An Update on Maternal Use of Antiepileptic Medications in Pregnancy and Neurodevelopment Outcomes

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Abstract

Antiepileptic drugs (AEDs) are prescribed commonly to women of childbearing age. In utero exposure to some AEDs can have significant cognitive and behavioral consequences for the unborn child. Recently, prospective studies of women taking AEDs during pregnancy have added significantly to our understanding of cognitive and behavioral teratogenic risks posed by fetal AED exposure. Valproate is clearly associated with impaired cognitive development as well as an increased risk of disorders such as autism and autism spectrum disorder. Exposure to carbamazepine, lamotrigine, levetiracetam, or phenytoin monotherapy is associated with more favorable cognitive and behavioral outcomes than valproate, but more data are required to clarify if these AEDs have more subtle effects on cognition and behavior. There are insufficient data on the developmental effects of other AEDs in humans. Further, the underlying mechanisms of cognitive teratogenesis are poorly understood, including the genetic factors that affect susceptibility to AEDs.

Keywords
- epilepsy
- pregnancy
- mood disorder
- antiepileptic
- valproic acid
- lamotrigine
- levetiracetam
- neurodevelopment

Introduction

Approximately 2% of women take antiepileptic drugs (AEDs) during their pregnancy. The most common indications for AED use in pregnancy are psychiatric disorders, followed by pain disorders and epilepsy.[1] The decision to continue AEDs during pregnancy is a difficult one, which is based on balancing the risks of AED exposure to the unborn child with the risks posed to both the mother and the child by discontinuing these medications. For many patients, the risk of seizures or untreated symptoms requires that they take AEDs during pregnancy.[2,3]

Until recently, information on the effects of in utero AED exposure was scarce. In the past two decades, data from several prospective pregnancy registries has greatly improved our understanding of the risks of major congenital malformations (MCMs) associated with several antiepileptic drugs: Valproate is now known to be associated with a significantly increased risk of anatomic teratogenesis compared with baseline population rates and other AEDs.[4–8] Carbamazepine, lamotrigine, phenytoin, and levetiracetam seem to carry less of a risk of MCMs as compared with valproate.[4–8] More data are needed about other drugs, but recent data on topiramate has raised concern about its teratogenic potential, particularly a specific association with oral clefting.[8–10] These data are tremendously important in helping clinicians manage and counsel women of childbearing age who need to take AEDs. However, the risk of MCMs is not the only consideration for women taking AEDs. The effects of cognitive and behavioral effects from in utero exposure are also extremely relevant to prospective parents and more difficult to study and predict. This article reviews

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the most recent data on the developmental outcomes of children exposed to AEDs during pregnancy, highlighting several recent prospective studies. In addition, data on potential mechanisms of cognitive and behavioral teratogenesis of animal and translational studies are presented. The most recent studies are summarized in ►**Tables 1** and **2**. A detailed table of studies published before 2011 is available in the excellent review by Nadebaum et al.[11] Only the most recent study from a given cohort is presented. Unless specified, all exposures are monotherapy and all studies prospective.

Human Studies

The majority of human studies on the developmental effects of AED exposure have been retrospective or prospective observational studies of pregnant women with epilepsy. In these studies, it is difficult to separate the effects of the AEDs from the effects of epilepsy or seizures. At least in one study, paternal epilepsy and use of AEDs does not seem to affect developmental outcomes significantly.[12] Additionally, children born to mothers with untreated epilepsy do not differ from controls in measures of intelligence[13] or behavior.[12,14] However, these studies are unable to account for the fact that women with untreated epilepsy likely have milder disease. Some studies have suggested a connection between seizures during pregnancy and decreased intelligence quotient (IQ) scores in exposed children[15–18] though others have not found this association.[19–21] While it may not be possible to completely disentangle the effects of epilepsy, seizures, and AEDs, human studies, some of which control for seizure frequency, seem to point toward differential effects of various AEDs on cognitive and behavioral development of exposed children.

Valproate

Of all the AEDs, valproate has been most clearly associated with cognitive and behavioral teratogenesis across several human studies.[11,13,14,16–18,20,22–30] When compared with controls, standardized norms and children exposed to other AEDs, children exposed to valproate in utero have been shown to have a delay in achieving developmental milestones and lower IQ scores with particular weaknesses in verbal skills. Valproate-exposed children are also more likely to demonstrate poor adaptive skills and are at an increased risk for neurodevelopmental disorders (NDD) such as attention-deficit hyperactivity disorder (ADHD), autism, and autism spectrum disorders (ASD).

Cognitive Effects

Most of the early studies of valproate exposure and cognitive development were either retrospective[15,31,32] or small prospective studies which included as few as 8 to 18 valproate-exposed children.[21,33–36] Despite some methodological limitations and heterogeneity in study designs, the majority of these studies demonstrated a consistent association between valproate exposure and developmental delay. A meta-analysis of three studies[13] with 67 children exposed to valproate estimated that fetal valproate exposure is associated with a six point decrease in full-scale IQ (FSIQ) compared with unexposed children.

A major limitation of most of the earlier studies is that they did not control for the effect of maternal IQ, although a few studies did demonstrate that maternal IQ tended to be lower in women taking valproate during pregnancy.[16,21,33] Maternal IQ is an important predictor of a child's IQ.[37] Estimates of maternal IQ were assessed and incorporated into the analyses of three later studies: the neurodevelopmental effects of antiepileptic drugs (NEAD) study,[20,23–26] the Liverpool and Manchester neurodevelopmental group (LMNG) study,[27,28] and the Australian cohort described by Nadebaum et al.[16,29]

Nadebaum et al[29] recruited 38 school age children (range: 6–8 years) from the Australian pregnancy register for epilepsy and allied disorders who had been prenatally exposed to valproate. Pregnant mothers were prospectively identified, but the families were subsequently recruited into the study. In this cohort, valproate exposure in both monotherapy and polytherapy was associated with an increased likelihood of the very low FSIQ (< 70) or borderline low FSIQ (70–79) compared with standardized norms. In another publication from the same valproate cohort, the group found that core language scores of children exposed to valproate were significantly below the test mean for the clinical evaluation of language fundamentals (4th ed.).[16]

The NEAD study was a prospective observational study of 310 women with epilepsy and their children that controlled for maternal FSIQ along with several other important factors, including maternal age, seizure type, convulsions during pregnancy, AED dose, gestational age at birth, and preconception folate use.[20,22–26] The study enrolled pregnant women from the United States and the United Kingdom who were taking valproate, carbamazepine, lamotrigine, or phenytoin monotherapy. Compared with the other groups, the children prenatally exposed to valproate had significantly lower FSIQ scores at 3, 4.5, and 6 years of age.[20,22,25] At 6 years, valproate exposure was associated with a 7- to 10-point decrease in FSIQ as compared with the other monotherapy exposures.[20] Furthermore, a strong correlation between maternal IQ and child IQ was present for all monotherapies except for valproate in which this important relationship was not found. Valproate exposure was associated with decreased performance across several domains, including verbal IQ (VIQ) and non-VIQ, memory, and executive function. Verbal scores were most severely affected.[20]

The LMNG also conducted a robust prospective observational study of prenatal AED exposures and cognitive development.[17,27] It should be noted that a subset of the patients in this cohort also participated in the NEAD study. The authors assessed and controlled for similar covariates as the NEAD study as well as alcohol and tobacco use. This study also incorporated a control group of 287 children born to women without epilepsy in addition to 243 children born to women with epilepsy. Compared with healthy controls, children prenatally exposed to high-dose (> 800 mg daily) valproate had an adjusted IQ that was 9.7 points lower and an eightfold increased need for educational intervention. Valproate

Table 1 Antiepileptic drug exposure and cognitive development: Recent studies

Study	Population	Age	Number	Control group	Measures	Maternal IQ	Findings	Comments
Baker et al (2014)[17]	UK LMNG: prospective cohort with antenatal recruitment from antenatal clinics	6.2 y (6–6.8 y)	CBZ = 50 LTG = 29 VPA (< 800 mg) = 21 (> 800 mg) = 30 VPA PolyTx = 19 Other PolyTx = 11 No AEDs = 25 Other AEDs = 13	Yes *n* = 210	DAS Need for IEP	Yes	VPA > 800 mg/d c/w controls: ↓ FSIQ (9.7 points) ↑ Risk of FSIQ < 85 (RR = 8) ↑ Need for IEP (RR = 8) VPA > 800 mg/d, c/w LTG, CBZ: ↓ FSIQ, nonverbal and spatial IQ, ↓ Verbal IQ c/w LTG only VPA < 800 mg/d c/w controls: No difference in mean FSIQ or FSIQ < 85 ↓ Verbal IQ ↑ Need for IEP (RR = 6) VPA < 800 mg/d c/w LTG, CBZ: No difference in FSIQ, verbal or spatial IQ ↓ Mean nonverbal IQ c/w CBZ only CBZ c/w controls: No difference in mean FSIQ ↑ Risk of FSIQ < 85 (RR = 3.5), ↓ Verbal IQ (4.6 pts) No difference in IEP LTG c/w controls: No difference in IQ scores or IEP PolyTx c/w controls: VPA PolyTx—↓ FSIQ (6.4 points) Other PolyTx—No change in IQ scores	VPA use strongly associated with IGE and CBZ with LRE making it difficult to independently assess effects but more of variance attributed to AED exposure than epilepsy type
Cummings et al (2011)[51]	Ireland WWE: UK epilepsy and pregnancy register (Irish subjects only) Controls: Child Health System Database	Subjects: 2.9 y (0.5–7.5 y) Controls: 4.34 y (1.1–6.5 y)	CBZ = 49 LTG = 35 VPA = 58	Yes *n* = 44	BSID GMDS	No	VPA c/w controls: ↑ Risk of delayed performance (40 vs. 5%) CBZ c/w controls: ↑ Risk of delayed performance (20 vs. 5%) LTG c/w controls: No increased risk of delayed performance	Antenatal identification of subjects but postnatal recruitment; recruitment rates: 58% exposed 15% controls No maternal IQ; VPA mothers had lower educational achievement Control group older than exposed groups

(*Continued*)

Table 1 (*Continued*)

Study	Population	Age	Number	Control group	Measures	Maternal IQ	Findings	Comments
Meador et al (2013)[20]	U. S. and UK NEAD study: prospective cohort with antenatal recruitment	6.2 y (6–7.25 y)	CBZ = 61 LTG = 74 PHT = 40 VPA = 49	No	BRIEF CMS DAS NEPSY DTVMI One-word picture vocabulary	Yes	FSIQ and subscores: CBZ = LTG = PHT VPA < CBZ, LTG, PHT VPA c/w CBZ, LTG, PHT: ↓ FSIQ and verbal IQ ↓ Memory scores, ↓ Nonverbal IQ c/w LTG only ↓ Executive index c/w LTG only VPA > 1,000 mg/d c/w < 1,000 mg/d: ↓ Verbal and nonverbal IQ, ↓ General memory and executive index scores	Included 46 mother–child pairs from Baker et al,[17] No control group
Nadebaum et al (2011)[16]	Australia Australian register for women with epilepsy and allied disorders	7.4 y (6–8 y)	CBZ = 34 LTG = 9 VPA = 23 Other = 2 VPA PolyTx = 15 Other PolyTx = 19	No	CELF-4	Yes	Language scores: VPA PolyTx < VPA < LTG CBZ = LTG = Other PolyTx = expected norm VPA dose in first trimester negatively correlated with language scores VPA PolyTx c/w expected norm: ↓ Language scores ↑ Risk language score < 85 VPA PolyTx c/w CBZ, LTG, VPA: ↓ Language scores c/w LTG and VPA only	Antenatal identification of subjects but postnatal recruitment; recruitment rate: 83% No control group; standardized test norms used for comparison LTG group small
Nadebaum et al (2011)[29]	Australia Australian register for women with epilepsy and allied disorders	7.4 y (6–8 y)	VPA = 23 Other = 2 VPA PolyTx = 15 Other PolyTx = 19	No	WISC-IV	Yes	VPA c/w expected norms ↓ VCI, WM ↑ Risks of IQ < 80 (17.3 vs. 8.9%) VPA dose inversely related to VCI VPA PolyTx c/w expected norms ↓ VCI, WM, PS ↑ Risk of IQ < 80 (40 vs. 8.9%) Other PolyTx c/w expected norms ↓ VCI, WM ↑ Risk of IQ < 80 (15.8 vs. 8.9%)	Same cohort as above

Table 1 (*Continued*)

Study	Population	Age	Number	Control group	Measures	Maternal IQ	Findings	Comments
Rihtman et al (2012)[60]	Israel Exposed: Teratogen information service Controls: Convenience sample	4 y (3–5.6 y)	TPM = 9	Yes *n* = 18	Beery DCDQ M-Fun SB5	No	TPM c/w controls: ↓ General IQ, VIQ, nonverbal IQ ↓ WM, quantitative and fluid reasoning ↓ Visual perception, motor scores	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates not reported Small exposed group; 3/9 subjects exposed in first-trimester only No assessment maternal IQ or education
Rihtman et al (2013)[52]	Israel Exposed: Teratogen information service Controls: Convenience sample	LTG: 3.5 y VPA: 4.3 y Controls 5 y (3–7 y)	LTG = 42 VPA = 30	Yes *n* = 52	Beery DCDQ M-Fun SB5 SP, SSP	No	General IQ and subscores: VPA = LTG = controls VPA c/w controls: No difference in IQ, ↓ motor and sensory scores LTG c/w controls: ↓ Visual perception, ↓ motor, and sensory scores VPA c/w LTG No differences on any scales	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates: 36% VPA 50% LTG No maternal IQ; educational achievement: LTG < VPA < controls Control group older
Shallcross et al (2014)[18]	UK WWE: UK epilepsy and pregnancy register Controls: LMNG	3.5 y (3–4.5 y)	LEV = 53 VPA = 44	Yes *n* = 131	GMDS Reynell	Yes	VPA c/w controls, ↓ motor, and personal skills ↓ Comprehensive language score VPA c/w LEV ↓ Gross motor skills (15.8 points) LEV c/w controls No difference in any tested scales	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates: 35% VPA 83% LEV

Abbreviations: ABAS-II, Adaptive Behavior Assessment System 2nd ed; AED, antiepileptic drug; ASD, autism spectrum disorder; ASQ, ages and stages questionnaire; BASC, behavior assessment system for children; Beery, Beery–Buktenica Developmental Test of Visual-Motor Integration 5th ed; BRIEF, behavior rating inventory of executive function; BSID, Bayley scales of infant development; c/w, compared with; CBZ, carbamazepine; CELF-4, Clinical Evaluation of Language Fundamentals 4th ed; CMS, children's memory scale; Conners', Conners' rating scales–revised; CZP, clonazepam; DAS, differential ability scales; DCDQ, developmental coordination questionnaire; DTVMI, developmental test of visual motor integration; ESAT, early screening of autistic traits questionnaire; FSIQ, full-scale intelligence quotient; GMDS, Griffiths mental development scales; IEP, individual educational plan; IGE, idiopathic generalized epilepsy; IQ, intelligence quotient; LMNG, Liverpool and Manchester Neurodevelopmental Group; LRE, localization-related epilepsy; LTG, lamotrigine; MCHAT, modified checklist of autism in toddlers; M-FUN, Miller function and participation scales; MoBA, the Norwegian mother and child cohort; NEAD, neurodevelopmental effects of antiepileptic drugs; NEPSY, developmental neuropsychological assessment; Other PolyTx, polytherapy without valproic acid; Oxc, oxcarbazepine; PHT, phenytoin; PS, processing speed; PSI-III, Parent Stress Index 3rd ed; Reynell, Reynell language development scale; RR, relative risk; SB5, Stanford–Binet Intelligence Scales 5th ed; SCQ, social communication questionnaire; SP, sensory profile; SSP, short sensory profile; TPM, topiramate; UK, United Kingdom; U.S., United States; VCI, verbal comprehension index; VPA PolyTx, polytherapy including valproic acid; VPA, valproic acid; WASI, Wechsler abbreviated score of intelligence; WISC IV, Wechsler Intelligence Scale for Children 4th ed; WM, working memory; WWE, women with epilepsy.

Table 2 Antiepileptic drug exposure and behavioral development: Recent studies

Study	Population	Age	Number	Control group	Measures	Maternal IQ	Findings	Comments
Bromley et al (2013)[28]	UK LMNG: prospective cohort with antenatal recruitment from antenatal clinics	6.2 y (6–6.8 y)	CBZ = 50 LTG = 30 VPA = 50 VPA PolyTx = 20 Other PolyTx = 11 No AEDs = 26 Other AEDs = 14	Yes *n* = 214	Diagnosis of NDD NDD = ADHD or ASD or dyspraxia	Yes	VPA c/w controls: ↑ Risk of NDD (12 vs. 1.87%) VPA PolyTx c/w controls: ↑ Risk of NDD (15 vs. 1.87%) CBZ, LTG c/w controls No difference in risk of NDD (CBZ 2%, LTG 6.7 vs. 1.87%) Other PolyTx, no AEDs c/w controls No difference in risk of NDD (Other PolyTx 9%, No AEDs 0 vs. 1.87%)	NDD were not analyzed individually due to small numbers Community specialist making NDD diagnosis not blinded
Cohen et al (2013)[26]	U. S. + UK NEAD study: prospective cohort with antenatal recruitment	6 y Mean and range similar to Meador et al[20]	CBZ = 53 LTG = 63 PHT = 31 VPA = 45	No	ABAS-II BASC PSI-III	Yes	ABAS-II general adaptive scores: CBZ = LTG = PHT VPA < LTG, PHT VPA c/w CBZ, LTG, PHT: ↓ Adaptive scores c/w LTG, PHT only ↑ Atypical behavior c/w LTG,PHT only ↑ Inattention c/w LTG, PHT only Adaptive score inversely related to VPA and PHT dose VPA c/w standard norm: ↑ Risk of ADHD based on combined parent and teacher assessment (21 vs. 75%)	Included 46 mother-child pairs from Bromley et al,[28] No control group; standardized norms used for ADHD assessment Parental assessments introduce possible bias
Christensen et al (2014)[14]	Denmark Population study: Civil registers of births and psychiatric diagnoses	8.84 y (4–14 y)	CBZ = 386 CZP = 269 LTG = 647 OXC = 321 VPA = 388	CBZ = 386 CZP = 269 LTG = 647 OXC = 321 VPA = 388	Diagnosis of autism or ASD	No	VPA c/w controls: ↑ Risk autism (2.5 vs. 0.48%) ↑ Risk ASD (4.42 vs. 1.48%) VPA > 750 mg/d c/w < 750 mg/d No difference in risk of autism or ASD CBZ, CZP, LTG, OXC c/w controls No difference in risk of autism or ASD	Exposure databased on filled prescription Controlled for parental psychiatric disorders Community specialist making diagnoses not blinded No difference if VPA prescribed for epilepsy or other diagnosis

(*Continued*)

Table 2 (*Continued*)

Study	Population	Age	Number	Control group	Measures	Maternal IQ	Findings	Comments
Rihtman et al (2012)[60]	Israel Exposed: Teratogen information service Controls: Convenience sample	4 y (3–5.6 y)	4 y (3–5.6 y)	Yes $n = 18$	BRIEF Conners'	No	TPM c/w controls: ↑ Parent reported inattention/cognitive problems ↑ Parent-reported perfectionism No difference in teacher ratings	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates not reported Small exposed group; 3/9 subjects exposed in first trimester only
Rihtman et al (2013)[52]	Israel Exposed: Teratogen information service Controls: Convenience sample	LTG 3.5 y VPA 4.3 y Controls 5 y (3–7 y)	LTG = 42 VPA = 30	Yes $n = 52$	BRIEF Conners'	No	VPA c/w controls: ↓ Parent-reported executive function ↑ ADHD, Connors' global index No difference in teacher-reported measures LTG c/w controls: No difference in parent or teacher measures VPA c/w LTG No differences on any scales	Antenatal identification of exposed subjects but postnatal recruitment; recruitment rates: 36% VPA 50% LTG No maternal IQ; educational achievement: LTG < VPA < controls Control group older
Veiby et al (2013)[12]	Norway MoBA: Prospective cohort with antenatal recruitment	1.5 and 3 y	Mothers with epilepsy: (1.5 y/3 y) CBZ = 41/31 LT = 65/44 VPA = 25/19 PolyTx = 26/25 No AED = 221/154 Fathers with epilepsy: (1.5 y/3 y) AED = 147/110 No AED = 216/173	Yes $n = 107{,}597$	ASQ ESAT MCHAT MoBA checklist for ADHD Sentence complexity SCQ	No	VPA c/w controls ↓ Gross motor at 1.5 y ↓ Language at 3 y CBZ c/w controls ↓ Fine motor at 1.5 y ↓ Social skills at 3 y ↑ Aggressive symptoms at 3 y LTG c/w controls ↑ Autistic traits at 3 y ↓ Language score at 3 y No AEDs c/w controls No difference in any scores Fathers with epilepsy c/w controls ↑ Autistic traits at 1.5 y if father on AEDs ↓ Fine motor at 1.5 y if father not on AEDs No difference in any scores at 3 y	Parent f/u by mail survey. Response rate: 73% at 1.5 y 60% at 3 y Parental assessments introduce possible bias Primary outcome aggregate AED effect. AED exposure associated with increased autistic traits, poor sentence skills, and gross motor skills at 3 y PolyTx not divided by type. PolyTx as a group had poor performance on all scores at 1.5 y but not at 3 y

Abbreviations: ABAS-II, Adaptive Behavior Assessment System 2nd ed; ADHD, attention deficit hyperactivity disorder; AED, antiepileptic drug; ASD, autism spectrum disorder; ASQ, ages and stages questionnaire; BASC, behavior assessment system for children; BRIEF, behavior rating inventory of executive function; c/w, compared with; CBZ, carbamazepine; CZP, clonazepam; ESAT, early screening of autistic traits questionnaire; IQ, intelligence quotient; LMNG, Liverpool and Manchester Neurodevelopmental Group; LTG, lamotrigine; MCHAT, modified checklist of autism in toddlers; MoBA, the Norwegian mother and child cohort; NDD, neurodevelopmental disorders; NEAD, neurodevelopmental effects of antiepileptic drugs; OXC, oxcarbazepine; PHT, phenytoin; PolyTx, polytherapy; PSI-III, Parent Stress Index 3rd ed; SCQ, social communication questionnaire; TPM, topiramate; UK, United Kingdom; U.S., United States; VPA, valproic acid.

exposure at doses < 800 mg daily, was not associated with reduced IQ, but was associated with impaired verbal abilities and a sixfold increase in need for educational intervention.[17]

A relationship between higher doses of valproate and worse developmental outcomes was also suggested in the Australian cohort as well as the NEAD study. Nadebaum et al[16] found that first-trimester valproate dose was significantly correlated with poorer core language scores in the school-age Australian children even when controlling for maternal IQ. In the NEAD study, higher standardized doses of valproate were correlated with lower scores for FSIQ, VIQ and non-VIQ as well as memory and executive function.[20] While this dose relationship supports the conclusion that valproate can cause neurodevelopmental toxicity, it is not clear that there are "safe" doses of valproate below which human cognitive teratogenesis does not occur. Further prospective data incorporating valproate levels are needed to address this important point.

Behavioral Effects

In addition to poorer cognitive outcomes, in utero valproate exposure has also been associated with impaired behavioral outcomes. Early case reports and case series highlighted the association between autism and fetal valproate syndrome (a syndrome of characteristic facial features and congenital malformations that can be associated with prenatal valproate exposure).[38–40] In addition, a small population-based study conducted in Aberdeen, Scotland reported elevated rates of autism and ASD in children prenatally exposed to valproate monotherapy. One of the five autistic children also had several MCMs.[41] Several recent studies that excluded MCMs have also found impaired social and adaptive functioning in children prenatally exposed to valproate. In a population-based study from Demark, school-age children who were born to mothers prescribed valproate monotherapy during pregnancy had a significantly increased risk of receiving a formal diagnosis of autism or ASD according the national psychiatric register.[14] The absolute risk in the valproate-exposed cohort was 2.5% for autism and 4.42% for ASD compared with 0.48 and 1.53% in the general population. Controlling for psychiatric disease in the parents did not affect the results, nor did the exclusion of mothers who took valproate for conditions other than epilepsy. The rates of autism and ASD in children of mothers with epilepsy who did not take valproate during pregnancy were not significantly different from baseline rates. Specifically, compared with the general population, exposure to carbamazepine, clonazepam, oxcarbazepine, or lamotrigine monotherapy was not associated with statistically significant differences in the risk for autism or ASD.[14]

The LMNG also found an increased risk of behavioral abnormalities in their prospective study of the antenatally recruited cohort when children were assessed at 6 years of age. Because of the low frequency of autism and relatively small numbers in this cohort, the study examined the aggregate risk of several different NDD in children exposed to AEDs, including autism, ASD, ADHD, and dyspraxia. An NDD was present in 6 of 50 (12%) children prenatally exposed to valproate monotherapy and 3 of 20 (15%) children prenatally exposed to valproate in polytherapy.[28] These rates were significantly elevated compared with a rate of 1.87% in 214 control children. Children were considered to have an NDD if they had received a formal diagnosis from a health care professional outside of the research team. Investigators were blinded to the exposure type, but a referral bias on the part of parents or treating physicians cannot be excluded in this[28] or the Denmark population study.[14]

Although they are also subject to some bias, standardized parental assessments have demonstrated consistent evidence of impaired social and adaptive functioning in children prenatally exposed to valproate. The LMNG obtained parental interviews for a retrospectively recruited cohort of children age 6 to 16 years.[42] Based on the Vineland adaptive behavior scales, children exposed to valproate in utero had lower daily living and socialization skills than children exposed to carbamazepine, phenytoin, or polytherapies without valproate. The prospective NEAD cohort was also evaluated with parental standardized assessments (the adaptive behavior assessment system and the behavior assessment system for children) at both 3 and 6 years of age.[24,26] At both time points, children prenatally exposed to valproate were significantly more likely to receive poor scores for adaptive functioning compared with children exposed to phenytoin or lamotrigine, but not carbamazepine. The dose of valproate was also positively correlated with poorer scores for adaptive functioning. In addition, valproate was associated with more signs of atypical (socially immature) behavior and inattention than phenytoin or lamotrigine. Based on parental reports of attention on the behavior assessment system for children, 10/45 (22%) of the 6-year-old children exposed to valproate were considered at risk for ADHD. Based on the teacher assessments (which were only available for a smaller subset), 11/29 (38%) valproate-exposed children were at risk for ADHD.[26] These numbers were well above the U. S. centers for disease control and prevention estimate that ADHD affects 7% of the population.[43] Because the diagnostic and statistical manual for psychiatric disorders requires concordance of two or more raters for the diagnosis of ADHD, the authors combined the scores of both the parents and teachers. Of the 29 children assessed by both parents and teachers, 21% of the children met criteria for being at risk for ADHD.[26]

Carbamazepine

Studies of carbamazepine's effect on cognitive development have been conflicting. Many have found no effect of carbamazepine on cognitive development or academic achievement when compared with controls,[15,21,32,33,36,44–48] other studies, however, did report increased rates of developmental delay in children exposed to carbamazepine.[31,34,49–51] A meta-analysis of five of the earlier studies published between 1994 and 2005[13] analyzed the IQ scores of 151 carbamazepine-exposed children age 6 months to 16 years and found no difference in FSIQ or VIQ when compared with controls, but did identify reduced performance IQ in the carbamazepine group. Of note, some of the included studies and the meta-analysis did not control for the effect of maternal IQ. In the NEAD study, negative correlations between carbamazepine

dose and VIQ as well as motor functioning were detected at 3 years of age but no specific or dose-related adverse effects were identified when the cohort was evaluated at 6 years of age.[20,22,24] The recent prospective study from the LMNG found no difference in the adjusted mean FSIQ scores between the 6-year-old carbamazepine-exposed children and controls, but VIQ was 4.2 points lower in the exposed children. Additionally, the relative risk of having a low FSIQ < 85 was significantly increased in the carbamazepine cohort.[17] Both the NEAD and LMNG studies demonstrated that prenatal carbamazepine exposure was less likely to be associated with adverse cognitive effects than valproate.[17,20]

In terms of social functioning, the LMNG found no increased risk for formally diagnosed NDD in 6-year-old children prenatally exposed to carbamazepine compared with controls.[28] Similarly, the large Danish population study by Christensen et al[14] found no increased risk of autism or ASD in school age and teen children that had been exposed to carbamazepine in utero. An earlier population-based study in Aberdeen, Scotland reported that 2/80 (2.5%) carbamazepine-exposed children had ASD, which is above the population rate (0.25%) but lower than the valproate group (8.9%). These findings are hard to interpret given the small number of cases. In addition, one of the two carbamazepine-exposed children also had MCMs.[41]

Parental reports of behavior in children exposed to carbamazepine suggest possible adverse effects but these need to be substantiated with objective evaluations. In a population-based survey of Norwegian parents, children exposed to carbamazepine in utero were reported to have impaired fine-motor and personal social skills at 18 months and more aggressive symptoms at 36 months.[12] In the NEAD study, the mean score on the adaptive behavior assessment system for valproate-exposed children at the age of 6 years was significantly lower than that of children exposed to lamotrigine or phenytoin but did not differ statistically from the mean adaptive score of carbamazepine-exposed children.[26] Since this study did not involve an unexposed control group, it is not known whether the scores for the carbamazepine group were significantly decreased from the norm. Carbamazepine exposure was also associated with an increased risk for ADHD by parental reports of behavior, but not by teacher reports. In contrast, a retrospective study found no difference between parentally reported adaptive behavior of carbamazepine-exposed children age 6 to 16 years compared with unexposed children.[42]

In summary, it is clear that carbamazepine poses less of a risk for cognitive and behavioral teratogenesis compared with valproate, and is comparable to healthy controls in regards to measures of FSIQ. However, whether certain individuals or behavioral domains are particularly susceptible to carbamazepine exposure needs further study.

Lamotrigine

Developmental scores of infants prenatally exposed to lamotrigine did not differ from those of controls in two independent cohorts in the United Kingdom.[27,51] At 6 years of age, the IQ scores of the lamotrigine-exposed children in the LMNG cohort did not differ from controls.[17] The NEAD study found that FSIQ scores in children exposed to lamotrigine were significantly higher than those of valproate-exposed children and did not differ from those of carbamazepine- or phenytoin-exposed children.[20,22,25] In the 6-year-old NEAD cohort, both valproate and lamotrigine exposure were associated with decreased VIQ relative to non-VIQ and both had a lower than expected incidence of right handedness.[20] These findings raised the question of whether lamotrigine and valproate might affect cerebral lateralization, however, the lack of information on parental handedness and verbal or nonverbal abilities make it difficult to draw firm conclusions. In contrast to the NEAD findings, a cohort of Israeli school-age children, had no differences between IQ scores of children prenatally exposed to valproate and those exposed to lamotrigine.[52] Instead of a differential effect on VIQ, this study found that lamotrigine and valproate were both associated with decreased non-VIQs when compared with controls. Of note, the mean non-VIQ in the control group was 7 points higher than the mean VIQ. Children were prospectively identified from a teratogen information service and families were retrospectively recruited, potentially introducing some bias. Maternal education level and socioeconomic status were higher in the control group and adjusted for in analyses, but maternal IQ was not measured.[52]

Impaired language functioning and an increase in autistic traits were reported by parents of lamotrigine-exposed infants compared with the reference population in a Norwegian prospective population-based survey.[12] Parental ratings of the 6-year-old NEAD children prenatally exposed to lamotrigine suggested that they may be at an increased risk for ADHD, but the teacher ratings in a subgroup of these children did not substantiate this finding and no tendency toward social impairment was detected.[26] In contrast to these parental observations, the LMNG found no lamotrigine-associated increased risk of formally diagnosed NDD in their prospective study of school-age children.[27]

Levetiracetam

Developmental effects of levetiracetam have been assessed in one study from the LMNG.[18,30] Levetiracetam-exposed pregnancies had been identified prospectively as part of the United Kingdom pregnancy register and subsequently invited to participate in the study. Overall, 51 children exposed to levetiracetam were evaluated at 3 to 24 months and again at 36 to 54 months of age.[18,30] The developmental scores of the prenatally exposed children did not differ from those of controls at either time point, but were better than a valproate-exposed group. Since this is the only investigation of developmental outcomes with levetiracetam exposure, it will need to be replicated in future human studies, though it is corroborated by animal studies which have suggested levetiracetam exposure does not cause the cellular changes seen with exposure to other AEDs.[53,54]

Phenobarbital

The largest prospective study of phenobarbital and cognitive outcomes evaluated a Danish birth cohort of 114 adult men

who were born in a single hospital between 1959 and 1961 and who had been prenatally exposed to phenobarbital.[55] The cohort was divided into two groups, which were assessed with different measures of intelligence and data were analyzed separately. The most common indication for phenobarbital in this study was pregnancy-related hypertension. Mothers with epilepsy were excluded from one group and did not appear to be present in the second. Compared with controls from the same birth cohort, the phenobarbital-exposed group had significantly lower IQ scores in both studies. In a subset of 33 subjects who were assessed with the Wechsler adult intelligence scale, this effect was driven by lower VIQ. The subjects prenatally exposed to phenobarbital during the third trimester were the most affected with respect to lower IQ scores. In another prospective study, Thomas et al[36] also found lower IQs in a group of 12 phenobarbital-exposed children compared with children prenatally exposed to other AED monotherapies. Retrospective studies of prenatal phenobarbital exposure have demonstrated mixed results with some showing an adverse impact on cognition and educational outcomes[46,56] and others not finding evidence of an effect.[31,57] None of the phenobarbital studies published have accounted for maternal IQ.

Phenytoin

Several prospective and retrospective studies have not found a difference between the cognitive performance of infants and children prenatally exposed to phenytoin and unexposed controls.[15,36,47,58] Wide et al[48] found prenatally-exposed toddlers had overall normal intelligence but noted a significant decrease in observed locomotor functioning. In contrast, in an earlier prospective study of 34 children prenatally exposed to phenytoin, Scolnik et al[45] found a significant mean difference in FSIQ: the phenytoin-exposed group had a mean IQ of 103, which was lower than that of controls by 10 points. Concerns were raised that the effects could have been due to lower maternal IQs in mothers taking phenytoin.[59] Dean et al[31] also reported an increased risk of developmental delay in phenytoin-exposed children as well as valproate and carbamazepine-exposed children compared with unexposed controls. The average FSIQ and average VIQ of the phenytoin-exposed children in the NEAD study were significantly higher than those of the valproate-exposed children and not significantly different from those of children prenatally exposed to carbamazepine or lamotrigine. Since the study did not include an unexposed control group, it is not known if the phenytoin group would differ from unexposed children. In terms of behavioral effects, Vinten et al[42] did not find any significant differences between parentally reported adaptive behaviors in the phenytoin-exposed Norwegian children when compared with unexposed controls born to mothers with epilepsy.

Topiramate

There has been one small preliminary study of cognitive, motor, and behavioral outcomes of nine school-aged children prenatally exposed to topiramate.[60] Compared with sex and age-matched controls, the topiramate-exposed children had lower IQ scores across several domains as well as poorer motor and visual spatial skills. Over half of the exposed children received speech, occupational or physical therapy. While this study points to the need for further research on the cognitive effects of topiramate, the authors caution that the results are only preliminary due to the small number of children enrolled. Furthermore, there was no control for maternal IQ, and families were recruited when the children were school-aged, so those with greater concern about their children's learning difficulties may have been more inclined to participate.

Other Antiepileptic Drugs

There is little to no information on the developmental outcomes associated with exposure to other AEDs including benzodiazepines, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, oxcarbazepine, perampanel, pregabalin, rufinamide, vigabatrin, and zonisamide. The manufacturers of lacosamide caution that the drug is known to antagonize the collapsin response mediator protein-2, which is involved in neuronal differentiation and axonal growth,[61] but its effects on human cognitive development are not known.

Polytherapy

Numerous studies have suggested that treatment with multiple AEDs during pregnancy is associated with worse developmental outcomes in exposed children[21,29,31,36,44,56,58,62] though a few have not found this association.[15,27,47,63] The reason for these discrepant findings is likely due to differential effects of various drug combinations. Several studies have now demonstrated that polytherapy combinations that include valproate are clearly associated with adverse developmental outcomes and it is possible that valproate combinations were largely responsible for the polytherapy effects seen in earlier studies. In their prospectively identified, Australian cohort, Nadebaum et al[16] demonstrated that polytherapy exposures including valproate resulted in significantly lower FSIQ and verbal comprehension scores compared with valproate monotherapy or polytherapy combinations that did not include valproate. The LMNG also found that only polytherapy combinations that included valproate were associated with decreased mean FSIQ and VIQ in school-aged children whereas other polytherapy combinations were not.[17] Future studies will need to look at specific polytherapy combinations to understand which drugs have an additive or synergistic effect on behavioral outcomes. Studies will also need to look at the effects of combinations of AEDs with other drugs that are commonly prescribed in conjunction with AEDs.

Potential Mechanisms of Cognitive and Behavioral Teratogenesis

Animal and translational studies have begun to uncover the mechanisms by which AED exposure may lead to intellectual

and behavioral abnormalities. The behavioral effects of AEDs in rodent models have been recently reviewed in excellent detail.[64] Rats exposed to several AEDs including benzodiazepines, lacosamide, lamotrigine, phenobarbital, valproate, and vigabatrin either in utero or in the early postnatal period exhibited behavioral abnormalities compared with unexposed controls.[61,64] Valproate exposure has been used to create a rat model of autism.[65] It is difficult to extrapolate rodent phenotypes to human data but rodent models do provide control over administration of medication and can separate drug exposure from the potential effect of maternal conditions, which is not possible in human observational studies. They also allow for visualization of changes in brain development at a molecular and cellular level. In rodent models, AED exposure has been shown to interfere with several important stages in brain development. These include neuronal proliferation and migration and as well as apoptosis, or programmed cell death.[53,54,66–80] Synapse formation, pruning, and synaptic plasticity also are affected by exposure to some AEDs.[81–84] An important consideration in interpreting animal studies is that the timing of exposure varies from study to study; in rat models, the early postnatal period is felt to approximate the third trimester of human pregnancy. Many of the rat studies presented here use a single exposure in the first two postnatal weeks whereas a minority administered the drug to rats throughout pregnancy.

Neuronal Migration and Proliferation

Lamotrigine or valproate treatment of pregnant rats during embryogenesis was associated with hippocampal or cortical dysplasias in the offspring, which is presumably due to abnormal neuronal migration. This did not occur with exposure to carbamazepine, levetiracetam, phenobarbital, or topiramate.[66,67] Treatment of pregnant rats with valproate during embryogenesis has also been shown to affect neuronal migration and differentiation of serotonergic neurons.[68]

AED exposure may also lead to aberrant neurogenesis. Rats treated with gamma-aminobutyric acid (GABA) agonists such as clonazepam, diazepam, or phenobarbital in the early postnatal period demonstrated decreased proliferation of new neurons in the dentate gyrus of the hippocampus.[69,70] Treatment with an N-methyl-d-aspartate (NMDA) antagonist had a similar effect.[69] Carbamazepine, lamotrigine, and topiramate exposures were not associated with decreased neurogenesis.[70,71] Treatment with valproate results in decreased hippocampal neurogenesis in some studies,[69,72] but not others.[70,71] In one study, prolonged valproate or lamotrigine treatment caused increased hippocampal neurogenesis.[71] The differences between these results may relate to differences in doses or duration of drug exposure. In the rat neocortex, valproate exposure during pregnancy appears to lead to an abnormally increased number of neurons resulting in increased cortical thickness.[73] Further studies are needed to clarify the mechanisms of abnormal neurogenesis and why this is seen with some drug exposures but not others. Based on these initial studies, it is felt that decreased excitation by NMDA antagonism or enhanced GABA activity may be responsible for changes in hippocampal neurogenesis.[69,70]

Magnetic resonance imaging studies in humans have also suggested that aberrant neuronal migration is associated with AED exposure. Iknonmidou et al[85] found that adults that had been exposed to AEDs in utero had smaller gray matter volumes in the basal ganglia and hypothalamus when compared with controls, but small sample sizes precluded evaluation of drug-specific effects. In a more recent magnetic resonance imaging study of 16 valproate-exposed children, Wood et al[86] found that these children had increased mean cortical thickness in the left inferior frontal gyrus and more common loss of right greater than left asymmetry compared with control children.

Apoptosis

In rats, early postnatal exposure to therapeutic doses of clonazepam, diazepam, phenytoin, phenobarbital, valproate, and vigabatrin can cause dose-dependent widespread apoptosis.[74,75,87] Specifically phenobarbital has been shown to cause increased cell death in several limbic nuclei[76] whereas phenytoin has been associated with increased cell death in the nucleus accumbens as well as the hippocampus and cerebellum.[77] Carbamazepine, lamotrigine and topiramate did not cause cell death when given to neonatal rats at doses within the therapeutic range for preventing induced seizures in rodents, but each of these medications did lead to increased apoptosis at doses above this range. Additionally, each of these drugs increased facilitated cell death when used in combination with phenytoin or phenobarbital.[54,78,80] In contrast, levetiracetam did not alter programmed cell death at any dose or in conjunction with phenytoin. At therapeutic doses, levetiracetam and carbamazepine together did not alter apoptosis[53,79] but supertherapeutic doses of levetiracetam and standard doses of carbamazepine did result in increased cell death in the thalamus.[79]

The apoptotic effects of AEDs on the developing brain are very similar to those seen in rat models of fetal alcohol syndrome.[87] The specifics of how these exposures lead to apoptosis are not known, but neuronal suppression, which is an effect common to all AEDs, has been suggested as a possible common mechanism. Reduced expression of neurotrophins and cell-growth signal proteins also likely contribute.[75] Finally, increased expression of tumor necrosis factor-α by astrocytes also seems to mediate valproate-induced neuronal apoptosis.[88]

Of note, synergistic effects of AEDs and other neuroactive agents also have the potential to affect programmed cell death. For example, the psychoactive component of marijuana, tetrahydrocannabinol, greatly facilitated the apoptotic effects of phenobarbital.[89] Similar studies looking at the combined effects of antiepileptic drugs and other medications commonly used in combination with these drugs such as selective serotonin reuptake inhibitors would be informative.

Synaptogenesis

In addition to affecting the creation and removal of neurons, antiepileptic drugs also, appear to affect the connections between neurons. For example, in the rat model of autism, rat pups exposed to valproate during embryogenesis were found to have an increased number of cortical to cortical connections but each of these connections was less efficient.[82] Synaptic plasticity (the ability for synapses to strengthen in response to a stimulus) is also enhanced in rats prenatally exposed to valproate leading to augmented long-term potentiation, which may improve learning and memory in exposed animals.[81,83] These alterations were postulated to underlie risk for autism perhaps by enhanced memories of fearful stimuli, which also occurred in the exposed animals.[83] It should be noted, however, that the observed enhancement of long-term potentiation in these young animal models does not imply that memory should be improved in children with fetal valproate exposure. In fact, valproate-exposed children have been shown to have impaired memory.[20,29]

Several AEDs other than valproate have also been shown to alter synaptogenesis. In a recent study, Forcelli et al[84] demonstrated that phenytoin, phenobarbital, and lamotrigine administered to rat pups on postnatal day 7 altered normal maturation of both inhibitory and excitatory synapses between days 10 and 14, increasing the connectivity of both inhibitory and excitatory synapses. When the pups were followed to day 18, the frequency of inhibitory potentials of lamotrigine-exposed pups did not differ from that of controls, but the inhibitory potentials of phenytoin and phenobarbital-exposed pups were still much less frequent. The authors concluded that drug-induced proapoptotic mechanisms also produce alterations in synaptic maturation because treatment with melatonin (which is used in animal models to block apoptosis) prevents the synaptic changes. Additionally, levetiracetam, which does not cause apoptosis, did not affect synaptic maturation.[84]

Genetic Modification

Genetic or more specifically, epigenetic mechanisms likely play an important role in AED teratogenesis, though to date this concept has been explored by only a few studies. In a zebrafish model, embryos exposed to valproate had decreased micro-RNA expression. MicroRNA are small noncoding components of DNA that regulate transcription of messenger RNA and hence play an important role in development.[90] Valproate has also been shown to alter transcription of messenger RNA in both zebrafish and rodent models.[91,92]

Valproate is thought to exert epigenetic effects by interfering with histone acetylation and DNA methylation, two interconnected processes that regulate gene transcription.[91,93–96] Changes in DNA methylation patterns may also be affected by other AEDs: Two human studies of cord blood[97,98] and placental tissue[98] of AED-exposed pregnancies demonstrated significant alterations in DNA methylation patterns in AED-exposed samples compared with controls. The larger series by Smith et al[98] demonstrated that duration of AED exposure correlated with global hypomethylation. Methylation patterns did not seem to be affected by the condition for which the mother was taking AEDs (mood disorder versus epilepsy). The majority of the patients in these two human studies were not exposed to valproate. Seventy percent of the 54 AED-exposed pregnancies in the study by Smith et al[98] were exposed to lamotrigine. The exact mechanism by which AEDs alter DNA methylation is not known but it is speculated that alterations in the folate/homocysteine metabolic pathways, which have been associated with many AEDs including lamotrigine and the enzyme-inducing AEDs, may be responsible.[97]

If epigenetic modification is found to mediate AED teratogenesis, it may also be possible to uncover individuals whose genomes are more or less susceptible to these effects. For example, in a population-based study in Aberdeen, Scotland, Dean et al[99] found that AED-exposed children with congenital malformations and fetal anticonvulsant syndrome were more likely to be born to mothers with a certain polymorphism of methylene-tetrahydrofolate reductase when compared with AED-exposed children who were unaffected. In the same study, AED-exposed children with NDD and/or fetal anticonvulsant syndrome were more likely to have polymorphisms of methionine synthase and methionine synthase reductase at trend levels as compared with the healthy children. Each of these enzymes plays an important role in folate/homocysteine metabolism. Similarly, in a study of children with epilepsy exposed to AEDs postnatally, those with certain polymorphisms of methylene-tetrahydrofolate reductase have higher homocysteine levels and may be more susceptible to the cognitive effects of antiepileptic drugs.[100] A better understanding of genetic susceptibility to the teratogenic effects of AEDs and the epigenetic mechanisms of teratogenesis may eventually lead to interventions that could help mitigate the adverse effects of AEDs or identify individuals at greatest risk. This will likely require large-scale population studies as well as more investigations on animals. Since the current literature suggests that individual AEDs affect both structural and cognitive function in unique ways, these investigations will need to look at more than just a class effect on the regulation of the genome.

Potential Factors Improving Cognitive Outcomes

Folic Acid

Folic acid supplementation is an example of the kind of intervention that might be able to prevent or reduce the epigenetic effects of AEDs, particularly those that are mediated by the DNA methylation pathway: In animal models, folate is able to prevent DNA hypomethylation and other metabolic changes associated with valproate exposure.[101,102] Folic acid supplementation for women with epilepsy who are of reproductive age has become standard of care, although the optimal dose is not known.[103–105] The rationale for the recommendation for folic acid supplementation is based

mainly on population studies that have associated supplementation with a decreased risk of neural tube defects.[106] To date, only a few studies have demonstrated a relationship between folate levels or folic acid supplementation and MCMs in women with epilepsy and larger studies are needed.[104,107,108] In the NEAD study, the mean FSIQ of 6-year-old children whose mothers reported periconceptional folic acid use was higher than the mean FSIQ of those who were not exposed to supplementation early in pregnancy, even after controlling for other factors such as maternal IQ.[20] When prenatal valproate-exposed children were excluded from the analysis, there also appeared to be a positive dose-related effect of maternal folic acid supplementation on the child's IQ. Information on periconceptional folic acid supplement use was obtained retrospectively by maternal interview. This finding suggests that folic acid supplementation may have a positive effect on cognitive development but it will need to be substantiated by further studies. LMNG did not find a significant effect of periconceptional folic acid supplementation on IQ of the offspring at 6 years of age.[17] Additionally, since the NEAD study only included AED-exposed pregnancies, it is not certain if the positive affect of folic acid supplementation was mitigating the effects of AEDs or would be associated with increased average IQ in children resulting from all pregnancies. Several recent studies have demonstrated a relationship between periconceptional folic acid supplementation and higher cognitive and behavioral outcomes in the general population.[109–112] At this point, there is insufficient evidence to conclude that folic acid supplementation mitigates the structural or developmental teratogenic effects of AEDs; at best it is likely only one of the necessary targets for intervention. More research in this area is greatly needed.

Breastfeeding

Breastfeeding is known to have several important health benefits for both mother and child and promotes mother–infant bonding.[113] Although controversy still exists, breastfeeding may also improve cognitive development.[114,115] This benefit appears to extend to AED-exposed children who are breastfed. In the NEAD study, AED-exposed children who were breastfed had higher age-6 FSIQ and verbal scores than those who were not breastfed, even after controlling for maternal IQ. Additionally, in the prospective Norwegian cohort, Veiby et al[62] also found a positive effect of breastfeeding for 6 and 18 months on the parent-reported developmental abilities of children. However, this effect did not persist at 36 months.[62] Neither study found adverse effects of breast milk exposure to the studied drugs (carbamazepine, lamotrigine, phenytoin, and valproate) on developmental outcomes. While further prospective studies of AED exposure via breast milk are necessary, for many AEDs the theoretical concern of prolonged infant exposure likely does not outweigh the known benefits of breastfeeding.

Future Directions

The treatment of women with epilepsy has been dramatically affected by the research on AED teratogenesis that has been expanding quickly in the last two decades. The effect of AEDs on the intellectual and behavioral functioning of exposed children has more recently gained traction. While there have been tremendous developments in our understanding of cognitive and behavioral teratogenesis, our knowledge still contains large gaps. We have come to recognize that valproate can have a detrimental effect on IQ and other neurodevelopmental outcomes of a prenatally exposed child and should be avoided whenever possible in women of childbearing age. More information is needed to clarify the effects of other AEDs on the cognitive and behavioral development of exposed children. While less likely to cause adverse cognitive and neurodevelopmental effects than valproate, the AEDs carbamazepine, lamotrigine and phenytoin have been associated with mixed outcomes. In both animal studies and human studies, levetiracetam seems to be emerging as a drug with minimal effects on cognitive development, but these findings need to be replicated in larger prospective human studies. The cognitive and behavioral effects of other commonly used AEDs are virtually unknown and need to be investigated. Future studies should be prospective in design and ideally follow children to school age or beyond. They should include a control group and account for important covariates such as maternal IQ, seizure frequency and other environmental factors. Given the marked changes in drug elimination during pregnancy for some AEDs and inter-individual differences in drug metabolism,[116] relative exposure to AEDs should be quantitated via blood levels rather than dose.

More detailed and objective evaluation is needed regarding the risks of behavioral abnormalities such as autism, ASD, ADHD and dyspraxia with in utero AED exposure. It is possible that some of the traits attributed to these diagnoses will be manifestations of mild to moderate developmental delay. In addition, as we investigate the risk of ASD and other NDD associated with AED exposure, it will be important to assess and control for parental socialization skills and learning disabilities.

In addition to more prospective human studies, further translational research is needed to clarify the mechanisms of AED-related teratogenesis in humans and clarify which mother-infant pairs are at greatest risk. Hopefully, understanding these mechanisms will lead to ways to avoid or at least minimize the adverse effects of AED use during pregnancy which is a necessity for many women with epilepsy, mood or pain disorders. Additionally to manage the delicate balance between adverse effects of AEDs and seizures, clinicians need more information about the effect of AED drug levels as well as a better understanding of how seizures types and frequency affects pregnancy outcomes and cognitive development.

Implications for Patient Care

Although there is still much more to be learned, it is imperative that physicians treating women taking AEDs be proactive in keeping up with the literature on both the structural and cognitive teratogenic risks of these drugs. They should

counsel all women of reproductive age on these risks early and often. Young women including teens and preteens should be appropriately counseled even before they are sexually active. Half of all pregnancies in women with epilepsy are unplanned,[117] thus waiting until a woman is planning pregnancy to counsel her or optimize her regimen is not sufficient. Contraceptive counseling is also extremely important for all women taking AEDs, particularly because many antiepileptic drugs have significant drug–drug interactions with hormonal contraception.[118] An intrauterine device is a highly effective form of reversible contraception appropriate for many patients who are not planning pregnancy.

Even with effective contraception, however, medication management of a reproductive-age woman should always strive to use drugs with lowest teratogenic potential first. Valproate should never be used as a first-line drug in girls or women. There is a minority of patients in whom seizures or mood symptoms cannot be adequately controlled without valproate. In these patients, the dose of valproate should be minimized and polytherapy should be avoided whenever possible. For women taking other AEDs, these should also be kept at minimal effective dose/level. It is also critical to make sure that AEDs are indicated. For example, women with seizures that do not respond to an antiepileptic drug or who have atypical histories should be referred for inpatient monitoring early in their treatment to exclude a diagnosis of nonepileptic seizures.

Choosing an AED for a woman of reproductive age and counseling her about teratogenic risks should take into account available information about cognitive outcomes. Counseling should not be limited to a discussion of structural teratogenesis or Food Drug Administration (FDA) pregnancy category. The FDA pregnancy categories are a useful guideline but the majority of AEDs are FDA category C (only topiramate and valproate are category D and valproate is category X for the treatment of migraine during pregnancy). Thus this classification scheme does not suffice to explain the differences between a drug for which we have some animal and human studies with relatively favorable outcome (i.e., carbamazepine, lamotrigine, levetiracetam) and those for which we have no significant human data but cause for concern based on animal studies (i.e., lacosamide, vigabatrin). The FDA has announced that the current pregnancy categories will be phased-out starting in June 2015 and should be replaced with more detailed information on teratogenic risk as well as information on how to enroll in pregnancy registries. This information might help clinicians provide a more comprehensive counseling on the risk of drug exposure in pregnancy.

An area of great controversy is whether AED regimens should be changed during pregnancy. Previously, when data on AED teratogenesis was mostly limited to data on MCMs, the window of opportunity to switch AEDs was felt to be mostly closed by the time a woman knew she was pregnant. Furthermore, the risk of cross-titrating AEDs was considered too great given that this exposed the fetus to polytherapy and increased the risk of seizures. Based on the recent data, however, the cognitive effects of AEDs likely occur throughout pregnancy and particularly during the third trimester. Therefore, some experts feel that in certain cases it is reasonable to change AEDs during pregnancy in patients taking valproate. This is a difficult decision that needs to be based on the patient's individual history including her seizure frequency and/or severity of her mood disorder, history of prior medication trials and effectiveness and likelihood of responding to the next drug as well as the ability to monitor her closely. There is insufficient evidence to argue for or against this approach.

Women taking antiepileptic drugs should also take folic acid supplements though the exact dose required is not known. In population studies, folic acid supplementation decreases risk of neural tube defects and may have a positive effect on cognitive development. Although data demonstrating a clear benefit of folic acid supplements for women taking AEDs beyond that of the benefits in the general population are limited, supplementation is typically recommended by professional organizations. Since several AEDs are known to interfere with folate metabolism, supplementation above the 0.4 mg recommended for all women of childbearing age is reasonable until more data are available. In the United States, 0.4 to 4 mg is recommended, and 5 mg is recommended in the United Kingdom, Europe, and Canada for women taking AEDs.[103–105,108]

Most women with taking AEDs should be encouraged to breastfeed. At least for women taking carbamazepine, lamotrigine, phenytoin or valproate monotherapy the benefits of breast milk have been shown to outweigh risks. Women taking other AEDs or combinations of AEDs should at least be engaged in a discussion about the known benefits of breast milk and the mostly theoretical concerns about infant exposure through breast milk to other AEDs. Supporting breastfeeding needs to be a team effort that includes the neurologist, obstetrician and pediatrician to avoid mixed messages that can frustrate a patient and undermine her efforts to breastfeed. A prebirth visit with a pediatrician to discuss the mother's medical history and breastfeeding plans is often very useful. Pediatricians treating children exposed to AEDs in utero should also be vigilant in monitoring the child's developmental progress and consider early intervention for children exposed to valproate or any AED-exposed child demonstrating signs of developmental delay.

Conclusions

Recent studies have substantially augmented our understanding of the developmental risks of in utero AED exposure. In particular, they have shown that, for at least some children, prenatal valproate exposure can have adverse cognitive and behavioral consequences. Continued prospective research is needed to characterize the effects of other antiepileptic drugs completely. Further animal, translational and human studies are also needed to identify the epigenetic mechanisms by which AED-mediated cognitive and behavioral teratogenesis occurs to identify at-risk patients and ideally develop interventions that mitigate the adverse effects of AEDs.

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