Do lamotrigine and levetiracetam solve the problem of using sodium valproate in women with epilepsy?

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Summary: Women with epilepsy, especially those of child-bearing age, are faced with difficult choices when it comes to choosing the most suitable antiepileptic drug (AED). This is particularly so for those with idiopathic generalized epilepsies, or those for whom seizure syndrome is not immediately apparent, where sodium valproate is still considered the drug of choice. While with treatment most might expect to become seizure free, without any adverse effects, other considerations for women mean that valproate is usually initially avoided, with other AEDs such as lamotrigine or levetiracetam being chosen in preference. Based on current information, this article attempts to provide an overview on whether or not the availability of these and other broad-spectrum AEDs have solved the difficulties of using valproate in women of child-bearing age.

Keywords: neurology, maternal–fetal medicine

INTRODUCTION

Epilepsy is the most common, chronic serious neurological disorder and affects 4–10 out of every 1000 people, in the developed world.¹ It can be defined as the condition, or more accurately the set of conditions, in which individuals have a tendency to recurrent, usually unprovoked epileptic seizures. These can be of many different types, be of multiple aetiologies and can be associated with markedly differing responses to treatment. When classifying the ‘epilepsies,’ a more useful approach is to classify by epilepsy syndrome (Table 1).² The epilepsy syndromes are groups of disorders which are characterized by clusters of symptoms and signs which customarily occur together. Individuals with a particular epilepsy syndrome will broadly speaking have similar types of seizures, will show similar investigation results, will demonstrate similar responses to treatment and have a similar long-term prognosis.

The idiopathic generalized epilepsies (IGEs) represent a number of disorders which are increasingly felt to have a genetic basis. They often present in an age-dependent fashion in individuals who are otherwise well with seizure types which include primarily generalized tonic-clonic, absence and myoclonic seizures. They encompass such epilepsy syndromes as juvenile myoclonic epilepsy, juvenile absence epilepsy and epilepsy with generalized tonic-clonic seizures on awakening. As a group they are usually very satisfying to treat with most individuals achieving long-term seizure freedom.³ Unlike partial onset seizures, however, they tend to respond to a limited number of antiepileptic drugs (AEDs), with other commonly used AEDs, including carbamazepine, phenytoin and oxcarbazepine having a tendency to exacerbate certain seizure types such as absences and myoclonus. Furthermore, for most, long-term prognosis is treatment dependent and there

is a significant risk of seizure relapse if treatment is withdrawn. Treatment is therefore considered to be necessary long term, if not lifelong. For women of child-bearing years with epilepsy this is of particular importance.

For the IGEs, AED choices are generally restricted to broad spectrum AEDs, which are generally considered to include valproate, lamotrigine, levetiracetam, topiramate and zonisamide. For those with generalized tonic-clonic seizures only and focal epilepsy, narrower spectrum AEDs such as carbamazepine can also be used.

Based on currently available information, valproate is considered the ‘gold standard’ AED for the treatment of the IGEs or those for whom classification is not possible. This was confirmed in the SANAD (Standard Against New Anti-epileptic Drug) trial which compared the effectiveness of valproate, lamotrigine and topiramate in those with generalized or unclassified epilepsy.⁴ Valproate does not always work, however, or may be contra-indicated. Furthermore, valproate is now considered not to be an AED of choice for women with epilepsy of child-bearing years.^{5,6} This view initially arose from the results of studies comparing major congenital malformation (MCM) rates in offspring exposed *in utero* to AEDs. More recently studies assessing the cognitive and behavioural impact of *in utero* AED exposure have also revealed significant concerns for valproate.^{7,8} It is therefore now held that for women of child-bearing age, in whom pregnancy could occur, particular caution must be exercised when using valproate, to the extent that where there are other options, valproate should not be considered a first-line treatment for women with epilepsy. The development of other AEDs such as lamotrigine and levetiracetam, but also topiramate and zonisamide, is therefore welcome.

This article aims to consider the evidence in favour of lamotrigine and levetiracetam over valproate in managing women with epilepsy, taking account of those issues relevant during the child-bearing years (Table 2). Where there is any information

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Table 1 International League Against Epilepsy classification of the epilepsies and epileptic syndromes (1989)

The ILAE classification of the epilepsies and epilepsy syndromes (1989)	
• 1 Generalized <ul style="list-style-type: none"> – Idiopathic with age-related onset <ul style="list-style-type: none"> • BNFC • BNC • Benign myoclonic epilepsy in infancy • CAE • JAE • JME • EGA • Other generalized epilepsies • Specific activation – Cryptogenic <ul style="list-style-type: none"> • West syndrome, Lennox-Gastaut, etc. – Symptomatic generalized epilepsies <ul style="list-style-type: none"> • Early myoclonic encephalopathies, etc. 	• 2 Localization-related <ul style="list-style-type: none"> – Idiopathic with age-related onset <ul style="list-style-type: none"> • BECTS • Childhood epilepsy with occipital paroxysms • Primary reading epilepsy – Symptomatic <ul style="list-style-type: none"> • EPC • TLE • Central region epilepsies – Cryptogenic
	• 3 Undetermined <ul style="list-style-type: none"> – With both generalized and focal seizures
	• 4 Special syndromes <ul style="list-style-type: none"> – Febrile convulsions – Isolated seizures or SE – Provoked – metabolic upset, alcohol, drugs, etc.

CAE=childhood absence epilepsy; TLE=temporal lobe epilepsy; BNFC=benign neonatal familial convulsions; JAE=juvenile absence epilepsy; JME=juvenile myoclonic epilepsy; BNC=benign neonatal convulsions; EGA=epilepsy with generalized tonic-clonic seizures on awakening only; BECTS=benign childhood epilepsy with centro-temporal spikes; EPC=epilepsia partialis continua; SE=status epilepticus

on topiramate and zonisamide this will be mentioned. Both areas of knowledge and uncertainty will be discussed.

VALPROATE, LAMOTRIGINE, LEVETIRACETAM AND APPEARANCE

Sodium valproate can cause hair loss, acne and hirsutism. In addition, it can also stimulate appetite leading to obesity. In contrast, lamotrigine and levetiracetam are not associated with an adverse effect on appearance.

VALPROATE, LAMOTRIGINE, LEVETIRACETAM AND CONTRACEPTION

Contraception in women with epilepsy is a topic of great practical importance for which there are plenty of guidelines to assist the clinician, including those of the National Health Service (NHS) Institute for Health and Clinical Excellence (NICE) epilepsy guidelines⁹ (<http://guidance.nice.org.uk>), the Scottish

Table 2 Areas for consideration for women with epilepsy of child-bearing age

Effects of AEDs on appearance
Effect of female hormones on seizure control
Effects of epilepsy and seizures and AEDs on fertility
Effects of AEDs on contraception and <i>vice versa</i>
Effects of epilepsy and AEDs on pregnancy
Effects of pregnancy on AEDs and seizure control
Effects of epilepsy and in particular seizures on the developing embryo/fetus
Effects of AEDs on the developing embryo/fetus

AED=antiepileptic drug

Intercollegiate Guidelines Network (SIGN) guidelines on the diagnosis and management of adults with epilepsy¹⁰ (<http://www.sign.ac.uk/guidelines/fulltext/70/index.html>), primary care guidelines on the management of epilepsy in women from the Royal Society of Medicine¹¹ (Epilepsy Guidelines Group, 2004) and Guidelines from the Royal College of Obstetricians and Gynaecologists Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit¹² (<http://www.ffprhc.org.uk>).

Neither valproate nor levetiracetam nor zonisamide exhibit any interactions with any methods of contraception. The situation for lamotrigine is not clear. While initially reported as not interfering with the combined oral contraceptive pill (COCP), there is one report in which lamotrigine was associated with a small decrease in the levels of the progestin used in this study, levonorgestrel, with the area under the curve reduced by 19% and maximal concentration by 12%.¹³ On the basis of this the manufacturer has recommended that women are informed of the potential for pill failure and that additional methods of contraception are used.

A second issue relating to co-administration of the COCP with lamotrigine is the effect the COCP has on systemic lamotrigine levels. In some women plasma lamotrigine levels are approximately halved by co-administration of the COCP.¹⁴ This may result in reduced seizure control after the addition of the COCP or conversely may result in lamotrigine toxicity following removal of the COCP. Therefore, substantial care should be taken when introducing the COCP in someone who is seizure free on a stable dose of lamotrigine as well as withdrawal of the COCP in patients on lamotrigine. Some consideration might be given to checking serum lamotrigine levels before and after starting the COCP with doses being adjusted to maintain seizure control and minimize toxicity.

Based on the above, the Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit of the Royal College of Obstetricians and Gynaecologists recently updated their guidance on AEDs and contraception to include lamotrigine as a 'condition' where the 'theoretical or proven risks of the COCP generally outweigh the advantages' stating that the 'provision of the COCP requires expert clinical judgement and/or referral to a specialist provider, since the use of the method is not usually recommended unless other methods are not available or not acceptable' (<http://www.ffprhc.org.uk>).¹² In contrast, lamotrigine therapy is listed as a condition for which there is no restriction on the use of either the progestogen-only pill or progestogen-only implant (<http://www.ffprhc.org.uk>).¹² Based on the results of the study from Sidhu *et al.*,¹³ there must however be doubt on the effectiveness of progestogen-only methods of contraception in women taking lamotrigine.

Topiramate is a CYP3A4 inducer, but the contraceptive efficacy of the COCP is thought not to be affected at monotherapy doses <200 mg/day.¹⁵ It might however be considered best practice to recommend that barrier methods are also used even at doses of topiramate <200 mg/day. Low-dose progestogen methods (such as the progesterone-only oral contraceptive) are not recommended when topiramate is being taken.

VALPROATE, LAMOTRIGINE, LEVETIRACETAM AND FERTILITY

Much has been written about the effects of individual AEDs on female fertility. A full review of this area is beyond the scope of

this article. Epilepsy and AEDs are associated with changes in hormones that may contribute to reproductive and sexual dysfunction in women, as well as abnormalities of bone health. The most common disorders of reproductive functioning in women with epilepsy are polycystic ovarian syndrome (PCOS) and hypothalamic amenorrhea.^{16,17}

PCOS, defined as the presence of multiple follicular cysts, ovulatory dysfunction (oligo-ovulation and anovulation) and clinical or serological evidence of hyperandrogenism, is estimated to occur in about 5% of women without epilepsy but in up to 20% of women with epilepsy. The relationship between PCOS and epilepsy is complicated, but since the original observation by Isojarvi and colleagues¹⁸ that sodium valproate may be associated with an increased incidence of PCOS, cross-sectional studies have produced conflicting results, either demonstrating a significant association between valproate and PCOS or reporting no significant association at all.¹⁹ Valproate-associated changes do seem to be reversible.^{20,21} In contrast to valproate, data relating to lamotrigine have failed to show an increased prevalence of PCOS.¹⁹ In a cross-sectional prospective, randomized, longitudinal trial, Morrell *et al.*²² evaluated the impact of valproate on the development of PCOS. Women with epilepsy and regular menstrual cycles were randomized to treatment with valproate or lamotrigine and followed for 12 months. Women starting valproate were significantly more likely to develop PCOS than those taking lamotrigine (9% versus 2% respectively, $P = 0.007$). So far, there is little evidence relating to the risks of PCOS with long-term treatment with levetiracetam.²³

VALPROATE, LAMOTRIGINE, LEVETIRACETAM AND BONE HEALTH

It is known that alterations of reproductive hormones by AEDs may have adverse consequences on bone health.^{24,25} While the negative impact on bone health may be a consequence of increased clearance of vitamin D by cytochrome P450 enzyme-inducing AEDs, it is clear that non-enzyme inducing AEDs including valproate^{26,27} may also be associated with an increased fracture risk. There are limited data on other commonly used AEDs, although drugs such as topiramate and zonisamide that inhibit carbonic anhydrase may theoretically affect bone health by inducing a metabolic acidosis.²⁵ There are no clinical studies on levetiracetam although animal data suggest levetiracetam may reduce bone strength without altering bone mass density.²⁸

VALPROATE, LAMOTRIGINE, LEVETIRACETAM AND PREGNANCY

Risks to the mother

The main concern to the mother during pregnancy is deterioration in seizure control. Not only is there a risk of harm from seizures, but there are psychosocial consequences, such as loss of driving rights and the perceived inability for someone to care for a new born child. As well as the risks from trauma during seizures there are also concerns from increased maternal mortality. The confidential enquiries into maternal deaths in the UK covering the period from 1997 to 1999 identified that maternal mortality was increased 10-fold for women with epilepsy compared with the prevalence of

epilepsy.²⁹ While the reasons for the increased risk are not fully understood follow-up reports have consistently reported that sudden, unexpected death in epilepsy (SUDEP) accounts for most of the excess deaths. In the most recent report spanning 2006–2008, 14 of the 261 maternal deaths were recorded as being due to epilepsy.³⁰ Of the 14, nine were taking lamotrigine, none of whom had their AED level measured in pregnancy and 11 were felt to have died as a result of SUDEP. Of the five who had AED levels measured at autopsy, three had a subtherapeutic level and two a low level.

For most women with well controlled epilepsy, seizure control does not deteriorate during pregnancy. This was shown in a study of 1956 prospectively identified cases. Using first trimester seizure control as the reference, seizure control was found to be unchanged throughout pregnancy in 63.6% of cases. Of these, 92.7% were seizure free during the entire pregnancy.³¹ Seizure control did however differ slightly depending on the AED taken, with approximately 90% of those women taking valproate compared with 83% of those taking lamotrigine being seizure free in pregnancy. Unfortunately no data were available for levetiracetam. While there are potentially many reasons why these differences were observed, it is interesting to compare the above with what is known about how AED levels change during pregnancy. For lamotrigine, apparent clearance increases steadily throughout pregnancy, peaking at about the 32nd gestational week, when a 330% increase from baseline has been observed.^{32–36} The observed fall in lamotrigine levels during pregnancy has been reported as being associated with deterioration in seizure control. Levetiracetam levels have also been shown to drop as much as lamotrigine in pregnancy.³⁷ Whether or not this is clinically relevant has not been studied.

There is currently no consensus on how best to monitor AED levels, in particular lamotrigine, during pregnancy. It has previously been advocated that a baseline, preconception, unbound (free) AED level, repeated at the beginning of each trimester and in the last four weeks of pregnancy, should be the minimum level of monitoring.³⁸ More frequent measurements will be necessary if seizure control deteriorates, side-effects ensue or compliance is an issue. For most AEDs routine monitoring of serum levels is probably not necessary. For lamotrigine, some are of the opinion that close monitoring is mandatory and that drug levels should be increased if serum levels fall, to prevent deterioration in seizure control.³⁹ That close monitoring may be effective at minimizing seizure deterioration was shown in 42 pregnant women receiving lamotrigine where monthly monitoring and dose adjustment was associated with only 19% having an increased seizure frequency.⁴⁰ Whether such practices expose the fetus to additional risks has not been established.

In an attempt to resolve the above difficulties, The National Institutes for Health Research (NIHR) have funded a large multicentre randomized controlled trial, EMPIRE (Antiepileptic drug management in Pregnancy: an evaluation of effectiveness, cost-effectiveness and acceptability of dose-adjustment strategies). This aims to identify the optimal monitoring method for pregnant mothers on various AEDs (http://www.icms.qmul.ac.uk/chs/pctu/current_projects/EMPIRE/37438.html).⁴¹ During the study if serum levels of AEDs fall, women will be randomized to a therapeutic drug-monitoring regimen or usual care involving monitoring clinical features. The primary outcome measure is seizure control with fetal outcome as a secondary measure. When completed, the study will be the largest trial in pregnant

mothers with epilepsy, involving more than 35 centres in UK, with a sample size of 1000 women.

Risks to the fetus

When considering the risks to the fetus these are usually taken to be the risk of:

- (1) MCMs, in other words malformations of such significance that they require medical or surgical intervention;
- (2) Minor abnormalities, which while occasionally disfiguring, do not require intervention;
- (3) Cognitive and behavioural delay/upset;
- (4) Intrauterine growth restriction.

Most of the available literature has concentrated on the risk of MCMs. Information is now also available on the risks to cognitive and behavioural development from *in utero* AED exposure.

Overall, the risk of MCMs from *in utero* AED exposure in monotherapy is increased by a factor of two to three, from the background risk of 2–3%.^{42,43} Exposure to polytherapy is associated with a greater risk for MCMs, which increases the more AEDs are taken.^{44–49}

Risks for MCMs

Based on available information valproate appears consistently to be the AED associated with the highest risk for MCMs.^{46,50,51} A wide range of risks has however been reported (Table 3). Possible reasons for this wide range include different methods of recruitment, different definitions of MCMs and differing times for follow-up.⁵² For a number of AEDs, dose is also an important determinant for the risk of MCM.^{46,51} This seems especially important for valproate where total daily doses less than between 700 and 1000 mg per day carry significantly lower risks for MCMs.^{46,51}

With regard to lamotrigine, the International Lamotrigine Pregnancy Registry recently reported an MCM rate of 2.2% (95% CI 1.6–3.1%) among 1558 first trimester lamotrigine-exposed pregnancies.⁵³ Data from the UK Epilepsy and Pregnancy Register revealed a similar malformation rate for pregnancies exposed to lamotrigine alone, with 21 of 647 (3.2%) infants having an MCM. A positive dose-response

was seen in keeping with exposure to other AEDs, with 5.4% of pregnancies exposed to more than 200 mg a day of lamotrigine having an MCM.⁴⁶ This was not that different from the MCM rate observed by the same investigators for pregnancies exposed to less than 1000 mg a day of valproate.⁴⁶ A positive dose response was also found by the EURAP investigators,⁵¹ but not by the North American Pregnancy Register or the International Lamotrigine Registry.^{53–55}

With regard to levetiracetam, published cases are limited. Three small reports of pregnancies exposed to levetiracetam have not raised any obvious concerns.^{56–58} The UK Epilepsy and Pregnancy Register have reported on 362 pregnancies exposed to levetiracetam. There were no MCMs among the 133 monotherapy exposures and nine among the 229 exposed to levetiracetam as part of a polytherapy regimen.⁵⁹

Less information is available for topiramate. The UK Epilepsy and Pregnancy Register reported on 203 pregnancies exposed to topiramate. Of the 70 cases that had just received topiramate, three (4.8%) had an MCM, of which two were clefting abnormalities and one a case of hypospadias.⁶⁰ In contrast, in another study of 52 pregnancies exposed to topiramate, no concerns were raised.⁶¹

The North American AED Pregnancy Registry has published data in abstract form for 197 monotherapy exposures to both topiramate and levetiracetam; eight and four MCMs were noted respectively equating to rates of 4.1% and 2.0%. In keeping with results from the UK, two of the eight MCMs with topiramate were cleft lip deformities.⁶²

For zonisamide, data for exposed pregnancies are even more limited. The only published report includes 25 pregnancies.⁶³ Considering some concerns were expressed in this small study, the lack of further information from many more pregnancies is clearly a concern.

With regard to specific MCMs, exposure to valproate in early pregnancy is associated with significantly increased risks for spina bifida, atrial septal defects, cleft palate, hypospadias and craniosynostosis.⁶⁴ The risk of spina bifida (1–2%)^{46,65,66} is dose dependent, with the greatest risk for those exposed to doses of greater than 1000 mg per day. Skeletal defects, including radial ray aplasia, rib and vertebral anomalies⁶⁷ and polydactyly, have also been reported.

No distinctive pattern of malformations has been reported for lamotrigine, although a 10.4-fold (95% CI 4.3–24.9) increase in the rate of clefting abnormalities was noted in the North

Table 3 MCMs reported by Pregnancy Registers

Epilepsy and Pregnancy Registry			
AED	UK epilepsy and pregnancy register (number of exposures; MCM rate (95% CI) (Ref)	North American pregnancy registry ^{22–24}	EURAP ²⁵
Valproate	<i>N</i> = 715. MCM rate 6.2% (4.6–8.2) ³⁹	<i>N</i> = 149. MCM rate 10.7% (6.3–16.9) ⁴³	<700 mg per day, <i>N</i> = 431. MCM rate 5.6% (3.60–8.17) ≥700 to 1500 mg per day <i>N</i> = 480. MCM rate 10.4% (7.83–13.50) ≥1500 mg per day <i>N</i> = 99. MCM rate 24.2% (16.19–33.89) ⁴⁴
Lamotrigine	<i>N</i> = 647. MCM rate 2.3% (2.1–4.9) ³⁹	<i>N</i> = 684. MCM rate 2.3% (1.3–3.8) ⁴⁸	<300 mg per day <i>N</i> = 836. MCM rate 2.0% (1.19–3.24) ≥300 mg per day <i>N</i> = 444. MCM rate 4.5% (2.77–6.87) ⁴⁴
Levetiracetam	<i>N</i> = 133. MCM rate 0% (NA) ⁵²	<i>N</i> = 197. MCM rate 2.0% (NA) ⁵⁵	<i>N</i> = 126. MCM rate 1.6% (0.4–5.6) ⁴⁴

NA=not available; MCM=major congenital malformation

American Pregnancy Registry.⁵⁵ In contrast, the UK Epilepsy and Pregnancy Register⁶⁸ and the European Surveillance of Congenital Anomalies found no evidence of increased isolated oro-facial clefts relative to other MCMs for lamotrigine.⁶⁹

RISKS FOR MINOR ANOMALIES/ FACIAL DYSMORPHISM

In addition to MCMs, minor anomalies have also been related to valproate exposure. A combination of facial dysmorphic features, which has been called the fetal valproate syndrome (Table 4),⁷⁰ and which is felt by some to be distinct from that seen with other AEDs such as phenytoin, has also been described. Dysmorphic features such as epicanthal folds, long philtrum, flat nasal bridge and hypertelorism do occur with other AEDs. The significance of dysmorphic features is still largely unknown, although a few recent studies have shown that there is a significant negative correlation between dysmorphic features and verbal intelligent quotients (IQs).^{7,71}

Risks for cognitive functioning/behavioural upset

The effects of *in utero* exposure to AEDs on cognitive functioning and behaviour have not been studied as comprehensively as studies on MCMs. A Cochrane review previously concluded that the majority of studies in this area were of limited quality with little evidence implicating one drug over another with respect to a detrimental effect on development.⁷² However, more recent studies have begun to clarify the impact of AEDs on neurodevelopment.

Studies have shown mean IQ to be significantly lower in the children of women with epilepsy compared with controls.^{73–76} While it has been suggested that these findings are independent of AED exposure, a growing body of evidence suggests AEDs do carry risks. To date, valproate has been reported as having the most detrimental effect. For example, in one study from the Merseyside Regional Epilepsy Centre, 30% of those exposed to valproate, and 20% exposed to polytherapy containing valproate, had additional educational needs.⁷⁷ In a further study, the same group found that verbal IQ was significantly lower in children exposed to valproate monotherapy (mean 83.6, 95% CI 78.2–89.0; $n = 41$) than in unexposed children (90.9, 87.2–94.6; $n = 80$) or in children exposed to carbamazepine (94.1, 89.6–98.5; $n = 52$) or phenytoin (98.5, 90.6–106.4; $n = 21$).⁷ Multiple regression analysis revealed that in addition to exposure to valproate, five or more tonic-clonic seizures in pregnancy and low maternal IQ were also associated with lower verbal IQ. Doses of valproate over 800 mg/day were associated with lower verbal IQ than lower doses.

The prospective Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study applied the Bayley Mental Developmental

Scale at three years in 309 children born to mothers taking AEDs.⁸ In the NEAD study, the valproate group global IQ was reduced by nine points compared with the lamotrigine group, seven points compared with the Phenytoin group and six points compared with the Carbamazepine group. The association between valproate use and global IQ was dose dependent: children born to mothers taking a valproate dose of less than 1000 mg per day had a global IQ that was not significantly different from that in children born to mothers taking carbamazepine, lamotrigine or phenytoin. In a further study in the same cohort,⁷⁸ dose-related effects of AED exposure on both verbal and non-verbal cognitive ability was assessed using a variety of measures. At the time of assessment (mean age 3 years), infants exposed to valproate scored worse on tests of verbal and non-verbal functioning (scores adjusted for maternal IQ, maternal age, dose, race, alcohol and folic acid use during pregnancy). No significant effects were observed for lamotrigine or phenytoin. A dose-dependent relationship was present for lower verbal and non-verbal abilities with valproate. Other groups have also reported that valproate is associated with worse cognitive outcomes, especially with regard to language skills, and also that the effect is dose related.^{79–81}

With regard to the effect of lamotrigine on cognitive development, data are more reassuring. This has been demonstrated by a number of groups (8, 78–81) and from a study from Northern Ireland, which did not find any significant effect of lamotrigine on cognitive development.⁸²

Data for the other newer AEDs are restricted to levetiracetam. In a study from the Liverpool and Manchester Neurodevelopmental Group and the UK Epilepsy and Pregnancy Register which compared cognitive development in children exposed to levetiracetam and valproate, children exposed to levetiracetam *in utero* were not at an increased risk of delayed early development compared with control children. In contrast, those exposed to valproate scored significantly worse.⁸³

VALPROATE, LAMOTRIGINE AND LEVETIRACETAM, AND BREASTFEEDING

Breastfeeding should be encouraged and may even have the additional advantage that it ensures the baby is gradually withdrawn from AED therapy. AEDs are excreted in breast milk at a level inversely proportional to the degree of maternal serum protein binding.^{84–86} Hence, the amount transferred to the infant in breast milk varies substantially between AEDs (Table 5). Valproate is heavily protein bound and therefore excreted in small quantities in breast milk.

Information on the concentration in breast milk of the newer AEDs is rather limited; however, preliminary data indicate that lamotrigine passes into breast milk in significant levels.³³ When combined with the effects of immature hepatic uridine diphosphate glucuronyltransferase enzyme systems, neonatal

Table 4 Features of fetal valproate syndrome

- Tall forehead
- Medial eyebrow deficiency
- Flat nasal bridge
- Broad nasal root
- Shallow philtrum
- Long upper lip
- Thin vermillion border

Table 5 Antiepileptic drugs studied in breast milk as a proportion of blood levels

Antiepileptic drug	Proportion appearing in breast milk (%)
Valproate ⁷⁹	3
Lamotrigine ⁸⁰	61
Topiramate ⁸¹	86
Levetiracetam ⁸²	105

exposure to lamotrigine might result in high blood concentrations in some infants, a problem that could be compounded if valproate is also taken.⁸⁷ Possibly of more importance, this may also call into question the safety of increasing lamotrigine doses to keep up with falling serum levels in the mother. So the effects of immature hepatic enzyme systems could mean that any increase in dose, to maintain maternal serum levels, could translate into a markedly elevated serum level in the infant.

There have been concerns that breastfeeding during AED therapy, especially for valproate, might have a detrimental effect on cognitive development. Data from the Neurodevelopmental Effects of Antiepileptic Drugs Study are therefore reassuring, albeit the numbers studied were small. IQs for breastfed children did not differ from those that were not breastfed either for all AEDs combined or for those exposed to the individual AEDs studied, which included valproate.⁸⁸

For levetiracetam, plasma concentrations in breastfed infants are low despite extensive transfer of levetiracetam into breast milk.⁸⁶

CONCLUSION

There are advantages of using lamotrigine and levetiracetam rather than valproate in women of child-bearing years with IGEs or unclassified epilepsy syndromes. In particular, their lesser propensity for causing MCMs, cognitive delay and behavioural upset in exposed fetuses makes them attractive alternatives. In addition, both appear to have a lesser impact on fertility and bone health.

Using lamotrigine instead of valproate is not however without its difficulties, especially considering its bidirectional interactions with hormonal methods of contraception and the tendency for serum levels to fall through pregnancy. How to manage these is not yet resolved. With regard to levetiracetam, there does not appear to be any interaction with hormonal methods of contraception and while as yet there are no reports of seizure deterioration in pregnancy, serum levels have been shown to fall as much as lamotrigine levels during pregnancy. There is clearly a need for further study to determine whether or not the issues which occur with lamotrigine apply to levetiracetam.

Of equal importance and maybe sometimes forgotten too readily, is that lamotrigine is not as good as valproate for treating generalized or unclassified epilepsy syndromes, and while clearly levetiracetam works for these syndromes,^{89,90} as yet there are no head to head studies comparing it with the gold standard treatment, valproate. Avoiding valproate therefore means that some women will suffer unnecessary seizures, with all the risks and psychosocial consequences thereof.

In conclusion, despite the increasing number of broad spectrum AEDs to choose from, women with epilepsy have difficult choices to make when choosing the most appropriate AED for them: should they choose valproate which has the best chance of rendering them seizure free, but which potentially exposes them to a number of undesirable side-effects or later their offspring to significant risks for MCMs and cognitive delay, or should they choose either lamotrigine or levetiracetam, potentially exposing themselves to unnecessary seizures in an attempt to minimize immediate and future problems with valproate, should they ever get pregnant?

DECLARATIONS

Competing interests: I have received grants to undertake research and honoraria for giving lectures from UCB-Pharma, Sanofi-Synthelabo, Glaxo Smith Kline, Janssen-Cilag, Pfizer and Eisai.

Funding: None.

Ethical approval: Not applicable.

Guarantor: JJC.

Author contribution: JJC researches literature and wrote article in its entirety.

REFERENCES

- Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. *Mayo Clin Proc* 1996;**71**:576–86
- Commission on Classification, Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**:389–99
- Mohanraj R, Brodie MJ. Outcomes of newly diagnosed idiopathic epilepsy syndromes in a non-pediatric setting. *Acta Neurol Scand* 2007;**115**:204–8
- Marson AG, Al-Kharusi AM, Alwaidh M, *et al.*, for the SANAD Study group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;**369**:1016–26
- Medicines and Healthcare products Regulatory Agency. Sodium valproate and prescribing in pregnancy. *Curr Probl Pharmacovigil* 2003;**29**:6
- Harden CL, Meador KJ, Pennell PB, *et al.* Management issues for women with epilepsy – focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: report of the quality standards subcommittee and therapeutics and technology subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009;**50**:1237–46
- 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**:1575–83
- Meador KJ, Baker GA, Browning N, *et al.* Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009;**360**:1597–605
- National Health Service (NHS) Institute for Health and Clinical Excellence (NICE) epilepsy guidelines. See <http://guidance.nice.org.uk> (last checked 7 January 2012)
- The Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the diagnosis and management of adults with epilepsy. See <http://www.sign.ac.uk/guidelines/fulltext/70/index.html>
- Stokes T, Shaw EJ, Juarez-Garcia A, Camosso-Stefinovic J, Baker R. *Clinical Guidelines and Evidence Review for the Epilepsies: Diagnosis and Management in Adults and Children in Primary and Secondary Care*. London: Royal College of General Practitioners, 2004
- Guidelines from the Royal College of Obstetricians and Gynaecologists Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. See <http://www.ffrhc.org.uk>
- Sidhu J, Job S, Singh S, Phillipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2006;**61**:191–9
- Sabers A, Bucholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res* 2001;**47**:151–4
- Doose DR, Wang SS, Padmanabhan M, Schwabe S, Jacobs D, Bialer M. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. *Epilepsia* 2003;**44**:540–9
- Luef G. Hormonal alterations following seizures. *Epilepsy Behav* 2010;**19**:131–3
- Pack AM. Implications of hormonal and neuro-endocrine changes associated with seizures and antiepilepsy drugs: a clinical perspective. *Epilepsia* 2010;**51**(Suppl. 3):150–3
- Isojärvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllylä VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 1993;**329**:1383–8
- Verrotti A, D'Egidio C, Mohn A, Coppola G, Parisi P, Chiarelli F. Antiepileptic drugs, sex hormones, and PCOS. *Epilepsia* 2011;**52**:199–211
- Isojärvi JI, Rättyä J, Myllylä VV, *et al.* Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. *Ann Neurol* 1998;**43**:446–51
- Mikkonen K, Vainionpää LK, Pakarinen AJ, *et al.* Long-term reproductive endocrine health in young women with epilepsy during puberty. *Neurology* 2004;**62**:445–50

- 22 Morrell MJ, Hayes FJ, Sluss PM, *et al.* Hyperandrogenism, ovulatory dysfunction, and polycystic ovary syndrome with valproate versus lamotrigine. *Ann Neurol* 2008;**64**:200–11
- 23 Taubøll E, Gregoraszcuk EL, Tworzydło A, Wójtowicz AK, Ropstad E. Comparison of reproductive effects of levetiracetam and valproate studied in prepubertal porcine ovarian follicular cells. *Epilepsia* 2006;**47**:1580–3
- 24 Pack AM, Reddy DS, Duncan S, Herzog A. Neuroendocrinological aspects of epilepsy: important issues and trends for future research. *Epilepsy Behav* 2011;**22**:94–102
- 25 Nakken KO, Taubøll E. Bone loss associated with use of antiepileptic drugs. *Expert Opin Drug Saf* 2010;**9**:561–71
- 26 Sato Y, Kondo I, Ishida S, *et al.* Decreased bone mass and increased bone turnover with valproate therapy in adults with epilepsy. *Neurology* 2001;**57**:445–9
- 27 Boluk A, Guzelipek M, Savli H, Temel I, Ozişik HI, Kaygusuz A. The effect of valproate on bone mineral density in adult epileptic patients. *Pharmacol Res* 2004;**50**:93–7
- 28 Nissen-Meyer LS, Svalheim S, Taubøll E, *et al.* Levetiracetam, phenytoin, and valproate act differently on rat bone mass, structure, and metabolism. *Epilepsia* 2007;**48**:1850–60
- 29 The Scottish Executive Health Department, The National Institute for Clinical Excellence, The Department of Health, Social Services, Public Safety: Northern Ireland. *Why Mothers Die – Report on Confidential Enquiry into Maternal Deaths in the UK, 1997–1999*. London: RCOG Press, 2001
- 30 Cantwell R, Clutton-Brock T, Cooper G, *et al.* Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. *BJOG* 2011;**118**(Suppl. 1):1–203
- 31 The EURAP Study Group. Seizure control and treatment in pregnancy. Observations from the EURAP Epilepsy Pregnancy Registry. *Neurology* 2006;**66**:354–60
- 32 Tomson T, Ohman I, Vitos S. Lamotrigine in pregnancy and lactation: a case report. *Epilepsia* 1997;**38**:1039–41
- 33 Ohman I, Vitos S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 2000;**41**:709–13
- 34 Tran TA, Leppik IE, Blesi K, *et al.* Lamotrigine clearance during pregnancy. *Neurology* 2002;**59**:251–55
- 35 Pennell PB, Newport DJ, Stowe ZN, *et al.* The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* 2004;**62**:292–95
- 36 Dehaan GJ, Edelbroek P, Segers J, *et al.* Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 2004;**63**:571–3
- 37 Tomson T, Palm R, Kallen K, *et al.* Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007;**48**:1111–16
- 38 Quality standards subcommittee of the American Academy of Neurology. Practice parameter: management issues for women with epilepsy (summary statement). *Neurology* 1998;**51**:944–8
- 39 Pennell PB, Peng L, Newport DJ, *et al.* Lamotrigine in pregnancy. Clearance, therapeutic drug monitoring and seizure frequency. *Neurology* 2008;**70**:2130–6
- 40 Sabers A, Pettenaite V. Seizure frequency in pregnant women treated with lamotrigine monotherapy. *Epilepsia* 2009;**50**:2163–6
- 41 EMPIRE – antiepileptic drug management in pregnancy: an evaluation of effectiveness, cost-effectiveness and acceptability of dose adjustment strategies. See http://www.icms.qmul.ac.uk/chs/pctu/current_projects/EMPIRE/37438.html
- 42 Samren EB, Van Duijn CM, Christiaens L, Hofman A, Lindhout D. Antiepileptic drug regimes and major congenital abnormalities in the offspring. *Ann Neurol* 1999;**46**:739–46
- 43 Holmes LB, Harvey EA, Coull BA, *et al.* The teratogenicity of anti convulsant drugs. *N Engl J Med* 2001;**344**:1132–8
- 44 Samren EB, Van Duijn C, Koch S, *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**:981–90
- 45 Olafsson E, Hallgrímsson JT, Hauser WA, Ludvigsson P, Gudmundsson G. Pregnancies of women with epilepsy: a population-based study in Iceland. *Epilepsia* 1998;**39**:887–92
- 46 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**:193–98
- 47 Canger R, Battino D, Canevini MP, *et al.* Malformations in offspring of women with epilepsy: a prospective study. *Epilepsia* 1999;**40**:1231–6
- 48 Kaneko S, Battino D, Andermann E, *et al.* Congenital malformations due to antiepileptic drugs. *Epilepsy Res* 1999;**33**:145–8
- 49 Kaaja E, Kaaja R, Hiilesmaa V. Major malformations in offspring of women with epilepsy. *Neurology* 2003;**60**:575–9
- 50 Wyszynski D, Nambisan M, Surve T, Alsdorf R, Smith C, Holmes L, for the Antiepileptic Drug Pregnancy Registry. Increased risk of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005;**64**:961–65
- 51 Tomson T, Battino D, Bonizzoni E, *et al.* Dose dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy pregnancy registry. *Lancet Neurol* 2011;**10**:609–17
- 52 Tomson T, Battino D, Craig J, *et al.* Pregnancy registries: differences, similarities, and possible harmonization. *Epilepsia* 2010;**51**:909–15
- 53 Cunningham MC, Weil JG, Messenheimer JA, Ferber S, Yerby M, Tennis P. Final results from 18 years of the International Lamotrigine Pregnancy Registry. *Neurology* 2011;**76**:1817–1823
- 54 Cunnington M, Ferber S, Quartey G. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. *Epilepsia* 2007;**48**:1207–10
- 55 Holmes LB, Baldwin EJ, Smith CR, *et al.* Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 2008;**70**:2152–8
- 56 Long L. Levetiracetam monotherapy during pregnancy: a case series. *Epilepsy Behav* 2003;**4**:447–8
- 57 Ten Berg K, Samren EB, Van AN, Oppen AC, Engelsman M, Lindhout D. Levetiracetam use and pregnancy outcome. *Reprod Toxicol* 2005;**20**:175–8
- 58 Hunt S, Craig J, Russell A, *et al.* Levetiracetam in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2006;**67**:1876–9
- 59 Kennedy F, Morrow J, Hunt S, *et al.* Malformation risks of anti-epileptic drugs in pregnancy: an update from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2010;**81**:e18 doi:10.1136/jnnp.2010.226340.7
- 60 Hunt S, Russell A, Smithson WH, *et al.* Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2008;**22**:272–6
- 61 Ornoy A, Zvi N, Arnon J, Wajnberg R, Schechtman S, Diav-Citron O. The outcome of pregnancy following topiramate treatment: A study on 52 pregnancies. *Reprod Toxicol* 2008;**25**:388–9
- 62 Holmes LB, Smith CR, Hernandez-Diaz S. Pregnancy Registries: Larger sample sizes essential. *Birth Defects Res (A)* 2008;**82**:307
- 63 Kondo T, Kaneko T, Amano Y, Egawa I. Preliminary report on teratogenic effects of zonisamide in the offspring of treated women with epilepsy. *Epilepsia* 1996;**37**:1242–4
- 64 Jentink J, Loane MA, Dolk H, *et al.*, for the EUROCAT Antiepileptic Study Working Group. Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med* 2010;**362**:2185–93
- 65 Omtzigt JG, Los FJ, Grobbee DE, *et al.* The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology* 1992;**42**(Suppl. 5):119–125
- 66 Lindhout D, Omtzigt JGC, Cornel MC. Spectrum of neural-tube defects in 34 infants prenatally exposed to antiepileptic drugs. *Neurology* 1992;**42**(Suppl. 5):111–8
- 67 Koch S, Losche G, Jager-Roman E, *et al.* Major birth malformations and antiepileptic drugs. *Neurology* 1992;**42**(Suppl. 5):83–8
- 68 Hunt SJ, Craig JJ, Morrow JI. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. *Neurology* 2009;**72**:1108
- 69 Dolk H, Jentink J, Loane M, Morris J, Jong-Van Den Berg LT, On behalf of the EUROCAT Antiepileptic Drug Working Group. Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? *Neurology* 2008;**71**:706–7
- 70 Diliberti JH, Farndon PA, Dennis NR, Curry CJR. The fetal valproate syndrome. *Am J Med Genet* 1984;**19**:473–81
- 71 Kini U, Adab N, Vinten J, Fryer J, Clayton-Smith J, on behalf of the Liverpool and Manchester Neurodevelopment Study Group. Dysmorphic features: an important clue to the diagnosis and severity of fetal anticonvulsant syndrome. *Arch Dis Fetal Neonatal Ed* 2006;**91**:90–5
- 72 Adab N, Tudur SC, Vinten J, *et al.* Common Antiepileptic Drugs in Pregnancy in Women with Epilepsy (Cochrane review). *The Cochrane Library*. Issue 3. Chichester, UK: John Wiley & Sons, Ltd, 2003
- 73 Gaily E, Kantola-Scorsa E, Granstrom ML. Intelligence of children of epileptic mothers. *J Pediatr* 1988;**113**:677–84
- 74 Scolnik D, Nulman I, Rovet J, *et al.* Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA* 1994;**271**:767–70
- 75 Dean JCS, Hailey H, Moore SJ, Lloyd DJ, Turnpenny PD, Little J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J Med Genet* 2002;**39**:251–9
- 76 Thomas SV, Sukumaran S, Lukose N, George A, Sarma PS. Intellectual and language functions in children in mothers with epilepsy. *Epilepsia* 2007;**48**:2234–40
- 77 Adab N, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2001;**70**:15–21

- 78 Meador KJ, Baker GA, Browning N, *et al.*, for the NEAD Study Group. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain* 2011;**134**:396–404
- 79 McVeary KM, Gaillard WD, Van Meter J, Meador KJ. A prospective study of cognitive fluency and originality in children exposed *in utero* to carbamazepine, lamotrigine, or valproate monotherapy. *Epilepsy Behav* 2009;**16**:609–16
- 80 Bromley RL, Mawer G, Love J, *et al.* Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010;**51**:2058–65
- 81 Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology* 2011;**76**:719–26
- 82 Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed *in utero* to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011;**96**:643–7
- 83 Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA, on behalf of the Liverpool Manchester Neurodevelopment Group and the UK Epilepsy and Pregnancy Register. Child development following *in utero* exposure. Levetiracetam vs sodium valproate. *Neurology* 2011;**76**:383–9
- 84 Nau H, Rating D, Koch S, Hauser I, Helge H. Valproic acid and its metabolites: placental transfer, neonatal pharmacokinetics, transfer via mother's milk and clinical status in neonates of epileptic mothers. *J Pharmacol Exp Ther* 1981;**219**:768–77
- 85 Ohman I, Vitolis S, Luef G, Soderfeldt B, Tomson T, *et al.* Topiramate kinetics during delivery, lactation and in the neonate: preliminary observations. *Epilepsia* 2002;**43**:1157–60
- 86 Tomson T, Palm R, Kallen K, *et al.* Pharmacokinetics of Levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007;**48**:1111–6
- 87 Berry DJ. The distribution of lamotrigine throughout pregnancy. *Ther Drug Monit* 1999;**21**:450
- 88 Meador KJ, Baker GA, Browning RN, *et al.*, on behalf of NEAD Study Group. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology* 2010;**75**:1954–60
- 89 Berkovic SF, Knowlton RC, Leroy RF, *et al.* Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. *Neurology* 2007;**69**:1751–60
- 90 Noachtar S, Andermann E, Meyvisch P, *et al.*, N166 Levetiracetam Study Group. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. *Neurology* 2008;**70**:607–16

(Accepted 6 November 2011)