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Cognitive Outcomes of Prenatal Antiepileptic Drug Exposure

Katherine Inoyama, MD* and Kimford J. Meador, MD*

*Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA

Abstract

Antiepileptic drugs (AEDs) have been known to have teratogenic effects for a little over 50 years. While early reports focused on fetal malformations, there has been an increasing amount of data over the last few decades exploring the cognitive outcomes of offspring exposed to AEDs in utero. Although the challenges of confounding factors and varied methodologies have led to inconsistent results, the negative impact of some of the agents, such as valproate, have become clear. Further studies are needed to evaluate the cognitive effects of prenatal exposure to many AEDs which have not been tested, to clarify the effects of existing AEDs which have yielded mixed results, and to better understand the effects of polytherapy. Research in animal models is warranted to screen AEDs for their effects on cognition in exposed offspring and to further our understanding of the underlying mechanisms by which AEDs exert their harmful effects on the developing brain. And finally, new AEDs without these harmful effects and agents which can prevent or reverse the negative consequences imparted by AED therapy on cognition should be sought.

Keywords

Antiepileptic drugs; cognitive; epilepsy; pregnancy; teratogen

1. Animal Studies

1.1. Cognitive and Behavioral Effects of Prenatal AED Exposure in Animal Models

There have been numerous animal studies demonstrating poor behavioral, cognitive, and motor functioning in offspring that were prenatally exposed to antiepileptic drugs (AEDs). The early studies included phenobarbital (Roger-Fuchs et al., 1992), valproate (Schneider and Przewlocki, 2005) and phenytoin (Vorhees, 1987). In the 1980s and 1990s, Vorhees published a series of studies examining the behavioral effects on the offspring of maternal rats that had received phenytoin during days 7–18 of gestation, the prime period of organogenesis, at serum levels comparable to the therapeutic range for humans. The offspring were found to have abnormal circling, impaired learning, hyperactivity, delayed

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Address correspondence: Katherine Inoyama, MD, Department of Neurology & Neurological Sciences, Stanford University School of Medicine, 300 Pasteur Drive (Room A343), Stanford, CA 94305-5235, Tel: 650:725-6648, Fax: 650:498-6326, kinoyama@stanford.edu.

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development of air righting reflex and abnormal reference memory-based spatial learning (Vorhees, 1987; Schilling et al., 1999; Weisenburger et al., 1990). More recently, studies have been conducted in which the maternal rat was exposed to phenytoin for the duration of the pregnancy and pre-weaning period to more closely resemble a human mother's experience of taking the medication throughout pregnancy and nursing. Higher order learning in which rats transitioned from appetitive (positive reinforcement) to aversive conditioning was impaired (Mowery et al., 2008), and the authors suggested a mechanism of impaired hippocampal development, which has been seen histologically in mice and rats exposed to phenytoin and other AEDs perinatally (Ogura et al., 2002; Vorhees et al., 1990).

1. 2. Cognitive and Behavioral Effects of Prenatal AED Exposure in Primates

Evaluation of infant monkeys with exposure to therapeutic maternal levels of phenytoin during gestation demonstrated significantly increased hyperexcitability during recognition testing which required attention to presented stimuli. Infant monkeys with prenatal phenytoin or phenytoin and stiripentol exposure demonstrated higher degrees of hyperexcitability marked by vocalizations, struggling, biting, inconsolability, and inattention to stimuli. In contrast, hyperexcitability was not seen in infant monkeys with prenatal exposure to carbamazepine or stiripentol alone (Phillips and Lockard, 1993, 1996).

1.3. Effects of AED exposure on early development at the cellular level

On the cellular level, several groups have demonstrated increased apoptosis and impairment of neurogenesis and synaptogenesis with some AEDs. Bittigau et al. (2002, 2003) found evidence of apoptosis in nearly every region of forebrain examined in postnatal rats 24 hours after exposure to benzodiazepines, phenytoin, phenobarbital, or valproate. The effects were dose dependent and were found to occur predominantly during a specific phase of development, between postnatal days 0 to 14, through a mechanism hypothesized to be due to impaired signaling of cell survival pathways. Evaluation specifically of the limbic system in rats with postnatal exposure revealed diffuse apoptosis with phenobarbital, apoptosis in the nucleus accumbens with phenytoin, and no increase in apoptosis with carbamazepine (Forcelli et al., 2011). There have been additional AEDs that were not found to cause apoptosis in the developing rat brain, including carbamazepine, lamotrigine, levetiracetam, and topiramate (Glier et al. 2004; Katz et al., 2007; Kim et al., 2007a & 2007b; Manthey et al., 2005). In combination, however, potentiation of the apoptotic effect in phenytoin was seen when combined with carbamazepine or topiramate, while levetiracetam did not alter the degree of apoptosis seen with phenytoin. Thus, not all AEDs result in apoptotic effect, and even amongst AEDs, the effect on apoptosis varies.

In mice exposed to phenytoin on postnatal days 5 to 14, which is comparable to a portion of the third trimester in human development, a thinner granule cell layer was seen in the dentate gyrus, and Purkinje cells were immature and abnormally arranged in the cerebellum, which is not only important for motor control, but likely for cognitive processing as well. The average brain weight was significantly lower in 56 day old mice in the group treated with phenytoin, and was most pronounced in the cerebellum, which was only 71% that of the control mice cerebellar weight. Impairments in spatial learning were also demonstrated in the phenytoin treated group, in the absence of motor deficits (Ogura et al., 2002).

Carbamazepine has also been shown to dramatically decrease neuronal numbers both in the hippocampus and cortex in mice exposed in utero; however, no changes were observed in their ability to perform cognitive tests at 5 weeks of age (Åberg et al., 2013). Decreased neuronal membrane order in the hippocampus has been shown in rats with prenatal exposure to phenytoin, during the same day 7–18 of gestation for which cognitive deficits were noted above in section 1.1. In a paralleled experiment using valproic acid, the synaptic membrane order was decreased not only in the hippocampus but also in the neocortex (Vorhees et al., 1991). Prenatal exposure to valproate and vigabatrin in rats has been noted to increase cortical and hippocampal dysplasias in the offspring, further reinforcing the evidence for impaired neurogenesis (Manent et al., 2007).

Not only is there structural evidence, but more recent work has confirmed that synaptic deficits result from the exposure as well. Abnormal function has been demonstrated at the synaptic level with a single exposure on postnatal day 7 to phenytoin, phenobarbital and lamotrigine but not to levetiracetam in rats examined up to postnatal day 18 (Forcelli et al., 2012). Interestingly, while lamotrigine has previously been shown to have apoptotic effects at supratherapeutic levels but not within the therapeutic range (Katz et al., 2007), a delay in synaptic maturation was seen with the single dose of therapeutic range which improved over time (Forcelli et al., 2012). We are only in the beginning stages of understanding how AEDs exert their harmful effects on the developing brain, and animal studies have begun to shed light on the potential underlying mechanisms.

2. Human Studies: A Historical Perspective

2.1. Recognition of the teratogenic effects of AEDs

The gravity of teratogenicity from medication exposure during pregnancy was brought to the forefront with the unfortunate thalidomide incident of the late 1950s and early 1960s. A medication that was reported to be safe, thalidomide was prescribed to pregnant women to combat morning sickness and resulted in numerous birth defects of which phocomelia was the most notorious (Franks et al., 2004). AEDs did not come under scrutiny for their teratogenic effects until the late 1960s, when physicians began reporting “hare lip and cleft palate...congenital heart lesions and minor skeletal abnormalities” among children of mothers taking the anti-epileptic medications of that time period, which included phenytoin, phenobarbitone, and primidone (Meadow, 1968). As an increasing number of reports were published over the 1970s, the risk of fetal malformations with these medications became more evident (Speidel and Meadow, 1972; Millar and Nevin, 1973). While the physical manifestations were initially the most obvious and well documented, the cognitive and behavioral effects began receiving attention later, from approximately the 1980s. More recently, with the development of pregnancy registries, larger scale and more well-controlled studies of AED anatomical teratogenesis in humans are available. In addition, studies with careful tracking and analysis of cognitive outcomes of children born with prenatal exposure to AEDs are being performed.

2.2. Cognitive outcome in children with prenatal AED exposure: Early Studies

The first studies evaluating the cognitive outcomes of children with prenatal AED exposure yielded inconsistent and at times misleading results. Shapiro et al., in a prospective cohort study, evaluated children at 8 months with mental and motor scores, and again at 4 years of age with intelligence quotients and did not find a significant difference between those who had prenatal exposure to phenytoin and/or phenobarbitone and those not exposed, but noted a trend in lower scores amongst the children of the mothers with epilepsy regardless of whether they were on an AED, compared to offspring of mothers without epilepsy. Combined with similar findings for malformations, this led to the idea that perhaps it was the presence of parental epilepsy, rather than the AEDs, which was responsible for the deficits (Shapiro et al., 1976). Similar results were seen with lower intelligence scores in children of mothers with epilepsy regardless of AED exposure; however, there was an association with lower scores and lower socioeconomic status, which was ranked based on parental education and job status. Maternal intelligence quotients were not formally tested, but note was made of 10 mothers in the epileptic study group with borderline intelligence (Gaily et al., 1988). While some studies found lower intellectual performance in children with prenatal AED exposure (Hanson et al., 1976; Hill et al., 1974), there were other studies which did not find a difference in intelligence even with the presence of maternal epilepsy, compared with control children (Steinhausen et al., 1982).

It was not until years later in 2000 that the question of whether the presence of maternal epilepsy itself causes cognitive dysfunction was systematically addressed, when Holmes et al. published results of a larger cohort of child-mother pairs comparing those without maternal epilepsy and those with a history of maternal epilepsy, excluding all who had taken AEDs during pregnancy or had tonic-clonic seizures while pregnant. Testing was performed to evaluate the intelligence of children ages 6–16 years and both parents, and there was no difference in scores between the groups, indicating that the presence of maternal epilepsy itself was not a risk factor for poor cognitive outcomes in the offspring (Holmes et al., 2000).

2.3. Cognitive outcome in children with prenatal AED exposure: 1990s to present

While most earlier studies had focused solely on malformations, from the 1990s onward, there has been increasing focus on cognitive outcomes, and more thorough assessments are being performed with improved methods and consideration of confounding factors.

2.3.1. Monotherapy and polytherapy—Of the AEDs, valproate has the strongest data showing poor cognitive outcomes with prenatal exposure, with the recommendation of avoidance during pregnancy rated as Level B evidence by the American Academy of Neurology (Harden et al., 2009). Children with prenatal exposure to valproate were found to have lower verbal IQ compared to children with prenatal carbamazepine monotherapy exposure or no AED exposure (Gaily et al., 2004). The Neurodevelopmental Effects of Antiepileptic Drug (NEAD) study group performed a multi-center, prospective study controlling for multiple potentially confounding variables. Their first report on cognitive outcomes evaluated children at 3 years of age, and found children with prenatal exposure to valproate had a reduction in mean IQ score of 9 points compared to lamotrigine, 7 points

compared to phenytoin, and 6 points compared to carbamazepine, with those exposed to higher valproate dosages faring worse (Meador et al., 2009). Follow-up evaluations at 4.5 years (Meador et al., 2012) and at 6 years of age demonstrated persistently worse cognitive outcomes in the valproate treated group, not only for IQ but also other measures such as verbal and memory abilities compared to the other monotherapy exposure groups (Meador et al., 2013). Further, children exposed to valproate had significantly fewer right handers and lower verbal than non-verbal index scores suggesting the possibility that valproate may affect normal development of cerebral lateralization (Meador et al., 2011a). Results from the Liverpool and Manchester Neurodevelopment Group (LMNG) and United Kingdom Epilepsy and Pregnancy Registry (UKEPR) demonstrated that children with prenatal valproate exposure scored lower on measures of motor skill, language comprehension, and language expression, even when controlling for maternal IQ (Shallcross et al., 2014). The same group found that even children exposed to valproate at low doses (i.e., <800mg/day) had impaired verbal IQ and increased need of educational assistance (Baker et al., 2015).

In 1995, Reinisch et al. published data demonstrating decreased verbal IQ in two cohorts of adult men who were prenatally exposed to phenobarbital, in the absence of maternal epilepsy or other central nervous system disorders. Verbal IQ was half a standard deviation lower in those exposed, with the greatest difference seen with those exposed during the third trimester and earlier, with verbal IQ being -10.22 that of predicted. Lower verbal IQ was also associated with lower socioeconomic class and with unwanted pregnancy (Reinisch et al., 1995).

Studies of prenatal phenytoin exposure have yielded mixed results for cognition. Lower full scale IQ scores at 7 years of age were found amongst children exposed to phenytoin compared to unexposed children whose mothers did not have epilepsy, controlling for socioeconomic status (Hanson et al., 1976). Another study had similar findings for prenatal phenytoin exposure with lower scores for full scale IQ, verbal IQ and the Visual Motor Integration Test, which was also controlled for socioeconomic status but not for maternal IQ (Vanoverloop et al., 1992). However, there have also been studies in which intellectual outcomes were not affected by phenytoin, such as was found in 2005 by Vinten et al. with a small sample size, but controlling for maternal IQ, as well as by Gaily et al. (1988) and Shapiro et al. (1976), with consideration for maternal IQ and socioeconomic status, respectively. The NEAD study found that children exposed in utero to phenytoin did not differ from those exposed to carbamazepine or lamotrigine, but fared better than with valproate (Meador et al., 2013).

The majority of studies evaluating carbamazepine have demonstrated no effect on cognition with prenatal exposure (Scolnik et al., 1994; Wide et al., 2002; Vinten et al., 2005; Meador et al., 2013), although lower intelligence scores have been reported (Ornoy and Cohen, 1996).

The NEAD study had a large cohort of children exposed to lamotrigine (n=100); these children had higher IQ, verbal index, non-verbal index, memory, and executive index scores than children exposed to valproate, but no differences compared to carbamazepine and

phenytoin (Meador et al., 2013). The children exposed to lamotrigine had significantly fewer right handers and lower verbal than non-verbal index scores similar to valproate.

Levetiracetam has been shown to not impact the cognition of children exposed in utero. Data from the LMNG and UKEPR demonstrated similar cognitive measures between the levetiracetam exposed group and the unexposed control group of children evaluated at 24 and 36–54 months of age (Shallcross et al., 2011; Shallcross et al., 2014). A selection of recent prospective studies assessing the cognitive effects of monotherapy AED use in pregnancy are summarized in Table 1.

There are preliminary findings that fetal topiramate exposure may have adverse cognitive effects. Rihtman et al. (2012) reported that children ages 3–6 years performed significantly worse on most measures of visual, motor, behavioral and cognitive function compared to controls from the general population. However, sample size was small (topiramate n=9), and the results must be interpreted with caution pending additional studies.

A small study has suggested a negative impact of prenatal benzodiazepine exposure (exposed group of n=17), which was used by the mothers for various medical conditions, on neurodevelopmental outcomes up to 18 months compared to those who were not exposed (Viggedal et al., 1993). However, prenatal exposure to benzodiazepines and benzodiazepine related compounds (e.g. zolpidem), again taken for various conditions, was recently evaluated in a large (exposed group of n=395), prospective study which utilized a questionnaire to assess language competency at 3 years of age, as reported by the mother, and no difference was found compared to the non-exposed group (Odsbu et al., 2014). Results for benzodiazepines are inconclusive given the limitations of the studies, including small sample sizes in the former study and lack of direct evaluation of the child in the latter.

Additional studies have found polytherapy to be associated with poor cognitive outcomes. In a follow-up study of children originally from a cohort evaluated through age 4–6 years which had demonstrated poorer scores up to preschool age with prenatal polypharmacy (Steinhausen et al., 1994; Lösche et al., 1994), follow-up evaluation of the children between 10–19 years of age revealed that those in the polypharmacy group continued to have lower intelligence scores, and it was specific to those whose medication list included primidone (Koch et al., 1999).

2.3.2. Maternal intelligence: A crucial confounding factor—Most studies conducted up to the 1990s lacked evaluation of the mother's IQ, which has been shown to be strongly correlated with the intelligence of her children (Meador et al., 2011b). A retrospective study by Adab et al. took this into account and assessed 249 children between 6 to 16 years of age and found lower verbal IQs in children with prenatal exposure to valproate but not in monotherapy with carbamazepine or phenytoin, even after adjusting for maternal IQ. Those with polytherapy exposure also had a tendency toward lower IQs, which did not reach statistical significance. Performance IQ, however, was not affected even with valproate exposure (Adab et al., 2004). In a prospective study with data on maternal IQ, mothers with epilepsy who were on valproate had lower IQ scores and lower education levels than mothers with epilepsy on carbamazepine monotherapy or not on AEDs.

However, after controlling for maternal IQ, there was no difference in child IQ amongst the groups, which could either be due to small sample size (total of 39 children) or other inherent differences in the valproate treated group (Eriksson et al., 2005). In contrast, the NEAD study found reduced IQ for children exposed to valproate even after control for maternal IQ (Meador et al., 2013). Although maternal and child IQ were strongly correlated for the other three AEDs like the normal population, the IQ of children exposed to valproate did not correlate with their mothers' IQ suggesting that fetal valproate exposure disrupts this normal relationship.

2.3.3. Assessment of AED dosage—The dose effect of valproate on verbal IQ was evaluated in the study by Adab et al., a factor that was not addressed in many studies prior to the new millennium. Although the sample size was small, a larger prenatal dose of valproate (>800 mg daily) was correlated with lower scores in the children (Adab et al., 2004). A similar negative association between intelligence scores and valproate dosing was noted by Gaily et al. in 2004 and Baker et al. in 2015. The NEAD study found an adverse dose-dependent effect of prenatal valproate exposure on IQ as well as multiple other cognitive measures (Meador et al., 2013). Hirano et al. noted that children at 1.5 years of age who had prenatal exposure to high dosages of various monotherapies had lower scores on language comprehension than those exposed to low dosages (Hirano et al., 2004). Lower IQ scores were also seen with higher dosages of primidone in the study by Koch et al., described in section 2.3.1 (Koch et al., 1999). However, additional studies found no correlation between AED dosage and child cognitive outcomes for phenytoin (Scolnik et al., 1994; Meador et al., 2013), carbamazepine (Gaily et al., 2004; Ornoy and Cohen, 1996; Scolnik et al., 1994; Meador et al., 2013), lamotrigine (Meador et al., 2013), or levetiracetam (Shallcross et al., 2014). As seen with polytherapy, a mother with more severe epilepsy and frequent seizures is more likely to require higher dosages of medication, further complicating the picture.

2.3.4. Autism spectrum disorders (ASD)—Several animal studies disclosed an increase in behaviors that mirror autism with prenatal AED exposure, raising concern that rates of ASD could also be increased in humans (see Rouillet et al., 2013 for a thorough review on this topic). Evaluation of prenatal AED exposure in children revealed that 8.9% exposed to valproate and 2.5% exposed to carbamazepine met diagnostic criteria for ASD (Rasalam et al., 2005) while a study from the LMNG had rates of 12% for the valproate monotherapy group compared to 1.8% in the control group not exposed to AEDs, with a positive trend for dosage effect which was not statistically significant. The proportion of children found to have ASD was further increased to 15% for valproate polytherapy. Other monotherapies suggested an increase in rates of ASD from the control group, but interpretation is limited due to small sample sizes (Bromley et al., 2013). A recent large population study from Norway reported that fetal valproate exposure was associated with an increase in autistic spectrum disorder and autism (Christensen et al., 2013).

2.3.5. Maternal epilepsy type—A few studies have found differences in child cognitive outcomes with regards to the mother's epilepsy type (partial or generalized onset). Hirano et al. in 2004 noted poorer social and linguistic scores in children of mothers with partial onset compared to generalized onset epilepsy, controlling for socioeconomic status. However,

other studies have not found an association between underlying epilepsy type of the mother and cognitive outcomes of offspring (Gaily et al., 2004; Meador et al., 2013) or for neurodevelopmental disorders including ASD (Bromley et al., 2013).

2.3.6. The effect of maternal seizures during pregnancy—There have been inconsistent results as to whether maternal seizures affect intellectual functioning of the offspring. Lower verbal IQ scores were found in children exposed to 5 or more maternal tonic-clonic seizures in utero (Adab et al., 2004; Vinten et al., 2005). In contrast, other studies have shown no such correlation (Scolnik et al., 1994; Ornoy and Cohen, 1996). Data from the LMNG and UKEPR study demonstrated no effect of exposure to maternal seizures in utero in children evaluated at 24 months of age (Shallcross et al., 2011), but did find poorer outcomes in language comprehension as well as gross motor skills, personal and social skills, hand and eye coordination, and performance skills during evaluations at 36–54 months of age (Shallcross et al., 2014).

2.3.7. Breastfeeding—As neurodevelopment continues beyond the womb, the effects of AED exposure through breast milk is of continued interest. In the NEAD study group, described in section 2.3.1., 42.9% of children were breastfed for an average of 7.2 months, and the adjusted mean IQ score was 4 points higher in 6 year old children who had been breastfed compared to those who had not, across all monotherapy treatment groups (Meador et al., 2014). A Norwegian study evaluating AED exposure prenatally and through breast milk also found less impairment on cognitive measures with breastfed children evaluated at 6 months and 18 months of age compared to nonbreastfed children, although there was no difference between the groups at 36 months of age (Veiby et al., 2013).

3. Future direction

3.1. Establishing risk

There are numerous possible reasons why studies have found inconsistent results for the cognitive effects of prenatal AED exposure. Various methodologies, including demographic differences in the sampled populations, age at which testing was performed, the types of cognitive tests utilized, and lack of control for confounding variables are at least in part responsible for the variability of results. Confounding factors include maternal IQ and education, which have been found to be closely correlated with child IQ (Meador et al., 2011b), but were not considered in most studies prior to 2000. In addition, maternal cognitive test scores may also be lowered due to the cognitive side effects of epilepsy and AEDs (Meador et al., 2007; Motamedi and Meador, 2004), further complicating interpretation.

Most of the newer AEDs have not been evaluated in animal or human studies for their cognitive effects in offspring through exposure in utero. Additional basic and genetic research is needed to determine the underlying mechanisms. From what little data we have on polypharmacy in animals and humans, the potentiation of harmful cognitive effects seen with certain combinations is concerning, and further studies are needed to assess the effects of other untested groupings. As we move forward, large scale prospective studies with standardized methods of cognitive evaluation controlling for confounding variables will be

essential. Identification of additional biomarkers, such as use of imaging modalities (Ikonomidou et al., 2007), or assessments of behavioral and physiologic outcomes may also be informative as screening tools or analytical methods for future studies.

The long term consequences of AED exposure during early infancy on cognitive effects are also not established and require attention. With animal data demonstrating impaired outcomes with AED exposure during the immediate postnatal period, which largely corresponds with a portion of the third trimester and neonatal period in humans, it is highly plausible that the deleterious effects of in utero AED exposure translate to neonatal exposure as well.

3. 2. Potential therapies

Beyond avoiding AEDs with the highest risks, there is a need to develop therapies, which block or reverse the adverse AED-induced effects.

3.2.1. 17 β -estradiol—Neuronal apoptosis may be seen in the immature brain with exposure to sodium channel blockade, activation of GABA_A receptors, or *N*-methyl-D-aspartate (NMDA) inhibition, but there may be other mechanisms. The AED-induced apoptosis has been determined to be at least in part due to inactivation of pro-survival proteins extracellular signal-related kinase (ERK-1/2), Raf, and AKT through altered gene expression (Bittigau et al., 2002). Asimiadou et al. (2005) have demonstrated that co-administration of 17 β -estradiol with agents that induce apoptosis with the above mechanisms of action (phenytoin, phenobarbital, and dizocilpine, respectively), prevented the excess apoptosis from occurring in the brains of 7 day old rats. Furthermore, addition of tamoxifen, an α - and β -estrogen receptor antagonist, blocked the anti-apoptotic effects seen with 17 β -estradiol, confirming that the mechanism of action is through the interaction with the estrogen receptor. Given that higher levels of activated kinase 1/2 and AKT were found with 17 β -estradiol, the authors suggested the protective effects of 17 β -estradiol occurred through secondary extracellular signaling leading to cellular survival.

3.2.2. Magnesium sulfate—Systematic reviews have found that antenatal administration of magnesium sulfate for the treatment of eclampsia or pre-term labor was associated with a decreased rate of cerebral palsy in the pre-term or low-birth weight infant (Conde-Agudelo and Romero, 2009; Doyle et al., 2009). In a French study, longer term follow-up of school-age children who had been exposed to magnesium sulfate in utero revealed no statistically significant differences in cognitive and motor outcomes, but the measures showed a trend toward better outcomes with the magnesium sulfate treated group (Chollat et al., 2014). However, another multi-center randomized control trial found no such trend on follow-up of school-age children (Doyle et al., 2014). In light of evidence that magnesium sulfate increases apoptosis in rat hippocampal culture (Dribben et al, 2010), the safety to both mother and fetus and the potential long-term neuroprotective benefits to the child are in need of further evaluation.

3.2.3. Vinpocetine—Vinpocetine, a phosphodiesterase type 1 inhibitor, which can enhance memory and LTP (long-term potentiation) in animals (Szatmari and Whitehouse,

2003), has been evaluated in several different neurological disorders for its potential cognitive and neuroprotective benefits. Clinical studies are limited, and a systematic review in 2003 only identified 3 double-blinded, randomized trials, which all evaluated vinpocetine's effect on cognition in the setting of dementia and found inconclusive results (Szatmari and Whitehouse, 2003). In a rat model of fetal alcohol syndrome, subsequent administration of vinpocetine was found to improve the performance in spatial learning to the level of control rats without prior alcohol exposure (Filgueiras et al., 2010). Prenatal alcohol exposure also disrupts visual cortex plasticity, and vinpocetine was able to restore ocular dependence plasticity in a ferret model (Medina et al., 2006). Thus, it is worth evaluating whether this agent could amend the cognitive deficits caused by prenatal AED exposure, considering the potential that basic science has revealed for this compound. Vinpocetine has also been reported to have anticonvulsant properties (Sitges et al., 2011), and its utility as an AED in maternal epilepsy could be of interest if prenatal exposure is found to be safe.

3.2.4. Genetic—Teratogens act on a genetically susceptibility substrate. This may account in large part for the individual variability in outcomes despite similar AED exposures. If we understood the underlying genetic factors, then we could theoretically avoid exposures in those with genetic risks to the adverse AED effects. Knowledge of the mechanisms could also lead to new therapeutic interventions to block the apoptosis and related neuronal abnormalities.

4. Conclusion

The last few decades have brought attention to the cognitive effects of in utero AED exposure. Continued treatment with AEDs through pregnancy is recommended for most women with epilepsy. Valproate has been shown to have the most deleterious consequences on cognition, and it is recommended that women with epilepsy avoid valproate during pregnancy if other therapeutic options exist. Although the data on human studies suggests a low risk for cognitive deficits with lamotrigine, levetiracetam, and carbamazepine, the effects of most other agents remain inconclusive or untested. We are only in the beginning stages of understanding the longterm consequences of these drugs in exposed offspring, and further research is urgently needed in order to properly treat the mother's epilepsy while minimizing the risk to her child.

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Highlights

Studies show the developing brain is vulnerable to antiepileptic drugs (AEDs).

Valproate has the worst impact on cognition of prenatally exposed children.

More studies are needed to evaluate the cognitive consequences of all AEDs in utero.

New therapies are needed to prevent cognitive impairment by prenatal AED exposure.

Table 1
Selected prospective studies assessing cognitive outcomes in children with prenatal AED exposure.

AED / Study	Study type and (n) of study group	Verbal abilities	Non-verbal abilities	FSIQ	Control Group IQ	Statistical Significance	Child's age at testing
Valproate							
Baker et al., 2015	LMNG study; prospective, observational, assessor-blinded Low dose (800 mg) n=21 High dose (>800mg) n=30	Low dose (800 mg) 94 (14); Mean (SD) High dose (>800mg) 90 (10); Mean (SD)	Low dose (800 mg) 98 (9); Mean (SD) High dose (>800mg) 96 (15); Mean (SD)	Low dose (800 mg) 98 (11); Mean (SD) High dose (>800mg) 93 (12); Mean (SD)	Mothers without epilepsy *; FSIQ= 107 (12) Verbal=103 (12) Non-verbal =106 (13); Mean (SD)	Verbal p=0.04 , Non-verbal p=0.10, FSIQ p=0.09 ----- Verbal ** p<0.001 , Non-verbal p=0.007 , FSIQ p<0.001	73.0 (2) months; Mean (SD) ----- 74.1 (4) months; Mean (SD)
Meador et al., 2013	NEAD study; prospective, observational, assessor-blinded n=49	97 (94-100); Mean (95% CI)	101 (98-104); Mean (95% CI)	98 (95-101); Mean (95% CI)	CBZ, LTG or PHT monotherapy	FSIQ and Verbal abilities of VPA exposed group was lower than all other AED groups; (see specific AEDs below for p values)	6 years
Gaily et al., 2004	Prospective, population-based, observational, assessor-blinded n= 13 (monotherapy) ----- n=17 (polytherapy with valproate)	Monotherapy 83.5 ± 3.8 (Mean ± SEM) Polytherapy 81.5 ± 2.8 (Mean ± SEM)	96.3 ± 4.8 (Mean ± SEM) ----- 96.1 ± 3.7 (Mean ± SEM)	89.7 ± 3.6 (Mean ± SEM) ----- 86.6 ± 2.4 (Mean ± SEM)	Other AED exposure: VIQ 94.8 (SEM 1.4)	VIQ of VPA exposed children to all other study group children p=0.003	7.0 (1.5; 2.1 to 11.1) years (SD; range)
Carbamazepine							
Baker et al., 2015	LMNG study; prospective, observational, assessor-blinded n=50	98 (15); Mean (SD)	108 (14); Mean (SD)	105 (15); Mean (SD)	Mothers without epilepsy *; FIQ= 107 VIQ=103 Non-verbal IQ=106	Verbal p=0.02 , Non-verbal p=0.16, FSIQ p=0.96	74.1 (4) months; Mean (SD)
Meador et al., 2013	NEAD study; prospective, observational, assessor-blinded n=61	104 (102-107) ; Mean (95% CI)	104 (102-107); Mean (95% CI)	106 (103-109) ; Mean (95% CI)	LTG, PHT or VPA monotherapy	VPA exposed group had worse outcome: Verbal p=0.0005 , Non-verbal p=0.08, FSIQ p=0.0010	6 years

AED /Study	Study type and (n) of study group	Verbal abilities	Non-verbal abilities	FSIQ	Control Group IQ	Statistical Significance	Child's age at testing
Gaily et al., 2004	Prospective, population-based, assessor-blinded n=86	96.2 ± 1.9; Mean ± SEM	103.1 ± 1.5; Mean ± SEM	99.7 ± 1.8; Mean ± SEM	No maternal epilepsy: VIQ 94.9 ± 1.2 Nonverbal IQ 102.4 ± 1.2 FIQ 97.6 ± 1.4	No significant difference from control group or unexposed group (latter data not shown).	7.0 (1.5; 2.1 to 11.1) years (SD; range)
Phenytoin							
Meador et al., 2013	NEAD study; prospective, observational, assessor-blinded n=40	106 (102-109); Mean (95% CI)	106 (103-109); Mean (95% CI)	109 (105-113); Mean (95% CI)	CBZ, LTG or VPA monotherapy	VPA exposed group had worse outcome: Verbal p=0.0005 , Non-verbal p=0.0514 , FSIQ p=0.006	6 years
Lamotrigine							
Baker et al., 2015	LMNG study; prospective, observational, assessor-blinded n=29	99 (13); Mean (SD)	103 (12); Mean (SD)	103 (11); Mean (SD)	Mothers without epilepsy*; FIQ=107 VIQ=103 Non-verbal IQ=106	Verbal p=0.23 , Non-verbal p=0.34 , FSIQ p=0.22	73.7 (SD) months; Mean (SD)
Meador et al., 2013	NEAD study; prospective, observational, assessor-blinded n=74	105 (102-107); Mean (95% CI)	108 (105-110); Mean (95% CI)	108 (105-111); Mean (95% CI)	CBZ, PHT or VPA monotherapy	VPA exposed group had worse outcome: Verbal p=0.003 , Non-verbal p=0.0015 , FSIQ p=0.0003	6 years
Levetiracetam							
Shallcross et al., 2014	LMNG-UK-EPR study; recruited from registry; assessor-blind; n=53	Reynell comprehension = 49.6 (10.3) and expressive = 52.0 (13.4); Mean (SD)	Griffiths motor 110.4 (17.2) and performance 109.9 (15.4); Mean (SD)	NA	Unexposed group and VPA exposed group	LEV did not differ than unexposed, but was better than VPA on gross motor skills p<0.001 , comprehension p=0.005 , and expressive language p<0.001	36 – 54 months

* An additional control group of children of mothers with epilepsy who did not take an AED during pregnancy, had similar IQ results as the general population control group.

** Nonverbal abilities also noted to be statistically significantly lower in the VPA high dose group compared to controls.

FSIQ = Full Scale Intelligence Quotient, VIQ = verbal IQ, PIQ = performance IQ, LMNG = Liverpool Manchester Neurodevelopmental Group, NEAD = Neurodevelopmental Effects of Antiepileptic Drugs, UK-EPR = UK Epilepsy Pregnancy Registry, CBZ = carbamazepine, LEV = levetiracetam, LTG = lamotrigine, PHT = phenytoin, VPA = valproate, NA = not applicable.