Published in final edited form as:

Curr Opin Neurol. 2009 April ; 22(2): 162–166. doi:10.1097/WCO.0b013e3283292401.

Cognitive abilities and behaviour of children exposed to antiepileptic drugs *in utero*

Rebecca L. Bromley^a, Gus A. Baker^a, and Kimford J. Meador^b

^aDepartment of Neurological Science, University of Liverpool, Liverpool, UK

^bDepartment of Neurology, Emory University, Atlanta, Georgia, USA

Abstract

Purpose of review—The last two decades have witnessed a growing concern over the treatment of epilepsy in women of childbearing age, with an increased risk of major congenital malformations and possible cognitive difficulties associated with certain antiepileptic drugs. The aim here is to review the literature regarding the possible cognitive and behavioural impact of exposure to antiepileptic drugs *in utero*.

Recent findings—Recent evidence from large prospective cohorts indicates that there is a longer term risk to the cognitive and behavioural development of the child exposed *in utero* to sodium valproate. Information on other antiepileptic agents is conflicting or nonexistent and more research in this area is urgently required.

Summary—Despite the methodological shortfalls of some of the research in this area, there is an accumulation of evidence highlighting an increased risk for cognitive and behavioural difficulties in children exposed to sodium valproate *in utero*. Although less certain, there may also be risks associated with phenobarbital and phenytoin exposure. Information regarding these risks should be communicated to the potential mother who has epilepsy.

Keywords

antiepileptic drugs; cognitive; epilepsy; *in utero*; pregnancy

Introduction

Cognitive impairment or intellectual disability and maladaptive behaviour have a large impact on the present and future functioning of the child. They place a large burden on the family and are reported to present an increased cost to the wider society in terms of lower potential future earnings and the need for extra support throughout the educational system [1,2]. It is, therefore, of paramount importance that the potential risks regarding cognitive and behavioural functioning in children exposed to antiepileptic drugs (AEDs) *in utero* are understood. Currently, there are several well designed prospective studies with preliminary results that should be communicated to the potential mother with epilepsy.

Intellectual and cognitive functioning

With regard to the first generation AEDs, published research completed both retrospectively and prospectively has indicated that exposure of children to either phenytoin (PHT) or

phenobarbital in monotherapy or polytherapy combinations can lead to adverse effects. Exposure may lead to nonverbal deficits within the areas of performance intelligence quotient (IQ) and spatial processing [3,4], difficulties with verbal skills [4–6], motor abilities [7] and poorer attentional abilities [5]. A large study investigating children exposed to phenobarbital monotherapy [8] has reported that children exposed to phenobarbital did not differ from control children in terms of their IQ at 4 years of age. Others have, however, reported a higher incidence of global impairment (IQ<70) following exposure to PHT and phenobarbital *in utero* [9–15]. Intellectual abilities of children exposed to PHT *in utero* have been reported to correlate significantly with the presence of dysmorphic features [16]. There is limited evidence regarding the cognitive and intellectual functioning of adolescents and adults who were exposed to AEDs *in utero*. Two completed studies [3,6], however, report that the deficits in cognitive abilities reported following exposure to phenobarbital and PHT persist into adulthood.

The majority of the published research has focused on two second generation AEDs, which are valproate (VPA) and carbamazepine (CBZ). VPA more than CBZ has been associated with more negative outcomes and concern over the cognitive functioning of children exposed to VPA *in utero* remains. The most consistent finding from the published results indicates that children exposed to VPA *in utero* have a poorer level of language functioning and in particular a lower verbal IQ [17–21]. In a relatively large retrospective study, children exposed to VPA *in utero* were found to have a mean verbal IQ that was seven points lower than that in other children in monotherapy drug groups and children born to women with epilepsy who were not medicated during the pregnancy [17,18]. This research also indicated that verbal IQ scores in the VPA exposed group correlated with the level of dysmorphic features [22] and that more children exposed to VPA *in utero* met the criteria (IQ<70) for intellectual disability [17,18, 23]. It has also been suggested that children exposed to VPA *in utero* are poorer in their ability to recall faces [24] and are more distractible [17]. Cognitive deficits such as those reported above are likely to be linked to the increased need for special education for children exposed to VPA *in utero*. In a retrospective questionnaire-based study [25], it was shown that a higher percentage of children exposed to VPA *in utero* required special education in comparison with children exposed to CBZ *in utero*.

There is both retrospective and prospective evidence suggesting that children exposed to CBZ *in utero* also appear to be poorer than controls on tasks of language and IQ [13,19]. There have also been reports of a more general developmental delay following exposure to CBZ *in utero* [26,27]. However, outcomes regarding the cognitive abilities of children exposed to CBZ *in utero* have been conflicting and the majority of studies have found that children exposed to CBZ *in utero* do not differ significantly from control children [7,14,20,28]. For example, Gaily *et al.* [20] documented no significant difference between the IQ scores of children exposed to CBZ monotherapy ($n = 86$) *in utero* and control children in a relatively large prospective study.

Recent research into the cognitive abilities of children exposed *in utero* to antiepileptic drugs

The onset of large prospective studies designed to answer the question regarding the longer term outcome of children exposed to AEDs *in utero* marks a large step forward in this area of research. The Kerala Registry of Epilepsy and Pregnancy (KREP) is a registry designed to examine the birth and later abilities of the child born to a mother with epilepsy. Recent published results from this registry report on the evaluation of 395 children under the age of 2 years [29••]. They found that children exposed to monotherapy VPA ($n = 71$) were significantly poorer in their motor abilities than those exposed to CBZ *in utero* ($n = 101$). Children exposed to VPA *in utero* also had the poorest mental development mean score and had the highest incidence of children falling within the impaired range (40.8%) among the other monotherapy groups (CBZ 29.7%, phenobarbital 26.8% and PHT 37.9%). These differences did not reach

statistical significance, however, and the group exposed to PHT *in utero* did not differ greatly from the VPA group. The incidence of impaired performance was higher but again not significantly different for the polytherapy-exposed children (48.7%) in comparison with the monotherapy-exposed children (33.7%). Maternal IQ, a strong correlate of child IQ, was not measured and a control group of children born to women without epilepsy was not included. These represent weaknesses in the methodology of this study.

Further research in this area has recently come from the multicentre Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study running in the USA and in the UK [30••,31]. Preliminary results focus on the intellectual functioning of 258 children exposed to monotherapy CBZ ($n = 73$), VPA ($n = 53$), lamotrigine (LTG; $n = 84$) and PHT ($n = 48$). After adjusting for maternal IQ and other influential factors, children of 3 years of age and younger who were exposed to VPA *in utero* were found to have a significantly lower level of intellectual functioning in comparison with children exposed to other AEDs [30••,31]. More children exposed to VPA (13%) than the other monotherapy groups (CBZ = 3%, LTG = 2% PHT = 5%) fell within the impaired range (IQ<70). There was a significant dose–effect relationship with VPA and not with the other monotherapy drugs. This is the first report regarding the cognitive abilities of children exposed to LTG *in utero*. As with the KREP study, the NEAD study does not have a control group to allow for comparison to be made between children exposed to an AED *in utero* and those representative of the general population. Both the KREP study and the NEAD study have protocols to follow their cohorts to the age of 6 years to allow for a more reliable documentation of the possible longer term effects of exposure to AEDs *in utero*.

There is recent evidence of the cognitive abilities of older children exposed to AEDs *in utero*. In a Finnish study [32••], the cognitive abilities of 154 children born to women with epilepsy with an IQ in the normal range were assessed along with 130 control children who were born to women without epilepsy. The cognitive domains assessed included attention, language, fine motor, visuospatial, memory and learning abilities. Analysis indicated no significant differences across any of the cognitive domains for the study group as a whole versus the control group. Interestingly, the children born to women without epilepsy who were not exposed to medication *in utero* were found to perform significantly poorer on the memory for names task. When children exposed to AEDs and control children were compared, children exposed to AED monotherapy performed poorer on attentional tasks than control children. Further, the children exposed to AED polytherapy performed poorer on auditory attention, sentence repetition and the fine motor task. Children exposed to VPA *in utero* (either as monotherapy or polytherapy; $n = 22$) had a significantly lower score in attentional tasks and memory tasks. Although these results may be complicated by the inclusion of both monotherapy and polytherapy cases, they indicate that despite intelligence within the normal range, children exposed to VPA *in utero* may show deficits in specific areas of cognition.

Another recent study has followed up adolescents of 10–20 years of age [33••], whose cognitive abilities were originally reported on by Steinhausen *et al.* [34]. In the previous assessment, children within this cohort were found to have a significantly poorer verbal and performance IQ if they had been exposed to medication *in utero*. The most recent assessment included 34% of the previous cohort. This represents a dropout rate of 4% per year, which highlights the difficulties in completing research over such a long follow-up period. The results from 116 adolescents (67 born to women with epilepsy and 49 controls) showed that exposure to all AEDs *in utero* with the exception of CBZ had a negative impact on later intellectual functioning. The number of participants in the follow-up study, however, was small and the lost to follow-up group was too big to allow drug comparisons. This study indicates the need for prospective studies to follow cohorts until adulthood.

The behaviour and neurodevelopmental disorders in children exposed *in utero* to antiepileptic drugs

The question of whether the child is at an increased risk of later behavioural difficulties has been inadequately addressed by research, although there is evidence to indicate that exposed children may be at an increased risk regardless of the individual drug exposure [19,35]. There have been case study and retrospective reports indicating that exposure to AEDs *in utero* may be associated with an increased risk of the later development of autistic spectrum disorders (ASDs) [35–37]. The incidence of ASD within a retrospective population [36] of 260 children exposed to AEDs *in utero* was 4.6%, which is higher than the reported incidence for nonexposed children and the reported incidence in the general population (0.06%) [38]. The incidences of ASD differed between drug groups. The incidence in the children exposed to VPA monotherapy *in utero* was 8.9% and even higher when both the monotherapy and polytherapy treatments were taken together (11.7%). The incidence of ASD in the group of children exposed to CBZ *in utero* was 2.5% for monotherapy and 4.5% for both monotherapy and polytherapy CBZ treatments together. These findings were retrospective and open to an inclusion bias, however.

In addition to the reports of the incidence of ASD, there have been concerns over the more general behavioural functioning of children exposed to AEDs *in utero*. In a prospective study in Finland [39], children exposed to VPA were rated as having a high level of behavioural difficulties. The differences in behavioural ratings between the children exposed to VPA and those exposed to CBZ or no AED were not significant; however, the number within each group was small ($n = 13$).

Recent research focusing on the behavioural abilities and neurodevelopmental disorders in children exposed to antiepileptic drugs *in utero*

The prospective study currently being undertaken by the Liverpool and Manchester Neurodevelopment Group has enrolled 632 children (296 born to women with epilepsy and 336 born to women without epilepsy) between 2000 and 2006 from maternity hospitals in the north west of England. Preliminary results from this study report an incidence of 6.3% of ASD in children exposed to VPA *in utero* [40••]. This represents a seven-fold increase in comparison with the control group (0.9%) from this cohort. The results from this prospective study are preliminary with 32% of the total cohort falling below the average age of detection and diagnosis of an ASD. At present, the increased incidence of ASD following exposure to CBZ reported previously [36] has not been found in this prospective cohort.

Summary

There is an accumulating body of evidence that children exposed to VPA *in utero* are at an increased risk of cognitive impairment at a young age and that exposure poses an increased risk for the later development of ASD. Research indicates that the deficits seen in younger children exposed *in utero* may also be evident in the adolescent years, but this requires further investigation. There is no conclusive evidence for the other AEDs but cognitive assessments following exposure to CBZ *in utero* have more often than not been associated with nonsignificant differences. As with VPA, there is an accumulation of negative results regarding the cognitive abilities of children exposed to either PHT or phenobarbital *in utero*. For all of these medications, there is insufficient evidence regarding the adaptive and maladaptive behavioural functioning of the child. Currently, there is no research into the cognitive or behavioural abilities of children exposed to most newer AEDs *in utero* (e.g. levetiracetam,

gabapentin, topiramate); the reason for this in part is due to the length of time it takes for a sufficient number of women with epilepsy on these medications to be enrolled and their offspring followed up for an adequate period.

There are methodological difficulties with research in this area (see Nicholai *et al.* [41••] for a critical review), which may account in part for conflicting results between studies. More well designed and methodologically sound research is urgently needed to inform more reliably and in more detail on the cognitive abilities of children exposed to AEDs *in utero* for all AEDs currently in use. Other factors that may be influential on the later cognitive abilities of the child, such as the underlying epilepsy syndrome, exposure to seizures *in utero* and a possible genetic predisposition, require research attention.

Conclusion

The accumulating body of evidence clearly identifies that exposure to AEDs *in utero* carries a risk of cognitive and behavioural problems. It is clear that more research is needed in order to allow comprehensive preconceptual advice to be given to women with epilepsy who are planning a pregnancy. Finally, there is recognition that the cognitive and behavioural impact on the child exposed to AEDs *in utero* cannot be ameliorated with surgical intervention and consequently greater effort should be placed on conducting research that identifies those most at risk.

Acknowledgments

G.B. has received educational grants from Sanofi Aventis, UCB and Pfizer of more than £10 000.

K.M. has received research support from GlaxoSmithKline, Eisai, Marius, Myriad, Neuropace, SAM Technology and UCB Pharma. K.M. has received an NIH grant to conduct the NEAD study (NIH 5R01-NS038455).

G.B. and R.B. have acted as expert witnesses relating to anticonvulsant syndrome.

The authors would like to thank George Mawer and Rebekah Shallcross for their comments on the draft of this review.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 196).

1. Baker BL, McIntyre LL, Blacher I, et al. Pre-school children with and without developmental delay: behaviour problems and parental stress over time. *J Intellect Disabil Res* 2003;47:217–230. [PubMed: 12787154]
2. Emerson E. Mothers of children and adolescents with intellectual disability: social and economic situation, mental health status and the self-assessed social and psychological impact of the child's difficulties. *J Intellect Disabil Res* 2003;47:385–399. [PubMed: 12787168]
3. Dessens AB, Cohen-Kettenis P, Mellenbergh G, et al. Prenatal exposure to anticonvulsant drugs and spatial ability in adulthood. *Acta Neurobiol Exp* 1998;58:221–225.
4. Vanoverloop D, Schnell RR, Harvey EA, Holmes LB. The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. *Neurotoxicol Teratol* 1992;14:329–335. [PubMed: 1454041]

5. Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, et al. Association of prenatal phenobarbital and phenytoin exposure with small head size at birth and with learning problems. *Acta Paediatr* 2000;89:533–541. [PubMed: 10852187]
6. Reinisch JM, Sanders S, Mortensen EL, Rubin DB. In utero exposure to phenobarbital and intelligence deficits in adult men. *JAMA* 1995;274:1518–1525. [PubMed: 7474220]
7. Wide K, Winbladh B, Sars-Zimmer K, Berggren E. Psychomotor development minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. *Dev Med Child Neurol* 2000;42:87–92. [PubMed: 10698324]
8. Shapiro S, Hartz SC, Siskind V, et al. Anticonvulsants and parental epilepsy in the development of birth defects. *Lancet* 1976;1:272–275. [PubMed: 55587]
9. Hill RM, Verniaud WM, Horning MG, et al. Infants exposed in utero to antiepileptic drugs. *Am J Dis Child* 1974;127:645–653. [PubMed: 4825584]
10. Hill, RM.; Verniaud, WM.; Rettig, GM., et al. Relationship between antiepileptic drug exposure of the infant and developmental potential. In: Janz, Dea, editor. *Epilepsy, Pregnancy and the Child*. New York: Ravens Press; 1982. p. 409–417.
11. van der Pol MC, Hadders-Algra M, Huisjes HJ, Touwen BCL. Antiepileptic medication in pregnancy: late effects on the children's central nervous system development. *Am J Obstet Gynecol* 1991;164:121–128. [PubMed: 1986598]
12. Parisi P, Francia A, Vanacore N, et al. Psychomotor development and general movements in offspring of women with epilepsy and anticonvulsant therapy. *Early Hum Dev* 2003;74:97–108. [PubMed: 14580750]
13. Rovet J, Cole S, Nulman I, et al. Effects of maternal epilepsy on children's neurodevelopment. *Neuropsychology* 1995;1:150–157.
14. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA* 1994;271:767–770. [PubMed: 7509419]
15. Ventosa L, Rocha L, Lourenco L, et al. Effects of epilepsy and antiepileptic drugs in children of mothers with epilepsy. *Epilepsia* 2002;43:511.
16. Holmes LB, Coull BA, Dorfman J, Rosenberger PB. The correlation of deficits in IQ with midface and digit hypoplasia in children exposed in-utero to anticonvulsant drugs. *J Pediatr* 2005;146:118–122. [PubMed: 15644835]
17. Vinten J, Adab N, Kini U, et al. Neuropsychological effects of exposure to anticonvulsant medication in utero. *Neurology* 2005;64:949–954. [PubMed: 15781806]
18. 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. [PubMed: 15491979]
19. Dean JCS, Hailey H, Moore SJ, et al. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J Med Genet* 2002;39:251–259. [PubMed: 11950853]
20. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 2004;62:28–32. [PubMed: 14718692]
21. Mawer G, Clayton-Smith J, Coyle H, Kini U. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. *Seizure* 2002;11:512–518. [PubMed: 12464511]
22. Kini U, Adab N, Vinten J, et al. Dysmorphic features: an important clue to the diagnosis and severity of fetal anticonvulsant syndromes. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F90–F95. [PubMed: 16239295]
23. Adab N, Vinten J, Kini U. The longer-term effects of antiepileptic drug exposure in utero. *Epilepsia* 2002;43:512.
24. Eriksson K, Viinikainen K, Monkkonen A, et al. Children exposed to valproate in utero – population based evidence of risks and confounding factors for long-term neurocognitive development. *Epilepsy Res* 2005;65:189–200. [PubMed: 16029946]
25. 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. [PubMed: 11118242]
26. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996;75:517–520. [PubMed: 9014606]

27. Lyons Jones K, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. *N Engl J Med* 1989;320:1661–1666. [PubMed: 2725616]
28. Wide K, Winbladh B, Kallen B. Major congenital malformations after intrauterine exposure to antiepileptic drugs especially carbamazepine and valproic acid. *Epilepsia* 2002;43:513.
- 29••. Thomas SV, Ajaykuma B, Indhu K, et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy Behav* 2008;13:229–236. [PubMed: 18346940] This paper presents findings from a large prospective study that reports on the cognitive outcomes of young children exposed to AEDs *in utero* in comparison with children not exposed to AEDs born to women with epilepsy.
- 30••. Meador KJ, Baker GA, Browning N, et al. Neurodevelopmental effects of fetal antiepileptic drug exposure. *N Engl J Med*. in press The NEAD study group report on a large prospective group of children exposed to AED monotherapy *in utero*. The study controls for confounding factors such as epilepsy type, seizures during pregnancy and maternal IQ.
31. Meador KJ, Baker GA, Browning N, et al. Neurodevelopmental effects of fetal antiepileptic drug exposure: 3 year old cognitive outcomes. *Epilepsia* 2008;49(s7):490.
- 32••. 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. [PubMed: 17521493] This paper describes the cognitive deficits of children exposed to AEDs *in utero* who are comparable in terms of intelligence with control children. This is a unique investigation and highlights that children exposed to AEDs *in utero* may have specific cognitive deficits despite falling within the average intelligence range.
- 33••. Titze K, Koch S, Helge H, et al. Prenatal and family risks of children born to mothers with epilepsy: effects on cognitive development. *Dev Med Child Neurol* 2008;50:117–122. [PubMed: 18177411] This paper is one of the few that have followed up a prospective cohort into their adolescent years. Findings here indicate that deficits seen in younger children exposed *in utero* may continue to be evident in adolescence.
34. Steinhausen HC, Losche G, Koch S, Helge H. The psychological development of children of epileptic parents. I: Study design and comparative findings. *Acta Paediatr* 1994;83:955–960. [PubMed: 7529600]
35. Moore SJ, Turnpenny PD, Quinn A, et al. A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet* 2000;37:489–497. [PubMed: 10882750]
36. Rasalam AD, Hailey H, Williams JH, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev Med Child Neurol* 2005;47:551–555. [PubMed: 16108456]
37. Williams G, King J, Cunningham M, et al. Fetal valproate syndrome and autism: additional evidence of an association. *Dev Med Child Neurol* 2001;43:202–206. [PubMed: 11263692]
38. Rutter M. Incidence of autism spectrum disorders: changes over time and their meaning. *Acta Paediatr* 2005;94:2–15. [PubMed: 15858952]
39. Viinikainen K, Eriksson K, Monkkonen A, et al. The effects of valproate exposure in utero on behaviour and the need for educational support in school-aged children. *Epilepsy Behav* 2006;9:636–640. [PubMed: 17049311]
- 40••. Bromley RL, Mawer G, Clayton-Smith J, Baker GA, Liverpool and Manchester Neurodevelopment Group. Autism spectrum disorders following in utero exposure to antiepileptic drugs. *Neurology* 2008;71:1923–1924. [PubMed: 19047565] This paper reports from a prospective cohort the incidence of ASDs in children exposed to AEDs *in utero*. The findings add to previous retrospective findings regarding the incidence of ASDs in children exposed *in utero* to AEDs.
- 41••. Nicolai J, Vles JS, Aldenkamp AP. Neurodevelopmental delay in children exposed to antiepileptic drugs in utero: a critical review directed at structural study-bias. *J Neurol Sci* 2008;271:1–14. [PubMed: 18479711] This review of literature regarding research into the cognitive abilities of children exposed to AEDs *in utero* focuses on the methodological differences and shortfalls of research completed to date.