REVIEW

# Neurodevelopmental effects of anti-epileptic drugs

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**Summary**    Use of medication with a desired effect on the central nervous system (as with anti-epileptic drugs) in children will undoubtedly cause concern about neurodevelopment. Data are emerging to suggest an effect of anticonvulsants on the developing brain of the unborn child when administered to mothers with epilepsy. This obviously requires detailed evaluation, especially when considering the risks of epilepsy itself. In the child with epilepsy, many of the early onset epilepsies are associated with developmental compromise as part of their clinical profile, and therefore determining the relative effects of the underlying cause, seizures and medication can be difficult. Although data are available with regard to some anti-epileptic drugs (AEDs) they remain lacking particularly in the very young with regard to efficacy as well as neurodevelopmental effects of the newer anti-epileptic drugs. Ongoing evaluation is required to ensure the best clinical practice in each individual.
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## Introduction

The choice of anti-epileptic drug in the management of epilepsy in childhood is based on the predominant seizure type and where possible the epilepsy syndrome. Whilst the underlying aetiology is a major contributor to cognitive outcome, the presumption in early onset epilepsy is that developmental compromise may be associated with ongoing seizure activity, seen or unseen, so called 'epileptic encephalopathy'. If this is the case, then treatment of the epilepsy should lead to improved developmental outcome. The natural history of many of the seizure disorders is, however, poorly understood; there is some evidence to suggest that children with longstanding epilepsy make little developmental progress and therefore have an intellectual quotient (IQ) that appears to fall over time. The difficulty we have therefore is that the cause of the developmental compromise is likely to be multifactorial in origin. The extent to which the effects of the anti-epileptic medication might contribute is essentially unknown and likely to vary according to the drug used, the requirement for polypharmacy and individual differences in sensitivity. Of course, the effects of anti-epileptic drugs may not only be seen in the developing child, but also in the unborn child of mothers taking these medications through pregnancy.

## Anti-epileptic drug use during pregnancy—the effect on the foetal brain

Exposure to anti-epileptic drugs (AEDs) during pregnancy is associated with an increased risk of congenital malformations and may have an adverse effect on foetal growth and psychomotor development. The first report of a malformation thought to be the result of phenytoin exposure was in 1963 (Mullers-Kuppers, 1963). Subsequently a retrospective survey concluded that congenital malformations were twice as common in infants of mothers on AEDs (Speidel and Meadow, 1972) as in a non-exposed population. However the relative risk of different anti-epileptic drugs has not been investigated until relatively recently, and even now with the existence of pregnancy registries (www.epilepsyandpregnancy.co.uk; www.eurapinternational.org), knowledge has been acquired about the apparent risk of the older more commonly used AEDs rather than that of the newer agents. It is also apparent that not all children born to mothers on anti-epileptic drugs are at risk. Reports show between 3.5% and 9.0% of all AED-exposed pregnancies will have a major congenital malformation, compared with a background risk of 1—2% (Canger et al., 1999; Holmes et al., 2004; Kaaja et al., 2003; Kaneko et al., 1992; Morrow et al., 2006; Samren et al., 1997). More recently the possible effects on psychomotor development in offspring manifesting at a later age have been highlighted (Adab et al., 2004; The NEAD Study Group, 2009), data not available from registry studies.

The risk to the unborn child has to be balanced against that of untreated epilepsy in the mother. The relative risk of malformations however is higher amongst those individuals with treated as opposed to untreated epilepsy, and higher in those on larger doses of AEDs as well as those on polytherapy vs monotherapy (Morrow et al., 2006). Many of the previous studies have been cohort studies, reviewing the effects of the older anticonvulsants such as phenytoin and phenobarbitone. The pregnancy registries now reveal information on use of sodium valproate, carbamazepine and lamotrigine but only to a limited extent on newer AEDs. Malformation rates vary across studies owing to differences in ascertainment, but no consistent differences in odds ratios are seen for phenytoin, phenobarbitone and carbamazepine, whereas sodium valproate is repeatedly associated with a higher risk in most studies (Wide et al., 2004; Artama et al., 2005; Morrow et al., 2006)

For lamotrigine there is some evidence that in monotherapy at lower dose risk approaches that of carbamazepine —3.2% for lamotrigine compared to 2.2% for carbamazepine (Morrow et al., 2006). The effect appears to be potentiated by combination therapy with valproate, (2.7% for exposure to lamotrigine with other AEDs and 12.5% for lamotrigine with valproate). However it also appears that there is a greater risk with increased dose, a higher risk seen with valproate doses above 600 mg/day and lamotrigine doses above 200 mg/day.

Carbamazepine and sodium valproate have been independently associated with the development of neural tube defects. Supplementation with folate may in part be protective, periconceptional supplementation reducing the risk in women with a previously affected pregnancy (MRC Vitamin Study Research Group, 1991; Mulinare et al., 1988; Seller and Nevin, 1984), but this may not apply to women taking AEDs (Yerby, 2003). Folate supplementation is nevertheless recommended in all women preconceptually, and many recommend for all women with epilepsy of child bearing age. In this situation doses of 4—5 mg daily are recommended, over and above the dose of 400 μg/day shown to be effective in trials in women not on AED's.

A possible increased risk of developmental delay in offspring born to mothers with epilepsy taking anti-epileptic drugs has long been noted, but not attributed to any specific anticonvulsant. (Gaily et al., 1988; Granstrom and Gaily, 1992; Speidel and Meadow, 1972). Many potential contributory factors have been considered such as maternal seizure type, number of seizures during pregnancy, IQ and education of parents, in addition to AED exposure (Table 1). The possible differential effect of sodium valproate on the developing brain was highlighted in a selected questionnaire study reported in 2001. 1267 women (all mothers with epilepsy) were approached of which 721 (57%) returned questionnaires. Information from about 590 children was gathered, including 400 school children (150 exposed to monotherapy, 74 polytherapy and 176 no AEDs). 349 were in mainstream education, 42 (10.5%) of whom were receiving some form of help and nine (2.25%) were in special education (Adab et al., 2001). Odds ratio of additional educational needs for those exposed to valproate monotherapy compared to unexposed children was 3.4 in contrast to 0.26 for carbamazepine and 0.54 for other monotherapy. No data are available as to whether mothers were prescribed folic acid. Although foetal anticonvulsant syndrome, including possible valproate embryopathy had been reported previously (Diliberti et al., 1984; Kelly, 1984) this was the first report suggesting that valproate could have an effect on cognitive development over and above other medications. However, this was recognised to be a highly selective retrospective

**Table 1** Summary of studies examining neurocognitive outcome of children or to mothers with epilepsy.

| Study | Type of study | Control group | AEDs monotherapy (polytherapy) | Findings | | | | Comments |
|---|---|---|---|---|---|---|---|---|
| Ornoy and Cohen (1996) | Retrospective, observational | Yes | CBZ 47 | | CBZ | Controls | | Variable time of review (age 6 months to 6 years) |
| | Semi-blinded (psychologist) | | | Bayley MDI | 101.1 | 112[*] | | No correction for maternal IQ |
| | | | | McCarthy GCI | 97.5 | 101[*] | | Six CBZ children dysmorphic, and much lower IQ |
| | Reviewed 6 months to 6 years | | | No significance between groups in motor performance | | | | |
| Koch et al. (1999) | Prospective, longitudinal | Yes | No exposure 13 | | VIQ | PIQ | IQ | 41% Ascertainment for callback |
| | | | All 31 (23) | Control | 103.1 | 106.7 | 105.5 | |
| | | | PHT 12 (12) | No exposure | 100.8 | 98.6 | 101.8 | Little detail on individual drugs, appear to be mainly PHT and PRM |
| | Reviewed 14 years | | PRM 9 (6) | Mono | 99.7 | 100 | 99.7 | |
| | | | Control 49 | Poly | 92.7[*] | 92.2[*] | 92.2[*] | |
| Adab et al. (2001) | Questionnaire based, retrospective | No | No drugs 176 | Odds ratio for children having SEN exposed to AEDS 1.94 | | | | Highly selective, self-reporting of mothers, likely bias |
| | Children age 3 months to 23 years | | CBZ 116 (43) VPA 56 (39) EZM 1 (?) LMT 13 (8) PHT 24 (21) PB 7 (?) | Valproate monotherapy 3.4 Carbamazepine monotherapy 0.26 | | | | |
| Wide et al. (2004) | Prospective, blinded | Yes | Control 66 | No difference between unexposed & exposed for global scores | | | | Small numbers except CBZ |
| | Reviewed age 4.5—5 years | | AEDs 67 CBZ 35 (43) PHT 16 (2) | Significant higher number mothers with AED treatment no further education | | | | |
| | | | VPA 3 (2) PB 2 (1) CLN 2 (0) | | | | | |
| Gaily et al. (2004) | Prospective, blinded | Yes | CBZ 86 (23) | CBZ VIQ 96, PIQ 103 | | | | Small numbers in VPA group; confounding factors polytherapy and maternal IQ |
| | Age 5—9 years | | VPA 13 (17) | VPA VIQ 82[*] PIQ 96 Control VIQ 95 PIQ 96 | | | | |
| Adab et al. (2004) | Retrospective non-blinded | No | For children >6 years | Children >6 years mean verbal IQ low average range in those exposed to VPA monotherapy and significantly lower than exposed and other monotherapy groups | | | | Retrospective ascertainment, low level participation (40%) |
| | Children age 6 months to 6 years | | No drugs 80 ALL 120 (49) VPA 41 (28) 8 | | | | | |

**Table 1** (*Continued*)

| Study | Type of study | Control group | AEDs monotherapy (polytherapy) | Findings | | Comments |
|---|---|---|---|---|---|---|
| | | | CBZ 52 (?) | | | |
| | | | PHT 21 (?) | | | |
| Liverpool and Manchester Neurodevelopmental Study Group (2005) | Retrospective, non-blinded | No | Unexposed 80 | VPA had largest odds ratio (3.47) for having an impaired VIQ compared to other drug groups (CBZ 1.03, PHT 0, POLY 1.09) and significantly higher odds ratio compared to non-exposed group (1.00) | | Same patient group as included in Adab et al. (2004) |
| | | | All 120 (49) | | | |
| | | | VPA 41 | | | |
| | Review 6—16 years | | CBZ 52 | | | |
| | | | PHT 21 | | | |
| Titze et al. (2008) | Prospective, observational | Yes | CBZ 4 (2) | Polytherapy exposure lower IQ than controls; all AEDs except CBZ had negative impact on IQ | Small numbers, individual AED effect difficult to assess | |
| | | | PB 3 (11) | | | |
| | Mean age at review 14.2 years (10—20 years) | | PHT 12 (12) | Early poor environment confounds effect | | |
| | | | VPA 3 (8) | | | |
| | | | PRM 9 (6) | | | |
| The NEAD Study Group (2009) | Prospective, multicentre, observational | No | | Mean IQ | | No control group, non-blinded, no randomisation, small numbers |
| | | | VPA 61 | VPA 92[*] | | |
| | Children reviewed at 3 years | | CBZ 93 | CBZ 98 | | |
| | | | PHT 55 | PHT 99 | | |
| | | | LMT 100 | LMT 101 | | |

[*] Significant $p < 0.05$.

study with obvious bias as mothers were self-presenting, and further data required.

A subsequent study from the same group examined neuropsychological performance of children over 6 years of age exposed to valproate and carbamazepine as monotherapy or polytherapy in utero, or to no anti-epileptic exposure. Again this was a selected sample as mothers had been invited to bring their children to participate in the study. Children exposed to valproate in mono or polytherapy had significantly lower performance and verbal IQ compared to those exposed to carbamazepine or no AEDs (Liverpool and Manchester Neurodevelopmental Study Group, 2005). This was also true when corrected for maternal IQ. However much of the data to date has been retrospective rather than prospective and therefore definitive conclusions are difficult to make. One prospective study, with blinded assessment and comparison to a control group, suggested carbamazepine did not impair intelligence in prenatally exposed offspring, but that exposures to valproate and polytherapy were associated with reduced verbal intelligence; however though there were a relatively high number of carbamazepine monotherapy exposures (86), exposures to valproate monotherapy were low (13) and independent effects of valproate unconfirmed in view of confounding of results by low maternal IQ and polytherapy (Gaily, 2004). One further study following children born to mothers with epilepsy to adolescence, matched with controls, found not only did children prenatally exposed to AEDs achieve lower IQ than controls (polytherapy > monotherapy), but also this was compounded by poor family environment at 2 years (Titze et al., 2008).

More recently preliminary data of developmental outcome at 3 years have been reported after prospective enrolment of infants in the 'neurodevelopmental effects of anti-epileptic drugs study group' (NEAD). This reports children exposed to vaproate in utero to have significantly lower IQ scores at 3 years than those exposed to other anti-epileptic drugs (phenytoin, lamotrigine and carbamazepine), even after adjusting for maternal IQ, maternal age, gestational age at birth and maternal preconception use of folate. Children exposed to valproate had a mean IQ score 9 points below those exposed to lamotrigine. There are recognised limitations to this study, in particular lack of randomisation, no existence of a control group, and small numbers and follow-up is ongoing (The NEAD Study Group, 2009).

Pregnancy registries are likely to provide answers to questions on the relative teratogenic risks of the common monotherapies, relative risks of the most common AED combinations, possible drug-specific malformations and the impact of dose or other major covariates. However only partial (if any) answers will be found for risks associated with the less commonly used AEDs or most combinations, or the role of any genetic predisposition or other potential confounders. Further, reliable data with regard to cognitive outcome will only be available from prospective non-selected studies.

The fact that not all children exposed display consistent abnormalities, and the increasing number of descriptions of exposed siblings (Kozma, 2001; Malm et al., 2002; Schorry et al., 2005) suggests a genetic susceptibility. How we counsel mothers embarking on pregnancy is therefore currently difficult. The possible risk of exposure to anti-epileptic drugs has to be weighed up against the risk of seizures should anti-epileptic drugs be discontinued or changed. The degree to which genetic susceptibility is responsible, and through what mechanism, remains to date unknown. Our duty remains to keep women informed of possible risks and from an early stage.

## Anti-epileptic drug use during the neonatal period

The neonatal period (<28 days) has the highest incidence of epileptic seizures throughout the life span (1.8—3.5/1000 life births) (Hauser et al., 1993). Despite the increasing number of AEDs now available to us generally, we still remain relatively limited in our choice of medication in this age range. A Cochrane Review concluded that there is little evidence to support the use of any of the anticonvulsants currently used in the neonatal period with regard to efficacy (Booth and Evans, 2004). We are further limited by the lack of available intravenous preparations; neonates presenting with seizures are often sick, maybe pre-term, unable to absorb adequately from the gut. Few newer agents have intravenous preparations available. Phenobarbitone and phenytoin, however, remain the predominant drugs used. Data are available on pharmacokinetic data as well as safety. The main determinant of efficacy has been the effect on the clinical seizures but there is some evidence that this may be misleading and potentially harmful. In a prospective observational study of 14 babies with neonatal seizures requiring treatment with phenobarbitone video electroencephalogram (EEG) performed before and up to 24 h following treatment showed a minimal effect with four responding, and an increase in electrographic seizures in 10 (Boylan et al., 2002).

An important problem in the treatment of neonatal seizures therefore is detection. Many clinical events will be subtle and difficult to recognise (Mizrahi and Kellaway, 1987). At risk babies may be ventilated and paralysed so the clinical detection is impossible unless video EEG recording is used, when the relative rate of electrical vs clinical seizures has been shown to be high (Boylan et al., 1999). What also remains unclear is the significance of electrical seizures alone. Do all seizures need to be treated? Evidence suggests that the underlying aetiology has the greater influence on neurological outcome rather than the presence or absence of seizures (Tekgul et al., 2006). The occurrence of electrographic seizures is associated with poor developmental outcome but again whether this is related to the aetiology is unknown (Boylan et al., 1999; McBride et al., 2000). Seizures do however confound the prognosis in neonates with hypoxic ischemic injury (Hall et al., 1998) and at the present time it is considered desirable to abolish seizure activity if possible: our problem is in determining what to use to achieve this.

Seizures presenting in the neonatal period are more likely to be acute symptomatic — the etiology in the majority is hypoxic ischemic encephalopathy, but other causes include acute cerebrovascular insults, systemic illness, central nervous system infection and metabolic disorders. The role of ongoing AED treatment could therefore be questioned if the neonate may only be prone to seizures in the

short-term, although accepting they may remain at a higher risk. Further, presentation with seizures in an otherwise well neonate in the first few days of life may be the initial presentation of one of the benign self-limited epilepsy syndromes (Benign Idiopathic Neonatal Convulsions or Benign Familial Neonatal Convulsions). AEDs may have different effects in the immature neonatal brain because of developmental changes seen in neuroreceptor function. Although unclear as to the primary in vivo mode of action of many of the AEDs, some studies have shown gamma amino-butyric acid (GABA) mediated inhibition is not fully developed until beyond the age equivalent in humans of more than 3 years, GABA being excitatory in some areas of the brain in the neonatal period (Dzhala et al., 2005; Sanchez and Jensen, 2001). Inhibition of receptors during different stages of brain development may also have consequences on brain development, and hence prophylactic administration of AEDs could have secondary adverse effects. The true extent of these are, however, unknown as when regular treatment is required, seizures are often difficult to treat and prognosis for neurodevelopmental outcome poor. Again the question arises as to the relative contributions of the underlying condition, the seizures and the AEDs.

The choice of AED in the neonatal period therefore continues to be driven by individual protocol rather than by any evidence base. Important research questions remain not only in the choice of AED with regard to efficacy, but also as to whether newer approaches considering the developmental changes within the brain deserve consideration. Discovery of genetic targets in the familial syndromes, and the developmental changes in expression of certain transporters have led to a rethink in how we may approach neonatal seizures. Over expression of the chloride importer NKCC1 in the neonatal rat brain (Dzhala et al., 2005) has led to the suggestion that the NKCC1 inhibitor bumetanide, a diuretic already in use, may be clinically useful in the management of neonatal seizures. Further trials will be imperative to evaluate such use, not only of newer novel agents but also newer AEDs.

## Anti-epileptic drug use during infancy

Outside the neonatal period, the incidence of epilepsy also remains high in the first year of life. Most published series document poor long-term outcome with continuing seizures and neurodevelopmental impairment in 40—60% (Battaglia et al., 1999; Cavazzuti et al., 1984; Chevrie and Aicardi, 1978; Chevrie and Aicardi, 1979; Czochanska et al., 1994; Matsumoto et al., 1983). Etiologies encompass a wide spectrum of developmental brain malformations, acquired brain injuries, genetic and metabolic conditions. Despite the previously reported poor clinical outcome there are infants whose epilepsy takes a more benign course but the incidence of these disorders remains low (Watanabe et al., 1990).

A catastrophic course with medication resistant seizures and severe impairment of developmental progress is characteristic of many of the epilepsies starting in infancy. As discussed above, it is presumed that the ongoing seizure and epileptic activity at least in part contribute to the poor neurodevelopmental progress. Seizure activity may have a negative impact on the immature brain impairing neurodevelopmental progress, so called 'epileptic encephalopathy' (Engel, 2001). Optimised diagnostic and therapeutic strategies that result in improved seizure control could therefore presume to have a significant impact on cognitive outcome in this age group. Problems arise however as there are few treatments evaluated for use in this age group as in neonates, and developmental data are even more lacking. The relevance of anti-epileptic treatment to developmental impairment in this group is not known. As has been discussed evidence from experimental work suggests that anti-epileptic drugs in theory may interfere with some of the normal maturation of receptor function. Some of the possible neurocognitive side effects of the anti-epileptics themselves, seen in a limited number of older children and adults may also be of concern in the child acquiring skills (Aldenkamp et al., 2000). Studies attempting to address the possible longer term cognitive effects of AEDs have shown conflicting results (Loring and Meador, 2004; Vermeulen and Aldenkamp, 1995). Studies have also evaluated older children and later use of AED's rather children in the longer term after AED use in infancy. The relative effects of the underlying disorder, the effects of the seizures and the anti-epileptic drugs are therefore impossible to tease apart in clinical practice. Only clinical experience and evidence base of efficacy (and safety) can lead to the best practice.

A further problem that remains is of course the limited evidence base for efficacy on which we base our decisions in practice. Studies on the whole evaluate efficacy in seizure type; many are designed to maximise data accumulation for regulatory requirements. As a result, many epilepsy syndromes may be grouped together. Clinical decisions on treatment in children in the majority should be based on syndrome diagnosis, for which data will not be available from grouped analysis. Increasingly studies are being performed with regard to syndrome diagnosis but this still remains limited in the very young. Such studies require multicentre participation and major investment to acquire numbers. This aside, certain groups have shown that this can be achieved with open label pragmatic trials (Mikaeloff et al., 2003) as well as small well designed crossover trials (Chiron et al., 2000).

## Infantile spasms

Data are available for the use of AEDs in the treatment of infantile spasms. Classically these children present between 3 and 9 months of age with recurrent bilateral symmetrical contraction of the muscles of the neck/trunk, causing the majority of children to flex forward. This occurs repeatedly, in clusters more commonly on waking. The majority of children has an associated marked high amplitude chaotic abnormality on EEG (hypsarrhythmia). Developmental plateau or regression (loss of skills) is also seen at presentation of spasms in most, the original triad of spasms, hypsarrhythmia, and developmental plateau first described by Charles West, so called ''West Syndrome''. A similar presentation will be seen with different etiologies as the presentation of spasms is an age related phenomena. The underlying pathophysiology is thought to be attributable to rapid involvement of sub cortical networks, particularly thalamocortical networks.

The developmental prognosis is highly related to the underlying cause, with some degree of learning impairment seen in up to 90% (Riikonen, 1982). The presumption has been that the epileptiform activity is the aetiology to the cognitive regression seen at presentation; limited data suggest developmental outcome is improved in those who are both treated with seizure cessation and have an early response to treatment (Rener-Primec et al., 2006). However, even with complete resolution of the spasms and EEG abnormality, the rate of long-term neurodevelopmental compromise remains high.

Steroids have long been used in the treatment of West syndrome. Open label, retrospective and randomised studies have reported cessation of spasms in 42—87%. Hancock and Osborne (2004) studies also suggest injectable steroids to be more favourable than oral steroids. The emergence of vigabatrin demonstrated an apparent selective efficacy in this syndrome, particularly in children with spasms the result of tuberous sclerosis (Aicardi et al., 1996; Chiron et al., 1997). Data from the UK infantile spasms study (UKISS) where children at presentation were randomised to steroids or vigabatrin, showed steroids to be more effective than vigabatrin with regard to outcome at 14 days (excluding children with tuberous sclerosis) (Lux et al., 2004). In the same study children were randomised further in the steroid group to injectable or oral steroids; no difference between these groups was seen. Developmental outcome from this study was assessed by Vineland telephone interview at 14 months in both the steroid and vigabatrin groups (Lux et al., 2005) and showed no difference in mean VABS score between the two groups. However in the IS group with no known aetiology the mean score was higher in the hormone treated group than the vigabatrin group. Further work is required to determine whether treatment can influence neurodevelopmental outcome.

### Severe myoclonic epilepsy of infancy (Dravet syndrome)

This is a further syndrome with onset in the first year where development is normal prior to the onset of seizures. Children present with prolonged lateralised seizures with normal continuing development; in the second year typically they develop multiple seizure types including myoclonic jerks, and developmental plateau. It has been presumed that this may be the model of an epileptic encephalopathy; presumed that the developmental compromise is the result of ongoing epileptic activity. Genetic studies have shown up to 80% have a mutation of the sodium channel SCN1A on chromosome 2 (Harkin et al., 2007), and that a proportion of the remainder have a complete exon deletion as determined on multiplex ligation-dependent probe amplification (MLPA) (Marini et al., 2007).

A randomised controlled crossover trial of stiripentol (a cytochrome P450 inhibitor) vs placebo added to clobazam and sodium valproate showed significant benefit in the treatment of this otherwise difficult to treat epilepsy (Chiron et al., 2000). This study demonstrated that evaluation in a particular syndrome is indeed possible; what remains unclear however is whether response to this AED is specific to Dravet. Further, it is also unclear whether there is a direct anticon-

vulsant effect itself from stiripentol or whether the result is the effect of raising the metabolites of clobazam and sodium valproate (as stiripentol is a cytochrome P450 inhibitor) (Giraud et al., 2006; Quilichini et al., 2006). It also remains unclear whether any impact can be made on neurodevelopment by treatment of seizures (Wolff et al., 2006); animal data suggest that seizures are not the whole story and that the genetic background may have some degree of influence on the natural history of the disorder (Martin et al., 2007). A further important finding with regard to management is that certain AEDs may lead to deterioration in seizures (e.g., lamotrigine (Guerrini et al., 1998), possibly related to the underlying genetic defect.

## Use of anti-epileptic drugs in the older child

As outlined certain epilepsy syndromes are associated with developmental compromise with onset under the age of 5 years; but some degree of epileptic encephalopathy, however, may also be seen in certain syndromes presenting in older children. Although the effects of seizures are believed to have the most effect in the younger age group (Muter et al., 1997) susceptibility may be seen up to 5—6 years of age with certain syndromes presenting with developmental regression alongside catastrophic onset of seizures. It could be assumed that AEDs may also have an impact at this early stage, but data still remain sparse and conflicting for both the older and newer anti-epileptic agents.

Most studies traditionally have evaluated efficacy over a relatively short time, which has limited any accumulation of neurodevelopmental data. Studies have on the whole been cross-sectional rather than longitudinal which limits the information available. (Loring and Meador, 2004). Of concern, however, is that even limited cognitive effects of a medication at any stage in the natural history of an epilepsy may have significant long-term consequences. Further, such effects may not be readily apparent from within a study as individuals are already likely to be on AEDs at recruitment, and therefore the possible true effect of AED's overall not detectable over time. Currently regulatory authorities stipulate a requirement that a paediatric programme should be planned in the development of any newer AED (European Union, 2006; www.fda.gov/cder/pediatric), and that neurodevelopmental outcome should be incorporated into such studies. However, standardised assessments are not available that can be applied in a cost effective manner, over less than a 12-month period, or across age groups. Further it is unlikely that any comparative data to a control group would be available.

This aside long-term effects on cognition have been shown from early treatment with phenobarbitone (Farwell et al., 1990; Wolf et al., 1981; Sulzbacher et al., 1999). Farwell et al. (1990) randomly assigned children with a history of febrile seizures (requiring prophylaxis at that time) to phenobarbitol or placebo. After 2 years neuropsychological assessment revealed a significantly lower IQ in the group assigned phenobarbitol than the placebo group, suggesting phenobarbitol suppressed cognitive performance. Concerns more recently have also been expressed in some individuals on topiramate, particularly with regard to verbal ability,

with deficits in working memory, short-term verbal memory, language skills including verbal fluency, verbal IQ, attention/concentration, processing speed, complex visuomotor ability and perception in certain individuals (Martin et al., 1999; Lee et al., 2003; Lee et al., 2006). This raises particular concern in early childhood where language development is at risk, although this has not been systematically evaluated and the effect of ongoing seizures may equally be of concern. It also does not appear to be a global effect with certain individuals appearing particularly susceptible, and with effects minimised if introduction of the medication is cautious and polytherapy avoided. It also appears to be reversible in older individuals (Thompson et al., 2000). Mixed findings have been seen with other newer and older agents with regard to an effect on cognition dependent on study design, but overall the newer agents (e.g., lamotrigine, levetiracetam) are thought to pose a lesser risk (Aldenkamp et al., 2003; Zhou et al., 2008; Bootsma et al., 2008), Their effects in the developing child, however, are largely unknown.

## Other alternatives to conventional AED's are also available.

The ketogenic diet, a high fat diet low in carbohydrate designed to mimic the effects of starvation, has been shown to be effective in the treatment of seizures resistant to anticonvulsants in older children (Neal et al., 2008). There is increasing evidence that it may be more effective in the younger age group, and should be considered earlier in the clinical course of the epilepsy (Kossoff et al., 2002; Kossoff et al., 2008; Nordli et al., 2002). Again however randomised controlled data is not available in children under 2 years of age; furthermore the risk benefit is not known in the developing brain. Animal studies suggest the diet could have some adverse effect on cognitive development (Zhao et al., 2004), but human data are limited in availability. Preliminary studies have suggested significant improvements in overall function and quality of life, not necessarily related to seizure control (Hallbrook et al., 2007; Pulsifer et al., 2001)

## Conclusions

There will always remain particular concern about the effects of medication on a developing child. This is especially pertinent at times of rapid brain development with regard to drugs primarily targeted at epileptic seizures, both in utero and in early childhood. There is evidence that certain AEDs may have an effect at particular times of exposure although the relative effects of the seizures, underlying aetiology and AEDs are unclear. Whenever the exposure, there is some evidence that some individuals may be more at risk than others and not all are susceptible to effect. Although there is no question that further data are required to inform our clinical decisions, each case must be considered on an individual basis as to the risk benefit of any particular AED used and the role of ongoing treatment.

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