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Review

Does in utero exposure of antiepileptic drugs lead to failure to reach full cognitive potential?

D. McCorry [a,*], R. Bromley [b,c]

[a] Department of Epilepsy, University Hospital Birmingham Queen Elizabeth NHS Foundation Trust, UK
[b] Institute of Human Development, University of Manchester, UK
[c] Royal Manchester Children's Hospital, Central Manchester University Foundation NHS Trust, Manchester, UK

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ABSTRACT

A clinical scenario of a young female on 800 mg of sodium valproate (VPA) who has recently failed lamotrigine (LTG) and levetiracetam (LEV) and who is currently planning a pregnancy is presented. Currently available data pertaining to the longer-term development of children exposed to antiepileptic drugs (AEDs) are reviewed along with considerations around the methodology and interpretation of such research. There is an accumulation of data highlighting significant risks associated with prenatal exposed to VPA, with the level of risk being mediated by dose. The majority of published evidence does not find a significant risk associated with carbamazepine (CBZ) exposure in utero for global cognitive abilities however the evidence for more specific cognitive skills are unclear. Limited data indicate that LTG may be a preferred treatment to VPA in terms of foetal outcome but further evidence is required. Too little data pertaining to LEV exposure is available and a lack of evidence regarding risk of this and other new AEDs should not be interpreted as evidence of safety.

1. Introduction

Consider a woman currently seizure free on sodium valproate (VPA) 800 mg daily, who has previously failed lamotrigine (LTG) and levetiracetam (LEV) through efficacy. She is taking folic acid and planning a pregnancy: what can we tell her about the future of her child? Pre-conceptual decision making is a complex balance of perceived risk and harm (Fig. 1). It is only through reliable research into the effect of individual antiepileptic drugs (AED) exposure in the womb, can we hope to provide the woman comprehensive information to allow an informed decision regarding choice and dose of AED. This review considers the key research that directly measures in utero AED exposure effects on future cognitive and behavioural development of the commonly used AEDs in clinical practice.

2. Indirect evidence

AEDs can cause neuronal injury at single dose exposures therapeutically relevant to humans during critical phases of brain development in rat models [1]. Evidence of harm is noted both with pathologic brain injury and in behavioural and cognitive changes in offspring and is mediated through a variety of putative mechanisms [1], with apoptosis most commonly reported [2]. The teratogenic effects of in-utero exposure of AEDs are established and discussed by Tomson in this supplement [3]. But in brief, pregnancy registers internationally consistently highlight in utero exposure to have an elevated dose-dependent risk from sodium valproate compared to other commonly used AEDs [4–6].

Understanding of the cognitive development of children exposed to in utero AEDs lags behind that of congenital malformations; despite early case reports pertaining to AED associated malformations often noting that cases also presented with impaired cognitive functioning [7–9]. Since the turn of the century increased attention to the potential cognitive risks that may be associated with specific AED exposures has occurred, however, data pertaining to newer drugs is still slow to accumulate. But why should specific attention be paid to the cognitive functioning of children exposed in the womb to AEDs?

Biological plausibility that this group of medications poses a risk to neuronal development is provided by data from animal models. Animal studies document altered neuronal development following exposure in utero to phenobarbital (PB) [10], phenytoin (PHT) [10], VPA [10–13], carbamazepine (CBZ) [14]. A small number of studies also indicate that LTG may also alter aspects of neuronal development [11,15], with LEV being the only AED not to

* Corresponding author. Tel.: +44 1213716850.
E-mail address: Dougallmccorry@yahoo.com (D. McCorry).

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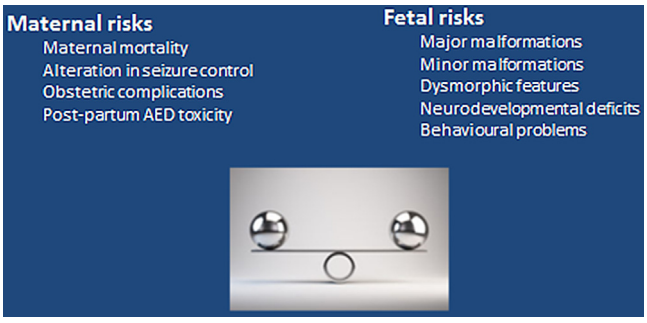

Fig. 1. The balance of benefit and risk of epilepsy drug treatment in pregnancy.

be associated with such affects to date [16] but research is still limited. An effective neuronal network is required to support cognitive functioning with decades of research highlighting lifelong implications for children who sustain damage to the neuronal system. Considering then that AEDs are noted in animals to alter typical neuronal development and the lifelong impact that such alterations may have for the human child, understanding the potential risks associated with the specific AED exposures is critical in ensuring optimum outcomes for both mother and child.

3. Measurement of cognitive abilities and lifelong implications

The longer term future academic and employment opportunities of the exposed offspring could only be assessed directly through a prospective longitudinal study which follows them up into adulthood. However, whether an AED is associated with an increased risk of cognitive difficulty needs to be determined much faster than such a method would allow and therefore the cognitive functioning of the child, which is predictive of later educational outcomes are utilized. The most commonly used method to assess cognitive functioning in school aged children in the intelligence test which produces an IQ quotient and is demonstrated to be relatively stable throughout the lifetime [17]. However, this measure is far from comprehensive and should be considered as a global summary for cognitive functioning with consideration given that substantial strengths and weaknesses in specific domains (i.e. language functioning or processing speed) may be masked by such a measure and that although certain memory systems contribute to IQ such a measure is unable to measure episodic memory or complex aspects of other specific cognitive skills.

Understanding the factors that contribute to cognitive development might reasonably be described as complex. Both genetic and epigenetic effects along with both prenatal and postnatal environmental factors interact to mediate cognitive outcome [18,19]. There are, however, a few stables within this set of complex interactions which are relevant to the study of AED teratogenicity. Firstly, IQ is a good predictor of educational attainment. Deary et al. [20] for example demonstrated in over 7000 children that having an IQ in the average range meant that 56% would get the expected average in formal educational examinations in comparison to just 16% of children whose IQ was below the average range. A second stable relevant to this topic is the finding that parental IQ is a strong predictor of child IQ [18]; stemming from both direct genetic influences and through the impact paternal IQ has on the child's postnatal [21], and you could even argue, prenatal environment. Thus, the measurement of cognitive function in the childhood years with the consideration and adjustment for confounding variables such as parental IQ is likely to provide a reliable indication of the child's future level of functioning and comparisons to unexposed children or children exposed to other AEDs allows us to delineate risks associated with specific AED treatments.

However, to understand and interpret key research into clinical decision making we should understand how such abilities are measured and interpreted. IQ is by far the most 'famous' cognitive function and has a number of negative historical connotations, however, its correlation with educational outcome means it remains in useful as a summary of global cognitive function. The majority of published paediatric IQ tests are available only to those with the correct training and academic background. Tests are developed based on cognitive theory and administered to hundreds or even thousands of children during development which form its normative population. Knowing how this normative population performed when given the assessment under standardized testing conditions means that inferences can be made about the child who has just completed the assessment either for clinical or research purposes. The most widely used measures of IQ are the Wechsler Intelligence Scales [22] which are produced for adults and children across a number of languages. The mean IQ score on these measures is 100 with a standard deviation of 15, with 68% of children assessed falling within the average range, with 13.6% falling over one standard deviation from the mean with 2.2% falling over two standard deviations from the mean (a score of below 70). Inferences can therefore be made based on the child's scores as to how the child performs in comparison to the normative population for their age group; reporting what quotient they are comparable to and also whether they fall within, below or above the average range (thus is their IQ comparable, above or below the majority of children their age).

At a group level the mean IQ scores of two groups can be statistically compared to see if one group provides a lower or higher mean IQ than the other. It is a common misconception that a group mean within the average range suggests that there is no concern for the children within that group. For example, a mean group IQ of 91, although in the average range, is lower than the normal population mean of 100 and therefore there will be increased numbers of children falling within the below average and impaired ranges as the Gaussian curve, which centres around the mean, shifts to the left. Therefore although at a group level the mean is within the average range there will be an increased frequency of children falling below the average range, which is critical information when assessing risks. Group means well above the expected mean of 100 also require investigation, as procedural or testing artefacts may be falsely inflating the mean scores. For example, a common error is the use of an old IQ test where the normative sample was collected over 10 years previously. Comparing a child's performance to a normative sample collected 10 or more years ago will lead to an inflation of the child's IQ score due to the phenomenon called the 'Flynn effect'. The Flynn effects demonstrate that there are gains in IQ over time to the magnitude of around 3 points per 10 years [23]. Therefore up to date tests and normative samples are required to ensure reliable assessment.

IQ is not, however, a measure of a specific cognitive skill and there is not a neuroanatomical correlate to IQ; IQ is in fact a 'summary score' for a range of more specific cognitive skills such as attention, semantic memory, language, processing speed, spatial and certain executive abilities such as goal orientated behaviour and task persistence. Thus reliance in research into potential cognitive effects following exposure in utero to AEDs on IQ may lead to the masking of more specific cognitive effects. An IQ score also will not tell you about certain cognitive skills including episodic memory, more complex aspects of attention or other cognitive skills and discrepancies between IQ level and such skills have been reported [24,25]. Therefore although useful to summarize cognitive function in a research context where you want to keep the number of statistical comparisons to a minimum and the

hours spent testing each child to a minimum, IQ score in isolation should not be considered to measure cognitive functioning in its entirety.

In younger children early developing cognitive abilities tend to be dependent on the emergence of early motor and language ability and therefore a slightly different assessment approach is required. The developmental quotient (DQ) is similar to IQ in that it provides a global summary of the development of skills across aspects of cognition and has been showed to be predictive of later cognitive functioning [26]. Two commonly used measures are the Bayley Scales of Infant and Toddler Development [27] or the Griffiths Mental Development Scales [28] and require the infant to be observed demonstrating certain responses (i.e. exploration, copying, verbalizations, pointing etc.) following the presentation of standardized toys with set instructions across a set number of trials. Typically, these measurements are used in children under school age and in particular in children under the age of three years or where a severe developmental delay is suspected. Similar to IQ tests, these measures have a normative sample where the mean is 100 and a standard deviation of 15 and therefore the aspects of IQ interpretation noted above apply here.

4. Other considerations in neurodevelopmental research

In addition to selecting the neurodevelopmental measures and interpreting them correctly there are a number of other methodological issues the clinician should consider when reviewing data pertaining to neurodevelopmental outcome studies in the context of children exposed to AEDs.

4.1. Power

Given that around 20% of normal developing children are expected to fall below the average range (over one standard deviation below the mean) it can be viewed that below average cognitive development is a fairly common outcome, certainly in comparison to rates of major congenital malformations which are rare outcomes in the general population (2–3%). The more common outcome under investigation the fewer participants needed to ensure an adequately powered cohort and therefore this works in favour of the researcher investigating neurodevelopmental outcomes [29]. Whilst large numbers of children are required to study the risk of major malformations, fewer children are required to investigate cognitive ability. Power is also affected by the size of the effect under investigation and therefore large effect sizes will be detectable with smaller groups than more moderate or milder effect sizes which will require larger numbers of participants. Typically papers in this area report power calculations to require between 40 and 50 participants per group for adequate power to detect moderate to large effect sizes [29–31], the detection of even larger effect sizes would be possible with smaller groups [29], however, knowing the effect size you are looking at prior to the onset of a study is difficult. Thus, although the assessment and follow up is more time consuming fewer children in comparison to malformation studies are required for neurodevelopmental studies to detect large effect sizes.

4.2. Groups

Historically, many research papers would simply report on the cognitive abilities of a single monotherapy AED exposed group. Given the differences in prescribing across countries and time points [32] no two monotherapy groups are likely to be comparable and conflicting findings become possible. Further, given the evidence reviewed below, differential outcomes across the different AEDs demonstrates that a single monotherapy group would not provide information required to counsel women about any potential risks. Therefore evidence to counsel women should come from specific AED treated groups and not from a single mixed AED group.

4.3. Blinded assessments

To ensure that the effects of unconscious biases are reduced more reliable data will be generated by research where the person assessing the child's performance is blinded to where the child belongs to an experimental or control group.

4.4. Confounders

As noted above when researching cognitive development a wealth of postnatal influences come into effect with the collection of information pertaining to confounders and adjusting for them statistically is vital. In both general cognitive research and research specific to AED exposure parental IQ, socioeconomic status, child age, gestational age at birth, child gender have all been documented to be significantly associated with child cognitive outcome and the more reliable studies should statistically address their impact on the measured outcome.

4.5. Registry studies/prospective studies

As randomized controlled trials are not thought to be ethical the gold standard for research into neurodevelopmental teratology studies such as those including AEDs would be a well-designed observational study. Prospective studies are thought to be more reliable than retrospective studies as they remove the challenges of recall bias around teratogen use [33,34]. The utilization of cohorts of children prospectively enrolled into a malformation register make use of available cohorts, however, recruitment would be considered retrospective, which in its self may lead to bias. However, recent meta-analysis finds a similar pattern of findings across these two study types [35].

A recently completed systematic review finds that quality of methodologies in neurodevelopment studies have been variable but that there is a trend for more recent studies to have more reliable methodologies [35], which is encouraging.

5. Review of current neurodevelopmental evidence

5.1. Carbamazepine

Carbamazepine has received the most research attention pertaining to the cognitive abilities of children exposed to AEDs. The majority of evidence fails to find an association between CBZ exposure and poorer global cognitive development in infancy or IQ in school aged children in comparison to control children [35–39]. The largest study to date recorded the IQ of 86 children exposed to CBZ in comparison to 141 children born to women without epilepsy and failed to find a significant difference at school age [36].

In the largest prospective study to compare children exposed to CBZ to other AEDs, the NEAD Study found that the IQ of children exposed to CBZ was significantly higher than that of the children exposed to VPA and did not differ significantly from the children exposed to either LTG or PHT when the children were assessed at 3, 4.5 and 6 years of age [30,40,41].

An increased prevalence of autistic spectrum disorders in children exposed to certain AEDs such a VPA has been documented. Rasalam et al. [42] reported an increased risk of autistic spectrum diagnosis in children exposed to CBZ, however, this has not been replicated by others [43,44], including a large population based study [44].

5.2. Sodium valproate

Despite its many years of use the cognitive risks associated with prenatal exposure to VPA were only really documented since the turn of the century. The work of Adab and colleagues [39,45] highlighted that children exposed to VPA were at an increased risk of requiring educational support and that their IQ was significantly poorer than both controls and children exposed to other AEDs. These retrospective findings have since been replicated and extended with prospective methodologies [30,36,38,40,41,46–50] and a recent meta analysis found that VPA exposure in the womb was associated with a significant mean difference of between seven to eleven IQ points in comparison to control children and children exposed to other AEDs [35]. In context, a mean IQ score reduction of this magnitude is substantial when it is considered the standard deviation of these measures is 15. Whilst meta-analysis is limited to unadjusted mean scores from already published data the vast majority of the prospective studies included made adjustment for confounding parental and child variables and maintained the conclusion; that prenatal exposure to VPA is associated with an increased risk of poorer cognitive outcome [30,36,38,40,41,46,47,50]. Of particular note, in the NEAD study children exposed to PHT, LTG and CBZ demonstrated the expected correlation between maternal IQ and child IQ, however, the group exposed to VPA showed no such correlation; increased maternal IQ was not linked to increased child IQ [41].

Looking across the ages of assessment it is apparent that the difficulties for the children exposed to VPA are present early in development [30,38,50] and remain into the school aged years [35]. Early language and motor developmental impairments are reported in young children exposed to VPA which are consistent with the report by Moore and colleagues [51] who documented an increased need to speech and language therapy in the children exposed to VPA and which has been replicated [39]. Vulnerabilities, in language functioning have also been noted at school age and appear to be global in nature [49].

There is also evidence from case reports, retrospective and more recently prospective studies that children exposed to VPA prenatally are at an increased risk of being diagnosed as having an autistic spectrum disorder [39,43,44,52]. Christensen et al. [44] utilized routinely recorded healthcare data to investigate whether children exposed to VPA were at an increased risk of autistic spectrum diagnosis and found an absolute risk of 4.42% based on 508 children exposed to VPA monotherapy. This prevalence is lower than an 8% prevalence which has been reported from observational studies [39,42,43] and this discrepancy is likely due to methodological differences across study types.

One of the most important considerations in relation to treatment in the child bearing years with VPA is its dose. The risk to cognitive development appears to be mediated by the dose of VPA with a number of studies reporting decreasing cognitive abilities with increasing dose [30,38–41,49]. Meador et al. [41] found doses equal or above 1000 mg per day VPA had a mean IQ of 94 compared to a mean IQ of 104 for doses below this value. Doses of less than 1000 mg of VPA were associated with a non-significantly lower IQ when compared to CBZ, PHT and LTG [41]. Across all AED exposures peri-conceptual folate was associated with a higher IQ [41], however, replication is required here.

5.3. Lamotrigine

Lamotrigine is widely used in the treatment of epilepsy in women of childbearing age [32,53], however, there is limited information on cognitive outcomes in children exposed to it in utero. Bromley and colleagues [38] found infants exposed to LTG and who were under the age of two years at assessment not to differ in their early global cognitive development from control children. Consistently, Cummings et al. [50] also found a non-significant difference in children exposed to LTG in comparison to controls. Further, data from the NEAD study found the IQ of children exposed to LTG to be significantly higher than the children exposed to VPA but not significantly different from children exposed to CBZ and PHT [30,40,41].

In terms of specific cognitive abilities Meador et al. [41] found superior verbal, non-verbal, memory and executive skills for school aged children exposed to LTG in comparison to the children exposed to VPA. Rihtman and colleagues [54], however, noted a significant correlation between dose of LTG and poorer fine motor abilities, but this was not replicated in the study by Veiby et al. [55]; although parental rating of motor abilities were used in the later study. Further research, is required into the cognitive abilities of children exposed to LTG with particular emphasis on dose.

In the study by Bromley and Colleagues [43] children exposed to LTG were not at an elevated risk of autistic spectrum diagnosis in comparison to control children and neither did the large population study by Christensen et al. [44]. However, Veiby et al. [55] using parental completed questionnaires reported that at 36 months of age parents indicated concern that their child may show traits of autistic spectrum disorders more frequently than the parents of control children.

5.4. Levetiracetam

There are only two published studies to date which assesses the cognitive abilities of children exposed to LEV in utero; which highlights the latency between widespread use and teratology risk or safety information.

The two studies by Shallcross and colleagues have a degree of overlap in their subjects with 32% of the under two year old cohort [47] being reassessed between the ages of 3 and 4.5 years [46]. The global cognitive ability and the language abilities of children exposed to LEV were comparable to control children at both age points, whilst significant differences were noted for some aspects of development in comparison to children exposed to VPA [46,47]. Within this data there was noted to be a significant effect of dose of LEV; although the correlation was reportedly weak [47]. Further research is urgently required and the absence of data should not be taken as an indication of foetal safety.

6. Unanswered questions and future research

VPA was introduced in the early 1970s yet it has taken over 40 years of use to comprehensively determine its harmful effects on the cognitive development of unborn child. Future research should occur more quickly following an AED entering standard usage. There is a need to conduct standardized blinded assessments, reporting data in a way that can be used to enable meta analysis. There is a need to understand how in-utero exposure effects cognitive and behavioural development not only in childhood but also with long-term follow-up into adolescent years. There should be caution about the reliability of risk estimates for VPA at offspring aged six years as it remains possible the difference between the VPA exposed children and their peers increase into adolescence as cognitive complexity increases.

Current practice has moved away from using VPA in women of childbearing age towards CBZ, LEV and LTG. Currently too little is known about LTG and LEV and cognitive outcomes in the child, particularly around potential dose effects. Therefore, the data on newer AEDs should be considered as very limited, and the controlled observational data on cognitive outcomes of children on polytherapy unknown and should not be simply extrapolated from monotherapy data. Further, too little evidence pertaining to

specific cognitive abilities is available for all AEDs. Counselling should include what we know and what we do not. A lack of evidence of risk should not be taken as evidence of safety.

Finally, while we as professionals try and understand the risks and benefits of AED usage in women of childbearing age and through pregnancy our goal is primarily to inform a woman's decision making. Professionals need to understand the woman's perspective, form a relationship of trust that allows their concerns over the tablets they choose to take to be expressed and appreciate that while we can attempt to give statistical risks in certain scenarios there is uncertainty both to our current knowledge and to what these risks mean to the individual.

7. Conclusions

A consistent theme has emerged that VPA exposure in the womb is a risk for a poorer cognitive outcome than other commonly used AEDs. The risks appear to lower the mean IQ for the exposed children by some seven to eleven points and, in addition, there is a greater number of children with special educational needs and learning difficulties. Prospective studies and a population based registry also indicate a higher than expected rate of abnormal behavioural development with autism and autistic spectrum disorder. VPA has a dose effect, with doses lower than 1000 mg daily appearing, based on current level of evidence, to be associated with better cognitive outcomes.

Women with epilepsy of childbearing age should ideally be on a single AED at the lowest effective dose to control seizures, VPA should generally be avoided when possible, however, the importance of seizure control should not be underestimated. Women should be offered high dose folic acid 5 mg peri-conceptually. Clinicians should be aware that unplanned pregnancy is common and, for example, accounts for around one third of pregnancies at the epilepsy-antenatal clinic at Birmingham Women's Hospital, UK.

Returning to the clinical scenario introduced at the beginning of this article of the women currently seizure free on VPA 800 mg daily, who has previously failed LTG and LEV through efficacy. She would need to be counselled about the teratogenic data of VPA and the concerns VPA may affect cognitive development highlighted above balanced with the risk of loss of seizure control; in light of her current level of dose which appears to carry lower risk if she elected to conceive on VPA we would support the informed decision. Whilst the risk posed in terms of malformations could be eliminated if VPA was introduced from 12 weeks, no such reassurance can be given for cognitive development with foetal brain maturation continuing throughout pregnancy (and into the postnatal years). Little is known about the cognitive outcomes of monotherapy or dual therapy with high dose LTG and LEV and this too would be presented to the female to aid her treatment decisions. Finally decisions on AED choice and dose are not one of the events and should there be loss of seizure control in pregnancy, consultation and risk information provision would be required and counselling should be seen as an ongoing discussion between the prescribing clinician and the patient.

Conflict of interest

Dr Dougall McCorry is the neurological lead for Antiepileptic drug (AED) management in Pregnancy: An evaluation of effectiveness, cost effectiveness and acceptability of dose adjustment strategies (EMPIRE) trial funded by the NIHR. Dr Bromley is currently supported by National Institute for Health Research (PDF-2013-06-041).

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