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Characterization of pregnancies among women with epilepsy using valproate before or during pregnancy - A longitudinal claims data analysis

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Abstract

Purpose

To characterize pregnancies among women with epilepsy who have filled a prescription for valproate at any time before or during pregnancy and to assess other antiepileptic drug (AED) prescriptions.

Methods

Based on health claims data (German Pharmacoepidemiological Research Database - GePaRD; covering ~20% of the population), we selected pregnancies beginning between 2014 and 2016 in women with at least three years of observation period before pregnancy and with at least one epilepsy diagnosis code in the year before pregnancy. Among those, we selected pregnancies with at least one valproate dispensation any time before or during pregnancy. We further described these pregnancies regarding patterns in the dispensation of valproate and other AED among the women from their first day in the database until the end of the pregnancy.

Results

Among 2,068 pregnancies fulfilling the inclusion criteria, we identified 454 pregnancies (89% ending in live births and 8% in induced abortions) in 430 women with at least one valproate dispensation before or during pregnancy. In 357 of these pregnancies (79%), valproate was only dispensed before pregnancy, while 97 pregnancies (21%) had a valproate dispensation during pregnancy and of these, 77% (N=75) during the first trimester. The proportion with a valproate dispensation during pregnancy declined from 2014 (25%) to 2016 (19%), also concerning exposure during the first trimester (2014: 20%, 2015: 17%, 2016: 12%), while the proportion ending in an induced abortion was increasing (2014: 5%, 2015: 8%, 2016: 13%). In 48% of exposed pregnancies (N=36), there was no other AED dispensed during the entire observation time before pregnancy. This proportion was lower for pregnancies beginning in 2016 (33%) than for those beginning in 2014 and 2015 (53% and 50%, respectively).

Conclusion

In most women with epilepsy using valproate before or during pregnancy, valproate was dispensed only well before pregnancy beginning. The proportion exposed to valproate during the first trimester declined between 2014 and 2016, but the low proportion treated with alternative AED before valproate treatment suggests there is still room for improvement.

Keywords

Valproate, epilepsy, pregnancy, antiepileptics, German claims data

1. Introduction

Valproate is very effective for the treatment of various forms of epilepsy (Elger and Berkenfeld, 2017), but since the 1980s it has been known that valproate exposure during pregnancy significantly increases the risk of congenital malformations (DiLiberti et al., 1984; Weston et al., 2016). More recently, valproate exposure during pregnancy was also found to increase the risk of delayed motor development (Veiby et al., 2013), reduced cognitive abilities (Meador et al., 2013), and autistic spectrum disorders in the child (Bromley et al., 2013; Christensen et al., 2013). Due to these risks, the Pharmacovigilance Risk Assessment Committee (PRAC[1]) of the European Medicines Agency recommended to strengthen the restrictions on the use of valproate in women and girls of childbearing age (European Medicines Agency, 2014, 2018). In 2014, PRAC stated that "valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated" (European Medicines Agency, 2014).

To assess whether these recommendations changed prescribing patterns, various different approaches are needed. In cross-sectional analyses, we found that the overall age standardized rate of women of childbearing age with at least one dispensation of valproate has declined by 28% between 2004 and 2016, with the largest decline in epilepsy patients (Wentzell et al., 2018a). In an ongoing study we investigate trends in the proportion of pregnant women with epilepsy exposed to valproate during the critical time window (study is being prepared for publication). In addition, long-term longitudinal data on women exposed to valproate before or during pregnancy are required in order to assess whether treatment patterns have changed over time in this very specific population, also with respect to the use of alternative drugs before using valproate. For Germany, there has been no study on the practice of prescribing valproate and its treatment alternatives to women with epilepsy before

[1] Abbreviations: ATC, Anatomical Therapeutic Chemical; AED, antiepileptic drug; GePaRD, German Pharmacoepidemiological Research Database; ICD-10-GM, International Classification of Diseases 10th revision, German modification, PRAC, Pharmacovigilance Risk Assessment Committee; WWE, women with epilepsy

or during pregnancy so far. Our objectives were therefore to characterize - based on German claims data - pregnancies among women with epilepsy to whom valproate was prescribed before or during pregnancy and to assess prescriptions of alternative drugs before and during pregnancy.

2. Material and methods

2.1 Data source

We used data from the German Pharmacoepidemiological Research Database (GePaRD) from 2004 until 2017. GePaRD is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on drug dispensations as well as outpatient (i.e., from general practitioners and specialists) and inpatient services and diagnoses. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented (Haug and Schink, 2020; Leibniz Institute for Prevention Research and Epidemiology - BIPS, 2020).

In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

In GePaRD, diagnosis codes are registered according to the International Classification of Diseases 10th revision, German modification (ICD-10-GM) in the in- and outpatient setting. Drugs can be identified by the respective Anatomical Therapeutic Chemical (ATC) code.

There is information on the date of both prescription and dispensation of drugs. For research on drug utilization and safety during pregnancy based on GePaRD, algorithms have been developed to identify pregnancy outcomes including the date of the outcome and to classify pregnancy outcomes (Mikolajczyk et al., 2013; Wentzell et al., 2018b), to estimate the beginning of pregnancy (Schink et al., 2020), and to link mothers with their offspring (Garbe et al., 2011). In brief, pregnancy outcomes are identified based on delivery dates and diagnosis and procedure codes from the in- and outpatient setting, classified into different outcome categories using a hierarchical approach (e.g. term birth, preterm birth, induced abortion, ectopic pregnancy) and a date is assigned to the outcome (Mikolajczyk et al., 2013; Wentzell et al., 2018b). The beginning of pregnancy is then calculated backwards from the outcome date based on information on the estimated delivery date (available for about 80% of pregnancies) or using the median length method if this information is not available (Schink et al., 2020).

2.2 Study population and study design

The following inclusion criteria were applied: We selected pregnancies i) in women of childbearing age (12–50 years), ii) beginning between 2014 and 2016, iii) with a database history (i.e., continuous observation time in GePaRD) for at least three years before the beginning of pregnancy, and iv) with a code indicating the presence of epilepsy in the year before the beginning of pregnancy. The presence of epilepsy was assessed based on diagnoses (ICD-10-GM codes F80.3, G40.-, G41.-) coded in the in- or outpatient setting in the year before pregnancy beginning.

Among all included pregnancies, we selected those where the woman had at least one dispensation of valproate use any time before or during pregnancy. We then described these pregnancies regarding patterns in the dispensation of valproate and other antiepileptic drugs (AEDs) recommended by the German guideline (Elger and Berkenfeld, 2017) among the women from their first day in the database until the end of the pregnancy (codes available from the author).

2.3 Definition of exposure windows

We divided the observation time into relevant time windows as illustrated in Figure 1 and described the dispensations of valproate and other AEDs for each of these time windows. We also determined the date of the first pregnancy-related examination. The latter date was considered relevant as it marks the point in time when it is certain that the pregnancy was known both to the woman and her treating physician.

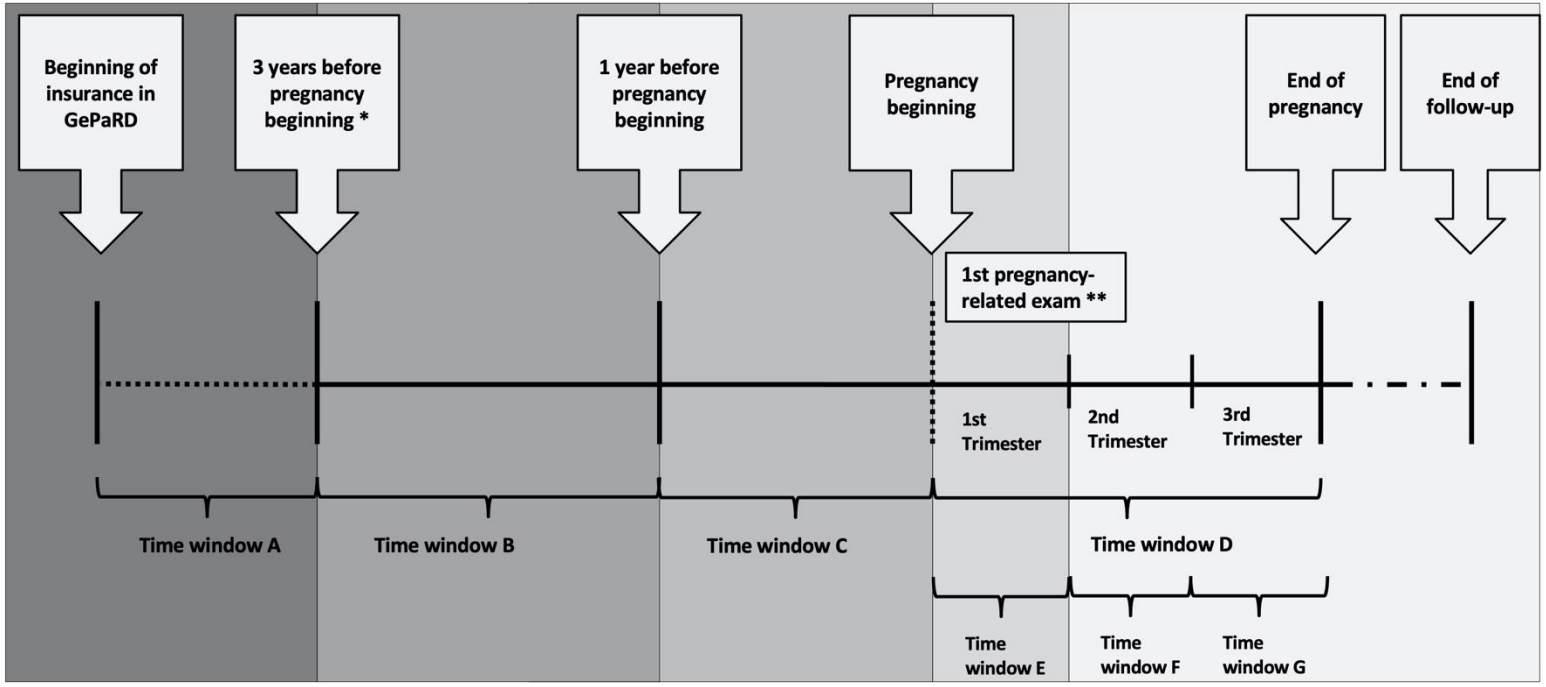

Figure 1: Division of the observation time into relevant time windows

* At least three years of continuous insurance before pregnancy beginning were required as inclusion criterion.

** The first pregnancy-related examination may also be after the 1st trimester.

2.4 Data analysis

We first assessed the total number of pregnancies fulfilling the inclusion criteria. We then focused on those with at least one dispensation of valproate before or during pregnancy. For these pregnancies, we assessed whether there was at least one dispensation of valproate and/or other antiepileptic treatment for each time window as defined above. We also calculated the number and proportion of pregnancies with a dispensation of valproate, other AEDs or no exposure to these drugs overall for each time window and per year of pregnancy beginning.

3. Results

Overall, 2,068 pregnancies fulfilled the inclusion criteria. Of those, 454 pregnancies (in 430 women) had at least one dispensation of valproate before or during pregnancy. Of the 454 pregnancies, 169 (37%) began in 2014, 156 (34%) in 2015, and 129 (28%) in 2016. The mean observation period before the beginning of pregnancy was about ten years (on average 6.9 years in addition to the fixed pre-observation period of three years required for inclusion). The mean age at the time of pregnancy outcome was 31.1 years. In more than 40% of pregnancies, there was at least one hospital main discharge diagnosis of epilepsy before pregnancy beginning. Overall, 89% of the pregnancies ended in live births and 8% in induced abortions. The proportion of induced abortions was higher in 2016 (13%) compared to 2014 (5%) (see Table 1).

Number of pregnancies fulfilling the inclusion criteria	Overall 454	Pregnancies beginning in 2014 169 (37.22%)	Pregnancies beginning in 2015 156 (34.36%)	Pregnancies beginning in 2016 129 (28.41%)
Type of pregnancy outcome				
Term birth	332 (73.13%)	128 (75.74%)	115 (73.72%)	89 (68.99%)
Preterm birth	35 (7.71%)	13 (7.69%)	13 (8.33%)	9 (6.98%)
Birth after due date	36 (7.93%)	16 (9.47%)	10 (6.41%)	10 (7.75%)
Stillbirth	2 (0.44%)	0 (0.00%)	1 (0.64%)	1 (0.78%)
Induced abortion	38 (8.37%)	9 (5.33%)	12 (7.69%)	17 (13.18%)
Ectopic pregnancy	8 (1.76%)	3 (1.78%)	3 (1.92%)	2 (1.55%)
Spontaneous abortion *	3 (0.66%)	0 (0.00%)	2 (1.28%)	1 (0.78%)
Duration of time window A in months (see Figure 1, time from start of observation in GePaRD until 3 years before pregnancy beginning)				
Mean (Std)	82.75 (30.68)	76.97 (24.06)	87.27 (28.79)	84.85 (38.65)
Median (Q1–Q3)	93 (66–104)	88 (66–92)	100 (84–104)	110 (56–116)
Mother's age at the time of pregnancy outcome				
Mean (Std)	31.09 (5.60)	31.21 (5.26)	31.26 (5.77)	30.73 (5.85)
Median (Q1–Q3)	31 (28–35)	31 (28–35)	32 (29–35)	31 (27–35)

Table 1: Characteristics of pregnancies

* As we focused on pregnancies with a clear outcome (defined by diagnosis or procedure codes), pregnancies ending in spontaneous abortions are underrepresented here as they may end without requiring medical care (i.e. without recording of procedure or diagnosis codes).

Table 2 shows the dispensation of valproate or other AEDs for the 454 pregnancies in the defined time windows, overall and stratified by year of pregnancy beginning. The proportion with any valproate dispensation gradually decreased, i.e. from 90% between the start of observation in GePaRD until 3 years before pregnancy beginning (=time window A) to 51% in three years before to one year before pregnancy beginning (=time window B) to 35% between one year before to pregnancy beginning (=time window C). In 357 of the pregnancies (79%), valproate was only dispensed before pregnancy, while 97 pregnancies (21%) had a valproate dispensation during pregnancy (2014: N=42, 2015: N=30, 2016: N=25) and of these, 77% (N=75) had a dispensation in the first trimester. The proportion of valproate-exposed pregnancies declined from pregnancies beginning in 2014 (25%) to pregnancies beginning in 2016 (19%), also concerning exposure during the first trimester (2014: 20%, 2015: 17%, 2016: 12%). Regarding pregnancies where the mother was exposed to valproate only before pregnancy (N=357 pregnancies), the last valproate dispensation was in median 3.9 years before the beginning of pregnancy (3.1 years in 2014, 3.9 years in 2015, and 4.5 years in 2016) (Figure 2).

Dispensations of antiepileptics	Overall 454	Pregnancies beginning in 2014 169 (37.22%)	Pregnancies beginning in 2015 156 (34.36%)	Pregnancies beginning in 2016 129 (28.41%)
Time window A: From the beginning of insurance until 3 years before pregnancy beginning				
Any valproate	408 (89.87%)	152 (89.94%)	139 (89.10%)	117 (90.70%)
Valproate only	150 (33.04%)	52 (30.77%)	48 (30.77%)	50 (38.76%)
Valproate and another AED *	258 (56.83%)	100 (59.17%)	91 (58.33%)	67 (51.94%)
Other AED only	18 (3.96%)	6 (3.55%)	6 (3.85%)	6 (4.65%)
None	28 (6.17%)	11 (6.51%)	11 (7.05%)	6 (4.65%)
Time window B: From 3 years before pregnancy beginning to 1 year before pregnancy beginning				
Any valproate	231 (50.88%)	99 (58.58%)	66 (42.31%)	66 (51.16%)
Valproate only	114 (25.11%)	50 (29.59%)	38 (24.36%)	26 (20.16%)
Valproate and another AED	117 (25.77%)	49 (28.99%)	28 (17.95%)	40 (31.01%)
Other AED only	147 (32.38%)	45 (26.63%)	62 (39.74%)	40 (31.01%)
None	76 (16.74%)	25 (14.79%)	28 (17.95%)	23 (17.83%)
Time window C: From 1 year before pregnancy beginning to pregnancy beginning				
Any valproate	161 (35.46%)	70 (41.42%)	47 (30.13%)	44 (34.11%)
Valproate only	93 (20.48%)	42 (24.85%)	29 (18.59%)	22 (17.05%)
Valproate and another AED	68 (14.98%)	28 (16.57%)	18 (11.54%)	22 (17.05%)
Other AED only	186 (40.97%)	58 (34.32%)	76 (48.72%)	52 (40.31%)
None	107 (23.57%)	41 (24.26%)	33 (21.15%)	33 (25.58%)

Dispensations of antiepileptics	Overall 454	Pregnancies beginning in 2014 169 (37.22%)	Pregnancies beginning in 2015 156 (34.36%)	Pregnancies beginning in 2016 129 (28.41%)
Time window D: From the beginning of pregnancy to the end of pregnancy (pregnancy overall)				
Any valproate	97 (21.37%)	42 (24.85%)	30 (19.23%)	25 (19.38%)
Valproate only	71 (15.64%)	32 (18.93%)	23 (14.74%)	16 (12.40%)
Valproate and another AED	26 (5.73%)	10 (5.92%)	7 (4.49%)	9 (6.98%)
Other AED only	208 (45.81%)	71 (42.01%)	80 (51.28%)	57 (44.19%)
None	149 (32.82%)	56 (33.14%)	46 (29.49%)	47 (36.43%)
Time window E: 1st trimester				
Any valproate	75 (16.52%)	34 (20.12%)	26 (16.67%)	15 (11.63%)
Valproate only	55 (12.11%)	26 (15.38%)	20 (12.82%)	9 (6.98%)
Valproate and another AED	20 (4.41%)	8 (4.73%)	6 (3.85%)	6 (4.65%)
Other AED only	183 (40.31%)	61 (36.09%)	68 (43.59%)	54 (41.86%)
None	196 (43.17%)	74 (43.79%)	62 (39.74%)	60 (46.51%)
Time window F: 2nd trimester				
Pregnancies lasting at least until 2nd trimester	405 (89.21%)	157 (92.90%)	139 (89.10%)	109 (84.50%)
Any valproate	65 (16.05%)	34 (21.66%)	15 (10.79%)	16 (14.68%)
Valproate only	54 (13.33%)	30 (19.11%)	12 (8.63%)	12 (11.01%)
Valproate and another AED	11 (2.72%)	4 (2.55%)	3 (2.16%)	4 (3.67%)
Other AED only	173 (42.72%)	59 (37.58%)	72 (51.80%)	42 (38.53%)
None	167 (41.23%)	64 (40.76%)	52 (37.41%)	51 (46.79%)

Dispensations of antiepileptics	Overall 454	Pregnancies beginning in 2014 169 (37.22%)	Pregnancies beginning in 2015 156 (34.36%)	Pregnancies beginning in 2016 129 (28.41%)
Time window G: 3rd trimester				
Pregnancies lasting until 3rd trimester	399 (87.89%)	154 (91.12%)	137 (87.82%)	108 (83.72%)
Any valproate	47 (11.78%)	24 (15.58%)	14 (10.22%)	9 (8.33%)
Valproate only	41 (10.28%)	22 (14.29%)	13 (9.49%)	6 (5.56%)
Valproate and another AED	6 (1.50%)	2 (1.30%)	1 (0.73%)	3 (2.78%)
Other AED only	155 (38.85%)	56 (36.36%)	54 (39.42%)	45 (41.67%)
None	197 (49.37%)	74 (48.05%)	69 (50.36%)	54 (50.00%)

Table 2: Use of valproate and other antiepileptic drugs before and during pregnancy

* AED = Antiepileptic drug (other than valproate)

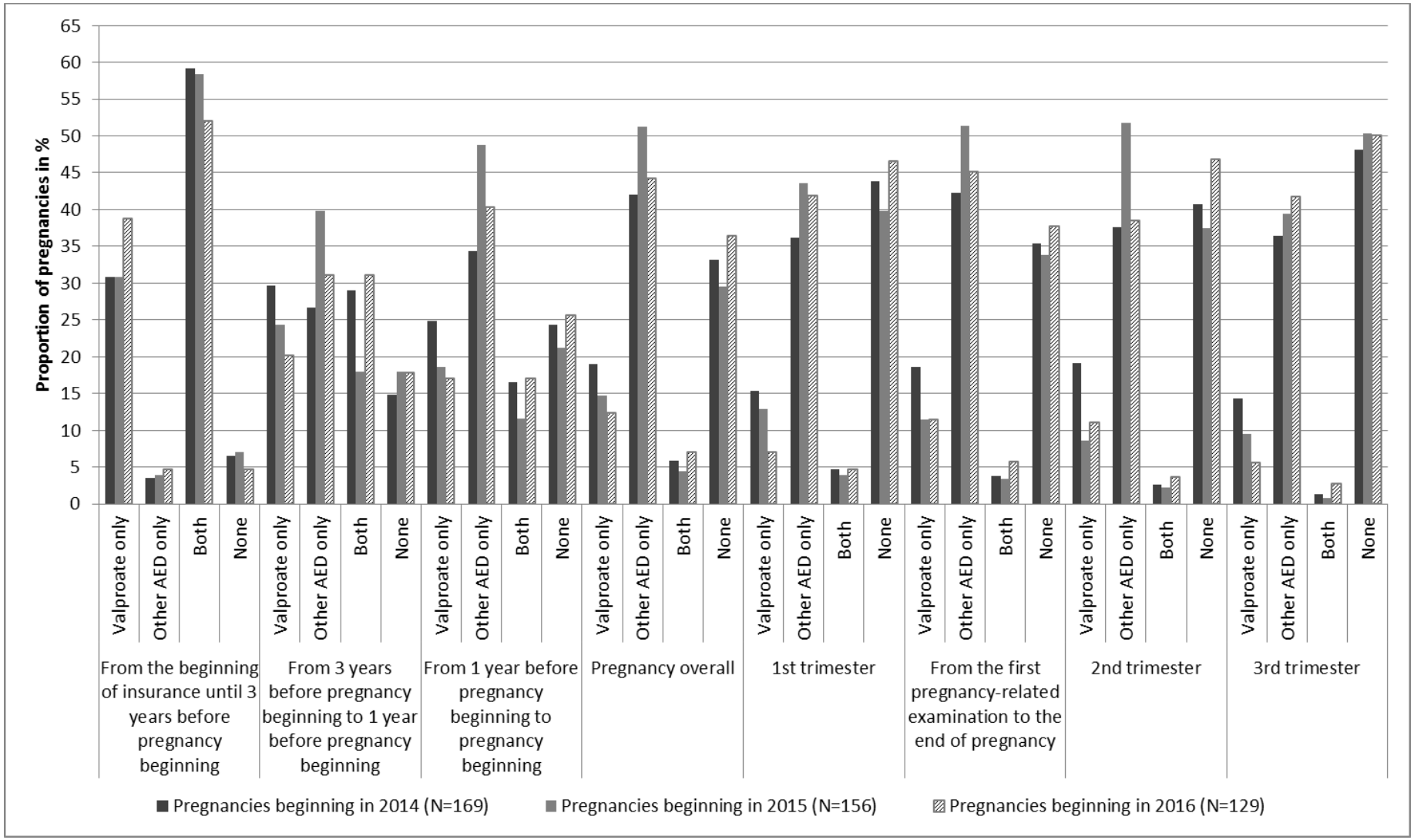

Figure 2: Use of valproate and other antiepileptic drugs (AEDs) before and during pregnancy, stratified by year of pregnancy beginning

Table 3 characterizes the 75 pregnancies exposed to valproate in the first trimester. In 58 of these pregnancies (77%), valproate was dispensed after the first pregnancy-related examination. The proportion of pregnancies ending in induced abortions increased from 3%, to 12% and 27% for pregnancies beginning in 2014, 2015, and 2016, respectively. In 36 of the 75 pregnancies (48%), there was no dispensation of another AED within the entire available observation time before pregnancy. This proportion decreased from 53% and 50% to 33% for pregnancies beginning in 2014, 2015, and 2016, respectively. Among the pregnancies with at least one other AED dispensed to the mother before the beginning of pregnancy (N=39), there was a record of only one other AED in 56% (N=22; mainly lamotrigine), of two other AEDs in 23% (N=9), and of more than two other AEDs in 21% (N=8). Overall, in 31 of these pregnancies, at least one dispensation of lamotrigine was observed and in 14, levetiracetam was dispensed before pregnancy beginning (Table 3).

	Overall N=75	Pregnancies beginning in 2014 N=34	Pregnancies beginning in 2015 N=26	Pregnancies beginning in 2016 N=15
Valproate dispensation after the first pregnancy-related examination	58 (77.33%)	28 (82.35%)	18 (69.23%)	12 (80.00%)
Type of pregnancy outcome				
Term birth	54 (72.00%)	26 (76.47%)	18 (69.23%)	10 (66.67%)
Preterm birth	7 (9.33%)	4 (11.76%)	2 (7.69%)	1 (6.67%)
Birth after due date	6 (8.00%)	3 (8.82%)	3 (11.54%)	0 (0.00%)
Stillbirth	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Induced abortion	8 (10.67%)	1 (2.94%)	3 (11.54%)	4 (26.67%)
Ectopic pregnancy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spontaneous abortion *	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Another AED ** before pregnancy	**39** (52.00%)	**16** (47.06%)	**13** (50.00%)	**10** (66.67%)
At least one dispensation of …				
Carbamazepine	5 (12.82%)	2 (12.50%)	2 (15.38%)	1 (10.00%)
Clobazam	3 (7.69%)	1 (6.25%)	0 (0.00%)	2 (20.00%)
Ethosuximide	2 (5.13%)	0 (0.00%)	1 (7.69%)	1 (10.00%)
Gabapentin	2 (5.13%)	1 (6.25%)	1 (7.69%)	0 (0.00%)
Lamotrigine	31 (79.49%)	13 (81.25%)	9 (69.23%)	9 (90.00%)
Levetiracetam	14 (35.90%)	5 (31.25%)	5 (38.46%)	4 (40.00%)
Midazolam	1 (2.56%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Oxcarbazepine	2 (5.13%)	0 (0.00%)	2 (15.38%)	0 (0.00%)
Perampanel	1 (2.56%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Pregabalin	1 (2.56%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Topiramate	8 (20.51%)	1 (6.25%)	3 (23.08%)	4 (40.00%)
Zonisamide	2 (5.13%)	0 (0.00%)	1 (7.69%)	1 (10.00%)

Number of different other AEDs used before pregnancy beginning				
Only one	22 (56.41%)	10 (62.50%)	8 (61.54%)	4 (40.00%)
Two different other AEDs	9 (23.08%)	5 (31.25%)	2 (15.38%)	2 (20.00%)
More than two different other AEDs	8 (20.51%)	1 (6.25%)	3 (23.08%)	4 (40.00%)
Pregnancies with another AED before pregnancy	39 (52.00%)	16 (47.06%)	13 (50.00%)	10 (66.67%)
Available observation period in months (time from start of observation in GePaRD until 3 years before pregnancy beginning				
Mean (Std)	78.72 (34.62)	78.24 (25.64)	82.74 (33.31)	74.25 (49.38)
Median (Q1–Q3)	92 (56–100)	91 (73–92)	100 (86–101)	103 (13–112)
Pregnancies with no other AED before pregnancy				
Available observation period in months (time from start of observation in GePaRD until 3 years before pregnancy beginning				
Mean (Std)	72.72 (35.89)	75.01 (25.74)	66.73 (44.65)	80.03 (47.58)
Median (Q1–Q3)	88 (46–98)	87 (56–92)	97 (19–103)	101 (59–116)

Table 3: Characteristics of pregnancies with a valproate dispensation during the first trimester

* As we focused on pregnancies with a clear outcome (defined by diagnosis or procedure codes), pregnancies ending in spontaneous abortions are underrepresented here as they may end without requiring medical care (i.e. without recording of procedure or diagnosis codes).

** AED = Antiepileptic drug (other than valproate)

4. Discussion

In our study, we identified 454 pregnancies in women with epilepsy and at least one dispensation of valproate before or during pregnancy among 2,068 pregnancies overall.

In nearly 80% of these 454 pregnancies, valproate was only used well before pregnancy. We observed changes between 2014 and 2016 which may be related to the risk minimization measures taken in 2014, such as a decreasing proportion of valproate-exposed pregnancies, also in the first trimester, and a decreasing proportion of valproate-exposed pregnancies without use of another AED during the observation period before pregnancy. In absolute terms, however, even though there was a downward trend, we still found a considerable number of pregnancies with a dispensation of valproate during the first trimester (N=75 overall, 2014: N=34, 2015: N=26, 2016: N=15).

A key element of the PRAC recommendations from 2014 is that valproate should not be used to treat epilepsy in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. In other words, it is recommended that other treatments are tested before valproate is used in these women. Still, our study showed that even in 2016, one third of pregnant women with epilepsy treated with valproate in the first trimester, were not treated with another AED within the entire observation period before pregnancy beginning. Of note, our estimate of the proportion not using other AEDs before pregnancy may even be an underestimate as we did not distinguish whether other AEDs were used before valproate or in combination with valproate. Of course, we cannot rule out that other treatments were tested before the start of the (on average) ten-year pre-observation period. However, we hypothesize that several physicians may have started treatment with valproate as first-line treatment before the PRAC recommendations were issued and did not re-consider the treatment decision in light of the new recommendations. Primary data studies among prescribing physicians would be needed to test this hypothesis as an important step towards the development of strategies to further reduce valproate exposure during pregnancy but avoiding social desirability bias in such studies is challenging (Toussi et al., 2021a). Such studies would also be helpful to understand potential reasons for

the increasing proportion of pregnancies with valproate exposure during the first trimester ending in an induced abortion (2014: 3%; 2015: 12%; 2016: 27%). A possible interpretation might be that this is also indicative of an increasing awareness of valproate's fetal hazard.

Overall, our findings are in line with the results of other studies. We previously conducted an analysis on the use of valproate in girls and women of childbearing age, which was not restricted to epilepsy patients. In that analysis, we observed an overall declining trend in valproate dispensations since 2004 and particularly since 2014. This trend was most pronounced in women between 21 and 35 years of age and in girls and women with epilepsy (Wentzell et al., 2018a).

Despite these positive trends, there are studies supporting our impression that the use of alternative drugs before valproate initiation is still suboptimal in Germany. A study assessing the proportion of women with newly diagnosed epilepsy using valproate as second-line rather than first-line therapy in various European countries–-before and after implementation of risk minimization measures–-did not observe a change in Germany, while the proportion increased in Sweden, the UK, and Spain (Toussi et al., 2021b). The same study also investigated changes in the incidence of valproate-exposed pregnancies, but for this part of the analysis, no data from Germany were available. In Sweden and France, there was a decrease in the incidence of valproate-exposed pregnancies which supports our findings, but the study designs are not fully comparable. For example, the Swedish data only included pregnancies of at least 23 weeks gestational age, so valproate-exposed pregnancies ending in induced abortions were likely often not captured.

Our study has specific strengths and limitations. We used a claims database covering 20% of the German population which has been shown to be representative of all persons with statutory health insurance coverage in Germany regarding drug prescriptions (Fassmer and Schink, 2014) and which offers a longer follow-up than most other claims databases in Germany. Given the nature of claims data, our analysis was not affected by recall or non-responder bias. GePaRD contains information on all reimbursable outpatient dispensations

and on all in- and outpatient diagnoses coded in the general and the specialized setting. Our results thus reflect the treatment situation in the real-world setting. Also, the information available to precisely estimate the beginning of pregnancy (Schink et al., 2020) and to determine and classify pregnancy outcomes (Wentzell et al., 2018b) is a strength. In contrast to many other studies, the latter also allowed us to take into account pregnancies ending in an induced abortion. Similar to other claims databases, however, pregnancies ending in a spontaneous abortion are underrepresented in our study. For the identification of spontaneous abortions we used a conservative approach focusing on pregnancies with a clear code for spontaneous abortion. As a consequence, our approach misses spontaneous abortions that did not require medical care. Unlike studies based on medical records or primary data, however, we lacked information on the severity of epilepsy, the prescribed dose, and the physicians' risk-benefit assessment. We could thus not assess to which extent the valproate-exposed pregnancies beginning in 2016 were medically justified, nor could we assess whether the physicians at least prescribed the lowest dosage possible, but one has to keep in mind that there is no safe dosage for the unborn child (Tomson et al., 2015). In the interpretation of our data, it should also be kept in mind that we only estimated exposure to valproate based on dispensations but could not directly determine or measure exposure. The uncertainty of whether or not a drug has actually been taken is inherent to almost all pharmacoepidemiological studies but varies according to the drug under study. In the case of valproate, we consider it unlikely that a woman aware of her pregnancy fills a prescription in early pregnancy in order to store it and take it after the end of pregnancy, so this scenario might only be relevant for women not aware of the pregnancy at the time of filling the prescription. In case this resulted in a certain proportion of pregnancies misclassified as exposed or non-exposed during the first trimester in our study, we do not see any reasons to assume that this potential misclassification was differential regarding calendar years, so we think the trends we observed in our study do not depend on this potential misclassification. Furthermore, a dispensation of valproate in the first trimester means that a physician has prescribed valproate to the woman immediately before or in an early phase of pregnancy,

which we think is also an important message irrespective of whether or not the woman has taken the drug. Dispensations of other AEDs during the defined time windows may also reflect combination therapy with valproate as we did not analyze the order of dispensations.

5. Conclusion

In our study including pregnancies among women with epilepsy and a valproate dispensation before or during pregnancy, valproate was mostly dispensed only well before pregnancy beginning. The proportion exposed to valproate during the first trimester declined between 2014 and 2016, but the low proportion treated with alternative AED before valproate treatment suggests there is still room for improvement. The use of valproate before and during pregnancy thus merits further monitoring and evaluation, also regarding the impact of further risk minimization measures recommended by the PRAC in 2018 (European Medicines Agency, 2014, 2018). Also, the fact that we observed a remarkable increase in the proportion of valproate-exposed pregnancies ending in an induced abortion requires further investigation.

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Data availability

In accordance with German data protection regulations, access to the data of the German Pharmacoepidemiological Research Database may only be given to third parties within the realm of collaborations with BIPS and after signing an agreement for guest researchers. Furthermore, as we are not the owners of the data we are not legally entitled to grant access to the data or to store data elsewhere, e.g., in a repository. This also relates for any kind of analysis datasets extracted from GePaRD.

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Competing interest

Nadine Wentzell and Ulrike Haug are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies (PASS) requested by health authorities. The design and conduct of these studies as well as the interpretation and publication are not influenced by the pharmaceutical industry. The study presented was not funded by the pharmaceutical industry.