Published in final edited form as:

Neurochem Res. 2017 July ; 42(7): 2065–2070. doi:10.1007/s11064-017-2262-4.

Neurodevelopmental Effects of Antiepileptic Drugs

Marissa Kellogg¹ and Kimford J. Meador²

¹Department of Neurology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Mail Code 120, Portland, OR 97239-3098, USA

²Department of Neurology & Neurological Sciences, Stanford University, Stanford CA, USA

Abstract

Increasing evidence suggests that exposure to certain antiepileptic drugs (AEDs) during critical periods of development may induce transient or long-lasting neurodevelopmental deficits across cognitive, motor and behavioral domains. The developing nervous system may endure prolonged chronic exposure to AEDs during pregnancy (in utero) or during childhood, which can lead to neurodevelopmental defects such as congenital neural tube defects, lower IQ, language deficits, autism and ADHD. To date, valproate is the most widely recognized AED to significantly negatively affect neurodevelopment, and demonstrates greater adverse effects than any other AEDs that have been assessed. Although some AEDs appear to have low risk (i.e., lamotrigine, levetiracetam), other AEDs have been implicated in a variety of studies detailed below, and many AEDs have not been adequately assessed. The purpose of this review article is to summarize our current understanding of the neurodevelopmental effects of AEDs.

Keywords

AED; Antiepileptic drugs; Anticonvulsant drugs; Neurodevelopmental effects; Neurodevelopment; AED exposure

Introduction

Antiepileptic drugs (AEDs) are neuroactive compounds that reduce seizure incidence by a variety of biochemical mechanisms which decrease pathological hyperexcitability of the cerebral cortex [1]. Since AEDs act on the central nervous system, they may induce neurocognitive, motor and behavioral side effects during active exposure, such as dizziness, sedation, balance impairment, and mood change. Increasing evidence suggests that exposure to certain AEDs during critical periods of development may induce transient or long-lasting neurodevelopmental deficits across cognitive, motor and behavioral domains [2]. Since epilepsy is a chronic condition, patients must take AEDs daily for years to decades to prevent seizures; consequently, the developing nervous system may endure prolonged chronic exposure to AEDs during pregnancy (in utero) or during childhood. At the same time, poorly-controlled seizures may also lead to adverse neurodevelopmental outcomes and

other medical complications, so it may be difficult to distinguish the effects of the drugs from the effects of the epilepsy in individuals with both.

The purpose of this review article is to summarize our current understanding of the neurodevelopmental effects of AEDs. First, we will discuss the existing body of research on the topic and how it was acquired. Second, we will review the evidence for neuro-anatomical, teratogenic, cognitive, and behavioral effects in dedicated sections organized by type of effect with a focus on neurocognitive effects. Finally, we will conclude with a survey of areas of ongoing research and gaps in knowledge.

Existing Research

Our current understanding of the neurodevelopmental effects of AEDs has exponentially increased over the past 30 years, but remains incomplete. Current evidence derives primarily from studies of in utero exposure to AEDs in both animals and humans, although some studies of childhood exposure are being conducted. Animal studies are typically randomized experiments of drug exposure, but human studies are inevitably observational (prospective or retrospective) given ethical constraints [2]. Human studies of fetal exposure are limited not only by ethical and practical factors, but also logistical and financial factors; it is expensive and time-intensive to closely follow exposed children over their many years of development. In children with epilepsy, randomized controlled trials of cognitive effects are possible, but few comparative studies have been conducted, especially over prolonged exposure [3]. However, in the development of newer generation AEDs, more standardized neuropsychological testing of children and adolescents have been incorporated in the clinical trials.

Most animal data on neurodevelopmental effects of AEDs derives from rodent studies, although some primate work has also been done [4]. In animal studies, factors such as dose, timing, genetic background, mechanism of epilepsy, can be precisely controlled so that direct comparisons between drugs and doses can be made. However, the applicability of this research is significantly limited by the fact that animals are not humans, and there are likely various mechanisms acting on various stages of development that cannot be directly modeled. While human and rodent molecular biology is nearly identical, higher level brain structure and function are different. Perhaps more importantly, neurocognitive and behavioral responses to the AEDs are markedly different and must be measured differently; for example, a human IQ test bears little resemblance to rodent cognitive tests and cannot be directly compared.

One of the most concerning findings of the animal studies is that many AEDs (at therapeutic levels) have repeatedly been found to be pro-apoptotic to certain populations of cells in the immature brain [5, 6]. Additional studies have demonstrated decreased cell proliferation or decreased number of cells in the hippocampus, hypothalamus, cerebellum [7, 8]. Similar to alcohol, AED-induced cognitive/behavioral deficits may be more related to altered physiology and synaptogenesis in surviving neurons than actual cell lost. Nevertheless, the drug-induced apoptosis in the immature brain appears to be a reliable marker of long-term cognitive/behavioral effects. AED-induced apoptosis in the immature animal brain has been

demonstrated for benzodiazepines, phenobarbital, phenytoin, valproate and vigabatrin. Apoptosis does not occur with monotherapy exposure to carbamazepine, levetiracetam, lamotrigine or topiramate, but these AEDs except levetiracetam may increase apoptosis in polytherapy with an AED that induces apoptosis in monotherapy [2]. Unfortunately, many AEDs have not been tested in this model.

It has been proposed that AEDs may induce different teratogenic deficits at different stages of exposure and may involve different mechanisms. For example, anatomical risks are most related to first trimester exposure, but cognitive/behavioral effects may be more related to third trimester exposure similar to alcohol [9]. Possible mechanisms for neurodevelopmental defects besides apoptosis and cell proliferation alterations include folate deficiency, reactive intermediates (e.g. epoxides or free radicals), ischemia, synaptic changes, and neuronal suppression—but there is no strong evidence for a single mechanism [10].

To assess the potential long-term neurodevelopmental effects of cell loss or altered physiology in the brain, more animal studies are being conducted measuring outcomes in learning, social behavior, motor performance, and emotional (eg fear) responses in head-to-head trials of different AEDs. For example, recent studies have shown that there is a decrease in spatial learning (via the water maze test) and decreased social exploration in adult rats exposed to phenobarbital, phenytoin, and lamotrigine on postnatal days 7–13 [11]. Numerous studies have shown variable abnormalities in cued fear conditioning, risk assessment, sensorimotor gating, motor coordination, startle response, risk assessment, and many other neurodevelopmental measures, depending on the AED, dose and timing; recent reviews by Bath and Scharfman and Verrotti et al. summarize the highlights of such studies [4, 12]. On the contrary, some studies have suggested neuroprotective effects of certain AEDs like levetiracetam and lamotrigine, especially in animals with seizures [13], so further research is indicated.

Given the potential risks of fetal exposure to AEDs, it would be ethically, logistically and practically very difficult to perform randomized controlled trials of exposure in pregnant women. As a result, the evidence on the topic derives primarily from registry studies such as the EURAP. Countries such as the Netherlands, Norway and Sweden, have nationalized healthcare with robust population-based databases that facilitate neuro-epidemiological studies of exposure and longitudinal neurodevelopmental outcomes. In the United States and Canada, the North American AED Pregnancy Registry (established in 1997) has been the largest source of data on the risk of major malformations from AED exposures during pregnancy; 10,200 women had enrolled as of May 2016 [14]. The US and UK-based Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study has been the most comprehensive prospective multicenter observational study of exposure and neurodevelopmental effects, assessing outcomes such as IQ and behavior in children many years post-exposure [15, 16]. This investigation is continuing with a new cohort examining both maternal and child outcomes in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study. The results of the registries have not only contributed critical data to the medical and scientific community for analysis, systematic review and incorporation into national and international treatment guidelines, but have also empowered women with epilepsy and have highlighted gaps in knowledge and care.

Anatomical Teratogenic Effects of AEDs

It has been recognized for over 50 years that fetal exposure to AEDs can increase the risk for major congenital malformations (MCMs). Categories of MCMs include neural tube defects (a neurodevelopmental abnormality), cardiac, craniofacial, skeletal, and urological malformations. Since the 1960s, physicians began reporting “hare lip and cleft palate... congenital heart lesions and minor skeletal abnormalities” among children of mothers taking AEDs of that time period, which included phenytoin, phenobarbitone, and primidone [17]. Currently, it is recognized that certain AEDs are more teratogenic than others, with valproate being the most teratogenic [18].

In 2016, the Cochrane Collaboration published a systematic review of on congenital malformation outcomes in children exposed to AED monotherapy in utero [18]. The review included 50 published studies, to calculate the relative risks of congenital malformations using pooled prevalences of malformations within AED groups. Children exposed to valproate had the highest risk of a MCM at 10.93%, and the level of risk of having a malformation was linked to the cumulative dose the child was exposed to in the womb. Additionally, children exposed to carbamazepine, phenytoin, phenobarbital, and topiramate were also at higher risk of malformations. The authors concluded the current evidence suggested levetiracetam and lamotrigine carried the lowest risks of malformations. The effect of timing of exposure was difficult to assess by the Cochrane team since not all 50 published studies clarified timing. A committee assembled by the American Academy of Neurology in 2009 reassessed the evidence related to the care of women with epilepsy during pregnancy and concluded that AED polytherapy probably contributes to the development of MCMs, especially when valproate is part of the drug regimen [19]. Since the topic of malformations has been extensively covered in these recent evidence-based systematic reviews, we refer readers to those articles and recent reviews for more details on the topic [1].

Cognitive Effects of AED Exposure

To date, the evidence suggests that in utero exposure to several AEDs does not significantly affect IQ after controlling for maternal IQ, with the notable exception of valproate exposure. However, many AEDs have not been adequately assessed. In 2014, the Cochrane Collaboration Epilepsy Group systematically reviewed the literature to assess the effects of prenatal exposure to commonly prescribed AEDs on neurodevelopmental outcomes in the child, and to assess the methodological quality of the literature [20]. The primary outcome examined was global cognitive functioning (IQ in adults and school-aged children, and developmental quotient or “DQ” in non-school-aged children), and secondary outcomes included deficits in specific cognitive domains or prevalence of neurodevelopmental disorders. They incorporated 22 prospective cohort studies and six registry-based studies into their analysis. The most salient finding was that children exposed to valproate in utero showed poorer cognitive development both in infancy and when school-aged. A link between valproate dose and child ability was found in six studies, with higher cumulative doses of the drug linked to a lower IQ ability in the child [21]. There was conflicting evidence on carbamazepine and phenytoin exposure in utero, which the authors thought was

most likely due to differences in study design. There was very limited high-quality data on newer medications, but the preponderance of the evidence suggests that lamotrigine and levetiracetam have no significant neurodevelopmental adverse effects. In fact, several studies have recorded above average IQ scores in children exposed to lamotrigine in utero [22, 23].

Innumerable studies have examined the immediate effects of active AED use on different cognitive domains, but a paucity of studies have examined the effects of fetal exposure on specific cognitive domains. Moreover, there is marked heterogeneity in cognitive domain assessment methodologies—especially since neurodevelopment is a dynamic process and different methodologies are appropriate at different ages—so comparisons across studies are challenging. With regards to motor development, phenytoin and valproate have been implicated in delayed motor milestones or impaired coordination, while carbamazepine, levetiracetam, and lamotrigine have shown no significant motor impairment [20]. In verbal or language domains, valproate has consistently been shown to worsen verbal outcomes [24]; there is no robust evidence for other AEDs affecting language, although carbamazepine has been implicated in some but not other studies [16, 21]. While topiramate is an AED known to affect verbal domains during active use [25], there is insufficient evidence to determine whether there is any neurodevelopmental effect. To date, no neurodevelopmental studies have identified isolated visuospatial deficits in the setting of AED exposure; when visuospatial deficits are found, such as with valproate exposure, they are inevitably associated with global and verbal deficits as well. In general, there is a paucity of neurodevelopmental studies specifically evaluating the cognitive domains of attention, memory and executive function—so further research is needed in these areas. A recent study of visual attention and orientating to faces in 7 month-old infants exposed to AEDs in utero found no significant effect of exposure [26]. In addition, the NEAD study found impairments in executive function, memory and non-verbal cognitive functions in children exposed in utero to valproate [16].

In assessing cognitive outcomes of AED exposure, there are a myriad of potential confounding factors. Maternal IQ is now well-recognized as one of the strongest predictors of offspring IQ, regardless of epilepsy status or medication use [27]. A recent review by Inoyama and Meador examined cognitive outcomes of prenatal AED exposure, summarizing the current evidence and chronicling its evolution over time [28]. They note that prior to 2000, most studies did not control for maternal IQ and therefore are subject to strong bias. Other potential confounding factors are total AED exposure (dose and duration), type and severity of maternal epilepsy (both during pregnancy and after), poly-pharmacy, socioeconomic status, presence of other comorbidities, and breastfeeding exposure. Further, studies to date have not examined AED blood levels, which may be important given variable changes in AED clearance during pregnancy.

Behavioral Outcomes of AED Exposure

Rates of behavioral disorders such as autism and attentional deficit disorders have been reported to be higher in children exposed to certain AEDs in utero [29]. Increased prevalence of autism spectrum disorders in children with fetal valproate exposure has been reported in several studies, with prevalences ranging from 3 to 15% [30–32]. The strongest

evidence linking valproate to autism risk comes from a Danish population-based study of 655,615 children including 508 with fetal valproate exposure; incidence of autism spectrum disorder was 4.42% (95% confidence interval [CI] 2.59–7.46%) and autism incidence was 2.50% (95% CI 1.30–4.81%) [31] in exposed children, compared to 2.44% (95% CI 1.88–3.16%) and 1.02% (95% CI 0.70–1.49%), respectively, in children not exposed. Additionally, rates of autism have been found to be higher with higher doses of sodium valproate exposure [32]. In other prospective studies of neurobehavioral outcomes, children whose mothers took valproate during their pregnancy had higher rates of ADHD, and received significantly higher parental ratings of behaviors consistent with poor attention regulation and social immaturity [33].

Postnatal AED Exposure Effects on Neurodevelopment

The neurodevelopmental effects of postnatal exposure to AEDs are methodologically much more difficult to study than prenatal exposure because, after breastfeeding, AEDs are almost exclusively given to children with seizures and epilepsy. Therefore, studies must tease apart the effect size of the various additional confounders: type of epilepsy, seizure control, underlying brain disease, reversible AED side effects, etc. One way to examine this would be to conduct neurobehavioral testing on children with age-related epilepsy syndromes who are exposed to various AEDs during randomized controlled trials of AED therapy, such as the Phase III clinical trial in newly diagnosed childhood absence epilepsy (CAE) [34]. This study demonstrated that attentional dysfunction was more common with valproic acid than with ethosuximide treatment (49 vs 33%, respectively; odds ratio, 1.95; 95% CI 1.12 to 3.41); it would be interesting to study whether this effect was completely reversible with discontinuation of these medications. Also, longer follow-up studies in children during chronic treatment are needed to assess long-term adverse neurodevelopmental effects. Fortunately, standardized neuropsychological testing of children and adolescents is now being routinely incorporated into clinical trials of the newer therapies, so we will better be able to assess neurodevelopmental effects going forward [3].

To date, the studies of the neurodevelopmental effects of AED exposure during breastfeeding indicate that the practice of breastfeeding while taking AEDs is generally safe with no documented worsening of adverse neurodevelopmental effects of AED exposure [35–37]. In fact, comparisons of infants of mothers on AEDs who breastfed versus bottle-fed often indicate that breastfeeding may be neurodevelopmentally advantageous despite risks of ongoing AED exposure. In a subpopulation analysis of the multicenter NEAD study, 42.9% of children exposed to AEDs prenatally were also exposed during breastfeeding for a mean of 7.2 months; the breastfed children exhibited higher IQ (adjusted IQ 4 points higher [95% CI 0–8]) and enhanced verbal abilities compared to the bottle fed children at age 6 years [37]. For details on this subject, a recent review by Veiby et al. summarizes the current understanding of the risks and benefits of breastfeeding in women with epilepsy [35].

Future Directions

Clearly, more evidence is needed to better define the neurodevelopmental effects and risks associated with AED exposure. The consequences of AED exposure may not manifest until

years or decades after exposure, so more longterm surveillance studies are needed. Countries with nationalized health systems and more comprehensive required national reporting data for congenital abnormalities or neurodevelopmental disorders, such as the Netherlands, Norway and Sweden could perform more prospective neurodevelopmental testing or correlations of public school and health care data. In the US, the North American Pregnancy Registry with combined effort from the Centers for Disease Control (CDC) has contributed significantly to our understanding of risk, but it remains a voluntary registry with incomplete data currently funded by a coalition of pharmaceutical industry partners. Ideally, congenital defects would require mandatory reporting, and the registry would be nationally funded. Additionally, the Food and Drug Administration could require follow-up reporting by pharmaceuticals on their neurodevelopmental effects years after approval, to better delineate risks. Finally, there needs to be improved NIH funding for basic science and prospective clinical research to identify the specific mechanisms responsible for the teratogenic effects, so they can potentially be blocked or minimized by future therapies.

Conclusions

Increasing evidence suggests that exposure to certain AEDs during critical periods of development may induce transient or long-lasting neurodevelopmental deficits across cognitive, motor and behavioral domains. The developing nervous system may endure prolonged chronic exposure to AEDs during pregnancy (in utero) or during childhood, which can lead to neurodevelopmental defects such as congenital neural tube defects, lower IQ, language deficits, autism and ADHD. To date, valproate is the most widely recognized AED to significantly negatively affect neurodevelopment, and demonstrates greater adverse effects than any other AEDs that have been assessed. Although some AEDs appear to have low risk, other AEDs have been implicated in a variety of studies detailed above, and many AEDs have not been adequately assessed. While lamotrigine and levetiracetam appear to be relatively safe, there is insufficient evidence to make definitive conclusions for most AEDs, and further studies and follow-up are needed to quantify risk.

References

1. Levy R, Mattson R, Meldrum B, Perucca E (2002) Antiepileptic drugs. Lippincott Williams & Wilkins, Philadelphia
2. Meador KJ, Loring DW (2016) Developmental effects of antiepileptic drugs and the need for improved regulations. *Neurology* 86:297–306 [PubMed: 26519545]
3. Lagae L (2016) The importance of assessing behaviour and cognition in antiepileptic drug trials in children and adolescents. *Acta Neurol Belg*. doi:10.1007/s13760-016-0734-y
4. Bath KG, Scharfman HE (2013) Impact of early life exposure to antiepileptic drugs on neurobehavioral outcomes based on laboratory animal and clinical research. *Epilepsy Behav* 26:427–439 [PubMed: 23305780]
5. Bittigau P et al. (2002) Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci* 99:15089–15094 [PubMed: 12417760]
6. Forcelli PA, Kim J, Kondratyev A, Gale K (2011) Pattern of antiepileptic drug-induced cell death in limbic regions of the neonatal rat brain. *Epilepsia* 52:e207–e211 [PubMed: 22050285]
7. Yanai J et al. (1989) Neural and behavioral alterations after early exposure to phenobarbital. *Neurotoxicology* 10:543–554 [PubMed: 2696900]

8. Morte MI et al. (2013) Evaluation of neurotoxic and neuroprotective pathways affected by antiepileptic drugs in cultured hippocampal neurons. *Toxicol In Vitro* 27:2193–2202 [PubMed: 24055897]
9. Ikonomidou C et al. (2000) Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. *Science* 287:1056–1060 [PubMed: 10669420]
10. Velez-Ruiz NJ, Meador KJ (2015) Neurodevelopmental effects of fetal antiepileptic drug exposure. *Drug Saf* 38:271–278 [PubMed: 25693658]
11. Forcelli PA, Kozlowski R, Snyder C, Kondratyev A, Gale K (2012) Effects of neonatal antiepileptic drug exposure on cognitive, emotional, and motor function in adult rats. *J Pharmacol Exp Ther* 340:558–566 [PubMed: 22129597]
12. Verrotti A, Scaparrotta A, Cofini M, Chiarelli F, Tiboni GM (2014) Developmental neurotoxicity and anticonvulsant drugs: a possible link. *Reprod Toxicol* 48:72–80 [PubMed: 24803404]
13. Halbsgut LR, Fahim E, Kapoor K, Hong H, Friedman LK (2013) Certain secondary antiepileptic drugs can rescue hippocampal injury following a critical growth period despite poor anticonvulsant activity and cognitive deficits. *Epilepsy Behav* 29:466–477 [PubMed: 24103817]
14. AED Pregnancy Registry (2016) <http://www.aedpregnancyregistry.org/>. Accessed 29 Dec 2016
15. Meador KJ et al. (2006) In utero antiepileptic drug exposure: fetal death and malformations. *Neurology* 67:407–412 [PubMed: 16894099]
16. Meador KJ et al. (2013) Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 12:244–252 [PubMed: 23352199]
17. Meadow SR (1968) Anticonvulsant drugs and congenital abnormalities. *Lancet Lond Engl* 2:1296
18. Weston J et al. (2016) *Cochrane database of systematic reviews*. Wiley, Hoboken
19. Harden CL et al. (2009) Management issues for women with epilepsy: focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes. *Epilepsia* 50:1237–1246 [PubMed: 19507301]
20. Bromley R et al. (2014) *Cochrane database of systematic reviews*. Wiley, Hoboken
21. Baker GA et al. (2015) IQ at 6 years after in utero exposure to antiepileptic drugs a controlled cohort study. *Neurology* 84:382–390 [PubMed: 25540307]
22. Bromley RL et al. (2010) Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 51:2058–2065 [PubMed: 20633039]
23. Rihtman T, Parush S, Ornoy A (2013) Developmental outcomes at preschool age after fetal exposure to valproic acid and lamotrigine: cognitive, motor, sensory and behavioral function. *Reprod Toxicol* 41:115–125 [PubMed: 23791930]
24. Nadebaum C et al. (2011) Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology* 76:719–726 [PubMed: 21339499]
25. Donegan S, Dixon P, Hemming K, Tudur-Smith C, Marson A (2015) A systematic review of placebo-controlled trials of topiramate: how useful is a multiple-indications review for evaluating the adverse events of an antiepileptic drug? *Epilepsia* 56:1910–1920 [PubMed: 26662191]
26. Videman M et al. (2016) Evidence for spared attention to faces in 7-month-old infants after prenatal exposure to antiepileptic drugs. *Epilepsy Behav* 64:62–68 [PubMed: 27732918]
27. Meador KJ et al. (2011) Relationship of child IQ to parental IQ and education in children with fetal antiepileptic drug exposure. *Epilepsy Behav* 21:147–152 [PubMed: 21546316]
28. Inoyama K, Meador KJ (2015) Cognitive outcomes of prenatal antiepileptic drug exposure. *Epilepsy Res* 114:89–97 [PubMed: 26088891]
29. Adab N et al. (2004) The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 75:1575–1583 [PubMed: 15491979]
30. Bromley RL et al. (2013) The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry* 84:637–643 [PubMed: 23370617]
31. Christensen J et al. (2013) Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 309:1696 [PubMed: 23613074]
32. Wood AG et al. (2015) Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy. *Epilepsia* 56:1047–1055 [PubMed: 25963613]

33. Cohen MJ et al. (2013) Fetal antiepileptic drug exposure: adaptive and emotional/behavioral functioning at age 6years. *Epilepsy Behav* 29:308–315 [PubMed: 24012508]
34. Glauser TA et al. (2010) Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 362:790–799 [PubMed: 20200383]
35. Veiby G, Bjørk M, Engelsen BA, Gilhus NE (2015) Epilepsy and recommendations for breastfeeding. *Seizure* 28:57–65 [PubMed: 25837494]
36. Veiby G et al. (2013) Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia* 54:1462–1472 [PubMed: 23865818]
37. Meador KJ et al. (2014) Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. *JAMA Pediatr* 168:729–736 [PubMed: 24934501]