



Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry

Torbjörn Tomson*, Dina Battino*, Erminio Bonizzoni, John Craig, Dick Lindhout, Emilio Perucca, Anne Sabers, Sanjeev V Thomas, Frank Vajda, for the EURAP Study Group†

Summary

Background Evidence for the comparative teratogenic risk of antiepileptic drugs is insufficient, particularly in relation to the dosage used. Therefore, we aimed to compare the occurrence of major congenital malformations following prenatal exposure to the eight most commonly used antiepileptic drugs in monotherapy.

Methods We did a longitudinal, prospective cohort study based on the EURAP international registry. We included data from pregnancies in women who were exposed to antiepileptic drug monotherapy at conception, prospectively identified from 42 countries contributing to EURAP. Follow-up data were obtained after each trimester, at birth, and 1 year after birth. The primary objective was to compare the risk of major congenital malformations assessed at 1 year after birth in offspring exposed prenatally to one of eight commonly used antiepileptic drugs (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate) and, whenever a dose dependency was identified, to compare the risks at different dose ranges. Logistic regression was used to make direct comparisons between treatments after adjustment for potential confounders and prognostic factors.

Findings Between June 20, 1999, and May 20, 2016, 7555 prospective pregnancies met the eligibility criteria. Of those eligible, 7355 pregnancies were exposed to one of the eight antiepileptic drugs for which the prevalence of major congenital malformations was 142 (10.3%) of 1381 pregnancies for valproate, 19 (6.5%) of 294 for phenobarbital, eight (6.4%) of 125 for phenytoin, 107 (5.5%) of 1957 for carbamazepine, six (3.9%) of 152 for topiramate, ten (3.0%) of 333 for oxcarbazepine, 74 (2.9%) of 2514 for lamotrigine, and 17 (2.8%) of 599 for levetiracetam. The prevalence of major congenital malformations increased with the dose at time of conception for carbamazepine ($p=0.0140$), lamotrigine ($p=0.0145$), phenobarbital ($p=0.0390$), and valproate ($p<0.0001$). After adjustment, multivariable analysis showed that the prevalence of major congenital malformations was significantly higher for all doses of carbamazepine and valproate as well as for phenobarbital at doses of more than 80 mg/day than for lamotrigine at doses of 325 mg/day or less. Valproate at doses of 650 mg/day or less was also associated with increased risk of major congenital malformations compared with levetiracetam at doses of 250–4000 mg/day (odds ratio [OR] 2.43, 95% CI 1.30–4.55; $p=0.0069$). Carbamazepine at doses of more than 700 mg/day was associated with increased risk of major congenital malformations compared with levetiracetam at doses of 250–4000 mg/day (OR 2.41, 95% CI 1.33–4.38; $p=0.0055$) and oxcarbazepine at doses of 75–4500 mg/day (2.37, 1.17–4.80; $p=0.0169$).

Interpretation Different antiepileptic drugs and dosages have different teratogenic risks. Risks of major congenital malformation associated with lamotrigine, levetiracetam, and oxcarbazepine were within the range reported in the literature for offspring unexposed to antiepileptic drugs. These findings facilitate rational selection of these drugs, taking into account comparative risks associated with treatment alternatives. Data for topiramate and phenytoin should be interpreted cautiously because of the small number of exposures in this study.

Funding Bial, Eisai, GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Sanofi-Aventis, UCB, the Netherlands Epilepsy Foundation, and Stockholm County Council.

Copyright © 2018 Elsevier Ltd. All rights reserved.

Introduction

The teratogenic risks associated with antiepileptic drugs are a concern for prescribers from many disciplines because epilepsy is often managed by primary care physicians and there has been an increasing use of these drugs for indications other than epilepsy. Evidence suggests that infants exposed to antiepileptic drugs are at

higher risk for major congenital malformations than are infants of untreated mothers with epilepsy.¹ Observational studies have reported that valproate has a higher teratogenic risk than other antiepileptic drugs,^{2–7} that this risk is dose dependent,^{2,3,5,7} and that offspring exposed prenatally to valproate are also at higher risk for impaired postnatal cognitive development^{8–10} and, possibly, autism

Lancet Neurol 2018; 17: 530–38

Published Online

April 18, 2018

[http://dx.doi.org/10.1016/S1474-4422\(18\)30107-8](http://dx.doi.org/10.1016/S1474-4422(18)30107-8)

See [Comment](#) page 485

*Contributed equally

†The appendix shows the complete list of collaborators

Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Prof T Tomson MD);

Department of Neurology, Karolinska University Hospital, Stockholm, Sweden (Prof T Tomson);

Epilepsy Center, Department of Neurophysiology and Experimental Epileptology, IRCCS Neurological Institute Carlo Besta Foundation, Milan, Italy (D Battino MD);

Department of Clinical Science and Community, Section of Medical Statistics, Biometry and Epidemiology, Faculty of Medicine and Surgery, University of Milan, Milan, Italy (E Bonizzoni PhD);

Department of Neurosciences, Acute and Unscheduled Care, Belfast Health and Social Care Trust, Belfast, UK (J Craig MB);

Department of Genetics, University Medical Center Utrecht, Utrecht, Netherlands (Prof D Lindhout MD);

Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, Netherlands (Prof D Lindhout);

Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy (Prof E Perucca MD);

Clinical Trial Center, IRCCS Mondino Foundation, Pavia, Italy (Prof E Perucca);

The Epilepsy Clinic, Department of Neurology, Rigshospitalet-Blegdamsvej, University State Hospital, Copenhagen, Denmark (Prof A Sabers MD);

Department of Neurology, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum,

Research in context

Evidence before this study

Although the use of antiepileptic drugs during pregnancy has been known for more than 50 years to be associated with increased risks of major congenital malformations in the offspring, it is not until more recent years, with emerging data from prospective pregnancy registries, that the teratogenic potential of different antiepileptic drugs had begun to be delineated. We refer to two recently published systematic reviews and meta-analyses. One review focused on newer antiepileptic drugs and searched, on Nov 12, 2014, PubMed and Embase for all newer antiepileptic drugs, congenital anomalies, and pregnancy. The second systematic review searched MEDLINE, Embase, and the Cochrane Central Register of Controlled trials from inception to Dec 15, 2015. We did a separate PubMed search for articles published from Dec 16, 2015, to Dec 15, 2017, using the search terms “anticonvulsants”, “antiepileptic drugs”, “teratogenicity”, and “birth defects”. Our search was limited to studies in English and we did not set any criteria for assessment of quality.

Although meta-analyses increase the statistical power, they combine data from heterogeneous studies sometimes with different outcome criteria, and do not provide direct within-study comparisons between antiepileptic drug treatments. Such internal comparisons have been made in individual reports from independent prospective antiepileptic drug and pregnancy registries but so far only between the most frequently used antiepileptic drugs. Taken together, these studies have consistently reported increased risk of major congenital malformations associated with valproate and phenobarbital compared with pregnancies unexposed to antiepileptic drugs, as well as compared with pregnancies exposed to other antiepileptic drugs such as carbamazepine and lamotrigine. Findings also suggest increased risks associated

with topiramate. Pregnancy registries have also reported that the risks associated with some drugs, in particular valproate, might be dose dependent.

Added value of this study

On the basis of the largest published prospective cohort of pregnancies in women with epilepsy so far, we provide the prevalence of major congenital malformations at 1 year after birth following exposure to the eight most frequently used antiepileptic drugs in monotherapy. Where a dose dependency relationship was apparent, risks are reported at different doses used at conception. In a multivariable analysis, we report 36 direct comparisons of risks between different treatment modalities.

Implications of all the available evidence

With epilepsy often managed by primary care physicians, and an increasing use of antiepileptic drugs for other indications, the risk of major congenital malformations is a concern for prescribers from many disciplines. Epilepsy, as well as some psychiatric conditions, might have serious consequences and require continuation of treatment during pregnancy. Treatment modalities should be reviewed regularly in all women of childbearing potential to assess risks and benefits of treatment alternatives and enable any appropriate modifications before pregnancy. Current evidence has made clear that, whenever possible, valproate should be avoided in the treatment of women of childbearing potential, but risks differ also between other treatments. Our comprehensive study, with comparisons of risks between a multitude of antiepileptic drug treatments and dosages, provides physicians with vital information when they consider alternatives for women of childbearing potential.

spectrum disorders.¹¹ On the basis of these observations, the US Food and Drug Administration¹² and the European Medicines Agency¹³ issued restrictions on the use of valproate in women of childbearing age and, in the case of the European Medicines Agency, also in girls.

The use of valproate for the treatment of epilepsy in pregnancy¹⁴ and in women of childbearing age has recently declined.¹⁵ By contrast, the use of valproate for other indications has increased,¹⁵ in particular for psychiatric conditions,¹⁴ which might reflect a gap in awareness among those outside the field of neurology.¹⁴ Prescription patterns, however, might also reflect the shortage of appropriate treatment alternatives and insufficient data for the teratogenicity of other antiepileptic drugs,¹⁶ particularly newer generation antiepileptic drugs, the use of which has increased substantially in pregnancy.^{14,17}

Information about comparative risks of major congenital malformations with different antiepileptic drugs comes primarily from prospective registries.^{2-5,18} However, because of power limitations, so far only the most frequently used antiepileptic drugs have been assessed.

Meta-analyses might increase statistical power, but are limited by methodological heterogeneity across included studies and fail to assess important variables such as the influence of the dose used.^{1,19} Therefore to overcome these limitations, we aimed to compare the risks of major congenital malformations for eight major antiepileptic drugs, including the risks associated with different doses of the most commonly used agents to provide physicians with novel tools for rational selection of these drugs.

Methods

Study design and participants

We did a longitudinal prospective, cohort study based on EURAP, an international registry collecting data for the assessment of risks of antiepileptic drugs during pregnancy. EURAP was established in 1999 and has since involved 42 countries with more than 1500 collaborators (appendix).

We included data for pregnant women for prospective assessment if they were exposed to antiepileptic drugs at conception, enrolled in EURAP within gestation week 16

Kerala, India (Prof S V Thomas MD); and Department of Medicine and Department of Neurology, University of Melbourne, Royal Melbourne Hospital, Melbourne, VIC, Australia (Prof F Vajda MD)

Correspondence to: Prof Torbjörn Tomson, Department of Neurology, Karolinska University Hospital, SE 171 76 Stockholm, Sweden torbjorn.tomson@sll.se

See Online for appendix

(based on the date of the last menstrual period), and fetal outcome was unknown. We excluded from the current analysis retrospectively identified pregnancies, those occurring in women without epilepsy, those for which physicians did not submit reports within preset deadlines, and those for which follow-up was not yet completed at the current census. We also excluded pregnancies in which antiepileptic drugs were switched

or withdrawn during the first trimester, those exposed to antiepileptic drug combination therapy or to other potentially teratogenic drugs, and those with comorbidities associated with teratogenic risks (appendix). Additionally, we excluded cases of

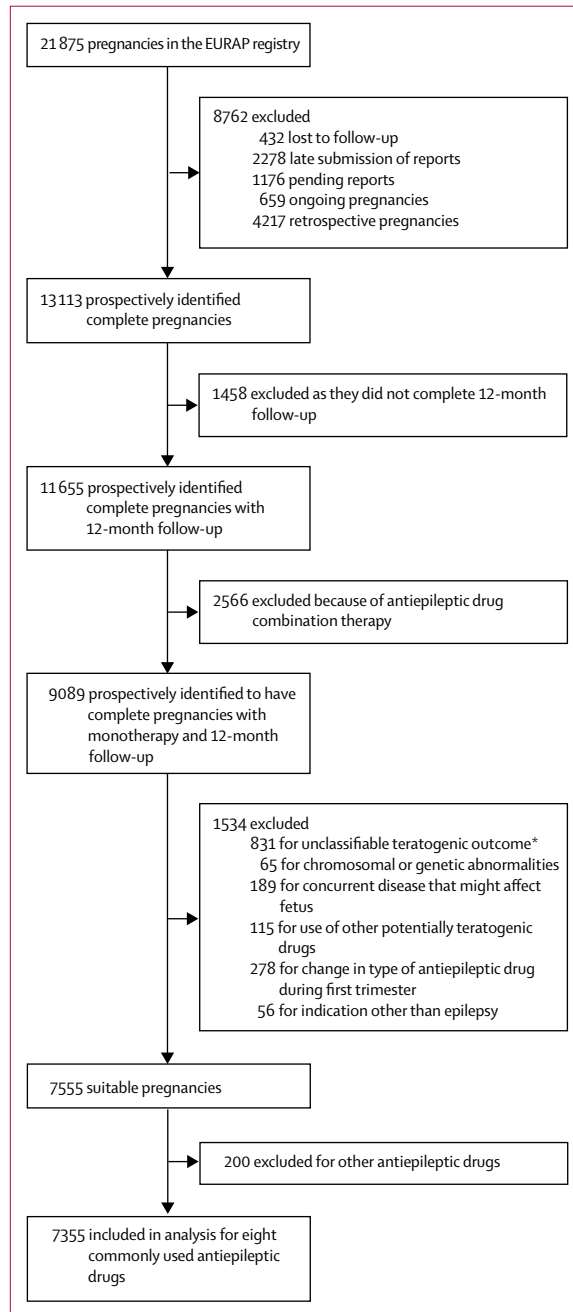


Figure: Study population and selection process

*Unclear whether there was a major malformation (n=27), intrauterine deaths (n=693), or induced abortions for causes other than fetal abnormalities (n=111).

Study cohort (n=7355)	
Mean maternal age at time of conception, years	29.8 (4.9)
Mean duration of pregnancy at time of enrolment, weeks	8 (3)
Parent history of major congenital malformations	
Negative	7228 (98%)
Positive	87 (1%)
Information missing	40 (1%)
Geographical region	
Americas	72 (1%)
Europe	6424 (87%)
Southeast Asia	226 (3%)
Western Pacific	633 (9%)
Parity	
0	4371 (59%)
1	2366 (32%)
2	479 (7%)
3 or more	138 (2%)
Information missing	1 (<1%)
Type of epilepsy	
Idiopathic generalised epilepsy	2868 (39%)
Localisation-related epilepsy	3675 (50%)
Undetermined or unclassifiable epilepsy	812 (11%)
Generalised tonic-clonic seizures during first trimester	
No	6807 (93%)
Yes	533 (7%)
Information missing	15 (<1%)
Educational level of the father*	
Low	1044 (14%)
Medium or high	5714 (78%)
Information missing	597 (8%)
Educational level of the mother*	
Low	934 (13%)
Medium or high	5986 (81%)
Information missing	435 (6%)
Folic acid intake†	
Appropriate	2795 (38%)
Inappropriate	4509 (61%)
Information missing	51 (1%)
Sex of the child	
Girl	3591 (49%)
Boy	3715 (51%)
Information missing	49 (1%)

Data are mean (SD) or n (%). *Parental educational level was categorised into low (≤9 years of education) or medium or high (>9 years of education). †Arbitrarily deemed appropriate if initiated at least 3 months before conception and maintained throughout the first trimester (dose ≥0.4 mg/day).

Table 1: Demographic and clinical details of the study cohort

spontaneous abortions, abortions induced for causes other than fetal abnormalities, pregnancies in which fetal outcome could not be determined, and pregnancies that resulted in offspring with genetic or chromosomal abnormalities (appendix).

We received approval from the ethics committees of participating centres for the protocol, and we obtained either written or oral informed consent from all women enrolled.

Procedures

We obtained information during early pregnancy about demographics, type of epilepsy, seizure frequency, comorbidities, family history of major congenital malformations, type of antiepileptic drug treatment used, and other risk factors. Additionally, we obtained follow-up data after each trimester, at birth, and 1 year after birth. The treating physician collected these data and transferred it online to a EURAP national coordinator, who reviewed the reports for completeness and accuracy before transmission to the EURAP central database in Milan, Italy.

Abnormalities in the offspring were reported descriptively by enrolling physicians, who were instructed to report anything they considered to be a potential abnormality. These reports were reviewed and classified by an outcome committee unaware of the type of exposure. When needed, the committee could request supplementary information from the reporting physician.

Outcomes

The primary objective was to compare the risk of major congenital malformations assessed at 1 year after birth in offspring exposed prenatally to one of eight different antiepileptic monotherapies (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate) and, whenever a dose dependency was identified, to compare the risks at different dose ranges.

Pregnancies were classified on the basis of type and dosage of antiepileptic drug used at conception. Seizures were classified as either generalised tonic-clonic or other types, and epilepsy syndromes broadly classified according to the International League Against Epilepsy criteria at the time EURAP was launched.²⁰ Major congenital malformations were defined as structural abnormalities with surgical, medical, functional, or cosmetic importance, and classified according to the 2005 EUROCAT criteria.²¹

Covariates for the analysis were selected a priori on the basis of those considered potentially relevant based on our previous analysis of pregnancy outcome in EURAP.⁵ Family history of major congenital malformations refers to the proband's parents, excluding cerebral malformations causally associated with the maternal epilepsy. Folate supplementation was arbitrarily deemed appropriate if initiated at least 3 months before conception and maintained throughout the first trimester irrespective of dose, provided that it was no less than 0.4 mg/day.

	Dose range (mg/day)	Number of pregnancies exposed	Number of major congenital malformation events	Prevalence of major congenital malformation events (95% CI)
Lamotrigine	25–1300	2514	74	2.9% (2.3–3.7)
Carbamazepine	50–2400	1957	107	5.5% (4.5–6.6)
Valproate	100–3000	1381	142	10.3% (8.8–12.0)
Levetiracetam	250–4000	599	17	2.8% (1.7–4.5)
Oxcarbazepine	75–4500	333	10	3.0% (1.4–5.4)
Phenobarbital	15–300	294	19	6.5% (4.2–9.9)
Topiramate	25–500	152	6	3.9% (1.5–8.4)
Phenytoin	30–730	125	8	6.4% (2.8–12.2)

Table 2: Prevalence of major congenital malformations in offspring exposed prenatally to one of eight different antiepileptic monotherapies

	Number of pregnancies exposed	Number of major congenital malformation events	Prevalence of major congenital malformation events (95% CI)	p value
Lamotrigine				
≤325 mg/day	1870	46	2.5% (1.8–3.3)	0.0145
>325 mg/day	644	28	4.3% (2.9–6.2)	..
Carbamazepine				
≤700 mg/day	1276	58	4.5% (3.5–5.8)	0.0140
>700 mg/day	681	49	7.2% (5.4–9.4)	..
Valproate				
≤650 mg/day	600	38	6.3% (4.5–8.6)	<0.0001
>650 to ≤1450 mg/day	666	75	11.3% (9.0–13.9)	..
>1450 mg/day	115	29	25.2% (17.6–34.2)	..
Phenobarbital				
≤80 mg/day	73	2	2.7% (0.3–9.5)	0.0390
>80 to ≤130 mg/day	161	10	6.2% (3.0–11.1)	..
>130 mg/day	60	7	11.7% (4.8–22.6)	..

When a dose dependency for the risk of major congenital malformation was identified, comparisons also included specific dose ranges at time of conception.

Table 3: Association between prevalence of major congenital malformations and exposure to one of the four monotherapies in which a dose response was detectable

Statistical analysis

A total sample of 7000 observations achieves 80% power at a two-sided 0.05 significance level to detect an odds ratio (OR) of 2.0, based on logistic regression of a binary response variable on a binary covariate with a prevalence ranging from 10% to 90% and a 2% frequency of teratogenic events in the group with the lowest frequency of events. On the basis of the empirical rule that the ratio between the overall number of events and the number of explanatory variables should be at least equal to ten, a total sample size of 7000 observations was deemed adequate to minimise the risk of overfitting in a multivariable logistic model, assuming a 5% frequency of teratogenic events in the pooled population and a selected number of clinically plausible predictors equal to 35.

To calculate frequencies of major congenital malformations, the numerator was the sum of all live births

plus pregnancy losses with confirmed major congenital malformations, whereas the denominator included live births, pregnancies terminated electively for suspected major congenital malformations, and perinatal deaths.

The EURAP dose categorisation algorithm⁵ was used to define dose categories. The Cochrane-Armitage test was used to confirm a dose response across the identified categories. A random effect logistic model was used to compare treatments after adjusting for potential confounders or prognostic factors, and to assess the effect of these factors on outcome. The logistic regression

was done by fitting data through a generalised mixed linear model with the logit-link function, a binomial distribution, and an indicator of mother as a random effect to adjust estimates for the presence of clustered data (women with more than one birth). Results are reported as ORs with associated two-tailed 95% CIs.

The primary analysis was done without replacement of missing values, which was considered justified because attrition occurred only for covariates and was less than 2%. However, a sensitivity analysis was also done by using a generalised estimating equations model with missing data filled in through multiple imputation to test the robustness of the findings of the primary analysis.

A two-tailed p value of 0.05 or less was used to define statistical significance. By setting type-2 error at the same severity level as the type-1 error, multiplicity generated by the 48 comparisons was handled by controlling the false discovery rate as an alternative to the classic Bonferroni-type adjustments.²² This adjustment was done by the Benjamini and Hochberg adaptive linear step-up approach.²³ All statistical calculations were done with SAS (version 9.4).

Role of the funding source

The funders 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 of EURAP had the final responsibility for the decision to submit for publication.

Results

Of the 21875 pregnancies registered in the database from June 20, 1999, to May 20, 2016, 9089 pregnancies were identified prospectively in women who had been exposed to antiepileptic drug monotherapy and had complete follow-up data up to 1 year. Of these pregnancies, 7555 met eligibility criteria (figure). 237 (3%) of the 7555 pregnancies were enrolled through the UK and Ireland Epilepsy and Pregnancy Register, 419 (6%) from the Australian Pregnancy Register, and 226 (3%) from the Kerala Registry of Epilepsy and Pregnancy. Of the 7555 eligible pregnancies, 2514 (33%) were exposed to lamotrigine, 1957 (26%) to carbamazepine, 1381 (18%) to valproate, 599 (8%) to levetiracetam, 333 (4%) to oxcarbazepine, 294 (4%) to phenobarbital, 152 (2%) to topiramate, and 125 (2%) to phenytoin. The remaining 200 (3%) pregnancies were associated with 13 other antiepileptic drug monotherapy exposures (ranging from one to 45 pregnancies in each group). Table 1 summarises the demographics of the 7355 pregnancies exposed to the eight most common monotherapies. These pregnancies resulted in 7275 live-born offspring, 43 perinatal deaths, and 37 elective terminations for fetal abnormalities.

810 women contributed two pregnancies, 71 women to three pregnancies, two women to four pregnancies, and

	Odds ratio (95% CI)	Adjusted p value†
Drug comparisons with lamotrigine ≤325 mg/day		
Valproate (>1450 mg/day)	13.52 (7.73–23.64)	0.0002
Phenobarbital (>130 mg/day)	5.81 (2.40–14.08)	0.0002
Valproate (>650 mg/day to ≤1450 mg/day)	4.72 (3.11–7.18)	0.0002
Valproate (≤650 mg/day)	2.70 (1.67–4.38)	0.0002
Carbamazepine (>700 mg/day)	2.68 (1.71–4.19)	0.0002
Phenobarbital (>80 mg/day to ≤130 mg/day)	2.46 (1.16–5.23)	0.0196
Phenytoin (≥30 mg/day to 730 mg/day)	1.93 (0.78–4.75)	0.1554
Carbamazepine (≤700 mg/day)	1.71 (1.12–2.61)	0.0143
Lamotrigine (>325 mg/day)	1.68 (1.01–2.80)	0.0463
Topiramate (≥25 mg/day to 500 mg/day)	1.67 (0.69–4.04)	0.2524
Oxcarbazepine (≥75 mg/day to 4500 mg/day)	1.13 (0.55–2.31)	0.7358
Levetiracetam (≥250 mg/day to 4000 mg/day)	1.11 (0.62–2.00)	0.7282
Phenobarbital (≤80 mg/day)	1.07 (0.25–4.60)	0.923
Within-drug comparisons		
Phenobarbital (>130 mg/day vs ≤80 mg/day)	5.41 (1.05–27.89)	0.0436
Valproate (>1450 mg/day vs ≤650 mg/day)	5.00 (2.79–8.97)	0.0002
Valproate (>1450 mg/day vs >650 mg/day to ≤1450 mg/day)	2.86 (1.67–4.89)	0.0002
Phenobarbital (>130 mg/day vs >80 mg/day to ≤130 mg/day)	2.36 (0.81–6.86)	0.1135
Phenobarbital (>80 mg/day to ≤130 mg/day vs ≤80 mg/day)	2.29 (0.47–11.05)	0.3028
Valproate (>650 mg/day to ≤1450 mg/day vs ≤650 mg/day)	1.75 (1.12–2.73)	0.0147
Lamotrigine (>325 mg/day vs ≤325 mg/day)	1.68 (1.01–2.80)	0.0463
Carbamazepine (>700 mg/day vs ≤700 mg/day)	1.56 (1.03–2.37)	0.0352
Other antiepileptic drug comparisons		
Valproate (>650 mg/day to ≤1450 mg/day) vs lamotrigine (>325 mg/day)	2.81 (1.70–4.65)	0.0002
Valproate (>650 mg/day to ≤1450 mg/day) vs carbamazepine (≤700 mg/day)	2.76 (1.82–4.19)	0.0002
Valproate (≤650 mg/day) vs levetiracetam (250–4000 mg/day)	2.43 (1.30–4.55)	0.0069
Carbamazepine (>700 mg/day) vs levetiracetam (250–4000 mg/day)	2.41 (1.33–4.38)	0.0055
Valproate (≤650 mg/day) vs oxcarbazepine (75–4500 mg/day)	2.39 (1.13–5.08)	0.0235
Carbamazepine (>700 mg/day) vs oxcarbazepine (75–4500 mg/day)	2.37 (1.17–4.80)	0.0169
Valproate (≤650 mg/day) vs carbamazepine (≤700 mg/day)	1.58 (0.98–2.55)	0.0626
Lamotrigine (>325 mg/day) vs levetiracetam (250–4000 mg/day)	1.51 (0.79–2.88)	0.2077
Lamotrigine (>325 mg/day) vs oxcarbazepine (75–4500 mg/day)	1.49 (0.70–3.17)	0.3051
Oxcarbazepine (75–4500 mg/day) vs levetiracetam (250–4000 mg/day)	1.02 (0.45–2.30)	0.9644
Carbamazepine (>700 mg/day) vs valproate (≤650 mg/day)	0.99 (0.60–1.65)	0.9708
Oxcarbazepine (75–4500 mg/day) vs carbamazepine (≤700 mg/day)	0.66 (0.33–1.32)	0.2393
Levetiracetam (250–4000 mg/day) vs carbamazepine (≤700 mg/day)	0.65 (0.36–1.16)	0.1412
Lamotrigine (>325 mg/day) vs carbamazepine (>700 mg/day)	0.63 (0.38–1.05)	0.0766
Lamotrigine (>325 mg/day) vs valproate (≤650 mg/day)	0.62 (0.36–1.09)	0.0959

(Table 4 continues on next page)

one woman to five pregnancies. There were 106 twin pregnancies and one triplet pregnancy. Each twin or triplet was considered a separate pregnancy. Therefore, the 7355 pregnancies occurred in 6393 women.

The patient's physicians submitted reports on potential abnormal fetal outcomes in 752 pregnancies; 383 (5%) of the total 7355 pregnancies were classified as major congenital malformations by the committee. The prevalence of major congenital malformations was 142 (10.3%) of 1381 pregnancies exposed to valproate, 19 (6.5%) of 294 to phenobarbital, eight (6.4%) of 125 to phenytoin, 107 (5.5%) of 1957 to carbamazepine, six (3.9%) of 152 to topiramate, ten (3.0%) of 333 to oxcarbazepine, 74 (2.9%) of 2514 to lamotrigine, and 17 (2.8%) of 599 to levetiracetam (table 2). Outcomes of pregnancies exposed to the 13 less frequently used antiepileptic drugs, which were not included in further analyses, are presented in the appendix. A dose dependency in the prevalence of major congenital malformations was identified for carbamazepine, lamotrigine, phenobarbital, and valproate (table 3).

Table 4 shows the comparisons between the treatment associated with the lowest frequency of major congenital malformations (lamotrigine ≤ 325 mg/day) and other antiepileptic drug treatments, within-drug comparisons of different dose categories, 15 other between-drug comparisons, and non-drug related comparisons. Compared with lamotrigine of 325 mg/day or less, the odds of major congenital malformations was significantly higher for all doses of carbamazepine and valproate, and for phenobarbital at doses of more than 80 mg/day. The low dose category of valproate (≤ 650 mg/day) was associated with increased odds compared with levetiracetam, whereas high-dose carbamazepine (>700 mg/day) was associated with increased odds compared with levetiracetam and oxcarbazepine. Low-dose valproate (≤ 650 mg/day) was not associated with increased odds compared with high-dose lamotrigine (>325 mg/day). Increased odds were also associated with parental history of major congenital malformations and with pregnancies from southeast Asia compared with those from Europe (table 4). Appropriate versus inappropriate or no use of folic acid supplementation was not associated with a reduced odds of major congenital malformations (table 4). No reduction in odds with appropriate use of folic acid was seen when results were analysed by different antiepileptic drugs or for different types of major congenital malformations (data not shown). The results of the sensitivity analysis are reported in the appendix and confirm the robustness of our primary analyses.

The different types of major congenital malformations observed in the 383 offspring are listed in the appendix. With respect to broad categories of malformations, cardiac congenital malformations were the most common, followed by hypospadias, multiple major congenital malformations, renal defects, and neural tube defects (table 5). An ultrasound examination was done in 365 of the

383 pregnancies ending with a major congenital malformation, revealing the malformation in 76 of these cases.

Discussion

In this large cohort study, we ascertained the comparative risk of major congenital malformations for eight commonly used antiepileptic drugs. We did multivariable analysis of 36 direct comparisons between treatment modalities by using, as a measure of exposure, the dose taken at time of conception, which is the dose that physicians can best relate to for treatment decisions before planned pregnancies. We are aware that dose at conception is only an approximate measure of exposure, not least because changes in plasma antiepileptic drug concentrations can occur during pregnancy, including the first trimester. In line with our earlier analysis based on much smaller cohorts,⁵ we identified a dose dependency of the major congenital malformation risk for lamotrigine, carbamazepine, valproate, and phenobarbital. Additionally, we found that even at the lowest dose category (≤ 650 mg/day), valproate was associated with significantly greater risk than most other treatments, with the exception of high-dose categories of carbamazepine and lamotrigine. The lowest risk was found with low-dose lamotrigine (≤ 325 mg/day). This study provides data on the largest published cohorts with levetiracetam ($n=599$) and oxcarbazepine ($n=333$) monotherapy exposure, for which the risk was not dose dependent and overall was comparable to that of low-dose lamotrigine and lower than high-dose carbamazepine. Our data for phenytoin and topiramate, for which no dose dependency was found, need to be interpreted more cautiously because of the comparatively fewer exposures.

Parental history of major congenital malformations was associated with an almost three-times increase in

	Odds ratio (95% CI)	Adjusted p value†
(Continued from previous page)		
Non-drug covariates		
Parental history of major congenital malformations	2.98 (1.52–5.87)	0.0023
Southeast Asia vs Europe	2.43 (1.48–3.99)	0.0009
Americas vs Europe	1.51 (0.62–3.70)	0.3673
Sex (boys vs girls)	1.33 (1.07–1.67)	0.0142
Folic acid (appropriate use vs no use or inappropriate use)	1.26 (0.99–1.60)	0.0579
Maternal age at conception‡	1.01 (0.98–1.03)	0.5166
Western Pacific vs Europe	0.94 (0.63–1.40)	0.7440
Generalised tonic-clonic seizures during first trimester	0.91 (0.58–1.43)	0.6890
Undetermined or unclassifiable vs localisation-related epilepsy	0.76 (0.51–1.14)	0.1893
Parity 1 vs 0	0.75 (0.58–0.98)	0.0329
Idiopathic generalised epilepsy vs Localisation-related epilepsy	0.74 (0.56–0.98)	0.0383
Parity ≥ 2 vs 0	0.72 (0.46–1.13)	0.1574

Within each category of comparison, treatments and other variables are listed in decreasing order of odds, from highest to lowest odds. * $n=7355$. †Multiplicity generated by the 48 comparisons was handled by controlling false discovery rate. ‡Continuous covariate.

Table 4: Results of multivariable analysis of major congenital malformations in the study cohort*

	Antiepileptic drugs								Total number of offspring (n=7355)			Time of detection	
	Carbamazepine (n=1957)	Lamotrigine (n=2514)	Levetiracetam (n=599)	Oxcarbazepine (n=333)	Phenobarbital (n=294)	Phenytoin (n=125)	Topiramate (n=152)	Valproate (n=1381)	Prenatally	Birth (≤2 months after delivery)	>2 months to ≤1 year	21	0
Cardiac	28 (1%)	15 (1%)	5 (1%)	4 (1%)	8 (3%)	5 (4%)	3 (2%)	34 (2%)	102 (1%)	10	71	21	0
Cleft lip or palate	2 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0	6 (<1%)	14 (<1%)	2	12	0	0
Hypospadias	10 (1%)	6 (<1%)	1 (<1%)	0	1 (<1%)	0	1 (1%)	22 (2%)	41 (1%)	0	40	1	0
Neural tube defects	7 (<1%)	1 (<1%)	0	0	2 (1%)	1 (1%)	0	16 (1%)	27 (<1%)	23	4	0	0
Polydactyly	2 (<1%)	0	0	1 (<1%)	2 (1%)	0	0	8 (1%)	13 (<1%)	0	13	0	0
Gastrointestinal	7 (<1%)	8 (<1%)	1 (<1%)	0	0	0	0	2 (<1%)	18 (<1%)	6	11	1	0
Renal	12 (1%)	8 (<1%)	1 (<1%)	0	1 (<1%)	0	0	7 (1%)	29 (<1%)	12	9	8	0
Other major congenital malformations	31 (2%)	27 (1%)	8 (1%)	4 (1%)	4 (1%)	2 (2%)	2 (1%)	30 (2%)	108 (1%)	14	66	28	0
Multiple major congenital malformations	8 (<1%)	6 (<1%)	0	0	0	0	0	17 (1%)	31 (<1%)	9	22	0	0
Total number of major congenital malformations	107 (5%)	74 (3%)	17 (3%)	10 (3%)	19 (6%)	8 (6%)	6 (4%)	142 (10%)	383 (5%)	76	248	59	0
No major congenital malformations reported	1850 (95%)	2440 (97%)	582 (97%)	323 (97%)	275 (94%)	117 (94%)	146 (96%)	1239 (90%)	6972 (95%)

Data are n (%) of affected offspring, unless stated otherwise.

Table 5: Major congenital malformations associated with eight different antiepileptic monotherapies and their time of detection

odds of major congenital malformations, suggesting a genetic predisposition to malformations or an individual susceptibility, or both, to the teratogenic effects of antiepileptic drugs. Earlier studies have found a high risk of major congenital malformations in the offspring of women who had multiple pregnancies associated with exposure to the same drug.^{24,25} Compared with inappropriate or no folate supplementation, appropriate folate supplementation was associated with a borderline (about 1.3-times) increase in the odds of major congenital malformations, although this finding was not significant. This finding might reflect a greater propensity to use folate in women considered to be at greater risk of an adverse pregnancy outcome and should not be considered as an argument against folate supplementation. The results, however, confirm the paucity of evidence for a protective effect of folate against major congenital malformations induced by antiepileptic drugs.²⁶ Our analysis also revealed about a 1.3-times increase in odds of major congenital malformations in offspring of the male sex. The sex difference was no longer present when the sex-specific hypospadias was removed from the analysis (data not shown).

EURAP has a time window for identification of major congenital malformations extending to 1 year after birth, whereas other registries mostly limit their follow-up to birth or 2 months after birth.^{2,3} Of the 383 cases with major congenital malformations, 59 (15%) cases were only detected after 2 months, which explains why the frequency of major congenital malformations is higher in EURAP than in studies with shorter follow-up. This extended duration of follow-up, together with differences in criteria of major congenital malformations, limits comparisons across registries²⁷ and affects the validity of meta-analyses.^{1,19}

It is concerning that only 20% of major congenital malformations were detected prenatally, despite the fact that 95% of the women had undergone an ultrasound examination, which even failed to detect four (15%) of 27 neural tube defects. The detection rate is known to vary markedly depending on the type of major congenital malformation, examination modalities used, and examiner's expertise. In a systematic review, a second trimester ultrasound scan was found to detect spina bifida in 67% of offspring, cardiac defects in 17%, gastrointestinal defects in 41%, and renal malformations in 67%.²⁸ The detection rates for cardiac defects, gastrointestinal defects, and renal malformations were lower in the EURAP registry than in this systematic review. In line with the observational nature of the registry, ultrasonography testing was not done according to a standardised protocol, but followed local standards in participating centres. Most of the pregnancies, however, had an examination in the second trimester.

EURAP and other prospective registries have previously reported frequencies of major congenital malformations after monotherapy exposure to the most commonly used antiepileptic drugs based on smaller cohorts.^{2-5,18} The

North American Antiepileptic Drug Pregnancy Registry reported a dose dependency in risk of major congenital malformations for valproate only, and found that in comparison with lamotrigine the risk was significantly greater for valproate (risk ratio 5.1, 95% CI 3.0–8.5), phenobarbital (2.9, 1.4–5.8), and topiramate (2.2, 1.2–4.0).³ The UK and Ireland Epilepsy and Pregnancy Registers reported greater risk of major congenital malformations with valproate than with lamotrigine and carbamazepine, and found a dose dependency in the risk associated with valproate and carbamazepine.² The Australian Pregnancy Register²⁹ and the Kerala Registry of Epilepsy and Pregnancy,⁴ both collaborating with EURAP, have reported dose dependency in the risk of major congenital malformation with valproate. The comparatively low frequency of major congenital malformations with levetiracetam and oxcarbazepine found in our study is in line with reports from smaller cohorts.^{3,29,30} By contrast with some studies,^{1,3,19,31} we did not find a particularly high risk with topiramate. Our results on topiramate should, however, be interpreted cautiously because of the smaller size of the cohort exposed to this drug.

Our analysis provides a large number of direct comparisons between treatments, including risks associated with specific dose ranges, which can guide treatment choices for women of childbearing potential who require antiepileptic drug treatment.

The main strengths of our study are the large size of the cohort, the prospective recording of exposure to antiepileptic drugs and other potentially relevant risk factors before outcome is known, and the meticulous follow-up with strict criteria for classifying major congenital malformations. A further strength, and a challenge, is the international scope with inclusion of data from more than 40 countries worldwide. One limitation is that the registry is not population based, and women are enrolled by reporting physicians who might have a special interest and expertise. Such possible selection bias should, however, not affect the validity of the internal comparisons between treatments, which is the main objective of the study. A further limitation is the absence of a control group of pregnancies without exposure to antiepileptic drugs, but the relevant question for physicians treating women with a serious condition that involves pregnancy is rarely whether to treat or not, but rather which of the available treatments is the safest. However, a recent large meta-analysis reported an average risk of major congenital malformations of 2.6% in children unexposed to antiepileptic drugs.¹ Although it is difficult to compare data across studies, the frequency of major congenital malformations associated with lamotrigine, levetiracetam, and oxcarbazepine in the EURAP registry are in the same range as those reported in the meta-analysis for unexposed offspring. One might also consider the fact that exposure was defined by antiepileptic drug dose rather than plasma concentration of the antiepileptic drug as a limitation, because plasma

concentration probably better reflects fetal exposure to the drug. However, standardised drug concentration sampling and measurement was not feasible in a large-scale international epidemiological study. Furthermore, there is no consensus on when samples should be drawn or how they should be analysed to best reflect fetal exposure during the critical time window for teratogenesis.

Because treatment allocation was not randomised, factors other than the type of antiepileptic drug used might affect outcome. For these reasons, we excluded pregnancies with exposure to other teratogenic drugs or with concurrent diseases known to increase the risk of adverse pregnancy outcomes. Information about other potential risk factors was collected prospectively and included in the multivariable analysis.

In conclusion, this study is the most comprehensive direct comparison of major congenital malformation risk with different antiepileptic drugs. Therefore, this study provides physicians with vital information when they consider different treatment alternatives for women that are of childbearing potential. Although our analysis was restricted to women with epilepsy, there is no reason why the data should not be applicable to fetal antiepileptic drug exposure regardless of indication.

Contributors

All authors contributed equally to the design of the study. EB did the statistical analysis. All authors contributed equally to the interpretation of the data. TT and DB drafted the first version of the manuscript, and all authors contributed equally to the input of the first draft and the finalisation of the submitted manuscript.

Declaration of interests

TT is an employee of Karolinska Institutet (Stockholm, Sweden) and is Associate Editor for the *Epileptic Disorders* journal. TT has also received speaker's honoraria to his institution from Eisai, UCB, Actavis, *BMJ* India, Livanova, and Sandoz; honoraria to his institution for advisory boards from UCB and Eisai; and research support from Stockholm County Council, CURE, GlaxoSmithKline, UCB, Eisai, Bial, and Novartis. DB has received speaker's honoraria from UCB and Sanofi. EB has received consultancy fees from Italfarmaco, Zambon, Polichem, Roche, and Sanofi-Aventis. JC has received research grants and speaker's honoraria from UCB Pharma, Eisai, GlaxoSmithKline, Sanofi Synthelabo, Pfizer, and Janssen-Cilag. DL has received research grants from Janssen-Cilag, GlaxoSmithKline, Pfizer, and the Netherlands Epilepsy Foundation. EP has received research funds from the European Union, the Italian Ministry of Health, the Italian Ministry for Education and University, and the Italian Medicines Agency; has received speaker's, consultancy fees, or research grants from Eisai, Livanova, Medichem, Sanofi, Sandoz, and Sun Pharma; and has been on the safety or advisory boards of UCB Pharma and GW Pharma. AS has received consultancy or lecture fees for Eisai Denmark and UCB Nordic; and has received travel support from Eisai, Biogen, and UCB Nordic. SVT has received research support from the Indian Council of Medical Research, speaker's honorarium from *BMJ* India, and Royalty from Wiley Publishing House. FV declares no competing interests.

Acknowledgments

EURAP has received financial support from Bial, Eisai, GlaxoSmithKline, Novartis, UCB, Janssen-Cilag, Pfizer, and Sanofi-Aventis. EURAP have continued to receive financial support after 2010 from Bial, Eisai, GlaxoSmithKline, Novartis, and UCB. Further financial support has been provided from the Netherlands Epilepsy Foundation (grant 03-18 [Lindhout]) and the Regional Agreement on Medical Training and Clinical Research (ALF) between Stockholm County Council and Karolinska Institute (Tomson). The Australian

Pregnancy Register has received funding from Sanofi/Genzyme, UCB, Janssen, Sci-Gen, Eisai, the Australian National Health and Medical Research Council, Epilepsy Society of Australia, Royal Melbourne Hospital Medical Research Foundation, and Epilepsy Action.

References

- Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. *BMC Med* 2017; **15**: 95.
- Campbell E, Kennedy F, Russell A, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry* 2014; **85**: 1029–34.
- Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012; **78**: 1692–99.
- Thomas SV, Jose M, Divakaran S, Sankara Sarma P. Malformation risk of antiepileptic drug exposure during pregnancy in women with epilepsy: results from a pregnancy registry in South India. *Epilepsia* 2017; **58**: 274–81.
- Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 2011; **10**: 609–17.
- Tomson T, Battino D, Perucca E. Valproic acid after five decades of use in epilepsy: time to reconsider the indications of a time-honoured drug. *Lancet Neurol* 2016; **15**: 210–18.
- Vajda FJ, O'Brien TJ, Graham JE, Lander CM, Eadie MJ. Dose dependence of fetal malformations associated with valproate. *Neurology* 2013; **81**: 999–1003.
- Baker GA, Bromley RL, Briggs M, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. *Neurology* 2015; **84**: 382–90.
- Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009; **360**: 1597–605.
- Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013; **12**: 244–52.
- Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013; **309**: 1696–703.
- US Food Drug Administration. FDA drug safety communication: valproate anti-seizure products contraindicated for migraine prevention in pregnant women due to decreased IQ scores in exposed children. June 5, 2013. <https://www.fda.gov/Drugs/DrugSafety/ucm350684.htm> (accessed Sept 12, 2017).
- European Medicines Agency. Assessment report: procedure under article 31 of directive 2001/83/EC resulting from pharmacovigilance data. Oct 9, 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_and_related_substances_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500177352.pdf (accessed April 10, 2015).
- Wen X, Meador KJ, Hartzema A. Antiepileptic drug use by pregnant women enrolled in Florida Medicaid. *Neurology* 2015; **84**: 944–50.
- Murphy S, Bennett K, Doherty CP. Prescribing trends for sodium valproate in Ireland. *Seizure* 2016; **36**: 44–48.
- Tomson T, Marson A, Boon P, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. *Epilepsia* 2015; **56**: 1006–19.
- Bobo WV, Davis RL, Toh S, et al. Trends in the use of antiepileptic drugs among pregnant women in the US, 2001–2007: a medication exposure in pregnancy risk evaluation program study. *Paediatr Perinat Epidemiol* 2012; **26**: 578–88.
- Vajda FJ, O'Brien TJ, Lander CM, Graham J, Eadie MJ. The teratogenicity of the newer antiepileptic drugs—an update. *Acta Neurol Scand* 2014; **130**: 234–38.
- de Jong J, Garne E, de Jong-van den Berg LT, Wang H. The risk of specific congenital anomalies in relation to newer antiepileptic drugs: a literature review. *Drugs Real World Outcomes* 2016; **3**: 131–43.
- Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League against Epilepsy. *Epilepsia* 1989; **30**: 389–99.
- EUROCAT. EUROCAT Guide 1.3 and reference documents: instructions for the registration and surveillance of congenital anomalies. Newtownabbey: EUROCAT Central Registry, 2005.
- Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol* 2014; **67**: 850–57.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol* 1995; **57**: 289–300.
- Vajda FJ, O'Brien TJ, Lander CM, Graham J, Roten A, Eadie MJ. Teratogenesis in repeated pregnancies in antiepileptic drug-treated women. *Epilepsia* 2013; **54**: 181–86.
- Campbell E, Devenney E, Morrow J, et al. Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero. *Epilepsia* 2013; **54**: 165–71.
- Morrow JI, Hunt SJ, Russell AJ, et al. Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2009; **80**: 506–11.
- Tomson T, Battino D, Craig J, et al. Pregnancy registries: differences, similarities, and possible harmonization. *Epilepsia* 2010; **51**: 909–15.
- Bricker L, Garcia J, Henderson J, et al. Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views. *Health Technol Assess* 2000; **4**: 1–193.
- Vajda FJ, O'Brien T, Lander C, Graham J, Eadie M. The efficacy of the newer antiepileptic drugs in controlling seizures in pregnancy. *Epilepsia* 2014; **55**: 1229–34.
- Mawhinney E, Craig J, Morrow J, et al. Levetiracetam in pregnancy: results from the UK and Ireland epilepsy and pregnancy registers. *Neurology* 2013; **80**: 400–05.
- Hunt S, Russell A, Smithson WH, et al. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2008; **71**: 272–76.