Developmental effects of antiepileptic drugs and the need for improved regulations

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ABSTRACT

Antiepileptic drugs (AEDs) are among the most common teratogenic drugs prescribed to women of childbearing age. AEDs can induce both anatomical (malformations) and behavioral (cognitive/behavioral deficits) teratogenicity. Only in the last decade have we begun to truly discriminate differential AED developmental effects. Fetal valproate exposure carries a special risk for both anatomical and behavioral teratogenic abnormalities, but the mechanisms and reasons for individual variability are unknown. Intermediate anatomical risks exist for phenobarbital and topiramate. Several AEDs (e.g., lamotrigine and levetiracetam) appear to possess low risks for both anatomical and behavioral teratogenesis. Despite advances in the past decade, our knowledge of the teratogenic risks for most AEDs and the underlying mechanisms remain inadequate. Further, the long-term effects of AEDs in neonates and older children remain uncertain. The pace of progress is slow given the lifelong consequences of diminished developmental outcomes, exposing children unnecessarily to potential adverse effects. It is imperative that new approaches be employed to determine risks more expediently. Our recommendations include a national reporting system for congenital malformations, federal funding of the North American AED Pregnancy Registry, routine meta-analyses of cohort studies to detect teratogenic signals, monitoring of AED prescription practices for women, routine preclinical testing of all new AEDs for neurodevelopmental effects, more specific Food and Drug Administration requirements to establish differential AED cognitive effects in children, and improved funding of basic and clinical research to fully delineate risks and underlying mechanisms for AED-induced anatomical and behavioral teratogenesis.

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GLOSSARY

AED = antiepileptic drug; **CAE** = childhood absence epilepsy; **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **FDA** = Food and Drug Administration; **HR** = hazard ratio; **NCBDDD** = National Center on Birth Defects and Developmental Disabilities; **NNNS** = NICU Network Neurobehavioral Scale.

Antiepileptic drugs (AEDs) are among the most common teratogenic drugs prescribed to women of childbearing age. Although classified as antiepileptic, over half of AED prescriptions are for neuropathic pain, migraine headaches, and psychiatric disorders. In addition, AED use during pregnancy is expanding overall, with a fivefold prescription increase in newer AEDs between 2001 and 2007.¹ The risks of malformations from AEDs have been studied primarily in women with epilepsy. The occurrence of major congenital malformation is 6.1% in offspring of women with epilepsy who were treated with AEDs, 2.8% in children of women with untreated epilepsy, and 2.2% in healthy controls.² However, risk is variable across AEDs. The most common malformations from fetal AED exposure are cardiac malformations, and other malformations include orofacial clefts, skeletal, urologic, and neural tube defects.²

Bromide, the first AED, was discovered in the 1850s. Initial reports noting increased malformation risk in children exposed in utero to AEDs were in the 1960s shortly after the thalidomide tragedy highlighted the risks of fetal drug exposure. The first congenital defect linked to a specific AED was spina bifida for valproate in 1982.³ Detailed differential anatomical and behavioral effects of in utero AED exposure did not appear until the 2000s.⁴ The extended delay in

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recognizing risks of AED exposure has caused significant adverse developmental outcomes that could have been prevented. Further, the risks for many additional AEDs remain unknown.

Studies on AED teratogenic effects are underpowered for most AEDs. Although AED pregnancy registries provide larger sample sizes for some AEDs, most registries rely on voluntary reporting and are thus subject to enrollment bias.² Even with increased knowledge in the last decade, the relative risks for both anatomical and behavioral deficits from fetal AED exposure remain uncertain for most AEDs. The present rate of expanding our knowledge remains slow, especially given the lifelong implications of diminished developmental outcomes. This article summarizes our present knowledge and proposes potential solutions to address the need for improved oversight, routine standardized assessments, and research funding directed at the developmental effects of AEDs.

FETAL AED RISKS FOR MAJOR CONGENITAL MALFORMATIONS Detailed reviews are available elsewhere.^{2,5}

Monotherapy. The risks of malformations for AED monotherapies are outlined in table 1. Approximately 400 cases are necessary to adequately establish overall risk of malformations combined, and larger samples are needed for specific malformations. The sample sizes for most of the AEDs listed in table 1 are inadequate not only to determine risks for specific defects, but also to establish dose-dependent risks. Data for the remaining AEDs not in the table are absent or inadequate to estimate overall risks.

Polytherapies. The American Academy of Neurology guidelines concluded that fetal exposure to AED polytherapy likely increases the risk of major congenital malformations as compared to monotherapy.⁴ Polytherapy regimens that include valproate appear to be a major contributor to this risk.^{2,6} Additional research is needed to characterize the risk of different polytherapy combinations, especially combinations with newer generation AEDs.

Summary of AED and malformations. Variability in findings across studies reflects differences in methodology, AED doses, and patient populations. Despite these differences, it is clear that valproate poses the greatest risk for congenital malformations of AEDs studied thus far. Phenobarbital and topiramate appear to pose intermediate risks, while carbamazepine, lamotrigine, and levetiracetam pose lower risks. The findings of the European and

International Registry of Antiepileptic Drugs in Pregnancy study demonstrating dose-dependent effects for the 4 AEDs with adequate sample sizes suggest that dose-dependent risks for malformations may exist for most AEDs.⁵ The malformation risks for many AEDs as well as specific AED combinations are not yet known.

FETAL AED RISKS FOR COGNITIVE IMPAIRMENT Detailed reviews are available elsewhere.^{7,8}

Monotherapy. The risks of cognitive/behavioral impairments in children from fetal AED exposure are listed in table 2 for carbamazepine, lamotrigine, levetiracetam, phenobarbital, phenytoin, and valproate. Data on cognitive effects of in utero exposure are not available for other AEDs in humans.

Polytherapies. The American Academy of Neurology guidelines concluded that cognitive outcomes are likely reduced in children exposed in utero to AED polytherapy as compared to monotherapy.⁴ However, the relative effects of various AED combinations are uncertain.

Summary of fetal AED risks for cognitive impairment. Present studies suggest that valproate poses a special risk for behavioral as well as anatomical teratogenesis. These risks are dose-dependent, but a safe low dose is not apparent. Some studies have suggested risks for other AEDs, but these risks have not yet been adequately characterized. Reasons for variability in individual children are unclear, and the risks of cognitive impairments for many AED monotherapies and polytherapy combinations are unknown.

FETAL AED RISKS FOR AUTISM AND AUTISTIC SPECTRUM DISORDER Cases and small series suggested that fetal valproate exposure poses autism risk.^{9–12} Several additional studies have demonstrated increased behavioral problems in children exposed to valproate in utero.^{13,14} However, the strongest evidence linking valproate to autism risk comes from a Danish population-based study (1996–2006), which examined 655,615 children including 508 with fetal valproate exposure. The incidence of autistic spectrum disorder was 4.42% (95% confidence interval [CI] 2.59%–7.46%) (adjusted hazard ratio [HR] 2.9) and autism incidence was 2.50% (95% CI 1.30%–4.81%) (adjusted HR 5.2) in children with fetal valproate exposure.¹⁵

POTENTIAL COGNITIVE RISKS FOR NEONATES AND OLDER CHILDREN **Importance of the problem.** Multiple AEDs have comparable overall efficacy for appropriate epilepsy syndromes, but may differ in effectiveness. Neuropsychological effects of AEDs contribute to differential effectiveness, and AED psychotropic effects can be positive or negative.^{7,16}

Table 1 Monotherapy AED risks of major congenital malformations (% malformations [95% confidence intervals]; sample size, except EUROCAT, with odds ratios [95% confidence intervals])

AED	CBZ	GBP	LTG	LEV	OXC	PB	PHT	TPM ^a	VPA
North American AED Pregnancy Registry ^{b,e1}	3.0 (2.1-4.2); 1,033	0.7 (0.02-3.8); 145	2.0 (1.4-2.8); 1,562	2.4 (1.2-4.3); 450	2.2 (0.6-5.5); 182	5.5 (2.8-9.7); 199	2.9 (1.5-5.0); 416	4.2 (2.4-6.8); 359	9.3 (6.4-13.0); 323
UK ^{a2-e4} and Ireland ^{a2} Epilepsy and Pregnancy Registers	2.6 (1.9-3.5); 1,657		2.3 (1.8-3.1); 2,098	0.70 (0.2-2.5); 304				4.8 (1.7-13.3); 70	6.7 (5.5-8.3); 1,220
Danish Medical Birth Registry ^{e5}		1.7 (0.1-5.1); 59	3.7 (1.15-2.2); 1,019		2.8 (0.6-2.2); 393			4.6 (0.8-4.9); 108	
Finnish Medical Birth Registry ^{e6}	3; 805						3; 38		11; 263
Swedish Medical Birth Registry ⁵	3; 1,318		3; 867				7; 119		5; 619
International Lamotrigine Pregnancy Registry ^{e7}			2; 1,558						
European and International Registry of Antiepileptic Drugs in Pregnancy ^{e8,6}	Low dose ^b 3.4 (1.1-7.7); high dose ^c 8.7 (5.2-13.4); total 1,402		Low dose ^d 2.0 (1.2-3.2); high dose ^e 4.5 (2.8-6.9); total 1,280			Low dose ^f 5.4 (2.5-10.0); high dose ^g 13.7 (5.7-26.3); total 217			Low dose ^h 5.9 (4.2-8.3); high dose ⁱ 24.0 (16.8-33.1); total 1,010
European Surveillance of Congenital Anomalies ^{e9,e10}	Odds ratio: spina bifida 2.6 (1.2-5.3)								Odds ratios: spina bifida 12.7 (7.7-20.7)
									Atrial septal defect 2.5 (1.4-4.4)
									Cleft palate 5.2 (2.8-9.9)
									Hypospadias 4.8 (2.9-8.1)
									Polydactyly 2.2 (1.0-4.5)
									Cranio-synostosis 6.8 (1.8-18.8)
Gabapentin Pregnancy Registry ^{e11}		4.5; 44							
GBP Multicountry Study ^{e12}		4.1; 170							

Abbreviations: AED = antiepileptic drug; CBZ = carbamazepine; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; TPM = topiramate; VPA = valproate.

^a Particular risk for cleft defects was noted in the North American and UK registries.

^b Low dose (<400 mg/d) for carbamazepine.

^c High dose ($\geq$ 1,000 mg/d) for carbamazepine.

^d Low dose (<300 mg/d) for lamotrigine.

^e High dose ($\geq$ 300 mg/d) for lamotrigine.

^f Low dose (<150 mg/d) for phenobarbital.

^g High dose ($\geq$ 150 mg/d) for phenobarbital.

^h Low dose (<700 mg/d) for valproate.

ⁱ High dose ($\geq$ 1,500 mg/d) for valproate.

Table 2 Fetal AED risks for cognitive/behavioral impairments

AED	Study designs	No. ^a	Age	Maternal IQ	Findings
CBZ	Prospective evaluator-blind study ^{e13}	36	>18 mo	No	CBZ = HCtrls on IQ
	Population-based, longitudinal study ^{e14}	35	4.5–5 y	No	CBZ = HCtrls locomotor
	Prospective assessor-blind study ^{e15}	86	7 y	Yes	CBZ = HCtrls > VPA on verbal IQ
	Observational cohort study ^{e16}	37	9–60 mo	No	VPA < CBZ < LTG and HCtrls on neurodevelopmental measures
	Prospective registry ^{e17}	34	6–7.2 y	No	CBZ = LTG > VPA on language scores
	Prospective assessor-blind study ^{e18–e20}	94	3–6 y	Yes	CBZ > VPA on FSIQ, verbal and memory scores; CBZ = LTG = PHT on FSIQ
	Prospective assessor-blind study ^{e21}	50	6 y	Yes	CBZ = HCtrls = LTG > VPA (>800 mg/d); CBZ < HCtrls on verbal IQ; CBZ > VPA (<800 mg/d) on nonverbal IQ
LTG	Prospective assessor-blind study ^{e18–e20}	100	3–6 y	Yes	LTG > VPA on FSIQ, verbal, nonverbal, memory, and executive scores; LTG = CBZ = PHT on FSIQ; LTG had fewer dextrals and lower verbal than nonverbal scores
	Observational cohort study ^{e16}	26	9–60 mo	No	VPA < CBZ < LTG and HCtrls on neurodevelopmental measures
	Prospective registry ^{e17}	9	6–7.2 y	No	LTG = CBZ > VPA on language scores
	Prospective assessor-blind study ^{e21}	29	6 y	Yes	LTG = HCtrls = CBZ > VPA (>800 mg/d); LTG > VPA (>800 mg/d) on verbal IQ
LEV	Prospective assessor-blinded study ^{e22}	43	42 mo	Yes	LEV = HCtrls > VPA on development and language scores
PB	Two assessor-blind studies on independent cohorts ^{e23}	33 and 81	Adult men	No	PB: Lower verbal IQ in both cohorts
PHT	Blinded-evaluator case-control study ^{e24}	20	4–8 y	No	PHT: Lower FSIQ and PIQ
	Prospective evaluator-blind study ^{e15}	36	7 y	Yes	PHT < CBZ and HCtrls on IQ, but PHT = CBZ when maternal IQ controlled
	Population-based, longitudinal study ^{e14}	21	4.5–5 y	No	PHT < HCtrls locomotor
	Prospective assessor-blind study ^{e18–e20}	55	6 y	Yes	PHT > VPA on FSIQ, verbal and memory; PHT = CBZ = LTG on FSIQ
VPA	Retrospective study ^{e25}	56	School age	No	3.4 OR risk for additional educational needs in monotherapy VPA vs unexposed
	Retrospective study ^{e26}	41	≥6 y	Yes	VPA < other monotherapies and unexposed on verbal IQ
	Prospective study ^{e27}	42	2 y	No	Delayed early development for VPA
	Observational cohort study ^{e16}	45	9–60 mo	No	VPA < CBZ < LTG and HCtrls on neurodevelopmental measures
	Prospective assessor-blind study ^{e15}	13	7 y	No	VPA < CBZ and HCtrls on verbal IQ
	Prospective registry ^{e17}	23	6–7.2 y	No	VPA < CBZ = LTG on language scores
	Prospective assessor-blind study ^{e18–e20}	62	3–6 y	Yes	VPA < CBZ = LTG = PHT on FSIQ, verbal, and memory; VPA < LTG on nonverbal and executive scores; VPA dose-dependent effects on all measures
	Prospective assessor-blind study ^{e21}	51	6 y	Yes	VPA (>800 mg/d) < HCtrls = CBZ = LTG on FSIQ; VPA (<800 mg/d) < HCtrls = CBZ on verbal IQ

Abbreviations: AED = antiepileptic drug; CBZ = carbamazepine; FSIQ = full-scale IQ; HCtrls = healthy controls; LEV = levetiracetam; LTG = lamotrigine; OR = odds ratio; PB = phenobarbital; PHT = phenytoin; PIQ = performance IQ; VPA = valproate.

^a Sample sizes (monotherapy).

Choosing between AEDs in children is based largely upon clinical experience rather than research due to absence of appropriate studies to form evidence-based recommendations.

The importance of cognitive and behavioral risks of AEDs in pediatric populations is recognized by multiple organizations. The American Academy of Neurology/Child Neurology Society practice guideline

asserts “behavioral and cognitive side effects need to be better evaluated, especially for new AED(s), and individual risks as well as group differences assessed on tests of cognition.”¹⁷ According to the American Academy of Pediatrics, “few studies have been comprehensive, and for most drugs, neuropsychological effects have been incompletely described.”¹⁸ An NIH workshop nearly 2 decades ago emphasized cognition and

behavioral outcomes as critical components for evaluating AED effectiveness in pediatric epilepsy.¹⁹ Drug tolerability is an important component of AED effectiveness,²⁰ with long-term AED retention rates more dependent on adverse neuropsychological side effects than on efficacy alone.²¹ Knowledge of differential neuropsychological AED effects in children is particularly important since AEDs may affect long-term brain maturation.

Despite recognition of their importance, inclusion of cognitive and behavioral measures in assessment of AED effectiveness and tolerability largely remains an aspirational goal. Neuropsychological AED data in children are limited²² and adult AED findings are not readily generalizable to children.²³ For example, the primary behavioral phenobarbital side effect is hyperactivity in children, depression in young adults, and sundowning in the elderly. Although neuropsychological impairment may be present at the time of initial diagnosis,²⁴ AED exposure during neurodevelopment can produce impairments that may continue into adulthood even after AED discontinuation.²⁵ Thus, neuropsychological morbidity associated with AED selection will have lifespan consequences with broad public health implications.

Cognitive AED outcomes in pediatric epilepsy. Results of the few well-designed studies and the methodologic limitations are detailed elsewhere.²² In an influential randomized clinical trial, phenobarbital for seizure prophylaxis was associated with an approximate 1/2 SD decline compared to controls, an effect that persisted following drug discontinuation.²⁶ The inability of children to fully catch up and compensate for lost time is important because it suggests the AEDs may alter developmental trajectory. The magnitude of phenobarbital's effect is large since IQ is a global score, and AEDs can have greater effect on attention and processing speed. Phenobarbital can also decrease verbal learning.²⁷ In contrast, a small randomized trial comparing phenobarbital to carbamazepine in children with partial epilepsy observed no IQ differences.²⁸ In a double-blind randomized clinical trial in childhood absence epilepsy, valproate was associated with poorer attentional performance compared to either ethosuximide or lamotrigine.²⁹

Study design issues. The literature on cognitive AED effects is rife with significant methodologic limitations,²² including open-label studies without randomization, underpowered sample sizes, and absence of appropriate control groups including direct comparison to other AEDs. The duration of most studies is inadequate to establish long-term cumulative AED effects on cognition (e.g., school performance and achievement). Many studies report

AED effects as global summary measures (e.g., IQ) rather than attention, memory, and processing speed domains, which are more sensitive to AED effects. Thus, cognitive effects could be missed due to inappropriate test selection.

Cognitive testing cannot easily be added to traditional AED efficacy studies designed to demonstrate seizure frequency reduction since these studies are conducted in patients with severe epilepsy and are designed to have treatment failures. Thus many patients will not complete the study, and comparable cognitive effects cannot be readily established. Decreased seizures may improve cognition, obscuring adverse AED cognitive effects. Since efficacy studies are designed to demonstrate differences in seizure control, one treatment group is expected to have a greater failure rate, resulting in a larger number of patient withdrawals. If patients failing treatment are tested at the time of AED withdrawal, the results are not comparable for multiple reasons. First, if they are withdrawn quickly due to adverse event such as rash, they will be off the AED when tested. Second, if patients fail treatment due to increased seizure frequency, the increase in seizures will adversely impact cognition. Third, the test-retest time interval for patients exiting the study will be shorter than for those who complete the trial, resulting in greater practice effects and less time for habituation. Thus, cognitive AED effects are best investigated in a study specifically designed to establish cognitive treatment side effects rather than as part of a design to investigate AED efficacy for seizure control.

Under appropriate conditions with established medications, cognitive testing may be included without the above biases. For example, differential effectiveness of established medications ethosuximide, lamotrigine, and valproate was investigated in a National Institute of Neurological Disorders and Stroke Phase III clinical trial in newly diagnosed childhood absence epilepsy (CAE).²⁹ Ethosuximide and valproate were more effective in treating CAE than lamotrigine. Ethosuximide emerged as the recommended CAE treatment based upon analyses demonstrating fewer adverse neuropsychological effects on attention compared to valproate. This trial was the first direct head-to-head comparative randomized clinical trial establishing optimal initial treatment for CAE specifically and pediatric epilepsy in general. Although the primary analyses identified a loser across the 3 AEDs (lamotrigine), the different neuropsychological profile between ethosuximide and valproate identified ethosuximide as the initial treatment choice for this population.

As acknowledged by the Agency for Healthcare Research and Quality, classification of treatment success for comparative evaluation of treatment effectiveness of AEDs should include school performance in

Table 3 Anatomical teratogenesis in animals

Antiepileptic drug	Anatomical malformations and defects
Carbamazepine	Malformations induced in animals include gastroschisis, omphaloceles, hydronephrosis, ventricular septal defects, hydrocephaly, and skeletal defects. ² The metabolism of carbamazepine involves oxidative formation of carbamazepine-10,11-epoxide, which is thought to be responsible for the teratogenicity of the parent drug. ^{e28}
Gabapentin	The most commonly observed malformations in animals include craniofacial defects (e.g., brachygnathia, pointed snouts, open eyes, cataracts, and thickened short necks) and limb defects. ^{e29}
Lamotrigine	Prenatal exposure can induce hippocampal and cortical malformations in a dose-dependent manner. ^{e30} Malformations observed in animals include exencephaly, cleft palate, arched palate, midfacial hypoplasia, urogenital abnormalities, and skeletal defects. ^{e31,e32}
Levetiracetam	An increased frequency of skeletal defects has been observed. ^{e33}
Phenobarbital	Anatomical defects seen after exposure to phenobarbital in animals include cleft palate, cardiac malformations, urogenital defects, hydronephrosis, skeletal ossification delays, and dilated cerebral ventricles. ^{e34}
Phenytoin	Malformations in animals include orofacial clefts, skeletal ossification delays. Dilated cerebral ventricles, renal agenesis, hydronephrosis, cutaneous and renal haemorrhage, and cardiac, digital, and ocular abnormalities. ^{e35,e36}
Topiramate	Increased fetal malformations (primarily craniofacial defects) and skeletal ossification defects have been noted in animals. ^{e37}
Valproate	A large variety of developmental defects have been observed in a dose-dependent manner such as skeletal, craniofacial, skeletal, cardiac, exencephalic, and neural tube defects. ^{e38,e39}

children.³⁰ Because clinical trials cannot evaluate study school performance outcomes due to time and resource limitations, standardized and validated approaches to assess cognition including attention provide a surrogate approach given the strong relationship between attention and school performance.³¹ The epilepsy community, including patients, families, and clinicians, increasingly recognized that classification of treatment success extends beyond counting seizures to involve patient-centric considerations (e.g., cognition and quality of life).³² A further discussion of specific recommended assessment approaches is included in appendix e-1 on the *Neurology*[®] Web site at Neurology.org.

Neonates. Neonatal seizures are common, with an overall incidence of 3/1,000 live births and a mortality of ~15% and morbidity of ~30%.³³ Prognosis is primarily related to the underlying etiology of the seizures rather than the seizures themselves. However, controlled studies of AED effectiveness in neonates including behavioral outcomes have not been conducted, and treatment is presently empirical. This is disconcerting given that animal studies demonstrate susceptibility of the immature brain to AED-induced neuronal apoptosis, including AEDs commonly used in neonates (see section on behavioral teratogenesis below).

There are a host of methodologic challenges in the design and execution of AED studies in neonates. Unlike the assessment of cognitive differences in older pediatric populations, in which various computerized approaches may serve as the primary outcome variables, characterization of potential cognitive AED differences and assessment of neonatal AED outcomes require face-to-face testing by a specialty trained

examiner. Although cognitive outcome studies have not yet been performed, a recommended instrument is the NICU Network Neurobehavioral Scale (NNNS),³⁴ which contains normative information and has been successfully used to characterize in utero exposure to cocaine, methamphetamine, alcohol, marijuana, and cigarettes, and the NNNS appears to be the best standardized measure for assessing early developmental outcomes. Further, such studies will ultimately require long-term follow-up evaluations with control of potential confounding variables.

Basic science research of AED teratogenesis. Detailed reviews of basic research on the teratogenic effects of AEDs are available.^{2,35} There is a great need for studies in animal models due to the limitations inherent in human epidemiologic and clinical AED studies. Although the mechanisms of AED teratogenicity remain largely unknown, one suspected mechanism for several AEDs is that their reactive metabolites (e.g., free radicals) are teratogenic.³⁶ AED-induced neuronal apoptosis and related neuronal dysfunction have been emphasized in the mechanisms of behavioral teratogenesis.³⁷

Anatomical teratogenesis in animals. See table 3 for a detailed listing.

Behavioral teratogenesis in animals. Beginning in the 1980s, the behavioral teratogenesis of AEDs became apparent.³⁸ Early studies demonstrated that phenobarbital reduces brain weight and impairs behavior in mice, phenytoin impairs coordination and learning in rats, phenytoin can cause hyperactivity in monkeys, and valproate produced adverse neurobehavioral effects.^{8,38,39}

Similar to alcohol,⁴⁰ certain AEDs can induce widespread neural apoptosis in immature brains.

Table 4 Proposed solutions to expedite discovery and mediation of teratogenic risks for AEDs

A mandatory national reporting system for congenital malformations
Federal funding for the North American AED Pregnancy Registry
Frequent cumulative meta-analyses of cohort studies should be conducted to detect early signal emergence of AED-associated congenital malformations
A national program to monitor prescription practices for AEDs with known teratogenic risks in women of childbearing age and intercede with educational programs where indicated
Routine preclinical testing in animal models of AED neurodevelopmental effects either by industry or the NIH AED Discovery Program
More specific FDA requirements to establish cognitive effects of AEDs in children and to allow comparisons across AEDs
Targeted funding by the NIH and other agencies for basic research on the mechanisms of AED-induced cognitive/behavioral deficits and for clinical research on the long-term cognitive effects of AEDs exposure in the fetus, neonate, and older child; research in this area should also attempt to discover therapies to block or ameliorate the AED-induced deficits

Abbreviations: AED = antiepileptic drug; FDA = Food and Drug Administration.

Studies in rats have shown that clonazepam, diazepam, phenobarbital, phenytoin, valproate, and vigabatrin induce apoptosis.^{41,42} These effects are not present for monotherapy exposures to carbamazepine, lamotrigine, levetiracetam, or topiramate monotherapy.^{43–46} However, all of these AEDs except levetiracetam can enhance the apoptosis when added to AEDs that induce it in monotherapy, suggesting that such polytherapy combinations may increase risks. These apoptotic effects may result from reduced expression of neurotrophins and extracellular signal proteins.⁴² More important than the apoptosis is dysfunction of the surviving neurons since functional and physiological alterations may occur in AEDs that do not produce apoptosis.^{37,47}

In addition, some preliminary animal studies suggest that there may be approaches that can block or ameliorate AED and other drug-induced apoptosis or behavioral deficits in the immature brain. For example, 17 β -estradiol treatment in animals can block AED-induced apoptosis by AEDs such as phenytoin and phenobarbital.⁴⁸ Melatonin can prevent anesthesia-induced neurodevelopmental apoptosis⁴⁹ and can prevent phenobarbital-induced disruption in maturation.³⁷ Vinpocetine is a phosphodiesterase type 1 inhibitor, which can enhance memory and long-term potentiation in animals.⁵⁰ In immature animals exposed to alcohol, subsequent administration of vinpocetine can restore performance on a spatial learning task⁵¹ and restore ocular plasticity.⁵²

Costs of anatomical and behavioral teratogenesis from fetal AED exposures. Direct estimates of the cost solely related to AED-induced congenital malformations and cognitive/behavioral deficits are not available, but can be inferred from other data to be extremely expensive across the lifetime of affected children. See appendix e-2 for detailed financial estimates. These estimates do not include the impact of

AED-induced behavioral deficits such as autism. In addition, beyond the financial impacts, the emotional costs of birth defects, cognitive impairments, and behavioral problems create substantial burdens for both the patient and family caregivers. An improved approach to reduce these financial and emotional costs is needed.

Proposed actions to improve the present situation. An estimated 7.9 million infants worldwide are born each year with a major congenital malformation.⁵³ Congenital malformations may have genetic, infectious, or environmental etiologies, including drug exposures. However, most malformations are due to unknown causes. Prescription drug exposures are a preventable cause once the risks have been established. There is a critical need to better understand the epidemiology of malformations in regards to fetal drug exposure.⁵³ In addition, prescription practice may not change even when the risk is clear. For example, a recent study examined utilization of AEDs in women during pregnancy who were enrolled in Florida Medicaid from 1999 to 2009; although the use of valproate use decreased during this decade, this decrease was only for women receiving AED for epilepsy and was not decreased for other indications. A summary of our recommendations is presented in table 4 and described in detail below.

Centers for Disease Control and Prevention–related. To address birth defects, the Centers for Disease Control and Prevention (CDC) via the National Center on Birth Defects and Developmental Disabilities (NCBDDD) and the Council of State and Territorial Epidemiologists works to identify causes of birth defects. The CDC’s NCBDDD funds 14 states to track major birth defects and funds the Centers for Birth Defects Research and Prevention. In addition, 16 of the grantees funded by CDC’s National Environmental Public Health Tracking Network also report birth defect data. However, these samples are only a portion of those exposed.⁵⁴

There are over 100 infectious diseases that require reporting on a national level, many of which have a smaller public health impact than congenital malformations. Despite the CDC activities, our present knowledge of AED risks has depended primarily on AED pregnancy registries. In the United States, the North American AED Pregnancy Registry has contributed valuable information but depends on pregnant women volunteering, which reduces the pregnancy data available for analysis. The registry began in 1997 and as of the fall of 2014, fewer than 10,000 women had enrolled. These numbers are inadequate to address risks for many AEDs. Thus, critical information to avoid AEDs with higher risks is delayed. In addition, the long-term funding on the North American registry is uncertain since it presently depends on a coalition of

pharmacy companies. Rather than depending on a consortium of pharmaceutical companies, the North American AED Pregnancy Registry should be federally funded, working in collaboration with the CDC.

The situation would be further improved if there were a national reporting system for congenital malformations to obtain population data resulting in much larger samples. The establishment of a national reporting system could also have implications for assessing other etiologies of malformations. Finally, there should be a plan to monitor prescription usage of drugs with known teratogenic risks, and intercede with appropriate educational programs when indicated.

A recent study offers insight into an approach to identify teratogenic signals at earlier time points. Tanoshima et al.⁵⁵ performed cumulative and conventional meta-analyses of cohort studies to determine the time profiles of signal emergence for valproic acid-associated congenital malformations. They found that a significant risk signal for valproic acid-associated combined major congenital malformations emerged in 1990 before the results of the large-scale registries. Such analyses should be routinely conducted by the CDC or Food and Drug Administration (FDA), and also could be done by industry and independent researchers.

FDA-related. The FDA should require preclinical testing of new AEDs in the apoptotic or other neurodevelopmental models to estimate potential risk for behavioral teratogenesis. The findings in apoptotic models mirror the risks of cognitive deficits in children with fetal AED exposure. However, some AEDs that do not produce apoptosis can alter normal neurophysiology. Thus further research is needed. In the interim, use of the apoptotic model would allow identification of AEDs with potential risk prior to marketing rather than being identified years after clinical introduction and widespread use by women. In addition, there should be more specific FDA guidelines on monitoring and evaluation of cognitive effects of AED exposure in neonates and older children.

NIH-related. There is a critical need for additional research to fully delineate the anatomical and behavioral teratogenic risks for many other AEDs and to identify the underlying mechanisms of AED-induced deficits. Since teratogens act on a susceptible genetic substrate, understanding the genetic factors underlying AED teratogenesis is critical. Further, research should also examine potential therapies to block, diminish, or ameliorate the AED-induced deficits. Examining the teratogenic risks of new AEDs should be part of the NIH drug discovery program, and the NIH and other funding agencies should strive to highlight and improve funding of basic and clinical research on this pressing issue.

DISCUSSION AEDs are among the most common teratogenic drugs prescribed to women of childbearing age, which includes prescriptions for epilepsy, neuropathic pain, migraine headaches, and psychiatric disorders. Many women require AED treatment throughout their pregnancies, so understanding the differential teratogenic risks of AEDs is important. Beyond the risks of fetal exposure, the immature brain remains susceptible to AED-induced neuronal apoptosis and dysfunction after birth. Despite advances in our knowledge in the last 2 decades, the precise risks for most AEDs and AED combinations remain unknown. In addition, new AEDs continue to be developed, and under the present approach to establishing cognitive risks, decades will pass before their teratogenic risks are known. Thus, many children may be exposed unnecessarily each year to potential adverse effects. It is imperative that new approaches be employed to determine these risks more expediently. Our recommendations include a national reporting system for congenital malformations, federal funding of the North American AED Pregnancy Registry in collaboration with the CDC, monitoring of prescription practices for AEDs with known teratogenic risks, requiring preclinical testing of all new AEDs in the apoptotic or similar models, and improved funding by the NIH and other organizations of basic and clinical research to fully delineate risks and underlying mechanisms for AED-induced anatomical and behavioral teratogenesis.

AUTHOR CONTRIBUTIONS

Dr. Meador contributed to the concept and design of the review, analyses, and data interpretation; drafted the manuscript; approved the final manuscript for submission; accepts accountability for all aspects of the work; and controlled the decision to publish. Dr. Loring contributed to the concept and design of the review, analyses, and data interpretation; edited and revised the manuscript; and approved the final manuscript for submission.

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