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Malformation risks of anti-epileptic drugs in pregnancy: A prospective study from the UK Epilepsy and Pregnancy Register.

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SUMMARY

Background – Anti-epileptic drugs (AEDs) taken during pregnancy are associated with an increased risk of major congenital malformations (MCMs). The risks for different AED regimes are difficult to define from earlier studies and are mostly unknown for those containing the newly licensed AEDs (vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam and pregabalin).

Methods – The UK Epilepsy and Pregnancy Register is a prospective, observational, registration and follow up study. Women with epilepsy who become pregnant, whether or not they are taking an AED, in any combination, and whose details are forwarded before the outcome of the pregnancy is known are included. The presence of MCMs recorded within the first three months of life is the main outcome measure.

Findings – Full outcome data was collected on 3607 cases. The overall MCM rate for all AED exposed cases was 4.2% (95% C.I. 3.6 – 5.0%). The MCM rate was significantly higher in polytherapy (6.0%) (n=770) compared with monotherapy exposures (3.7%) (n=2598) (crude OR 1.63 [p=0.010]; adjusted OR 1.83 [p=0.002]). The MCM rate for women with epilepsy who had not taken AEDs during pregnancy (n=239) was 3.5% (95% C.I. 1.8 – 6.8%). The MCM rate was significantly greater for pregnancies exposed only to valproate (6.2% ; 95% C.I. 4.6 – 8.2) compared with those exposed only to carbamazepine (2.2% ; 95% C.I. 1.4 – 3.4)(OR 2.78 [p<0.001]; adjusted OR 2.97 [p<0.001]). There were also fewer MCMs for pregnancies exposed only to lamotrigine (3.2% ; 95% C.I. 2.1 – 4.9) compared with those exposed only to valproate OR 0.52 [p=0.015]; though statistical significance was lost using multivariable analysis (adjusted OR 0.59 [p=0.064]). While there was a trend towards more MCMs with increasing doses of valproate this was not significant. A positive dose response for MCMs was noted for lamotrigine (p=0.006) with a MCM rate of 5.4% (95% C.I. 3.3 -8.7%) for total daily doses of more than 200mg. This MCM rate was similar to those receiving doses of 1000mg or less of valproate (5.1% ; 95% C.I. 3.5 – 7.3). For pregnancies exposed to more than 1000mg of valproate a day the MCM rate was 9.1% (95% C.I. 5.8 – 14.1%). For polytherapy combinations, those containing valproate in any combination had a significantly higher risk of MCM than polytherapy combinations not containing valproate (O.R. 2.49 [95% C.I. 1.31 – 4.70]).

Interpretation – Almost 96% of live-births born to women with epilepsy did not have a MCM. The MCM rate for polytherapy exposed pregnancies was significantly
greater than for monotherapy exposures. Polytherapy regimes containing valproate had significantly more MCMs than those not containing valproate. For monotherapy exposures, carbamazepine was associated with the lowest risk of MCM. While there was a trend towards lamotrigine being associated with fewer MCMs than valproate, the differences were minimised in those infants exposed to more than 200mg each day of lamotrigine.

KEY WORDS: Epilepsy, Pregnancy, Teratogenicity, Antiepileptic drugs.
BACKGROUND

Epilepsy is the most common serious chronic neurological condition, with a prevalence of between 4 and 10 people per 1000 [1]. Most of those affected, including women of childbearing years, will require long-term treatment with antiepileptic drugs (AEDs) to prevent seizures. Although the interactions between epilepsy and pregnancy are multiple, it is the potential effect of AEDs on the developing foetus that raises most concern. With an estimated three to four pregnancies in every thousand occurring to women with active epilepsy [2, 3], this means between 1800 to 2400 children are born to such women in the UK each year.

It is widely accepted that prenatal exposure to AEDs increases the risk of a major congenital malformation (MCM) from the background risk of 1-2% [3, 4] to between 4-9% [4-7]. With regard to the spectrum of MCM, physicians are generally aware that neural tube defects have been associated with in-utero exposure to sodium valproate and carbamazepine [8-10] and barbiturates (phenobarbital, primidone) and phenytoin have been associated with congenital heart defects and facial clefts [11-13]. Other MCMs including urogenital and skeletal abnormalities have also been reported [13,14].

The information from these studies, which form the basis for how we counsel women with epilepsy, who are contemplating pregnancy or who are already pregnant, up until recently did not include any data on the newly available AEDs, of which eight (vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam and pregabalin) have been introduced in the UK since 1989. While animal studies on many of these AEDs are encouraging when compared to older AEDs [15], human data are sparse. In an attempt to provide information on the risks of MCMs for prenatal exposure to the ever increasing number of AEDs, pregnancy registries have been developed. The UK Epilepsy and Pregnancy Register, established in 1996, was one of the first modern independent pregnancy registers to be established. Here we present our findings up to March 31 2005.
METHODS
This is a prospective, observational, registration and follow-up study which commenced in December 1996. Ethical approval was obtained from the North Thames Multicentre Research Ethics Committee and subsequently from all UK local research ethics committees.

Cases suitable for inclusion were defined as pregnant women with epilepsy, whether or not they were taking an AED, either in monotherapy or polytherapy, and who were referred to the register before the outcome of the pregnancy was known. Cases where any prenatal test (fetal ultrasound, blood test) had shown an abnormality and cases resulting in a pregnancy loss, in which an abnormality had been identified before referral to the register had been made, were excluded. Cases that were on no AEDs during the first trimester but then had second or third trimester exposure to an AED were also excluded. Cases that had exposure to more than one AED during the first trimester, or who had additional AEDs started in the second or third trimesters were counted as polytherapy exposures.

Cases were referred to the register by neurologists, epilepsy nurse specialists, obstetricians and midwives, general practitioners, and other health care professionals caring for women with epilepsy, and from women with epilepsy themselves through our freephone (0800 3891248) or by downloading registration forms from our website www.epilepsyandpregnancy.co.uk.

Information was collected at registration from the referring source and as required from any other relevant health care professionals. Details collected included general demographic information, epilepsy details, including cause of epilepsy if known, seizure types and frequency, AED exposure details up to three months before conception and during the pregnancy up to the date of referral with any changes made, and other drug exposure details including folic acid prescription with details of dose and whether commenced pre-conceptually. Outcome data were collected at three months after the expected date of delivery firstly by sending the patient’s general practitioner a standardized questionnaire for completion. Information collected at this time included changes to AEDs during pregnancy, previous pregnancy details, relevant family history, current pregnancy details including the
results of prenatal testing and details on current pregnancy outcome. At this time any others (clinical geneticist, paediatrician etc.) who had either been identified during the pregnancy or at follow up were also contacted for further information.

**Data Analysis**

Outcomes were classified by one of the authors (PM) into those without birth defects, those with MCMs and those with other defects (minor defects, and chromosomal disorders and single gene defects). For each of these categories, outcomes were further sub-divided into live births and pregnancy losses (spontaneous pregnancy losses or induced abortions). The results were also stratified by whether exposure was part of a monotherapy or polytherapy regime.

A MCM was defined as an abnormality of an essential embryonic structure requiring significant therapy and present at birth or discovered during the first six weeks of life.

Disorders not conforming to this definition were assigned as minor malformations based on the definitions and lists of disorders in the EUROCAT registry. Developmental delay and cases of fetal anticonvulsant syndrome, where there was a combination of dysmorphic features but no major defects as defined above, although significant defects in themselves were coded as minor structural malformations.

**Statistical analysis**

The MCM rate was calculated as; the total number of live births with a MCM + the total number of pregnancy losses with a MCM / the total number of live births + the total number of pregnancy losses with a MCM. Spontaneous pregnancy losses and induced abortions where no abnormalities were reported were not included for analysis as we do not know if they were examined in detail and therefore can not know the outcome. Total numbers presented for each grouping are therefore either total number of outcomes or total number of informative outcomes i.e. pregnancy losses with no abnormalities reported excluded. For each MCM rate 95% confidence intervals were calculated based on Wilson, using *Confidence Interval Analysis (CIA) for Windows*. For pregnancies exposed to carbamazepine, valproate or lamotrigine in monotherapy the effect of dose on the occurrence of MCMs was also analyzed using the Mann-Whitney U test. Individual logistic regression analyses
were conducted using the presence of an MCM as the dependent variable, and age of mother at birth, parity of mother, family history of MCM, peri-conceptional folic acid intake, sex of infant and category of AED exposure (monotherapy, polytherapy and no AED exposures and individual AED exposures with more than 25 recorded cases [carbamazepine, valproate, lamotrigine, phenytoin, gabapentin]) as the independent variables. Crude and adjusted odds ratios (OR) and their 95% confidence intervals were calculated with no AED exposure and carbamazepine for individual monotherapy exposures being used as the comparators. \( P \) values of <0.05 were considered significant. Calculations were performed using SPSS Version 13.
FINDINGS
On March 31, 2005, 4414 pregnancies had been registered, of which 3607 had full outcome data. Three hundred and fifty six cases (8.1%) were lost to follow up. The reasons for loss to follow up were, withdrawal of consent (n=22), change of address/GP (n=75), failure to respond to follow up questionnaire (n=198) and incomplete details returned (n=61). A number of pregnancies are ongoing and outcome is awaited (n=451). With regard to exclusions, 5 spontaneous abortions that had occurred prior to registration were excluded, in addition 2 patients were excluded from analysis because of abnormal scans prior to registration - both were late registrations (>20 weeks) in one case Fallot’s teratology had been diagnosed and in the other case spina bifida had been queried (though was later excluded). The register has also been informed about a number of previously completed pregnancies but this retrospective data has not been considered here.

Two thousand five hundred and ninety eight (72.0%) cases had been exposed to a single AED in pregnancy, 770 (21.3%) to more than one AED and 239 (6.7%) were reported to have epilepsy but were not exposed to any AEDs during their pregnancy. Figure 1. illustrates the total number of monotherapy exposures per drug.

Two hundred and seven (5.7%) resulted in a pregnancy loss. Of these 21 were recorded as having any type of birth defect, with thirteen being a MCM. Of the live births (n=3400), 316 (9.3%) were recorded as having any type of birth-defect of which 129 were recorded as having an MCM. The MCM rate for all AED exposed pregnancies was 4.2% (95% C.I. 3.6 – 5.0%). Table 1 shows the MCM rate by type of AED exposure. The MCM rate was significantly higher in polytherapy compared with monotherapy exposures. (crude OR 1.63 [p=0.010]; OR adjusted for age at birth, parity, family history of MCM, folic acid exposure, sex of infant 1.83 [p=0.002]).

Table 2 shows MCM details for monotherapy exposures with over 25 outcomes. The MCM rate was significantly less for carbamazepine compared with valproate. There was a trend towards fewer MCMs for lamotrigine compared with valproate exposed pregnancies (unadjusted OR 0.517 [p=0.015]; however when adjusted for age at birth, parity, family history of MCM, folic acid exposure, sex of infant statistical
significance was lost (OR 0.589 [p=0.064]). Two infants exposed to topiramate (35
exposures) had an MCM (one case of cleft lip and palate, one case of hypospadias)
and one infant exposed to gabapentin had a ventriculoseptal defect. No MCMs were
recorded from any other monotherapy exposures (levetiracetam n=25, ethosuximide
n=12, clonazepam n=9, vigabatrin n=6, oxcarbazepine n=7, and piracetam n=1). The
types of malformations recorded for individual monotherapy exposures are shown in
table 3.

DOSE RESPONSE
The mean daily dose of AED was not different for those cases with and without a
MCM respectively for either carbamazepine (657.5mg and 611.7mg; p=0.56) or
valproate (1053.5mg and 936.0; p=0.153). For lamotrigine the mean daily dose was
significantly higher for those with an MCM compared with those without an MCM
respectively (352.4mg and 250.6mg; p=0.005). The MCM rates by exposure to
carbamazepine, valproate and lamotrigine as a function of dose are shown in table 4
and illustrated in figure 2.

POLYTHERAPY
There were 126 different combinations among the 770 cases exposed to AEDs in
polytherapy. The MCM rates for the 388, 430 and 304 cases exposed respectively to
carbamazepine, lamotrigine and valproate as part of a polytherapy combination were
4.1% (95% C.I. 2.5 – 6.7%), 4.8% (95% C.I. 3.1 – 7.3%) and 9.0% (95% C.I. 6.3 –
12.8%). For polytherapy combinations, those containing valproate in any
combination had a significantly higher risk of MCM than polytherapy combinations
not containing valproate (O.R. 2.49 [95% C.I. 1.31 – 4.70]). Considering the most
commonly used polytherapy combinations, the MCM rate for pregnancies exposed to
carbamazepine and valproate (n=62) was 8.8% (95% C.I. 3.8 – 18.9) and for
pregnancies exposed to valproate and lamotrigine (n=141) was 9.6% (95 C.I. 5.7 –
15.7%). No MCMs were recorded in pregnancies exposed to carbamazepine and
lamotrigine (n=118) [MCM rate 0.0% (95% C.I. 0.0 – 3.3%).
INTERPRETATION

In this study which reports on the largest number of pregnancy outcomes for infants born to women with epilepsy, we found that almost 96% of infants exposed to AEDs in utero did not have a MCM. However, for those exposed to AEDs as part of a polytherapy regime the MCM rate was significantly higher than for monotherapy exposures. In our study, most monotherapy exposures were for carbamazepine, valproate and, increasingly during the study period, to lamotrigine. Differences were noted between drugs, with significantly fewer MCMs being noted for carbamazepine compared with valproate. There was a trend towards fewer MCMs with lamotrigine compared with valproate, which was statistically significant on univariate analysis though significance was lost on multivariable analysis. Further analysis of the data revealed that a disproportionate number of cases exposed to valproate and with a malformation had been excluded from the multivariable analysis as information on one or more of the variables was incomplete. This may have affected the result by underestimating the MCM rate for valproate in the multivariable analysis. For monotherapy exposures, a positive dose response was observed for lamotrigine. While we observed a trend towards a dose response for valproate this did not reach statistical significance. However, infants exposed to more than 1000mg of valproate had the highest MCM rate for any monotherapy exposure at 9.1%. The types of MCMs found in pregnancies exposed to carbamazepine, valproate and phenytoin in monotherapy were similar to those previously reported, neural tube defects, facial clefts, cardiac defects, hypospadias and skeletal abnormalities being most frequently reported. For lamotrigine the types of MCM were not dissimilar from other AEDs, although genito-urinary abnormalities (eg hypospadias) (28%) and unusual gastrointestinal defects (eg duodenal / oesophageal atresia) (14%) appeared to be over represented. However, it would take many more outcomes to reliably comment on the prevalence of individual malformations. For polytherapy combinations containing valproate the MCM rate was between two and three times higher than combinations not containing valproate.

One of the strengths of this study was that women with epilepsy from a single country were enrolled during pregnancy before outcome was known. As a result we were able to include adverse outcome data from pregnancy losses of all kinds. The exclusion of cases in whom an abnormality had been identified prior to registration might have introduced the potential to underestimate the MCM rate, but in fact this proved to be
more a theoretical consideration than a practical one, as apart from a small number of spontaneous abortions that occurred early and prior to registration (and would, in any case, have been excluded from calculation of MCM rate) only two cases were excluded from the study due to abnormal scans prior to registration – both were late referrals (>20 weeks) (and in one case the abnormality was later excluded by further tests).

The identification and recruitment of women with a diagnosis of epilepsy who did not take AEDs during pregnancy was another strength of the study, although this group may not constitute a control group as women with epilepsy, who do not require AEDs may not be considered as directly comparable to those having to continue on drugs. That our referrals came from a wide range of sources including antenatal booking clinics and women themselves likely helps the generalizability of the results.

Another strength of the study was the General Practitioner system within the UK. As through this single source we were able to obtain outcome data. Although a number of other specialists and others may have been involved in the care of the infants, one would expect that any abnormality identified would have been reported back to the child’s/mother’s General Practitioner.

The principal weakness of the study is that it is not a randomised controlled trial, it is simply an observational study. Women were not randomly assigned to receive different AEDs, and the selection of a particular agent and its dosage depended on individual environmental and genetic variables that in themselves may have had a bearing on the risk of MCM. However, a randomised controlled trial in this area would be deemed unethical and impracticable, indeed risk of pregnancy is often an exclusion criteria in regulatory trials of AEDs. Another weakness is that even when recruitment was occurring at its maximum (between 70 and 80 cases each month), we were still only being informed of between 40 and 50% of all eligible cases in the UK. This clearly has the potential to introduce biases although we feel that recruiting from a broad range of sources may have minimized these. We also did not set an absolute time limit beyond which cases were excluded. It is therefore possible that referrers did have some a priori knowledge of outcome, based for example on the results of early ante-natal screening tests, which were not passed on to us at the time of referral.
We also did not record all potentially relevant confounding variables, for example socio-economic class, smoking, and alcohol habits. That we only recorded MCMs noted at three months is also potentially problematic as some MCMs may present much later in life, although the majority of major defects would be detectable at 3 months.

All of the older AEDs have been previously linked with an increased risk of MCMs [4-7]. However, the quality of information available on any potential for teratogenic effects, even for those AEDs which have been widely used for decades, is difficult to assess. Results from earlier studies are often methodologically flawed, for example, many studies were retrospective and were often were carried out in specialised epilepsy centres, which could affect the generalizability of the results. More importantly, the numbers of patients included on each drug in monotherapy were often inadequate to carry out comparisions between the agents used and even when the amalgamated findings from smaller (but not methodologically exact) studies were performed the numbers were often still too small to reliably perform statistical analysis. Furthermore, until recently there has been no information on the safety of the newer AEDs and how these compare with established AEDs.

In an order to address these deficiencies pregnancy registers have been developed across the world, which include those conducted by the pharmaceutical industry as well as those managed by independent groups of physicians and scientists [19-24]. The International Lamotrigine Pregnancy Register was the first to report on a substantial number of pregnancies exposed to one of the newer AEDs.[25] Initial results based on 334 first trimester lamotrigine outcomes, showed an MCM rate for 168 monotherapy outcomes of 1.8%(95% C.I. 0.5 –5.5%) and 6.0% for 166 polytherapy exposures. Similar to our results, they found an MCM rate of 10% (95% C.I. 3.7 – 22.6%) in those infants exposed to lamotrigine and valproate. Rather than being specific to this combination, and difficult to interpret, we feel our results suggest that it is likely that it is the valproate that contributes to the increased risk. Updated figures from The International Lamotrigine Pregnancy Register, published in 2005, from 414 first trimester monotherapy exposures were closer to those we found with a MCM rate of 2.9% (95% CI 1.6% - 5.1%). [26] Of the other pregnancy registers, the Australian Pregnancy Register for Women on Anti-epileptic Medication
has presented the results of 61 monotherapy exposures to lamotrigine with no MCMs being noted. [27] In another study from Denmark the overall MCM rate for lamotrigine exposed pregnancies (n=51) was 2.0%. [28] Information on the safety of the other newer AEDs data are still sparse. [15] A recent report of 55 exposures (20 polytherapy and 35 monotherapy) to oxcarbazepine only noted one MCM. [29].

Our findings for valproate, either taken singly or in combination, are in broad agreement with the results so far published or presented by the other pregnancy registers in suggesting an increased risk in this group, though the magnitude of this risk appears lower in our study than others. The North American AED Pregnancy Registry recently published 16 affected cases among 149 VPA-exposed women (10.7%; 95% CI : 6.3-16.9%). Assuming a background prevalence of 1.62% for major congenital defects, they suggested a relative risk for MCM in valproate exposed pregnancies of 7.3 (95% CI 4.4 –12.2) [30]. Figures published from the Australian Pregnancy Register for Women on Anti-epileptic Medication revealed a malformation rate for valproate exposed pregnancies of 16.0%. Although this included both monotherapy and polytherapy exposure, once again the number of exposed pregnancies (n= 97) was considerably less than in our current study [31]. In the Australian study the mean daily dose of valproate was higher in those with a malformation, a finding that has previously been reported. [5,7]. While we noted a trend in the same direction our findings did not reach significance.

In keeping with our findings, that MCMs are more likely with valproate taken in monotherapy compared with carbamazepine taken in monotherapy was reported in a recent much smaller study from Sweden (O.R. 2.51 [1.43 – 4.48]) [32]. Whilst our results may suggest that there is a higher relative risk of MCM in the offspring of women exposed to valproate than carbamazepine the absolute risk in both groups remains low. It must also be recognised that the two groups are not absolutely comparable as carbamazepine and valproate may be used to treat different forms of epilepsy, with valproate being more commonly used in the idiopathic generalised epilepsies. This may not only introduce a further confounding variable but also mitigate against the switching of the drugs if pregnancy is contemplated.
Recent reviews of the subject have suggested caution in the prescription of valproate in women with epilepsy planning to become pregnant and suggested the consideration of the prescription of other equally effective and safer AEDs [33]. Lamotrigine has a spectrum of efficacy similar to that of valproate and has been suggested as an alternative to it in certain patient groups. Our results provide the first information collected from large numbers of pregnancies comparing outcomes on these two drugs in pregnancy. The results suggest that the group of women exposed to lamotrigine appear to have a lower overall risk of having a child with a MCM, particularly at doses of 200mg or less, than those taking valproate. However it should be noted that for women taking dose of lamotrigine greater than 200mg per day the MCM rate (5.4% ; 95% CI 3.3 – 8.7%) was no different to pregnancies exposed to 1000mg or less per day of valproate ( 5.1% ; 95% CI 3.5 – 7.3%).

Clearly there is a need for further data to be collected to estimate the risks of all available AEDs in pregnancy, and not only for MCMs. Notwithstanding some methodological concerns pregnancy registers seem the only feasible way of collecting the data required to signal such safety concerns for particular AEDs or regimes. The UK Epilepsy and Pregnancy Register continues to collect information and welcomes new referrals. Our study supports the idea that there are differences between AEDs and highlights areas of concern. That almost 96% of infants born to women with epilepsy did not have a MCM however, is a message that is likely to be reassuring both to women with epilepsy and to those who care for them.
**Sources of Funding**

This study was made possible by a research grant from the Epilepsy Research Foundation and a number of educational grants from pharmaceutical companies (Glaxo-Smith-Kline, Sanofi-Aventis, UCB –Phama, Janssen-Cilag, Pfizer.) An internet based web-site detailing the aims of the UK Epilepsy and Pregnancy register was made possible by a grant from Glaxo-Smith-Kline.

**REFERENCES.**


<table>
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<th>Drug exposure</th>
<th>Number of informative outcomes*</th>
<th>Number of MCM</th>
<th>Crude MCM rate (95% C.I.)</th>
<th>Odds ratio (95% C.I.)</th>
<th>P value</th>
<th>Adjusted odds ratio# (95% C.I.)</th>
<th>P value#</th>
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<td>No AED</td>
<td>227</td>
<td>8</td>
<td>3.5 (1.8 – 6.8)</td>
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<td>-</td>
<td>1.0 (1.8 – 6.8)</td>
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<td>Monotherapy</td>
<td>2468</td>
<td>91</td>
<td>3.7% (3.0 – 4.5)</td>
<td>1.05 (0.50 – 2.19)</td>
<td>0.90</td>
<td>1.03 (0.49 – 2.17)</td>
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<td>43</td>
<td>6.0% (4.5 – 8.0)</td>
<td>1.71 (0.79 – 3.69)</td>
<td>0.17</td>
<td>1.76 (0.80 – 3.86)</td>
<td>0.16</td>
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</table>

*Pregnancy losses with no MCM excluded.

# Adjusted for age at delivery, parity of mother, family history of MCM, periconceptional folic acid exposure and sex of infant.

Table 1. Overall MCM rates by type of AED exposure.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of informative outcomes*</th>
<th>Number of MCM</th>
<th>MCM rate (95% C.I.)</th>
<th>OR (95% C.I.)</th>
<th>P value</th>
<th>Adjusted OR (95% C.I.)#</th>
<th>P value#</th>
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<td>Carbamazepine</td>
<td>900</td>
<td>20</td>
<td>2.2% (1.4 – 3.4)</td>
<td>1.0</td>
<td>-</td>
<td>1.0</td>
<td>-</td>
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<td>Valproate</td>
<td>715</td>
<td>44</td>
<td>6.2% (4.6 – 8.2)</td>
<td>2.78</td>
<td>&lt;0.001</td>
<td>2.97 (1.65 – 5.35)</td>
<td>&lt;0.001</td>
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<td>Lamotrigine</td>
<td>647</td>
<td>21</td>
<td>3.2% (2.1 – 4.9)</td>
<td>1.44</td>
<td>0.253</td>
<td>1.71 (0.88 – 3.32)</td>
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<td>Phenytoin</td>
<td>82</td>
<td>3</td>
<td>3.7% (1.3 – 10.2)</td>
<td>1.64</td>
<td>0.433</td>
<td>1.60 (0.43 – 5.95)</td>
<td>0.484</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>31</td>
<td>1</td>
<td>3.2% (0.6 – 16.2)</td>
<td>1.33</td>
<td>0.782</td>
<td>1.76 (0.22 – 14.49)</td>
<td>0.596</td>
</tr>
<tr>
<td>Topiramate</td>
<td>28</td>
<td>2</td>
<td>7.1% (2.0 – 22.6)</td>
<td>2.75</td>
<td>0.185</td>
<td>3.46 (0.73 – 16.39)</td>
<td>0.119</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>22</td>
<td>0</td>
<td>0.0% (0.0 – 14.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Pregnancy losses with no MCM excluded

# Adjusted for age at delivery, parity of mother, family history of MCM, periconceptional folic acid exposure and sex of infant.

Table 2. MCM rate by monotherapy drug exposures.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of cases</th>
<th>N.T.D</th>
<th>Facial cleft</th>
<th>Cardiac</th>
<th>Hypo-spadias/ G.U.T</th>
<th>G.I.T.</th>
<th>Skeletal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>900</td>
<td>2 (0.2%)</td>
<td>4 (0.4%)</td>
<td>6 (0.7%)</td>
<td>2 (0.2%)</td>
<td>2 (0.2%)</td>
<td>3 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>VPA</td>
<td>715</td>
<td>7 (1.0%)</td>
<td>11 (1.5%)</td>
<td>5 (0.7%)</td>
<td>9 (1.3%)</td>
<td>2 (0.3%)</td>
<td>8 (1.1%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>LTG</td>
<td>647</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>4 (0.6%)</td>
<td>6 (0.9%)</td>
<td>3 (0.5%)</td>
<td>2 (0.3%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>PHT</td>
<td>82</td>
<td>0 (0.0%)</td>
<td>1 (1.2%)</td>
<td>1 (1.2%)</td>
<td>0 (0.0%)</td>
<td>1 (1.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Table 3. Types of MCMs by AED (CBZ = carbamazepine, VPA = valproate, LTG = lamotrigine, PHT = phenytoin; NTD = neural tube defect, GUT genitourinary tract, GIT = gastrointestinal tract defects)
<table>
<thead>
<tr>
<th>AED</th>
<th>Maximum daily dose (mg)</th>
<th>Total number of informative exposures</th>
<th>Number of MCM</th>
<th>MCM rate% (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>&lt;400</td>
<td>401</td>
<td>7</td>
<td>1.7(0.8 – 3.6)</td>
</tr>
<tr>
<td></td>
<td>400 – 1000</td>
<td>385</td>
<td>10</td>
<td>2.6(1.4 – 4.7)</td>
</tr>
<tr>
<td></td>
<td>&gt;1000</td>
<td>92</td>
<td>3</td>
<td>3.3(1.1 – 9.2)</td>
</tr>
<tr>
<td>Valproate</td>
<td>&lt;600</td>
<td>266</td>
<td>11</td>
<td>4.1(2.3 – 7.3)</td>
</tr>
<tr>
<td></td>
<td>600 – 1000</td>
<td>247</td>
<td>15</td>
<td>6.1(3.7 – 9.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;1000</td>
<td>286</td>
<td>17</td>
<td>9.1(5.8 – 14.1)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>&lt;100</td>
<td>151</td>
<td>2</td>
<td>1.3(0.4 – 4.7)</td>
</tr>
<tr>
<td></td>
<td>100 – 200</td>
<td>208</td>
<td>4</td>
<td>1.9(0.8 – 4.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;200</td>
<td>279</td>
<td>15</td>
<td>5.4(3.3 – 8.7)</td>
</tr>
</tbody>
</table>

Table 4. MCM rate for monotherapy exposure to carbamazepine, valproate and lamotrigine by dose.
Conflicts of Interest
The authors JC, AR, LP, PM, RW, BI and JM have attended meetings with the support of various pharmaceutical companies, including Glaxo-Smith-Kline. The authors JC, LP, PM, and JM have given lectures at the bequest of pharmaceutical companies, including Glaxo-Smith-Kline, for which they have received honoraria. The authors IR and CMcG have declared no conflicts of interest.

I declare that as the corresponding author I had full access to all the data and had final responsibility for submission of the article for publication.

Dr James Morrow, Consultant Neurologist/Principal Investigator UK Epilepsy and Pregnancy Register group.

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Figure 1. Total Monotherapy outcomes.
Figure 2. MCM rate (%) by dose.

![Bar chart showing MCM rate by dose for CBZ, VPA, and LTG.

Legend:
- CBZ < 400mg, VPA < 600mg, LTG < 100mg
- CBZ 400-1000mg, VPA 600-1000mg, LTG 100-200mg
- CBZ > 1000mg, VPA > 1000mg, LTG > 200mg]