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Comparing the General Practice Research Database and the UK Epilepsy and Pregnancy Register as Tools for Postmarketing Teratogen Surveillance

Anticonvulsants and the Risk of Major Congenital Malformations

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Abstract

Background: Use of pregnancy registries is a common method of postmarketing surveillance of pregnancy outcomes to identify potential teratogens. However, with the increase in electronic capture of healthcare data for administrative, audit and research purposes, data generated during routine clinical practice might be used to address questions similar to those explored using pregnancy registries.

Objectives: To establish how data from the UK General Practice Research Database (GPRD) compares with data from the UK Epilepsy and Pregnancy Register and to assess how it can contribute to postmarketing surveillance of pregnancy outcomes.

Methods: Pregnancy outcomes were identified from the GPRD for women aged 14–49 years with a diagnosis of epilepsy and supporting evidence. Outcomes with a major congenital malformation (MCM) were identified and the relative risks (RRs) of an MCM following a range of first-trimester antiepileptic drug (AED) exposures were calculated and compared with those reported by the UK Epilepsy and Pregnancy Register. In addition, we also evaluated whether the known association between valproate and spina bifida could be identified using data from the GPRD. The study period ran from 1 January 1990 until 31 December 2006.

Results: A total of 1766 live mother-baby pairs were identified, as well as 551 pregnancy terminations, 13 stillbirths and 1 neonatal death. Including those that resulted in a termination, there were 62 unique pregnancy outcomes with an MCM. An increased risk of spina bifida was identified using the GPRD

following first-trimester monotherapy exposure to valproate when compared with those with no AED exposure (RR 8.02; 95% CI 1.5, 43.5). More generally, comparing the GPRD with the UK register, the GPRD ascertained a lower number of first-trimester AED exposures: monotherapy 711 versus 2468; polytherapy 156 versus 718. We reproduced the UK register results of an increased MCM risk following first-trimester polytherapy AED exposure compared with no AED exposure (RR 2.89; 95% CI 1.43, 5.84). Using the GPRD, we identified similar point estimates to the UK register following monotherapy and polytherapy exposures (4.1% vs 3.7% and 7.1% vs 6.0%, respectively) but we were unable to reproduce the level of statistical significance. For individual AEDs, the MCM rate following valproate exposure was 4.9% (11/225) in the GPRD compared with 6.2% (44/715) in the UK register.
Conclusions: The GPRD has potential for the identification of malformations and of a teratogenic association. For epilepsy, the GPRD does, however, identify fewer exposed pregnancies than a pregnancy registry. Therefore, in many circumstances pregnancy registries are likely to remain preferable as a method of surveillance. The GPRD may be better suited to monitoring medicines used in the treatment of more prevalent conditions, such as depression, or for monitoring medicines that have been on the market for a long time and for which no registry has been set up.

Background

Prescription medications are commonly used by women of childbearing age.[1,2] With an estimated 30–50% of pregnancies being unplanned[3,4] and some medical conditions (e.g. epilepsy and depression) making it inadvisable to stop treatment, there is the potential for women to be exposed to medications during the first trimester of pregnancy, which is the critical time period for organ and tissue development. Usually pregnant women are excluded from clinical trial programmes,[5] and consequently the safety of medicine use during pregnancy and its impact on the risk of congenital malformations cannot be fully assessed until the drug has been marketed.

Pregnancy registries have been used commonly over the past 2 decades to monitor the safety of a new product on the market. Registries aim to detect any substantial increase in the risk of major congenital malformations (MCMs), which are generally defined as those that are life threatening, require major surgery or result in the child having a considerable disability.[6] Pregnancy registries require primary data collection, which can be time consuming and costly. Given the recent increase in electronic capture of healthcare data for administrative, audit and research purposes, in some circumstances data obtained during routine clinical practice might be able to address the same questions as those explored using pregnancy registries.

The UK General Practice Research Database (GPRD) has been identified as a potential data source for the postmarketing surveillance of drug exposure during pregnancy.[7] Methods have been developed to identify pregnancies on the database[8-10] and to link the mothers' medical records with those of the offspring.[11] Congenital malformations remain the primary outcome of interest following drug exposure during pregnancy and studies have begun to verify the GPRD (Read/OXMIS) coding system with respect to the identification of some specific defect types (cardiac defects[12] and neural tube defects[13]).

This study aimed to examine further the potential of the GPRD to serve as a pregnancy registry. Given the presence of a number of pregnancy

registries monitoring antiepileptic drug (AED) use, this study aimed to replicate their findings concerning the risk of all MCMs by AED therapy type, and focused the comparison on those reported by the UK Epilepsy and Pregnancy Register.[14] The UK Epilepsy and Pregnancy Register and the GPRD capture similar geographic populations and in both the information on outcome of pregnancy is primarily from the general practitioner (GP), which facilitates a comparison of results. This study also assessed the utility of the GPRD to identify a known teratogenic association, namely the association between first-trimester exposure to valproate and the risk of spina bifida.[15,16] Replication of this known teratogenic association has also formed part of a validation study by the European network of population-based registers for the epidemiological surveillance of congenital anomalies (EUROCAT) to assess the validity of using EUROCAT data to detect AED-associated risks of specific malformations.[17]

Methods

Data Sources

The GPRD is the world's largest computerized database of anonymized, longitudinal medical records from primary care.[18] The GPRD contains over 55 million person-years of data and currently captures approximately 4 million active patients (approximately 7% of the UK population) registered with approximately 500 practices within the UK.[19] Virtually all prescriptions, non-drug interventions and referrals issued by GPs are recorded in the database, as are medical diagnoses, including pregnancy.

The UK Epilepsy and Pregnancy Register is a prospective, observational, registration and follow-up study.[14] Women can either enrol directly into the UK register themselves or they can be enrolled by their healthcare professional (GP, epilepsy specialist, neurologist, etc.). Information on AED exposure and demographic variables are collected from the referring source before the pregnancy outcome is known. Information on pregnancy outcome and the presence of an MCM is collected approximately 3 months after the estimated date of delivery via a GP questionnaire. Pregnancies can be reported to the UK register retrospectively, after the pregnancy outcome is known, but these are excluded from the standard prevalence estimates to avoid selection bias towards more severe outcomes.

General Practice Research Database Maternal Study Population

The GPRD study followed a retrospective cohort design, and women were eligible for inclusion if they were, or had been, permanently registered at a GP practice considered by the GPRD division at the Medicines and Healthcare products Regulatory Agency (MHRA) to be contributing data up to standard for the purposes of research. The number of eligible pregnancies and MCMs reported in this paper are a subgroup of those reported in an earlier publication by Charlton et al.[20] More stringent inclusion criteria for epilepsy have been used in the study presented here owing to the need to ensure that the GPRD study population was as comparable as possible to those enrolling in the UK Epilepsy and Pregnancy Register. Sensitivity analyses were carried out to assess the impact on risk estimates of using more stringent inclusion criteria.

In the current study, women were identified as having epilepsy if they had any of the following within their medical record:

- at least two epilepsy diagnosis codes;
- one epilepsy diagnosis code and at least one AED prescription;[1]
- at least two seizure codes (excluding febrile or neonatal seizures) and at least one AED prescription;
- one epilepsy code and at least two seizure codes (excluding febrile or neonatal seizures).

Of those identified with epilepsy, women with a record relating to a pregnancy outcome between

1 AEDs included acetazolamide, beclamide, carbamazepine, clobazam, clonazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital (phenobarbitone), phenytoin, pregabalin, tiagabine, topiramate, valproate and vigabatrin.

1 January 1990 and 31 December 2006 were identified.

Identifying Pregnancy Outcomes

For live- and stillbirths (≥24 weeks' gestation) the pregnancy outcome date was considered to be the date of the first record of a pregnancy outcome when no additional records were identified in the preceding 90 days. For terminations of pregnancy, the date of the termination was taken as the last recorded termination of pregnancy code, within a 6-week window, as earlier termination of pregnancy codes commonly related to requests and referrals for an elective termination rather than the termination itself. Pregnancy outcomes specifically stating that they were a spontaneous abortion or miscarriage were excluded as they are beyond the scope of a pregnancy registry because of the likelihood of inconsistent identification of defects. Women could contribute more than one pregnancy outcome to the study and each unique pregnancy outcome was considered separately.

Pregnancies were excluded from the cohort if the woman was not aged 14–49 years at the date of the pregnancy outcome and if she did not have any codes indicating a pregnancy (e.g. last menstrual period [LMP], pregnant, positive pregnancy test, antenatal care, etc.) in the 280 days before the pregnancy outcome date. Women were required to be continuously enrolled in the GPRD for the 4 months before the estimated LMP date and throughout the pregnancy to allow reliable assessment of AED exposure. Further pregnancies were excluded if the evidence of epilepsy was not recorded before the first medical record indicative of a pregnancy.

Linking Mother-Baby Pairs

The offspring of women meeting all inclusion criteria described above were identified where possible (based on having the same family and GP practice numbers, and the child's year and month of birth being equal to the mother's year and month of delivery). To enable comparison with the UK register, which collects outcome data approximately 3 months after the expected delivery date,[14] infants of mother-baby pairs were required to be registered on the GPRD at 3 months of age or to have been registered and died before 3 months of age.

Major Congenital Malformations (MCMs)

Live Births

Medical codes relating to any type of congenital malformation were identified using a list of search terms that was created based on the conditions listed in the 'congenital anomalies' chapter of the *International Classification of Diseases 9th Edition* (ICD-9 codes 740–759).[21] Children of women in the cohort who had ≥1 of these codes or relevant codes within their hierarchical vicinity were identified within the GPRD.

As pregnancy registries are primarily concerned with major malformations, the malformations identified were categorized as major or minor. To ensure consistency in terms of classification, malformations were categorized according to the classification used by EUROCAT. The same classification had been used by the UK Epilepsy and Pregnancy Register.[14] Minor defects and malformations associated with prematurity, when isolated, are excluded from EUROCAT reports. There is also a small number of malformations (e.g. hypospadias, hydronephrosis, talipes, syndactyly) that are only classified as major if certain criteria are met.[22,23] All congenital malformation codes identified within the cohort were reviewed independently by two of the authors (RC, JW).

Malformations identified via the computerized records were confirmed or refuted, for those still registered with the practice, by scrutinizing a photocopy of the child's anonymized full medical record, enabling access to all referral letters, letters from specialists, hospital discharge reports, etc. For children who had transferred out of the practice and for those where the GP did not return photocopied records, information recorded in the free-text fields of the patients' entire medical record was obtained and reviewed. Each time a GP records a medical code within the GPRD they have the opportunity to record any additional information in the free-text field. This may include a more detailed description of symptoms, test results or information relating to diagnostic

procedures and surgery. All information in the photocopied records and free text was anonymized by the MHRA before being returned to the investigators. The analyses in the remainder of this study include all confirmed malformations that were classified as major and all confirmed malformations where there was insufficient information to classify them as minor. For the purpose of this study, chromosomal defects, congenital malformations known to be of genetic origin and malformations where there was clear evidence that the malformation was not drug-induced (e.g. hydrocephalus that was secondary to an intraventricular haemorrhage) were excluded.

Terminations, Stillbirths and Neonatal Deaths

To identify terminations of pregnancy that followed an MCM diagnosis, the free-text comments recorded in the women's electronic medical record during the 2 months before and 4 months after the termination date were obtained. This was because these comments were likely, in some cases, to contain additional information relating to antenatal scans, diagnostic tests and malformation diagnoses. For terminations where the free text did contain information relating to an MCM, this was taken to be sufficient evidence and no further supporting evidence was required. For pregnancies ending in a stillbirth or a neonatal death, free text was obtained for the 2 months before and 6 months after the event. This extended time period was chosen to allow any post-mortem results to be reported back to the GP.

First-Trimester Exposure

To identify the first trimester (first 13 weeks following the LMP), the start date of a pregnancy (LMP) for a live birth was assumed to be 280 days before the pregnancy outcome date unless there was a record in the woman's medical file indicating that the delivery was pre- or post-mature, in which case the assumed LMP date was adjusted accordingly.

Prescriptions for AEDs, masked to outcome status, were identified and used to establish AED exposure status. Prescriptions were mapped based on the assumption that one prescription could not start until the previous one had finished unless it was being taken as polytherapy or there was clear evidence of drug switching. Where there was evidence of drug switching (i.e. where there were continuous prescriptions for a new drug treatment and no more prescriptions for the original drug), the first drug was deemed to have been discontinued on the date the second one was prescribed. Based on these assumptions, exposure status of study participants was determined for each AED on each day and women were subsequently classified as having been exposed in the first trimester to specific AEDs as well as whether the exposure was mono- or polytherapy.

Terminations of Pregnancy

For terminations of pregnancy, gestational age and first-trimester exposure to AEDs was ascertained, for MCM cases, by the manual independent review of the patient's electronic prescription records by two of the authors (RC, CdV), masked to the type of MCM and the pregnancy start and end dates.

Analyses

The prevalence of non-chromosomal MCMs meeting the inclusion criteria following a range of different AED exposures was calculated. The MCM rate was calculated as equation 1:

$$\frac{\text{The number of live births with an MCM} + \text{the number of pregnancy losses with an MCM}}{\text{The total number of live births} + \text{the number of pregnancy losses with an MCM}} \quad \text{(Eq. 1)}$$

Pregnancy losses (spontaneous abortions, elective terminations and stillbirths) without an MCM were excluded from the denominator. This approach is commonly taken by pregnancy registries because of the likelihood of inconsistent identification of defects across pregnancy losses.[14,24] Multiple births were included in the analyses but it was decided *a priori* that if there was a case of a multiple birth where both/all infants had the same MCM they would only be counted once in the numerator and once in the denominator. Relative risks (RRs) with 95% confidence

intervals (CIs) were calculated using STATA (version 9; StataCorp LP, College Station, TX, USA) to compare the risk of a pregnancy outcome with an MCM following mono- and polytherapy AED exposure with those who had no AED exposure during the first trimester. Comparisons of MCM risk were also made for the three most commonly used AEDs. For this, carbamazepine was selected as the baseline prevalence as it was the comparator chosen in the UK register analyses and it had the largest number of exposures. Comparisons with the UK Epilepsy and Pregnancy Register were made with the figures that they reported in their publication of January 2006.[14] The above analyses were also completed to investigate the association between first-trimester monotherapy exposure to valproate and spina bifida on the GPRD.

Results

Study Cohort

The GPRD study cohort is depicted in figures 1 and 2. The cohort consisted of 2019 live mother-baby pairs, 551 pregnancy terminations, 13 stillbirths and 1 neonatal death. Approximately 49% of the mother-baby pair cohort had been exposed to ≥1 AED during the first trimester of pregnancy. For mother-baby pairs who had at least 2 years of data before the start of pregnancy (n = 1497), there was evidence that 15.8% had discontinued AED use in the 2 years before becoming pregnant. Of those exposed to an AED during the first trimester, 83.2% were exposed to monotherapy and 16.8% to polytherapy. The three AEDs most frequently prescribed as monotherapy were carbamazepine, valproate and lamotrigine (table I).

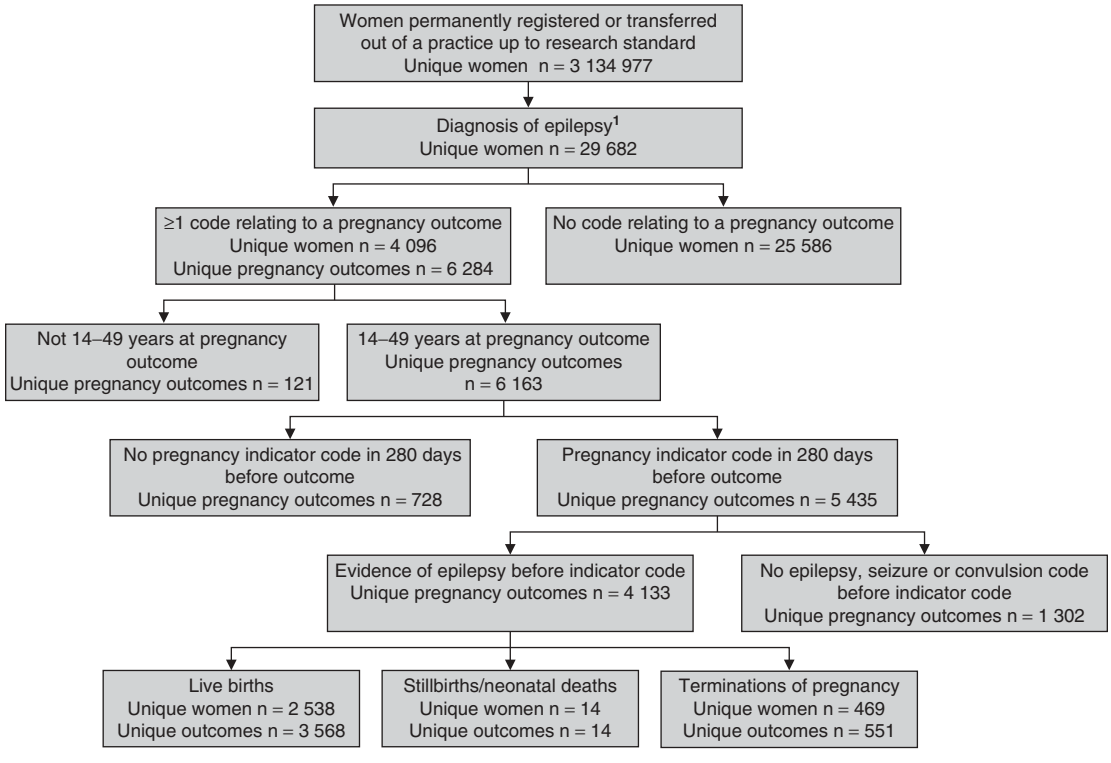

Fig. 1. Identifying eligible mother-baby pairs. **1** Women were identified as having epilepsy if they had any of the following within their medical record: (i) at least two epilepsy diagnosis codes; (ii) one epilepsy diagnosis code and at least one antiepileptic drug (AED) prescription; (iii) at least two seizure codes (excluding febrile or neonatal seizures) and at least one AED prescription; or (iv) one epilepsy code and at least two seizure codes (excluding febrile or neonatal seizures).

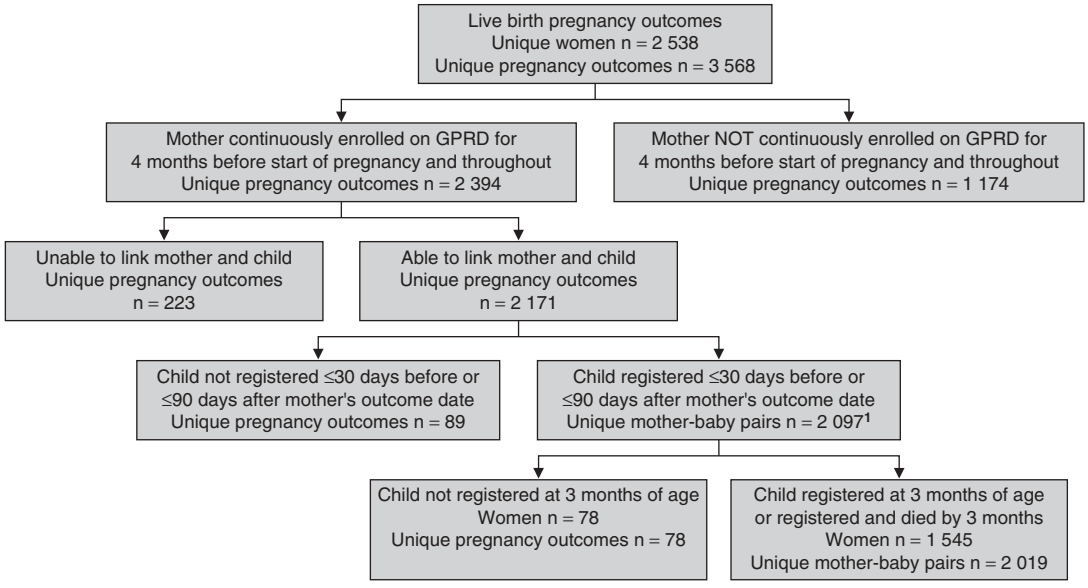

Fig. 2. Identifying eligible women and pregnancies. **1** Including twins and triplets. **GPRD** = General Practice Research Database.

MCMs

By Pregnancy Outcome

A total of 82 MCMs in 62 unique live-born individuals were identified and met the confirmation criteria. Review of the free text confirmed 14 pregnancies met the inclusion criteria and had been terminated following a prenatal MCM diagnosis (table II). No further MCMs were identified following review of the free text for either the stillbirths or neonatal deaths.

By Infant Follow-Up

Of the 82 confirmed MCMs, 53 (64.6%) had been recorded on the GPRD by 3 months of age and 71 (86.6%) by 1 year of age; a breakdown is shown in table III. Given that <65% of confirmed MCMs had been recorded during the first 3 months of life, it was decided to calculate the prevalence of MCMs at 1 year of age. The analysis cohort therefore included only those infants still present on the GPRD at age 1 year, those who had registered and died by 1 year of age and those pregnancy losses with a non-chromosomal MCM. Of the 2019 mother-baby pairs within our initial cohort, 1766 (87.5%) met these criteria and, including terminations, there were 62 unique pregnancy outcomes with an MCM. The characteristics of mother-baby pairs still present on the GPRD at 1 year of age were not found to differ substantially from those who were still present at 3 months of age (table I).

Prevalence of MCMs

Type of Antiepileptic Drug Therapy

Table IV shows the prevalence of MCMs diagnosed by 1 year of age following different types of first-trimester AED exposure. An increased risk of an MCM was observed on the GPRD following first-trimester polytherapy exposure when compared with women having no AED exposure. The point estimates (absolute risks) for each exposure category were similar for the GPRD and the UK register; however, on the GPRD, the increased risk following polytherapy compared with monotherapy did not reach statistical significance (RR 1.73; $p = 0.10$ compared with RR 1.63; $p = 0.01$, in the UK register).

Monotherapy

Table V shows the prevalence of MCMs for the three most commonly prescribed monotherapy exposures. The GPRD observed a higher carbamazepine MCM prevalence than was found in the UK register, which, surprisingly, found a lower prevalence of MCMs in pregnancies

Table I. Population characteristics for mother-baby pairs where offspring were registered on the General Practice Research Database

Characteristic	Live births registered at 3 months of age[a]	Live births registered at 1 year of age[b]
No. of mother-offspring pairs	2019	1766
No. of unique women	1545	1355
Average age at pregnancy outcome [years; mean (SD)]	30.0 (5.6)	30.1 (5.6)
Sex of offspring – male (%)	51.2	51.1
Average number of years infant was followed up/present on the database (SD)	5.4 (4.0)	6.1 (3.9)
First-trimester exposure [n (%)]	994 (49.2)	871 (49.3)
monotherapy	818	706
polytherapy	164	154
drug switching	12	11
Unexposed (n)	1025	895
First-trimester monotherapy (n)		
carbamazepine	355	310
valproate	248	221
lamotrigine	128	98
phenytoin	57	52
phenobarbitone	11	11
clonazepam	6	4
topiramate	5	4
gabapentin	4	2
ethosuximide	3	3
levetiracetam	1	1

a Or registered and died before reaching 3 months of age.

b Or registered and died before reaching 1 year of age.

exposed to carbamazepine than in unexposed pregnancies. As can be seen from table V, this had implications for the RR estimates of exposure when carbamazepine was used as the baseline prevalence. Bearing in mind the known issues with selection bias to pregnancy registers, we considered the possibility that for the pregnancy register, carbamazepine may have been an inappropriate reference group and it might have been more appropriate to compare all exposures with the unexposed population. Owing to the lower carbamazepine MCM prevalence, we therefore calculated the RR estimates both for the GPRD and the UK register, with the unexposed populations as the baseline prevalence (table V). As a result, risk estimates for carbamazepine and lamotrigine were in the opposite direction in the GPRD compared with the UK register, and the point estimate for valproate was higher on the GPRD than in the UK register, although, as in the register, it did not reach statistical significance (RR 2.00; 95% CI 0.99, 4.07; p = 0.05).

Valproate and Spina Bifida

The UK register did not report on the rate of spina bifida among monotherapy valproate-exposed pregnancies. It did, however, publish the rate of all neural tube defects following monotherapy valproate exposures, and this was estimated at 1.0% compared with 2.2% in the GPRD. Further analysis on the GPRD identified seven cases of spina bifida; one was a live birth and six were terminations of pregnancy. Of these, during the first trimester, four cases were exposed to valproate in monotherapy, one was exposed to other AEDs in polytherapy and two were unexposed to any AEDs. The prevalence of spina bifida in valproate monotherapy-exposed pregnancies (resulting in a live birth, stillbirth or termination of pregnancy) was

1.78% (95% CI 0.05, 3.50) compared with 0.22% (95% CI 0.00, 0.53) for pregnancies with no first-trimester AED exposure. The prevalence of spina bifida was significantly higher in the valproate-exposed group compared with those unexposed to AEDs (RR 8.02; 95% CI 1.5, 43.5).

Table II. No. of malformations identified meeting the major congenital malformation inclusion criteria

Malformation	No. of malformations – live births	No. of malformations – terminations
Neural tube defect		
Hydrocephalus	2	1
Spina bifida	1	6
Anencephaly	0	2
Cardiac		2[a]
Atrial septal defect	4	0
Ostium secundum atrial septal defect	2	0
Coarctation of aorta	1	0
Patent ductus arteriosus	1	0
Pulmonary stenosis	3	0
Pulmonary artery atresia	1	0
Tetralogy of Fallot	3	0
Ventricular septal defect	10	0
Transposition of great arteries	0	1
Facial cleft		
Cleft palate	3	0
Cleft lip and palate	2	0
Hypospadias/genitourinary tract		
Absence of kidney	1	0
Atrophy of kidney	1	0
Hydronephrosis	5	0
Hypospadias	11	0
Cystic kidney disease	1	0
Renal tract disorder	0	1
Gastrointestinal tract defects		
Hirschsprung's disease	1	0
Imperforate anus	2	0
Tracheo-oesophageal fistula	1	0
Other		
Congenital cataract	1	0
Fetal valproate syndrome	4	0
Hip dislocation/dysplasia	3	0
Limb reduction	4	0
Talipes equinovarus	4	0
Talipes unspecified	1	0
Polydactyly	3	0
Syndactyly	2	0
Multiple abnormalities	0	1
Reference to 'congenital anomaly'.[b] See also table III	4	0

a Unable to determine exact malformation type but given that they resulted in an induced pregnancy termination they have been assumed to be major.

b Review of photocopied medical records or free text found these to be club hand, club foot, syndactyly and a limb defect.

Discussion

In this study we were able to identify a known teratogenic association in the GPRD, suggesting there may be instances where the GPRD can be used for the evaluation of drug safety in pregnancy. Differences were found, however, when comparing overall MCM rates for AEDs on the GPRD with UK register data. Below we discuss some of the key findings along with strengths and limitations of using the GPRD as a tool for postmarketing teratogen surveillance.

Table III. The age by which malformations in live-born infants were recorded in the General Practice Research Database

Malformation	No. of major congenital malformations – live births	Recorded by 3 months	Recorded after 3 months and before 1 year	Recorded after 1 year
Neural tube defect				
Hydrocephalus	2	0	1	1
Spina bifida	1	1	0	0
Cardiac				
Atrial septal defect	4	3	0	1
Ostium secundum atrial septal defect	2	2	0	0
Coarctation of aorta	1	0	1	0
Patent ductus arteriosus	1	1	0	0
Pulmonary stenosis	3	2	0	1
Pulmonary artery atresia	1	1	0	0
Tetralogy of Fallot	3	3	0	0
Ventricular septal defect	10	6	4	0
Facial cleft				
Cleft palate	3	3	0	0
Cleft lip and palate	2	2	0	0
Hypospadias/genitourinary tract				
Absence of kidney	1	0	0	1
Atrophy of kidney	1	0	1	0
Hydronephrosis	5	5	0	0
Hypospadias	11	8	1	2
Cystic kidney disease	1	0	0	1
Gastrointestinal tract defects				
Hirschsprung's disease	1	0	0	1
Imperforate anus	2	2	0	0
Tracheo-oesophageal fistula	1	1	0	0
Other				
Congenital cataract	1	0	1	0
Fetal valproate syndrome	4	1	1	2
Hip dislocation/dysplasia	3	3	0	0
Limb reduction	4	1	3	0
Talipes equinovarus	4	2	1	1
Talipes unspecified	1	1	0	0
Polydactyly	3	1	2	0
Syndactyly	2	1	1	0
Reference to 'congenital anomaly'.[a] See also table II	4	3	1	0

a Review of photocopied medical records or free text found these to be club hand, club foot, syndactyly and a limb defect.

Table IV. Prevalence of major congenital malformations (MCMs) following different types of first-trimester antiepileptic drug exposure

Exposure type	General Practice Research Database			UK Epilepsy and Pregnancy Register		
	no. of exposures	unique offspring with MCMs[a] [n (%)]	relative risk (95% CI)	no. of exposures	unique offspring with MCMs[b] [n (%)]	unadjusted odds ratio (95% CI)
Unexposed	902	22 (2.4)	Reference	227	8 (3.5)	Reference
Monotherapy	711	29 (4.1)	1.67 (0.97, 2.89); p = 0.06	2468	91 (3.7)	1.05 (0.50, 2.19); p = 0.90
Polytherapy	156	11 (7.1)	2.89 (1.43, 5.84); p = 0.005	718	43 (6.0)	1.71 (0.79, 3.69); p = 0.17

a Recorded in child's electronic medical record by 1 year of age.

b Outcome data collected approximately 3 months after expected delivery date.

Sample Size

The relatively small number of AED exposures on the GPRD was a limitation that resulted in wide CIs around many of the MCM prevalence estimates. It was known from the outset that the number of first-trimester AED exposures on the GPRD was likely to be small, given the low prevalence of epilepsy and the fact that the database captures only about 7% of the UK population. The GPRD is therefore likely to be better suited to more prevalent conditions and the identification of exposures that result in a substantial increase in risk. However, the AED drug class was selected for this study in view of the large amount of comparator information already available from AED pregnancy registries and, more specifically, the presence of the UK register.

Cohort Identification and Disease Status

Not all women with epilepsy will be recorded explicitly as such. Instead, some women with epilepsy will only have records of seizures or convulsions on the GPRD. This results from the possibility that an epilepsy diagnosis may have been made in a hospital setting and not actually recorded within the woman's electronic medical record. GPs are not required to, and do not, record the indication for prescribing with repeat prescriptions. For the purposes of this study, we

Table V. Prevalence of major congenital malformations (MCMs) following different monotherapy first-trimester antiepileptic drug exposures with carbamazepine as the reference category and with unexposed as the reference category

Monotherapy exposure	General Practice Research Database			UK Epilepsy and Pregnancy Register		
	no. of exposures (%)	unique offspring with MCMs[a] [n (%)]	relative risk (95% CI)	no. of exposures (%)	unique offspring with MCMs[b] [n (%)]	unadjusted odds ratio (95% CI)
Carbamazepine	**311 (49.1)**	**13 (4.2)**	**Reference**	**900 (39.8)**	**20 (2.2)**	**Reference**
Lamotrigine	98 (15.5)	3 (3.1)	0.73 (0.21, 2.52); p = 0.77	647 (28.6)	21 (3.2)	1.44 (0.77, 2.67); p = 0.25
Valproate	225 (35.5)	11 (4.9)	1.17 (0.53, 2.56); p = 0.70	715 (31.6)	44 (6.2)	2.78 (1.62, 4.76); p < 0.001
Unexposed	**902**	**22 (2.4)**	**Reference**	**227**	**8 (3.5)**	**Reference[c]**
Carbamazepine	311	13 (4.2)	1.71 (0.87, 3.36); p = 0.11	900	20 (2.2)	0.63 (0.28, 1.41); p = 0.26
Lamotrigine	98	3 (3.1)	1.26 (0.38, 4.17); p = 0.73	647	21 (3.2)	0.92 (0.41, 2.05); p = 0.84
Valproate	225	11 (4.9)	2.00 (0.99, 4.07); p = 0.05	715	44 (6.2)	1.75 (0.83, 3.65); p = 0.13

a Recorded in child's electronic medical record by 1 year of age.

b Outcome data collected approximately 3 months after expected delivery date.

c Calculated by the authors and not reported by the UK Epilepsy and Pregnancy Register.

wanted to ensure we captured all epilepsy cases but excluded women without epilepsy and women who received AEDs for indications other than epilepsy (e.g. trigeminal neuralgia). Therefore, for women to be taken as having epilepsy, they were required to have either ≥2 epilepsy diagnosis codes (without the need for supporting evidence) or a single epilepsy code or ≥2 seizure or convulsion codes (plus additional supporting evidence within their medical record).

It is possible that these inclusion criteria may still have resulted in the inclusion of a small number of women in the GPRD cohort who did not actually have epilepsy and therefore would not have been eligible for inclusion in the UK Epilepsy and Pregnancy Register. These women are likely to fall into the 'AED unexposed' category and therefore this may, in part, explain the different proportions in the exposure categories between the two data sources. An alternative or additional explanation for some of the difference in the proportion of exposed versus unexposed pregnancies could be that women with epilepsy who are not taking AEDs, or who have discontinued using AEDs in preparation for their pregnancy, are less likely to choose to enrol and be captured in a pregnancy register. Within the GPRD it was found that 15.8% of those who had ever received an AED prescription, had discontinued AED therapy during the 2 years before becoming pregnant. A number of sensitivity analyses were carried out to assess the effect of different epilepsy inclusion criteria within the GPRD cohort but these were found not to materially alter the risk estimates.

Outcome Assessment

It was possible to identify and verify a wide range of congenital malformations in the GPRD. The ability to identify pregnancies in the GPRD with an MCM that resulted in a termination of pregnancy was critical in the identification of the teratogenic association between first-trimester exposure to valproate and an increased risk of a pregnancy outcome with spina bifida. The severe nature of spina bifida and the fact it is often diagnosed prenatally meant that without the terminated pregnancies and supporting free text this association would not have been identified. The inclusion of pregnancy terminations is important for the identification of any severe or life-threatening malformation diagnosed prenatally. Registries have the benefit of a review of MCM cases by an experienced teratologist, but a potential strength of using the GPRD is the ability to capture more completely than registries those pregnancies that do not result in a live birth.

Exposure Assessment

The GPRD has the advantage that prescription data is recorded prospectively and independently of the pregnancy outcome. The level of certainty with which it is possible to determine timing of exposure on the GPRD is limited by the level of precision with which it is possible to estimate the exact LMP date and subsequently the first trimester. The GPRD is therefore more appropriate for medicines used to treat chronic, rather than episodic, conditions where exposure is likely to be continuous. Exposure assessment on the GPRD is, however, purely based on the issue of prescriptions and there is no way of establishing if and when the medicine has been taken. Exposure information on the GPRD is also limited to medicines available for use in the UK that require a prescription; it does not capture over-the-counter medicines.

Both the GPRD and the UK register reported carbamazepine, valproate and lamotrigine as the most commonly used AED monotherapies during the first trimester of pregnancy. The UK register observed a higher proportional representation of lamotrigine exposures than the GPRD. Given that lamotrigine was not launched in the UK until 1992 and would have taken time to penetrate the market, this difference could be the result of the different time periods of data collection, with the GPRD study including pregnancy outcomes from 1990 and the UK register starting in December 1996. Further analyses restricting the GPRD data to the same time period as the UK register, however, still found the register to have a higher proportion of lamotrigine use. This difference could therefore be an ex-

ample of selection bias within the UK register, with women and healthcare professionals being more likely to report lamotrigine exposures as it is a relatively new drug on the market.

Differences in Risk Assessment

The UK register reported comparative risk analyses between AED monotherapy-exposure groups using carbamazepine as the reference exposure category. However, the prevalence of MCMs associated with carbamazepine use in the UK register was lower than that observed for the unexposed group and lower than corresponding risk estimates in the GPRD. This, in great part, underlies the differences in comparative results between the UK Register and the GPRD, and illustrates the problem of choosing an appropriate comparator group for these studies of drug safety in pregnancy. Indeed, it highlights the issue of whether a comparator group should be chosen for pregnancy registry studies monitoring for a signal of major teratogenicity where the effects, if present, are likely to be so great they usually will need no comparison groups or consideration of confounding variables.[25,26]

Irrespective of any comparator group, both data sources reported a lower prevalence of MCMs following first-trimester exposure to valproate than has been reported in a number of studies outside the UK.[27-31] The reason for this is unclear and further investigation would be required to determine whether it is related to differences in recording, differences in the use of valproate in the UK, differences in the use of concomitant folic acid, or other factors.

Follow-Up

Outcome information is often requested by pregnancy registries close to the expected date of delivery (often within the first 3 months of life). Within the GPRD, fewer than 65% of MCMs were recorded by 3 months of age, which may demonstrate a need to follow infants for longer in the GPRD than in registries in order to obtain representative outcome data. Loss to follow-up is an issue with all prospective observational studies. Although in the UK register loss to follow-up was only 8.1%, in some registries it can be as high as 27%.[24] Within the GPRD there is the potential for infant follow-up to extend beyond the period immediately after birth, with the mean length of infant follow-up within this study cohort being 6.1 years (SD 3.9).

Confounders

In order to encourage enrolment, and given that pregnancy registries are designed to identify major teratogens, the amount of information requested in terms of potential confounding factors is often limited. Although not evaluated in this study, information is available within the GPRD on potential confounders such as age, smoking status, alcohol status, body mass index, co-morbidity and other prescription medications; however, further work is required to look at the completeness, accuracy and reliability of these variables.

Comparison of Data Sources

The UK Epilepsy and Pregnancy Register was set up with an entirely different aim than that of the GPRD. Consequently, the methods of data collection used by computerized medical record databases and pregnancy registries do differ and these differences have implications for the type of information available and the extent to which direct comparisons can be made. Pregnancy registries often rely on voluntary enrolment and therefore may not always capture a truly representative sample of those either with the disease of interest or using the medication of interest. Whilst such selection bias is an issue, the indication for prescribing is usually unambiguous and typically pregnancy registries have detailed information regarding birth defects identified at birth. In contrast, whilst in the GPRD selection bias is negligible or absent, the indication for prescribing is implicit rather than explicit because it is influenced from the presence of diagnostic and symptom records and the absence of alternative explanations. In addition, to obtain detailed information regarding malformations identified, exploring the electronic records does not suffice. Instead, free text or hospital letters need to be consulted.[20]

Conclusions

Postmarketing surveillance of pregnancy outcomes to identify potential teratogens is essential because of the lack of evidence available when a new product is first marketed regarding its safety when used during pregnancy. The GPRD has proven useful in the identification of malformations and of a major teratogenic association. The GPRD does, however, identify fewer exposed pregnancies than a pregnancy registry, especially for less prevalent conditions; therefore, in many circumstances pregnancy registries are likely to remain the optimum method of surveillance. Given limitations in sample size, the GPRD is going to be most capable of identifying major risk factors rather than those that result in a relatively small increase in risk. The GPRD may also be better suited to monitoring medicines used to treat more prevalent conditions, such as depression, or medicines that have been on the market for a long time for which no registry has been set up.

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