Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry

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Summary

Background **Prenatal exposure to antiepileptic drugs is associated with a greater risk of major congenital malformations, but there is inadequate information on the comparative teratogenicity of individual antiepileptic drugs and the association with dose. We aimed to establish the risks of major congenital malformations after monotherapy exposure to four major antiepileptic drugs at different doses.**

Methods **The EURAP epilepsy and pregnancy registry is an observational cohort study representing a collaboration of physicians from 42 countries. We prospectively monitored pregnancies exposed to monotherapy with different doses of four common drugs: carbamazepine, lamotrigine, valproic acid, or phenobarbital. Our primary endpoint was the rate of major congenital malformations detected up to 12 months after birth. We assessed pregnancy outcomes according to dose at the time of conception irrespective of subsequent dose changes.**

Findings **After excluding pregnancies that ended in spontaneous abortions or chromosomal or genetic abnormalities, those in which the women had treatment changes in the first trimester, and those involving other diseases or treatments that could affect fetal outcome, we assessed rates of major congenital malformations in 1402 pregnancies exposed to carbamazepine, 1280 on lamotrigine, 1010 on valproic acid, and 217 on phenobarbital. An increase in malformation rates with increasing dose at the time of conception was recorded for all drugs. Multivariable analysis including ten covariates in addition to treatment with antiepileptic drugs showed that the risk of malformations was greater with a parental history of major congenital malformations (odds ratio 4·4, 95% CI 2·06–9·23). We noted the lowest rates of malformation with less than 300 mg per day lamotrigine (2·0% [17 events], 95% CI 1·19–3·24) and less than 400 mg per day carbamazepine (3·4% [5 events], 95% CI 1·11–7·71). Compared with lamotrigine monotherapy at doses less than 300 mg per day, risks of malformation were significantly higher with valproic acid and phenobarbital at all investigated doses, and with carbamazepine at doses greater than 400 mg per day.**

Interpretation **The risk of major congenital malformations is influenced not only by type of antiepileptic drug, but also by dose and other variables, which should be taken into account in the management of epilepsy in women of childbearing potential.**

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Introduction

Between 0·3% and 0·7% of all pregnancies are in women with epilepsy.[1] Most of these women need to continue use of antiepileptic drugs during pregnancy because uncontrolled seizures might harm the mother and fetus. This continuation is of concern to physicians, because antiepileptic drugs as a class might cause major congenital malformations[2,3] and adverse effects on cognitive development after prenatal exposure.[4]

In the past decade, the teratogenicity of antiepileptic drugs has been compared through large prospective registries.[5] A recent systematic review[3] concluded that "it is highly probable that intrauterine first-trimester exposure to valproic acid has a higher risk of major congenital malformations compared with carbamazepine, and possibly compared with phenytoin or lamotrigine". Subsequent case-control studies have confirmed that, compared with other antiepileptic drugs, treatment with valproic acid has a greater risk of spina bifida, atrial septal defects, cleft palate, and craniosynostosis,[6] and carbamazepine a greater risk of spina bifida.[7] However, the associations reported in these observational studies could be influenced by confounders such as type or severity of epilepsy, socioeconomic status, and family history of birth defects. The findings of several studies also suggest an association between dose and risk of malformations, at least for valproic acid.[8–13] However, none of the previous studies had sufficient statistical power to compare risks associated with different doses of the most common drugs or to assess the influence of potential confounders. In this study, we aimed to assess data collected prospectively over 11 years by the International Registry of Antiepileptic Drugs and Pregnancy (EURAP)[14] to establish the risks of major congenital malformations after monotherapy exposure to four major antiepileptic drugs at different doses.

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Methods

Participants

The EURAP registry was established in 1999 and at present involves 42 countries with more than 700 collaborators. The eligibility criteria for prospective assessment in EURAP were treatment with antiepileptic drugs for any indication at conception, enrolment within gestation week 16, and enrolment before fetal outcome is known. Information is obtained in early pregnancy on demographics, type of epilepsy, seizure frequency, comorbidities, family history of major congenital malformations, drug treatment (including folate intake), smoking, alcohol, and other potential risk factors. Follow-up data are collected once each trimester, at birth, and at 12 months after birth. Data are obtained by the physicians responsible for the women's care and transferred online to a EURAP national coordinator for review before transmission to the central database in Milan, Italy. Missing data are recovered and inconsistencies are corrected through online interaction.

We excluded pregnancies that were ascertained retrospectively, pregnant women without epilepsy, women lost to follow-up or for whom physicians did not submit data within preset deadlines, and those for whom follow-up was not yet completed or had updates or corrections pending. Pregnancies in which antiepileptic drugs were switched or withdrawn during the first trimester, women who were exposed to antiepileptic drug polytherapy or other potentially teratogenic drugs, and women who had comorbidities that could increase the risk of major congenital malformations (eg, diabetes, toxoplasmosis, and HIV) were also excluded. Other reasons for exclusion were spontaneous abortions, abortions induced for causes other than fetal abnormalities, pregnancies in which fetal outcome could not be established, and pregnancies that resulted in children with genetic or chromosomal abnormalities. Informed consent was obtained from all women, in writing or orally depending on the requirements in the different countries. The protocol was approved by ethics committees of participating centres.

Procedures

Our primary objective was to assess the prevalence of major congenital malformations 12 months after birth in offspring exposed in utero to four main antiepileptic monotherapies (carbamazepine, lamotrigine, valproic acid, or phenobarbital), split into dose-range intervals. We classified pregnancies on the basis of the type of drug and the dose at conception. The registry did not collect information on the brand or formulation of the drugs. In accordance with the intention-to-treat principle, we assessed pregnancies in which dose was changed during pregnancy on the basis of dose at conception, irrespective of subsequent dose changes. We classified seizures as either generalised tonic-clonic (GTC) or other types, and epilepsy syndrome in accordance with the International League Against Epilepsy criteria.[15] Parental history of major congenital malformations excludes cases of cerebral malformations causally associated with the maternal epilepsy. We did not include history of major congenital malformations in siblings because of their possible prenatal exposure to similar or other antiepileptic drugs. Folate supplementation was arbitrarily deemed appropriate if started at least 3 months before conception and maintained throughout the first trimester irrespective of dose. Parental educational level was categorised into low (up to 9 years of education) or medium or high (more than 9 years of education).

Abnormalities in the offspring were recorded descriptively by the reporting physician and classified by an ad hoc independent classification committee that was masked to type of exposure. Physicians were instructed to report anything they thought possibly abnormal in the offspring, rather than restricting descriptions to a fixed checklist. The physicians' assessment was based on interviews with the mothers and, for liveborn offspring, data from the infants' medical records, supplemented by direct examination of the infants whenever needed and possible. These reports were reviewed by the classification committee, which could request additional information from the reporting physician when needed. We defined major congenital malformations as structural abnormalities with surgical, medical, functional, or cosmetic importance, and classified them in accordance with European Surveillance of Congenital Anomalies criteria.[16]

Statistical analysis

We computed that a total sample of 4000 observations would achieve 80% power at a two-sided 0·05 significance level to detect an odds ratio (OR) equal to or greater than 2·5. This calculation was based on logistic regression of a binary response variable on a binary covariate with a prevalence ranging from 10% to 90% and a 2% rate of teratogenic events in the lowest-rate group. Furthermore, on the basis of the general empirical rule that the ratio between the overall number of events and the number of explanatory variables should be at least equal to ten, we deemed a total sample size of 4000 observations adequate to minimise the risk of over fitting in a multivariable logistic model, assuming a 6% frequency of teratogenic events in the pooled population[2,3] and a maximum number of clinically plausible predictors equal to 24.

We identified dose-range categories by a non-arbitrary approach that consisted of splitting each treatment into three (carbamazepine, lamotrigine, valproic acid) or two (phenobarbital) dose categories depending on available sample size. We identified the cutoffs that separate dose categories by testing all possible numerical values by logistic regressions and selecting the one with the largest C-Index, a parameter that shows the predictive value of the cutoffs. Because of the empirical nature of this categorisation algorithm, the appropriateness of the identified categories also depends on their clinical

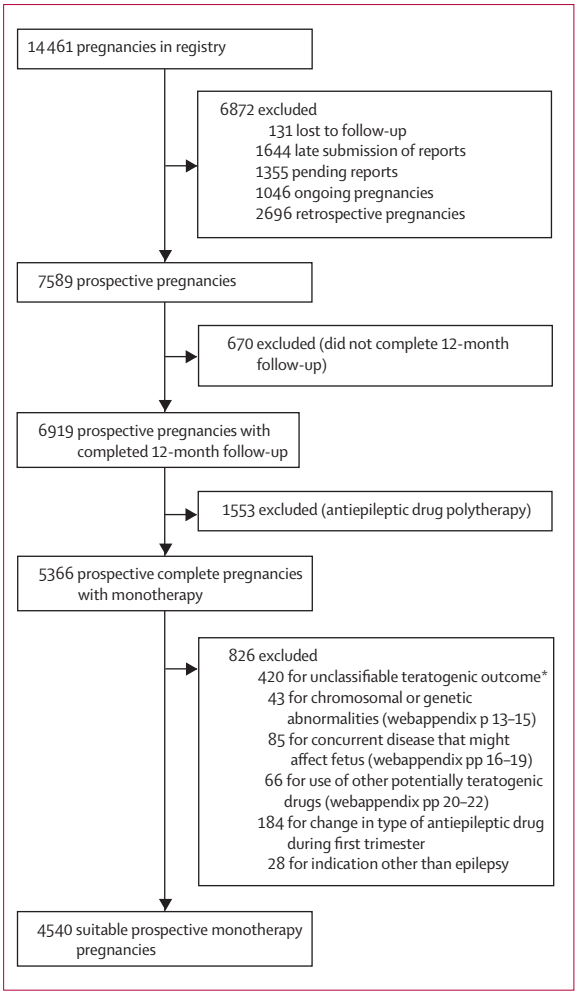

Figure: **Study population and selection process**
*Unclear whether there was a major malformation (n=11), spontaneous abortions (n=343), or induced abortions for non-fetal reasons (n=66).

	Median (range) or number (%)
Maternal age at time of enrolment (years)	29·7 (14·1–44·3)
Duration of pregnancy at time of enrolment (weeks)	8 (1–16)
Parental history of major congenital malformations	
Negative	3839 (98%)
Positive	52 (1%)
Information missing	18 (1%)
Geographical region	
Americas	40 (1%)
Europe	3354 (86%)
Southeast Asia	108 (3%)
Western Pacific	407 (10%)
Parity	
0	2353 (60%)
1	1208 (31%)
2	259 (7%)
3 or higher	89 (2%)
Type of epilepsy	
Idiopathic generalised epilepsy	1540 (39%)
Localisation-related epilepsy	1842 (47%)
Undetermined or unclassifiable	527 (14%)
Generalised tonic-clonic seizures during first trimester	
No	3600 (92%)
Yes	297 (8%)
Information missing	12 (0%)
Paternal educational level	
Low	617 (16%)
Medium or high	2864 (73%)
Information missing	428 (11%)
Maternal educational level	
Low	557 (14%)
Medium or high	3010 (77%)
Information missing	342 (9%)
Folic acid use	
Appropriate	1358 (35%)
Inappropriate	2519 (64%)
Information missing	32 (1%)
Sex of child	
Female	1900 (49%)
Male	1899 (49%)
Information missing	110 (3%)

Includes data for pregnancies in which exposure was to one of the four most common monotherapies (n=3909).

Table 1: **Demographic and clinical data**

See Online for webappendix

plausibility. Because of the small number of pregnancies in the lowest lamotrigine dose category, we combined the lowest and the intermediate lamotrigine dose categories.

To calculate malformation rates, the sum of all pregnancies with confirmed major congenital malformations (including prenatally detected malformations that resulted in elective terminations and stillbirths) was the numerator and the sum of all included cases was the denominator. We used multiple logistic regression to assess the four monotherapies divided into dose categories (ten different treatment categories overall) after adjusting for potential confounders or prognostic factors, and to assess the effect of these factors on prognosis. Our logistic model was parameterised with generalised estimating equations with an exchangeable working correlation matrix to take into account clustered data (women with more than one birth). We did not identify any fit improvements when we included selected interaction terms between the covariates in the multivariable model, confirming that the additivity assumption (model with main effects only) was adequate. For goodness-of-fit, we compared recorded and predicted teratogenic events in ten subgroups of women with identical values of explanatory variables (Hosmer–Lemeshow test; probability=0·967). We computed the heuristic shrinkage estimator of van Houwelingen and le Cessie to quantify over fitting. We selected the final covariates included in

	Sample size	Congenital malformation up to birth to 2 months	Congenital malformation up to 1 year	Number seizure free (%)
Carbamazepine				
<400	148	2 (1·3%, 0·16–4·80)	5 (3·4%, 1·11–7·71)	95 (64%)
≥400 to <1000	1047	34 (3·2%, 2·26–4·51)	56 (5·3%, 4·07–6·89)	699 (67%)
≥1000	207	16 (7·7%, 4·48–12·25)	18 (8·7%, 5·24–13·39)	129 (62%)
Lamotrigine				
<300	836	14 (1·7%, 0·92–2·79)	17 (2·0%, 1·19–3·24)	562 (67%)
≥300	444	16 (3·6%, 2·07–5·79)	20 (4·5%, 2·77–6·87)	303 (68%)
Phenobarbital				
<150	166	7 (4·2%, 1·71–8·50)	9 (5·4%, 2·51–10·04)	117 (71%)
≥150	51	7 (13·7%, 5·70–26·26)	7 (13·7%, 5·70–26·26)	35 (69%)
Valproic acid				
<700	431	18 (4·2%, 2·49–6·52)	24 (5·6%, 3·60–8·17)	306 (71%)
≥700 to <1500	480	43 (9·0%, 6·56–11·88)	50 (10·4%, 7·83–13·50)	316 (66%)
≥1500	99	23 (23·2%, 15·33–32·79)	24 (24·2%, 16·19–33·89)	63 (63%)

Data are events (rate, 95% CI) unless otherwise stated.

Table 2: **Number of offspring with malformations for the four monotherapies at different doses at conception (mg per day)**

our multivariable model to achieve adequate predictive accuracy (goodness of fit) without compromising model calibration (over fitting), and we used multiple imputation[17] to replace missing values for covariates. The Monte Carlo Markov Chain technique implemented in SAS Proc MI was used to obtain 50 imputed datasets. Rubin's rules implemented in SAS Proc MIANALYZE were used to combine effect estimates and estimate CIs to allow for uncertainty due to missing data.

We chose a two-tailed p value of 0·05 or less to define statistically significant results. Because we judged type 2 error a greater concern, the type 1 error rate was quantified without adjustment for multiplicity of comparisons across treatments.[18] We did all statistical calculations with SAS version 9.1.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The data are the property of the EURAP study group and the authors had full access to all data. The Central Project Commission had final responsibility for the decision to submit for publication.

Results

For our present analysis, a cutoff date of June 9, 2010, was arbitrarily established, at which point 14461 pregnancies had been registered. Of these pregnancies, we prospectively identified 5366 in which the women were exposed to antiepileptic monotherapy and had completed the 12-month follow-up (figure). 826 pregnancies were subsequently excluded (demographics listed webappendix pp 7–8), whereas 4540, representing 20 different antiepileptic drugs, fulfilled the eligibility criteria. These 4540 pregnancies resulted in 4424 liveborn infants, 70 stillbirths, and 46 elective terminations because of fetal abnormalities. The webappendix (p 9) lists the major congenital malformations and exposures to each of the 20 different monotherapies. Of all eligible pregnancies, 3909 (86%) were exposed to the four most common monotherapies: carbamazepine (1402 pregnancies), lamotrigine (1280), valproic acid (1010), and phenobarbital (217). The webappendix (p 10) lists the countries in which the pregnant women reside.

Demographic and clinical data for the 3909 pregnancies that we included in our final analysis (table 1) were similar to those of the 631 pregnancies exposed to less commonly used monotherapies (webappendix p 11). Some women contributed more than one pregnancy to the study (291 with two pregnancies, 12 with three, and one with four). There were 51 twin pregnancies and one triplet pregnancy, and each of the twins or triplets was treated as a separate pregnancy. Thus, the 3909 pregnancies represent 3521 women. Of these, 2625 women were completely free from seizures throughout pregnancy, 563 had GTC seizures at least once, and 698 had other types of seizure excluding GTC; seizure information was missing or incomplete in 23 pregnancies. Table 2 shows the proportions of women remaining seizure free throughout pregnancy for the different treatments.

230 (6%) of the pregnancies included in our final analysis produced offspring with major congenital malformations identified up to 12 months after birth. Of these pregnancies, malformations were detected in 49 prenatally (resulting in elective termination in 23 and stillbirth in one), in 148 within 2 months after birth, and in 33 after the second month. Six of 51 twin pregnancies produced offspring with major congenital malformations. In four pairs, only one twin was affected, whereas

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	Number (%)
Carbamazepine <400 mg per day (n=148)	
Cardiac	2 (1%)
Hypospadias	2 (1%)
Other malformations	1 (1%)
No fetal anomalies	143 (97%)
Carbamazepine ≥400 to <1000 mg per day (n=1047)	
Cardiac	16 (2%)
Oro-facial cleft	2 (0%)
Hypospadias	6 (1%)
Neural-tube defect	1 (0%)
Polydactyly	1 (0%)
Renal	5 (1%)
Other malformations	22 (2%)
Multiple malformations	3 (0%)
No fetal anomalies	991 (95%)
Carbamazepine ≥1000 mg per day (n=207)	
Cardiac	4 (2%)
Hypospadias	1 (1%)
Neural-tube defect	4 (2%)
Polydactyly	1 (1%)
Renal	2 (1%)
Other malformations	2 (1%)
Multiple malformations	4 (2%)
No fetal anomalies	189 (91%)
Lamotrigine <300 mg per day (n=836)	
Cardiac	3 (0%)
Hypospadias	2 (0%)
Renal	2 (0%)
Other malformations	9 (1%)
Multiple malformations	1 (0%)
No fetal anomalies	819 (98%)
Lamotrigine ≥300 mg per day (n=444)	
Cardiac	5 (1%)
Oro-facial cleft	2 (1%)
Hypospadias	2 (1%)
Renal	1 (0%)
Other malformations	8 (2%)
Multiple malformations	2 (1%)
No fetal anomalies	424 (96%)
Phenobarbital <150 mg per day (n=166)	
Cardiac	2 (1%)
Hypospadias	1 (1%)
Neural-tube defect	1 (1%)
Polydactyly	1 (1%)
Renal	1 (1%)
Other malformations	3 (2%)
No fetal anomalies	157 (95%)
(Continues in next column)	

	Number (%)
(Continued from previous column)	
Phenobarbital ≥150 mg per day (n=51)	
Cardiac	4 (8%)
Oro-facial cleft	1 (2%)
Polydactyly	1 (2%)
Other malformations	1 (2%)
No fetal anomalies	44 (86%)
Valproic acid <700 mg per day (n=431)	
Cardiac	5 (1%)
Oro-facial cleft	3 (1%)
Hypospadias	3 (1%)
Neural-tube defect	2 (1%)
Polydactyly	1 (0%)
Renal	2 (1%)
Other malformations	8 (2%)
No fetal anomalies	407 (94%)
Valproic acid ≥700 to <1500 mg per day (n=480)	
Cardiac	10 (2%)
Oro-facial cleft	1 (0%)
Hypospadias	9 (2%)
Neural-tube defect	7 (2%)
Polydactyly	4 (1%)
Renal	3 (1%)
Other malformations	12 (3%)
Multiple malformations	4 (1%)
No fetal anomalies	430 (90%)
Valproic acid ≥1500 mg per day (n=99)	
Cardiac	7 (7%)
Hypospadias	5 (5%)
Neural-tube defect	2 (2%)
Other malformations	3 (3%)
Multiple malformations	7 (7%)
No fetal anomalies	75 (76%)

Table 3: **Types of malformations for the four different monotherapies at different doses**

in one pair both twins had polydactyly and in the remaining pair both twins had hypoplastic left heart syndrome. Table 2 shows the rates of major congenital malformations at different dose ranges defined by our categorisation algorithm. The webappendix (p 12) shows the dose distributions within different dose categories. Table 2 also shows a comparison of rates of major congenital malformations at 2 months and 12 months after birth. The most common major congenital malformations missed at 2 months were cardiac (ten), hip (eight), and renal (six) malformations.

Cardiac defects were the most common major congenital malformations recorded after exposure to the four study antiepileptic drugs (table 3). There were 11 neural-tube defects in the 1010 valproic acid exposures, five in the 1402 carbamazepine exposures, and one in the 217 phenobarbital exposures. 15 neural-tube defects were detected prenatally by ultrasound, and folate had been prescribed appropriately according to the definition used in our study in seven of the 17 pregnancies in which the offspring had neural-tube defects.

Table 4 summarises the results of our multiple logistic regression analyses including the ten treatment categories (four antiepileptic drugs at two or three doses) and potential confounders or prognostic factors. The treatment associated with the lowest rate of malformations (<300 mg per day lamotrigine) served as a reference for internal comparisons. Compared with less than 300 mg per day lamotrigine, the risk of major congenital malformations was significantly increased for all doses of valproic acid and phenobarbital and for the two highest doses of carbamazepine. For the covariates that we assessed, significantly increased ORs were associated with a parental history of major congenital malformations and folate use (table 4).

We provide details on pregnancies excluded from our analysis in the webappendix. These include pregnancies resulting in chromosomal and genetic abnormalities (webappendix pp 13–15) and those associated with other diseases that might be associated with adverse pregnancy outcomes (overall rate of major congenital malformations at 1 year was 5·9%; webappendix pp 17–21) or with other potential teratogens (overall rate of major congenital malformations at 1 year was 9·1%; webappendix pp 22–24). Ten pregnancies in which there were major congenital malformations were among the 184 pregnancies that were excluded because of a change in the type of antiepileptic drug during the first trimester.

	Odds ratio (95% CI)	p value
Drug comparisons with lamotrigine <300 mg per day		
Carbamazepine (<400 mg per day)	1·6 (0·56–4·53)	0·3803
Carbamazepine (≥400 to <1000 mg per day)	2·5 (1·45–4·48)	0·0012
Carbamazepine (≥1000 mg per day)	4·6 (2·28–9·31)	<0·0001
Phenobarbital (<150 mg per day)	2·5 (1·11–5·85)	0·0275
Phenobarbital (≥150 mg per day)	8·2 (3·16–21·53)	<0·0001
Valproic acid (<700 mg per day)	2·8 (1·46–5·30)	0·0019
Valproic acid (≥700 to <1500 mg per day)	5·8 (3·27–10·13)	<0·0001
Valproic acid (≥1500 mg per day)	16·1 (8·22–31·54)	<0·0001
Within-drug comparisons		
Carbamazepine (≥400 to <1000 *vs* <400 mg per day)	1·6 (0·63–4·07)	0·3265
Carbamazepine (≥1000 *vs* <400 mg per day)	2·9 (1·04–8·00)	0·0413
Lamotrigine (≥300 *vs* <300 mg per day)	2·2 (1·12–4·35)	0·0221
Phenobarbital (≥150 *vs* <150 mg per day)	3·2 (1·11–9·45)	0·0316
Valproic acid (≥700 to <1500 *vs* <700 mg per day)	2·1 (1·25–3·43)	0·0047
Valproic acid (≥1500 *vs* <700 mg per day)	5·8 (3·07–10·92)	<0·0001
Non-drug covariates		
Americas *vs* Europe	2·1 (0·82–5·33)	0·1227
Southeast Asia *vs* Europe	1·3 (0·59–2·94)	0·5064
Western Pacific *vs* Europe	1·0 (0·67–1·63)	0·8570
Parental history of major congenital malformations	4·4 (2·06–9·23)	0·0001
Maternal age	1·0 (0·97–1·04)	0·8209
Educational level father (low *vs* medium or high)	1·0 (0·64–1·55)	0·9941
Educational level mother (low *vs* medium or high)	1·1 (0·70–1·73)	0·6829
Generalised tonic-clonic seizures during first trimester	0·6 (0·31–1·11)	0·103
Folicate use (appropriate *vs* inappropriate)	1·4 (1·02–1·82)	0·035
Sex (male *vs* female)	1·0 (0·75–1·29)	0·8982
Idiopathic generalised epilepsy *vs* localisation-related epilepsy	0·9 (0·62–1·23)	0·4421
Undetermined or unclassifiable *vs* localisation-related epilepsy	0·8 (0·47–1·22)	0·2531
Parity	0·8 (0·67–1·04)	0·1074

Lamotrigine <300 mg per day was selected as comparator since this treatment was associated with the lowest point estimate of the risk for major congenital malformations (table 2). Odds ratios for maternal age and parity show the risk associated with an increase of 1 year in age and an increase of 1 point in parity, respectively.

Table 4: **Results of multivariable logistic analysis**

Discussion

Our findings show that the risk of major congenital malformations increases dose-dependently with all assessed antiepileptic drugs. We recorded particularly high malformation rates for 1500 mg per day or greater doses of valproic acid. Doses of valproic acid of less than 700 mg per day were associated with a malformation rate in a similar range to that of carbamazepine doses of 400 mg per day to less than 1000 mg per day, phenobarbital of less than 150 mg per day, and lamotrigine of 300 mg per day or higher (table 2), although we cannot firmly conclude that these treatments are equivalent because our study was not powered to assess a formal equivalence or non-inferiority between treatments. A parental history of major congenital malformations was independently associated with a four-times greater risk (table 4). There was no association between epilepsy type or GTC seizures in the first trimester and a greater risk of major congenital malformations. Seizure control was similar across the different treatment categories (table 2). This similarity should not be interpreted as evidence of similar efficacy of all antiepileptic drugs irrespective of dose but, probably, as a result of treatment being adjusted to meet individual needs. It is important to emphasise that the dose categories used in our analysis, and reported in table 2, are based on the dose at the time of conception. It is often necessary to adjust drug doses to maintain seizure control as pregnancy progresses,[14,19] and previous reports from EURAP have suggested that such dose adjustments are more common with lamotrigine or oxcarbazepine, for which the decline in plasma concentrations during pregnancy seems to be particularly pronounced.[14]

Folate supplementation was associated with a greater risk of major congenital malformations, which possibly shows confounding by indication because women at greater risk are more likely to take folate. The UK registry[20] reported rates of major congenital malformations in offspring of women on antiepileptic drugs with appropriate folate intake that were at least as high as those in women on antiepileptic drugs without appropriate folate intake, and a recent case-control study[21] also show that folate was not effective in preventing spina bifida associated with exposure to valproic acid. However, these findings should not be used as an argument against the common recommendation of providing low-dose folate supplementation to women with epilepsy who are planning pregnancy.[19]

Greater rates of major congenital malformations after exposure to antiepileptic drugs and, in particular, valproic acid have been reported in other studies (panel).[2–3,8–13,22–24] Our rates are slightly higher than those reported in population-based studies and two other major registries,[11,23–27] a difference probably explained by our extended follow-up until 12 months after birth.

Although dose-dependent teratogenic effects of valproic acid have been reported before, the cutoffs used to identify higher risk were selected arbitrarily and varied across studies—from 600 to 1500 mg per day.[4,8–12,28] A greater risk of major congenital malformations with lamotrigine doses greater than 200 mg per day was reported by the UK registry,[13] but was not confirmed in subsequent studies.[29,30] We are not aware of previous reports on dose-dependent risk of major congenital malformations with carbamazepine or phenobarbital, although in the UK registry there was suggestive evidence of higher risk at high carbamazepine doses,[13] and a recent prospective observational study found verbal performance at age 3 years was negatively associated with maternal carbamazepine dose in pregnancy.[31]

Our study has some limitations. First, our assessment of major congenital malformations was based on descriptions from reporting physicians and supportive medical records. The risk of under-reporting and biased reporting was managed by instruction of physicians to report anything they thought possibly abnormal, leaving the final determination and classification to the independent classification committee. Although uncertain cases could be resolved by interaction between the central registry and reporting physicians, there were 11 cases for which it was not possible to establish whether criteria for major congenital malformations were met. These cases were not clustered in a specific treatment category, and their exclusion is unlikely to have affected our results. Second, our registry does not include untreated women with epilepsy or healthy women as controls and therefore we cannot establish the influence of individual treatments versus no treatment. However, the value of untreated controls in assessing treatment effects is limited by the fact that the severity of the seizure disorder and other covariates is unlikely to be similar in all groups (confounding by indication). Likewise, we do not provide data on background risk in the general population. Even if such information were available for the 42 countries involved, it would be of questionable value. Malformation rates associated with any given antiepileptic drug vary substantially across different pregnancy registries, probably because of differences in methods such as time windows of assessment and methods used to identify and define malformations.[5] Therefore, comparisons with external control populations can be misleading unless these populations are assessed in exactly the same way as the exposed cohorts. The choice for physicians and for women with active epilepsy considering pregnancy is rarely between treatment or no treatment; instead, the challenge is to identify the safest effective treatment.

A further limitation of our study is that we did not include in our analysis data on dose adjustments after conception. Hence, our dose categories represent the exposure to antiepileptic drugs at the beginning of pregnancy and not necessarily the average exposure during the first trimester. In our view, however, the risks associated with different doses at conception are the most relevant information when considering treatment alternatives for women with epilepsy who plan to become pregnant. Furthermore, EURAP is not population based and relies on collaboration mostly from hospital physicians who have a special interest in epilepsy and tend to manage selected patient populations.[32] This could affect overall rates of major congenital malformations, but should not invalidate internal comparisons between treatments, our primary objective. A final potential concern with our cohort is heterogeneity: more than 30 countries participated, with uneven contributions (webappendix p 10), and prescription patterns for antiepileptic drugs vary between countries. In the

Panel: Research in context

Systematic review

We refer to a recently published systematic review[3] done by the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society, which covered relevant articles published between 1985 and June, 2007. That search was done with Medline, Medline-In-Process, Current Contents, Biological Abstracts, and BIOSIS previews. The search terms were "seizures or epilepsy", "catamenial epilepsy", "pregnancy", "anticonvulsants", "antiepileptic drugs", "teratogenesis", "birth defects", "pregnancy registry", "cognitive outcome", "vitamin K", "folate or folic acid", "breastfeeding", "oral contraceptives", "polycystic ovary syndrome", "hormone replacement therapy", "menopause", "perimenopause", and "fertility". The search was confined to articles with human participants and included all languages for which there was an abstract in English. A secondary search for missed references was done by reviewing the bibliographies of review articles and meta-analyses identified in the primary search. We did a separate PubMed search for articles published from June, 2007, to February, 2011. For this additional search we used the search terms "anticonvulsants", "antiepileptic drugs", "teratogenicity", and "birth defects". Our search was limited to studies in English. We did not set any criteria for assessment of quality.

Interpretation

Women with active epilepsy need effective treatments during pregnancy, for their own wellbeing and that of their fetus. Findings from previous studies and systematic reviews suggested that intrauterine exposure to valproic acid is associated with a greater risk of major congenital malformations than is exposure to some other antiepileptic drugs, but little guidance is available on how to manage women whose seizures cannot be controlled by other drugs. In our study, we established the risks of major congenital malformations after monotherapy exposure to four major antiepileptic drugs—carbamazepine, lamotrigine, valproic acid, and phenobarbital—at different doses. Our analysis, which controlled for ten covariates in addition to type of treatment, showed a dose-dependent risk of major congenital malformations with all four drugs. Our findings suggest that many women can enter pregnancy at comparatively low doses and maintain seizure control. Our study gives the prescriber the possibility of assessing, before pregnancy, how teratogenic risks with an individual woman's treatment compare with the risks associated with alternative treatments at various doses.

countries in EURAP that enrol 20–25% of all eligible patients, the use of antiepileptic drugs seems to follow the general national prescription patterns.[29] Geographical region of enrolment did not affect outcome in our multivariable analysis (table 4) and, from a worldwide perspective, the multinational contribution to our cohort might increase the generalisability of our results.

We still have little understanding of maternal and fetal risks associated with uncontrolled seizures. Randomised studies comparing pregnancy outcomes in women with treated versus untreated active epilepsy are not ethically justified. However, reports from the UK[33] suggest that the risk of maternal death is greater in women with epilepsy than those without epilepsy and that this risk could be related to withdrawal of antiepileptic drugs. The same study reported poorer cognitive outcomes in schoolchildren who had been exposed to frequent GTC seizures in utero. Such reports support the opinion generally accepted by physicians that women with active epilepsy need effective treatments during pregnancy, for their own wellbeing and that of their fetus. It is in this context that our findings bridge a longstanding gap in knowledge that has hampered a rational approach to the management of women with epilepsy of childbearing potential. Present guidelines caution on the use of valproic acid during pregnancy,[6] but offer little guidance on alternative options and how to manage women whose seizures cannot be controlled by other drugs. This is particularly problematic for women with idiopathic generalised epilepsies, in whom valproic acid seems to be the most effective drug.[34] Our results show that dose selection is as crucial as the choice of the drug. The approach generally accepted by physicians so far has been to identify, before conception, the lowest effective dose of the drug that is most appropriate for the woman's epilepsy. Our study gives the prescriber the possibility of assessing how teratogenic risks at that dose compare with the risks associated with alternative treatments at various doses. Our data suggest that many women can enter pregnancy at low doses and maintain seizure control, although in many such cases dose adjustment might be needed later in pregnancy. Such low doses, particularly with lamotrigine and carbamazepine, seem to be associated with low malformation rates. The EURAP registry continues to enrol pregnancies, with the aim of providing more information on teratogenic risks with these four and other antiepileptic drugs in the future.

Contributors

DB is the central study coordinator and manager of the EURAP database. EB was responsible for the statistical analysis. All authors contributed to the concept, design, and data interpretation. TT and DB drafted the first report and all authors contributed to and approved the final report.

EURAP study group

A complete list of collaborators is given in the webappendix pp 1–6. Central project commission: D Battino (central study coordinator), E Bonizzoni, J Craig, D Lindhout, E Perucca, A Sabers, T Tomson, (chair), F J E Vajda. Outcome assessment committee: R Finnell, USA; F Faravelli, Italy; E Robert-Gnansia, France. Scientific advisory board: B Schmidt, Germany; M J Brodie, UK. Regional coordinators: S Kochen, Argentina; F J E Vajda, Australia; G Luef, Austria; D Lindhout and S Bulk, Benelux; A de Marinis, Chile; D Vitezic, Croatia; J Zarubova and R Kuba, Czech Republic; A Sabers, Denmark; R Kälviäinen, Finland; M Beaussart, France; O Toidze and S Kasradze, Georgia; B Schmitz, Germany; P Kwan, Hong Kong; G Barcs, Hungary; S V Thomas, India; M Neufeld, Israel; A Paggi, Italy; H Ohtani, Japan; R Mameniskiene, Lithuania; G Kiteva-Trencevska, Macedonia; K O Nakken, Norway; W Liao, China; L Cabral-Lim, Philippines; J Jedrzejczak, Poland; A Guekht and O Lokshina, Russia; D Sokic, Serbia and Montenegro; V Safcak, Slovakia; B Cebular, Slovenia; M Martinez Ferri, Spain; T Tomson, Sweden; B Tettenborn and G Baumgarten, Switzerland; C W Lai and A Yu, Taiwan; C Ozkara and D Kinay, Turkey; J Craig and A Russell, UK. Central registry staff (Italy): B Moche Kamga (data manager and supervisor), S Doñe and K Turner (auditors), G Nardini, L Prato.

Conflicts of interest

DB has received speakers' fees from UCB Pharma and Sanofi-Aventis. EB has received consultancy fees from Italfarmaco, Newron, Nicox, Roche, and Ferring. JC received research grants and speakers' fees from UCB Pharma, Eisai, GlaxoSmithKline (GSK), Sanofi-Aventis, Pfizer, and Janssen-Cilag. DL received research grants from Janssen-Cilag, GSK, Pfizer, UCB Pharma, and Netherlands Epilepsy Foundation. AS received consultancy or lecture fees from, and is on advisory boards of, Eisai Denmark and UCB Nordic, and has received travel support from Eisai Denmark, GSK, and UCB Nordic. EP received research funds from the European Union, the Italian Ministry of Health, the Italian Ministry for Education and University, and the Italian Medicines Agency; he also received speakers' or consultancy fees, research grants, or both from Bial, Eisai, GSK, Johnson and Johnson, Novartis, Pfizer, Sanofi-Aventis, SK Holdings, Supernus, UCB Pharma, and Valeant, and has been on advisory boards of Bial, Valeant, GSK, Johnson and Johnson, UCB Pharma, Eisai, Novartis, Pfizer, and Sanofi-Aventis. TT received research grants, speakers' honoraria, or both from Eisai, GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Sanofi-Aventis, and UCB-Pharma. FV declares no conflicts of interest.

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