Child development following in utero exposure

Levetiracetam vs sodium valproate

R. Shallcross, BSc
R.L. Bromley, PhD
B. Irwin, RGN, RM
L.J. Bonnett, MMathStat
J. Morrow, MD, PhD
G.A. Baker, PhD, FBPsS
On behalf of the Liverpool Manchester Neurodevelopment Group and the UK Epilepsy and Pregnancy Register

Address correspondence and reprint requests to Professor Gus Baker, Department of Neurological Science, Clinical Sciences Centre for Research and Education, Lower Lane, Liverpool, L9 7LJ UK
g.baker@liv.ac.uk

ABSTRACT

Objective: Children born to women with epilepsy (WWE), exposed in utero to levetiracetam (LEV, n = 51), were assessed for early cognitive development and compared to children exposed to sodium valproate in utero (VPA, n = 44) and a group of children representative of the general population (n = 97).

Methods: Children were recruited prospectively from 2 cohorts in the United Kingdom and assessed using the Griffiths Mental Development Scale (1996), aged <24 months. Information regarding maternal demographics were collected and controlled for. This is an observational study with researchers not involved in the clinical management of the WWE.

Results: On overall developmental ability, children exposed to LEV obtained higher developmental scores when compared to children exposed to VPA ($p < 0.001$). When compared, children exposed to LEV did not differ from control children ($p = 0.62$) on overall development. Eight percent of children exposed to LEV in utero fell within the below average range (DQ score of <84), compared with 40% of children exposed to VPA. After controlling for maternal epilepsy and demographic factors using linear regression analysis, exposure to LEV in utero was not associated with outcome ($p = 0.67$). Conversely, when compared with VPA exposure, LEV exposure was associated with higher scores for the overall developmental quotient ($p < 0.001$).

Conclusion: Children exposed to LEV in utero are not at an increased risk of delayed early cognitive development under the age of 24 months. LEV may therefore be a preferable drug choice, where appropriate, for WWE prior to and of childbearing age. *Neurology*® 2011;76:383–389

GLOSSARY

AED = antiepileptic drug; **CM** = congenital malformation; **GMDS** = Griffiths Mental Development Scale; **LEV** = levetiracetam; **LMNDG** = Liverpool and Manchester Neurodevelopment Group; **NART** = National Adult Reading Test; **SES** = socioeconomic status; **UKEPR** = UK Epilepsy and Pregnancy Register; **VPA** = valproate; **WWE** = women with epilepsy.

There is growing evidence that the development and cognitive functioning of children is affected by exposure in utero to antiepileptic drugs (AEDs).[1,2] The most consistent finding throughout the literature is that VPA significantly increases the risk of congenital malformations (CM), developmental delay, and lower IQ scores in children.[2–4] Consequently, practice guidelines suggest that VPA should be avoided, where possible, by WWE of childbearing age.[5] This has led to decreasing use of VPA in WWE as clinicians aim to reduce the risk to the fetus.[6,7] Conversely, increases in the use of LEV in WWE of childbearing age have been reported.[7] LEV is indicated for both focal and idiopathic generalized epilepsy.[8] The UK Epilepsy and Pregnancy Register (UKEPR, www.epilepsyandpregnancy.co.uk) reports a low occurrence of CM following LEV use in pregnancy.[9,10] In addition, animal data report a lower

From the Division of Neurosciences (R.S., R.L.B., G.A.B., L.J.B.) and the Centre for Medical Statistics and Health Evaluation (L.J.B.), University of Liverpool; and The Department of Neurology (B.I., J.M.), Royal Group of Hospitals, Belfast, UK.

Study funding: Sponsored by UCB. Work carried out by the UK Epilepsy and Pregnancy Register is supported by a research grant from the Epilepsy Research Foundation and a number of unrestricted educational grants from pharmaceutical companies (GlaxoSmithKline, Sanofi-Aventis, UCB, Janssen-Cilag, Novartis, Pfizer Inc., Eisai Inc.). A Web site detailing the aims of the UK Epilepsy and Pregnancy Register was made possible by a grant from GlaxoSmithKline and UCB. The work presented is also in part a programme (RP-PG-0606-1062) that received financial support from the National Institute for Health Research (NIHR) Programme Grants for Applied Research funding scheme. The Liverpool and Manchester Neurodevelopment Group have received an educational grant from Sanofi-Aventis and have received support from the NEAD study National Institute of Health Grant (2 R01 NS038455) and also by grants from Epilepsy Research UK RB219738 (National Lottery Charities Board). The views and opinions expressed within this article do not necessarily reflect those of the NIHR or the Department of Health.

Disclosure: Author disclosures are provided at the end of the article.

CM rate in comparison to other AEDs.[11,12] Reliable information on the neurodevelopment and cognitive abilities of children exposed to LEV in utero has not been published to date. In response to this lack of information, the Liverpool and Manchester Neurodevelopment Group (LMNDG) and the UKEPR have initiated a prospective follow-up study aimed at documenting the early cognitive development of children exposed to LEV in utero.

METHODS

Recruitment. Women taking LEV and VPA during their pregnancy were recruited from the UKEPR (enrollment methodology has previously been published).[13] Criteria for enrollment into this study included the use of monotherapy LEV or VPA in women with an IQ above 70 and whose children were below the age of 2 years at the time of assessment. Information on whether women taking VPA were taking immediate release, delayed release, or extended release was not available. The women identified were sent a letter asking if they would like to take part in a continuation of the UKEPR study. For those who did not respond, a follow-up letter was sent.

In addition to the comparison group of children exposed to VPA collected from the UKEPR, children exposed to VPA enrolled and already assessed through the LMNDG program of research were all included if seen on or after January 1, 2003. This ensured an adequately sized comparison group. A second comparison group of children born to women without epilepsy, not taking medication during pregnancy, was also recruited from the LMNDG program of research if previously assessed on or after January 1, 2003. Children recruited into both comparison groups have previously been reported.[2,4]

The methodology of the LMNDG prospective study and the present study were similar, allowing for reliable comparisons to be made between the groups.[4] Both studies include prospective enrollment (i.e., while mothers were pregnant before pregnancy outcome was known) and prospective collection of pregnancy data. The exception to this was the collection of data regarding socioeconomic status (SES), alcohol, nicotine, and seizure exposure, which was collected retrospectively for the mothers from the UKEPR. Prospective collection of seizures in pregnancy at time of registration was collected by the UKEPR. Retrospective collection of seizures occurring throughout gestation was subsequently collected for the current study. Epilepsy type was reconfirmed following the collection of data regarding seizure type, with a detailed description of seizures being taken from mothers and then classified into partial, generalized, or unclassified by a neurologist.

Assessment of the child. Mothers recruited from the UKEPR who returned the reply slip agreeing to assessment of their child were contacted by telephone and offered a home visit appointment. Mothers who were recruited from the LMNDG had already been assessed at either a home visit or a hospital appointment, and therefore were not contacted again. Children were assessed under the age of 24 months (mean age 14 months, range 3–24 months) by an assistant psychologist or by authors R.S. and R.L.B. All children within the study completed the Griffiths Mental Development Scale (GMDS[14]) between 2003 and 2010. The GMDS measures, individually and collectively, 5 areas of development for the 0–2 age group: locomotor skills, personal and social skills, hearing and language skills, eye and hand coordination skills, and nonverbal performance skills. Administration of the Griffiths requires a high degree of objectivity on the part of the examiner. All examiners were trained in use of the Griffiths to ensure uniform objectivity in testing.[14]

All mothers were asked to complete the National Adult Reading Test (NART[15]) in order to gain a measure of maternal IQ. Feedback was provided to the families of the children assessed and, where necessary, referrals were made to specialist services.

Data analysis was completed by author L.J.B. *t* Tests were used to assess whether the means of comparative groups were significantly different. Linear regression analysis was then utilized to assess the influence of confounding variables on overall development quotient. Variables of clinical importance (seizures in pregnancy, gestational age, maternal IQ, child age at assessment, SES, AED type) were included in the model. The Bonferroni correction was used to address the multiple testing issue; to maintain the 5% significance level despite testing 6 hypotheses, each individual hypothesis was tested at a statistical significance level of $0.05/6 = 0.008$.

Standard protocol approvals, registrations, and patient consents. Ethical approval for the study was granted by the Northwest Research Committee. Written informed consent was obtained from all mothers. The current study is supported by UCB Pharma, which played no part in the design, undertaking, or write-up of this study. This is an observational study with researchers playing no part in the clinical management of the WWE.

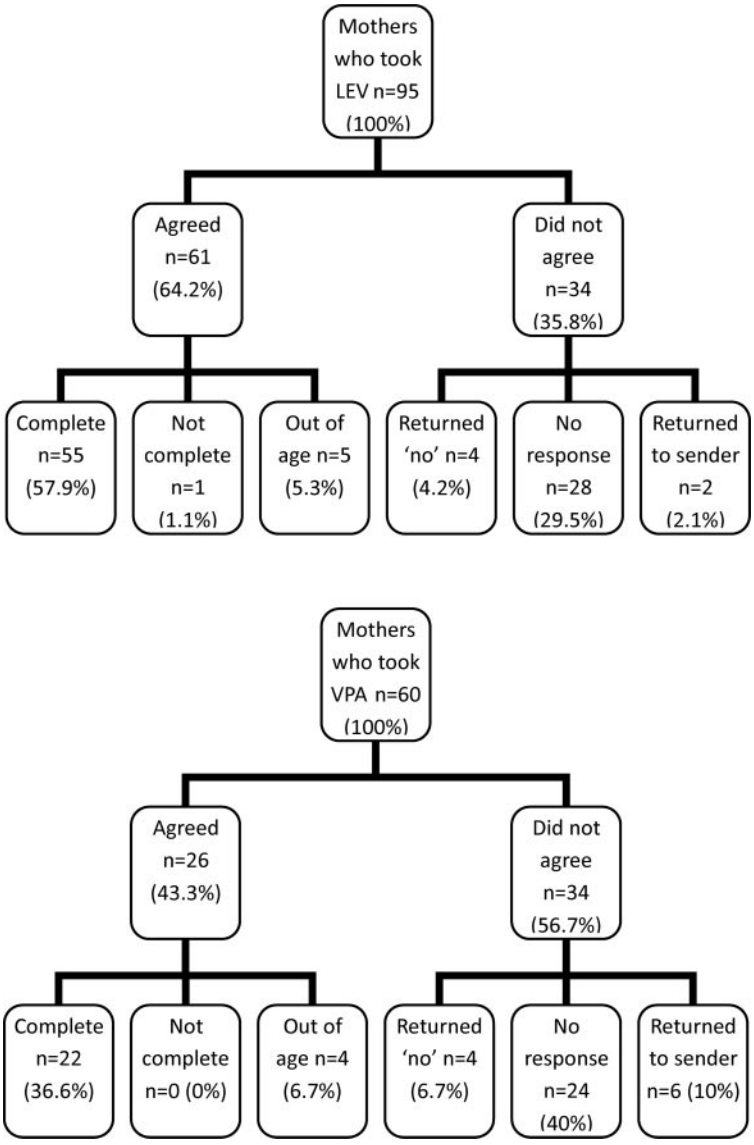
RESULTS

A total of 155 children under the age of 24 months were identified from the UKEPR, 95 of whom were exposed to LEV monotherapy and 60 exposed to VPA monotherapy throughout pregnancy. Figure 1 demonstrates the response rate of those women contacted for each group.

Women recruited from the UKEPR who responded positively were older than women who did not respond or responded negatively for both mothers who took LEV ($p < 0.001$) and mothers who took VPA ($p = 0.028$) during pregnancy.

Children exposed to LEV (n = 55) recruited from the UKEPR were assessed. Children exposed to VPA, previously prospectively recruited by the LMNDG (n = 22), were added to the VPA-exposed group of children from the UKEPR (n = 22) in order to make the total number of children exposed to VPA assessed 44. No differences were noted between the LMNDG or UKEPR mothers taking VPA in terms of maternal IQ ($p = 0.51$) or overall developmental outcome of the children ($p = 0.84$), demonstrating the similarity of the groups and justifying their combination. Control children born to women without epilepsy, not exposed to medication in pregnancy, previously prospectively recruited and assessed by the LMNDG, were used as a control group (n = 98).

Figure 1 Responses of women recruited from the UK Epilepsy and Pregnancy Register



LEV = levetiracetam; VPA = valproate.

Within the control group, one child was excluded as the mother was prescribed warfarin throughout pregnancy. Therefore, 97 control children were included in the analysis.

Of the 55 children exposed to LEV in utero, 4 were excluded (one child had inconsistently high score and was therefore assumed to be an outlier, one mother discontinued medication throughout pregnancy, one mother was also taking Lamictal from 2 to 8 weeks gestation, one mother has a diagnosis of Landau Kleffner syndrome). Therefore, 51 children exposed to LEV were included in the analysis. No children were excluded from the group of children exposed to VPA. From here only children not excluded from the analysis are described. A total of 192 children were included in the analysis, 95 born to WWE and 97 born to control women.

In terms of maternal variables, mothers taking VPA and mothers taking LEV had lower mean full-scale IQ compared to control mothers ($p = 0.01$ and $p = 0.04$). No differences were found in maternal IQ between mothers taking LEV or VPA during pregnancy ($p = 0.60$). The age of the mothers at conception did not differ between controls and mothers taking LEV ($p = 0.43$) or VPA ($p = 0.44$) throughout pregnancy. Nor did it differ between mothers taking VPA and mothers taking LEV throughout pregnancy ($p = 0.99$). For consumption of alcohol, no differences were found between the control group of mothers and mothers taking LEV ($p = 0.14$) and mothers taking VPA ($p = 0.95$). Nor were there differences between mothers taking LEV or VPA during pregnancy on alcohol consumption ($p = 0.37$). No differences were found for smoking during pregnancy between the control group of mothers and mothers taking LEV ($p = 0.51$) and mothers taking VPA ($p = 0.95$). Nor were there differences between mothers taking LEV or VPA for smoking during pregnancy ($p = 0.46$). Differences in SES were found between those taking LEV and control mothers ($p = 0.01$) with a higher number of controls within SES 3 (SES 1 = professional, SES 2 = skilled, SES 3 = manual/unemployed). No other significant differences were found between the groups in regards to SES.

For the children, no differences in age at assessment were found between control mothers and those taking LEV during pregnancy ($p = 1.0$) or mothers taking VPA during pregnancy ($p = 0.57$). Nor were differences found between mothers taking LEV and mothers taking VPA in regards to age at assessment ($p = 0.66$). Similarly, no differences were found in regards to gestational age between control mothers and mothers taking LEV during pregnancy ($p = 0.54$) or mothers taking VPA during pregnancy ($p = 0.98$), nor were differences noted between mothers taking LEV and mothers taking VPA ($p = 1.0$) (see table 1).

Out of 95 children born to WWE, 27 (28.4%) mothers had focal epilepsy, 51 (53.7%) had idiopathic generalized epilepsy, and 16 (16.8%) had unclassified epilepsy. Data were missing regarding epilepsy type for 1 (1.1%) woman. For women with focal epilepsy, 24 (88.9%) were receiving LEV monotherapy and 3 (11.1%) were receiving VPA monotherapy throughout pregnancy. For women with generalized epilepsy, 17 (33.3%) were receiving LEV monotherapy and 34 (66.7%) were receiving VPA monotherapy throughout pregnancy. For mothers taking LEV during pregnancy, the mean

Table 1 Demographic variables of mothers who took part in the study

	Mean maternal IQ	Mean maternal age, y	Mean age of child at assessment, mo	Mean gestational age, wk	% Smoked	% Consumed alcohol	% SES 1	% SES 2	% SES 3
LEV	100.4	29.6	13.8	39.2	13.7	31.4	35.3	23.5	33.3
VPA	98.1	29.6	16.4	39.3	22.7	22.7	36.4	18.2	45.5
Control	105.1	30.3	14.0	39.7	20.6	20.6	26.8	9.3	62.9

Abbreviations: LEV = levetiracetam; SES = socioeconomic status; VPA = valproate.

dose was 1,700 mg (250–4,000 mg), and for mothers taking VPA, the mean dose was 800 mg (200–1,600 mg).

Seizures of any type were experienced by 40 (42.1%) WWE during pregnancy. Seizure data were missing for 4 WWE (4.2%). Seventeen women (63%) with focal epilepsy reported experiencing seizures during pregnancy compared with 17 women (33.3%) with generalized epilepsy and 6 women (37.5%) with unclassified epilepsy. There was no difference in overall developmental outcome in the children exposed to seizures during pregnancy and those who were not ($p = 0.16$).

On overall developmental ability, children exposed to LEV obtained higher developmental scores when compared to children exposed to VPA ($p < 0.001$). When compared, children exposed to LEV did not differ from the control group of children ($p = 0.62$) on overall development (table 2 and figure 2). For overall development, 8% of children exposed to LEV in utero fell within the below average range (developmental quotient score of <84), compared with 40% of children exposed to VPA and 12% of children born to control mothers. The relative risk of delayed development for the children exposed to VPA was 3.38 in comparison to children exposed to LEV. In comparison to exposure to LEV, the relative risk for control children for delayed development was 1.42.

Children exposed in utero to LEV had higher mean score on all subscales when compared to children exposed in utero to VPA (see table 2). This difference reached significance for locomotor skills ($p < 0.001$), hand and eye coordination ($p < 0.001$), and performance skills ($p < 0.001$), and showed a trend toward significance for hearing and language ($p = 0.01$). In contrast, LEV did not differ significantly from control children on any subscale (see table 3).

Finally, linear regression analysis was performed controlling for the following variables: seizures in pregnancy, gestational age, maternal full-scale IQ, maternal age, child age at assessment, SES, exposure to nicotine, exposure to alcohol, and drug used in pregnancy. Cases where data on specific variables were missing were not included in the analysis. After controlling for confounding factors, exposure to LEV in utero was not associated with overall developmental outcome ($p = 0.67$). In the second linear regression analysis, LEV-exposed children were compared to VPA-exposed children for overall developmental ability. When compared with VPA exposure, LEV exposure was associated with higher scores for the overall developmental quotient ($p < 0.001$).

Table 2 Mean scores (95% confidence interval [CI]) by antiepileptic drug type across all developmental areas

	LEV (n = 51), mean (CI)	VPA (n = 44),[a] mean (CI)	Controls (n = 97), mean (CI)
Locomotor	97.35 (93.66–98.29)	84.66 (78.72–90.59)	95.24 (92.18–98.29)
Personal and social	98.00 (93.73–102.27)	89.82 (83.62–96.02)	97.95 (94.69–101.21)
Hearing and language	100.57 (96.89–104.24)	90.48 (84.29–96.66)	101.27 (98.09–104.45)
Hand and eye coordination	101.88 (97.46–106.30)	88.21* (82.07–94.35)	97.43 (93.75–101.11)
Performance	101.75 (98.02–105.47)	88.88* (83.29–94.48)	101.48 (98.03–104.94)
Overall development quotient	99.96 (97.16–102.76)	87.93* (82.68–93.18)	98.87 (96.05–101.68)

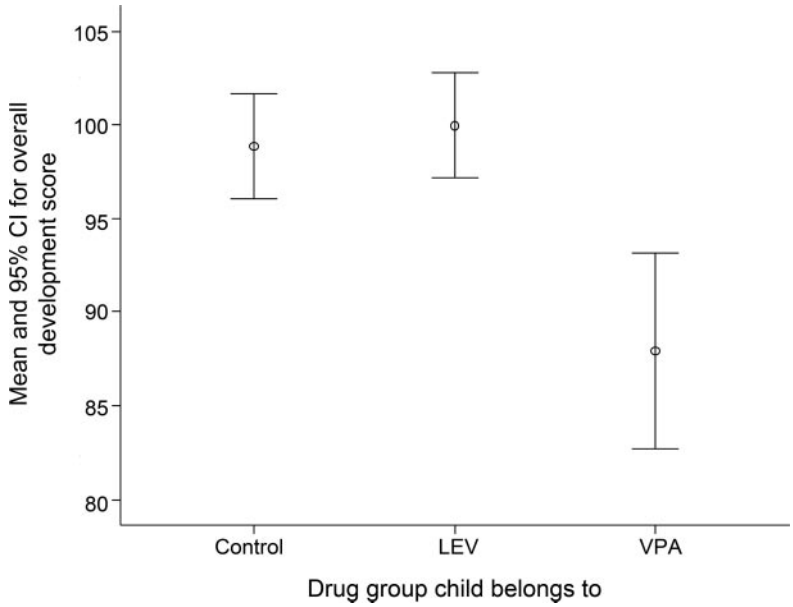
Abbreviations: LEV = levetiracetam; VPA = valproate.
[a] One child in the VPA group did not obtain an overall development quotient as not all subscales of the test could be completed, including eye and hand coordination and performance subscales. Therefore, only 43 children were included in the analysis for the subscales marked *.

DISCUSSION The study compared the development of 55 children exposed to LEV in utero, 44 children exposed to VPA in utero, and 97 control children, all under the age of 24 months.

Mothers enrolling into the follow-up study from the UKEPR were older than those refusing participation or who did not respond. This is consistent with the published research from the LMNDG.[4]

The results indicate that children exposed to LEV in utero have less risk of poorer overall development than children exposed to VPA in utero. Children exposed to LEV did not differ significantly on any subscale of development when compared to control children. For their overall development, 8% of children exposed to LEV in utero fell below the average range (developmental quotient score of <84), compared with 40% of children exposed to VPA and 12% of children born to control mothers. Therefore,

Figure 2 Child overall development quotient, mean and 95% confidence intervals (CI) by antiepileptic drug type



LEV = levetiracetam; VPA = valproate.

children exposed to VPA in utero are 3.38 times more likely to have a below average overall development quotient that those children exposed to LEV in utero. This indicates that there is a clinically significant difference between children exposed to LEV and VPA. After controlling for confounding variables using linear regression analysis, LEV was not associated with overall development outcome, whereas VPA was significantly associated with poorer developmental outcome.

Studies into the motor and cognitive functions of rat offspring exposed in utero to LEV have documented no effect of LEV exposure upon rats functioning.[16] While further human studies are needed, our results support this previous finding and suggest that, if all other factors are equal, LEV may be a preferable AED for WWE of childbearing age.

The findings are consistent with previous studies assessing children's development after exposure in utero to VPA[1–2,4,17,18] and contribute to the growing body of evidence surrounding the negative impact of prenatal exposure to VPA. Performance of children exposed to LEV was significantly higher than the children exposed to VPA on all subscales apart from the hearing and language subscale. It has previously been documented that children exposed to VPA have problems with expressive language.[19] Expressive language use is minimal in children under 24 months of age, and therefore may explain the failure to reach significance.

Some differences were found between the WWE and the control women; however, confounding variables were controlled for using linear regression analysis. No significant difference was found between the children who were exposed to seizures in utero and those who were not. Similarly, seizures during pregnancy were not predictive of developmental outcome in the linear regression analysis. This supports previous studies[2,4,18,20,21] but is refuted by others.[1,22]

In the developing rat brain, in utero exposure to VPA has been shown to cause apoptotic neurodegeneration,[23] whereas LEV is not reported to cause apoptosis.[24,25] The possible differences in the potential to cause apoptotic neurodegeneration between LEV and VPA may go some way in explaining the differences in scores on developmental assessments presented in this study.

Strengths of this study include its prospective enrollment of participants through either the LMNDG study or the UKEPR. Further strengths include a large sample size relative to this type of research, control of confounding variables, utilization of a control group, as well as a comprehensive neuropsychological assessment. Limitations of this study include the fact that the group of children not born to a WWE and around half of the VPA group utilized here have previously been reported by the LMNDG[4] and 6% by NEAD.[2] This was, however, necessary to provide useful comparison groups within the restraints of funding and time. A further limitation of the study is the unblinded nature of the assessor. Despite this, the rate of children falling below average (40%) is similar to, although slightly higher than, the rates previously reported by the LMNDG (29%), who used the same methodology but with blinded assessment.[4] This increase may be explained by the higher mean dose of VPA for women enrolled onto the UKEPR (864 mg/

Table 3 Levels of significance for differences between groups on development quotient subscales

	Overall developmental, *p* value	Locomotor, *p* value	Personal and social, *p* value	Hearing and language, *p* value	Hand and eye coordination, *p* value	Nonverbal performance, *p* value
LEV vs controls	0.62	0.40	0.99	0.79	0.14	0.92
LEV vs VPA	<0.001[a]	<0.001[a]	0.03[b]	0.01[b]	<0.001[a]	<0.001[a]

Abbreviations: LEV = levetiracetam; VPA = valproate.
[a] Significant to a level of 0.008.
[b] Significant to a level of 0.05.

daily) compared with the LMNDG article (735 mg/daily),[4] as a dose effect has been reported for VPA,[2,4] although was not found to be significant in this study. The lack of dose effect reported here may be due to the young age of the children, sample size, or it may be that even at lower doses some children were scoring low for developmental level. Children exposed in utero to LEV are currently being blindly assessed, between ages 6 and 9, by the LMNDG and the UKEPR in order to address the limitation of unblinded assessment raised in the current study. Blood level monitoring of the mothers throughout pregnancy is not carried out by the UKEPR and therefore was beyond the scope of this study. Finally, the study includes the retrospective data collection of seizures during pregnancy, use of alcohol and smoking during pregnancy, as well as SES information. It was felt that asking mothers retrospectively for detail of types of seizure and number of seizures during pregnancy would be difficult to recall and therefore not accurate, thus only "yes/no" responses to whether seizures occurred at any point during pregnancy were collected. The same applies to the collection of information regarding cigarette and alcohol use during pregnancy.

A consideration of this study is the young age of the children. Further assessment of children at older developmental stages is essential for obtaining a comprehensive understanding of any possible longer-term effects of LEV exposure in utero. Therefore, separate cohorts of children at 3 and 6 years of age will also be assessed for cognitive development to ensure that the conclusion here regarding a lack of increased risk of impairment from LEV use in pregnancy is reliable. Research needs to be effectively communicated to health care professionals and in turn to WWE so that informed decisions can be made as to the best possible AED treatment for WWE prior to and during childbearing age.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by L.J. Bonnett.

CONTRIBUTORS

Liverpool and Manchester Neurodevelopment Group (during the period of this work)—Alder Hey Children's Hospital, Liverpool, UK: Alan Fryer, MD, Rachel Kneen, MD; St Mary's Hospital, Manchester, UK: Siddharth Banka, MRCP(Ch), Maria Briggs, RGN, Jill Clayton-Smith, MD, George Mawer, FRCP(E), PhD; The University of Liverpool, UK: Gus Baker, PhD, FBPsS, Rebecca Bromley, PhD, Pete Dixon, PhD, Alison Gummery, BSc, Rebekah Shallcross, BSc; Walton Centre for Neurology and Neurosurgery, Liverpool, UK: Loretta Kerr. UK Epilepsy and Pregnancy Register (during the period of this work)—The Belfast Trust Group of Hospitals, UK: John Craig, MRCP, Stephen Hunt, MRCP, Beth Irwin, RGN, RM, Patrick Morrison, MD, James Morrow, MD; The Beaumont Hospital Dublin: Norman Delanty, MD, Brenda Liggan, RGN; Southern General Hospital, Glasgow: Aline Russell, MD; Academic Unit of Primary Care, University of Sheffield, UK: Henry Smithson, MD; Luton and Dunstable Hospitals, UK: Linda Parsons, MD; Royal Preston Hospital, UK: Iain Robertson, MD.

ACKNOWLEDGMENT

The authors thank Dr. Arif Shukralla, MRCP, Division of Neuroscience, The University of Liverpool, UK for his classification of seizure types.

DISCLOSURE

Dr. Shallcross reports no disclosures. Dr. Bromley has served as an expert witness in a medico-legal case. Dr. Irwin and Dr. Bonnett report no disclosures. Dr. Morrow has served on a scientific advisory board for GlaxoSmithKline and has provided expert medical opinions in medico-legal cases. Dr. Baker has served on a scientific advisory board for sanofi-aventis; serves on the editorial board of *Epilepsy and Behaviour*; has received speaker honoraria from Eisai Inc.; has received educational support from UCB, sanofi-aventis, and Pfizer Inc; and receives research support from Epilepsy Research UK, Medical Research Council UK, and Epilepsy Action UK.

Received May 28, 2010. Accepted in final form September 24, 2010.

REFERENCES

1. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004;75:1575–1583.
2. 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;360:1597–1605.
3. Samren EB, Duijn CM, Hiilesmaa VK, et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. Epilepsia 1997;38:981–990.
4. Bromley RL, Mawer G, Love J, et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010;51:2058–2065.
5. Harden CL, Hopp J, Ting TY, et al. Management issues for women with epilepsy: focus on pregnancy (an evidence-based review): I: obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009;50:1229–1236.
6. Ackers R, Besag FM, Wade A, Murray ML, Wong IC. Changing trends in antiepileptic drug prescribing in girls of child-bearing potential. Arch Dis Child 2009;94:443–447.
7. Vajda FJ, Hollingworth S, Graham J, et al. Changing patterns of antiepileptic drug use in pregnant Australian women. Acta Neurol Scand 2010;121:89–93.
8. Abou-Khalil B. Levetiracetam in the treatment of epilepsy. Neuropsychiatr Dis Treat 2008;4:507–523.
9. Morrow J, Russell A, Guthrie E, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006;77:193–198.
10. Hunt S, Craig J, Russell A, et al. Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. Neurology 2006;67:1876–1879.
11. Isoherranen N, Spiegelstein O, Bialer M, et al. Developmental outcome of levetiracetam, its major metabolite in humans, 2-pyrrolidinone N-butyric acid, and its enantio-

mer (R)-alpha-ethyl-oxo-pyrrolidine acetamide in a mouse model of teratogenicity. Epilepsia 2003;44:1280–1288.
12. Genton P, Van VB. Piracetam and levetiracetam: close structural similarities but different pharmacological and clinical profiles. Epileptic Disord 2000;2:99–105.
13. Russell A, Craig J, Morrison P, et al. UK Epilepsy and Pregnancy Group. Epilepsia 2004;45:1467.
14. Huntley M. The Griffiths Mental Development Scales: From Birth to 2 Years, 2nd ed. Oxford: The Test Agency Limited; 1996.
15. Nelson H, Willison J. The National Adult Reading Test, 2nd ed. Windsor: Nfer-Nelson Publishing; 1991.
16. Ozyurek H, Bozkurt A, Bilge S, Ciftcioglu E, Ilkaya F, Bas DB. Effect of prenatal levetiracetam exposure on motor and cognitive functions of rat offspring. Brain Dev 2010; 32:396–403.
17. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004;62:28–32.
18. Kantola-Sorsa E, Gaily E, Isoaho M, Korkman M. Neuropsychological outcomes in children of mothers with epilepsy. J Int Neuropsychol Soc 2007;13:642–652.
19. Bromley RL, Gummery A, Shallcross R, et al. IQ, memory, language and attention in children exposed to antiepileptic drugs in utero: preliminary outcomes at 6 years of age. Epilepsia 2009;50:491. Abstract.
20. Thomas SV, Ajaykumar B, Sindhu K, Nair MK, George B, Sarma PS. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy Behav 2008;13:229–236.
21. Thomas SV, Sukumaran S, Lukose N, George A, Sarma PS. Intellectual and language functions in children of mothers with epilepsy. Epilepsia 2007; 48:2234–2240.
22. Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. Arch Neurol 2009;66:979–984.
23. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci USA 2002;99:15089–15094.
24. Kim J, Kondratyev A, Gale K. Antiepileptic drug-induced neuronal cell death in the immature brain: effects of carbamazepine, topiramate, and levetiracetam as monotherapy versus polytherapy. J Pharmacol Exp Ther 2007; 323:165–173.
25. Manthey D, Asimiadou S, Stefovska V, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. Exp Neurol 2005;193:497–503.