Drugs - Real World Outcomes (2023) 10:639–649
https://doi.org/10.1007/s40801-023-00394-y

ORIGINAL RESEARCH ARTICLE

Impact of Risk Minimisation Measures on Valproate Use among Women of Reproductive Age in Latvia Between 2013 and 2020: A 7-Year Nationwide Prescription Database Study

Ieva Rutkovska[1,2] · Andis Seilis[1] · Zane Neikena[1] · Elita Poplavska[1,2,3]

Accepted: 11 September 2023 / Published online: 12 October 2023

Abstract

Background A relevant safety concern for the use of valproate (VPA) in women of reproductive age is its teratogenicity. In 2014 European Medicines Agency (EMA) introduced risk minimisation measures (RMMs) to reduce the VPA use by women of reproductive age, where the impact on VPA use was not as large as expected. In 2018, the EMA introduced additional RMMs, and it is essential to assess impact of these interventions.

Objective The objective of this study was to evaluate the impact of the EMA-published RMMs in 2014 and 2018 on the prevalence of VPA use and to describe trends in the prevalence rate and incidence proportion of VPA use in epilepsy, bipolar disorder and off-label indications in Latvia.

Methods This was a nationwide population-based study using a primary care prescription database. The study included women in age groups < 15, 15–49 and > 49 years and men in age group 15–49 years who have received VPA. This study assessed the prevalence rate and the incidence proportion of VPA use. The impact of RMMs on the two study intervention periods [fourth quarter (Q4) 2014 and Q4 2018] in men and women was evaluated using causal impact analysis.

Results In the study cohort, VPA use in women in the age group 15–49 years decreased after the first and second intervention periods, where after the first intervention period the relative reduction in prevalence of VPA consumption was −7.7 [95% confidence interval (CI) −10%, −5.1%] and after both study periods −6.4% (95% CI −11%, −1.5%). In girls < 15 years of age, valproate use decreased after both intervention periods, while in women > 49 years old VPA use increased. In men aged 15–49 years, an increase after the first period and a non-significant decrease after both intervention periods was observed. The prevalence of valproate use in girls < 15 years and women 15–49 years of age with bipolar disorder, epilepsy and off-label indications decreased per 1000 people during the study period. The incidence proportion of VPA use in women aged 15–49 years decreased each year since the beginning of the study period.

Conclusions A statistically significant decrease in the prevalence of VPA use was identified among girls < 15 years and women 15–49 years of age. In Latvia, an overall good reaction to the EMA RMMs was observed. The effects go beyond the target population and affect the use of VPA in young girls as well.

1 Introduction

Valproic acid and sodium valproate (VPA) have been used worldwide as antiepileptic drugs (AEDs) for epilepsy since 1967 and for bipolar disorder since 1995. A relevant safety concern for VPA is its teratogenicity. Among medications for epilepsy and bipolar disorder, VPA poses the highest risk of malformations and neurodevelopmental disorders [1–3]. In 2009, the indication of VPA for bipolar disorders was restricted by the European Medicines Agency (EMA). Now it is recommended only for manic episodes if lithium is contraindicated or not tolerated [4]. In 2013, additional RMMs were introduced, such as educational materials and warnings in product information. VPA in women could be

✉ Ieva Rutkovska
ieva.rutkovska@zva.gov.lv

1 State Agency of Medicines of the Republic of Latvia, Jersikas Street 15, Riga 1003, Latvia

2 Department of Applied Pharmacy, Faculty of Pharmacy, Riga Stradins University, Konsula Street 21, Riga 1007, Latvia

3 Institute of Public Health, Riga Stradins University, Kronvalda bulvaris 9, Riga 1010, Latvia

Key Points

Risk minimisation measures (RMMs) had a statistically significant impact on the prevalence of valproate (VPA) use among girls < 15 years and women 15–49 years of age per month in Latvia after interventions in 2014 and 2018.

The influence of RMMs goes beyond the intended target population, affecting the use of VPA in girls.

The overall response to these measures in Latvia is a favourable contribution to safer medication practises. As no plateau phase was observed in our study after intervention in 2014, further long-term influence of RMMs should be assessed.

used along with an effective contraception method if alternative therapy is ineffective or is not tolerated. Further RMMs to reduce the use of VPA by women of reproductive age were published in the third quarter (Q3) of 2014 [4]. The impact of RMMs on the VPA use in Europe was not as large as expected, raising concerns about the effectiveness of the measures implemented. As a consequence, the EMA introduced the pregnancy prevention programme (PPP) and additional changes in product information and educational materials in the second quarter (Q2) of 2018 [5, 6].

Latvia is a Baltic country, a member of the European Union with a universal health coverage, a single-purchaser national health system funded by general tax revenues. There are limited epidemiological data on epilepsy and bipolar disorders in Latvia, but some authors have estimated the prevalence of epilepsy at 4820 [95% confidence interval (CI) 939–9715] based on modelling data [7]. The prevalence of bipolar disorder according to a cross-sectional study is 0.5% (95% CI 0.2–1.0) for bipolar I disorders and 0.9% (95% CI 0.6–1.6) for bipolar II disorders [8]. Within the national drug reimbursement system, AEDs are fully reimbursed for epilepsy, with 25% co-payment for bipolar disorders for all permanent residents of Latvia [9].

The national competent authority, the Latvian State Agency of Medicines (SAM), is responsible for the national implementation of the published RMMs. A direct healthcare professional communication (DHPC) letter and educational materials for prescribers, pharmacists and patients on the use of valproate were distributed in Latvia at the end of the fourth quarter (Q4) of 2014 [10]. Furthermore, a DHPC letter and PPP materials were distributed in Q4 2018. In August 2020, information on the VPA PPP was updated and disseminated again [11]. DHPC and educational materials were disseminated to health care professionals (HCPs) and are available electronically in the national Medicinal Product Register.

Recent studies in Europe, including other Baltic countries, indicated a decrease in VPA use in women after the RMMs in 2014 [12–17]; however, there are not many studies that have assessed the impact of additional RMMs introduced by the EMA in 2018. Kurvits et al. [17] discussed the need for more population-based studies in different European regions to investigate whether regional patterns of awareness of VPA risks differ so that national regulatory authorities can better explain the differences. The Latvian study provides an opportunity to compare the consistency of changes following the publication of the EMA RMMs with other countries of the European Union (EU).

The objective of this study was to evaluate the impact of RMMs published by the EMA in 2014 and 2018 on the prevalence of VPA use and describe the trends of VPA use in epilepsy, bipolar disorder and off-label indications in Latvia. Our hypothesis was that there would be a statistically significant decrease in VPA consumption after the first and second EMA intervention periods, comparing actual VPA usage with predicted counterfactual post-intervention VPA usage, in women 15–49 years of age; however, no changes would be observed in girls < 15 years, women > 49 years and men 15–49 years old.

2 Materials and Methods

2.1 Study Period

The study period was January 2013 to June 2020. The chosen time frame included the period before and after the publication of the VPA safety information and RMMs by the EMA in 2014 and 2018.

2.2 Study Design

This was a nationwide population-based study using outpatient prescription data from the national drug reimbursement system within the Latvian National Health Service (NHS) database covering all permanent residents of Latvia. NHS data were anonymised and a unique identifier was assigned to each patient and physician, to allow tracking of medication prescribing and dispensing for each individual patient included in the study cohort. According to local data protection regulations, no approval from the ethics committee was required for this study [18].

2.3 Data Sources and Study Data

Data were obtained from the NHS information system database, which includes data from the Latvian healthcare digital database 'e-Veselība' (e-Health).

The following data were collected from the NHS database: anonymous unique patient identifier, sex, age, Anatomical Therapeutic Chemical (ATC) code, brand name and International Non-proprietary Name (INN) of prescribed, and subsequently dispensed, medicines (referred to as 'used' in the text from now on), main diagnosis code for which the medicine was prescribed and co-diagnosis code, the speciality of the prescriber, and anonymous unique identification number of the prescriber. The data set included the majority of the Latvian population to whom AEDs are prescribed, as these medications are included in the national reimbursement system.

The database covers data on the following medications: valproic acid, sodium valproate, clonazepam, carbamazepine, gabapentin, levetiracetam, lamotrigine, oxcarbazepine, and topiramate.

Lacosamide, pregabalin and stiripentol are not reimbursed by the state, thus not covered by the database; however, these medications are available on the market and can be purchased by patients out of pocket. Consumption data suggest that the use of these medications is rather low. Stiripentol and lacosamide were consumed at 0.0 up until 2020 in a defined daily dose per 1000 inhabitants per day (DID). The highest consumption was for pregabalin (0.48 DID in 2020), but we cannot differentiate whether it was used for epilepsy or for neuropathic pain [19, 20].

Brivaracetam, cenobamate, fenfluramine, eslicarbazepin, perampanel, rufinamide, vigabatrin and zonisamide are authorized in Latvia, but were not available on the market during the study period [21].

Data on the number of women in the eligible age group of the general population of Latvia were obtained from the Latvian Official Statistics Portal [22].

For impact analysis, we analysed monthly data while for prevalence and incidence proportion calculations we used half-yearly data. VPA is prescribed for 3 months within the reimbursement system; therefore, the 3–6-month period covers one VPA prescribing episode.

2.4 Study Population

The study included all women and men in the age range of 15–49 years, girls < 15 years and women > 49 years who have received AEDs (ATC code N03) within the Latvian NHS reimbursement system from 2013 to 2020. The age range 15–49 years corresponds to the reproductive age as defined by the World Health Organization. The inclusion of girls and women outside this limit allowed us to evaluate the spillover effects of the RMM.

We excluded the cases where VPA was prescribed but never dispensed to a patient in a pharmacy.

Women were stratified by indication (label and off-label), which was determined by the International Classification of Diseases tenth edition (ICD-10) diagnosis codes G40, used for epilepsy, and F31, used for bipolar disorder. All other indications for which AEDs were prescribed were classified as off-label use, including G41 (status epilepticus).

2.5 Data Analysis

To describe the trend in use, we calculated the prevalence rate of VPA use in women in each age group (< 15, 15–49 or > 49 years) and in each indication (epilepsy, bipolar disorder and off-label). The prevalence rate of VPA use was defined as the number of unique women in the study cohort in a particular age group with a given indication who used VPA during a period of 6 months per 1000 women in a general population in a particular age group (< 15, 15–49 or > 49 years) in a particular year.

The incidence proportion of VPA use was calculated as a number of unique women during a period of 6 months in the age group 15–49 years who used VPA for the first time per 1000 women in a general population in the age group 15–49 years. Only VPA users who did not use VPA in any of the previous half-year periods were included. To minimise the overestimation of the number of 'new users', we calculated the incidence from the second available half-year (HY) timepoint (second HY of 2013).

2.6 Causal Effect Analysis

We used a Bayesian structural time series model (BSTM) proposed by Brodersen et al. [23] to assess the causal impact of the EMA interventions on VPA utilisation. Causal impact is a specific type of causal inference analysis method for time series data in which a data model is created on the basis of time series data prior to an intervention and subsequently is used to forecast a series of baseline values for the time period after the intervention (counterfactual values), which are the expected observations of how the dependent variable might have evolved after the event in the case where the event had not occurred. Causal impact provides a BSTM to model counterfactual values and quantify the uncertainty of the model. The algorithm for posterior inference is based on Markov chain Monte Carlo (MCMC). The absolute impact of the intervention is the difference between the observed and counterfactual post-intervention data. The relative impact expresses the absolute change as a percentage, where the numerator is the difference between the observed and

counterfactual post-intervention data multiplied by 100 and the denominator is the counterfactual post-intervention data [23].

The effect of the intervention was determined using monthly prevalence data for both study periods in women in age groups < 15, 15–49 and > 49 years and in men in the age group 15–49 years to investigate whether the results obtained in women 15–49 years of age are stable and if statistically significant reductions are not observed in all populations and age groups.

The statistical significance of the monthly effect was evaluated by examining whether its Bayesian credible interval, with a confidence level of 95%, included zero.

The prior standard deviation of the Gaussian random walk of the local level of 0.05 was used. The estimation of the model involved drawing 1000 samples using MCMC.

The trend and seasonality of VPA users were included as time series components of the BSTM within a basic structural model containing a regression component with a static coefficient. Data analyses were carried out using the statistical software R (version: 4.1.1); for causal impact analysis, we used the CausalImpact package.

2.7 Definition of a Time Period

We chose two data points for the impact analysis with respective pre- and post-intervention periods.

The first study period was Q4 2014 (October 2014), when the RMMs were published by the EMA and distributed to HCPs by the SAM. The pre-intervention period was defined from January 2013 to November 2014 and the post-intervention period was defined from December 2014 to October 2018.

The second study period was Q4 2018 when additional information on RMMs, including PPP, was distributed for Latvia's HCP (in November 2018). The pre-intervention period was defined from January 2013 to October 2018 and the post-intervention period was defined from November 2018 to June 2020. The second period reflected the entire intervention period, including data from 2014, as the impact of the first and second intervention cannot be separated.

3 Results

3.1 Trends in VPA Use in 2013–2020

The prevalence of VPA use in women aged 15–49 years decreased each year during the study period, while the prevalence of other use of AEDs (not including VPA) increased (Fig. 1). This trend was also observed in girls < 15 years of age, but, on the contrary, the use of VPA increased in women > 49 years of age (Appendix 1, Fig. 1).

Among all indications for VPA, the highest prevalence (per 1000 people) of VPA users was observed in women 15–49 years of age in the epilepsy group, although the prevalence decreased from 2.20 to 1.70 between 2013 and 2020. Off-label indications had the second highest prevalence of

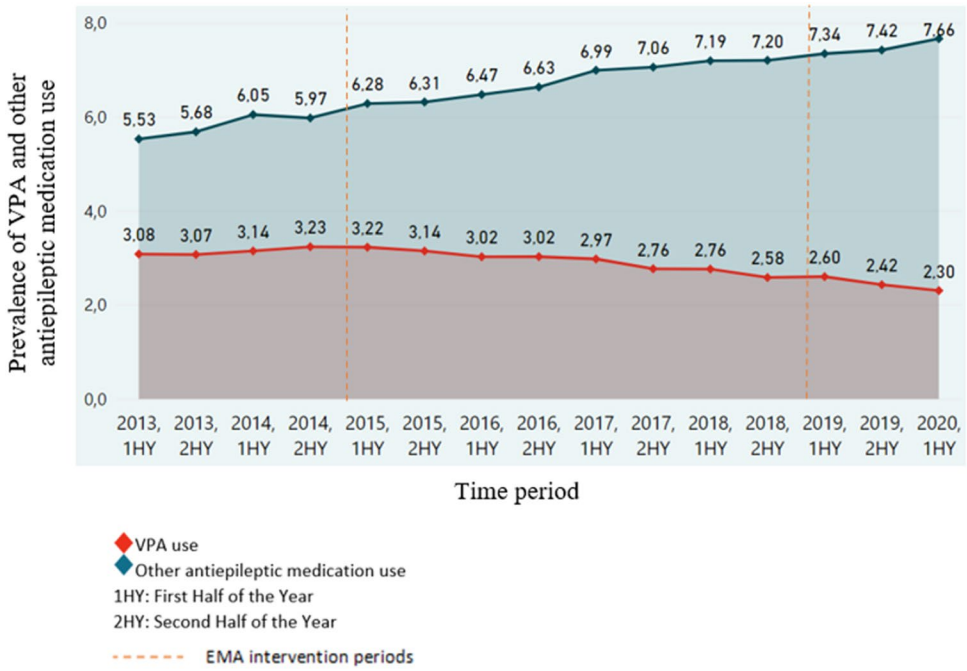

Fig. 1 Prevalence of VPA use and other antiepileptic medications in the study cohort in women aged 15–49 years per 1000 women aged 15–49 years in the general population of Latvia

VPA use in the age group 15–49 years, 0.86 in 2013 and 0.59 in 2020. The prevalence of VPA use in bipolar disorder decreased from 0.05 to 0.03 between 2013 and 2020 (Fig. 2). The same trend was observed in girls < 15 years old, while in women > 49 years old, an increase in the prevalence of VPA use was observed between 2013 and 2020 in all indications (Appendix 1, Fig. 1).

3.2 Incidence Proportion of VPA Use

The incidence proportion of VPA use in women aged 15–49 years has decreased each year since the beginning of the study period (Fig. 4), with a slight increase in the first half of 2019. In the first half of 2014, the incidence proportion reached 0.6 per 1000 women, while in the first half of 2020, it decreased to 0.11 (Fig. 3).

3.3 Characteristics of VPA Prescribers by Indications

In the population of 15–49 years old women, the most frequent prescribers of VPA were general practitioners (GPs) who indicated VPA for epilepsy. In the dataset, 945 unique GPs prescribed VPA for 1576 unique women with epilepsy. Psychiatrists who prescribed VPA to women for off-label indications were the second most frequent prescribers; this was followed by neurologists and psychiatrists prescribing VPA for epilepsy and GPs prescribing VPA for off-label indications.

3.4 Changes in VPA Use After Two Intervention Points

The prevalence of VPA use in women in age groups < 15 years and 15–49 years decreased after both intervention points – after the introduction of RMMs in 2014 and the PPP in 2018. No reduction was observed in the male population after RMMs in 2014, and a non-significantly small reduction was observed after 2018. A significant increase in the prevalence of VPA use was observed in women > 49 years of age after both periods. The actual and expected (counterfactual) numbers and the absolute and relative causal effect of each intervention with posterior probability in the VPA user groups are summarised in Table 1.

3.4.1 Impact of RMM on the Prevalence of VPA Use in Women 15–49 Years Old

3.4.1.1 After the First Intervention Period (Q4 2014) In the post-intervention period, the average prevalence of VPA use per month was 1.2. If the intervention had not occurred in the first period, the average prevalence of VPA use per month would have been expected to be 1.3 (95% CI 1.3, 1.4). Subtracting the predicted prevalence from the observed prevalence yields an absolute effect of the intervention or a reduction in the use of VPA of −0.1 (95% CI −0.14, −0.065).

The relative reduction in VPA users after period one was −7.7% (95% CI −10%, −5.1%), and was statistically significant ($p < 0.001$) (Fig. 4).

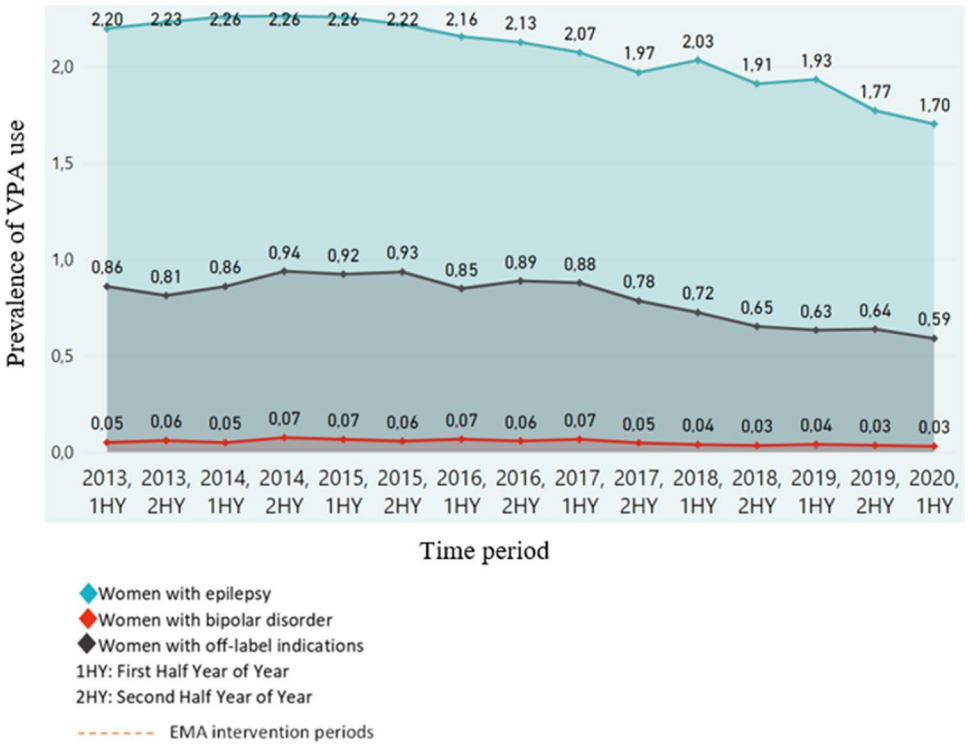

Fig. 2 Prevalence of the VPA use in the study cohort in women aged 15 to 49 years with bipolar disorder, epilepsy and off-label indications per 1000 women aged 15–49 years in the general population in Latvia

Fig. 3 Incidence proportion of VPA use in the study cohort in women aged 15–49 years per 1000 women aged 15–49 years in the general population in Latvia

Table 1 Forecasting the prevalence of VPA use per month in post-intervention period and causal impact of the EMA RMMs using Bayesian structural time series

Group	Period	Observed average prevalence of VPA use per month	Average expected prevalence of VPA use per month (95% CI)	Absolute effect (95% CI)	Relative effect (95% CI)	Posterior probability (*p* value)	Posterior probability of causal impact (%)
Women 15–49 years old	1	1.200	1.3 (1.3, 1.4)	−0.1 (−0.14, −0.065)	−7.7% (−10%, −5.1%)	0.001	99.9%
	2	1.00	1.100 (1, 1.2)	−0.072 (−0.13, −0.016)	−6.4% (−11%, −1.5%)	0.007	99.3%
Girls <15 years old	1	0.810	1 (0.95, 1.1)	−0.220 (−0.3, −0.14)	−21% (−27%, −14.0%)	0.001	99.9%
	2	0.670	0.75 (0.66, 0.84)	−0.077 (−0.17, 0.012)	−10% (−20%, 1.9%	0.042	95.8%
Women > 49 years old	1	1.200	1.100 (1.1, 1.1)	0.034 (0.009, 0.062)	3.1% (0.8%, 5.7%)	0.006	99.4%
	2	1.200	1.200 (1.1, 1.2)	0.024 (−0.006, 0.057)	2.1% (−0.5%, 5.0%)	0.066	93.4%
Men 15–49 years old	1	2.200	1.9 (1.9, 2)	0.210 (0.16, 0.28)	11% (7.8%, 15%)	0.001	99.9%
	2	2.200	2.2 (2.1, 2.3)	−0.002 (−0.087, 0.078)	−0.04% (−3.8%, 3.6%)	0.490	51.0%

3.4.1.2 After the First and Second Intervention Periods (Q4 2018) In the post-intervention period, the average prevalence of VPA use per month was 1.0. If the second intervention had not occurred, the average prevalence of VPA use per month would have been expected to be 1.10 (95% CI 1, 1.2). Subtracting the predicted prevalence from the observed prevalence yields an absolute effect of the intervention or a reduction in the use of VPA of −0.072 (95% CI −0.13, −0.016). The relative reduction in the use of VPA after the first and second intervention periods was −6.4% (95% CI −11%, −1.5%) and was statistically significant ($p < 0.007$) (Fig. 4). The impact of the intervention in 2018 cannot be truly differentiated from the impact of intervention in 2014, as the reduction in VPA use continued from 2014 to 2018 without stabilisation or plateau period.

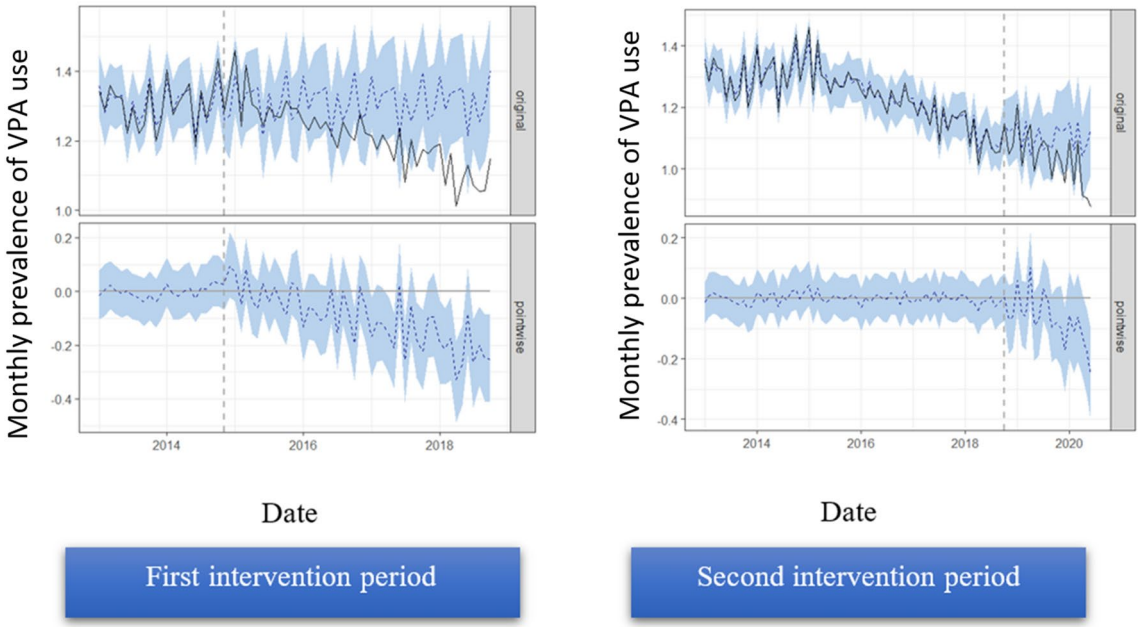

Fig. 4 The predicted and actual prevalence of VPA use in women aged 15–49 years per 1000 women aged 15–49 years in the general population in Latvia, with confidence intervals up until the beginning of the second intervention period (left) and including both periods (right). Original charts: black line – prevalence (actual data) of VPA use per month in women 15–49 years of age. Dashed blue line – predicted prevalence (counterfactual) of VPA use per month in women 15–49 years old. Shaded blue area – margin of error for the monthly predicted number (95% confidence interval). Vertical dashed grey line – date of intervention (December 2014 and November 2018). Point-wise charts: monthly variance of actual versus predicted (counterfactual) data

3.4.2 Impact of RMM on Prevalence of VPA Use in Women in Age Groups < 15 years and > 49 Years and Men in Age Group 15–49 Years After the First Intervention Period (Q4 2014)

In girls < 15 years of age, a statistically significant relative decrease of 21% (95% CI −24%, −5.1%) was observed in the post-intervention period (Appendix 1, Fig. 2). In women > 49 years of age a statistically significant relative increase of 3.1% (95% CI 0.75%, 5.7%) was observed in the post-intervention period (Appendix 1, Fig. 3). In the male population (15–49 years of age) a statistically significant relative increase of 11% (95% CI 7.8%, 15%) was observed (Appendix 1, Fig. 4).

3.4.3 Impact of RMMs on Prevalence of VPA Use in Women in Age Groups < 15 Years and > 49 Years and Men in Age Group 15–49 Years After the First and Second Intervention Periods (Q4 2018)

In the female population < 15 years of age, a statistically significant relative decrease of −10% (95% CI −20%, 1.9%) was observed in the post-intervention period (Appendix 1, Fig. 2). In women > 49 years of age, a relative increase of 2.1% (95% CI −0.5%, 5%) was observed, but was not statistically significant (Appendix 1, Fig. 3).

In the male population (15–49 years of age), a small and statistically non-significant relative decrease of −0.044% (95% CI −3.8%, 3.6%) was observed (Appendix 1, Fig. 4).

4 Discussion

This study describes VPA prescribing patterns and the impact of the RMMs implemented in 2014 and 2018 on the prevalence of VPA use in women in age groups < 15 years, 15–49 years and > 49 years, and men 15–49 years.

In our study, the prevalence of VPA use in women 15–49 years of age in 2013 was 3.08 per 1000 women and in 2020 it decreased to 2.30 per 1000 women. A similar prevalence rate was observed in Estonia, where the annual prevalence rate per 1000 women aged 15–44 years was 3.3 in 2013 and decreased to 3.1 per 1000 in 2018 [17].

For comparison, in 2014, the prevalence of VPA use per 1000 women aged 16–44 years in Ireland was approximately 2, but by 2019 it had decreased to approximately 1.5 [24]. The data of other countries suggest that the monthly prevalence rate of VPA use ranged from 1.9 to 2.2 per 1000 women of reproductive age in Denmark between 2010 and 2020, from 1.6 to 1.2 in the Netherlands and from 3.2 to 1.9 in the UK [25].

While the definitions of reproductive age and the calculation methods varied between the studies, most published studies describing trends in the use of VPA have shown that the annual prevalence and incidence of VPA prescribing declined or stabilized after 2014 in women of reproductive age [12, 14, 16, 17, 24, 26–28]. In Latvia, a decline in prevalence and incidence of VPA use continued after 2018 as well. Similar observations were made by McTaggart et al. in Scotland and Hughes et al. in Ireland [24, 26].

Impact analysis of prevalence of VPA use per month in women 15–49 years of age revealed a decrease after the first intervention period in 2014 and also after both intervention periods in 2014 and 2018. This reduction is statistically significant, where after the first intervention period in 2014, a relative reduction in prevalence was −7.7% (95% CI −10%, −5.1%) and after both intervention periods the reduction in prevalence was −6.4% (95% CI −11%, −1.5%).

The decline in prevalence of VPA use started after intervention in 2014, and persisted up until 2018. Furthermore, the decrease in VPA usage also continued after the intervention in 2018. The measured impact of the intervention after 2018 is somewhat influenced by the positive and statistically significant impact of the intervention in 2014, indicating that the intervention in 2018 had a smaller impact than the intervention in 2014.

The impact of the 2018 intervention cannot be truly differentiated from the impact after the 2014 intervention, as the reduction in prevalence of VPA use continued from 2014 to 2018 without stabilisation or plateau period. The impact after the 2018 intervention could be considered rather limited, yet the finding of our BSTS model of a significant reduction in VPA use after the entire study period (2013–2020) suggests that the 2018 intervention contributed to a further decline in VPA use in women of reproductive age in Latvia. At the same time, the use of other antiepileptics increased in women aged 15–49 years during the study period.

Several published studies evaluated the impact or effectiveness of RMM in 2014 on VPA use in the EU [14, 15, 17, 24–26, 29–31]. The methods differ between the studies, making direct comparison difficult; however, the 2014 RMMs have had a positive impact on incident prescriptions, VPA prescribing rates, VPA initiations as second-line therapy, incidence of VPA-exposed pregnancies and the use of effective contraception by patients in many countries [14, 17, 26, 29, 31]. Only a few studies identified a limited impact on the proportion of initiations of VPA, suggesting that the national context could play a role in the effectiveness of RMMs [30]. For example, in Sweden, after the EMA RMMs in 2014, the number of new VPA users in the epilepsy group has not decreased, while the number of new VPA users for psychiatric indications has decreased. The authors of the study argued that this could be explained by a decrease in the number of VPA users for epilepsy over a longer period before the EMA RMMs [14], which has not been observed in other studied countries, including Latvia.

Only a few studies have evaluated the effectiveness or impact of RMMs in 2018 [15, 24, 25]. Similar to Latvia, the prevalence of VPA use in Scotland decreased significantly after 2018 when PPP was implemented [26]. This finding could be explained by the relatively higher prevalence of VPA use before the intervention and the lack of a plateau effect after 2014.

In contrast, a study in Denmark, Italy, Spain, the Netherlands and the UK found that only the prevalence, not the incidence rate, or the discontinuation of VPA in reproductive age, decreased significantly after the interventions in 2018. The authors argue that a possible explanation could be a change in the duration of therapy observed in the study cohort or a general declining trend in the absolute number of valproate utilisation from 2010 to 2020 [25]. The authors conclude that there was a limited impact of RMMs in 2018 in the countries studied.

As part of our study, we also evaluated the impact of RMMs in girls < 15 years and women > 49 years of age. In girls < 15 years of age, VPA use decreased statistically significantly after both intervention periods and the decrease was more pronounced compared with the reproductive age group, suggesting that the impact of RMMs intervention could extend beyond the target population. On the contrary, in women > 49 years of age, the use of VPA has statistically significantly increased. A similar trend was observed in other published studies, in which girls and women outside

the reproductive age range were included [12, 15, 17, 28], while in Scotland, the prescribing of VPA decreased in all age groups of women [26].

When analysing the indications for which VPA was used in Latvia, a fairly high proportion of study patients used VPA for psychiatric indications, where 42% of women in study cohort used VPA for a psychiatric diagnosis between 2013 and 2020, including bipolar disorder and off-label indications. For off-label indications, VPA was prescribed most frequently by psychiatrists, while VPA was prescribed most commonly for patients with schizophrenia and moderate intellectual disabilities. We observed that the use of VPA decreased substantially in psychiatric disorders, including the use for off-label indications, which could be explained by the fact that the RMMs materials were widely disseminated.

In Estonia, 40% of all women who used VPA between 2005 and 2018 had psychiatric indications [17], but no reduction in the use of VPA was observed among psychiatrists. On the contrary, a study in Finland found that approximately half of patients received VPA for indications other than epilepsy, and the consumption of VPA for psychiatric indications decreased during the study period 2012–2016 [12]. In Sweden [14], 43.9% of VPA users had psychiatric diagnoses with a tendency to decrease between 2011 and 2017. In Ireland, in contrast, the prescription of VPA is increasing for indications other than epilepsy [16].

More studies are needed in different regions to better understand the long-lasting effects of RMMs on VPA use patterns in the EU. As no plateau phase was observed in our study after the intervention in 2014, the long-term influence of the EMA RMMs should be further assessed. Due to the limitations of routinely collected health data, we were unable to assess the appropriateness of VPA prescribing and adherence to PPP, including the use of contraceptives in women of reproductive age. Such studies would be of great importance to better understand the unintended effects of RMM, such as the decrease in VPA use in women outside the reproductive age range or the unnecessary withholding of VPA treatment in women of reproductive age. Although there are many available antiepileptic treatments, for some patients VPA remains the only effective option, and efforts must continue to take the necessary precautions in women of reproductive age and to prevent exposure to VPA during pregnancies [32].

An additional limitation of our study is that patients may purchase their medications outside of the reimbursement system for various reasons and it would not be captured in the database. It was not possible to estimate the number of such patients, but it is unlikely that these data would alter the conclusions of this study. To our knowledge, there were no changes in the regulation of reimbursed medications during the study period. Some new AEDs have been authorised during this period, but this may not have an impact on our results, as most of the new AEDs are not available on the Latvian market.

Previous research has noted that the choice of interrupted time series (ITS) method can lead to divergent conclusions regarding the impact of the intervention [33]. To analyse ITS data, segmented linear regression models have often been applied, using various estimation methods, such as ordinary least squares regression (OLS), which fails to adjust for autocorrelation, autoregressive integrated moving average (ARIMA), and restricted maximum likelihood (REML). Several studies that examine the impact of RMM have employed these methods. However, we utilise the BSTS method in our study, which employs state-space models that allow for the analysis of trends, seasonality, and regression components individually. Research has suggested that compared to ARIMA, BSTS models have a better predictability of future counterfactual values [34].

In analyses of the impact of RMM, we used periods that included information disseminated by SAM. The results indicate that the introduction of RMM and communication to HCP at the national level had an impact on the use of VPA. It is important to note that in addition to RMM introduced by EMA, SAM conducted additional activities from 2017 to 2020 to raise awareness of the risks of VPA such as publishing articles in professional journals, presenting at professional meetings and educational events, and co-authoring e-lectures for HCPs.

5 Conclusions

A statistically significant decrease in the use of VPA was identified in Latvia for women after the introduction of RMMs for VPA in 2014 and 2018. A decrease in prevalence and incidence of VPA users was observed in all indications studied: epilepsy, bipolar disorder and off-label indications. The results indicate a good reaction to the published RMMs with respect to the use of VPA in women. To understand the long-lasting effects of RMMs on VPA prescription patterns in the EU, further research is needed. In addition, studies that assess the appropriateness of VPA prescribing, as well as adherence to PPP, would allow a more nuanced understanding of the impact of RMM on VPA use.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-023-00394-y.

Acknowledgements Authors thank the Latvian National Health Service for providing the data. The authors also thank four anonymous reviewers for their comments that improved the manuscript.

Declarations

Funding This research did not receive specific grants from funding agencies in the public, commercial, or non-profit sectors.

Conflict of interest The authors have declared that no competing interests exists.

Ethical approval The analyses for this study were conducted retrospectively using deidentified patient data; according to local data protection regulations, no approval from the ethics committee was required for this study [18].

Consent to participate Not applicable.

Consent for Publication Not applicable.

Availability of data and material Upon reasonable request, study authors will provide access to data.

Author contributions All authors met the below criteria for authorship: substantial contributions to the conception or design of the work; the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; and final approval of the version to be published. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by I.R. and E.P. The first draft of the manuscript was written by I.R. and all authors reviewed and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol. 2018;17:530–8. https://doi.org/10.1016/S1474-4422(18)30107-8.
2. Tomson T, Battino D, Perucca E. Teratogenicity of antiepileptic drugs. Curr Opin Neurol. 2019;32:246–52. https://doi.org/10.1097/WCO.0000000000000659.
3. Güveli BT, Rosti RÖ, Güzeltaş A, Tuna EB, Atakl D, Sencer S, et al. Teratogenicity of antiepileptic drugs. Clin Psychopharmacol Neurosci. 2017;15:19–27. https://doi.org/10.9758/cpn.2017.15.1.19.
4. European Medicines Agency. Assessment report. Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data. Substances related to valproate. Procedure number: EMEA/H/A-31/1387. 2014.
5. European Medicines Agency. New measures to avoid valproate exposure in pregnancy endorsed. Member State representatives agree new restrictions and pregnancy prevention programme. . EMA/375438/2018 2018. https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-new-measures-avoid-valproate-exposure-pregnancy-endorsed_en-0.pdf (**accessed Sep 6, 2021**).
6. European Medicines Agency. New measures to avoid valproate exposure in pregnancy endorsed. . EMA/145600/2018 2018. https://www.ema.europa.eu/en/documents/press-release/new-measures-avoid-valproate-exposure-pregnancy-endorsed_en.pdf; (**accessed Sep 6, 2021**).
7. Beghi E, Giussani G, Abd-Allah F, Abdela J, Abdelalim A, Abraha HN, et al. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18:357–75. https://doi.org/10.1016/S1474-4422(18)30454-X.
8. Rancans E, Renemane L, Kivite-Urtane A, Ziedonis D. Prevalence and associated factors of mental disorders in the nationwide primary care population in Latvia: a cross-sectional study. Ann Gen Psychiatry. 2020. https://doi.org/10.1186/s12991-020-00276-5.
9. The National Health Service of Latvia. List of reimbursed medicines n.d. https://www.vmnvd.gov.lv/lv/kompensejamo-zalu-saraksti (**accessed Sep 20, 2022**).
10. State Agency of Medicines of the Republic of Latvia. A Dear Healthcare Professional letter "Drugs containing valproate and related compounds: risk of abnormal pregnancy outcomes" 2014. https://www.zva.gov.lv/lv/jaunumi-un-publikacijas/jaunumi/vestule-veselibas-aprupes-specialistam-valproatus-un-tam-radniecigus-savienojumus-saturosas-zales (**accessed Sep 6, 2021**).
11. State Agency of Medicines of the Republic of Latvia. A Dear Healthcare Professional letter. "Valproate: new restrictions on use; Pregnancy Prevention Programme to be introduced" 2018. https://www.zva.gov.lv/lv/jaunumi-un-publikacijas/jaunumi/vestule-veselibas-aprupes-specialistam-valproats-jauni-lietosanas-ierobezojumi-jaievies-grutniecibas (**accessed Sep 6, 2021**).
12. Virta LJ, Kälviäinen R, Villikka K, Keränen T. Declining trend in valproate use in Finland among females of childbearing age in 2012–2016 – a nationwide registry-based outpatient study. Eur J Neurol. 2018;25:869–74. https://doi.org/10.1111/ene.13610.
13. Jacob L, Schmitz B, Bohlken J, Kostev K. Trends in valproate use in patients in Germany between 2009 and 2017. Epilepsy Behav. 2019;92:26–30. https://doi.org/10.1016/j.yebeh.2018.12.002.
14. Karlsson Lind L, Komen J, Wettermark B, von Euler M, Tomson T. Valproic acid utilization among girls and women in Stockholm: impact of regulatory restrictions. Epilepsia Open. 2018;3:357–63. https://doi.org/10.1002/epi4.12228.
15. Puteikis K, Medžiaušaitė I, Mameniškienė R. Valproate utilisation trends among girls and women from 2013 to 2018. Seizure. 2019;70:77–81. https://doi.org/10.1016/j.seizure.2019.07.001.
16. Murphy S, Bennett K, Doherty CP. Prescribing trends for sodium valproate in Ireland. Seizure. 2016;36:44–8. https://doi.org/10.1016/j.seizure.2016.01.019.
17. Kurvits K, Laius O, Uusküla M, Haldre S, Rakitin A. Valproic acid prescription trends among females of childbearing age in Estonia: a 14-year nationwide prescription database study. Seizure. 2020;76:28–31. https://doi.org/10.1016/j.seizure.2020.01.004.
18. Latvian Association of Sociologists. Latvian Association of Sociologists Professional Code for Conducting Social and Market Research 2008. http://sociologija.lv/etika-2/lsa-kodekss/.

19. The State Agency of Medicines of Latvia. Statistics on medicines consumption n.d. https://www.zva.gov.lv/lv/jaunumi-un-publikacijas/publikacijas/zalu-paterina-statistika (**accessed Sep 20, 2022**).
20. The State Agency of Medicines of Latvia. Consumption of medicines by DDD per 1000 inhabitants per day 2017-2021 n.d. https://www.zva.gov.lv/lv/publikacijas-un-statistika/zalu-paterina-statistika-ddd (**accessed Sep 20, 2022**).
21. State Agency of Medicines of Republic of Latvia. Medicinal Product Register of Latvia n.d. https://dati.zva.gov.lv/zalu-registrs/en (**accessed Sep 20, 2022**).
22. Official Statistics Portal od Latvia. Population in regions and cities by age and gender at the beginning of year 1971 - 2022 n.d. https://data.stat.gov.lv/pxweb/en/OSP_PUB/START__POP__IR__IRD/IRD040 (**accessed Sep 20, 2022**).
23. Brodersen KH, Gallusser F, Koehler J, Remy N, Scott SL. Inferring causal impact using Bayesian structural time-series models. Ann Appl Stat. 2015;9:247–74. https://doi.org/10.1214/14-AOAS788.
24. Hughes JE, Buckley N, Looney Y, Curran S, Mullooly M, Bennett K. 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;31:661–9. https://doi.org/10.1002/pds.5427.
25. Klungel O, Sturkenboom M, Abtahi S, Pajouheshnia R, Durán Salinas C, Riera Arnau J, et al. Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends 2022https://doi.org/10.5281/ZENODO.7074588
26. McTaggart S, MacColl G, Gronkowski K, Wood R, Leach JP, Bennie M. Impact of regulatory safety notices on valproate prescribing and pregnancy outcome among women of child-bearing potential in Scotland: a population-based cohort study. BMJ Open. 2022. https://doi.org/10.1136/bmjopen-2021-058312.
27. Gaudio M, Konstantara E, Joy M, van Vlymen J, de Lusignan S. Valproate prescription to women of childbearing age in English primary care: repeated cross-sectional analyses and retrospective cohort study. BMC Pregnancy Childbirth. 2022. https://doi.org/10.1186/s12884-021-04351-x.
28. Han SH, Lee H, Shin JY, Moon HJ, Lee SY. Real-world prescribing trends of valproate in women with epilepsy in Korea. Epilepsy Beh. 2021. https://doi.org/10.1016/j.yebeh.2020.107700.
29. Ehlken B, Nishikawa C, Kaplan S, Dresco I, Granados D, Toussi M. 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;38:461–8. https://doi.org/10.1080/03007995.2021.1997286.
30. Toussi M, Shlaen M, Coste F, de Voogd H, Dimos V, Kaplan S. Effectiveness of risk minimisation measures for valproate: a drug utilisation study in Europe. Pharmacoepidemiol Drug Saf. 2021;30:292–303. https://doi.org/10.1002/pds.5166.
31. Degremont A, Polard E, Kerbrat S, Grimaud O, Jonville-Béra A-P, Ringa V, et al. Impact of recommendations on sodium valproate prescription among women with epilepsy: an interrupted time-series study. Epilepsy Behav. 2021;125: 108449. https://doi.org/10.1016/j.yebeh.2021.108449.
32. Mostacci B, Ranzato F, Giuliano L, la Neve A, Aguglia U, Bilo L, et al. Alternatives to valproate in girls and women of childbearing potential with Idiopathic Generalized Epilepsies: state of the art and guidance for the clinician proposed by the Epilepsy and Gender Commission of the Italian League Against Epilepsy (LICE). Seizure. 2021;85:26–38. https://doi.org/10.1016/j.seizure.2020.12.005.
33. Turner SL, Karahalios A, Forbes AB, Taljaard M, Grimshaw JM, McKenzie JE. Comparison of six statistical methods for interrupted time series studies: empirical evaluation of 190 published series. BMC Med Res Methodol. 2021;21:134. https://doi.org/10.1186/s12874-021-01306-w.
34. Navas-Thorakkattle M, Farhin S, Khan AA. Forecasting the Trends of Covid-19 and Causal Impact of Vaccines Using Bayesian Structural time Series and ARIMA. Ann Data Sci. 2022;9:1025–47. https://doi.org/10.1007/s40745-022-00418-4.