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REVIEW ARTICLE

Neurodevelopmental Effects of Fetal Antiepileptic Drug Exposure

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Abstract Many studies investigating cognitive outcomes in children of women with epilepsy report an increased risk of mental impairment. Verbal scores on neuropsychometric measures may be selectively more involved. While a variety of factors contribute to the cognitive problems of children of women with epilepsy, antiepileptic drugs (AEDs) appear to play a major role. The mechanisms by which AEDs affect neurodevelopmental outcomes remain poorly defined. Animal models suggest that AED-induced apoptosis, altered neurotransmitter environment, and impaired synaptogenesis are some of the mechanisms responsible for cognitive and behavioral teratogenesis. AEDs that are known to induce apoptosis, such as valproate, appear to affect children's neurodevelopment in a more severe fashion. Fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across a range of domains, and these appear to persist at least until the age of 6. Some studies have shown neurodevelopmental deficiencies associated with the use of phenobarbital and possibly phenytoin. So far, most of the investigations available suggest that fetal exposures to lamotrigine or levetiracetam are safer with regard to cognition when compared with other AEDs. Studies on carbamazepine show contradictory results, but most information available suggests that major poor cognitive outcomes should not be attributed to this medication. Overall, children exposed to polytherapy prenatally appear to have worse cognitive and behavioral outcomes compared with children exposed to monotherapy, and with the unexposed. There is an increase risk of neurodevelopmental deficits when polytherapy involves the use of valproate versus other agents.

Key Points

Neurodevelopmental abnormalities can occur following fetal exposure to antiepileptic drugs.

Antiepileptic drugs that are known to induce apoptosis, such as valproate, appear to affect children's neurodevelopment in a more severe fashion.

Children exposed to polytherapy prenatally appear to have worse cognitive and behavioral outcomes compared with children exposed to monotherapy, and with the unexposed.

1 Introduction

Epilepsy is a common neurological disorder that frequently requires continuous treatment during pregnancy, and antiepileptic drugs (AEDs) are one of the most commonly prescribed teratogens in women of child bearing potential [38]. Approximately, 1.5 million women with epilepsy are of childbearing age in the USA, and three to five births per 1,000 will be to women with epilepsy [22]. However, the

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total number of children exposed in utero to AEDs is likely greater because AEDs are used for the treatment of other conditions, such as headache, pain, and mood disorders. Neurodevelopmental abnormalities can occur following fetal exposure to AEDs. Through data from animal models and analysis of clinical outcomes in humans, the current state of knowledge can be elucidated [20].

2 Animal Studies

AED-induced cognitive/behavioral deficits (i.e., behavioral teratogenesis) have been observed in rat offspring at dosages lower than those associated with somatic malformations [3]. Phenobarbital, for example, produces neuronal deficits, reduces brain weight and brain catecholamine levels, and impairs development of normal behaviors in rats [16]. Phenytoin produces dose-dependent, long-term, impaired coordination and learning in mice [34]. A recent study has shown a range of behavioral deficits with some of the older AEDs such as phenobarbital, phenytoin and valproate, but also impaired rotorod performance for adult rats with neonatal exposure to lamotrigine [17]. AED-induced functional and anatomical defects may involve different mechanisms since anatomical risks are related to first trimester exposure, and functional deficits may be related primarily to third trimester exposure. Neonatal rats have been used in AED studies because their cerebral developmental period parallels the human third trimester. AED exposure during the third trimester may have severe and enduring consequences on the brain because functional properties and connectivity are developing and susceptible to AED-induced apoptosis and altered synaptogenesis, as demonstrated in rat models [15]. Proposed possible mechanisms underlying functional teratogenicity of AEDs include folate deficiency, reactive intermediates (e.g., epoxides or free radicals), ischemia, apoptosis-related mechanisms, and neuronal suppression [20].

The leading hypothesis for the mechanism behind behavioral/cognitive dysfunction involves AED-induced apoptosis and altered synaptogenesis. Similar to alcohol, exposure of the immature brain to some AEDs can produce widespread neuronal apoptosis in rodents and non-human primates [47]. *N*-Methyl-D-aspartate (NMDA) antagonist and gamma-aminobutyric (GABA) mimetic traits of ethanol may be responsible for its apoptogenic action, as other drugs that block NMDA glutamate receptors also trigger apoptosis in the developing brain. This is clinically significant because many AEDs used therapeutically in humans have NMDA antagonist or GABA mimetic properties (e.g., barbiturates and benzodiazepines) [35]. The associated cognitive deficits are likely more related to dysfunction in the surviving neurons than to the actual neuronal loss. There is evidence in neonatal rats that demonstrates that exposure to AEDs during a sensitive postnatal period impairs synaptic maturation in neurons that survive the initial exposure [15]. Genetic predisposition likely plays a role and could involve interaction of teratogens with multiple liability genes [14]. This, in part, may explain the observed individual variability.

The findings of alcohol-induced apoptosis in fetal animal brain led to the use of the apoptotic model in studies with AEDs in neonatal rats. This model is likely to reflect the susceptibility period to AED-induced adverse effects in the immature human brain. AEDs that have been shown to produce widespread neuronal apoptosis in the neonatal rat brain include phenytoin, vigabatrin, valproate, clonazepam, diazepam, and phenobarbital [4, 5]. The effect can occur with single-dose exposure, is dose-dependent, and occurs at therapeutically relevant blood levels [20]. Further, when two of these AEDs are given at below threshold dosages, the full apoptotic response is triggered, suggesting a synergistic effect.

Valproate's increased risk may be because apoptosis is induced beginning below its typical therapeutic range [5]. Many AEDs have not been tested in this model, but similar apoptotic effects were not seen at therapeutic dosages for carbamazepine, lamotrigine, levetiracetam, or topiramate in monotherapy. However, addition of these AEDs (except for levetiracetam) to an AED that produces apoptosis in monotherapy will increase the apoptotic effect, which may suggest polytherapy risk [23, 24]. The addition of levetiracetam has not been shown to enhance cell death in the developing brain. These observations in animals raise serious concern that certain AEDs, which are commonly used in women of childbearing potential, could produce similar adverse effects in children exposed in utero or in the neonatal period. Additional studies are needed to examine the effects of other AEDs in animal models and determine if a similar mechanism occurs in humans.

AEDs target neurotransmitters, ion channels, and second messenger systems in the brain. Diazepam, phenobarbital, valproate, and vigabatrin, for example, act on GABA signaling. Alterations to neurotransmitter systems could potentially induce teratogenesis. The neurotransmitter medium in the developing brain plays a large role in the regulation of neuronal differentiation and migration. Based on rat studies, enhanced GABA inhibition and blockade of NMDA receptors impairs neurogenesis and cell migration [27, 45]. This can lead to cortical dysplasias and reduced brain volume. In children exposed in utero to AEDs, the neurotransmitter changes and resultant cellular changes may account for impaired cognition [36].

AEDs alterations of genetic factors could affect plasticity-related genes as a possible mechanism leading to behavioral teratogenesis. A novel study examined mouse

pups exposed in uterus to valproate, measuring physical development, impaired olfactory discrimination, and dysfunctional pre-weaning social behavior [41]. In situ hybridization experiments revealed lower cortical expression of brain-derived neurotrophic factor (BDNF) messenger RNA (mRNA) in valproate animals [41]. These results suggest that alterations in plasticity-related genes may contribute to behavioral phenotypes associated with this AED. Further, valproate-treated mice displayed physical developmental delays, behavioral abnormalities, and modifications at the level of gene expression reported in autism [41]. This finding opens up the possibility to examine specific factors like BDNF in the development of autistic-related traits.

3 Human Studies

3.1 Limitations

Although the risks for birth defects and neurodevelopmental deficits are increased in children of women with epilepsy, the role of AEDs and differential risks of AEDs remain only partially delineated [22]. Disparities across studies are partly a result of differences in methodology and patient populations. Some of the studies had a small sample size and were based on detailed follow-up with a variety of neuropsychological tests. These studies are useful to identify differences in the distribution of the recorded variables, but not to identify uncommon effects. To assess the risk of relatively low-frequency events, large studies and clinical diagnoses are required. Formal assessments of mental performance were made in most studies, but in many it is unclear whether investigators were blind as to AED exposure when assessments were made. In many prospective studies, follow-up began after birth rather than during pregnancy. In other studies, the influences of possible confounding factors were not addressed in an empirical fashion [e.g., parental intelligence quotient (IQ) and education, seizure type and frequency, AED dose/blood levels, maternal age, and socioeconomic status].

3.2 General Findings

The majority of investigations report an increased risk for developmental delay and mental retardation in children of mothers with epilepsy [22]. The risk for mental impairment in children of mothers with epilepsy has been related to intrauterine growth retardation, reduced head circumferences, major malformations, numerous minor malformations, and in utero AED exposure [22]. Although contradictory findings have been reported, human studies suggest that AEDs play a major role.

3.3 Carbamazepine

A population-based, longitudinal, follow-up study of 35 preschool children born to women with epilepsy on treatment with carbamazepine did not show a difference in the Griffith's test scores for locomotor function, personal and social behavior, hearing and speech, eye and hand coordination, performance, and practical reasoning, when compared with unexposed children [50]. In a prospective, evaluator-blinded study published in 1994, 36 children exposed in utero to carbamazepine did not differ from their matched controls on any of the neurobehavioral tests, including IQ scores [42]. Another prospective, blinded study observing 86 children with fetal exposure to carbamazepine revealed mean verbal and nonverbal IQ scores of 96 [95 % confidence interval (CI) 93–100] and 103 (95 % CI 100–106). They did not differ from control subjects, whose mean verbal and nonverbal IQ scores were 95 (95 % CI 92–97) and 102 (95 % CI 100–105) [18]. More recently published data by the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group showed that IQ scores in children with prenatal exposure to carbamazepine followed longitudinally were as follow: 98 at 3 years, 106 at 4.5 years, and 105 at 6 years [29, 31, 32] (Table 1). These IQ scores did not differ from those of children exposed to lamotrigine or phenytoin. However, children exposed to any of these three AEDs had better IQ outcomes than children of mothers using valproate during pregnancy. Follow-up investigations showed a dose-dependent relationship for lower verbal abilities compared with nonverbal abilities with carbamazepine at age 3 years [30], but this resolved by the age of 6 [32]. This finding requires replication in separate cohorts to determine if language abilities are particularly susceptible to fetal carbamazepine exposure. In addition, other sub-investigations within the NEAD study revealed a significant dose-related

Table 1 Neurodevelopmental effects of antiepileptic drugs (NEAD)[a] Study

AED	Mean IQ[b]		
	3 years	4.5 years	6 years
Lamotrigine	101	106	108
Phenytoin	99	105	108
Carbamazepine	98	106	105
Valproate	92	96	97

AED antiepileptic drug, *IQ* intelligence quotient

[a] Prospective observational study that followed children exposed to AEDs in utero longitudinally

[b] Mean IQ of children exposed to each AED in utero, adjusted for factors significantly related to child IQ, such as maternal IQ

performance decline in motor functioning for carbamazepine exposure at age 3 years [9].

3.4 Lamotrigine

In the NEAD study, after adjustment for maternal IQ, maternal age, antiepileptic-drug dose, gestational age at birth, and maternal preconception use of folate, the mean IQ for children exposed to lamotrigine was 101 at 3 years, 106 at 4.5 years, and 108 at 6 years [29, 31, 32] (Table 1). These IQ scores did not differ from those of children exposed to carbamazepine or phenytoin, but were better than those of children with fetal exposure to valproate. Additional sub-investigations within the NEAD study have shown that lamotrigine appears to be better than valproate and carbamazepine with regard to motor development, and better than valproate and phenytoin with regard to adaptive and emotional/behavioral functioning [9, 10]. A study published by the Liverpool and Manchester Neurodevelopment Group showed no significant increase in the risk of neurodevelopmental disorders in children exposed to monotherapy with lamotrigine [6].

3.5 Levetiracetam

During a prospective study comparing the early cognitive development of children <24 months, born to women with epilepsy, exposed in utero to levetiracetam ($n = 51$) versus sodium valproate ($n = 44$), and a group of children representative of the general population ($n = 97$), children exposed to levetiracetam did not differ from the control group ($p = 0.62$) on overall development [44]. Eight percent of children exposed to levetiracetam in utero fell below the average range (Griffiths Mental Development Scale, Developmental Quotient <84), compared with 40 % of children exposed to valproic acid. After controlling for maternal epilepsy and demographic factors using linear regression analysis, exposure to levetiracetam in utero was not associated with adverse outcomes ($p = 0.67$) [44]. Conversely, when compared with valproic acid exposure, levetiracetam exposure was associated with higher scores for the overall developmental quotient ($p < 0.001$) [44]. A recently published follow-up study evaluating these children at age 36–54 months showed that children exposed to levetiracetam in utero did not differ from unexposed controls on any scale administered [43]. In comparison, children exposed to valproic acid in utero scored lower on measures of gross motor skills, comprehension and expressive language abilities [43].

3.6 Phenobarbital

Reduced cognitive outcomes have been reported with phenobarbital monotherapy [37]. Two double-blind studies were conducted on independent samples of adult men prenatally exposed to phenobarbital and matched controlled samples using different measures of general intelligence. Study 1 included 33 men, and study 2 included 81 men. In both, men exposed prenatally to phenobarbital had significantly lower verbal intelligence scores (approximately 0.5 SD) than predicted [40]. Exposure that included the last trimester was the most detrimental [40]. In a study assessing the effect of post-natal exposure to phenobarbital in 217 patients with febrile seizures aged 8–36 months, after 2 years, the mean IQ was 7.03 points lower in the group assigned to phenobarbital than in the placebo group (95 % CI −11.52 to −2.5, $p = 0.0068$) [13]. Six months later, after the medication had been tapered and discontinued, the mean IQ was 5.2 points lower in the group assigned to phenobarbital (95 % CI −10.5 to 0.04, $p = 0.052$) [13]. The investigators retested 139 of these children 3–5 years later, after they entered school, and they found that the phenobarbital group scored significantly lower than the placebo group on the Wide Range Achievement Test-Revised (WRAT-R) reading achievement standard score (87.6 vs. 95.6; $p = 0.007$) [46]. In addition, albeit not statistically significant, there was a mean difference of 3.71 IQ points on the Stanford-Binet, with the phenobarbital-treated group scoring lower (102.2 vs. 105.7; $p = 0.09$) [46]. The proportion of children remaining free of subsequent seizures did not differ significantly between the treatment groups. It appears that phenobarbital depresses cognitive performance in children, and the disadvantage on the verbal developmental skills may outlast the administration of the drug. Given phenobarbital's known apoptotic potential, adverse effects would be expected with prenatal exposure to this AED. However, further investigations are required to determine if this assumption holds true.

3.7 Phenytoin

The fetal hydantoin syndrome is a variable pattern of altered growth and performance that includes unusual facies, distal phalangeal hypoplasia, and other defects occurring in some infants exposed in utero to hydantoins, including phenytoin. Reduction of intellectual ability in infants with the fetal hydantoin syndrome is the area of greatest concern. A prospective study of 35 infants exposed prenatally to this class of anticonvulsants showed that 11 % had sufficient features to be classified as having the fetal hydantoin syndrome [21]. An additional 31 % displayed some features compatible with the prenatal effects of hydantoins [21]. A case-control study of 104 infants whose mother received hydantoins during pregnancy supports these conclusions [21].

In a blinded-evaluator, case-control study published in 1992, 20 phenytoin-exposed children between 4 and

8 years of age had significantly lower scores for performance IQ (PIQ), full scale IQ (FSIQ), and visual motor integration test (VMIT) [48]. In a prospective study published 2 years later, 36 children exposed to phenytoin in utero had a mean (±SD) global IQ 10 points lower (95 % CI 4.9–15.8) than their matched controls (113.4 ± 13.1 and 103.1 ± 25; $p = 0.038$) [42]. In addition, phenytoin-exposed children had a global IQ of ≤84 significantly more often than the control group ($p < 0.1$) [42]. While controls were matched for maternal age and socioeconomic status, maternal IQ was not taken into consideration. However, it was measured, and the mother–child IQ differences were similar for carbamazepine- and phenytoin-exposed children. In the same study, the Reynell language development scores followed a similar trend, with children exposed to phenytoin scoring significantly lower than their controls [42]. Also, a study evaluating the psychomotor development in preschool children exposed to phenytoin in utero showed a subtle but significant reduction in the scores for locomotor development at 4.5–5 years compared with unexposed children (mean scores 98 vs. 106; 95 % CI −14 to −0.4) [50]. In the NEAD study, after adjustment for maternal IQ, maternal age, antiepileptic-drug dose, gestational age at birth, and maternal preconception use of folate, the mean IQ for children exposed to phenytoin was 99 at 3 years, 105 at 4.5 years, and 108 at 6 years [29, 31, 32] (Table 1). These IQ scores did not differ from those of children exposed to carbamazepine or lamotrigine, but were better than those of children with fetal exposure to valproate. Additional sub-investigations within the NEAD study have shown a significant dose-related performance decline in parental ratings of adaptive functioning at age 6 for phenytoin [10].

3.8 Valproate

A retrospective survey that evaluated the relative risks of additional educational needs in children exposed to AEDs in utero, published in 2001, showed that children exposed to valproate monotherapy had an odds ratio (OR) of 3.4 (95 % CI 1.63–7.10) by contrast with an OR of 2.06 (95 % CI 0.06–1.15) for carbamazepine [1]. Polytherapy including valproate had similarly high ORs for additional educational needs (2.51 (95 % CI 1.04–6.07)) compared with those unexposed and also an increased ORs of 1.51 (95 % CI 0.56–4.07) versus polytherapy excluding valproate [1]. Another retrospective study published in 2004 controlled for maternal IQ and demonstrated a lower verbal IQ (approximately 10 points) in children exposed in utero to valproate ($n = 41$) versus other monotherapy groups and an unexposed group [2]. The decrease in IQ in the valproate group was dose dependent. A 2005 population-based study of 39 children aged 6.6–13.4 years showed that the prevalence of low intelligence (FSIQ <80) was 19 % (4/21) and the prevalence of exceptionally low intelligence (FIQ <70) 10 % (2/21) in valproate monotherapy-exposed children [12]. However, in this study, the mothers using valproate scored significantly lower ($p < 0.05$) in FIQ, and other cognitive measures, and had also significantly lower educational level ($p = 0.035$) [12].

In a prospective study evaluating the early cognitive development of children of women with epilepsy ($n = 198$), published in 2010, children exposed to sodium valproate had a statistically significant increased risk of delayed early development in comparison with the control children ($n = 230$) [7]. In an observational cohort study conducted in 210 children aged 9–60 months born to mothers enrolled in the UK Epilepsy and Pregnancy Register, there was evidence of mild or significant developmental delay in 23 children (39.6 %) exposed in utero to valproate, ten (20.4 %) exposed to carbamazepine, and one (2.9 %) exposed to lamotrigine compared with two children (4.5 %) in the control group [11]. Multivariate analysis demonstrated that in utero exposure to valproate (OR 26.1, 95 % CI 4.9–139; $p < 0.001$) and carbamazepine (OR 7.7, 95 % CI 1.4–43.1; $p < 0.01$) had a significant detrimental effect on neurodevelopment, but no adverse effects were seen for lamotrigine [11].

In the prospective NEAD study, after adjustment for maternal IQ, maternal age, antiepileptic-drug dose, gestational age at birth, and maternal preconception use of folate, children who had been exposed to valproate in utero had significantly lower IQ scores than those who had been exposed to other AEDs. For children exposed to valproate, the mean IQ was 92 at 3 years, 96 at 4.5 years, and 97 at 6 years [29, 31, 32] (Table 1). On average, children exposed to valproate had an IQ score 6–9 points lower than those exposed to lamotrigine, phenytoin, or carbamazepine. The association between valproate use and IQ was dose dependent. Children's IQs were significantly related to maternal IQs among children exposed to carbamazepine, lamotrigine, or phenytoin, but not among those exposed to valproate. In this study, children exposed to valproate also did poorly on measures of verbal and memory abilities compared with those exposed to the other AEDs, and on non-verbal and executive functions compared with children exposed to lamotrigine (but not carbamazepine or phenytoin) [32]. Dose-dependent adverse effects were seen in valproate-exposed children at age 6 years on IQ, verbal, non-verbal, memory, and executive functions. A substudy of the NEAD investigation also found that cognitive fluency and originality were lower in the group of children exposed to valproate in utero versus lamotrigine and carbamazepine groups [28]. Additional sub-investigations within the NEAD study have shown a significant dose-related decline in motor functioning and parental ratings of adaptive functioning for valproate. Also, on the basis of

parent ratings of attention span and hyperactivity, children of mothers who took valproate during their pregnancy appear to be at a significantly greater risk for a future diagnosis of attention-deficit/hyperactivity disorder [9, 10].

Another investigation, published in 2011, had findings similar to those of the NEAD study with regard to the effects of valproate exposure. In this investigation of 57 children exposed to valproate monotherapy ($n = 23$), polytherapy with valproate ($n = 15$), or polytherapy without valproate ($n = 19$), all groups had elevated frequencies of extremely low (<70) or borderline (70–79) FSIQ (15.8–40.0 %) [33]. Verbal Comprehension and Working Memory scores in all groups fell significantly below the standardized test mean [33]. Multivariate analysis of covariance analysis revealed significant main effects of valproate on verbal comprehension and working memory, and of polytherapy on verbal comprehension and processing speed [33]. Moreover, a 2009 study found poorer adaptive behavior in children with fetal exposure to valproate [49], which is consistent with the NEAD findings.

In a 20-year study, published in 2005, evaluating 260 children born to mothers taking AEDs, sodium valproate was the drug more commonly associated with autistic disorder. Five out of 56 study children (8.9 %) exposed to sodium valproate alone fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for autistic disorder ($n = 4$) or Asperger syndrome ($n = 1$) [39]. A recent study of 415 children exposed to AEDs in utero, published in 2013, found an increase in risk of neurodevelopmental disorders in children exposed to monotherapy sodium valproate (6/50, 12 %; adjusted OR 6.06, 95 % CI 1.65–24.53, $p = 0.007$) and in those exposed to polytherapy with sodium valproate (3/20, 15 %; adjusted OR 9.97, 95 % CI 1.82–49.40, $p = 0.005$) compared with control children (4/214; 1.87 %) [6]. Autistic spectrum disorder was the most frequent diagnosis. A prospective, population-based birth cohort study from Denmark was published in 2013 and included 655,615 children born in 1996–2006, of which 5,437 had autism spectrum disorder, including 2,067 with childhood autism. The 508 children exposed to valproate had an absolute risk of 4.42 % (95 % CI 2.5–7.46) for autism spectrum disorder, with an adjusted hazard ratio (HR) of 2.9 (95 % CI 1.7–4.9), and an absolute risk of 2.50 % (95 % CI 1.30–4.81) for childhood autism, with an adjusted HR of 5.2 (95 % CI 2.7–10.0) [8]. Thus, fetal valproate exposure is associated with a significantly increased risk of autism spectrum disorder and childhood autism.

3.9 Other AEDs as Monotherapy

The risks to cognition and behavior of fetal exposure from other AEDs are unknown secondary to a lack of adequate data in human studies.

3.10 Polytherapy

Several investigations have shown worse cognitive and behavioral outcomes with in utero exposure to polytherapy versus monotherapy. A study published in 1994 showed that children with prenatal exposure to polytherapy had significantly lower scores than controls for a large number of psychological tests [26]. A study published a few years later revealed increasing frequency of neurological dysfunction from the control group to the no drug or monotherapy group to the polytherapy group [25]. In addition, there were compromised intelligence scores in the polytherapy group [25]. In a study designed to investigate the effect of AEDs on intelligence in prenatally exposed children of mothers with epilepsy, significantly reduced verbal IQs were found in children exposed to polytherapy (mean 85, 95 % CI 80–90) compared with other study group children (e.g., carbamazepine monotherapy mean 96, 95 % CI 93–100) and control subjects (mean 95, 95 % CI 92–97) [18]. A population-based study evaluating the long-term effects in neurodevelopment at age 16 in children born to women with epilepsy during pregnancy reported that children exposed to polytherapy had an increased risk of not receiving a final grade or finishing the school year [19]. Note that these data predominately involved older AEDs, so the risk of polytherapy using the newer AEDs is not clear.

3.11 Other Variables

There are many other variables that can influence the neurodevelopmental outcomes of children born to women with epilepsy and exposed prenatally to AEDs. Some studies have shown a correlation between the type of maternal epilepsy and an increase in abnormal electroencephalogram (EEG) patterns in the child. Children of women with focal EEG findings and generalized tonic clonic seizures have an increased risk of developing focal paroxysmal discharges in their EEGs [25]. Also a retrospective study published in 2004 revealed that frequent tonic clonic seizures (five or more) in pregnancy were significantly associated with a lower verbal IQ despite adjusting for other confounding factors [2]. The NEAD study showed evidence of a relationship between the children's IQ and maternal IQ in most cases [29]. Also, in the NEAD study, there was evidence of a positive association of periconceptional folate use and IQ [32]. Mean IQ adjusted for other variables was 108 (95 % CI 106–111) with folate use versus 101 (95 % CI 98–104, $p = 0.0009$) without it [32]. While all these and other factors contribute to our understanding of neurodevelopmental deficits in children born to women with epilepsy, their discussion is beyond the scope of this review paper.

4 Conclusions

As summarized in this article, many studies investigating cognitive outcomes in children of women with epilepsy report an increased risk of mental impairment. Verbal scores on neuropsychometric measures may be selectively more involved. While a variety of factors contribute to the cognitive problems of children of women with epilepsy, AEDs appear to play a major role. The mechanisms by which AEDs affect neurodevelopmental outcomes remain poorly defined. While animal models suggest that AED-induced apoptosis, altered neurotransmitter environment, and impaired synaptogenesis are some of the mechanisms responsible for cognitive and behavioral teratogenesis, further research in this area is needed. Both animal and human studies suggest that not all AEDs are the same with regard to neurodevelopmental outcomes. AEDs that are known to induce apoptosis, such as valproate, appear to affect children's neurodevelopment in a more severe fashion. Fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across a range of domains, and these appear to persist at least until the age of 6. If possible, the use of sodium valproate should be avoided during pregnancy. The increased likelihood of neurodevelopmental disorders should be communicated to women for whom sodium valproate treatment is considered. Although the risk appears to be lower than with valproate, some studies have shown neurodevelopmental deficiencies associated with the use of phenobarbital and possibly phenytoin. The current guidelines of the American Academy of Neurology and the American Epilepsy Society recommend avoidance of both phenobarbital and phenytoin during pregnancy if possible. However, more conclusive determinations on the risks of phenytoin will require additional studies. So far, most of the investigations available suggest that fetal exposures to lamotrigine or levetiracetam are safer with regard to cognition when compared with other AEDs. However, attention needs to be paid to some recent animal investigations in which fetal exposure to lamotrigine was associated with subtle deficits, such as impaired rotorod performance in adult rats. Studies on the effect of levetiracetam are limited, and continued caution should be exercised when utilizing this AED in clinical practice. Studies on carbamazepine show contradictory results, but most information available suggests that, similar to lamotrigine, major poor cognitive outcomes should not be attributed to this medication. The risks to cognition and behavior of fetal exposure from other AEDs are unknown secondary to a lack of adequate data in human studies. Overall, children exposed to polytherapy prenatally appear to have worse cognitive and behavioral outcomes compared with children exposed to monotherapy, and with the unexposed. However, several studies suggest that all polytherapy is not the same. There is an increase risk of neurodevelopmental deficits when polytherapy involves the use of valproate versus other agents. In addition to the long-term neuropsychological effects described for each individual drug in this paper, there are other subtle effects, including reduced right-handedness and verbal (vs. non-verbal) abilities that might be attributable to changes in cerebral lateralization induced by exposure to AEDs [32]. It is important to evaluate the current therapeutic paradigms and develop new ones to minimize AEDs' effect on the developing brain, while maximizing clinical benefits.

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