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Impact of early life exposure to antiepileptic drugs on neurobehavioral outcomes based on laboratory animal and clinical research

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Abstract

Epilepsy affects approximately 1% of children under the age of 15, making it a very common neurological disorder in the pediatric population (Russ et al., 2012 [1]). In addition, ∼0.4–0.8% of all pregnant women have some form of epilepsy (Hauser et al., 1996a,b; Borthen et al., 2009; Krishnamurthy, 2012 [2–5]). Despite the potential deleterious effects of antiepileptic drugs (AEDs) on the developing brain, their use is still required for seizure control in pregnant women (Krishnamurthy, 2012 [5]), and they represent the standard approach for treating children with epilepsy (Chu-Shore and Thiele, 2010; Quach et al., 2010; Verrotti et al., 2011 [6–8]). Even when AEDs are effective, there are potential side effects, including cognitive and affective changes or altered sleep and appetite. The consequences of AED exposure in development have been studied extensively (Canger et al., 1999; Modi et al., 2011a,b; Oguni, 2011 [9–12]). Despite intensive study, there is still debate about the long-term consequences of early life AED exposure. Here, we consider the evidence to date that AED exposure, either prenatally or in early postnatal life, has significant adverse effects on the developing brain and incorporate studies of laboratory animals as well as those of patients. We also note the areas of research where greater clarity seems critical in order to make significant advances. A greater understanding of the impact of AEDs on somatic, cognitive and behavioral development has substantial value because it has the potential to inform clinical practice and guide studies aimed at understanding the genetic and molecular bases of comorbid pathologies associated with common treatment regimens. Understanding these effects has the potential to lead to AEDs with fewer side effects. Such advances would expand treatment options, diminish the risk associated with AED exposure in susceptible populations, and improve the quality of life and health outcomes of children with epilepsy and children born to women who took AEDs during pregnancy.

Keywords

Development; Valproate; Phenytoin; Phenobarbital; Behavior; Teratogenicity; Epilepsy; Comorbidity

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1. Introduction

Approximately 0.4 to 0.8% of pregnant women have epilepsy [2–5]. In humans, nearly all AEDs freely cross the placental barrier and can accumulate in the fetus [13–16]. In utero exposure to AEDs in humans has been associated with a variety of effects on somatic, cognitive, and behavioral development. The functional consequences of in utero AED exposure appear to depend upon the type of AED as well as the use of the AED as monotherapy or polytherapy [17,18]. Here, we review the effects of in utero AED exposure on somatic, cognitive and behavioral development using both human and animal data. The effects of in utero exposure are then compared to the effects of exposure in early postnatal life. The focus of the comparison between human and animal research is based on data from the best-studied AEDs: phenytoin, phenobarbital, and valproate.

2. In utero exposure of the fetus to AEDs

2.1. Effects of maternal AED use on somatic development of the newborn

2.1.1. Phenytoin—In the initial studies of prenatal exposure to phenytoin, an association was found between drug exposure and a group of developmental abnormalities that was termed “fetal hydantoin syndrome” [19,20]. This syndrome includes abnormal head and facial development, including microencephaly, short nose, cleft palate, low nasal bridge, and a fold of skin on the upper eyelid (epicanthal fold), abnormal ears, wide mouth and low hairline [20,21]. In general, fetal phenytoin exposure has been associated with a 2–3-fold increase in the likelihood of offspring to develop a congenital anomaly [22,23]. These anomalies include those mentioned above as well as heart defects, and abnormalities of the genitalia [23–28]. In addition, phenytoin exposure has been associated with decreased rate of body growth [27,29]. Despite early reports that showed a strong association between outcome and prenatal phenytoin exposure, a number of larger studies that were conducted more recently, in which phenytoin monotherapy was evaluated, did not find a significant association between phenytoin monotherapy and the symptoms previously identified as fetal hydantoin syndrome [30–32]. Nevertheless, concerns remain that phenytoin use in pregnancy could affect the fetus. What seems possible is that the adverse effects of phenytoin monotherapy are not universal because they require genetic predisposition or additional environmental influences to be fully expressed. If so, consideration of genes and environment could explain some of the variability of past studies and potentially lead to genetic or other approaches to more clearly define the risk in mothers taking AEDs. Another issue is that folic acid supplementation, a current standard of care during pregnancy which may diminish some of the adverse effects of phenytoin on somatic and neural development, is somewhat recent and may not have been universal in previous studies of prenatal AEDs.

2.1.2. Phenobarbital—Some of the earliest studies investigating the potential teratogenic effects of phenobarbital demonstrated a possible increase in risk of congenital anomalies [33]; however, many of these studies were single case reports. More recently, better powered studies have found that phenobarbital exposure can lead to a slight but significant increase in the risk of birth defects. Typically, these effects are restricted to an increased risk of cleft palate and cardiovascular anomalies [34–37]. Fetal phenobarbital exposure has also been associated with a decrease in birth weight and a reduced head circumference at birth [38]. Some studies suggest that in utero exposure to phenobarbital can lead to more widespread problems, similar to those reported in fetal hydantoin syndrome [39]. Given the different mechanisms of action of these drugs, it is unclear why in utero exposure to phenytoin and phenobarbital would lead to such similar effects on organ development. One hypothesis is that the epilepsy is teratogenic — not the AED. However, while pregnant women whose seizures are not controlled during pregnancy have an increased risk of premature birth and infants with lower birth weight [5], many of the teratogenic effects on

the offspring can be attributed to prenatal exposure to anticonvulsant drugs [40]. In the future, animal models could be valuable to further our understanding of the effects of uncontrolled epilepsy on the developing brain, particularly when epilepsy can be induced without widespread damage to the brain and reproductive system [41]. It is also possible to compare vehicle- and AED-treated groups under better controlled environmental conditions if laboratory animals are used. Recent studies of this kind are elucidating many effects of uncontrolled seizures during pregnancy in female laboratory rats; to date, there is both evidence for and against adverse effects of seizures during pregnancy on development of the offspring [42–45].

2.1.3. Valproate—Prenatal exposure to valproate is associated with a variety of birth defects in humans (effects that occur in approximately 5–10% offspring) [31,46,47,48], a rate that is significantly higher than has been associated with any of other AEDs currently in use. These effects appeared to be dose-dependent, with doses over 1000 mg/day leading to effects in 15–30% children [46,47]. Adverse effects include neural tube defects, decreased brain volume, heart defects, craniofacial dysmorphism (oral cleft), and abnormalities in the urethra in males (hypospadias) [28,46,47,49–60]. Children exposed to valproate in utero also showed intrauterine growth restriction (IUGR), other growth deficiencies, and increased risk of microcephaly [29,50,51]. Based upon the spectrum of effects, children exposed to valproate are said to exhibit “valproate syndrome”. Children with valproate syndrome also have facial dysmorphisms which include mid-facial hypoplasia, epicanthal folds, a short nose with a broad ridge, and a thin upper lip [50,51]. Again, the similarity of these effects to those of phenytoin and phenobarbital, AEDs that have distinct mechanisms of action, suggests either a risk inherent to pregnant women with epilepsy or a common teratogenic effect of these drugs that is not currently understood. Understanding a common mechanism – if it exists – deserves attention because it could lead to a treatment to stop adverse effects of AEDs in the fetus.

2.1.4. Other/polytherapy—In addition to the AEDs described above, carbamazepine has been associated with an increased risk of spina bifida, neural tube defects, cardiovascular anomalies, cleft palate, skeletal anomalies, and brain malformations [22,31,47,61–65] leading to the term “carbamazepine syndrome” [66,67]. Fetal carbamazepine exposure is also associated with a decrease in birth weight and premature delivery [68]. Despite a number of published reports showing teratogenic effects of carbamazepine, other studies have failed to replicate these findings [69]. Furthermore, related drugs (oxcarbazepine) have not been associated with a significant increase in birth defects [32,70–72]. However, it should be noted that oxcarbazepine, when used in combination with other AEDs, has been associated with an increased risk of malformations [25,70,73–75]. It has been shown that newer AEDs including lamotrigine have lower rates of major malformations [76–78] that increase when the AED is used in combination with other AEDs [47,79]. To date, detailed studies of newer generations of AEDs (topiramate, tiagabine, and levetiracetam) are still emerging. Rigorous study of the new AEDs is important to clarify whether they reduce risk to the fetus and whether AED effects on the fetus could share common mechanisms — even if the mechanisms that reduce seizures are distinct.

2.2. Effects of maternal AED use on cognition and behavior of the newborn

2.2.1. Phenytoin—Some of the earliest studies to identify a potential effect of AEDs on cognitive function in the offspring come from studies of phenytoin, where it was shown that there was an increased risk to cognitive function following prenatal exposure [19,24]. These findings were, in part, confirmed by follow-up studies in which trends were found toward decreased IQ in children (aged 4, 5, and 7 years) exposed to phenytoin in utero [20,34,80–85]. In a significant proportion of those studies, phenytoin was used as part of a polytherapy,

so the direct contribution of phenytoin to cognitive outcomes could not be assessed. Some groups have found that intellectual impairments only occurred in children who were exposed to phenytoin in utero who also presented with clear morphological anomalies [82]. Still, others have failed to find significant impairments in the intellectual abilities of children exposed to phenytoin in utero [86]. In addition to defects in cognitive functioning, some studies have identified delays in motor development in children who were exposed to phenytoin in utero [87,88].

2.2.2. Phenobarbital—In a variety of studies, in utero exposure of the fetus to phenobarbital has been associated with a significantly lower mean IQ score when tested as children [89]. More specifically, phenobarbital exposure is associated with a significant decrease in verbal IQ and verbal functioning [90] when compared with children that were not exposed to phenobarbital in utero. One study that is notable because it was prospective and included controls showed that prenatal exposure to phenobarbital led to worse neurological outcome, which was detected as early as 8 weeks of age [87,91]. Other data suggest the timing of prenatal exposure to phenobarbital is particularly important, because exposure in the third trimester was associated with learning disabilities and decreased cognitive functioning [27], with measurable effects in adulthood [90]. As with phenytoin, some groups report that intellectual impairments presented primarily in those subjects with obvious somatic abnormalities [92]. In contrast to these findings, several groups have failed to find an association between fetal phenobarbital exposure and altered cognitive function [93,94]. The variability of study results for phenobarbital makes a current consensus hard to define. Instead of viewing these results as conflicting, however, it is possible that they merely reflect that all variables (genes, environment) were not the same and both genes and environment play an underappreciated role in the development of adverse effects of fetal AED exposure.

2.2.3. Valproate—Valproate exposure during fetal development appears to have some of the most consistently negative effects on cognitive and emotional functioning of the offspring. In utero exposure to valproate has been associated with a 7–8-fold increase in the incidence of autism spectrum disorders (ASD) compared with unexposed populations [95–97]. Newborns of mothers taking valproate tend to have lower Apgar scores, increased perinatal distress, hypertonia, and developmental delays [51,98]. It has been shown that valproate levels at birth correlate with neurological functioning at 6 years of age [93]. Children exposed to valproate in utero are more likely to have mental impairment [85,86,99,100] and lower IQs [101–106]. Children who were exposed to valproate in utero also appear to have difficulty adapting to new routines, attention deficits, and depressed mood [85,100,102–107]. Valproate exposure is also associated with developmental delays in motor performance [96] and speech [108,109].

2.2.4. Other/polytherapy—The effects of other common AEDs, such as carbamazepine, on cognitive functioning of the offspring are less well defined, with some reports associating exposure with significant impairments in cognitive functioning [66,67] and others that do not support this conclusion [63,69,86,87,103]. Those studies that do report effects of prenatal carbamazepine have suggested that there are developmental delays in offspring [66]. However, in most reports, children exposed to carbamazepine in utero have normal IQ [88,103], and the risk of ASD is similar to unexposed children [96].

Based upon the results described above, there has been increasing concern regarding the potential effects of AEDs on cognitive and neural development, which have prompted larger scale studies to investigate the effects of these drugs in pediatric populations. A prime example of such a study, in which a great deal of information is emerging, is the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, which evaluated

children of mothers with epilepsy between 1999 and 2004. Meador and colleagues found no effect of phenytoin, carbamazepine or lamotrigine on IQ at 4.5 years, but there was an adverse effect of valproate [110].

3. Exposure of children to AEDs in early postnatal life

3.1. Effects of early postnatal exposure to AEDs on somatic development

Despite the number of studies assessing the impact of prenatal AED exposure on morphological development (e.g., fetal hydantoin syndrome, valproate syndrome, described above), the effects of AEDs on children (we focus here primarily on ages 0–15) that were unexposed prenatally and began AED treatment in early postnatal life are not as well defined. This is critical since AEDs have not been formally approved for use in the newborn, yet they were continued to be widely prescribed [111]. Furthermore, additional studies investigating the impact of acute and chronic seizures in children and the effects of acute or chronic AEDs in these populations are warranted.

One AED that has been studied in children, specifically with respect to somatic development, is valproate. Recent research has found that children with epilepsy who were treated with valproate tend to be shorter in stature and have higher body mass index (BMI) than children who had not taken valproate [112,113]. In a different series of studies with a similar approach, valproate use in children with epilepsy was associated with increased weight gain [114–122]. It has been suggested that weight gain is due to altered expression of growth hormones or ghrelin [113,123]. Other AEDs, such as carbamazepine, when administered to children with epilepsy, have also been associated with weight gain, an effect that may be related to changes in thyroid hormones [112,118,119].

3.2. Effects of early postnatal exposure to AEDs on cognitive and behavioral development

Interpreting the cognitive and behavioral effects of AEDs in children is difficult because, similar to adults, it is hard to dissociate the effects of AEDs from the effects of seizures. Moreover, the rapid and changing pace of neural and behavioral development across early life can contribute to significant variability, depending upon the age when treatment begins (i.e., there could be significant effects at a young age but no clear effects at an older age, or vice-versa). Furthermore, the serum levels of AEDs are also difficult to compare across ages 0–15 due to differences in drug metabolism during development [124]. Another source of variability is that behavioral effects of AEDs appear to be inconsistent, particularly in young children. Furthermore, the type of neuropsychiatric symptoms in children changes with age — regardless of epilepsy or AED use. For example, children who are institutionalized may exhibit externalizing disorders (hyperactivity, defiance, etc.) initially and then change gradually, ultimately exhibiting internalizing disorders (anxiety, depression, etc.) [125].

In addition to the potential problems described above, diagnosis of comorbid conditions in very young pediatric populations is often difficult. In addition, it is often difficult to interpret the data, because some effects of drugs may occur as soon as drugs are administered, whereas other effects of drugs may occur well after drug use has stopped, because the drug altered neurodevelopment when it was administered. Furthermore, in relation to psychiatric symptoms, epilepsy can have significant effects on the level of stress and mental well-being of the caregiver, which can significantly influence the health and well-being of the child.

Selection of control groups is also difficult. For example, concurrent evaluation of AEDs in controls with no epilepsy may be hard to find. They are not the only control group that is necessary, because there can be a complex pathology in patients with epilepsy involving both brain and periphery, whereas this is not the case in healthy individuals. However,

despite all of these caveats, there are some conclusions that can be made about the behavioral effects of AEDs in pediatric epilepsy.

3.2.1. Phenytoin—Despite the long-standing use of phenytoin in the treatment of epilepsy, few studies exist assessing the behavioral effects of its use in pediatric populations. A recent article by Glauser et al. [126] reviewed the current status of this literature and cited 5 published reports of children receiving phenytoin monotherapy [127–131]. In those reports, phenytoin was associated with somnolence (∼30% of users), apathy (∼11%), and anxiety (∼12%). In addition to these effects, Aman and colleagues have found minimal effects of phenytoin on psychomotor performance [132]. In rare instances, phenytoin exposure has also been associated with psychosis, delirium [133], and transient effects on visual functioning [134].

3.2.2. Phenobarbital—In some of the earliest studies of the behavioral effects of AEDs, infants taking phenobarbital as a consequence of a febrile seizure had higher incidence of behavioral effects (“fussiness”) and sleep disturbance [135], and there was an increased incidence of “cognitive” problems that appeared to increase with duration of treatment [135]. In a different study, children (∼1–3 years) treated with phenobarbital for febrile seizures had decreased IQ compared with placebo-treated controls [136]. In a more recent randomized placebo-controlled study with preterm infants with no epilepsy (<34 weeks) at risk for intracranial hemorrhage, perinatal administration of phenobarbital led to poor performance at age 2 on the Bayley Mental Developmental Index [137]. However, drug exposure was not predictive of IQ, achievement, or cognitive functioning at age 7 [138]. Similar studies of exposure to phenobarbital (at or just prior to delivery) have failed to find effects of drug exposure on the cognitive outcomes at 18 and 22 months of age [94]. Therefore, even if there are early postnatal effects of phenobarbital, there has been no consensus that these lead to long-term effects on behavior [135,139–142]. However some recent reviews continue to stress caution, especially when considering phenobarbital for seizure control in children [126].

In later stages of childhood (∼3–18 years), phenobarbital has been associated with significant behavioral side effects (ranging from as many as 30–76% of patients reporting adverse effects depending upon the study) [127,143–147]. In a series of large open-labeled studies, the most commonly reported adverse effects were irritability, sleep disturbances, and hyperactivity [127,129,135,143,144]. In a small group of children (∼43) aged 6–16, Brent et al. [148] found that phenobarbital was associated with depression in 40% of children on phenobarbital, with suicidal ideations being reported in 47% of phenobarbital users. Such effects have been replicated by other groups in which phenobarbital exposure was associated with poor self-concept scores [149] and a significant increase in hyperactivity [150,151]. Exposure to phenobarbital has also been associated with significant effects on cognitive functioning, including decreased IQ, slowed reaction times, and impaired concentration [140,150,151]. However, in those studies, many of the subjects remained on treatment during testing, making it hard to determine whether the results were due to adverse effects of drugs on brain development or acute effects of ongoing medication. Despite such shortcomings, these findings suggest that the potential adverse effects of drug exposure on behavior are not limited to early developmental periods. However, it is unclear whether the effects that are reported from 5 to 20 years continue later in life.

3.2.3. Valproate—Studies of the effects of valproate exposure on behavior have been mixed. In multiple studies, minimal to no effect of drug exposure (between 6 and 15 years old) has been identified on measures of cognitive functioning when the dose of valproate was low [151,152]. Some studies have actually identified possible improvements in cognitive functioning and IQ scores in individuals with epilepsy on valproate [150]. Such

beneficial effects could be related to reduced seizures or recent identification of potential epigenetic effects of valproate [153]. However, these studies contradict previous work that failed to identify beneficial effects of valproate on cognitive outcomes and identified potential negative effects on motor performance and visuospatial functioning [154].

3.2.4. Other/polytherapy—Pediatric use of topiramate in children (0.5–18 years) with epilepsy was associated with possible adverse effects on psychomotor function, verbal fluency, and attention [155–157]. Levetiracetam has been associated with somnolence and dizziness, but these effects often remit shortly after the beginning of treatment [158].

In summary, there are a number of effects of AEDs in children, which include gross morphological development, intellectual development and behaviors such as anxiety, mood, and attention. However, many studies do not agree, and there are also effects in adults in some cases. Therefore, it is difficult to interpret the existing findings, as noted above. As a result, some of what has been learned from studies of AEDs in laboratory animals has been very helpful.

4. Animal (rodent) in utero AED exposure

The use of animal models allows for careful assessment of the effects of AEDs on brain and behavior during development. Using these models, the timing, dose, class of drug, and mechanism can be assessed on a uniform genetic background. However, care must be taken when considering which effects can be generalized to humans. Despite the increased control that animal research provides, significant differences exist between species with regard to the timing of neurodevelopmental events, including neurulation, peak periods of neurogenesis, synaptogenesis, apoptosis, gliogenesis, and myelination. Therefore, care must be taken in generalizing results of studies about drug exposure in animals to humans. Several reviews do an excellent job of describing species differences in neurodevelopmental events to place the results from laboratory animals in context [159]. In addition to potential difficulties because of species differences, there also are difficulties in generalizing from animal models of epilepsy to clinical epilepsy syndromes. In this section, we review data from rodent models of early life AED exposure in animals with no epilepsy, eliminating the second issue. However, it is acknowledged that using the data based on animals with no epilepsy to address clinical epilepsy poses problems, and data from laboratory animal with epilepsy are useful.

A third issue to note is that the behavioral evaluation of animals is often difficult. What behavioral test in a rodent can be used to gain insight into psychiatric illness such as depression? To address this complex issue, behavioral scientists are moving toward a better approach for behavioral assessment, endophenotyping. An endophenotype is considered a subclinical trait that is either a component of the broader disorder or represents a disruption in a core process that can be traced back to a biological or genetic root cause. The endophenotypic approach eliminates the need to recapitulate a multicomponent/syndromic disorder in the animal and allows for a more accurate assessment of disrupted processes without the burden of attempting to recapitulate diagnostic criteria that are inaccessible in animals (such as hallucinations or ideations). Below, we address gross anatomical effects first, which are not as difficult to interpret. Secondarily, we present the data that are available about the effects of AED use on cognitive and behavioral development. Although difficult, the data, still, are useful and have the potential to shed light on the adverse effects of AED use in children.

4.1. Effects of maternal AED administration on somatic development of the offspring

4.1.1. Phenytoin—Similar to what has been observed in patient populations, prenatal exposure of normal rodents to phenytoin impacts the development of the fetus. In pregnant rats, phenytoin (when administered for most of gestation) led to an increase in stillbirth and higher mortality during the first week of life [160,161]. For pups that survived, some groups reported a decrease in postnatal weight gain [160] while other groups detected differences in body weight but not until after the time of weaning (which usually is 21–23 days after birth in the rat) [162]. Pregnant rats that received doses of phenytoin had pups with decreased somatic weight and decreased brain volume [163]. Phenytoin exposure in utero in rats has also been associated with significant effects on skeletal development (e.g., increased prevalence of limb, spinal column, and rib defects [164]).

4.1.2. Phenobarbital—In mice, prenatal phenobarbital exposure was associated with significant effects on birth weight and litter size [165]. However, in more recent studies in two different strains of mice (C3H and C57BL/6J), exposure to phenobarbital (∼0.5 mg/day) throughout gestation, a dose that is considered close to what would be a therapeutic dose in patients, had no effect on litter size or weight of the offspring [166]. In a separate study, exposure of mice (C57BL/6 and CBA) to phenobarbital in utero did not lead to a detectable effect on weight at birth, but weight of exposed mice was reduced at postnatal day (P)18 compared with controls [167]. Consistent with reports of decreased weight of offspring, prenatal phenobarbital has been associated with a decrease in muscle mass at 12 weeks of age (adulthood begins at 8 weeks in rodents) [168]. The studies of Sedowofia [167] and Ihemelandu [168] are hard to compare because different doses and times of treatment during gestation were used. Nonetheless, effects on somatic development were found, suggesting it is a common effect that may occur regardless of dose and duration of in utero exposure.

Related to effects on brain development, exposure to phenobarbital during gestation led to a significant decrease in cell proliferation in an area of the hypothalamus (the medial preoptic area) of female Sabra mice [169], decreased number of hippocampal pyramidal cells [170–173], and decreased number of cerebellar Purkinje and granule cells [174]. In light of data showing a similar effect after phenytoin, it has been suggested that early life exposure to AEDs can cause increased programmed cell death, a potentially devastating effect for the developing brain (discussed further below). On the other hand, there may be a reserve of cells present or sufficient developmental plasticity so that a small increase in apoptosis could occur without impairing development.

4.1.3. Valproate—Valproate has potent effects on fetal development in rodents. In utero exposure of Wistar rats to valproate (at a range of doses and throughout pregnancy) led to a ∼50% decrease in litter size, but no significant effects on either the weight gain of the mother during pregnancy or the weight of the offspring when measured one week after birth or shortly after puberty [175]. Acute valproate injection (one dose only of 600 mg/kg at E9) in pregnant Wistar rats led to an ∼25% decrease in litter size, a remarkable effect, but there were no detectable effects on weight gain of the surviving offspring [176]. The same dose, injected in Wistar rats at E12.5, led to a decrease in the body weight of the offspring starting at P23, an effect that continued to P180 [177]. The adverse effects of acute exposure to valproate at one time in gestation seem to generalize across rodents, as the administration of a single dose of valproate (800 mg/kg orally at E9 or E10) in a mixed strain of mice led to a similar decrease in weight gain to what was observed in rats. The effects were also similar in that they emerged following weaning [178].

In utero exposure to valproate also impacts neurodevelopmental milestones and leads to birth defects in rodents. Both mice and rats exposed to valproate during gestation have delays in eye opening by approximately 2 days [177,178], which is a significant delay. In several strains of mice, in utero exposure to valproate at a range of doses and times in gestation, including single dosing as well as longer treatment, has been associated with increased resorption of fetuses, the development of limb defects and neural tube defects (including exencephaly), and the development of skeletal malformation (including fused vertebrae, fused ribs, syndactyly, and dysplasias) [179–183]. In utero exposure to valproate (600 mg/kg at E12.5) in Long–Evans rats has also been associated with microcephaly and cerebellar abnormalities [184] which could be reproduced in Sprague–Dawley rats with a 600-mg/kg dose of valproate from E7–E18 [185].

4.2. Effects of maternal AED administration on cognitive and behavioral development of the offspring

4.2.1. Phenytoin—Because of the observations (described above) that phenytoin can have adverse effects on cognitive functioning in children with epilepsy, a number of groups have begun to assess the consequences of this drug on neurobehavioral development in rodents. Sprague–Dawley rats exposed to phenytoin during the second half of gestation (approximately the second trimester of human development) led to the development of impairments in memory performance of the offspring. Specifically, rats exposed to phenytoin in utero, when tested at P50 (early adulthood), showed impaired reference-based spatial learning in a straight channel swimming task and impairments in both the learning and reversal phases of the Morris water maze task [186]. These effects suggest a robust effect on memory systems, but there also could have been additional adverse effects. Fortuitously, other studies have filled this gap, showing that prenatal phenytoin exposure leads to abnormal circling behavior [161,187–189]. Lesions of the striatum can lead to similar effects on circling and may represent an area that was probably affected. Importantly, the abnormal circling did not confound studies of tasks like the Morris water maze, because significant effects of prenatal phenytoin on these tasks could still be observed in rats that did not express the abnormal circling phenotype. Earlier studies found significant effects on early motor development, including impairments in the righting reflex, rotarod performance, and cliff avoidance [163].

Studies by Weisenburger and colleagues found similar effects of in utero exposure of Sprague–Dawley rats to phenytoin on spatial learning in both the Morris water maze and the radial arm maze tasks [189]. In utero exposure was also associated with developmental delays in offspring, such as the age when auditory startle develops and delays in the ability to swim. There also are reports that phenytoin-exposed offspring have reduced rearing, have increased swimming maze errors, have impaired passive avoidance retention, and are hyperactive [161,187,188]. In a series of studies which examined correlations between the timing of drug exposure and behavior, the behavioral effects were most closely associated with exposure to phenytoin during days E11–E14 [161], suggesting a “critical” period for drug effects on neurobehavioral development. E11–E14 is an early time relative to cortical, hippocampal, and cerebellar development (E17 and later), so it is an interesting finding. It is a contrast to the morphological development after prenatal phenytoin, which seems to cause adverse effects regardless of the time of exposure.

4.2.2. Phenobarbital—In human studies, the effects of phenobarbital exposure on cognitive functioning have been mixed. In contrast, in utero exposure of rats to phenobarbital has been more clearly associated with cognitive impairments. Prenatal exposure of Sprague–Dawley rats to phenobarbital during the second half of gestation led to impairments in working memory and spatial learning as well as delays in ontogeny of

swimming behavior [160,161,188]. In a similar series of studies using lower doses of phenobarbital, there were deficits in performance on the eight-arm radial maze, spontaneous alternation, and Morris water maze tasks [190–192] indicative of impairments in hippocampal function. Similarly, prenatal exposure of mice to large doses of phenobarbital (3 g/kg from E9–E18) led to impaired performance on the eight-arm maze, spontaneous alteration, and Morris water maze tasks [173,192,193]. In C3H mice, low doses of phenobarbital (∼0.5 mg/day throughout gestation) led to decreased locomotor activity, increased startle response, and effects on motor coordination [194]. Conversely, exposure to moderate doses of phenobarbital (80 mg/kg) during the final week of gestation (∼E14–E20) in C57BL/6J mice led to hyperactivity in the offspring, decreased habituation to an open field [166,195,196], and impaired responding on an incremental operant reinforcement task [197–199], suggesting either strain differences in drug effects or contrasting effects dependent on the timing of drug administration. Related to recent work implicating AED exposure with the development of autistic spectrum disorder (ASD) (see below), some groups have found that E10–E16 treatment of the mother with phenobarbital (60 mg/kg) led to decreased play-soliciting behavior [200].

4.2.3. Valproate—Prenatal exposure to valproate has recently been proposed as a possible drug-induced model of ASD [177,201], and, thus, has received significant attention with regard to behavioral outcomes. Offspring of rats treated with high doses of valproate (500–600 mg/kg at E12.5) had significantly reduced socialization and play behaviors during adolescence, decreased exploratory activity, and an increase in repetitive and stereotypic-like behaviors [177,202], which are used as animal correlates of ASD-like syndromes [203]. Interestingly, a similar treatment regimen (600 mg/kg at E12.5) led to impairments in the ability of offspring to locate odors in bedding material at P9 but not at P10 or P11 [177]. These effects, similar to ASD-like endophenotypes, have been replicated in mice in which 800 mg/kg of valproate is administered to the pregnant dam at E11 [178].

The effects of in utero exposure to valproate may have effects that are related to symptoms of schizophrenia, which in a rodent are suggested to be simulated by altered prepulse inhibition, which indicates abnormal sensorimotor gating. In utero exposure to valproate has been associated with altered startle in the prepulse inhibition paradigm [177,202]. Offspring born to mothers that were administered valproate also show increased anxiety-like behavior on the elevated plus maze as adolescents [202] and were hyperactive during early life (P15) when tested in the open-field task [175,176]. Prenatal valproate exposure was also associated with significantly more freezing behavior in the cued and context portions of the contextual fear conditioning task, diminished fear extinction, and enhanced context and cue generalization [202]. These phenotypes suggest increased anxiety-like behavior or related deficits which are relevant not only to schizophrenia but also to many other types of psychiatric syndromes. Interestingly, rats that were exposed to valproate prenatally did not show impairments in learning on the Morris water maze task [202]. However, there were delays in the ontogeny of swimming behavior [177], impairments in negative geotaxis, and impairments in accelerating rotarod performance [175], suggesting adverse effects on motor development and coordination. Similar impairments have been noted in mouse models of late gestational (E12–E17) exposure to valproate at lower doses (200 mg/kg), where valproate was associated with impaired surface righting, impaired midair righting, decreased wire hanging strength and impaired learning in the Morris water maze task in early life [204]. Finally, high doses of valproate (825 mg/kg) administered throughout pregnancy led to decreased sensitivity of offspring in the tail flick, hot plate, and filament tests [175], suggesting a significant effect of drug exposure on pain and tactile sensitivities. These data, taken together, suggest a broad spectrum of effects of in utero valproate exposure on neurobehavioral development across several domains of somatic and cognitive functioning.

5. Animal (rodent) postnatal exposure

5.1. Effects of early postnatal AED administration on somatic development of young rodents

5.1.1. Phenytoin—Early postnatal administration of phenytoin (10–35 mg/kg) in mice (Jcl:ICR) leads to a reduction in total brain weight relative to saline-treated controls. Subdividing the brain, phenytoin exposure led to robust decreases specifically in the cerebral cortex and cerebellum [205–207]. In a separate study using similar doses in Sprague–Dawley rats but with administration that continued until the equivalent of early adolescence (P0–P30), significant elevation in neuronal apoptosis was found in nearly all brain regions studied [208], providing a potential explanation for effects on brain weight. The effects on apoptosis were dose-dependent, with neurons being most susceptible when phenytoin was administered from P0–P14 [209–211]. Similar effects of phenytoin on brain development have been observed by other groups and expanded upon. Postnatal phenytoin exposure has been shown to lead to delayed neuronal migration and impairments in the maturation of subsets of cerebellar cells [205,207,212,213]. The effects of phenytoin on cerebellar neurons can be recapitulated in vitro, where phenytoin induces apoptotic cell death of cultured cerebellar granule cells and degeneration of Purkinje cells [214–216]. These effects in rats are also observed in mice, where postnatal treatment with phenytoin (35 mg/kg) during the first two weeks of life leads to increased apoptosis in the hippocampus and cerebellum and the development of neurons with immature and irregular processes [217].

5.1.2. Phenobarbital—Adverse effects of phenobarbital on brain growth have also been studied relatively extensively. Postnatal administration of rats with a range of doses of phenobarbital (15–60 mg/kg) during the first three weeks of life leads to reduced brain weight of exposed rats relative to saline-treated controls [218,219]. As with phenytoin, the effects of phenobarbital are widespread with reduced numbers of Purkinje and granule cells in the cerebellum [173,219–222] and pyramidal and granule cells in the hippocampus [171,173]. The decrease in neuronal number in these regions is associated with widespread induction of apoptosis that increases with dose [208,209,223]. As with phenytoin, the effects of phenobarbital on apoptosis were most robust when exposure occurred between P0 and P14 [209]. Other groups have also shown that brief exposure (P7–P8) to higher doses of phenobarbital (75 mg/kg) led to decreased neuronal number in the thalamus, striatum, frontal cortex, and hippocampus of rodents [171,210,224]. In addition, phenobarbital exposure from P7–P34 leads to a decrease in hippocampal progenitor cell proliferation, decreased expression of a marker of immature cells, and decreased survival of postnatally generated neurons in the adolescent animal [225,226], suggesting that drug exposure affects postnatal neurogenesis in the hippocampus. Rats exposed to phenobarbital during the first three weeks of life also have impaired development of olfactory bulb (∼25% reduction in medial olfactory bulb volume), with the greatest reductions in neuronal number in the external layers (mitral and glomerular neurons) and significant but more modest effects on the granule cell layer [227].

5.1.3. Valproate—In humans, pediatric valproate exposure is associated with increased weight gain and an elevated body mass index (BMI). Interestingly, administration of valproate (200–400 mg/kg) to young mice at P13 was associated with a decrease in body weight, an effect that lasted until P23 [204]. Similar dosing regimens in rats (200 mg/kg from P4–P18) also led to a decrease in weight [228]. The decrease in weight could be rescued by gastric feeding to control caloric intake, suggesting the decrease in body weight was due to a decrease in feeding rather than in altered metabolism. More recent studies using lower doses of valproate in young Long–Evans rats (150 mg/kg from P6–P12) did not lead to detectable differences in weight gain relative to control rats [229]. Interestingly, in

the studies by Diaz and Shields [228], there was also a decrease in the brain weight of valproate-treated rats, but unlike somatic weight, this effect could not be rescued by gastric feeding, suggesting that brain development was impaired. Decreased brain growth could actually mean that there was also excess programmed cell death (apoptosis) during development, which would be consistent with other studies demonstrating that postnatal valproate exposure is associated with a dose-dependent increase in neuronal apoptosis [208,209,211]. In addition to brain and body development, valproate may also impact neurodevelopmental milestones. In Sprague–Dawley rats, valproate treatment (P6–P20) is associated with a delay in eye opening [230]. However, in separate studies using Long–Evans rats, in which valproate treatment is stopped around the period in which eye opening occurs (P6–P12), no effect of valproate on eye opening was found [229].

5.1.4. Other AEDs—When administered at doses that approximate therapeutic doses in humans, the drugs that were developed after phenytoin and phenobarbital, such as topiramate, lamotrigine, and levetiracetam, had no neurotoxicity in the young rat brain [231–233]. However, high doses of topiramate (>50 mg/kg), carbamazepine (200–400 mg/kg), diazepam (5–30 mg/kg), vigabatrin (50–200 mg/kg), and clonazepam (0.5–4 mg/kg) caused widespread apoptotic neuronal death when administered to young rats [188,211,231]. Taken together, AED use clearly predisposes the young rodent brain to apoptosis of neurons. The mechanism of this effect is not clear; some investigators suggest that it is related to decreased neuronal activity during development, since that is the one potential mechanism that all AEDs have in common, while others argue for decreased trophic support leading to loss of neurons [209]. Such changes may lead to altered development and even a predisposition to seizures, given that silencing neuronal populations in the visual system or hippocampus can lead to inappropriate development [234] and increased excitability [235,236], respectively.

5.2. Effects of early postnatal AED administration on cognitive and behavioral development of young rodents

5.2.1. Phenytoin—In rodents, early postnatal AED exposure has been shown to impact a variety of neurobehavioral outcomes. In mice, the early postnatal administration (P2–P4) of phenytoin (25–35 mg/kg) was associated with deficits in the righting reflex and head control from P5–P9 [206] and ongoing effects on motor function, including poorer performance on the rotarod test and increased locomotor activity in the open-field test [207]. However, in those studies, grip strength and gait were normal [207], suggesting that drug effects were not due to gross effects on muscle function. It should also be noted that ∼30% of the pups died when phenytoin was administered at these doses, suggesting non-specific effects. More studies are required to understand the high mortality, which could be due to many deficits ranging from acute toxicity to failure to nurse. Exposure of mice to similar doses of phenytoin later in postnatal development (P5–P14) has been shown to impact later performance on spatial tasks, such as the radial arm maze task and Morris water maze task [217], cued fear conditioning [237], and motor coordination [238].

5.2.2. Phenobarbital—Mice treated with phenobarbital (50 mg/kg) during the first weeks of life (P2–P21) showed significant impairments in the eight-arm radial maze task [190] and impaired performance on the Morris water maze spatial memory task [226,239]. Yanai and colleagues [240] showed that phenobarbital treatment during this same period led to strain-specific effects in mice on tests that evaluate anxiety-like behavior, such as the open-field test, with DBA/I mice being particularly affected and C57BL/10 mice being less affected. In rats, additional studies have shown that phenobarbital treatment leads to impairments in midair righting reflex, basic associative learning, sensorimotor gating, and anxiety-like behavior [238,241]. Others have shown impairments in working memory [242], impairments

in spatial learning [238,243,244], impairments in striatal-dependent reversal learning [237], disruptions in attention [242,245], and, possibly, hyperactivity [218].

5.2.3. Valproate—Postnatal exposure of mice to valproate had widespread effects on behavior. In BALB/c mice, postnatal valproate (200 or 400 mg/kg at P14) led to significant impairments in midair righting and modest effects on negative geotaxis but no change in basal locomotor activity when tested early in life (<P20) [204,246]. These same mice, when tested later in life, were found to have significant deficits in learning in the Morris water maze task [204]. It should be noted that in that study, mice receiving the higher dose also had impairments in performance in the visible platform portion of the task, indicating potential drug effects on sensory function or swimming abilities, along with a transient decrease in performance on the passive avoidance task [204]. Similar to prenatal exposure to valproate, postnatal valproate administration in rats led to a significant reduction in play behavior, suggesting an impact on social functioning [230]. Early postnatal treatment of rats (P6–P12) with valproate also led to a decreased acoustic startle response when tested at P23 (males) and at P45 (males and females), along with impairments in sensorimotor gating as assessed by prepulse inhibition [229]. Interestingly, in those studies, males and females showed significant impairment in manual dexterity in the vermicelli-handling task [229], suggesting potential effects on fine motor functioning.

6. Conclusions

Prenatal and postnatal exposure to AEDs is associated with many potential impairments. However, a consistent view of these impairments with respect to the type of AED, dose and timing of treatment that lead to the most risk is much less clear, leading to clinical concern but insufficient data to choose the best course during pregnancy in women with epilepsy and during early postnatal life in children with epilepsy. Furthermore, whether to treat and how to treat offspring of women with epilepsy so that any effects of prenatal exposure are remediated or reversed are currently unclear. Many of these approaches could benefit from initial studies in laboratory animals, but there are many complex issues related to the evaluation of animals to better treat humans. For example, in animals, AED administration to the mother or offspring has shown dramatic effects on neuronal cell number and behavior even if the exact type, dose, and timing of administration are not the same in all studies. These adverse effects of prenatal AEDs appear to generalize to humans because brain size often is decreased by maternal AED use, but it does not always seem far less striking in humans than in rodents (Tables 1–3).

Less is known about the effects of AEDs on young animals that have acute or chronic seizures, although this is clearly an important population to address. One of the reasons why information is limited is related to the difficult dissociation between effects of AEDs vs. seizures; AEDs may directly alter somatic, cognitive and behavioral development, but AEDs may also do so indirectly — by reducing seizures. This leads to a clinical dilemma: which is worse, uncontrolled seizures or the potential adverse effects of chronic AED exposure? The hope is that in the future, epileptogenesis can be prevented or new drugs will be more effective and have fewer potential adverse effects.

In summary, the field is at a crossroad. It is an exciting time with more AEDs available than ever and some, apparently, with low teratogenicity, but data are still emerging. On the other hand, comprehensive studies and a current consensus are unavailable — for both humans and laboratory animals. The financial resources that are necessary to fill this gap will be a challenge because the number of subjects required to address AED type, dose, and follow-up is substantial. Fortunately, the methods are available to study development of the CNS and behavioral outcomes in detail in both children and animals.

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Table 1

Effects of prenatal or early life exposure to phenytoin in children and laboratory animals.

Phenytoin	Effects on offspring of maternal AED use		Effects on offspring of early postnatal use	
	Human	Rodent	Human	Rodent
Somatic				
General body size	Decreased	Decreased, high mortality		High mortality
Facial features	Mixed results			
Limbs, skeleton	Mixed results	Increased limb, spinal, and rib defects		
Developmental milestone		Delayed righting reflex and swimming		Delayed righting reflex
CNS				
General brain size		Decreased		Decreased brain weight
Specific brain areas				
Cerebellum				Fewer neurons
Hippocampus				Fewer neurons
Sensory systems		Impaired cliff avoidance	Transient visual disturbance	
Motor systems	Possible transient effects	Hyperactivity, circling behavior	Rare instances	Hyperactivity, impaired rotarod
Cognitive functions				
IQ, BMDI score	Mixed results			
Learning and memory		General impairments		General impairments
Behavior				
Mood (depression)			Increased apathy	
Attention deficits				
Autistic-like behavior				
Schizophrenia-like				
Anxiety		Impaired cliff avoidance	Increased anxiety	Possible hyperactivity in open field

Somatic, cognitive and behavioral effects are shown for prenatal exposure (left) and early postnatal exposure (right). The table indicates common findings, and where variability is noted, it may be due to differences in the study parameters/methods, doses, or times of exposure. References are provided in the text.

Abbreviation: BMDI, Bayley Mental Developmental Index.

Table 2

Effects of prenatal or early life exposure to phenobarbital in children and laboratory animals.

Phenobarbital	Effects on offspring of maternal AED use		Effects on offspring of early postnatal use	
	Human	Rodent	Human	Rodent
Somatic				
General body size	Mixed results	Decreased (*)		
Facial features	Mixed results—cleft palate			
Limbs, skeleton				
Developmental milestones			Delays on BMDI (*)	Impaired righting reflexes
CNS				
General brain size	Decreased head circumference	Decreased weight		Decreased weight
Specific brain areas				
Cerebellum		Decreased cell number		Decreased cell number/apoptosis; mismigration
Hippocampus		Decreased cell number		Decreased cell number/apoptosis; mismigration
Sensory systems				
Motor systems	Delayed neurological development	Decreased muscle, delayed swimming	Hyperactivity/reduced reaction times	Hyperactivity
Cognitive functions				
IQ, BMDI score	Decreased (*)		Decreased	
Learning and memory	Decreased (*)	General impairments	Transient, variable	General impairments
Behavior				
Mood (depression)			Fussiness, depression, irritability	
Attention deficits		Working memory impairments	Impaired concentration	Working memory impairments and attention
Autistic-like behavior		Decreased play behavior		
Schizophrenia-like				Impaired prepulse inhibition
Anxiety				Increased (*)

Somatic, cognitive and behavioral effects are shown for prenatal exposure (left) and early postnatal exposure (right). The table indicates common findings, and where variability is noted, it may be due to differences in the study parameters/methods, doses, or times of exposure.

* indicates presence of conflicting reports in the literature. References are provided in the text.

Abbreviations: BMDI, Bayley Mental Developmental Index.

Table 3

Effects of prenatal or early life exposure to valproate in children and laboratory animals.

Valproate	Effects on offspring of maternal AED use		Effects on offspring of early postnatal use	
	Human	Rodent	Human	Rodent
Somatic				
General body size	Decreased	Mixed results, high mortality	Short stature, high BMI	Decreased weight gain
Facial features	Dysmorphic			
Limbs, skeleton	Dysmorphic	Dysmorphic		
Developmental milestones	Decreased Apgar scores, motor delays	Delayed eye opening, righting reflexes		Delayed eye opening, righting reflexes
CNS				
General brain size	Decreased	Decreased		Decreased brain weight
Specific brain areas	Decreased gray matter			
Cerebellum		Decreased		High doses lead to apoptosis
Hippocampus				High doses lead to apoptosis
Sensory systems		Impaired olfaction, decreased pain	Impaired visuospatial function	
Motor systems	Hypertonia	Hyperactivity, impaired on rotarod	Impaired motor performance	Impaired fine motor performance
Cognitive functions				
IQ, BMDI score	Low IQ			
Learning and memory	Delayed	General impairments	Improvements (*)	General impairments
Behavior				
Mood (depression)	Increased depression			
Attention deficits	Poor attention			
Autistic-like behavior	6–8-fold increased risk	Decreased play, increased stereotypies		Decreased play
Schizophrenia-like		Pre-pulse inhibition deficits		Pre-pulse inhibition deficits
Anxiety	Perinatal distress/low adaptability	Increased anxiety-like behaviors		

Somatic, cognitive and behavioral effects are shown for prenatal exposure (left) and early postnatal exposure (right). The table indicates common findings, and where variability is noted, it may be due to differences in the study parameters/methods, doses, or times of exposure.

* indicates conflicting reports in the literature. References are provided in the text.

Abbreviation: BMDI, Bayley Mental Developmental Index.