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Cognitive/behavioral teratogenetic effects of antiepileptic drugs

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Abstract

The majority of children of mothers with epilepsy are normal, but they are at increased risk for developmental delay. Antiepileptic drugs (AEDs) appear to play a role. Our current knowledge is reviewed, including research design issues and recommendations for future research. In animals, exposure of the immature brain to some AEDs can produce widespread neuronal apoptosis and behavioral deficits. The risks of AEDs in humans are less clear, but recent studies raise concerns, especially for valproate. There is a critical need for well-designed systematic research to improve our understanding of AED effects on the fetal brain.

Keywords

Antiepileptic drugs; Anticonvulsant drugs; Pregnancy; Teratogenesis; Development; Cognition; Behavior

1. Animal studies on behavioral effects of in utero AED exposure

Animal studies have demonstrated that in utero antiepileptic drug (AED) exposure can produce behavioral as well as anatomical defects, which can occur at dosages lower than those required to produce somatic malformations [1,2]. Gestational or neonatal exposure to benzodiazepines can affect brain chemistry and behavior causing hyperactivity or learning deficits [3,4]. Despite the common use of carbamazepine in humans, very few neurobehavioral studies in animals have been conducted with this AED. In utero carbamazepine exposure did not produce hyperexcitability in primates [5]. Perinatal phenobarbital exposure in rats reduces brain weight [6]. Mice exposed prenatally to phenobarbital have neuronal deficits, reduced brain weight, and impaired development of reflexes, open-field activity, schedule-controlled behavior, spatial learning, and cate- cholamine brain levels [7–12]. Gestational or neonatal exposure to phenytoin reduces brain weight [13,14], alters neuronal membranes in the hippocampus [15], delays neurodevelopment [16], and impairs spatial learning and motor coordination [17–25]. Hyperactivity has been observed in rats and primates following prenatal exposure to phenytoin [5,23,25]. Gestational primidone in rats produces learning deficits and reduces open-field activity [26]. In utero valproate exposure can alter neuronal membranes [27], decrease brain weight in mice [28], and result in adverse neurobehavioral effects [29,30].

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2. Mechanisms underlying adverse AED effects on neurodevelopment

2.1. Proposed mechanisms

Teratogens interact with genotype to produce both anatomical and behavioral defects. Whether a defect occurs depends on a susceptible genotype and may involve the interaction of multiple-liability genes [31]. Proposed mechanisms underlying teratogenicity of AEDs include folate, ischemia, neuronal suppression, reactive intermediates (e.g., epoxides or free radicals), and AED-induced neuronal apoptosis [32]. The mechanisms of anatomical and behavioral teratogenesis may well differ, because it appears that the highest risk of anatomical defects is from first-trimester AED exposure, whereas the highest risk of behavioral defects appears to be from exposure during the third trimester. One of the leading hypotheses of anatomical teratogenesis involves oxidative macromolecular damage from free radicals formed as reactive intermediates of AED metabolism [33]. However, it is unclear if this mechanism contributes to AED-induced behavioral teratogenesis. Folate deficiency during pregnancy reduces neurogenesis and increases apoptosis [34], but folate nutritional status during pregnancy has not been shown to impact neurodevelopment [35]. As discussed below, there is mounting evidence that AED-induced apoptosis is the most likely candidate for the behavioral deficits. However, it is possible that one of the other noted mechanisms could contribute to triggering the apoptosis.

2.2. AED-induced neuronal apoptosis

The immature brain is susceptible to widespread neuronal apoptosis secondary to a variety of insults including trauma, seizures, excessive oxygen, and certain drugs [36–43]. The observation that third-trimester gestational ethanol exposure can produce widespread neuronal apoptosis and neurobehavioral deficits led to the hypothesis that the adverse behavioral effects of AED exposure might bedue to asimilar mechanism[40,44]. The effect of ethanol is mediated by combined NMDA glutamate receptor blockade and $GABA_A$ receptor activation [40,45], which are receptor mechanisms affected by some AEDs. Recently, several AEDs have been tested for similar effects in a neonatal rat model. Widespread neuronal apoptosis occurs as a result of neonatal exposure to clonazepam, diazepam, phenobarbital, phenytoin, vigabatrin, or valproate [37,46]. The effect is dose dependent, occurs at therapeutically relevant blood levels, and requires only a relatively brief exposure. Further, AEDs can interact synergistically such that two AEDs, given at dosages that would not produce apoptosis when given in monotherapy, trigger the full apoptosis. This suggests that polytherapy may be more likely to result in neuronal apoptosis. The mechanism underlying the apoptosis appears to be related to reduced expression of neurotrophins and levels of protein kinases, which are important for neuronal growth and survival. Of note, the adverse effects were ameliorated by β-estradiol, which has neurotrophic effects [37,46,47]. A preliminary report found that neonatal rats dosed with carbamazepine slightly above the ED50 for anticonvulsant action developed widespread neuronal apoptosis [48]. In contrast, similar apoptotic effects were not seen at therapeutic dosages for carbamazepine, levetiracetam, lamotrigine, or topiramate in monotherapy dosages [41,49–52]. However, preliminary results suggest that carbamazepine, lamotrigine, and topiramate, but not levetiracetam, may potentiate cell death when given in combination with pro-apoptotic agents such as other AEDs. These observations raise a serious concern that certain AEDs, which are commonly used in women of child-bearing 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 this animal model, extend the studies to gestational animal models, determine if a similar mechanism occurs in humans, and delineate the factors triggering the apoptosis.

3. Human studies on cognitive effects of in utero AED exposure

Standard IQ testing is the best method to provide data that are comparable across different ages, exposure groups, and studies, as well as to pick up cognitive impairments milder than mental deficiency. IQ tests are well standardized with age norms and are predictive of school performance. Studies reporting outcome in infants or toddlers without IQ testing usually do not add significant information on cognitive outcome. Therefore, this review focuses on the studies that report IQ (or Griffiths DQ) scores in children of women with epilepsy (WWE).

3.1. Carbamazepine

Although prenatal exposure to carbamazepine has been suggested to result in a typical pattern of minor anomalies and developmental delay [53], there is little evidence of a carbamazepine syndrome [54]. Pooled data from two prospective population-based studies [55,56] showed a 1.9% (2/105) incidence of mental deficiency in carbamazepine monotherapy-exposed children of WWE. One of the two children had West syndrome in infancy as a possible etiology.

Carbamazepine monotherapy was the most common AED exposure in two recent prospective, controlled, population-based studies [56,57] with blinded evaluation of outcome. These studies included approximately 50% of the population of children born to WWE in their catchment areas: carbamazepine monotherapy exposures numbered 35 in the former and 86 in the latter study. Blinded assessment of DQ or IQ was done at ages 2–8 using the Griffiths test [57] or at 5–11 years with the age-appropriate Wechsler scale [56]. No IQ impairment was found in the children exposed to carbamazepine monotherapy compared with nonexposed children of WWE or controls.

A retrospective population-based study [58] investigated the risk of autism spectrum disorder (ASD) in children exposed to AEDs. Participants represented 42% of the population and included 80 children exposed to carbamazepine monotherapy. The prevalence of ASD was found to be 2.5% in the children exposed to carbamazepine alone; this was not statistically significantly different from the prevalence in the general population. The study is described more in detail in Section 3d on valproate.

3.2. Phenobarbital

The largest number of children exposed to phenobarbital monotherapy in utero has been reported by Shapiro et al. [59] from a prospective controlled study. Thirty-five exposed children of WWE and 4705 children of mothers without epilepsy but with phenobarbital exposure did not differ from control children with respect to IQ measured at 4 years of age.

Cognitive effects of fetal phenobarbital exposure have also been investigated in 114 male offspring of mothers without epilepsy [60]. Demographic, socioeconomic, and medical variables (including drug treatment) were recorded prospectively, and phenobarbital exposure was determined to have occurred if maternal treatment had lasted for at least 10 days during pregnancy. Cumulative phenobarbital dosages varied from 225 to 22,500 mg. Controls were matched for potential confounders, including a variable reflecting indication for phenobarbital. The study subjects were tested in young adulthood. Men exposed to phenobarbital had IQ scores approximately 0.5 SD lower than expected. The IQ impairment was most marked after exposure in the third trimester.

Long-term cognitive effects of early postnatal phenobarbital exposure have been investigated in a randomized, placebo-controlled, blinded study [61] in which 217 toddler-aged children with febrile seizures were randomized to receive either phenobarbital 4–5 mg/kg/day or placebo. At age 7, several years after discontinuation of phenobarbital, 64% of these children were examined with the Wide Range Achievement Test (WRAT-R) and the Stanford–Binet

Intelligence Scale [62]. Phenobarbital-exposed children had significantly impaired performance in WRAT-R reading scores, but not in the Stanford–Binet Scale, compared with the placebo group.

3.3. Phenytoin

Fetal exposure to phenytoin has been suspected to cause cognitive impairment since Hanson and Smith [63] described the fetal hydantoin syndrome in five unrelated children of WWE. Four children had been exposed to 100–400 mg of phenytoin (one monotherapy, three combined with barbiturates, one also to phensuximide) and one to 300 mg of mephenytoin during the fetal period. The features of the syndrome consisted of a characteristic pattern of craniofacial abnormalities, nail and distal phalangeal hypoplasia, postnatal growth deficiency, and mental deficiency.

The incidence of the fetal hydantoin syndrome is unknown. A cohort study by Hanson et al. [64] estimated that 11% of phenytoin-exposed children showed enough unusual features to justify the diagnosis of the syndrome. In contrast, a prospective, controlled, exposure-blinded, population-based study found low intelligence (<85), an important feature of the syndrome, in only 2 of 103 phenytoin-exposed children (1.9%) [55].

Prospective data on IQ scores after prenatal phenytoin exposure have been reported from two controlled population-based studies [55,59] with blinded evaluation of outcome. The results were controlled for socioeconomic class or maternal educational level. A total of 297 children of WWE were included, which covered approximately 50–60% of the population. Two hundred five children were exposed to phenytoin, 81 of them to monotherapy. IQ assessments were done at age 4 (Stanford–Binet) or 5.5 years (age-appropriate Wechsler scale), blinded to prenatal exposure. Comparison groups included 40 nonexposed children of WWE and more than 27,000 control children of mothers without epilepsy. Phenytoin doses were not reported, but maternal phenytoin levels during pregnancy were available in the study by Gaily et al. [55]. Both studies reported lower IQ values in children of WWE compared with controls, but no significant associations were observed to phenytoin or other drug exposure.

Hanson et al. [64] reported IQ results for a different cohort from the same database as Shapiro et al. [59]. The mean IQ at age 7 of 83 children exposed to phenytoin (maximum 25% monotherapy) was five points lower than that of control children of mothers without epilepsy, controlled for socioeconomic status. However, as all children of WWE in this study were exposed to phenytoin, the independent effect of the drug cannot be estimated.

3.4. Valproate

Developmental delay is one of the main features of the fetal valproate syndrome [54,65–67], which is otherwise characterized by a typical pattern of minor anomalies: trigonocephaly, bifrontal narrowing with indentation of the outer orbital ridge, medial deficiency of eyebrows, long shallow philtrum with long and thin upper lip, and broad or flat nasal bridge. Major malformations, especially neural tube and limb defects, may also occur. All studies describing the syndrome are case reports or retrospective clinic-based studies, leaving the incidence of fetal valproate syndrome unknown.

At present, prospective data on IQ scores in children with prenatal valproate monotherapy exposure are available only for 26 children from two population-based, evaluator-blinded studies [56,68]. In both studies, verbal IQ was 11–13 points lower in the valproate monotherapy-exposed group than in children not exposed to AEDs or exposed to carbamazepine monotherapy. Pooled population-based data from the same studies showed that 3 of 34 (8.8%) children exposed to valproate monotherapy had mental deficiency, compared

with 1 of 94 (1.1%) children of WWE who used other monotherapy during pregnancy. In both studies, maternal education level or IQ was significantly lower in the valproate group than in children of WWE exposed to other AEDs, which may have contributed to the difference.

The largest number of valproate monotherapy-exposed children reported so far ($n = 41$) comes from a retrospective study by Adab et al. [69]. Verbal IQ was significantly lower in the valproate group than in the unexposed and other monotherapy groups. The magnitude of the difference was approximately the same (10 points) as in the prospective studies. Maternal IQ scores were assessed, and no difference was found between valproate users and other WWE. A previous retrospective questionnaire survey in the same study population [70] reported increased educational needs in children exposed to valproate monotherapy.

Social or behavioral difficulties were reported by the parents to be present in 26 of 260 children of WWE (42% of the population) in a retrospective population-based study [58]. Review of the case records confirmed the diagnosis of an ASD by DSM-IV criteria in 12 of 26 children, 9 of whom had been exposed to valproate (5 in monotherapy). The minimum prevalence of ASD was estimated to be 1.9% in children of WWE, which was significantly higher than that of the general population. Of the 56 valproate monotherapy-exposed children, 5 (8.9%) were diagnosed with ASD.

Finally, recent preliminary results from an ongoing multicenter prospective study in the United States and United Kingdom also found lower cognitive outcomes for children exposed in utero to valproate monotherapy [71]. These preliminary results are based on cognitive assessments at 2 years of age.

3.5. Polytherapy

Polytherapy exposure in utero carries an increased risk of malformations and lower cognitive functioning [56,72,73]. Although attempts should be made to avoid polytherapy in pregnancy, there are women whose seizures, pain, or psychiatric disorders cannot be controlled with monotherapy. Significantly impaired verbal IQ was observed in 30 children exposed to AED polytherapy compared with 107 monotherapy-exposed children in a prospective, population-based study controlling for maternal education [56]. Although not statistically significant, the lowest mean verbal IQ was observed after exposure to polytherapy including valproate (17/30); for 13 of the 17, polytherapy consisted of valproate with carbamazepine. Polytherapy exposure (23 children) was associated with impaired verbal and nonverbal IQ also in a prospective clinic-based study by Koch et al. [74], in comparison to 31 children exposed to monotherapy. The most common drugs were phenytoin and primidone. Forty-one percent of the original cohort were examined at ages 10–19. The large prospective population-based study by Shapiro et al. [59] included 107 children exposed to a combination of phenytoin and phenobarbital. Their mean IQ did not differ from that of other children of WWE. Pooled data from two prospective population-based studies [55,56] showed mental deficiency in 1 of 84 (1.2%) polytherapy-exposed children. The child had been exposed to phenytoin, carbamazepine, and alcohol.

3.6. Conclusions from current literature on humans

The results of prospective population-based studies give no definite evidence that fetal exposure to phenytoin or carbamazepine impairs intelligence. Data on developmental effects of fetal valproate exposure are very limited, and confounding by genetic and environmental factors cannot be excluded. Nevertheless, the results of both prospective and retrospective studies raise concern that valproate may have a harmful effect on cognitive and, possibly, also on social development. It is not understood why verbal but not nonverbal IQ has been affected in all studies except one [68]. The data on fetal phenobarbital effects are insufficient and incongruent. Different designs, subjects, and ages at outcome measurement probably

contribute to the controversy. The limited studies on polytherapy exposure suggest that combining drugs may increase the risk of harmful effects. There are no data to suggest whether some combinations would be safer or more hazardous than others. Future studies need to examine monotherapies with the most commonly used drugs, especially valproate, and evaluate frequently used combinations in situations where monotherapy is not sufficient to control maternal seizures. Future studies also need to focus on the newer AEDs as there are no published studies on cognitive effects of prenatal exposure to these AEDs.

4. Studies on cognitive effects of maternal seizures during pregnancy in humans

No IQ impairment was found in two prospective population-based studies in which 14% of 189 [56] and 37% of 148 [55] children had been exposed to self-limiting generalized tonic–clonic seizures (GTCS). No episodes of status epilepticus were included. In the retrospective study by Adab et al. [69], 35% of 249 children had been exposed to GTCS, and verbal IQ was significantly reduced in those children (17% of all) who had been exposed to more than four GTCS. Although the results of cohort studies that have included mainly exposures to brief maternal GTCS are controversial, case reports have clearly documented that prolonged seizures and status epilepticus are a serious hazard for both the mother and the fetus [75].

5. Study design issues for studies in humans

Animal studies can control for a variety of confounding factors, examine underlying mechanisms, and provide information to guide human studies. However, interspecies differences and the lack of comparative information on pharmacokinetics and developmental outcome preclude direct extrapolation of animal results to human risks. Retrospective studies in humans may provide some insight, but are ultimately flawed because of subject selection bias and potential inaccuracy or lack of critical data. There is a compelling need for prospective, properly controlled studies in humans to establish the effects of in utero AED exposure on intellectual development. A randomized clinical trial with blind assignment of AED prior to pregnancy is not practical and raises some ethical concerns. Nevertheless, the effects of AEDs on the unborn child can be practically assessed by an appropriately designed observational study. Many prior studies have been flawed by inadequate control and statistical assessment of confounding factors, uncertain accuracy of historical and clinical information, or insufficient outcome criteria to provide delineation of subtle deficits. In recent years, several studies have provided useful information, but additional studies are needed to demonstrate the relative effects across all AEDs and to determine possible interactive effects of factors such as inheritance, psychosocial environment, and seizures during pregnancy. Future studies need to employ a prospective design beginning early in pregnancy (or, if possible, even prior to pregnancy); use adequate sample sizes (with power analysis); assess objective measures or apply blinded assessments; control for hereditary factors (e.g., genetic testing in somatic or behavioral outcome studies and formal neuropsychological evaluations of both parents in studies of cognitive/behavioral outcomes); include type, syndrome, and etiology of maternal epilepsy; and collect comprehensive data to statistically assess other possible confounding factors. Population-based studies would be required to determine actual as opposed to relative rates of poor outcomes. Inclusion and exclusion criteria may vary as a function of the goals of the specific study. The effect of potential confounding factors can be assessed statistically provided that the sample size is adequate and the pertinent data are collected. Enrollment early in pregnancy before any outcome data (e.g., ultrasound) are known should either be an inclusion criterion or this population should be targeted for separate analyses. Final results should be expressed with means and confidence intervals for continuous variables obtained from formal testing. In addition, serious affections (such as mental deficiency or significant behavioral disorders) should be clearly defined and the proportion of affected children indicated.

Heritability accounts for 30–50% of phenotypic IQ variance. IQ correlation for monozygotic twins reared together is 0.85, and for those raised apart, 0.67 [76]. Correlation for parental and child IQs is 0.42 [77]. Maternal IQ is not only a measure of inherited influences, but also has a strong association with fostering experiences. When maternal IQ is controlled, no other single environmental factor has a significant influence on child IQ in group studies [76]. Maternal education and socioeconomic status, often substituted for IQ as a control measure, correlate with the child's IQ but at a lower level. In one study that obtained both maternal IQ and education, matching groups on education was inadequate to control for the effects of maternal IQ [78,79]. Paternal IQ would be important data, as women with epilepsy may have a social disadvantage in partner choice [80]. It is also possible that maternal IQ could be affected by factors related to epilepsy and its treatment. Thus, consideration of obtaining the IQ of a first-degree maternal relative could be considered as a method to control for the effects of epilepsy and AEDs on the mother's IQ.

On a group level, obstetrical complications appear unrelated to IQ, and perinatal anoxia has a minimal correlation to IQ ($r = 0.06$) [76]. However, individual children could be affected by complications of pregnancy (e.g., placenta abruptio) or subsequent severe childhood illnesses. Malnutrition, as experienced in developed countries, does not have a substantial impact on intelligence, but malnutrition may affect mental and physical growth for individual children. Further, nutritional factors (e.g., folate) could possibly interact with AED exposure. Drug abuse (e.g., alcohol) during pregnancy influences development adversely. Routine childhood illnesses show no relationship to test scores, but hearing loss or more severe childhood diseases might impact development. The confluence model of family configuration (i.e., birth order, family size, and birth intervals) has not been clearly refuted, but a great deal of evidence suggests that the model is inadequate [81]. Socioeconomic status is correlated with behavioral adaptation ($r = 0{:}4 – 0.6$) [82]. A broad range of social variables are known to predispose a child to biomedical risks, the most salient of which, poverty, represents a complex accumulation of risks factors [83]. Socioeconomic status and specific home environmental factors (e.g., pressure for achievement) are related to IQ, but are not independent of family background, and may "serve as surrogate measures of parental IQ and education" [76]. Gender, ethnic origin, geographic location, maternal age, and parity are additional factors that also could potentially affect IQ scores.

Models of the epidemiology of mental retardation emphasize multiple risk factors [84]. Individuals with the same biomedical condition express different levels of cognitive deficits, demonstrating that other factors modulate the effects of the condition. Approximately 50% of patients with mental retardation have more than one risk factor, and mental retardation often reflects the cumulative or interactive effects of more than one factor [85]. Some risk factors, such as drug abuse, are embedded in a matrix of other risk factors; for example, women who abuse drugs are more likely to engage in other high-risk behaviors. Low socioeconomic status may interact with drug exposure to enhance the adverse effects. As an example, the retrospective study by Reinisch et al. [60] reviewed above found that the overall 7-point decrement in verbal IQ in men exposed in utero to phenobarbital increased to 20 points if the men were also born from an unwanted pregnancy and low socioeconomic status. In contrast to the effects of low socioeconomic status, high status may ameliorate adverse biomedical effects [86]. Thus, a variety of factors have to be monitored to assess their impact on cognitive/behavioral outcomes.

In summary, future studies ideally should employ a prospective design enrolling mother/child pairs early in pregnancy. AED dosages and blood levels should be obtained in each trimester. Objective measures or blinded assessment should be used to determine results irrespective of whether the investigation is directed at somatic or behavioral outcomes. Potentially confounding factors that should be assessed and controlled depending on the study goals may

include: maternal and paternal age, IQ, education, and race; socioeconomic status of household; maternal medical disorders (e.g., diabetes); maternal and family history of prior pregnancy abnormalities; maternal use of alcohol, tobacco, and other drugs (i.e., illicit, over-the-counter, and prescription) during pregnancy; maternal preconception and pregnancy nutrition, folate use, and folate/ homocysteine blood levels; epilepsy syndrome and etiology; seizure types and frequency during pregnancy; gestational age at enrollment; obstetrical complications; birth weight and head circumference; childhood diseases; and home environment during childhood, including languages spoken.

6. Issues related to cognitive/behavioral assessment of children

Previous studies on developmental outcome have tended to focus on intellectual functioning as the primary outcome variable and have generally ignored the use of assessment protocols that would allow for the evaluation of other domains of higher cortical functioning, such as executive functioning, language, visual–spatial and visual–motor/ constructional functioning, learning and memory, fine and gross motor skills, academic performance, adaptive functioning, and emotional/behavioral functioning.

To best determine the early developmental profiles and needs of these children, the optimal method for studying potential cognitive effects is a prospective, longitudinal design with adequate sample sizes through the age of 8. This will allow researchers to determine if various AED-exposed groups have significantly lower intellectual profiles, and to report the frequency of various learning disabilities (reading, written expression, mathematical reasoning/ calculation), other neurobehavioral disorders (specific language impairment, attention deficit/ hyperactivity disorder), and behavioral disorders commonly seen in childhood.

Future studies should attempt to evaluate the impact that in utero AED exposure has not only on intellectual functioning, but all aspects of higher cortical functioning as well. Please refer to Table 1, which provides a list of the major domains that should be investigated along with some suggested tests that may be used to assess each domain adequately. It is important to note that this list in not exhaustive, and inclusion/exclusion should not be considered an endorsement of any particular test. In addition, Table 2 provides a list of demographic and medical variables that can influence the outcome of studies in this area significantly. Efforts should be taken to carefully control for the potential impact of these variables.

Finally, cross-sectional studies may also be useful, as longitudinal studies take years to provide answers. Retrospective, cross-sectional studies that include samples of adolescents exposed to AEDs in utero can also provide important information about the emergence of cognitive deficits that may not appear until later in development (e.g., executive function deficits). Closer attention to factors listed in Table 2 can improve the ability to draw conclusions.

7. Proposed future research on the impact of in utero AED exposure

7.1. AED monotherapies

Data on older AEDs are incomplete, and there is little or no evidence of the impact of the newer AEDs, the majority which have a license as add-on therapies for partial refractory epilepsy. Future investigations are necessary to establish the cognitive/behavioral teratogenic effects of in utero exposure for all AEDs. Large cohort studies, however, are necessary and should include a sufficient number of women exposed to these newer AEDs.

7.2. AED polytherapy

Animal data demonstrate synergistic effects of polytherapy on apoptosis and suggest that risk may vary across different polytherapy combinations, but no such data are available for humans.

Future studies should focus on specific polytherapy combinations in situations where monotherapy is not sufficient to control maternal seizures.

7.3. Design issues

Ideally, future studies should employ a prospective design enrolling mother/child pairs early in pregnancy using sample sizes to provide adequate power. Objective measures and/or blinded assessment should be used to determine outcomes. Potentially confounding factors must be assessed and controlled as described previously. Additional specific design issues are discussed below.

7.4. Neuropsychological tests

A range of neuropsychological tests have been employed to investigate the neurodevelopment effects of exposure to AEDs in utero. These include the Wechsler Intelligence Scale for Children [56,68,69], Bayley's developmental scale [87], NEPSY [68], and the Griffith developmental scales [57,88]. The tests have demonstrated psychometric properties, but there is often little evidence for a rationale for their application to this research. The variation of tests also has significant implications for the generalizability of results across different studies. Further, failure to use a standardized approach restricts the use of meta-analysis.

The majority of investigations into the cognitive implications of in utero exposure to AEDs have focused on full-scale, performance (nonverbal), and verbal intellectual capabilities. Neuropsychological functioning, however, does not simply mean an assessment of intellectual functioning and, in fact, includes other processes such as language, hand/eye coordination abilities, executive functions, ability to hold concentration and apply attention to a task, creativity, and behaviors such as mood and social interaction. It is, therefore, paramount that future research comprises a comprehensive assessment of neuropsychological abilities that are investigated, as this will allow researchers to identify both expected and unexpected effects of exposure in utero.

7.5. Use of control groups

To understand the impact of exposure in utero, it is essential that future research gathers information from control groups, of children born either to mothers with epilepsy but not taking AEDs during pregnancy, to mothers without epilepsy, and to fathers with epilepsy. The control group will allow documentation of the natural history of neuropsychological development from which various comparisons can be made. The presence of a control group will also allow for the establishment of individual variation in a nonexposed group, which may act as a reference point for the interpretation of results.

7.6. Paternal IQ measurements

The majority of studies in the literature investigating the impact of in utero exposure to AEDs has attempted to control the hereditary aspects of intellectual functioning by taking a measure of maternal IQ or an IQ equivalent (e.g., The National Adult Reading Test). Collection of maternal IQ is usually easier than collection of paternal IQ, as the mother and the child are both enrolled into the study at the beginning from pregnancy clinics. Some mothers are no longer in contact with the father or do not wish for the father to be involved, or the father is unable or unwilling to attend. However, the nature of epilepsy causes disruption of cognitive processes and seizure activity impacts on intellectual functioning [89] as well as social interactions, which may result in a disadvantage in partner choice. Therefore, is taking a measure from the mother with epilepsy the most predictive of a child's intellectual functioning or would the IQ of the father (in most cases without epilepsy) be more reliable? Future research

should focus on obtaining a more reliable assessment of IQ from both parents along with social demographic data.

7.7. Influence of hereditary factors

Epileptic seizures result from biological dysfunction of the brain, which may in some cases be hereditary. The predisposition to abnormal activity in the brain may be contributory to the lower performance of children born to WWE. Koch et al. [74] found abnormal spike activity in children born to mothers with epilepsy. Certain types of epilepsy are considered to have higher rates of hereditary traits and the type of epilepsy is usually associated with a first drug of choice, for example, juvenile myoclonic epilepsy and valproate. This introduces bias into the investigation. To remove this bias of a family history of epilepsy, it would appear to be reasonable to consider a comparison between a group of women taking AEDs for epilepsy and a group of women taking AEDs for other conditions such as migraine and mood disorders. However, the issues of therapeutic dose ranges will need to be considered carefully.

7.8. Pharmacogenetics

Despite the observation of increased risk for poor outcomes in children exposed in utero to AEDs, there is considerable unexplained variability in the outcomes across children. It is likely that differences in responses to AED exposure are mediated by genetic factors. A systematic application of pharmacogenetics could provide insight in this regard. However, there are practical, methodological, and theoretical hurdles to overcome [90,91].

7.9. Basic mechanisms

Beyond the influence of pharmacogenetic factors, the basic mechanisms underlying AED-induced cognitive/ behavioral teratogenesis need to be delineated. Demonstrations in animals that AEDs can induce neuronal apoptosis in the developing brain raise concern that similar adverse effects may occur in children exposed in utero or the neonatal period. Future studies should determine the effects of other AEDs in the neonatal rat model, extend the studies to gestational animal models, and determine if a similar mechanism occurs in humans. In addition, it should be determined if other mechanisms contribute by triggering the apoptosis or directly cause the AED-induced behavioral teratogenesis. Investigations of basic mechanisms not only may lead to better AED selection on an individual basis, but also could lead to preventive therapies. For example, nicotinamide can protect against ethanol-induced apoptotic neurodegeneration in the developing mouse brain [92].

7.10. Neurodevelopment of the child: Imaging techniques

It is hypothesized that differences in the development of cognitive networks account for individual differences in cognitive abilities in both normal and abnormal development [93, 94]. As a consequence, the importance of using brain imaging techniques to inform on neurocognitive development is recognized. It is proposed that future research should focus on imaging of children exposed to AEDs in utero in comparison to a control group (either children of women without epilepsy or children of WWE taking no medication during pregnancy) to investigate if differences in the development of cognitive networks exist. Such knowledge would not only be of theoretical interest, but also would be of potential benefit in planning rehabilitation programs for those children with developmental problems as a result of exposure.

Functional magnetic resonance imaging (fMRI) provides a method to map the developing cognitive networks of children [95]. Additionally, the method can be used to compare two groups and could possibly highlight any neural network difference between children who were exposed to AEDs in utero and those who were not. A comparison group of children with a family history of epilepsy but who were not exposed to medication in utero would also make

for an interesting investigation. However, there are methodological and interpretational challenges to this type of investigation with children [94].

Recent studies have found lower verbal IQ or language functioning in children exposed to valproate in utero [56,69]. Imaging may provide important knowledge with respect to our understanding of the neural network supporting language processing and how this might be affected by exposure to AED treatment, compared with a nonexposed group where typically language networks are established by the age of 5 [95].

7.11. Maternal and physician understanding of risks

Future research should be conducted to investigate to what degree both women and their physicians understand the risks of exposure to AEDs during pregnancy. There is little past research on women's understanding of the risk associated with AED treatment during pregnancy and the risk of seizures during pregnancy [96].

8. Conclusions

Animal studies clearly demonstrate that AEDs can produce neuronal apoptosis and behavioral teratogenesis in the developing brain. Children exposed in utero to AEDs are at risk for poor cognitive/behavioral outcomes. Further, the animal studies raise the possibility that neonates may also be at risk of AED-induced apoptosis. Human data are incomplete, but children exposed in utero to AEDs are at risk for poor cognitive/behavioral outcomes, and present studies raise concerns, especially with regard to valproate. Many issues remain uncertain, and there is a critical need for further research to delineate the effects of AEDs on the immature brain.

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Table 1
Recommended neuropsychological testing protocol

Intelligence	
	Differential ability scales: preschool and school age levels
	Wechsler intelligence scales: preschool and school age levels
Executive functioning	
	Wisconsin Card Sorting Test
	Tower of London Test—NEPSY
	Verbal Fluency—NEPSY
	Visual Attention—NEPSY
	Behavior Rating Inventory of Executive Functioning (BRIEF)
Linguistic functioning	
	Expressive One-Word Picture Vocabulary Test
	Peabody Picture Vocabulary Test IV
	Phonological Processing—NEPSY
	Comprehension of Instructions—NEPSY
	Sentence Repetition—NEPSY
	Preschool Language Scale 4
	Comprehensive Evaluation of Language Fundamentals 4
Visual–spatial/motor functioning	
	Arrows—NEPSY
	Developmental Test of Visual–Motor Integration, 5th edition
Learning and memory	
	Children's Memory Scale (CMS)
	Wide Range Assessment of Learning and Memory 2
Fine-motor functioning	
	Grooved pegboard test
	Finger oscillation test
Academic functioning	
	Bracken Basic Concept Scale—Revised
	Wide Range Achievement Test 4
	Wechsler Individual Achievement Test II
	Gray Oral Reading Test 4
Adaptive functioning	
	Adaptive Behavior Assessment System II
	Vineland Adaptive Behavior Scale II
Behavior Ratings	
	Behavior Assessment System for Children 2 (parent and teacher ratings)
	Parent Stress Index

Table 2

Factors potentially affecting outcomes

Demographic variables	Medical variables
Maternal age	Seizure type and frequency
Maternal IQ	Epilepsy type and syndrome
Maternal education level	AED dosage and blood level
Maternal race	Etiology of maternal epilepsy
Socioeconomic status	Alcohol, tobacco, and other drugs
Paternal IQ	Folate use
	Gestational age and birth weight
	Hearing impairment
	Childhood illnesses