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ORIGINAL RESEARCH ARTICLE

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

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Abstract

Introduction Due to established teratogenicity of valproates, the EU risk minimisation measures (RMMs) with a pregnancy prevention programme (PPP) for valproate were updated in March 2018.

Objectives To investigate the effectiveness of the 2018 EU RMMs on valproate utilisation in five European countries/regions.

Methods A multi-database, times series study of females of childbearing potential (12–55 years) was conducted using electronic medical records from five countries/regions (01.01.2010–31.12.2020): Denmark, Tuscany (Italy), Spain, the Netherlands, and the UK. Clinical and demographic information from each database was transformed to the ConcePTION Common Data Model, quality checks were conducted and a distributed analysis was performed using common scripts. Incident and prevalent use of valproate, proportion of discontinuers and switchers to alternative medicine, frequency of contraception coverage during valproate use, and occurrence of pregnancies during valproate exposure were estimated per month. Interrupted time series analyses were conducted to estimate the level or trend change in the outcome measures.

Results We included 69,533 valproate users from 9,699,371 females of childbearing potential from the five participating centres. A significant decline in prevalent use of valproates was observed in Tuscany, Italy (mean difference post-intervention −7.7%), Spain (−11.3%), and UK (−5.9%) and a non-significant decline in the Netherlands (−3.3%), but no decline in incident use after the 2018 RMMs compared to the period before. The monthly proportion of compliant valproate prescriptions/dispensings with a contraceptive coverage was low (<25%), with an increase after the 2018 RMMs only in the Netherlands (mean difference post-intervention 12%). There was no significant increase in switching rates from valproates to alternative medicine after the 2018 intervention in any of the countries/regions. We observed a substantial number of concurrent pregnancies during valproate exposure, but with a declining rate after the 2018 RMMs in Tuscany, Italy (0.70 per 1000 valproate users pre- and 0.27 post-intervention), Spain (0.48 and 0.13), the Netherlands (0.34 and 0.00), and an increasing rate in UK (1.13 and 5.07).

Conclusion There was a small impact of the 2018 RMMs on valproate use in the studied European countries/regions. The substantial number of concurrent pregnancies with valproate exposure warrants a careful monitoring of implementation of the existing PPP for valproate in clinical practice in Europe, to see if there is any need for additional measures in the future.

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Key Points

Valproate use has generally declined among females of childbearing potential in Europe between 2010 and 2020.

After the 2018 EU risk minimisation measures for valproate, a significant decline in valproate utilisation was observed among females of childbearing potential in Tuscany (Italy), Spain, and UK, while there was a non-significant decline in the Netherlands, compared to the time period before.

The contraceptive coverage during valproate use was low across countries/regions, and increased only in the Netherlands after the 2018 intervention.

Switching from valproate to alternative medicine (for indications of valproate) was not increased after the 2018 risk minimisation measures in any of the studied countries/regions.

There was a substantial number of concurrent pregnancies with valproate exposure in the studied countries/regions.

1 Introduction

Valproate and related substances are licensed for the treatment of epilepsy and acute mania in patients with bipolar disorder in Europe, and also as prophylaxis for bipolar disorders and migraine headaches in some EU member states. The teratogenic risk associated with the use of valproates in pregnant women are well established [1, 2]. Previous studies showed that > 10% of children exposed to valproates in utero had a congenital malformation, and between 30 and 40% showed degrees of neurodevelopmental or behavioural disorders at an older age [3, 4]. In comparison with other antiepileptics among women with similar indications, children exposed in utero to valproate had a two- to six-fold increased risk of congenital malformations [2]. The risk is dose dependent with no safe threshold below which no risk exists [5].

In 2014, the European Medicines Agency (EMA) announced recommendations and set in place risk minimisation measures (RMMs) to warn against valproate use in all females of childbearing potential, especially during pregnancy [6]. The RMMs included a set of educational materials and Direct Healthcare Professional Communication (DHPC) to raise the understanding and awareness of prescribers and patients on the risks associated with valproates during pregnancy.

A review by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) in 2018 showed that despite the 2014 RMMs many patients were still not informed on the risks of using valproates during pregnancy, a high level of exposure to sodium divalproate and valpromide among females of childbearing potential persisted and prescribing conditions were not adhered to, especially in the bipolar disorder indication [7]. In March 2018, the PRAC recommended an update of the RMMs including the introduction of a pregnancy prevention programme (PPP) [8]. This included an assessment of each patient's potential to become pregnant, pregnancy tests before starting and during treatment with valproates, counselling about the risks of valproate treatment, the need for effective contraception throughout treatment, an annual review of ongoing treatment by a specialist and changes to the product information including a visual boxed warning. Furthermore, according to the 2018 measures by PRAC, valproates are contraindicated in females of childbearing potential for all indications (epilepsy, bipolar disorders and prophylaxis of migraine attacks) unless the conditions of a PPP, which has to be implemented in all EU Member States, are fulfilled.

The aim of this study was to investigate the use of valproates authorised in the EU before and after implementation of the 2018 revised measures for pregnancy prevention in clinical practice, and effectiveness of the 2018 RMMs, using longitudinal data collected in five electronic healthcare databases (EHDs) from five European countries. To answer this, we completed various objectives to measure the utilisation of valproates, contraceptive coverage, alternative medication use and occurrence of concurrent pregnancies with valproate exposure in females of childbearing potential.

2 Methods

2.1 Setting and Data Sources

This was a retrospective cross-sectional time series study, using data from five data sources in five European countries. A detailed description of the included data sources is provided in Online Resource S.1.a. In short, this included Danish National Registries (DNR) that consists of administrative and clinical registers in Denmark with information on all hospitalisation episodes, dispensations, birth records and vital statistics with a nationwide coverage of about 5.8 million individuals [9–11] (please see Online Resource S.1.b). The Agenzia regionale di sanità della Toscana (ARS Tuscany) is a regional administrative claims database in Italy, with information on outpatient prescriptions, hospital admissions, diagnostic tests and exemptions from co-payment,

linked to a birth registry, with a coverage of 3.6 million inhabitants. The PHARMO Data Network is an electronic medical record (EMR) database with data linked from different primary and secondary health care settings in the Netherlands (such as general practitioner [GP] visits, in- and outpatient pharmacies, hospitals, and perinatal registry), with a coverage of 4.2 million active patients [12, 13]. The Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria (BIFAP) is an EMR database from multiple regions in Spain, with information on GP visits, prescriptions/dispensations, diagnostic procedures, laboratory tests and specialist referrals, with a coverage of 9.4 million active patients [14]. The Clinical Practice Research Datalink (CPRD) is a primary care database from the UK, with data on all GP visits, prescriptions and laboratory tests from ~10 million active patients enrolled [15]. All these covers a source population of > 30 million persons with approximately 15–20 million females of childbearing potential.

2.2 Study Population

All females of childbearing potential (aged 12–55 years) between 01.01.2010 and 31.12.2020 were included from five databases (up to 31.12.2018 for DNR). The definitions of the study population, exclusion criteria applied, and main study time points are shown in Online Resource S.1.c. Women entered the cohort on the latest of 01.01.2010 (having one year of previous valid data), the 12th birthday and database registration. The cohort exit was defined as the earliest of 31.12.2020 (study end), the 56th birthday, sterilisation, death and database deregistration.

2.3 Exposures of Interest

2.3.1 Valproates

Valproate-containing medicinal products (valproic acid, sodium valproate, valproate pivoxil, valproate semi-sodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium) were the main study exposure. Prescription or dispensing events were extracted from drug files by ATC/CPRD product code or product name. Treatment episodes were separately constructed for valproate exposure following an existing methodology [16, 17]. An episode for a product with a given ATC/BNF code started on the date of incident prescription/dispensing. Each data access partner (DAP) recommended the approach that was expected to minimise exposure misclassification in their database, given their available data (Online Resource S.1.d). Overlap between prescription refills of valproates was accounted for by adding the overlapping days to the end of the treatment episode. A permissible gap of 30 days between episodes was implemented by combining episodes when the gap between them was shorter than 30 days.

Based on the constructed treatment episodes, subjects were counted as prevalent (or current) users of valproate in a month if they had a treatment episode that overlapped with that month by at least one day. A person was counted as an incident (or new) user in a specific month if they started a first ever treatment episode that month since the start of study in 01.2010, also considering the 1-year look-back period of 2009. Discontinuation of valproates was defined as no record of prescription/dispensing within 90 days following the theoretical end of the last valproate prescription/dispensing within a valproate episode. Females meeting criteria for discontinuation may re-initiate, leading to multiple episodes of treatment. Duration of use was defined as the time from initiation of treatment based upon the first recorded prescription/dispensing in the look-back or study periods until a specific month. Treatment duration per episode was stratified as follows: < 6 months, 6–12 months, and > 1 year.

2.3.2 Alternative Medications

Alternative medications used for epilepsy were including: Carbamazepine, phenobarbital, phenytoin, primidone, clobazam, clonazepam, eslicarbazepine acetate, lamotrigine, oxcarbazepine, perampanel, rufinamide, topiramate, zonisamide, brivaracetam, ethosuximide, gabapentin, lacosamide, levetiracetam, pregabalin, tiagabine, vigabatrin. Alternatives for bipolar disorder treatment (as maintenance) were: Lithium, quetiapine, olanzapine or lamotrigine. Alternatives for migraine prophylaxis were: beta-blockers, topiramate, amitriptyline, flunarizine, pizotifen, clonidine. Prescription or dispensing events of alternative medications were extracted from drug files by ATC/CPRD product code or product name.

The occurrence of switches from valproate to alternative medications was defined as the occurrence of a prescription of an alternative medication during an episode of valproate use or within the discontinuation period. If an alternative medication started after valproate discontinuation (after 90 days of the episode end), this was not considered as a switch.

2.4 Outcomes of Interest

2.4.1 Contraception

Contraception was defined as at least one user-independent method applied by the woman, or a hormone-based method combined with a barrier method. As the barrier method cannot be assessed reliably, it was not considered. Contraception coverage episodes were constructed based upon ATC/BNF and procedure codes, prescription dates, units prescribed for each method, and a fixed assumed duration for each method.

Hormone-based user-dependent methods consisted of: vaginal ring (28 days, including 21 days using and one week off), contraceptive patch (28 days, using for 3 weeks, one week off), progestogen-only pill or desogestrel progestogen-only pill (28 days continuously), and combination pills (28 days, as 21 days using and one week off). User-independent non-permanent methods included: contraceptive implant (3 years), contraceptive injection (12 weeks), intrauterine device (3 years), intrauterine system (3 years). User-independent permanent methods were female sterilisation and hysterectomy. Because of no family linkage available from data sources, male sterilisation (vasectomy) was not considered. Subjects were censored when a record of sterilisation or hysterectomy was observed, as they no longer were in the population of females of childbearing potential.

2.4.2 Pregnancies

Pregnancies were identified across databases using a pregnancy algorithm developed by Gini et al within the framework of the ConcePTION project (https://www.imi-conception.eu/). This builds directly on top of a published algorithm for detecting pregnancies [18]. Briefly, the proposed pregnancy algorithm allowed the identification of past and ongoing pregnancies from four main streams: perinatal or birth registries, administrative data banks using diagnosis codes, and a tailored-combined stream, which uses additional data from medical observations (item-sets).

The algorithm first identifies pregnancies from any possible records and subsequently establishes the start and end date of pregnancy by processing all the available information on a hierarchical manner. Hierarchy is based on the quality of records with four colour indicators: "Green" was assigned when both pregnancy start and end dates were recorded in the database; "Yellow" shows that pregnancy end date was recorded but pregnancy start date was imputed; "Blue" indicates that pregnancy start date was recorded in the database and end date was imputed; and the colour code "Red" represents a pregnancy event for which both pregnancy start and end dates were imputed. Hence, green shows the highest quality and red indicates the lowest one to ascertain a pregnancy event from all data available in the database. This framework was applied for ARS, PHARMO and BIFAP while CPRD used a different strategy [19]. However, PHARMO was only able to include in the algorithm the perinatal registry except in the first few years of the study period (Online Resource S.2).

2.5 PRAC Intervention

Although EMA released a statement on the recommendations and PPP in March 2018, the actual implementation dates varied across countries. The estimated start and end dates for the implementation of the PPP were, respectively, 16.07.2018 and 11.10.2018 in Denmark, 08.08.2018 and 02.10.2018 in Italy, 10.08.2018 and 12.12.2018 in the Netherlands, 24.07.2018 and 01.12.2018 in Spain, and 30.04.2018 and 31.07.2018 in the UK.

2.6 Strategy for Distributed Analyses

This study has been conducted in a distributed manner using the ConcePTION Common Data Model (CDM) and common analytics [20, 21]. This approach was taken to support the standardisation of analyses across data sources in the study and to improve transparency of the process of evidence generation. According to the ConcePTION CDM pipeline, codes are linked to concepts but remain in their original format. Then, an Extract, Transform and Load (ETL) process converts original data to the ConcePTION CDM tables, assisted by an ETL standard template defining the link between source data and the target tables of the CDM [22]. All intermediate data sets remained local with each DAP, and data processing and analysis steps were performed by DAPs using common analytic scripts provided by the core team. Only the results of the data quality checks and analyses were uploaded to a central, secure platform of Utrecht University (YODA). All analyses scripts are open source and are publicly available at: https://github.com/Lot4/Lot4Studies.

2.7 Statistical Analyses

Descriptive statistics were provided on the source and study population in addition to baseline characteristics of valproate users. Monthly prevalent and incident use of valproates were estimated over the study period, for each DAP, and stratified by age group, indication and duration of treatment. The change in overall trend in current (prevalent) use of valproate was calculated across the study period for all centres. Furthermore, the numbers of discontinuers of valproates were counted per month, for each DAP, and stratified by age group, indication, and duration of treatment. Compliance of prescribers with 2018 RMMs for valproate was analysed with the monthly proportion of valproate use during an episode of contraception, per each DAP, and stratified by age group, indication and duration of valproate use. Use of alternative medications in prevalent users of valproate was counted during the study period as the monthly number of prescriptions/dispensings, for each DAP, and reported separately for each of the three indications for valproates. The monthly incidence of treatment switches was estimated as the number of women who switched in a month divided by the total number of current valproate users that month.

To test the effect of the 2018 RMMs on outcomes, interrupted time series (ITS) analyses were conducted. Segmented generalised least squares regression analysis was used to compare the pre-intervention (2010–2018) and post-intervention (2018–2020) level and trend changes in each of the outcome measures mentioned above. The cut-off point for intervention to run the ITS analysis was set as the first month of the implementation window (mentioned in 2.5), and the remaining months of the implementation window were excluded from the ITS model to avoid mingling of the pre- and post-intervention periods. Based on the actual implementation windows and for consistency, a 2- or 3-month intervention period was chosen for ITS models, as Aug–Sep 2018 for ARS Tuscany, Aug–Oct 2018 for PHARMO, Aug–Oct 2018 for BIFAP, and May–Jul 2018 for CPRD. A slope and level-change impact model with two segments was used: segment 1 modelled constant pre-intervention outcome, segment 2 modelled post-intervention outcome, by estimating the regression coefficients and *p* values. The beta coefficients of the ITS analyses produced for each DAP were presented using forest plots. Additionally, the impact of the 2018 RMMs was quantified for various outcome measures using the beta coefficients of ITS analyses, in form of mean rate difference post-intervention, *p* value and percentage of change compared to the mean counterfactual value had the intervention not occurred [23].

The occurrence of a pregnancy event with a valproate exposure have been assessed in two ways: in "Analytic method A", we counted the monthly occurrence of a valproate prescription/dispensing during a pregnancy time window, as medication use during pregnancy. Here we counted only the first date of a valproate prescription/dispensing and removed any other prescription/dispensing dates to avoid duplicate counting of events during the same pregnancy for each unique patient. In "Analytic method B", we counted the monthly occurrence of start of a pregnancy during a treatment episode of valproate. For this we did not remove multiple potential pregnancies that might have occurred in the same patient during a (long) treatment with valproate, as each could represent the teratogenic risk to a unique foetus. In both methods, rates were produced per number of prevalent users of valproates each month, and also aggregated counts and rates per each year and for the whole study period before and after the 2018 RMMs, for each database.

Additionally, sensitivity analyses were conducted by setting the start of pre-intervention time period for ITS analyses to 01.01.2015 (instead of 01.01.2010), to minimise any effect from the 2014 RMMs on the overall trends, and restricting the end of the study period to 02.2020, to consider the impact of the COVID-19 pandemic on the time period afterwards.

2.8 Data Management and Quality Checks

The study was conducted according to the guidelines for Good Pharmacoepidemiology Practice [24], and according to the ENCePP code of conduct [25]. It bears an ENCePP Seal and is registered in the EU PAS register (EUPAS31001).

We conducted three levels of data quality and characterisation checks to ensure that the ETL process has been properly conducted and the analytic datasets produced by DAPs are complete and valid enough to be used in the main analyses. *Level 1 data checks* reviewed the completeness and content of each variable in each table to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.). *Level 2 data checks* assessed the logical relationship and integrity of data values within a variable or between two or more variables, within and between tables. And *Level 3 data checks* examined data distributions and trends over time, by examining output by year and month, for each DAP's databases. To help with evaluating the output of these checks, especially tailored quality check sheets were used in weekly 1–1 meetings between DAPs and the core team.

3 Results

A total of 9,699,371 females of childbearing potential from the five participating centres were included in the study population between 2010 and 2020 (until 2018 for DNR, and 2019 for PHARMO), where 69,533 individuals had used valproates at least once during the study period. The largest subpopulation of valproate users was from ARS Tuscany ($N = 29{,}093$), being also the highest percentage of its total population (2.6%) (Table 1). The median follow-up time ranged between 4.4 years (interquartile range [IQR] 3.9 years) for CPRD and 11.0 years (IQR 4.4 years) for ARS Tuscany. The mean age at the start of follow-up was always > 30 years, ranging between 33.9 years (for DNR) and 37.0 years (for CPRD). Similar across all databases, most patients were started to follow up at the highest age stratum (i.e., 41.0–55.0 years).

The utilisation of valproates generally declined across the study period and in most centres. While there was a 2.2% increase in prevalent use of valproates in ARS Tuscany (between 01.2010 and 12.2020), a 24.4%, 29.1%, and 37.7% decline was observed in current use, respectively, in PHARMO (01.2010 and 12.2019), BIFAP (01.2010 and 12.2020), and CPRD (01.2010 and 10.2020). The monthly prevalent use of valproate ranged between 1.9 and 2.2 per 1000 women of childbearing potential in DNR, between 6.1 and 7.7 in ARS database, between 1.2 and 1.6 in PHARMO

Table 1 Baseline characteristics of the valproate users within the different databases in Denmark, Italy, the Netherlands, Spain, and the UK

	Denmark, DNR	Italy, ARS Tuscany	The Netherlands, PHARMO	Spain, BIFAP	UK, CPRD
Total number of study population	1,575,216[†]	1,117,251	591,500	5,066,393	1,349,011
Number of valproate users (% of total population)	9159 (0.6%)	29,093 (2.6%)	2725 (0.5%)	22,325 (0.4%)	6231 (0.5%)
Median follow-up, years (IQR)	8.7 (2.0)	11.0 (4.4)	10.0 (1.4)	10.0 (3.9)	4.4 (3.9)
Age					
Mean age at index date* (years, SD)	33.9 (12.4)	36.5 (11.3)	34.4 (12.3)	34.7 (12.1)	37.0 (11.7)
12.0–20.9 years (%)	1801 (19.7%)	3648 (12.5%)	510 (18.7%)	3630 (16.3%)	699 (11.2%)
21.0–30.9 years (%)	1749 (19.1%)	4216 (14.5%)	455 (16.7%)	3903 (17.5%)	1098 (17.6%)
31.0–40.9 years (%)	2281 (24.9%)	8612 (29.6%)	693 (25.4%)	6362 (28.5%)	1554 (24.9%)
41.0–55.0 years (%)	3328 (36.3%)	12,617 (43.4%)	1067 (39.2%)	8430 (37.8%)	2880 (46.2%)

CPRD Clinical Practice Research Datalink, *DNR* Danish National Registries, *IQR* interquartile range, *SD* standard deviation

*Index date is defined as the date of entry into the study (the latest of 01 January 2010, the date the individual entered the underlying population of data source, or the individual's 12th birthday)

[†]Baseline numbers in Denmark are calculated from a different source (please see Online Resource S.1.b). The cumulative number here shows the included females of childbearing age in 01.2010

database, between 1.3 and 2.0 in BIFAP, and between 1.9 and 3.2 in CPRD. Additionally, we observed a declining trend in incident use of valproate in all databases across the study period (2010–2020).

The stratified analyses by age showed that most of the prevalent users of valproates were in the age stratum 41–55 years (Online Resource S.3.a). The stratification by treatment duration showed that there was an observable trend for a lower proportion of short-term users (≤ 6 months) and a higher proportion of long-term users (> 1 year) towards the end study period in most databases.

There was a statistically significant change in the trend of prevalent use of valproate after the implementation of the 2018 RMMs in most of the studied regions/countries, including ARS Tuscany, BIFAP and CPRD, without a significant change in the level (Fig. 1b–e). The quantification of the impact showed that the prevalent use of valproate decreased in average by 7.7% after the 2018 intervention versus before in ARS Tuscany (mean difference post-intervention −0.590 per 1000 person months, p value < 0.01), while this decline was 11.3% in BIFAP (− 0.198, < 0.01), and 5.9% in CPRD (0.143, 0.02) (Table 2). In PHARMO, we observed a non-significant decline of 3.1% in prevalent use post-intervention (− 0.043, 0.19). It was not possible to model the ITS analyses on data from DNR, because not enough data points were available here after the 2018 RMMs (Fig. 1a). Running the sensitivity analysis by excluding the first five years and COVID-19 period (with follow-up between 01.2015 and 02.2020) resulted in similar findings in ARS Tuscany, and PHARMO compared with the main analyses (Fig. 1b, c), but a significant change in both level and trend post-intervention in BIFAP (Fig. 1d) and non-significant changes in CPRD (Fig. 1e). The forest plots in Fig. 2 summarise the beta coefficients of ITS analyses of both main and sensitivity analyses for a level and trend change in prevalent use after the 2018 RMMs across centres.

There was no statistically significant change in level or trend of incident use seen in any of the studied databases after the implementation of the 2018 EU RMMs in the main models (Online Resource S.3.b). Quantification of the impact showed a 6.0%, 12.7%, 39.3% increase in valproate incident use post-intervention versus before, respectively, in ARS Tuscany, PHARMO, BIFAP, and a 16.5% decrease in CPRD, although none were statistically significant (Table 2). The only significant change in the sensitivity analyses was observed in PHARMO for an increase in level immediately after the intervention.

The monthly proportion of discontinuers ranged between 1.3 and 2.6% in DNR, 4.4–7.5% in ARS, 1.5–5.3% in PHARMO, 3.2–5.2% in BIFAP and 0.8–3.2% in CPRD. The ITS analyses showed that there was a significant change in both level and trend of valproate discontinuers in ARS Tuscany (0.6% mean difference post-intervention, p value = 0.81) and CPRD (− 28.8%, < 0.01), but no significant changes in PHARMO (9.1%, 0.29) and BIFAP (6.2%, 0.31) after the 2018 EU RMMs versus before (Table 2, and Online Resource S.3.c). Running the sensitivity analysis yielded non-significant estimates for a change in proportion of valproate discontinuers after the 2018 RMMs in ARS Tuscany and PHARMO, but a significant change in level in BIFAP, and a significant change in trend in CPRD.

Only between 5.8 and 9.3% of monthly valproate dispensings in DNR, 11.9–22.5% in PHARMO, 0.2–3.3% in BIFAP, and 10.1–24.9% of valproate prescriptions in CPRD have occurred during an episode of contraceptive use. The ITS analyses showed no significant change in level or trend of

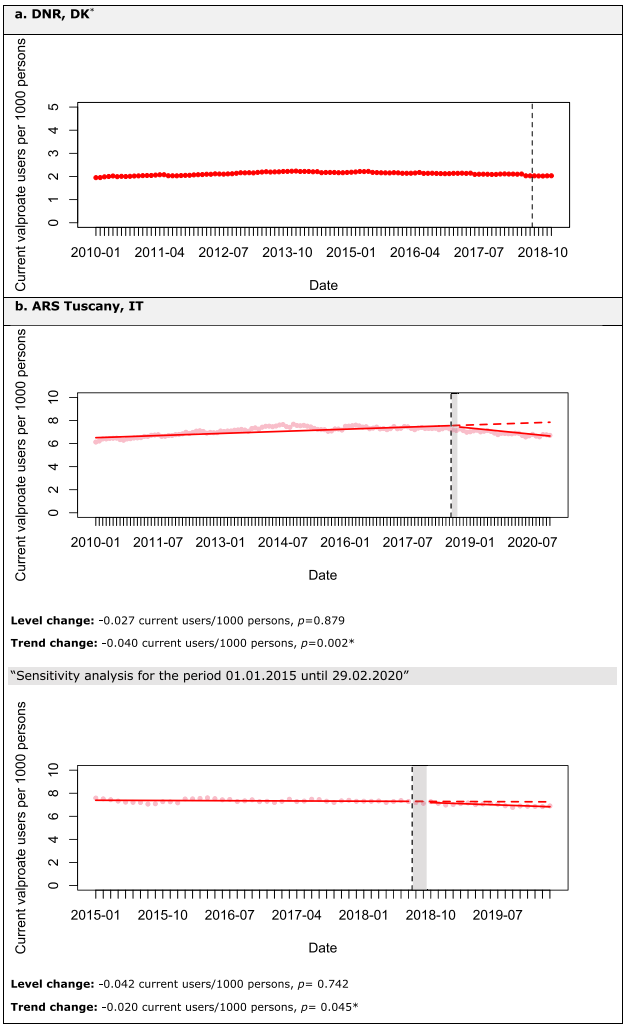


Fig. 1 Change in level and trend in rates of prevalent use of valproate in five participating centres over the study period, modelled by interrupted time series (ITS) analysis. The time of implementation of the 2018 risk minimisation measures for valproate is shown with a light grey bar (starts with a dashed black line), and the counterfactual trend (had the intervention not occurred) is shown with the dashed red line thereafter. Note that the end of study period differs per data source. In case of DNR, the trends of prevalent use over time have been shown instead, as an ITS modelling was not possible due to limited time points after the 2018 intervention

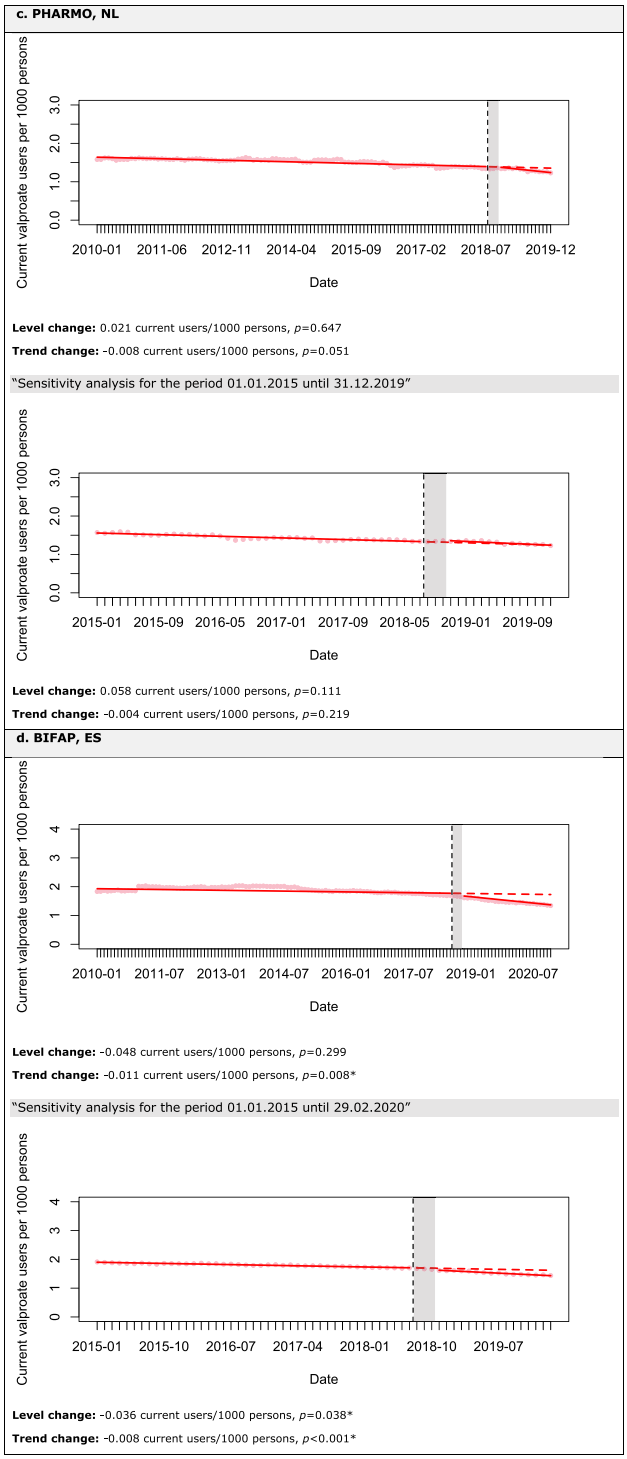


Fig. 1 (continued)

proportion of compliant valproate dispensings after the 2018 intervention in the studied databases, in either the main or in the sensitivity analyses (Online Resource S.3.d). The quantification of the impact showed that there was a significant 12.0% increase in compliant valproate dispensings with contraceptive coverage after the 2018 RMMs in PHARMO ($p = 0.02$), a non-significant 6.5% decrease in BIFAP (0.39), and a significant 26.6% decrease in CPRD (< 0.01), compared with the time before. In case of DNR, only the general trend during the study period is shown. We could retrieve limited information on contraceptive use during (parts of) the study period from ARS Tuscany, thus no trend has been shown.

The trend in alternative medication use per various indications of valproates across databases are given in Online Resource S.3.e. In summary, the trends for epilepsy and

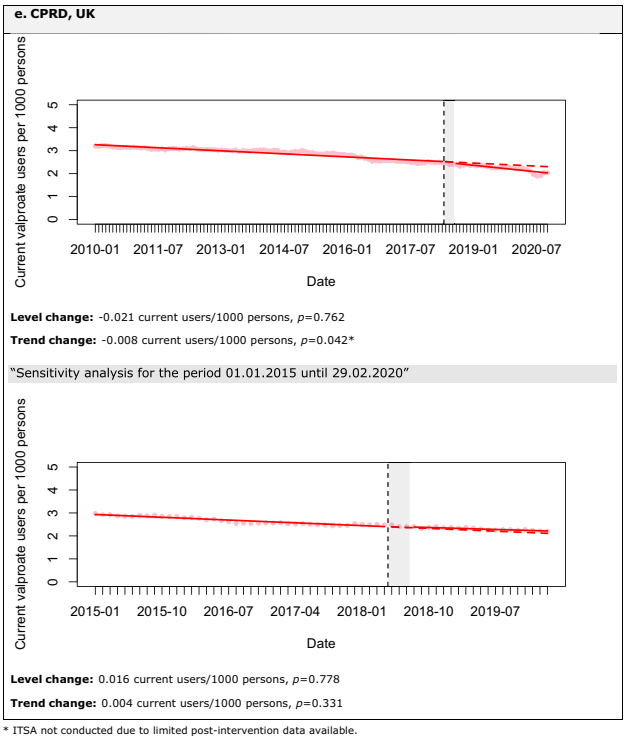


Fig. 1 (continued)

bipolar disease drugs were generally increasing in DNR, ARS, and PHARMO during the study period, while the trend in use of migraine drugs remained steady. The trends in use of alternative medications for all indications were levelling in BIFAP, and increasing in CPRD over the study period.

The monthly rate of switching from valproates to alternative medications during the study period ranged between 0.9 and 3.2% in DNR, 1.9–4.5% in ARS Tuscany, 0.7–3.0% in PHARMO, 1.0–3.7% in BIFAP, and 0.9–3.2% in CPRD. The ITS analysis of switching rates from valproates to alternative medicine before versus after the 2018 RMMs revealed that there was a statistically significant change in level and trend of switchers in ARS Tuscany, and non-significant changes in BIFAP (Online Resource S.3.f). The sensitivity analyses yielded non-significant changes in both centres. The quantification of the impact showed that there was a 3.3% decline in switching rates from valproate to alternative medicine after the 2018 RMMs versus before in ARS ($p = 0.47$), and 14.8% decrease in BIFAP (0.22), both statistically non-significant. It was not possible to model the ITS analysis in PHARMO and CPRD because the counts of switchers after 2018 were too small to fit a stable model, and in DNR there were insufficient time points after the 2018 intervention.

In general, we observed a substantial number of concurrent pregnancies with a valproate exposure in ARS Tuscany, BIFAP and CPRD, and fewer concurrent events in PHARMO (Table 3). With "Analytic method A", we found 386 first dates of a valproate dispensings in ARS Tuscany that occurred during a pregnancy time window (with the quality colour codes green and yellow) before implementation of the 2018 RMMs, with a rate of 0.70 per 1000 valproate users. The count and rate of such concurrent events in ARS declined to 40 and 0.27, respectively, after the 2018 RMMs. In PHARMO, we observed only 27 first dates of a concurrent valproate dispensing with a pregnancy event (all with a colour code green) with a rate of 0.34 per 1000 users, in the whole study period before 2018 RMMs, while there was no single event in the time period after. In BIFAP, there were 330 prescriptions/dispensings of valproate during a pregnancy episode (all with a quality colour code yellow) with a rate of 0.48 per 1000 drug users before the 2018 RMMs. The number of concurrent drug use/pregnancy events reduced to 20 events with a rate of 0.13 in the time period after. In contrast to other databases, we observed an increasing rate of simultaneous valproate prescriptions during pregnancy in CPRD, where 204 such events happened before 2018 RMMs (with a rate of 1.13 per 1000 users) and 56 events post-2018 intervention (rate 5.07). The findings of the "Analytic method B" (i.e., start of a pregnancy during a treatment episode of valproates) were similar to those mentioned above (Table 3). There were no data on pregnancy counts available from DNR.

The time distance between start of a pregnancy and prescription/dispensing date of a valproate during a pregnancy episode has been calculated in some DAPs. In ARS Tuscany, the median distance between a pregnancy start and dispensing date of a valproate was 27 days (IQR 48 days, maximum 278 days). While in PHARMO, the median length was 38 days (IQR 63, maximum 272), and in CPRD the median was 19 days (IQR 23, maximum 277).

4 Discussion

This study investigated the use of valproates before and after the 2018 RMMs and the effectiveness of the revised PPP in females of childbearing potential in five European countries. The utilisation of valproates, both incident and prevalent use, generally declined across the study period (2010–2020) in all centres, besides a small increase of prevalent use in ARS Tuscany (Italy). We observed a significant decline in prevalent use of valproate in ARS Tuscany (Italy), BIFAP (Spain) and CPRD (UK), and a non-significant decline in PHARMO (Netherlands) after the 2018 RMMs compared to the period before, but neither a significant decline in incidence rates, nor a significant increase in valproate discontinuation. This discrepancy might be explained by a general decline in the prevalent use of valproate since 2010 due to prior (partly successful) RMMs and specialists being discouraged from

Table 2 Quantification of the impact of the 2018 risk minimisation measures derived from the ITS analysis (of main models) on various outcome measures, including incident and prevalent use of valproates, discontinuation of valproates, contraceptive coverage during valproate use, and switching from valproates to alternative medications, across the participating centres

	ARS Tuscany, IT		PHARMO, NL		BIFAP, ES		CPRD, UK	
	Mean difference post-intervention* (%)	*p* value	Mean difference post-intervention* (%)	*p* value	Mean difference post-intervention* (%)	*p* value	Mean difference post-intervention* (%)	*p* value
Incident use of valproates (per 1000 person months)	0.009 (6.0)	0.53	0.002 (12.7)	0.48	0.003 (39.3)	0.37	− 0.002 (− 16.5)	0.43
Prevalent use of valproates (per 1000 person months)	**−0.590 (−7.7)**	**< 0.01**	−0.043 (−3.1)	0.19	**− 0.198 (− 11.3)**	**<0.01**	**− 0.143 (− 5.9)**	**0.02**
Discontinuation of valproates (percentage per month)	0.032 (0.6)	0.81	0.244 (9.1)	0.29	0.255 (6.2)	0.31	**−0.422 (− 28.8)**	**<0.01**
Contraceptive coverage during valproate use (percentage per month)	NA		**2.114 (12.0)**	**0.02**	− 0.186 (− 6.5)	0.39	**−6.196 (−26.6)**	**<0.01**
Switching from valproates to alternative medications (percentage per month)	−0.092 (−3.3)	0.47	NA		− 0.276 (− 14.8)	0.22	NA	

Because no ITS model could be fit for DNR, due to limited time points after the 2018 intervention, such quantification of the impact was not possible here

CPRD Clinical Practice Research Datalink, *DNR* Danish National Registries, *ES* Spain, *IT* Italy, *ITS* interrupted time series, *NA* not available, *NL* the Netherlands, *UK* the United Kingdom

Statistically significant rate ratios are shown in bold

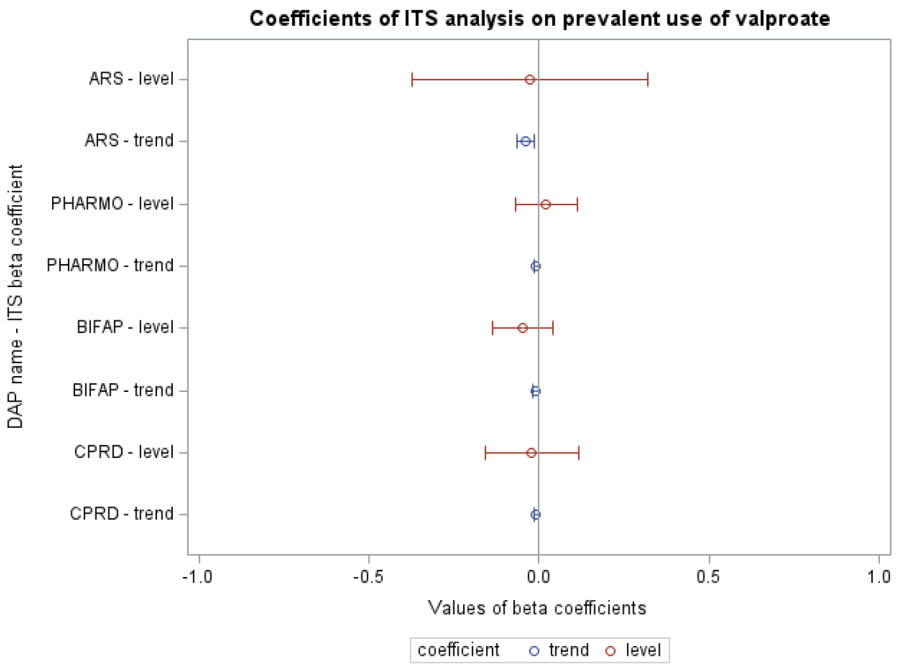
*The rates of mean difference post-intervention show the change in various outcome measures after the 2018 risk minimisation measures, combining the level and trend change from the ITS model. The percentage in parenthesis shows the mean percent change of rates of various outcome measures after the 2018 intervention compared to the mean counterfactual values had the intervention not occurred

initiating valproate in females of childbearing potential. A changing pattern in treatment duration in most centres, with lower proportion of short-term (≤ 6 months) and a higher proportion of long-term valproate users (> 1 year) towards the end of study period, can partly explain this hypothesis.

Additionally, the rate of contraceptive coverage at the start of valproate treatment was low across all DAPs, as always below a quarter of new valproate treatment episodes had started during contraceptive use. The only significant increase in compliant valproate prescriptions/dispensings with a contraceptive coverage after the 2018 RMMs was observed in PHARMO (Netherlands). Regarding the alternative medications, we found an increasing trend in rates of use for the indications epilepsy and bipolar diseases across the study period in most databases (i.e., DNR [Denmark], ARS [Italy], PHARMO [Netherlands] and CPRD [UK]), while the rates for migraine were mostly steady. The monthly rate of switch from a valproate to an alternative medication was similar across all DAPs (< 5%), with no significant increase in switching rates after the 2018 intervention versus the time before.

Finally, there was a substantial number of concurrent pregnancies with valproate exposure in ARS (Italy), BIFAP (Spain) and CPRD (UK), with fewer events in PHARMO (Netherlands). The occurrence of concurrent pregnancies in PHARMO (Netherlands) may be underestimated, as most of the study period pregnancies were identified only from a perinatal registry (i.e., pregnancies ending in a later stage). On the other hand, the higher occurrence of valproate exposure during pregnancy in ARS (Italy), BIFAP (Spain) and CPRD (UK) could mean that they captured pregnancies ending prematurely. The rate of concurrent pregnancies during valproate use declined in ARS (Italy), BIFAP (Spain) and PHARMO (Netherlands) after the 2018 intervention, but not in CPRD. This may suggest that often assessing that a pregnancy has started in a woman exposed to valproate or assessing that a pregnant woman has been exposed to valproate, results in termination of the pregnancy. The higher rate of concurrent pregnancies in CPRD (UK) before versus after the 2018 RMMs may be due to the known attrition of the CPRD GOLD databases in recent years and

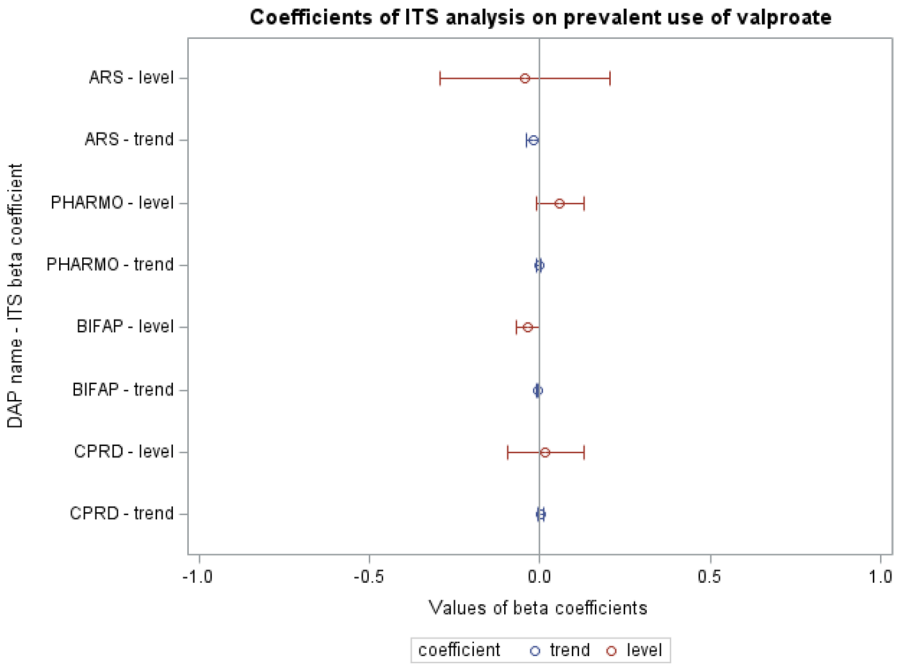
a) Main analysis (01.2010-12.2020)*



Abbreviations, DAP: Data Access Partner, ITS: interrupted time series.

* The end of study period was 12.2019 for PHARMO and 10.2020 for CPRD.

b) Sensitivity analysis (01.2015-02.2020)*



Abbreviations, DAP: Data Access Partner, ITS: interrupted time series.

* The end of study period was 12.2019 for PHARMO.

Fig. 2 Forest plots showing the level and trend beta coefficients of the interrupted time series analyses of prevalent use of valproate after the implementation of the 2018 risk minimisation measures across centres, in the: **a** main, and **b** sensitivity analysis

artificial inflation of rates with smaller denominators (loss to follow-up) towards the end of study period.

A drug utilisation study that evaluated the 2014 RMMs for valproate use in five European countries (France, Germany, Spain, Sweden and UK) found limited effectiveness of the measures based on the varying proportions of valproate initiation as second-line therapy from pre- to post-implementation period, and a decrease in incidence of

Table 3 Aggregated concurrent pregnancy events during valproate exposure, stratified by the analytic method (A: valproate use during a pregnancy time window, and B: pregnancy occurrence during a valproate treatment episode) and by time period of pre- and post-2018 risk minimisation measures, across databases

	ARS Tuscany, IT			PHARMO, NL			BIFAP, ES			CPRD, UK		
	Concurrent pregnancies	Prevalent users of valproates†	Rate per 1000 user	Concurrent pregnancies	Prevalent users of valproates†	Rate per 1000 user	Concurrent pregnancies	Prevalent users of valproates†	Rate per 1000 user	Concurrent pregnancies	Prevalent users of valproates†	Rate per 1000 user
A. Valproate use during a pregnancy time window												
Pre-2018 RMMs*	386	552,506	0.70	27	79,197	0.34	330	694,549	0.48	204	181,054	1.13
Post-2018 RMMs*	40	150,769	0.27	0	10,896	0	20	157,981	0.13	56	11,043	5.07
B. Start of pregnancy during a treatment episode of valproate												
Pre-2018 RMMs*	374	552,506	0.68	24	79,197	0.30	316	694,549	0.45	200	181,054	1.10
Post-2018 RMMs*	50	150,769	0.33	0	10,896	0	21	157,981	0.13	68	11,043	6.16

Noteworthy, only those pregnancy events with a quality colour code green and yellow have been considered in this table. Also, the observed concurrent events in the two analytic methods (A and B) are overlapping

ES Spain, *IT* Italy, *NL* the Netherlands, *RMM* risk minimisation measures, *UK* the United Kingdom

*The cut-off point for a demarcation between pre- and post-intervention time periods was selected as Aug. 2018 for all DAPs, based on the implementation period of RMMs across countries

†The number of prevalent users of valproates, used as the denominator for the rates here, is actually the sum of monthly prevalent use counts for the time period pre-2018 RMMs (i.e., Jan. 2010–Jul. 2018) and post-2018 RMMs (i.e., Aug. 2018 – end of study period for each database) in each database, which represent the sum of unique patients who were exposed each month to valproate

pregnancies exposed to valproate only in Sweden and UK [26]. However, the value of these findings remains limited due to the descriptive nature of the study and reliance on absolute counts instead of standardised rates. Running an ITS model on the UK data from the same group showed that there was no statistically significant change in period (level) or trend in the proportion of valproate initiation as second-line therapy before versus after the 2014 RMMs [27]. Another study in France reported an overall decrease in valproate use among females of childbearing potential with epilepsy after the 2014 RMMs, in an ITS study with a control group (males with epilepsy) [28].

There are few studies that focused on the risk awareness and adherence with EU RMMs for valproates in 2014 and 2018. A cross-sectional survey among physicians across France, Germany, Spain, Sweden and UK concluded that a majority of physicians had good knowledge of prescribing valproates in females of childbearing potential, where 96% of physicians responded that they only prescribe valproate to women with epilepsy or bipolar disorders when other treatments were ineffective/not tolerated [29]. Another study on the risk awareness and adherence with the 2018 RMMs in eight European centres (in Belgium, Denmark, Greece, Latvia, Portugal, the Netherlands, Slovenia and Spain) found that there was high awareness of the teratogenic risks associated with valproate use during pregnancy among patients (71%), prescribers (94%), and pharmacists (95%) [30]. However, in both these qualitative studies, the use of educational materials and information tools (such as patient card, risk acknowledgement forms, and healthcare professional guides) was low, and according to respondents, the most beneficial tool was the warning symbol on packaging of drugs. These results can complement what we found in this quantitative study with declining trend in utilisation of valproates since 2010 and after the 2018 RMMs, but still low rates of coverage by contraceptive methods.

It is of note that valproate RMMs have been in place for many years [7]. The referral in 2014 further strengthened the restrictions in use of valproate in females of childbearing potential, and this has become even more strengthened in 2018 [8]. A clear cut-off in 2018 to detecting an effect might not be visible on all outcomes studied, as for example the advice to use contraceptive measures was already in place before 2018, and the use of valproate in females of childbearing potential had been declining since 2010. While our findings confirmed this latter finding (a declining trend in valproate utilisation between 2010 and 2020), the influence from previous RMMs may have prevented us from detecting a significant change for some of the outcomes studied.

This study had several strengths. Selection bias was mitigated by including all females of childbearing potential registered in each database at any time during the study period (with a total sample size of ~10 million), in addition to

setting minimal exclusion criteria. Using several databases from different countries across the continent has led to a large and diverse study population with good representation and generalisability to a European and global setting. A key strength of this study was use of the ConcePTION CDM and common analytics to minimise unwanted heterogeneity among databases, and the rigorous quality checks that were conducted. Furthermore, to evaluate the implementation and the 2018 RMMs on valproate use, we benefited from the ITS analysis (a quasi-experimental design), which is one of the strongest methods for studying the impact of an intervention on drug utilisation and other outcomes when conducting an RCT is not feasible [31–33]. We were able to extract and use a large number of data points and observations, especially before the intervention, which helped us to reduce any effect from fluctuations, variability and outliers in medication use across the study period.

Our study was not free from limitations. No single European data source contains all the information required in this study, as the primary aim of data collection was not medical research. By using retrospectively collected data from EHDs, misclassification of exposure might have happened [34]. We had only dispensing information available from ARS, BIFAP and PHARMO and GP prescriptions available from CPRD, which are 1 or 2 steps behind the actual drug use by patients, respectively, with no information on adherence to medication. Misclassification of outcome, especially in case of pregnancy records, was another limitation. To minimise any issues with this, we used an adapted version of a previously validated algorithm [12]. Also, lack of data on over-the-counter contraceptives, which are not captured in any of the databases, might have resulted in an underestimation of the proportion of compliant valproate use with a contraceptive coverage. Moreover, not considering a longer look-back period (> 1 year) might have limited our ability to ascertain a true new (incident) use of valproate among the included individuals, especially in the first years of study period. The occurrence of the COVID-19 pandemic was a major obstacle, where it shortened our post-intervention period. It also brought us practical difficulties in accessing data from various databases, due to concurrent COVID-19 projects and slower approval and releasing of data by competent authorities, particularly in case of DNR (Online Resource S.1.b). To overcome this, we defined sensitivity analyses that excluded the COVID-19 period (after 02.2020).

5 Conclusions

In conclusion, there was a small impact of the 2018 RMMs on valproate utilisation and prescribing in the studied European countries/regions, considering a declining trend in utilisation patterns of valproates since 2010 and after the implementation of 2018 RMMs in Europe, an increase in compliant valproate prescriptions/dispensings with a contraceptive coverage only in PHARMO (Netherlands), no significant increase in switching rates from valproates to alternative medications, and declining rates of concurrent pregnancy events with valproate exposure in most countries/regions. But the substantial number of concurrent pregnancy events with valproate exposure warrants a careful monitoring of implementation of the existing PPP for valproate in clinical practice in Europe, to see if there is a need for additional measures in the future.

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Declarations

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Ethics approval In Denmark, the Danish National Prescription Registry was accessed through the Research Service Unit of Statistics Denmark (FSEID-00004357/DST-project no. 707524), and approval for processing of personal health data was obtained through the UCPH (ref. no.: 514-0301/19-3000). In Italy, the participation to the EMA Lot4 study on valproates was included in ARS Toscana workplan and it did not require any further ethical approval. In the Netherlands, the EMA Lot4 study on valproates has been approved for compliance with the general data protection regulation by the Institutional Review Board of 'Stichting Informatie voorziening voor Zorg en Onderzoek' (dd. 10 Oct 2019).

In Spain, the favourable approval was received from BIFAP scientific committee (reference num. 19_2019) on 23.02.2020, and from the Comité de Ética de la Investigación Con Medicamentos Regional de la Comunidad de Madrid-CEIm-R (Acta 02/20) on 10.02.2020. In the UK, the study proposal was reviewed and approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (reference 20_009), which is responsible for reviewing protocols for scientific quality.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials This multicentre study used anonymised patient data from electronic health care databases in different countries/regions. These data remained local within each centre and will not be distributed publicly. No additional data available.

Code availability All analyses scripts are open source and are publicly available at: https://github.com/Lot4/Lot4Studies.

Author contributions All authors contributed to intellectual concept and design of the research. SA, RP, CED, MG and EA wrote and checked the common analysis scripts for distributed analyses and conducted the final aggregated analyses. MA, SBK and CEH conducted the data acquisition and data analysis for Danish National Registries, Denmark. RG, AG, CB, GL, OP and GR performed the data acquisition and data analysis for ARS Tuscany, Italy. EH and KS carried out the data acquisition and data analysis for PHARMO, the Netherlands. PGP, CH, MMP carried out the data acquisition and data analysis for BIFAP, Spain. JB and KW conducted the data acquisition and data analysis for CPRD, UK. All authors contributed to data interpretation. SA, RP, CED, JRA and VH were in charge of quality control processes. SA and RP wrote the manuscript. All authors were involved in editing the manuscript. All authors are accountable for their own contribution, in addition to all aspects of the manuscript. All authors have approved the (re)submitted version of the manuscript.

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