Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register

J Morrow, A Russell, E Guthrie, L Parsons, I Robertson, R Waddell, B Irwin, R C McGivern, P J Morrison, J Craig

Objective: To assess the relative risk of major congenital malformation (MCM) from in utero exposure to antiepileptic drug (AEDs).

Methods: Prospective data collected by the UK Epilepsy and Pregnancy Register were analysed. The presence of MCMs recorded within the first three months of life was the main outcome measure.

Results: Full outcome data were collected on 3607 cases. The overall MCM rate for all AED exposed cases was 4.2% (95% confidence interval (CI), 3.6% to 5.0%). The MCM rate was higher for polytherapy (6.0%) (n = 770) than for monotherapy (3.7%) (n = 2598) (crude odds ratio (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% (1.8% to 6.8%). The MCM rate was greater for pregnancies exposed only to valproate (6.2% (95% CI, 4.6% to 8.2%) than only to carbamazepine (2.2% (1.4% to 3.4%) (OR = 2.78 (p < 0.001); adjusted OR = 2.97 (p < 0.001)). There were fewer MCMs for pregnancies exposed only to lamotrigine than only to valproate. A positive dose response for MCMs was found for lamotrigine (p = 0.006). Polytherapy combinations containing valproate carried a higher risk of MCM than combinations not containing valproate (OR = 2.49 (1.31 to 4.70)).

Conclusions: Only 4.2% of live births to women with epilepsy had an MCM. The MCM rate for polytherapy exposure was greater than for monotherapy exposure. Polytherapy regimens containing valproate had significantly more MCMs than those not containing valproate. For monotherapy exposures, carbamazepine was associated with the lowest risk of MCM.

Epilepsy is the most common serious chronic neurological condition, with a prevalence of between 4 and 10 people per 1000. Most of those affected, including women of childbearing age, 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 fetus that raises most concern. With an estimated three to four pregnancies in every thousand occurring to women with active epilepsy, this means between 1800 to 2400 children are born to such women in the United Kingdom 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% to 4–9%. 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 and barbiturates (phenobarbitone (phenobarbital), primidone) and phenytoin have been associated with congenital heart defects and facial clefts. Other MCMs, including urogenital and skeletal abnormalities, have also been reported.

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, did not until recently 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 in comparison with the earlier ones, 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 began in December 1996. Ethics 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 or who had additional AEDs starting in the second or third trimesters were included. For polytherapy exposures more than one AED during the first trimester, or who had additional AEDs starting in the second or third trimesters, were counted as polytherapy exposures.

Abbreviations: AED, antiepileptic drug; EUROCAT, European Surveillance of Congenital Anomalies; MCM, major congenital malformation
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 the cause of the 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 started preconception. Outcome data were collected at three months after the expected date of delivery by sending the patient’s general practitioner a standardised 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 (for example clinical geneticist, paediatrician) who had been identified either during the pregnancy or at follow up were also contacted for further information.

Data analysis
Outcomes were classified by one of us (PM) into those without birth defects, those with MCMs, and those with other defects (minor defects, chromosomal disorders, and single gene defects). For each of these categories, outcomes were further subdivided 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 a polytherapy regimen.

An MCM was defined as an abnormality of an essential embryonic structure requiring significant treatment 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—were coded as minor structural malformations, although they are significant defects in themselves.

Statistical analysis
The MCM rate was calculated as \( \frac{\text{total number of live births with an MCM} + \text{total number of pregnancy losses with an MCM}}{\text{total number of live births} + \text{total number of pregnancy losses with an MCM}} \times 100 \). 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 cannot know the outcome. The total numbers presented for each group are therefore the total number of outcomes or the total number of informative outcomes—that is, excluding pregnancy losses with no abnormalities reported. For each MCM rate, 95% confidence intervals (CI) were calculated, based on Wilson’s method, 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 analysed 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, periconceptional folic acid intake, sex of infant, and category of AED exposure (no AED exposures, monotherapy, polytherapy, 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, using no AED exposure or carbamazepine for individual monotherapy exposures as the comparators. Probability (p) values of <0.05 were considered significant. Calculations were done using SPSS, version 13.

RESULTS
On 31 March 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). Four hundred and fifty one pregnancies are ongoing and outcome is awaited. Exclusions were as follows: five spontaneous abortions that had occurred before registration, and two women with abnormal scans before registration (both were late registrations (>20 weeks); in one case Fallot’s teratology had been diagnosed and in the other, spina bifida had been queried (though later excluded)). The register has also been informed about a number of previously

Table 1 Overall major congenital malformation rates by type of antiepileptic drug exposure

<table>
<thead>
<tr>
<th>Drug exposure</th>
<th>Informative outcome* [n]</th>
<th>MCMs [n]</th>
<th>Crude MCM rate (95% CI)</th>
<th>OR (95% CI)</th>
<th>p Value</th>
<th>Adjusted OR† (95% CI)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AED</td>
<td>227</td>
<td>8</td>
<td>3.5 (1.8 to 6.8)</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>2468</td>
<td>91</td>
<td>3.7% (3.0 to 4.5)</td>
<td>1.05 (0.90 to 2.19)</td>
<td>0.90</td>
<td>1.03 (0.49 to 2.17)</td>
<td>0.94</td>
</tr>
<tr>
<td>Polytherapy</td>
<td>718</td>
<td>43</td>
<td>6.0% (4.5 to 8.0)</td>
<td>1.71 (0.79 to 3.69)</td>
<td>0.17</td>
<td>1.76 (0.80 to 3.86)</td>
<td>0.16</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.
AED, antiepileptic drug; CI, confidence interval; MCM, major congenital malformation; OR, odds ratio.
completed pregnancies but these retrospective data have not been considered here. In all, 2598 cases (72.0%) 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 13 being an MCM. Of the live births (n = 3400) 365 (10.7%) were recorded as having any type of birth defect, with 129 recorded as having an MCM. The MCM rate for all AED exposed pregnancies was 4.2% (95% CI, 3.6% to 5.0%). Table 1 shows the MCM rate by type of AED exposure. The MCM rate was significantly higher in polytherapy than with monotherapy exposures (crude OR = 1.63 (p = 0.010); OR adjusted for age at birth, parity, family history of MCM, folic acid exposure, and 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 than for valproate. There was a trend towards fewer MCMs for lamotrigine compared with valproate, which had the highest rate of MCMs, 6.2% (4.6% to 8.2%) compared with 2.78 (1.62 to 4.76) (p < 0.001) for carbamazepine and lamotrigine (n = 141) it was 9.6% (5.7% to 15.7%). No MCMs were recorded in pregnancies exposed to carbamazepine and lamotrigine (n = 118) (MCM rate 0.0% (0.0% to 3.3%).

**DISCUSSION**

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 an MCM. However, for those exposed to AEDs as part of a polytherapy regimen the MCM rate was significantly higher than for monotherapy exposures. In our study, most monotherapy exposures were to carbamazepine, valproate, and lamotrigine, and, increasingly during the study period, gabapentin. Differences were noted between drugs, with significantly fewer MCMs occurring with carbamazepine than with valproate. There was a trend towards fewer MCMs with lamotrigine than with valproate. This was statistically significant on univariate analysis, but significance was lost on multivariable analysis. Further analysis of the data showed 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

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Major congenital malformation rate by monotherapy drug exposures</th>
</tr>
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<tbody>
<tr>
<td>Drug</td>
<td>MCMs (n)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>900</td>
</tr>
<tr>
<td>Valproate</td>
<td>715</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>647</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>82</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>31</td>
</tr>
<tr>
<td>Topiramate</td>
<td>28</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>22</td>
</tr>
</tbody>
</table>

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

CI, confidence interval; MCM, major congenital malformation; OR, odds ratio.

**Polotherapy**

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% CI, 2.5% to 6.7%), 4.8% (3.1% to 7.3%), and 9.0% (6.3% to 12.8%). For polytherapy combinations, those containing valproate in any combination had a significantly higher risk of MCM than polytherapy combinations not containing valproate (OR = 2.49 (1.31 to 4.70)). Considering the most commonly used polytherapy combinations, the MCM rate for pregnancies exposed to carbamazepine and valproate (n = 62) was 8.8% (3.8% to 18.9%) and for pregnancies exposed to valproate and lamotrigine (n = 141) it was 9.6% (5.7% to 15.7%). No MCMs were recorded in pregnancies exposed to carbamazepine and lamotrigine (n = 118) (MCM rate 0.0% (0.0% to 3.3%).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Types of major congenital malformation by antiepileptic drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Cases (n)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>900</td>
</tr>
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<tr>
<td>Lamotrigine</td>
<td>647</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>82</td>
</tr>
</tbody>
</table>

GIT, gastrointestinal tract defects; GUT, genitourinary tract defects; NTD, neural tube defects.
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 directly comparable to those who have to continue on drugs. That our referrals came from a wide range of sources including antenatal booking clinics and women themselves probably helps the generalisability of the results.

Another strength of the study was the general practitioner system within the United Kingdom, as through this single source we were able to obtain outcome data. Although various different 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 GP.

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 dose 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 criterion in regulatory trials of AEDs. Another weakness is that even when recruitment was occurring at its maximum (between 70 and 80 cases a month), we were still only being informed of between 40% and 50% of all eligible cases in the United Kingdom. This clearly has the potential to introduce biases, although we feel that recruiting from a broad range of sources may have minimised 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 antenatal 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 socioeconomic 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 three months.

All of the older AEDs have been previously linked with an increased risk of MCMs. 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 carried out in specialised

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**Table 4** Major congenital malformation rate for monotherapy exposure to carbamazepine, valproate, and lamotrigine by dose

<table>
<thead>
<tr>
<th>AED</th>
<th>Maximum daily dose (mg)</th>
<th>Total informative exposures (n)</th>
<th>MCMs (n)</th>
<th>MCM rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>&lt;400</td>
<td>401</td>
<td>7</td>
<td>1.7 (0.8 to 3.6)</td>
</tr>
<tr>
<td></td>
<td>400 to 1000</td>
<td>385</td>
<td>10</td>
<td>2.6 (1.4 to 4.7)</td>
</tr>
<tr>
<td></td>
<td>&gt;1000</td>
<td>92</td>
<td>3</td>
<td>3.3 (1.1 to 9.2)</td>
</tr>
<tr>
<td>Valproate</td>
<td>&lt;600</td>
<td>266</td>
<td>11</td>
<td>4.1 (2.3 to 7.3)</td>
</tr>
<tr>
<td></td>
<td>600 to 1000</td>
<td>247</td>
<td>15</td>
<td>6.1 (3.7 to 9.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;1000</td>
<td>186</td>
<td>17</td>
<td>9.1 (5.8 to 14.1)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>&lt;100</td>
<td>151</td>
<td>2</td>
<td>1.3 (0.4 to 4.7)</td>
</tr>
<tr>
<td></td>
<td>100 to 200</td>
<td>208</td>
<td>4</td>
<td>1.9 (0.8 to 4.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;200</td>
<td>279</td>
<td>15</td>
<td>5.4 (3.3 to 8.7)</td>
</tr>
</tbody>
</table>

AED, antiepileptic drug; CI, confidence interval; MCM, major congenital malformation.
epilepsy centres, which could affect the generalisability of the results. More importantly, the numbers of patients included on each drug in monotherapy were often inadequate to carry out comparisons between the agents used and even when the amalgamated findings from smaller (but not methodologically exact) studies were included the numbers were often still too small to carry out statistical analysis reliably. 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.26–28 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% CI, 0.5% to 5.5%) and 6.0% for 166 polytherapy exposures. As with our results, they found an MCM rate of 10% (3.7% to 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 the valproate that contributes to the increased risk. Updated figures from the International Lamotrigine Pregnancy Register (2005), from 414 first trimester monotherapy exposures, were closer to those we found, with an MCM rate of 2.9% (1.6% to 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 a 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 are still sparse.29 A recent report of 55 exposures to oxcarbazepine (20 polytherapy and 35 monotherapy) noted only 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 valproate exposed women (10.7% (95% CI, 6.3% to 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 (4.4 to 12.2).30 Figures published from the Australian Pregnancy Register for Women on Anti-epileptic Medication revealed a malformed 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 malformed, a finding that has been reported previously.32 While we noted a trend in the same direction our findings did not reach significance.

In keeping with our findings, a recent much smaller study from Sweden reported that MCMs are more likely with valproate taken in monotherapy than with carbamazepine taken in monotherapy (OR = 2.51 (1.43 to 4.48)).33 While 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 that other equally effective and safer AEDs should be considered.34 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 an MCM—particularly at doses of 200 mg or less—than those taking valproate. However, it should be noted that for women taking doses of lamotrigine greater than 200 mg/day (the MCM rate (5.4% (95% CI, 3.3% to 8.7%)) was no different from pregnancies exposed to 1000 mg or less per day of valproate (5.1% (3.5% to 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 an MCM, however, is a message that is likely to be reassuring both to women with epilepsy and to those who care for them.

ACKNOWLEDGEMENTS

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Authors’ affiliations

J Morrow, Department of Neurology, Royal Group of Hospitals, Grosvenor Road, Belfast, UK
A Russell, Department of Clinical Neurophysiology, Southern General Hospital, Glasgow, UK
E Guthrie, General Practitioner, Dumbarton Road, Glasgow
L Parsons, Department of Neurology, St Albans City Hospital, Waverley Road, St Albans, Herts, UK
I Robertson, Shropshire Green Unit, Lancashire Teaching Hospitals NHS Trust, Preston, Lancashire, UK
R Wooddell, B Irwin, Royal Group of Hospitals, Grosvenor Road, Belfast
R C McGivern, Northern Ireland Regional Medical Physics Agency, Royal Group of Hospitals, Grosvenor Road, Belfast
P J Morrison, Department of Medical Genetics, Belfast City Hospital Trust, Belfast & School of Biological Sciences, University of Ulster, Coleraine, UK
J Craig, Department of Neurology, Royal Group of Hospitals, Grosvenor Road, Belfast

Competing interests: JC, AR, LP, PM, RW, BI, and JM have attended meetings with the support of various pharmaceutical companies, including Glaxo-Smith-Kline. JC, LP, PM, and JM have given lectures at the bequest of pharmaceutical companies, including Glaxo-Smith-Kline, for which they have received honoraria. IR and CMC-G have declared no conflicts of interest.
REFERENCES


