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Review

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.

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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

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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

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.

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

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.

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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References

[1] Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics 2012;129(2):256–64. [Epub 2012/01/25].
[2] Hauser E, Freilinger M, Seidl R, Groh C. Prognosis of childhood epilepsy in newly referred patients. J Child Neurol 1996;11(3):201–4. [Epub 1996/05/01].
[3] Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc 1996;71(6):576–86. [Epub 1996/06/01].
[4] Borthen I, Eide MG, Veiby G, Daltveit AK, Gilhus NE. Complications during pregnancy in women with epilepsy: population-based cohort study. BJOG 2009;116(13):1736–42. [Epub 2009/09/29].
[5] Krishnamurthy KB. Managing epilepsy during pregnancy: assessing risk and optimizing care. Curr Treat Options Neurol 2012;14(4):348–55. [Epub 2012/06/20].
[6] Chu-Shore CJ, Thiele EA. New drugs for pediatric epilepsy. Semin Pediatr Neurol 2010;17(4):214–23. [Epub 2010/12/25].
[7] Quach MM, Mazin A, Riviello Jr JJ. Newer anticonvulsant medications in pediatric neurology. Curr Treat Options Neurol 2010;12(6):518–28. [Epub 2010/09/18].
[8] Verrotti A, Loiacono G, Coppola G, Spalice A, Mohn A, Chiarelli F. Pharmacotherapy for children and adolescents with epilepsy. Expert Opin Pharmacother 2011;12(2):175–94. [Epub 2011/01/07].
[9] Canger R, Battino D, Canevini MP, et al. Malformations in offspring of women with epilepsy: a prospective study. Epilepsia 1999;40(9):1231–6. [Epub 1999/09/16].
[10] Modi AC, Ingerski LM, Rausch JR, Glauser TA. Treatment factors affecting longitudinal quality of life in new onset pediatric epilepsy. J Pediatr Psychol 2011;36(4):466–75. [Epub 2011/02/01].
[11] Modi AC, Rausch JR, Glauser TA. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. JAMA 2011;305(16):1669–76. [Epub 2011/04/28].
[12] Oguni H. Treatment of benign focal epilepsies in children: when and how should be treated? Brain Dev 2011;33(3):207–12. [Epub 2010/11/26].
[13] Barzago MM, Bortolotti A, Stellari FF, et al. Placental transfer of valproic acid after liposome encapsulation during in vitro human placenta perfusion. J Pharmacol Exp Ther 1996;277(1):79–86. [Epub 1996/04/01].
[14] Hovinga CA, Pennell PB. Antiepileptic drug therapy in pregnancy II: fetal and neonatal exposure. Int Rev Neurobiol 2008;83:241–58. [Epub 2008/10/22].
[15] Pennell PB, Hovinga CA. Antiepileptic drug therapy in pregnancy I: gestation-induced effects on AED pharmacokinetics. Int Rev Neurobiol 2008;83:227–40. [Epub 2008/10/22].
[16] De Santis M, De Luca C, Mappa I, et al. Antiepileptic drugs during pregnancy: pharmacokinetics and transplacental transfer. Curr Pharm Biotechnol 2011;12(5):781–8. [Epub 2011/02/24].
[17] Hill DS, Wlodarczyk BJ, Palacios AM, Finnell RH. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 2010;10(6):943–59. [Epub 2010/06/04].
[18] Vajda FJ, Hitchcock AA, Graham J, O'Brien TJ, Lander CM, Eadie MJ. The teratogenic risk of antiepileptic drug polytherapy. Epilepsia 2010;51(5):805–10. [Epub 2009/10/13].
[19] Hanson JW, Smith DW. Fetal hydantoin syndrome. Lancet 1976;1(7961):692. [Epub 1976/03/27].
[20] Hanson JW, Buehler BA. Fetal hydantoin syndrome: current status. J Pediatr 1982;101(5):816–8. [Epub 1982/11/01].
[21] Pennell PB, Klein AM, Browning N, et al. Differential effects of antiepileptic drugs on neonatal outcomes. Epilepsy Behav 2012;24(4):449–56. [Epub 2012/07/04].
[22] Nulman I, Scolnik D, Chitayat D, Farkas LD, Koren G. Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. Am J Med Genet 1997;68(1):18–24. [Epub 1997/01/10].
[23] Ornoy A. Neuroteratogens in man: an overview with special emphasis on the teratogenicity of antiepileptic drugs in pregnancy. Reprod Toxicol 2006;22(2):214–26. [Epub 2006/04/20].
[24] Hanson JW, Myrianthopoulos NC, Harvey MA, Smith DW. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr 1976;89(4):662–8. [Epub 1976/10/01].
[25] Lindhout D, Omtzigt JG. Pregnancy and the risk of teratogenicity. Epilepsia 1992;33(Suppl. 4):S41–8. [Epub 1992/01/01].
[26] Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, Koppe JG, Poll NE, Boer K. Association of prenatal phenobarbital and phenytoin exposure with genital anomalies and menstrual disorders. Teratology 2001;64(4):181–8. [Epub 2001/10/13].
[27] Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, Koppe JG, van De Poll NE, Boer K. Association of prenatal phenobarbital and phenytoin exposure with small head size at birth and with learning problems. Acta Paediatr 2000;89(5):533–41. [Epub 2000/06/14].
[28] Juarez-Olguin H, Belmont-Gomez A, Flores-Perez J, Barranco-Garduno LM, Flores-Perez C. Malformations in newborns associated to anticonvulsant consumption during pregnancy. Experience in third level hospital of Mexico. Rev Invest Clin 2008;60(1):15–20. [Epub 2008/07/01].
[29] Wide K, Winbladh B, Tomson T, Kallen B. Body dimensions of infants exposed to antiepileptic drugs in utero: observations spanning 25 years. Epilepsia 2000;41(7):854–61. [Epub 2000/07/18].
[30] Meyer JG. The teratological effects of anticonvulsants and the effects on pregnancy and birth. Eur Neurol 1973;10(3):179–90. [Epub 1973/01/01].
[31] Samren EB, van Duijn CM, Christiaens GC, Hofman A, Lindhout D. Antiepileptic drug regimens and major congenital abnormalities in the offspring. Ann Neurol 1999;46(5):739–46. [Epub 1999/11/30].
[32] Artama M, Auvinen A, Raudaskoski T, Isojarvi I, Isojarvi J. Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology 2005;64(11):1874–8. [Epub 2005/06/16].
[33] McMullin GP. Teratogenic effects of anticonvulsants. Br Med J 1971;4(5784):430. [Epub 1971/11/13].
[34] Shapiro S, Hartz SC, Siskind V, et al. Anticonvulsants and parental epilepsy in the development of birth defects. Lancet 1976;1(7954):272–5. [Epub 1976/02/07].
[35] Waters CH, Belai Y, Gott PS, Shen P, De Giorgio CM. Outcomes of pregnancy associated with antiepileptic drugs. Arch Neurol 1994;51(3):250–3. [Epub 1994/03/01].
[36] Olafsson E, Hallgrimsson JT, Hauser WA, Ludvigsson P, Gudmundsson G. Pregnancies of women with epilepsy: a population-based study in Iceland. Epilepsia 1998;39(8):887–92. [Epub 1998/08/13].
[37] Arpino C, Brescianini S, Robert E, et al. Teratogenic effects of antiepileptic drugs: use of an International Database on Malformations and Drug Exposure (MADRE). Epilepsia 2000;41(11):1436–43. [Epub 2000/11/15].
[38] Battino D, Kaneko S, Andermann E, et al. Intrauterine growth in the offspring of epileptic women: a prospective multicenter study. Epilepsy Res 1999;36(1):53–60. [Epub 1999/08/27].
[39] Jones KL, Jonhson KA, Chambers CC. Pregnancy outcome in women treated with phenobarbital monotherapy. Teratology 1992;45:453–4.
[40] Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001;344(15):1132–8. [Epub 2001/04/12].
[41] Scharfman HE, Malthankar-Phatak GH, Friedman D, et al. A rat model of epilepsy in women: a tool to study physiological interactions between endocrine systems and seizures. Endocrinology 2009;150(9):4437–42. [Epub 2009/05/16].
[42] Raffo E, de Vasconcelos AP, Boehrer A, Desor D, Nehlig A. Neurobehavioral maturation of offspring from epileptic dams: study in the rat lithium–pilocarpine model. Exp Neurol 2009;219(2):414–23. [Epub 2009/07/01].
[43] do Vale TG, da Silva AV, Lima DC, et al. Seizures during pregnancy modify the development of hippocampal interneurons of the offspring. Epilepsy Behav 2010;19(1):20–5. [Epub 2010/08/17].
[44] Lima DC, Vale TG, Arganaraz GA, et al. Behavioral evaluation of adult rats exposed in utero to maternal epileptic seizures. Epilepsy Behav 2010;18(1–2):45–9. [Epub 2010/05/13].
[45] Lima DC, Cossa AC, Perosa SR, et al. Neuroglobin is up-regulated in the cerebellum of pups exposed to maternal epileptic seizures. Int J Dev Neurosci 2011;29(8):891–7. [Epub 2011/07/20].
[46] Vajda FJ, O'Brien TJ, Hitchcock A, et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. J Clin Neurosci 2004;11(8):854–8. [Epub 2004/11/03].
[47] Vajda F, Lander C, O'Brien T, et al. Australian pregnancy registry of women taking antiepileptic drugs. Epilepsia 2004;45(11):1466. [Epub 2004/10/29].
[48] Kaneko S, Battino D, Andermann E, et al. Congenital malformations due to antiepileptic drugs. Epilepsy Res 1999;33(2–3):145–58. [Epub 1999/03/27].
[49] Robert E, Guibaud P. Maternal valproic acid and congenital neural tube defects. Lancet 1982;2(8304):937. [Epub 1982/10/23].

[50] DiLiberti JH, Farndon PA, Dennis NR, Curry CJ. The fetal valproate syndrome. Am J Med Genet 1984;19(3):473–81. [Epub 1984/11/01].
[51] Ardinger HH, Atkin JF, Blackston RD, et al. Verification of the fetal valproate syndrome phenotype. Am J Med Genet 1988;29(1):171–85. [Epub 1988/01/01].
[52] Gigantelli JW, Braddock SR, Johnson LN. Blepharoptosis and central nervous system abnormalities in combined valproate and hydantoin embryopathy. Ophthal Plast Reconstr Surg 2000;16(1):52–4. [Epub 2000/02/16].
[53] Moore SJ, Turnpenny P, Quinn A, et al. A clinical study of 57 children with fetal anticonvulsant syndromes. J Med Genet 2000;37(7):489–97. [Epub 2000/07/07].
[54] Bescoby-Chambers N, Forster P, Bates G. Foetal valproate syndrome and autism: additional evidence of an association. Dev Med Child Neurol 2001;43(12):847. [Epub 2002/01/05].
[55] Lajeunie E, Barcik U, Thorne JA, El Ghouzzi V, Bourgeois M, Renier D. Craniosynostosis and fetal exposure to sodium valproate. J Neurosurg 2001;95(5):778–82. [Epub 2001/11/13].
[56] McMahon CL, Braddock SR. Septo-optic dysplasia as a manifestation of valproic acid embryopathy. Teratology 2001;64(2):83–6. [Epub 2001/07/19].
[57] Williams G, King J, Cunningham M, Stephan M, Kerr B, Hersh JH. Fetal valproate syndrome and autism: additional evidence of an association. Dev Med Child Neurol 2001;43(3):202–6. [Epub 2001/03/27].
[58] Holmes LB. Teratogen-induced limb defects. Am J Med Genet 2002;112(3): 297–303. [Epub 2002/10/03].
[59] Meador KJ. Neurodevelopmental effects of antiepileptic drugs. Curr Neurol Neurosci Rep 2002;2(4):373–8. [Epub 2002/06/05].
[60] Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005;64(6):961–5. [Epub 2005/03/23].
[61] Hiilesmaa VK, Teramo K, Granstrom ML, Bardy AH. Fetal head growth retardation associated with maternal antiepileptic drugs. Lancet 1981;2(8239):165–7. [Epub 1981/07/25].
[62] Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. N Engl J Med 1991;324(10):674–7. [Epub 1991/03/07].
[63] Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA 1994;271(10): 767–70. [Epub 1994/03/09].
[64] Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Is carbamazepine teratogenic? A prospective controlled study of 210 pregnancies. Neurology 2001;57(2):321–4. [Epub 2001/07/27].
[65] Matalon S, Schechtman S, Goldzweig G, Ornoy A. The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures. Reprod Toxicol 2002;16(1):9–17. [Epub 2002/04/06].
[66] Jones KL, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. N Engl J Med 1989;320(25):1661–6. [Epub 1989/06/22].
[67] Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. Arch Dis Child 1996;75(6):517–20. [Epub 1996/12/01].
[68] Diav-Citrin O, Shechtman S, Gotteiner T, Arnon J, Ornoy A. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. Teratology 2001;63(5):186–92. [Epub 2001/04/26].
[69] Czeizel AE, Bod M, Halasz P. Evaluation of anticonvulsant drugs during pregnancy in a population-based Hungarian study. Eur J Epidemiol 1992;8(1):122–7. [Epub 1992/01/01].
[70] Meischenguiser R, D'Giano CH, Ferraro SM. Oxcarbazepine in pregnancy: clinical experience in Argentina. Epilepsy Behav 2004;5(2):163–7. [Epub 2004/05/05].
[71] Montouris G. Safety of the newer antiepileptic drug oxcarbazepine during pregnancy. Curr Med Res Opin 2005;21(5):693–701. [Epub 2005/06/23].
[72] Artama M, Ritvanen A, Gissler M, Isojarvi J, Auvinen A. Congenital structural anomalies in offspring of women with epilepsy—a population-based cohort study in Finland. Int J Epidemiol 2006;35(2):280–7. [Epub 2005/11/11].
[73] Lindhout D. Pharmacogenetics and drug interactions: role in antiepileptic-drug-induced teratogenesis. Neurology 1992;42(4 Suppl. 5):43–7. [Epub 1992/04/01].
[74] Lindhout D, Meinardi H, Meijer JW, Nau H. Antiepileptic drugs and teratogenesis in two consecutive cohorts: changes in prescription policy paralleled by changes in pattern of malformations. Neurology 1992;42(4 Suppl 5):94–110. [Epub 1992/04/01].
[75] Kaaja E, Kaaja R, Hiilesmaa V. Major malformations in offspring of women with epilepsy. Neurology 2003;60(4):575–9. [Epub 2003/02/26].
[76] Vajda FJ, Graham JE, Hitchcock AA, O'Brien TJ, Lander CM, Eadie MJ. Is lamotrigine a significant human teratogen? Observations from the Australian Pregnancy Register. Seizure 2010;19(9):558–61. [Epub 2010/08/27].
[77] Cunnington MC, Weil JG, Messenheimer JA, Ferber S, Yerby M, Tennis P. Final results from 18 years of the International Lamotrigine Pregnancy Registry. Neurology 2011;76(21):1817–23. [Epub 2011/05/25].
[78] Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10(7):609–17. [Epub 2011/06/10].
[79] Sabers A, Dam M, AR-H B, et al. Epilepsy and pregnancy: lamotrigine as main drug used. Acta Neurol Scand 2004;109(1):9–13. [Epub 2003/12/05].
[80] Gaily E, Granstrom ML, Hiilesmaa V, Bardy A. Minor anomalies in offspring of epileptic mothers. J Pediatr 1988;112(4):520–9. [Epub 1988/04/01].
[81] Gaily E, Kantola-Sorsa E, Granstrom ML. Intelligence of children of epileptic mothers. J Pediatr 1988;113(4):677–84. [Epub 1988/10/01].
[82] Adams J, Vorhees CV, Middaugh LD. Developmental neurotoxicity of anticonvulsants: human and animal evidence on phenytoin. Neurotoxicol Teratol 1990;12(3):203–14. [Epub 1990/05/01].
[83] van der Pol MC, Hadders-Algra M, Huisjes HJ, Touwen BC. Antiepileptic medication in pregnancy: late effects on the children's central nervous system development. Am J Obstet Gynecol 1991;164(1 Pt 1):121–8. [Epub 1991/01/01].
[84] Vanoverloop D, Schnell RR, Harvey EA, Holmes LB. The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. Neurotoxicol Teratol 1992;14(5):329–35. [Epub 1992/09/01].
[85] Dean JC, Hailey H, Moore SJ, Lloyd DJ, Turnpenny PD, Little J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. J Med Genet 2002;39(4):251–9. [Epub 2002/04/16].
[86] Vinten J, Adab N, Kini U, Gorry J, Gregg J, Baker GA. Neuropsychological effects of exposure to anticonvulsant medication in utero. Neurology 2005;64(6):949–54. [Epub 2005/03/23].
[87] Wide K, Winbladh B, Tomson T, Sars-Zimmer K, Berggren E. Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. Dev Med Child Neurol 2000;42(2):87–92. [Epub 2000/03/04].
[88] Wide K, Henning E, Tomson T, Winbladh B. Psychomotor development in preschool children exposed to antiepileptic drugs in utero. Acta Paediatr 2002;91(4):409–14. [Epub 2002/06/14].
[89] Koch S, Titze K, Zimmermann RB, Schroder M, Lehmkuhl U, Rauh H. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia 1999;40(9):1237–43. [Epub 1999/09/16].
[90] Reinisch JM, Sanders SA, Mortensen EL, Rubin DB. In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA 1995;274(19):1518–25. [Epub 1995/11/15].
[91] Leavitt AM, Yerby MS, Robinson N, Sells CJ, Erickson DM. Epilepsy in pregnancy: developmental outcome of offspring at 12 months. Neurology 1992;42(4 Suppl 5): 141–3. [Epub 1992/04/01].
[92] Holmes LB, Coull BA, Dorfman J, Rosenberger PB. The correlation of deficits in IQ with midface and digit hypoplasia in children exposed in utero to anticonvulsant drugs. J Pediatr 2005;146(1):118–22. [Epub 2005/01/13].
[93] Koch S, Jager-Roman E, Losche G, Nau H, Rating D, Helge H. Antiepileptic drug treatment in pregnancy: drug side effects in the neonate and neurological outcome. Acta Paediatr 1996;85(6):739–46. [Epub 1996/06/01].
[94] Shankaran S, Woldt E, Nelson J, Bedard M, Delaney-Black V. Antenatal phenobarbital therapy and neonatal outcome. II: Neurodevelopmental outcome at 36 months. Pediatrics 1996;97(5):649–52. [Epub 1996/05/01].
[95] Christianson AL, Chesler N, Kromberg JG. Fetal valproate syndrome: clinical and neuro-developmental features in two sibling pairs. Dev Med Child Neurol 1994;36(4):361–9. [Epub 1994/04/01].
[96] Rasalam AD, Hailey H, Williams JH, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 2005;47(8):551–5. [Epub 2005/08/20].
[97] Bromley RL, Mawer G, Clayton-Smith J, Baker GA. Autism spectrum disorders following in utero exposure to antiepileptic drugs. Neurology 2008;71(23): 1923–4. [Epub 2008/12/03].
[98] Jager-Roman E, Deichl A, Jakob S, et al. Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. J Pediatr 1986;108(6):997–1004. [Epub 1986/06/01].
[99] Meador KJ, Baker G, Cohen MJ, Gaily E, Westerveld M. Cognitive/behavioral teratogenetic effects of antiepileptic drugs. Epilepsy Behav 2007;11(3):292–302. [Epub 2007/11/13].
[100] Vinten J, Bromley RL, Taylor J, Adab N, Kini U, Baker GA. The behavioral consequences of exposure to antiepileptic drugs in utero. Epilepsy Behav 2009;14(1): 197–201. [Epub 2008/11/11].
[101] Adab N, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001;70(1): 15–21. [Epub 2000/12/16].
[102] Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004;75(11):1575–83. [Epub 2004/10/20].
[103] Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004;62(1):28–32. [Epub 2004/01/14].
[104] Eriksson K, Viinikainen K, Monkkonen A, et al. Children exposed to valproate in utero—population based evaluation of risks and confounding factors for long-term neurocognitive development. Epilepsy Res 2005;65(3):189–200. [Epub 2005/07/21].
[105] Thomas SV, Ajaykumar B, Sindhu K, Nair MK, George B, Sarma PS. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy Behav 2008;13(1):229–36. [Epub 2008/03/19].
[106] Bromley RL, Mawer G, Love J, et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010;51(10):2058–65. [Epub 2010/07/17].
[107] Viinikainen K, Eriksson K, Monkkonen A, et al. The effects of valproate exposure in utero on behavior and the need for educational support in school-aged children. Epilepsy Behav 2006;9(4):636–40. [Epub 2006/10/20].
[108] Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills of school-aged children prenatally exposed to antiepileptic drugs. Neurology 2011;76(8):719–26. [Epub 2011/02/23].
[109] Nadebaum C, Anderson V, Vajda F, Reutens D, Barton S, Wood A. The Australian brain and cognition and antiepileptic drugs study: IQ in school-aged children exposed to sodium valproate and polytherapy. J Int Neuropsychol Soc 2011;17(1): 133–42. [Epub 2010/11/26].
[110] Meador KJ, Baker GA, Browning N, et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. Neurology 2012;78(16):1207–14. [Epub 2012/04/12].

[111] Sankar R, Painter MJ. Neonatal seizures: after all these years we still love what doesn't work. Neurology 2005;64(5):776–7. [Epub 2005/03/09].
[112] Mikkonen K, Knip M, Pakarinen AJ, Lanning P, Isojarvi JI, Vainionpaa LK. Growth and lipid metabolism in girls and young women with epilepsy during pubertal maturation. Epilepsia 2005;46(7):1114–20. [Epub 2005/07/20].
[113] El-Khayat HA, Aly GS, Tomoum HY, Mamdouh RM, Al-Badani AK, Mohamed EI. Growth hormone levels in children and adolescents with epilepsy. Eur J Paediatr Neurol 2010;14(6):508–12. [Epub 2010/03/17].
[114] Demir E, Aysun S. Weight gain associated with valproate in childhood. Pediatr Neurol 2000;22(5):361–4. [Epub 2000/07/29].
[115] Wirrell EC. Valproic acid-associated weight gain in older children and teens with epilepsy. Pediatr Neurol 2003;28(2):126–9. [Epub 2003/04/18].
[116] El-Khayat HA, Abd El-Basset FZ, Tomoum HY, et al. Physical growth and endocrinal disorders during pubertal maturation in girls with epilepsy. Epilepsia 2004;45(9):1106–15. [Epub 2004/08/27].
[117] Grosso S, Mostardini R, Piccini B, Balestri P. Body mass index and serum lipid changes during treatment with valproic acid in children with epilepsy. Ann Pharmacother 2009;43(1):45–50. [Epub 2008/12/11].
[118] Verrotti A, D'Egidio C, Coppola G, Parisi P, Chiarelli F. Epilepsy, sex hormones and antiepileptic drugs in female patients. Expert Rev Neurother 2009;9(12): 1803–14. [Epub 2009/12/03].
[119] Verrotti A, Laus M, Scardapane A, Franzoni E, Chiarelli F. Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate. Eur J Endocrinol 2009;160(1):81–6. [Epub 2008/11/06].
[120] Verrotti A, la Torre R, Trotta D, Mohn A, Chiarelli F. Valproate-induced insulin resistance and obesity in children. Horm Res 2009;71(3):125–31. [Epub 2009/02/04].
[121] Masuccio F, Verrotti A, Chiavaroli V, et al. Weight gain and insulin resistance in children treated with valproate: the influence of time. J Child Neurol 2010;25(8): 941–7. [Epub 2010/03/09].
[122] Cansu A, Serdaroglu A, Camurdan O, Hirfanoglu T, Cinaz P. Serum insulin, cortisol, leptin, neuropeptide Y, galanin and ghrelin levels in epileptic children receiving valproate. Horm Res Paediatr 2011;76(1):65–71. [Epub 2011/06/11].
[123] Gungor S, Yucel G, Akinci A, Tabel Y, Ozerol IH, Yologlu S. The role of ghrelin in weight gain and growth in epileptic children using valproate. J Child Neurol 2007;22(12):1384–8. [Epub 2008/01/05].
[124] Crepeau AZ, Moseley BD, Wirrell EC. Specific safety and tolerability considerations in the use of anticonvulsant medications in children. Drug Healthc Patient Saf 2012;4:39–54. [Epub 2012/07/14].
[125] Bos K, Zeanah CH, Fox NA, Drury SS, McLaughlin KA, Nelson CA. Psychiatric outcomes in young children with a history of institutionalization. Harv Rev Psychiatry 2011;19(1):15–24. [Epub 2011/01/22].
[126] Glauser TA. Behavioral and psychiatric adverse events associated with antiepileptic drugs commonly used in pediatric patients. J Child Neurol 2004;19(Suppl. 1): S25–38. [Epub 2004/11/06].
[127] Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. Epilepsia 1988;29(6):794–804. [Epub 1988/11/01].
[128] de Silva M, MacArdle B, McGowan M, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. Lancet 1996;347(9003): 709–13. [Epub 1996/03/16].
[129] Thilothammal N, Banu K, Ratnam RS. Comparison of phenobarbitone, phenytoin with sodium valproate: randomized, double-blind study. Indian Pediatr 1996;33(7):549–55. [Epub 1996/07/01].
[130] Guerreiro MM, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res 1997;27(3):205–13. [Epub 1997/06/01].
[131] Pal DK, Das T, Chaudhury G, Johnson AL, Neville BG. Randomised controlled trial to assess acceptability of phenobarbital for childhood epilepsy in rural India. Lancet 1998;351(9095):19–23. [Epub 1998/01/20].
[132] Aman MG, Werry JS, Paxton JW, Turbott SH. Effects of phenytoin on cognitive–motor performance in children as a function of drug concentration, seizure type, and time of medication. Epilepsia 1994;35(1):172–80. [Epub 1994/01/01].
[133] Marin LL, Garcia-Penas JJ, Herguedas JL, et al. Phenytoin-induced visual disturbances mimicking Delirium Tremens in a child. Eur J Paediatr Neurol 2011;14(5): 460–3. [Epub 2010/08/24].
[134] Verrotti A, Manco R, Matricardi S, Franzoni E, Chiarelli F. Antiepileptic drugs and visual function. Pediatr Neurol 2007;36(6):353–60. [Epub 2007/06/15].
[135] Camfield CS, Chaplin S, Doyle AB, Shapiro SH, Cummings C, Camfield PR. Side effects of phenobarbital in toddlers; behavioral and cognitive aspects. J Pediatr 1979;95(3):361–5. [Epub 1979/09/01].
[136] Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. N Engl J Med 1990;322(6):364–9. [Epub 1990/02/08].
[137] Thorp JA, O'Connor M, Jones AM, Hoffman EL, Belden B. Does perinatal phenobarbital exposure affect developmental outcome at age 2? Am J Perinatol 1999;16(2):51–60. [Epub 1999/06/04].
[138] Thorp JA, O'Connor M, Belden B, Etzenhouser J, Hoffman EL, Jones PG. Effects of phenobarbital and multiple-dose corticosteroids on developmental outcome at age 7 years. Obstet Gynecol 2003;101(2):363–73. [Epub 2003/02/11].
[139] Mitchell WG, Chavez JM. Carbamazepine versus phenobarbital for partial onset seizures in children. Epilepsia 1987;28(1):56–60. [Epub 1987/01/01].
[140] Calandre EP, Dominguez-Granados R, Gomez-Rubio M, Molina-Font JA. Cognitive effects of long-term treatment with phenobarbital and valproic acid in school children. Acta Neurol Scand 1990;81(6):504–6. [Epub 1990/06/01].
[141] Chen YJ, Kang WM, So WC. Comparison of antiepileptic drugs on cognitive function in newly diagnosed epileptic children: a psychometric and neurophysiological study. Epilepsia 1996;37(1):81–6. [Epub 1996/01/01].
[142] Chen Y, Chi Chow J, Lee I. Comparison the cognitive effect of anti-epileptic drugs in seizure-free children with epilepsy before and after drug withdrawal. Epilepsy Res 2001;44(1):65–70. [Epub 2001/03/20].
[143] Wolf SM, Carr A, Davis DC, et al. The value of phenobarbital in the child who has had a single febrile seizure: a controlled prospective study. Pediatrics 1977;59(3):378–85. [Epub 1977/03/01].
[144] Knudsen FU, Vestermark S. Prophylactic diazepam or phenobarbitone in febrile convulsions: a prospective, controlled study. Arch Dis Child 1978;53(8):660–3. [Epub 1978/08/01].
[145] Wolf SM, Forsythe A. Behavior disturbance, phenobarbital, and febrile seizures. Pediatrics 1978;61(5):728–31. [Epub 1978/05/01].
[146] Herranz JL, Armijo JA, Arteaga R. Effectiveness and toxicity of phenobarbital, primidone, and sodium valproate in the prevention of febrile convulsions, controlled by plasma levels. Epilepsia 1984;25(1):89–95. [Epub 1984/02/01].
[147] Willis J, Nelson A, Black FW, Borges A, An A, Rice J. Barbiturate anticonvulsants: a neuropsychological and quantitative electroencephalographic study. J Child Neurol 1997;12(3):169–71. [Epub 1997/04/01].
[148] Brent DA, Crumrine PK, Varma RR, Allan M, Allman C. Phenobarbital treatment and major depressive disorder in children with epilepsy. Pediatrics 1987;80(6): 909–17. [Epub 1987/12/01].
[149] Ferrari M, Barabas G, Matthews WS. Psychologic and behavioral disturbance among epileptic children treated with barbiturate anticonvulsants. Am J Psychiatry 1983;140(1):112–3. [Epub 1983/01/01].
[150] Vining EP. Cognitive dysfunction associated with antiepileptic drug therapy. Epilepsia 1987;28(Suppl. 2):S18–22. [Epub 1987/01/01].
[151] Vining EP, Mellitis ED, Dorsen MM, et al. Psychologic and behavioral effects of antiepileptic drugs in children: a double-blind comparison between phenobarbital and valproic acid. Pediatrics 1987;80(2):165–74. [Epub 1987/08/01].
[152] Trimble MR, Thompson PJ. Sodium valproate and cognitive function. Epilepsia 1984;25(Suppl. 1):S60–4. [Epub 1984/01/01].
[153] Jessberger S, Nakashima K, Clemenson Jr GD, et al. Epigenetic modulation of seizure-induced neurogenesis and cognitive decline. J Neurosci 2007;27(22): 5967–75. [Epub 2007/06/01].
[154] Sommerbeck KW, Theilgaard A, Rasmussen KE, Lohren V, Gram L, Wulff K. Valproate sodium: evaluation of so-called psychotropic effect. A controlled study. Epilepsia 1977;18(2):159–67. [Epub 1977/06/01].
[155] Meador KJ. Newer anticonvulsants: dosing strategies and cognition in treating patients with mood disorders and epilepsy. J Clin Psychiatry 2003;64(Suppl. 8):30–4. [Epub 2003/08/02].
[156] Reith D, Burke C, Appleton DB, Wallace G, Pelekanos J. Tolerability of topiramate in children and adolescents. J Paediatr Child Health 2003;39(6):416–9. [Epub 2003/08/16].
[157] Meador KJ, Loring DW, Vahle VJ, et al. Cognitive and behavioral effects of lamotrigine and topiramate in healthy volunteers. Neurology 2005;64(12): 2108–14. [Epub 2005/06/30].
[158] Briggs DE, French JA. Levetiracetam safety profiles and tolerability in epilepsy patients. Expert Opin Drug Saf 2004;3(5):415–24. [Epub 2004/09/01].
[159] Ikonomidou C, Turski L. Antiepileptic drugs and brain development. Epilepsy Res 2010;88(1):11–22. [Epub 2009/10/15].
[160] Vorhees CV. Fetal anticonvulsant syndrome in rats: dose– and period–response relationships of prenatal diphenylhydantoin, trimethadione and phenobarbital exposure on the structural and functional development of the offspring. J Pharmacol Exp Ther 1983;227(2):274–87. [Epub 1983/11/01].
[161] Vorhees CV. Fetal anticonvulsant syndrome in rats: effects on postnatal behavior and brain amino acid content. Neurobehav Toxicol Teratol 1985;7(5):471–82. [Epub 1985/09/01].
[162] Sharp PE, LaRegina MC. The laboratory rat. Florida: CRC Press LLC; 1998.
[163] Elmazar MM, Sullivan FM. Effect of prenatal phenytoin administration on postnatal development of the rat: a behavioral teratology study. Teratology 1981;24(2): 115–24. [Epub 1981/10/01].
[164] Orup Jr HI, Holmes LB, Keith DA, Coull BA. Craniofacial skeletal deviations following in utero exposure to the anticonvulsant phenytoin: monotherapy and polytherapy. Orthod Craniofac Res 2003;6(1):2–19. [Epub 2003/03/12].
[165] Abel EL, Tan SE, Subramanian M. Effects of delta 9-tetrahydrocannabinol, phenobarbital, and their combination on pregnancy and offspring in rats. Teratology 1987;36(2):193–8. [Epub 1987/10/01].
[166] Middaugh LD, Thomas TN, Simpson LW, Zemp JW. Effects of prenatal maternal injections of phenobarbital on brain neurotransmitters and behavior of young C57 mice. Neurobehav Toxicol Teratol 1981;3(3):271–5. [Epub 1981/01/01].
[167] Sedowofia SK, Innes J, Alleva E, Manning A, Clayton RM. Differential effects of prenatal exposure to phenobarbital on the behaviour and neurochemistry of CBA and C57BL/6J mice. Psychopharmacology (Berl) 1989;97(1): 123–30.
[168] Ihemelandu EC. Effect of maternal phenobarbital consumption on muscle development in mice. Acta Anat (Basel) 1993;148(1):22–6. [Epub 1993/01/01].
[169] Yanai J, Woolf M, Feigenbaum JJ. Morphological alterations in the medial preoptic area after prenatal administration of phenobarbital. Acta Anat (Basel) 1982;114(4):347–54. [Epub 1982/01/01].
[170] Yanai J, Rosselli-Austin L, Tabakoff B. Neuronal deficits in mice following prenatal exposure to phenobarbital. Exp Neurol 1979;64(2):237–44. [Epub 1979/05/01].
[171] Yanai J, Bergman A. Neuronal deficits after neonatal exposure to phenobarbital. Exp Neurol 1981;73(1):199–208. [Epub 1981/07/01].

[172] Yanai J, Iser C. Stereologic study of Purkinje cells in mice after early exposure to phenobarbital. Exp Neurol 1981;74(3):707–16. [Epub 1981/12/01].
[173] Yanai J, Fares F, Gavish M, et al. Neural and behavioral alterations after early exposure to phenobarbital. Neurotoxicology 1989;10(3):543–54. [Epub 1989/01/01].
[174] Bergman A, Roselli-Austin L, Yedwab G, Yanai J. Neuronal deficits in mice following phenobarbital exposure during various periods in fetal development. Acta Anat (Basel) 1980;108(3):370–3. [Epub 1980/01/01].
[175] Frisch C, Husch K, Angenstein F, et al. Dose-dependent memory effects and cerebral volume changes after in utero exposure to valproate in the rat. Epilepsia 2009;50(6):1432–41. [Epub 2009/04/21].
[176] Dufour-Rainfray D, Vourc'h P, Le Guisquet AM, et al. Behavior and serotonergic disorders in rats exposed prenatally to valproate: a model for autism. Neurosci Lett 2010;47(1):55–9. [Epub 2009/12/29].
[177] Schneider T, Przewlocki R. Behavioral alterations in rats prenatally exposed to valproic acid: animal model of autism. Neuropsychopharmacology 2005;30(1):80–9. [Epub 2004/07/09].
[178] Roullet FI, Wollaston L, Decatanzaro D, Foster JA. Behavioral and molecular changes in the mouse in response to prenatal exposure to the anti-epileptic drug valproic acid. Neuroscience 2010;170(2):514–22. [Epub 2010/07/07].
[179] Paulson RB, Sucheston ME, Hayes TG, Paulson GW. Teratogenic effects of valproate in the CD-1 mouse fetus. Arch Neurol 1985;42(10):980–3. [Epub 1985/10/01].
[180] Padmanabhan R, Hameed MS. Exencephaly and axial skeletal malformations induced by maternal administration of sodium valproate in the MF1 mouse. J Craniofac Genet Dev Biol 1994;14(3):192–205. [Epub 1994/07/01].
[181] Faiella A, Wernig M, Consalez GG, et al. A mouse model for valproate teratogenicity: parental effects, homeotic transformations, and altered HOX expression. Hum Mol Genet 2000;9(2):227–36. [Epub 1999/12/23].
[182] Massa V, Cabrera RM, Menegola E, Giavini E, Finnell RH. Valproic acid-induced skeletal malformations: associated gene expression cascades. Pharmacogenet Genomics 2005;15(11):787–800. [Epub 2005/10/13].
[183] Menegola E, Di Renzo F, Broccia ML, et al. Inhibition of histone deacetylase activity on specific embryonic tissues as a new mechanism for teratogenicity. Birth Defects Res B Dev Reprod Toxicol 2005;74(5):392–8. [Epub 2005/09/30].
[184] Ingram JL, Peckham SM, Tisdale B, Rodier PM. Prenatal exposure of rats to valproic acid reproduces the cerebellar anomalies associated with autism. Neurotoxicol Teratol 2000;22(3):319–24. [Epub 2000/06/07].
[185] Vorhees CV. Teratogenicity and developmental toxicity of valproic acid in rats. Teratology 1987;35(2):195–202. [Epub 1987/04/01].
[186] Schilling MA, Inman SL, Morford LL, Moran MS, Vorhees CV. Prenatal phenytoin exposure and spatial navigation in offspring: effects on reference and working memory and on discrimination learning. Neurotoxicol Teratol 1999;21(5):567–78. [Epub 1999/09/24].
[187] Shore CO, Vorhees CV, Bornschein RL, Stemmer K. Behavioral consequences of prenatal diazepam exposure in rats. Neurobehav Toxicol Teratol 1983;5(5):565–70. [Epub 1983/09/01].
[188] Vorhees CV, Rindler JM, Minck DR. Effects of exposure period and nutrition on the developmental neurotoxicity of anticonvulsants in rats: short and long-term effects. Neurotoxicology 1990;11(2):273–83. [Epub 1990/01/01].
[189] Weisenburger WP, Minck DR, Acuff KD, Vorhees CV. Dose–response effects of prenatal phenytoin exposure in rats: effects on early locomotion, maze learning, and memory as a function of phenytoin-induced circling behavior. Neurotoxicol Teratol 1990;12(2):145–52. [Epub 1990/03/01].
[190] Kleinberger N, Yanai J. Early phenobarbital-induced alterations in hippocampal acetylcholinesterase activity and behavior. Brain Res 1985;354(1):113–23. [Epub 1985/09/01].
[191] Picker M, Thomas J, Koch C, Poling A. Effects of phenytoin, phenobarbital, and valproic acid, alone and in selected combinations, on schedule-controlled behavior of rats. Pharmacol Biochem Behav 1985;22(3):389–93. [Epub 1985/03/01].
[192] Yanai J, Pick CG. Studies on noradrenergic alterations in relation to early phenobarbital-induced behavioral changes. Int J Dev Neurosci 1987;5(4):337–44. [Epub 1987/01/01].
[193] Beer A, Slotkin TA, Seidler FJ, Aldridge JE, Yanai J. Nicotine therapy in adulthood reverses the synaptic and behavioral deficits elicited by prenatal exposure to phenobarbital. Neuropsychopharmacology 2005;30(1):156–65. [Epub 2004/10/22].
[194] Christensen HD, Gonzalez CL, Rayburn WF. Chronic prenatal exposure to phenobarbital and long-term behavior effects on mice offspring. J Matern Fetal Neonatal Med 2004;15(6):351–5. [Epub 2004/07/29].
[195] Middaugh LD, Blackwell LA, Boggan WO, Zemp JW. Brain concentrations of phenobarbital and behavioral activation or depression. Pharmacol Biochem Behav 1981;15(5):723–8. [Epub 1981/11/01].
[196] Middaugh LD, Simpson LW, Thomas TN, Zemp JW. Prenatal maternal phenobarbital increases reactivity and retards habituation of mature offspring to environmental stimuli. Psychopharmacology (Berl) 1981;74(4):349–52. [Epub 1981/01/01].
[197] Middaugh LD, Santos III CA, Zemp JW. Effects of phenobarbital given to pregnant mice on behavior of mature offspring. Dev Psychobiol 1975;8(4):305–13. [Epub 1975/07/11].
[198] Middaugh LD, Santos III CA, Zemp JW. Phenobarbital during pregnancy alters operant behavior of offspring in C57BL/6J mice. Pharmacol Biochem Behav 1975;3(6):1137–9. [Epub 1975/11/01].
[199] Zemp JW, Middaugh LD. Some effects of prenatal exposure to D-amphetamine sulfate and phenobarbital on developmental neurochemistry and on behavior. Addict Dis 1975;2(1–2):307–31. [Epub 1975/01/01].
[200] Laviola G, Terranova ML, Sedowofia K, Clayton R, Manning A. A mouse model of early social interactions after prenatal drug exposure: a genetic investigation. Psychopharmacology (Berl) 1994;113(3–4):388–94. [Epub 1994/01/01].
[201] Narita N, Kato M, Tazoe M, Miyazaki K, Narita M, Okado N. Increased monoamine concentration in the brain and blood of fetal thalidomide- and valproic acid-exposed rat: putative animal models for autism. Pediatr Res 2002;52(4):576–9. [Epub 2002/10/03].
[202] Markram K, Rinaldi T, La Mendola D, Sandi C, Markram H. Abnormal fear conditioning and amygdala processing in an animal model of autism. Neuropsychopharmacology 2008;33(4):901–12. [Epub 2007/05/18].
[203] Bambini-Junior V, Rodrigues L, Behr GA, Moreira JC, Riesgo R, Gottfried C. Animal model of autism induced by prenatal exposure to valproate: behavioral changes and liver parameters. Brain Res 2011;1408:8–16. [Epub 2011/07/20].
[204] Wagner GC, Reuhl KR, Cheh M, McRae P, Halladay AK. A new neurobehavioral model of autism in mice: pre- and postnatal exposure to sodium valproate. J Autism Dev Disord 2006;36(6):779–93. [Epub 2006/04/13].
[205] Ohmori H, Yamashita K, Hatta T, et al. Effects of low-dose phenytoin administered to newborn mice on developing cerebellum. Neurotoxicol Teratol 1997;19(3):205–11. [Epub 1997/05/01].
[206] Hatta T, Ohmori H, Murakami T, Takano M, Yamashita K, Yasuda M. Neurotoxic effects of phenytoin on postnatal mouse brain development following neonatal administration. Neurotoxicol Teratol 1999;21(1):21–8. [Epub 1999/02/19].
[207] Ohmori H, Ogura H, Yasuda M, et al. Developmental neurotoxicity of phenytoin on granule cells and Purkinje cells in mouse cerebellum. J Neurochem 1999;72(4):1497–506. [Epub 1999/03/31].
[208] Bittigau P, Sifringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci 2003;993:103–14. discussion 23-4. [Epub 2003/07/11].
[209] Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci U S A 2002;99(23):15089–94. [Epub 2002/11/06].
[210] Katz I, Kim J, Gale K, Kondratyev A. Effects of lamotrigine alone and in combination with MK-801, phenobarbital, or phenytoin on cell death in the neonatal rat brain. J Pharmacol Exp Ther 2007;322(2):494–500. [Epub 2007/05/08].
[211] Kim J, Kondratyev A, Gale K. Antiepileptic drug-induced neuronal cell death in the immature brain: effects of carbamazepine, topiramate, and levetiracetam as monotherapy versus polytherapy. J Pharmacol Exp Ther 2007;323(1):165–73. [Epub 2007/07/20].
[212] Ohmori H, Kobayashi T, Yasuda M. Neurotoxicity of phenytoin administered to newborn mice on developing cerebellum. Neurotoxicol Teratol 1992;14(3):159–65. [Epub 1992/05/01].
[213] Yan GM, Irwin RP, Lin SZ, et al. Diphenylhydantoin induces apoptotic cell death of cultured rat cerebellar granule neurons. J Pharmacol Exp Ther 1995;274(2):983–90. [Epub 1995/08/01].
[214] Blank NK, Nishimura RN, Seil FJ. Phenytoin neurotoxicity in developing mouse cerebellum in tissue culture. J Neurol Sci 1982;55(1):91–7. [Epub 1982/07/01].
[215] Neale EA, Sher PK, Graubard BI, Habig WH, Fitzgerald SC, Nelson PG. Differential toxicity of chronic exposure to phenytoin, phenobarbital, or carbamazepine in cerebral cortical cell cultures. Pediatr Neurol 1985;1(3):143–50. [Epub 1985/05/01].
[216] Tauer U, Knoth R, Volk B. Phenytoin alters Purkinje cell axon morphology and targeting in vitro. Acta Neuropathol 1998;95(6):583–91. [Epub 1998/07/03].
[217] Ogura H, Yasuda M, Nakamura S, Yamashita H, Mikoshiba K, Ohmori H. Neurotoxic damage of granule cells in the dentate gyrus and the cerebellum and cognitive deficit following neonatal administration of phenytoin in mice. J Neuropathol Exp Neurol 2002;61(11):956–67. [Epub 2002/11/15].
[218] Diaz J, Schain RJ. Phenobarbital: effects of long-term administration on behavior and brain of artificially reared rats. Science 1978;199(4324):90–1. [Epub 1978/01/06].
[219] Bergman A, Feigenbaum JJ, Yanai J. Neuronal losses in mice following both prenatal and neonatal exposure to phenobarbital. Acta Anat (Basel) 1982;114(2):185–92. [Epub 1982/01/01].
[220] Fishman RH, Ornoy A, Yanai J. Ultrastructural evidence of long-lasting cerebellar degeneration after early exposure to phenobarbital in mice. Exp Neurol 1983;79(1):212–22. [Epub 1983/01/01].
[221] Fishman RH, Yanai J. Long-lasting effects of early barbiturates on central nervous system and behavior. Neurosci Biobehav Rev 1983;7(1):19–28. [Epub 1983/01/01].
[222] Yanai J, Waknin S. Comparison of the effects of barbiturate and ethanol given to neonates on the cerebellar morphology. Acta Anat (Basel) 1985;123(3):145–7. [Epub 1985/01/01].
[223] Ikonomidou C, Bittigau P, Ishimaru MJ, et al. Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science 2000;287(5455):1056–60. [Epub 2000/02/11].
[224] Forcelli PA, Kim J, Kondratyev A, Gale K. Pattern of antiepileptic drug-induced cell death in limbic regions of the neonatal rat brain. Epilepsia 2011;52(12):e207–11. [Epub 2011/11/05].
[225] Chen J, Cai F, Cao J, Zhang X, Li S. Long-term antiepileptic drug administration during early life inhibits hippocampal neurogenesis in the developing brain. J Neurosci Res 2009;87(13):2898–907. [Epub 2009/05/14].
[226] Stefovska VG, Uckermann O, Czuczwar M, et al. Sedative and anticonvulsant drugs suppress postnatal neurogenesis. Ann Neurol 2008;64(4):434–45. [Epub 2008/11/11].
[227] Rosselli-Austin L, Yanai J. Neuromorphological changes in mouse olfactory bulb after neonatal exposure to phenobarbital. Neurotoxicol Teratol 1989;11(3):227–30. [Epub 1989/05/01].
[228] Diaz J, Shields WD. Effects of dipropylacetate on brain development. Ann Neurol 1981;10(5):465–8. [Epub 1981/11/01].
[229] Reynolds S, Millette A, Devine DP. Sensory and motor characterization in the postnatal valproate rat model of autism. Dev Neurosci 2012. [Epub 2012/05/26].
[230] Chomiak T, Karnik V, Block E, Hu B. Altering the trajectory of early postnatal cortical development can lead to structural and behavioural features of autism. BMC Neurosci 2010;11:102. [Epub 2010/08/21].

[231] Glier C, Dzietko M, Bittigau P, Jarosz B, Korobowicz E, Ikonomidou C. Therapeutic doses of topiramate are not toxic to the developing rat brain. Exp Neurol 2004;187(2):403–9. [Epub 2004/05/18].
[232] Manthey D, Asimiadou S, Stefovska V, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. Exp Neurol 2005;193(2): 497–503. [Epub 2005/05/05].
[233] Kim JS, Kondratyev A, Tomita Y, Gale K. Neurodevelopmental impact of antiepileptic drugs and seizures in the immature brain. Epilepsia 2007;48(Suppl. 5):19–26. [Epub 2007/10/04].
[234] Hubel DH, Wiesel TN. Effects of monocular deprivation in kittens. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol 1964;248:492–7. [Epub 1964/08/19].
[235] Galvan CD, Hrachovy RA, Smith KL, Swann JW. Blockade of neuronal activity during hippocampal development produces a chronic focal epilepsy in the rat. J Neurosci 2000;20(8):2904–16. [Epub 2001/02/07].
[236] Swann JW, Smith KL, Lee CL. Neuronal activity and the establishment of normal and epileptic circuits during brain development. Int Rev Neurobiol 2001;45: 89–118. [Epub 2000/12/293].
[237] Forcelli PA, Janssen MJ, Vicini S, Gale K. Neonatal exposure to antiepileptic drugs disrupts striatal synaptic development. Ann Neurol 2012;72(3):363–72. [Epub 2012/05/15].
[238] Forcelli PA, Kozlowski R, Snyder C, Kondratyev A, Gale K. Effects of neonatal antiepileptic drug exposure on cognitive, emotional, and motor function in adult rats. J Pharmacol Exp Ther 2012;340(3):558–66. [Epub 2011/12/02].
[239] Rogel-Fuchs Y, Newman ME, Trombka D, Zahalka EA, Yanai J. Hippocampal cholinergic alterations and related behavioral deficits after early exposure to phenobarbital. Brain Res Bull 1992;29(1):1–6. [Epub 1992/07/01].
[240] Yanai J, Guttman R, Stern E. Genotype-treatment interaction in response of mice to early barbiturate administration. Biol Neonate 1989;56(2):109–16. [Epub 1989/01/01].
[241] Forcelli PA, Janssen MJ, Stamps LA, Sweeney C, Vicini S, Gale K. Therapeutic strategies to avoid long-term adverse outcomes of neonatal antiepileptic drug exposure. Epilepsia 2010;51(Suppl. 3):18–23. [Epub 2010/07/22].
[242] Shannon HE, Love PL. Effects of antiepileptic drugs on working memory as assessed by spatial alternation performance in rats. Epilepsy Behav 2004;5(6): 857–65. [Epub 2004/12/08].
[243] Kant GJ, Wylie RM, Vasilakis AA, Ghosh S. Effects of triazolam and diazepam on learning and memory as assessed using a water maze. Pharmacol Biochem Behav 1996;53(2):317–22. [Epub 1996/02/01].
[244] Keith JR, Pitts RC, Pezzuti T, Galizio M. Effects of positive GABA(A) modulators on a multiple-component, repeated-acquisition test of spatial learning. Behav Pharmacol 2003;14(1):67–75. [Epub 2003/02/11].
[245] Holley LA, Turchi J, Apple C, Sarter M. Dissociation between the attentional effects of infusions of a benzodiazepine receptor agonist and an inverse agonist into the basal forebrain. Psychopharmacology (Berl) 1995;120(1):99–108. [Epub 1995/07/01].
[246] Yochum CL, Dowling P, Reuhl KR, Wagner GC, Ming X. VPA-induced apoptosis and behavioral deficits in neonatal mice. Brain Res 2008;1203:126–32. [Epub 2008/03/05].