual	6 monthly
GP Rx	Yes (no prescription data)	Yes	Yes	Yes	Yes
Outpatient Rx	Yes	Yes	Yes	No	No
Private Rx	Yes	No	No	No	No
Inpatient hospital Rx	No	No	Yes (not used here)	No	No
Date of Rx	Yes	Yes	Yes	Yes	Yes
Quantity of Rx	Yes	Yes	Yes	Yes	Yes
Duration of Rx	Yes	Based on DDD	Yes	Yes	Yes
Daily dose	Yes	Based on DDD	Yes	Yes	Yes
Brand/generic	Yes	Yes	Yes	Yes	Yes
Registered diagnosis compatible with indication of valproate	Diagnosis codes in history	Diagnosis codes in history	Diagnosis codes in history	Linked to prescription and diagnosis codes in medical history	Read diagnosis as a proxy

Coding of drugs	ATC	ATC	ATC	ATC	Gemscript/BNF product codes
Dosing regimen	No	No	Yes	Yes	Yes (incomplete)
Pregnancy testing	No	No	No (mainly OTC)	Yes	Yes
Pregnancy prevention					
Oral contraceptives	Yes	No	Yes	Yes (only those dispensed with a prescription)	Yes
Duration OC	Yes (based on DDDs)	No	Yes	Yes	Yes
Intrauterine device/system					
Date fitted	Yes (not copper IUD)*	No	Yes	No	Yes
Date removed	No	No	Yes	No	No
Implanon/Nexplanon/etonogestrel					
Date inserted	Date of prescription fill	No	Proxy based on date of prescription fill	Not systematically	Yes
Date removed	No	No	Proxy based on date of prescription fill	Not systematically	No
Noristerat/norethisterone enantate					
Date injected	Not marketed	No	Not marketed	Yes	Yes
Depo-provera					
Date injected	Date of prescription fill	No	Proxy based on date of prescription fill	Yes	Yes
Written record of OC advice	No	No	Free text, if recorded by GP	Free text potentially	Yes (partial)
Hysterectomy	Yes*	Yes	Yes	If recorded by GP	Yes (HES linkage)
Oophorectomy	Yes*	Yes	Yes	If recorded by GP	Yes (HES linkage)
Sterilisation	Yes*	Yes	Yes	If recorded by GP	Yes (HES linkage)

Partner vasectomy	No	No	No	No	No
Completed Menopause	No	No	Free text potentially	If recorded by GP and free text potentially	No
Outcomes					
Reasons for stopping Valproate	No	No	No	Free text potentially	No
Coding of disease	ICD-10*	ICD-9 CM/ICD-10	ICPC, ICD-9, ICD-10	ICPC-2, ICD-9, ICD 10, snomed	CPRD: Read HES: ICD-10 and OPCS-4
Pregnancy outcomes	Linkage to birth register*	Linkage to birth register, hospitalizatio n, mental health registry	Linkage to perinatal registry	From mother's records, if recorded by the GP	Mother-Baby Link via algorithm in CPRD
Number of pregnancies per year	60.000 births/year	Not yet known	29000 linked pregnancies / year	100,000	Not yet known

Abbreviations, ADM: Administrative; ATC: Anatomical Therapeutic Chemical; EMR: Electronic Medical Records; ICD: International Classification of Disease, ICPC: International Classification of Primary Care; DDD: defined daily dose; DNR: Danish national registers.

* Due to data access delays for the DNR, diagnosis, procedure and pregnancy information will not be available during the study; only information on prescriptions will be available

Denmark: Danish National Registries (DNR)

Denmark has a tax-funded health care system ensuring easy and equal access to health care for all its citizens, and all contacts with the system are recorded in administrative and medical registers. The records carry a unique personal identification number, called the CPR-number, assigned to every Danish citizen at birth. Linkage between registers at an individual level is possible because this CPR-number is used in all Danish registers.[1] All registers have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.8 million inhabitants plus historical information. For the purpose of this study information was obtained from the following registries: The Danish National Patient Registry (DNPR) includes all hospitalisation records since 1977, and incorporating all outpatient diagnoses and services also starting from 1995 using the International Classification of Diseases, 10th Reversion (ICD-10).[2] The Danish National Prescription Registry includes data on all drugs dispensed from Danish pharmacies from 1995 and onwards, including dispensing date, ATC code, product code and amount.[3] Sociodemographic data is available from the Danish Civil Registration System, such as sex, date of birth, migration, vital status and civil status recorded since 1968.

Italy: ARS

The Italian National Healthcare System is organised at regional level: the national government sets standards of assistance and a tax-based funding for each region, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. The Agenzia regionale di sanit`a della Toscana (ARS Tuscany) is a research institute of

the Tuscany Region. ARS database comprises all the data that are collected by the Tuscany Region to account for the healthcare delivered to its inhabitants. Moreover, ARS collects data from regional initiatives. The data in the ARS data source can be linked with each other at the individual level, through a pseudonymous identifier. ARS database routinely collects primary care and secondary care prescriptions of drugs for outpatient use, and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from co-payment, dispensings of diagnostic tests and procedures, causes of death, mental health services registry. A pathology registry is available, mostly recorded in free text, but with morphology and topographic Snomed codes. Mother-child linkage is possible through the birth registry.

The Netherlands: PHARMO and the Netherlands Perinatal registry

The PHARMO Database Network is a population-based network of electronic healthcare databases (EHDs) and combines data from different primary and secondary healthcare settings in the Netherlands.[4] These different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms.[5] Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere.[6]

The longitudinal nature of the PHARMO Database Network system enables to follow up more than nine million individuals in the Netherlands, which equals to more than half of the Dutch population, with an average follow-up of 12 years in 2018.[4] Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is one year. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other available information depends on the data source. To address the objectives of the present study the following PHARMO databases were used: General Practitioner Database, Out-patient Pharmacy Database and Pregnancy Register.

The General Practitioner (GP) Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/ drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System.[7] Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC), which can be mapped to ICD codes, but can also be entered as free text.

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO ATC Classification System. Oral contraceptives are mostly prescribed by GPs, but can also be obtained directly in the pharmacy, this was captured in PHARMO as was proven before.[8] PHARMO is listed under the ENCePP resources database.[9]

The Netherlands Perinatal Registry (PRN) is maintained by Perined and comprises data on pregnancies, births and neonatal outcomes of births in the Netherlands, voluntarily collected by perinatal caregivers, mainly for benchmarking.[10] For research purposes the data can be linked with the PHARMO Database Network via a trusted third party. Records include information on mothers (e.g., maternal age, obstetric history, parity), pregnancy (e.g., mode of conception, mode of delivery) and children (e.g., birth weight, gestational age, Apgar score). Diagnoses and symptoms are coded according to the Perinatal Registry code lists. For more information: https://www.perined.nl

Permission on a project-basis is needed from PHARMO as well as Perined to obtain these data. Combined Out-patient Pharmacy and PRN data currently cover a catchment area representing 0.5 million residents for the data cut up to 2015. Additional linkages to the other PHARMO databases can be performed on a patient-level. Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included.

Spain: BIFAP

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerised database of medical records of primary care (www.bifap.aemps.es) is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). The project started in 2001 and currently includes data on 12 million patients with clinical information from 14810 physicians (GPs and paediatricians) from nine participant Autonomous Regions.[11] BIFAP database currently includes anonymised clinical and prescription/dispensing data of around 14 million (9.4 active population) patients representing 85% of the population in participating regions, and 29% of the total Spanish population. Mean duration of follow up in the database is 8.7 years. Information collected by PCPs includes administrative, socio-demographic, lifestyle, and other general data, clinical diagnosis and health problems, results of diagnostic procedures, interventions, and prescriptions/dispensations. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2, ICD-9CM and SNOMEDCT system, and a variable proportion of clinical information is registered in "medical notes" in free text fields in the EMR. Additionally, information on hospital discharge diagnoses coded in ICD-10 terminology is linked to patients included in BIFAP for a subset of periods and regions participating in the database. All information on prescriptions of medicines by the PCP is incorporated and linked by the PCP to a health problem (episode of care), and information on the dispensing of medicines at pharmacies is extracted from the e-prescription system that is widely implemented in Spain BIFAP. A mother-child linkage has not been made so far and no private/specialist prescribing is available.

United Kingdom: Clinical Practice Research Datalink

The Clinical Practice Research Datalink (CPRD) comprises computerised medical records of general practitioners (GPs) from 1987 onwards. CPRD is one of the world's largest collections of primary care data, sourced from a UK-wide network of over 1,100 primary care practices.[12] CPRD comprises two complementary databases – Gold (from practices with VISION software) and Aurum (from practices with EMIS software). Combined, they include around 10 million currently registered active patients, representative of the UK population, of whom 75% have at least 20 years of follow up. The data covers ~15% of the population. GPs play a gatekeeper role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are affiliated to a practice, which centralises the medical information from the GPs, specialist referrals, hospitalisations and tests. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, laboratory results, hospital admissions and death. The validity of a wide range of drug exposure data is routinely tested. Only those practices that meet quality standards are used for research (about 10% of the practices that send data to CPRD do not meet the quality standards). Furthermore, validation studies are conducted regularly by comparing CPRD data to written notes of general practitioners.[13] A subset of CPRD records (from practices in England) are linked to the national Hospital Episode Statistics (HES) database. HES is a national dataset containing data on in-patient, out-patient and emergency care from all NHS hospitals in England. Administrative details, information on ICD-10 coded clinical diagnoses and OPCS-4-coded procedures are included. Office for National Statistics (ONS) mortality data recording causes of death from death certificates are collated by ONS and routinely linked to CPRD and HES. Of relevance for this proposal, collaborative work between LSHTM and CPRD researchers has recently established a pregnancy register within the CPRD, identifying instances of pregnancy and pregnancy outcomes since 1987.

b) Limitations regarding Danish National Registries (DNR)

Due to restrictions caused by COVID-19 pandemic, a limited dataset was used as the Danish data source for this study. This limited dataset was from an existing project on evaluation of risk minimisation measures, and included only data from the Danish National Prescription Registry. This caused several limitations to various sections of this study including data acquisition and analysis, as the following:

- Study population: All females of childbearing age with valproate dispensing (aged 12-55 years) resident in Denmark between 01.01.2010 and 31.12.2018 were included, as data from the originally intended last 2 years of study period (i.e., 2019 and 2020) were not available. Due to this limitation, no ITS analyses could be performed due to the few time points available after the implementation of 2018 risk minimisation measures in Denmark. The Danish female population of childbearing age (including non-valproate users) and thus all the related denominators in various analyses of this study (such as for calculating incidence or prevalence rates) was estimated based on public Danish population numbers from Statistics Denmark.[14]

- Indications: Information on indications for valproate use was not available in the data used for this study.

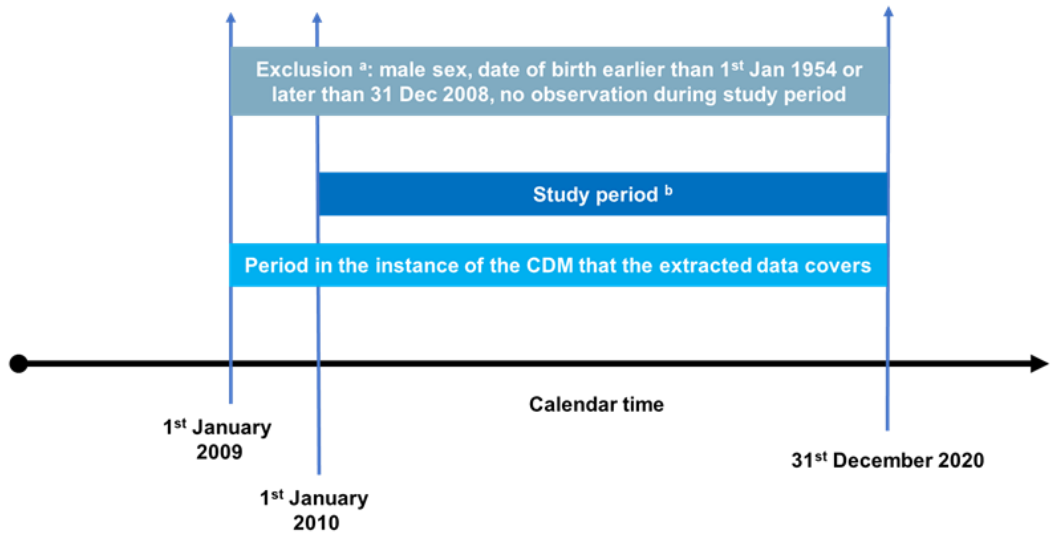
- Contraception: User-independent permanent methods of contraception were not available in the data used for this study.

- Alternative medications: Dispensing information on beta-blocker, and clonidine (Co2AC01) as alternatives for migraine were not captured in the data used for this study.

- Pregnancy: information about pregnancies and pregnancy testing was not captured in the data used for this study.

c) Schematic representation of data coverage and establishment of study population

Figure 1 – schematic of data coverage and definition of study population



a. Subjects may be excluded during initial data processing if they meet the general exclusion criteria. This will help to reduce data volume. DAPs may apply these exclusion criteria during their ETL, but they must report this (it will also be detected when assessing at patient flow). Subjects with any record of male sex will be excluded.
b. Time series of cross-sectional analyses is performed over this period (monthly analyses). The final month will begin December 1st 2020.

d) Data source-specific algorithms to define treatment episodes of valproate

In this study, DAPs provided, based on their knowledge and experience with their respective data sources, data source-specific algorithms to define study variables in their data sources, including treatment episodes with valproates. Algorithms differed between data sources to account for differences in the availability or quality of information captured across different data sources. For example, different algorithms to define the number of days of treatment were needed per data source, as some data sources contained prescribing information and others dispending information, and different levels of detail on products were captured. Furthermore, based on discussions with regional clinicians and pharmacists, some DAPs opted for certain strategies to define the number of days of treatment per record in their data to account for issues with measures such as defined daily dose (DDD). The algorithms are described in Table S.1.b-1.

Table S.1.b-1 Data source-specific algorithms to define number of days of treatment in an individual prescription or dispensing of valproate.

Data source	**Algorithm**
DNR	90-days fixed duration of valproate per dispensing
ARS	30-days fixed duration of valproate per dispensing
PHARMO	Algorithm based on standardised macros from the PHARMO database network. These macros utilise dispensing and product information to estimate the duration of an individual dispensed medicine. Missing values were imputed with a value of 30 days.
BIFAP	Algorithm based on the following strategy: 1. First step: if the duration of the prescription/dispensing has been written by the doctor but there is also enough data to calculate it* (this means that both the written duration and the calculated one exist) the shorter of the two is chosen. For example: if the physician wrote a duration of 35 days but the quantity dispensed is 30 tablets and the posology 3 tablets/day, the calculated duration is 10 days, and it is set as the duration. *Duration is calculated as number of prescribed/dispensed units in the product's package divided by the number of units to be taken per day (i.e., posology). 2. Second Step: when only one written or calculated duration is available, this is the one chosen. 3. Third step: when no duration is available, the distance between prescriptions/dispensings is used. This distance must be within the precalculated range of duration values for the medicinal product. 4. Fourth step: if none of the above steps could be reached, then the mode or the median (it is the researcher's choice) of the prescription/dispensing duration is set (mode or mean are calculated at the product level, from those prescriptions for which written or calculated duration was available).

	5. If none of the above options apply, the prescription/dispensing duration is considered a missing value. Missing values were imputed with a value of 30 days.
CPRD	1. Clean prescribed quantity per day and dispensed number of medicinal product with reference to prescribed quantity unit 2. Calculate days of treatment as dispensed number of medicinal product / prescribed quantity per day Missing values were imputed with a value of 30 days.

References

1. Pedersen CB. The Danish Civil Registration System. Scand J Public Health. 2011 Jul;39(7 Suppl):22-5.
2. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015 Nov 17;7:449-90.
3. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011 Jul;39(7 Suppl):38-41.
4. Bakker M, Herings R. PHARMO Database Network. In: Sturkenboom M, Schink T, Eds. Databases for Pharmacoepidemiological Research. Cham: Springer International Publishing AG; 2021:109-118.
5. Herings RM, Pedersen L. Pharmacy-based medical record linkage systems. In: Strom B, Kimmel S, Hennessy S. Eds. Pharmacoepidemiology. 5th ed. Hoboken: Wiley; 2012:270–86.
6. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. *Eur J Cancer.* 2010 Jan;46(2):395-404.
7. ATC/DDD Index 2018. WHO Collaborating Centre for Drug Statistics Methodology. 20.12.2017. Accessed: 11.03.2022. Available from: https://www.whocc.no/atc_ddd_index/
8. Bezemer ID, Verhamme KM, Gini R, et al. Use of oral contraceptives in three European countries: a population-based multi-database study. *Eur J Contracept Reprod Health Care.* 2016;21(1):81-7.
9. Resources Database: PHARMO Database Network. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®). Last updated: 10/01/2022. Accessed: 11.03.2022. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=45066
10. Goossen WT, Arns-Schiere AM. Information Architecture for Perinatal Registration in the Netherlands. *J Obstet Gynecol Neonatal Nurs.* 2017 Mar-Apr;46(2):310-321.
11. Maciá-Martínez MA, Gil M, Huerta C, et al. Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP): A data resource for pharmacoepidemiology in Spain. *Pharmacoepidemiol Drug Saf.* 2020 Oct;29(10):1236-1245.
12. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol.* 2015 Jun;44(3):827-36.
13. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol.* 2010 Jan;69(1):4-14.
14. Statistics Denmark. FOLK1A: Population at the first day of the quarter by region, sex, age and marital status. Accessed 31.08.2022. Available at: https://www.statbank.dk/statbank5a/selectvarval/define.asp?PLanguage=1&subword=tabsel&MainTable=FOLK1A&PXSId=199113&tablestyle=&ST=SD&buttons=0