

## Use of valproate in pregnancy and in women of childbearing age between 2014 and 2018 in Switzerland: a retrospective analysis of Swiss healthcare claims data

Spoendlin Julia<sup>ab</sup>, Blozik Eva<sup>cd</sup>, Graber Sereina M.<sup>c</sup>, Rauch Marlene<sup>ab</sup>, Marxer Carole A.<sup>ab</sup>, Rüegg Stephan<sup>e</sup>, Meier Christoph<sup>ab</sup>, Winterfeld Ursula<sup>f</sup>, Panchaud Alice<sup>gh</sup>

<sup>a</sup> Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Switzerland

<sup>b</sup> Hospital Pharmacy, University Hospital Basel, Switzerland

<sup>c</sup> Department of Health Sciences, Helsana Insurance Group, Zurich, Switzerland

<sup>d</sup> Institute of Primary Care, University and University Hospital of Zurich, Switzerland

<sup>e</sup> Division of Clinical Neurophysiology, Department of Neurology, University Hospital Basel and University of Basel, Switzerland

<sup>f</sup> Swiss Teratogen Information Service and Clinical Pharmacology Service, CHUV, Lausanne, Switzerland

<sup>g</sup> Service of Pharmacy, Lausanne University Hospital and University of Lausanne, Switzerland

<sup>h</sup> Institute of Primary Health Care (BIHAM), University of Bern, Switzerland

### Summary

**AIMS OF THE STUDY:** The prevalence of the use of valproate during pregnancy and by women of childbearing age in Switzerland is not known. We aimed to study the use of antiseizure drugs by these women in Switzerland, with a particular focus on valproate.

**METHODS:** We conducted a retrospective descriptive study using the healthcare claims database of the Swiss health insurance Helsana (2014–18). We established two separate study populations: (1) a cohort of pregnancies leading to a delivery, and (2) all women of childbearing age (15–45 years) who were insured with Helsana for at least one year during the study period. We identified the dispensation of valproate, lamotrigine, carbamazepine, levetiracetam, topiramate, pregabalin, gabapentin, phenobarbital, and phenytoin (1) between delivery and three months prior to the estimated date of the last menstrual period, and (2) by calendar year. We quantified exposure prevalence of each antiseizure drug as the number of women with  $\geq 1$  prescription fill per 10,000 (1) pregnancies, and (2) women by calendar year. Results were weighted for the demographic distribution of the Helsana population relative to the Swiss population.

**RESULTS:** We identified a weighted pregnancy population of 387,418 pregnancies, with a mean maternal age at delivery of 31.9 years (standard deviation 5.1). Lamotrigine was the most frequently dispensed antiseizure drug during pregnancy (20/10,000), followed by levetiracetam (11/10,000), and pregabalin (3.8/10,000). Valproate was dispensed to 1.9/10,000 women during pregnancy and to 1.3/10,000 women within 90 days prior to the last men-

strual period but not during pregnancy. The weighted study population of women aged 15–45 years consisted of 2,781,151 women, of whom 74,080 (270/10,000) were exposed to  $\geq 1$  of the evaluated antiseizure drugs. Pregabalin was the most frequently dispensed antiseizure drug (64/10,000), followed by lamotrigine (46/10,000), topiramate (32/10,000), and valproate (25/10,000). The use of valproate decreased from 28/10,000 women in 2014 to 21/10,000 women in 2018.

**CONCLUSIONS:** The prevalence of exposure to valproate during pregnancy was comparable to Denmark and lower than in other European countries. Despite decreasing exposure prevalence, the use of valproate in women of childbearing age in Switzerland seems higher than the actual clinical need.

**Keywords:** valproic acid, valproate, antiseizure drugs, Switzerland, claims database, pregnancy, women of childbearing age, drug utilisation, electronic database, pharmacoepidemiology

### Introduction

Valproate has been available in Switzerland since 1972 for the treatment of epilepsy, and since the mid-1990s also for bipolar disease [1]. Since the 1980s, a congenital valproate syndrome has been characterised, which occurs in up to 10% of children after in utero exposure to valproate during the first trimester [2]. The syndrome comprises neural tube defects, cardiovascular anomalies, limb defects, hypospadias, oral clefts, and dysmorphic facial features [3–6]. In the early and mid-2000s, case series described developmental delays in children with in utero valproate expo-

### Correspondence:

Prof. Alice Panchaud, PhD,  
Head of Primary care  
Pharmacy at BIHAM, Uni-  
versity of Bern, Mittel-  
strasse 43, CH-3012 Bern,  
alice.panchaudmon-  
nat[at]biham.unibe.ch

sure [7–9]. In 2009, a prospective cohort study, including 309 children exposed in utero to antiseizure drugs, reported significantly lower mean cognitive test scores at 3 years of age in 96 children with valproate exposure when compared to children exposed to lamotrigine, carbamazepine, or phenytoin [10]. Since then, several observational studies substantiated these findings, consistently reporting an increased risk of autism, attention deficit hyperactivity disorders, decreased cognitive function, and learning difficulties in children after in utero valproate exposure [10–17]. Some studies suggest that the risk of developmental disorders may be as high as 30–40% for children with in utero exposure to high doses of valproate [18].

The US Food and Drug Administration (FDA) issued a warning in 2011 [19], followed by the European Medicines Agency (EMA) in 2014 [20] and Swissmedic in 2015 [21]. They advised that valproate should not be used during pregnancy or by women of childbearing age unless other substances are ineffective or not tolerated. Since 2015, an increasingly heated public debate has unfolded, first in France, and then in Switzerland and other European countries, about whether or not authorities issued sufficiently appropriate and timely warnings. Until today, the number of exposed pregnant women in Switzerland, and thus the estimated number of affected children, remains unknown. We conducted an observational study using the Helsana claims database to quantify the number of prescriptions of valproate and other antiseizure drugs filled by pregnant women and women of childbearing age between 2014 and 2018 in Switzerland.

## Methods

### Data source

We conducted a retrospective descriptive study using the healthcare claims database of the Swiss health insurance Helsana for the years 2014–18. The Helsana group is one of Switzerland's leading health insurance companies, covering 1.1 million individuals with mandatory health insurance from all 26 cantons (approximately 15% of the Swiss population). The database includes information on inpatient and outpatient healthcare services, including drug dispensations, as well as demographics. For dispensation of prescription drugs, the corresponding codes of the anatomical therapeutic chemical (ATC) classification system are available [22]. All data are anonymous, and all analyses were conducted internally by the department of health sciences of the Helsana group.

## Pregnancy cohort

### Identification of delivery date

We identified inpatient and outpatient deliveries (including live births and stillbirths) covered by mandatory health insurance in the Helsana claims database between January 2014 and December 2018. Inpatient deliveries were recorded by means of SwissDRG (Drug Related Diagnosis) codes, and outpatient deliveries by means of Tarmed codes or billed deliveries by midwives (appendix 1, see separate PDF file for download). Delivery codes recorded within a period of 30 days were regarded as pertaining to the same pregnancy [23], and the date of delivery was defined as the first recorded code. Delivery codes separated by more than 300 days were considered as two separate pregnancies (fig. 1). When two subsequent codes were separated between 30 to 300 days, the date of delivery was set at the inpatient SwissDRG code, whereas women ( $n = 80$  women) were excluded if no SwissDRG code was recorded. We excluded pregnancies during which women were not continuously covered by mandatory insurance at Helsana between their last menstrual period and delivery ( $n = 9166$  pregnancies). Some women contributed more than one pregnancy to the cohort. Twins were treated as single births.

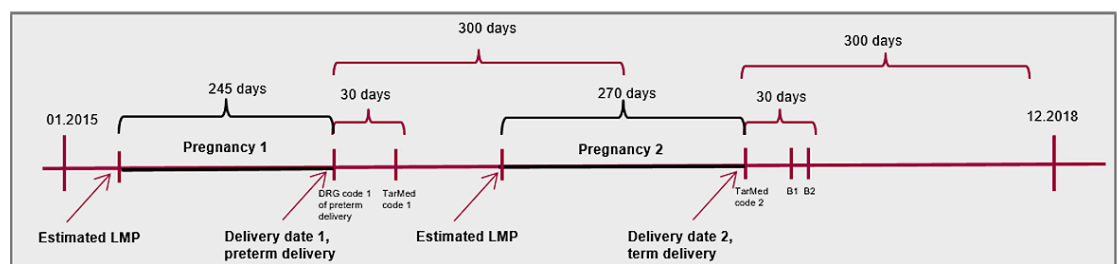
### Identification of the date of the last menstrual period and pregnancy trimesters

The date of the last menstrual period (i.e., start of pregnancy) was estimated, because gestational length or start of pregnancy are not recorded in healthcare claims data. According to an algorithm validated in US claims data [19], the date of the last menstrual period was assigned to be 245 days before the date of delivery for pregnancies that had a DRG code indicative of preterm delivery (<37 weeks, O01A, O01B, O01C, O01D, O60A), and 270 days before the date of delivery for all other pregnancies. A pregnancy trimester was defined to be 90 days, whereby the third trimester was shortened in case of a preterm delivery (fig. 1).

### Cohort of women of childbearing age

The cohort of women of childbearing age included all women aged 15–45 years between 2014 and 2018, irrespective of whether they were pregnant or not. Women were eligible to contribute data to any given year if they were continuously insured with Helsana's mandatory health insurance for the entire year (January–December).

**Figure 1:** Definition of delivery and last menstruation period (LMP) scheme.



### Covariates and descriptive analyses

For all pregnancies, we captured maternal age at delivery, the year of delivery, and whether the recorded codes (SwissDRG and Tarmed) indicated a caesarean section. For women of childbearing age, we captured age in the year of interest and the year the drug was dispensed.

Antiseizure drugs were identified based on recorded ATC codes of recorded prescription fills of drugs in claims data, and included valproate (N03AG01), lamotrigine (N03AX09), carbamazepine (N03AF01), levetiracetam (N03AX14), topiramate (N03AX11), pregabalin (N03AX16), gabapentin (N03AX12), phenobarbital (N03AA02), and phenytoin (N03AB02). Due to the data structure of electronic claims data, we were not able to take into account the indication for the use of individual antiseizure drugs. We quantified the prevalence of prescription fills for specific antiseizure drugs in both cohorts, defined as women/pregnancies, with  $\geq 1$  recorded claim for an antiseizure drug divided by the total number of enrolled women/pregnancies during the respective time period. Prevalence of antiseizure drug exposure is presented as absolute numbers per 10,000 women/pregnancies by calendar year. In women of childbearing age, prevalence of antiseizure drug exposure is also presented by age groups.

For the pregnancy cohort, we further categorised whether the last valproate prescription was filled between the date of the last menstrual period and delivery, or within 90 days before the last menstrual period (discontinuers), excluding pregnancies with less than 90 days of enrolment before the last menstrual period.

We weighted results of both cohorts, accounting for the demographic distribution of the population insured with mandatory insurance with Helsana relative to the Swiss population. Weighting factors included calendar year, canton, age, and sex. Because sample size was small, absolute numbers of women/pregnancies exposed to specific anti-

seizure drugs are not shown to preserve patient confidentiality. In order to focus on the relevant antiseizure drugs with regard to prescription frequency, only antiseizure drugs with a minimum weighted prevalence of 50 exposed pregnancies are presented. All analyses were conducted using the statistical programming language R (R version 3.6.1).

### Protocol approvals

This retrospective observational study using anonymous data did not require an ethics committee approval.

## Results

### Pregnancy cohort

Between January 2014 and December 2018, we identified a weighted population of 387,418 pregnancies leading to a delivery. The mean age at delivery ranged between 31.8 (standard deviation 5.1) and 32.1 (standard deviation 5.0) years between 2014 and 2018 (table 1). Of those, between 24,832 (33.0%) and 27,392 (33.5%) deliveries were caesarean sections, which is in accordance with data of the Swiss federal statistical office [24].

After weighting, valproate was dispensed during 1.9/10,000 pregnancies between 2014 and 2018. Overall, valproate was less frequently dispensed during pregnancy than other antiseizure drugs. Lamotrigine was the most frequently dispensed antiseizure drug during pregnancy (20.0/10,000), followed by levetiracetam (11.0/10,000), and pregabalin (3.8/10,000, table 2, fig. 2). For 1.3/10,000 pregnancies, a valproate prescription was filled within 90 days prior to the last menstrual period but not during pregnancy (discontinuers). The prevalence of antiseizure drug exposure in the unweighted pregnancy population is not shown for confidentiality reasons.

**Table 1:** Demographics of the weighted pregnancy population (2014–18)

	2014	2015	2016	2017	2018
No. of pregnancies	75,462	76,321	78,609	81,888	75,137
Mean age at delivery in years (standard deviation)	31.8 (5.1)	31.9 (5.2)	31.8 (5.2)	32.0 (5.2)	32.1 (5.0)
<20 years	446 (0.6%)	389 (0.5%)	479 (0.6%)	354 (0.4%)	376 (0.5%)
20–25 years	8279 (11%)	8599 (11.3%)	8345 (10.6%)	8324 (10.2%)	6938 (9.2%)
26–30 years	21,082 (27.9%)	21,286 (27.9%)	22,487 (28.6%)	23,113 (28.2%)	21,232 (28.3%)
31–35 years	27,654 (36.6%)	27,360 (35.8%)	28,480 (36.2%)	29,612 (36.2%)	27,686 (36.8%)
36–40 years	14,836 (19.7%)	15,215 (19.9%)	15,374 (19.6%)	16,596 (20.3%)	15,725 (20.9%)
41–45 years	3000 (4.0%)	3246 (4.3%)	3166 (4.0%)	3572 (4.4%)	2931 (3.9%)
>45 years	165 (0.2%)	225 (0.3%)	278 (0.4%)	318 (0.4%)	250 (0.3%)
Caesarean section	25,983 (34.4%)	26,177 (34.3%)	26,200 (33.3%)	27,392 (33.5%)	24,832 (33.0%)

**Table 2:** Weighted prevalence of exposure to antiseizure drugs (per 10,000) during pregnancy (2014–18)

	Valproate	Lamotrigine	Carbamazepine	Levetiracetam	Topiramate	Pregabalin
Exposed pregnancies (per 10,000)	1.9	20.0	3.0	11.0	2.4	3.8
Discontinuers*	1.3	0.7	0.4	0.8	3.3	9.3
<b>Exposed pregnancies by year</b>						
2014	NA†	20.0	3.8	10.0	2.9	2.7
2015	3.8	18.0	3.4	12.0	5.2	5.6
2016	2.2	18.0	2.4	7.0	0.9	3.2
2017	2.6	22.0	0.4	13.0	1.3	2.3
2018	1.1	20.0	0.1	10.0	1.9	5.6

\*  $\geq 1$  filled prescription between 90 days before the last menstrual period and the last menstrual period, but none during pregnancy. † No information available as the cell contained a 0 in the Helsana cohort.

### Cohort of women of childbearing age

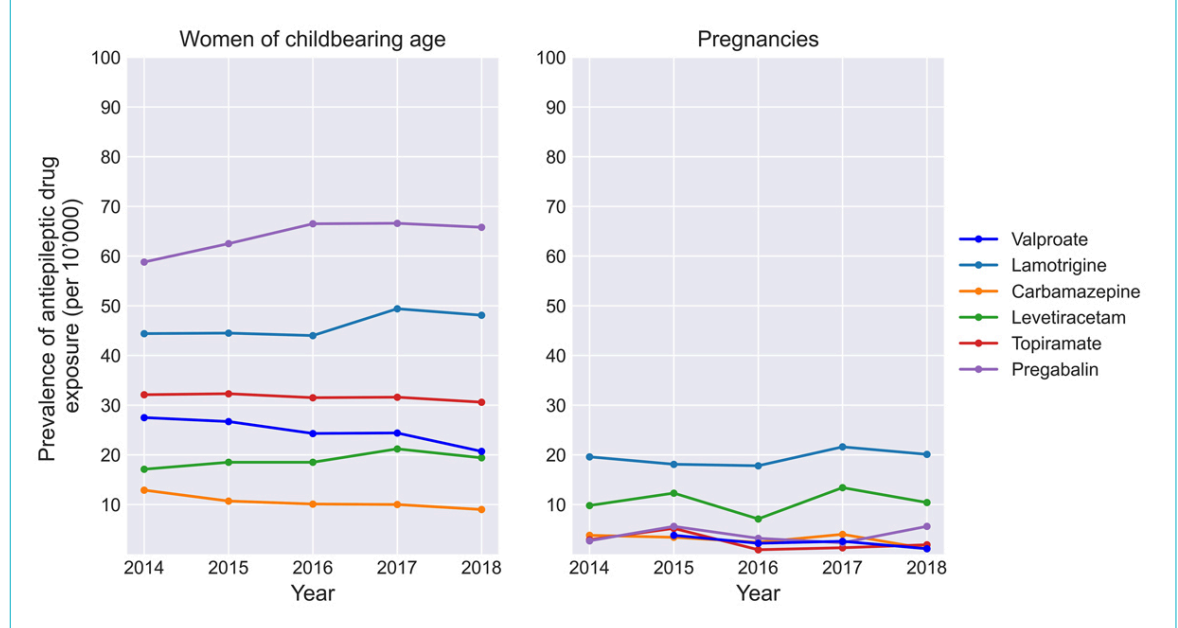
The weighted study population of women aged 15–45 years consisted of 2,781,151 women, of whom 74,080 (2.66%) were exposed to at least one of the evaluated antiseizure drugs during the study period. Pregabalin was the most frequently dispensed antiseizure drug in women of childbearing age, with an exposure prevalence of 59–67/10,000 women, followed by lamotrigine (44–49/10,000), and topiramate (31–32/10,000). Valproate was the fourth most frequently dispensed antiseizure drug; 28/10,000 women filled  $\geq 1$  prescription in 2014, decreasing to 21/10,000 women in 2018 (absolute decrease –25%). The likelihood of filling at least one valproate prescription increased with increasing age, from 24/10,000 women aged 20–25 years to 44/10,000 women aged 41–45 years (table 3, fig. 2). The prevalence of antiseizure drug exposure in the unweighted population of women of childbearing age is not shown for confidentiality reasons.

### Discussion

We estimated that approximately 1.9/10,000 pregnancies were exposed to valproate between 2014 and 2018 in Switzerland. Valproate exposure among women of childbearing age was more than 10-fold higher during the same time period, and decreased from 28/10,000 in 2014 to 21/10,000 women in 2018.

Our results are consistent with a reported valproate exposure of 2/10,000 pregnancies in Denmark in 2016 [25]. Contrary to the Danish study, however, our results are based on a relatively small sample of the Swiss population (15%), and thus our estimates may be subject to variability introducing some uncertainty. Reported prevalence of in utero valproate exposure vary by country and region; the Italian region of Tuscany reported that 15/10,000 pregnancies were exposed to valproate between 2007 and 2016 [26]. The French national agency of drug safety revealed a valproate exposure prevalence of 25/10,000 pregnancies in 2007, which declined to 14/10,000 pregnancies in 2014, and to 3/10,000 pregnancies in 2018 [27, 28], based on an

**Figure 2:** Prevalences of antiseizure drugs in pregnant women and women of childbearing age.



**Table 3:** Weighted prevalence of exposure to antiseizure drugs (per 10,000) in women of childbearing age (2014–18).

	Valproate	Lamotrigine	Carbamazepine	Levetiracetam	Topiramate	Pregabalin
<b>Exposure prevalence (/10,000 women) by year</b>						
2014 (N women total = 1,591,025)	28.0	44.0	13.0	17.0	32.0	59.0
2015 (N women total = 1,598,009)	27.0	45.0	11.0	19.0	32.0	63.0
2016 (N women total = 1,608,054)	24.0	44.0	10.0	19.0	32.0	67.0
2017 (N women total = 1,610,897)	24.0	49.0	10.0	21.0	32.0	67.0
2018 (N women total = 1,601,858)	21.0	48.0	9.0	19.0	31.0	66.0
<b>Exposure prevalence (/10,000 women) by age</b>						
≤20	11.0	22.0	3.6	13.0	23.0	23.0
21–25	24.0	48.0	5.1	24.0	46.0	54.0
26–30	27.0	58.0	10.0	25.0	47.0	76.0
31–35	31.0	63.0	17.0	28.0	50.0	109.0
36–40	36.0	58.0	16.0	21.0	54.0	155.0
41–45	44.0	64.0	23.0	21.0	63.0	232.0



analysis of national claims data. However, an EMA funded study suggested that valproate exposure prevalence in France was lower (11/10,000 pregnancies) as of 2011 [26]. Both the UK and the Emilia-Romagna region in Italy reported valproate exposure in 5/10,000 pregnancies in 2008 and 15/10,000 pregnancies in 2016 [26].

Characteristics of Swiss billing codes did not allow inclusion of pregnancies that ended in termination or abortion into our study population. (This was the same for the studies from Denmark and Emilia-Romagna. In France, 38% of valproate exposed pregnancies accounted for terminations and abortions in 2013 [27], rising to 50% in 2018 [28], which is more than two-fold higher compared to the reported number of terminations and abortions reported for the overall French population [29]. It is unclear to what extent these numbers are applicable to the Swiss population, but it is likely that (elective) pregnancy terminations and abortions are also proportionally more frequent among valproate users than in the overall Swiss population [30].

In the study population of women of childbearing age, between 28/10,000 and 21/10,000 women in Switzerland filled at least one prescription for valproate per year between 2014 and 2018. Analyses of national claims data revealed a similar prevalence of valproate exposure among women of childbearing age for Denmark (21-19/10,000 women between 2001 and 2016) [25], Germany (30-25/10,000 women between 2004 and 2016) [31], Ireland (35-31/10,000 between 2008 and 2013) [32], and a higher prevalence for Finland (50-40/10,000 between 2012 and 2016) and France (75-25/10,000 between 2007-2018) [33,34].

The exact number of women of childbearing age who require valproate for seizure control in Switzerland is not known, but it has been shown that between 5-15% of women with idiopathic (genetic) generalised epilepsy do not achieve seizure control with antiseizure drugs other than valproate [35,36]. Other forms of epilepsy, bipolar disease, and other off-label indications such as migraine prophylaxis, should not be treated with valproate in this patient population. Based on data from other European countries, we estimate that between 0.3-1.5/10,000 pregnancies and between 0.3-1.7/10,000 women of childbearing age absolutely require valproate for seizure control (calculations in appendix 2, see separate PDF file for download). Small sample size of pregnancies exposed to valproate in our study population, and several assumptions underlying our estimation of women absolutely requiring valproate, prevents a conclusion on whether or not valproate was prescribed too often in Switzerland during pregnancy. However, the more than 10-fold higher prevalence of valproate exposure among women of childbearing age observed suggests that despite decreasing exposure prevalence, valproate is still prescribed to women for whom alternative drug treatment may exist. This is critical, since studies from US epilepsy registers have reported that up to 65% of pregnancies among women with epilepsy are unplanned [37]. We do not have information on birth control use in Swiss claims data, but given that for approximately 1.3/10,000 pregnancies the last valproate prescription was filled within 90 days before the last menstrual period, pregnancies seem to be unplanned in a large proportion of valproate users in Switzerland. Ideally, treatment switch to a

new antiseizure drug should be completed a year before the last menstrual period to allow for a seizure-free year before conception [38].

In Switzerland, several media reports escalated public attention on children who had developed birth defects after in utero valproate exposure. This attention increased uncertainty among patients and healthcare providers and was driven by a lack of reliable data and subsequent speculations on the magnitude of the problem. Swissmedic concluded that valproate exposure in pregnant women has been low over the last two decades, based on the observation that only 29 cases of congenital malformations, and 10 cases of developmental disorders, had been reported to the Swiss spontaneous reporting system between 1994 and 2019 [21]. However, such systems do not capture drug exposure, and are highly susceptible to underreporting and bias. Rarely more than 10% of adverse drug events are reported, and the underreporting is especially pronounced if the events develop slowly (e.g., developmental disorders), or if the drug has been on the market for a long time [39]. In Switzerland, healthcare claims data are underused on an institutional level, and drug utilization on a national level is largely unknown. Other western countries, such as all Scandinavian countries, France, Germany, and the United States, have used healthcare claims data for surveillance of drug use and safety for decades, enhancing them with external data to study vulnerable populations such as pregnant women [40–43]. The Swiss federal council's health policy strategy 2020–2030 declared that the technological and digital transformation of the healthcare sector was one of its four main goals in order to improve public health over the next decade [44]. We hope that our study stimulates the discussion on how to make better use of existing data sources on an institutional level for the greater good of the Swiss population, and especially for vulnerable patient groups such as pregnant women.

Besides the strengths of this study, some limitations need to be considered. First, due to the claims data from 2019 being incomplete, the observational period ends in 2018; accordingly, we could not evaluate the effectiveness of the comprehensive 'pregnancy prevention program' for women treated with valproate, which has been implemented by EMA and Swissmedic in 2018 [45]. Second, healthcare claims data do not provide information on whether or not all tablets of a filled prescription were taken. We are therefore unable to evaluate how many of the women who filled a prescription for valproate within 90 days before the last menstrual period stopped the drug before conception, and how many still took it during the first most vulnerable weeks of pregnancy. Third, we were not able to evaluate the indication for the use of antiseizure drugs in this study. It is likely that the majority of women using pregabalin and topiramate did not have an underlying epilepsy diagnosis, but used these drugs for neuropathic pain and migraine respectively. Fourth, results have to be interpreted carefully, as they were estimated based on 15% of the Swiss population from all parts of the country with mandatory health insurance insured with Helsana, and weighted based on specific demographic factors. Thus, reported numbers do not necessarily represent the exact true exposure prevalence in the overall Swiss population of pregnant women or women of childbearing age. Fifth, given the descriptive nature of

this study, we did not perform an a priori sample size calculation. However, results have to be interpreted carefully given the small sample size of women exposed to certain antiseizure drugs, and further studies should aim to replicate our results using different data sources. Sixth, as characteristics of Swiss billing codes did not allow inclusion of pregnancies which ended in termination or abortion into our study population, our prevalence of use is underestimated. The underestimation range is however difficult to predict, as the prevalence of terminations and spontaneous abortions in Switzerland is unknown.

In conclusion, the prevalence of valproate exposure in pregnancy was comparable to Denmark, and lower than in other European countries. As in most other European countries, the use of valproate in women of childbearing age between 2014 and 2018 was higher than what we estimated to be indicated. This study demonstrates the value of electronic claims databases in the evaluation of drug exposure during pregnancy. Future projects are needed to systematically monitor utilisation of drugs using healthcare claims data, especially in vulnerable patient populations such as pregnant women. Results of such projects may build the basis for interventions to increase drug safety in the pregnant women in Switzerland.

#### Disclosure statement

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