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Fetal antiepileptic drug exposure: Adaptive and emotional/behavioral functioning at age 6 years

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Abstract

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study is a prospective observational multicenter study in the USA and UK, which enrolled pregnant women with epilepsy on antiepileptic drug (AED) monotherapy from 1999 to 2004. The study aimed to determine if differential long-term neurodevelopmental effects exist across four commonly used AEDs (carbamazepine, lamotrigine, phenytoin, and valproate). In this report, we examine fetal AED exposure effects on adaptive and emotional/behavioral functioning at 6 years of age in 195 children (including three sets of twins) whose parent (in most cases, the mother) completed at least one of the rating scales. Adjusted mean scores for the four AED groups were in the low average to average range for parent ratings of adaptive functioning on the Adaptive Behavior Assessment System—Second Edition (ABAS-II) and for parent and teacher ratings of emotional/behavioral functioning on the Behavior Assessment System for Children (BASC). However, children whose mothers took valproate during pregnancy had significantly lower General Adaptive Composite scores than the lamotrigine and phenytoin groups. Further, a significant dose-related performance decline in parental ratings of adaptive functioning was seen for both valproate and phenytoin. Children whose mothers took valproate were also rated by their parents as exhibiting significantly more atypical behaviors and inattention than those in the lamotrigine and phenytoin groups. Based upon BASC parent and teacher ratings of attention span and hyperactivity, children of mothers who took valproate during their pregnancy were at a significantly greater risk for a diagnosis of ADHD. The increased likelihood of difficulty with adaptive functioning and ADHD with fetal valproate exposure should be communicated to women with epilepsy who require antiepileptic

medication. Finally, additional research is needed to confirm these findings in larger prospective study samples, examine potential risks associated with other AEDs, better define the risks to the neonate that are associated with AEDs for treatment of seizures, and understand the underlying mechanisms of adverse AED effects on the immature brain.

Keywords

Antiepileptic drugs; Child development; Behavioral neurology; Epilepsy; Pregnancy; Valproate

1. Introduction

Animal studies have demonstrated that fetal exposure to some antiepileptic drugs (AEDs) at doses lower than those that result in structural malformations can produce cognitive and behavioral deficits, alter neurochemistry, and reduce brain weight [1,2]. Further, AEDs including clonazepam, diazepam, phenobarbital, phenytoin, vigabatrin, and valproate can produce widespread neuronal apoptosis similar to alcohol in the immature rat brain [3–9]. This effect is dose-dependent, occurs at therapeutically relevant blood levels, requires only relatively brief exposure (single injection), and has been related to reduced expression of neurotrophins and levels of protein kinases that promote neuronal growth and survival.

These observations suggest that certain AEDs might produce similar adverse effects in children exposed in utero or in the neonatal period. In fact, several AEDs have been associated with reduced cognitive abilities (e.g., IQ) in children exposed in utero [10–14]. Further, in the NEAD follow-up study at 3 years of age [13], fetal valproate exposure was also shown to significantly impair verbal as well as nonverbal abilities, whereas carbamazepine significantly impacted only verbal abilities. In addition, there were dose-dependent relationships between both lower verbal and nonverbal abilities and valproate and between lower verbal abilities and carbamazepine. Six-year cognitive outcomes recently reported by the NEAD study group [15] indicated that children with fetal valproate exposure continued to exhibit significantly lower IQ than children exposed to carbamazepine, lamotrigine, or phenytoin. In addition, valproate-exposed children performed more poorly than children exposed to the other three AEDs on measures of linguistic functioning and learning/memory. Only a higher valproate dose continued to be negatively associated with performance on measures of intelligence, linguistic functions, nonverbal abilities, learning/memory, and executive functions. Finally, children exposed to preconception folate exhibited higher mean IQ scores.

Previously, we reported [16] a significant dose-related performance decline in motor function for children whose mothers took valproate or carbamazepine during pregnancy. A similar decline in adaptive functioning was reported by parents in the valproate group, and a trend in the same direction was also noted for the carbamazepine group. On the basis of parent ratings of attention span and hyperactivity, the children of mothers who took valproate during pregnancy appeared to be at a significantly greater risk for attention-deficit/hyperactivity disorder (ADHD). In this report, we examine the effects of fetal AED exposure on adaptive and emotional/behavioral functioning at 6 years of age (the final time point of the study) in children of women with epilepsy.

2. Methods

2.1. Design

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study is a prospective observational investigation with blinded assessments that examined the possible cognitive

and behavioral teratogenesis of AEDs. Pregnant women with epilepsy on one of four AED monotherapies (i.e., carbamazepine, lamotrigine, phenytoin, or valproate) were enrolled from October 1999 through February 2004 across 25 epilepsy centers in the USA and UK. During the enrollment period, no other AEDs were being prescribed in numbers adequate enough to study. Polytherapy was not included because of its association with poorer outcomes [17,18]. A nonexposed control group was not included at the unanimous direction of the NIH review panel. This study is registered at clinicaltrials.gov as NCT00021866.

2.2. Participants

The Institutional Review Boards at each center approved the study. Consent for participation was obtained according to the Declaration of Helsinki. A National Institutes of Health Data Safety Monitoring Board monitored study conduct and safety. Pregnant women with epilepsy on carbamazepine, lamotrigine, phenytoin, or valproate monotherapy were enrolled. Mothers with an IQ below 70 were excluded to avoid floor effects and because maternal IQ is a major predictor of child IQ in population studies [19]. Other exclusion criteria included positive syphilis or HIV serology, progressive cerebral disease, other major diseases (e.g., diabetes), exposure to teratogenic agents other than AEDs, poor AED compliance, drug abuse in the prior year, or drug abuse sequelae.

2.3. Procedure

Information was collected on potentially confounding variables, including maternal IQ; age; education; employment; race/ethnicity; seizure/epilepsy types and frequency; AED dosages; compliance; socioeconomic status [20]; UK/USA site; preconception folate use; use of alcohol, tobacco, or other drugs during pregnancy; unwanted pregnancy; abnormalities or complications in the present pregnancy or prior pregnancies; age at enrollment and birth; birth weight; breastfeeding; and childhood medical diseases. Children were classified as breastfed if they were currently breastfeeding at the time of the 3-month follow-up phone call after delivery. Because separate investigations with similar research designs in the US and UK were merged after the investigations were initiated, maternal IQs were assessed using different measures. These measures included the Test of Non-verbal Intelligence—3rd Edition (TONI-3) [21] in 267 mothers, the Wechsler Abbreviated Scale of Intelligence (WASI) [22] in 20, and the National Adult Reading Test (NART) [23] in 17. To allow for comparisons across AEDs, the dosages were standardized. Average AED dose during pregnancy was standardized relative to the ranges observed within each group by the following calculation: $100 \times (\text{observed dose} - \text{minimum dose}) \div \text{range of doses}$.

To assess adaptive functioning, the child's mother/father and teacher (if the child was attending school) were asked to complete the Adaptive Behavior Assessment System—Second Edition (ABAS-II) [24]. Emotional/behavioral functioning was measured by having the child's mother/father and teacher complete the Behavior Assessment System for Children (BASC) [25]. Finally, the level of stress in the parent-child relationship was assessed by having the child's mother/father complete the Parent Stress Index—Third Edition (PSI-III) [26].

The number of completed parent ratings scales varied between 176 and 189 depending upon the scale (ABAS-II: $n = 176$; BASC: $n = 189$; PSI-III: $n = 179$). Many parents did not wish to have their child's school made aware of their involvement in this study. This resulted in a much smaller number of completed forms for teacher ABAS (81) and teacher BASC (123). Only 71 children had both teacher and parent ABAS scores available; by AED group, the number varied from only 12 to 24. Because of the very poor teacher ABAS completion rate, it was decided to analyze the parent ratings only for this scale.

Each rating scale was scored by assessors blinded to the AED used. Training and monitoring of the neuropsychological evaluations were conducted to assure quality and consistency across sites. As part of each training, workshops were conducted for all neuropsychological test batteries annually. In addition, each assessor was required to identify errors and provide the appropriate correction for videotaped testing sessions containing errors in administration and scoring. Assessors were also required to submit their own videotape of a practice test session (with a nonstudy child) with corresponding record forms to the Neuro-psychology Core Director for review, feedback, and approval. If assessors failed, they submitted additional video assessments for approval prior to testing study children.

2.4. Data analysis

The primary analysis in this study included 195 children (including three sets of twins) with complete adaptive and/or emotional/behavioral assessment at 6 years of age. Outcome data were missing for 116 of the 311 originally enrolled children. Multivariate regression models were used to examine AED group differences, adjusting for covariates. The a priori hypothesis for each dependent variable was that the specific AED, maternal IQ, standardized AED dose, gestational age at birth, and preconception folate use were important covariates, and thus, these were included as predictors in a linear model with child adaptive and emotional/behavioral ratings as outcomes. The dependent variables were the General Adaptive Composite score (standard score; mean = 100, standard deviation = 15) from the ABAS-II, the 9 individual clinical scale scores (*T* score; mean = 50, standard deviation = 10) from the BASC, and the Parent and Child Domain scores (measured as a percentile score) from the PSI-III.

Secondary analyses examined the following: 1) the relative relationships of AED exposures to child adaptive and emotional/behavioral ratings, and 2) the relationship of the significant covariates within each model to AED exposure. Analyses were performed at the NEAD Data and Statistical Center using SAS statistical software and R software (www.R-project.org).

3. Results

The primary analysis included 192 mothers and 195 children (including 3 sets of twins). Baseline maternal characteristics are depicted in Table 1. This table also shows a comparison of baseline characteristics in these mothers with the 113 mothers of children who were excluded from the analysis because of missing data. Mothers who were excluded from the analysis did not differ statistically on any of these characteristics from those who were included in the analysis.

3.1. Adaptive functioning

The statistical results for parent ratings on the ABAS-II are presented in Table 2. The results of an analysis of covariance model depicted in Table 2 indicate that the adjusted mean General Adaptive Composite score on the ABAS-II for the children whose mothers took valproate was significantly lower than the mean ratings for lamotrigine ($p = 0.0252$) and phenytoin ($p = 0.0014$). Adjusted age 6 mean composite scores along with 95% confidence intervals (CIs) for each AED group are listed in Table 3. Standardized AED dose was also significantly related ($p = .0006$) to performance ratings on the ABAS-II: a higher dose was associated with lower scores. Pearson correlations with standardized AED dose are presented in Table 4, and scatterplots of the dose-dependent effects are depicted in Fig. 1. Significant dose-dependent effects were seen for valproate ($p < .001$) and for phenytoin ($p = .03$) which indicated that higher average dosages of both of these AEDs were associated

with lower adaptive performance ratings of the children whose mothers took these AEDs during their pregnancies.

3.2. Emotional/behavioral functioning

The results of the analysis of covariance models for the 9 parent and teacher BASC clinical scales (Hyperactivity, Aggression, Conduct Problems, Anxiety, Depression, Somatization, Atypicality, Withdrawal, and Attention Problems) are presented in Tables 5A and 5B, respectively. Analysis of Table 5A indicates that the adjusted mean parent ratings of the four AED groups significantly differed for Atypicality and Attention Problems. In both instances, children whose mothers took valproate were rated as exhibiting significantly more atypical behaviors and inattention than the children whose mothers took lamotrigine ($p = 0.0167$ for the comparison on Atypicality; $p = 0.0197$ for the comparison on Attention Problems) and phenytoin ($p = 0.0123$ for the comparison on Atypicality; $p = 0.0019$ for the comparison on Attention Problems). Adjusted age 6 mean BASC scale scores along with 95% confidence intervals (CIs) for each AED group are listed in Tables 6A and 6B. Further analysis in Table 5A indicates that preconception folate usage during pregnancy is negatively associated with parent ratings on the Somatization and Atypicality scales. Specifically, mothers who took folate endorsed significantly fewer physical concerns ($p = 0.002$) and atypical behaviors ($p = 0.008$) in their children than mothers who did not. In addition, parent ratings of attention problems were marginally ($p = 0.06$) associated with standardized AED dose. However, partial correlations controlling for maternal IQ, folate use, and gestational age did not reveal a significant association within individual AED groups. Analysis of the BASC Teacher ratings indicated that the adjusted AED group means did not significantly differ across any of the 9 clinical scales. However, teacher ratings of anxiety were positively related to gestational age ($p = 0.03$) and negatively related to preconception folate usage during pregnancy ($p = 0.04$).

In order to evaluate the frequency of children who may be at risk for attention-deficit/hyperactivity disorder (ADHD: both inattentive and combined types), the frequency/percentage of children with at-risk parent and teacher ratings on the Attention Problems scale of the BASC (inattentive type) and at-risk ratings on both the Attention Problems and Hyperactivity scales (combined type) was calculated for each AED group. An at-risk score was defined as being greater than one standard deviation above the mean for the standardization sample (T score > 60) [25]. Table 7 presents the frequency/percentage of children with rating patterns consistent with ADHD primarily inattentive type vs combined type by AED group. The frequency/percentage of children in each AED group with either type of ADHD was compared with the 7% estimate of ADHD in the U.S. population reported in the 2006 National Health Interview Survey conducted by the Centers for Disease Control and Prevention [27]. This estimate was based upon parental endorsement of an ADHD diagnosis made by a professional in their children 3–17 years of age. T -test analysis of the parental report data (Table 7) indicated that both the valproate (22.2%; $p = .0001$) and carbamazepine (17.3%; $p = .004$) groups had a significantly greater percentage of children at risk for ADHD than the national CDC estimate. T -test analysis of the teacher report data (Table 7) indicated that the valproate (37.9%; $p < .0001$), carbamazepine (23.1%; $p = .0001$), and lamotrigine (19.44; $p = 0.003$) groups all had significantly greater percentages of children at risk for ADHD than the national CDC estimate (see Fig. 2). Finally, given that the Diagnostic and Statistical Manual of Mental Disorders—IV [28] requires that ADHD behaviors be problematic across multiple settings/raters (home and school), the frequency/percentage of children with at-risk scores on both the parent and teacher rating scales (within the subset of children with both forms completed; $n = 108$) was examined. Analysis of Table 8 reveals that when this diagnostic criterion is considered, only the valproate group (21.4%; $p = .003$) is significantly elevated compared to the CDC national estimate of 7%.

In order to determine if the AED groups significantly differed on the frequency of parents reporting elevated levels of stress in the parent–child relationship, the frequency/percentage of children with at-risk parent ratings on either the Parent or Child Domain scores from the PSI-III was calculated for each AED group. At-risk scores were defined as being greater than the 90th percentile. For both the Parent Domain and the Child Domain, a logistic regression model was fit with the at-risk score (yes/no) as the outcome, controlling for maternal IQ, AED group, standardized dose, gestational age, and folate usage as covariates. Based on a Wald chi-square test, there were no significant group differences for the Parent Domain ($p = .97$) or the Child Domain ($p = .35$).

4. Discussion

The NEAD study is the largest prospective investigation of cognitive and behavioral outcomes following fetal exposure to valproate, carbamazepine, lamotrigine, and phenytoin. The study seeks to determine if differential long-term neurodevelopmental effects exist across these four commonly used AEDs. In this report, we examined the effects of fetal AED exposure on adaptive and emotional/behavioral functioning at 6 years of age (the end point of the study) in children of women with epilepsy.

The major results of this study indicate that although adjusted mean scores for the four AED groups were in the average range for adaptive functioning, the adjusted mean score for the children whose mothers took valproate was significantly lower than the mean scores for the lamotrigine and phenytoin groups. Further, a significant dose-related performance decline in parental ratings of adaptive functioning was seen for valproate, with a less significant performance decline evident for phenytoin. The current findings for valproate are consistent with those previously reported in the NEAD study children at age three [16]. They are also consistent with the 6-year cognitive outcome data (intelligence, linguistic functions, nonverbal abilities, learning/memory, and executive functions) recently reported by the NEAD study group [15]. This finding provides additional support for the contention that fetal valproate exposure can impact not only cognitive development but also the daily adaptive functioning of children whose mothers took this AED, especially at higher dosages.

Children whose mothers took valproate during their pregnancy also received significantly higher parental ratings of behaviors consistent with poor attention regulation and atypicality (social immaturity) as compared with the children of mothers that took lamotrigine or phenytoin. Further, based upon BASC parent rating scales and combined parent and teacher rating scales of attention problems and hyperactivity, children of mothers who took valproate during pregnancy continue to be at a significantly greater risk for a diagnosis of ADHD consistent with our previous report of NEAD children at age three [16]. This finding also supports prior studies demonstrating that children exposed to valproate in utero may be at increased risk for neurodevelopmental disorders such as autism spectrum disorder [29–33]. As such, a raised index of suspicion should translate into more careful follow-up and evaluation of these children with appropriate referral for early interventional services/therapies when indicated.

Finally, our results appear to provide some additional support for maternal use of preconception folate. Specifically, parents who reported maternal folate use also endorsed fewer physical complaints and atypical behaviors in their children, and teachers endorsed lower levels of anxiety in these offspring. However, even though these findings support the work of recent studies which report the positive association of folate use with child IQ and its negative association with language delay and neurodevelopmental outcomes [15,34,35], these findings should be interpreted with caution as folate use was assessed as one of a multitude of confounding variables and was established by maternal interview.

The strengths of the NEAD study include its prospective design, blinded cognitive assessments using standardized measures, and detailed monitoring of multiple potential confounding factors. Caution is advised because of study limitations which include a relatively small sample size, loss of enrolled subjects to analysis, lack of randomization, incomplete data on AED blood levels, and absence of an unexposed control group during pregnancy. As a result, future studies should employ AED blood levels to assess intrauterine exposure. Observational studies, such as the NEAD study, are vulnerable to confounding factors related to baseline characteristics; however, randomized trials of fetal AED exposure in humans are not possible. Although our analysis suggests that baseline group differences do not explain our findings, additional research is needed to confirm these findings in larger prospective study samples, examine the potential risks of other AEDs, better define the risks to the neonate that are associated with AEDs for treatment of seizures as well as other indications, and understand the underlying mechanisms of adverse AED effects on the immature brain.

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Appendix A

A.1. NEAD study group

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Fig. 1. Scatterplots of ABAS-II General Adaptive Composite scores vs. standardized dose for each antiepileptic drug (AED) during pregnancy.

Fig. 2.

Percentage of children at risk for ADHD by AED group. Note: The horizontal line depicts the 7% estimate of ADHD in the U.S. population reported in the 2006 National Health Interview Survey conducted by the Centers for Disease Control and Prevention [27].

Demographics and IQ results for mothers of children included in the analyses (complete data on GAC and/or both attention and hyperactivity subscales of the BASC).

Table 1

	All mothers in analysis	Antiepileptic drug group				Missing mothers ^d
		Carbamazepine	Lamotrigine	Phenytoin	Valproate	
Mothers (n)	192	53	63	31	45	113
Mean maternal IQs (95% CI)	99 (97:102)	100 (95:105)	103 (99:107)	95 (89:101)	96 (91:100)	96 (93:99) [p = 0.08]
Mean maternal ages (95% CI)	30 (29:31)	30 (30:32)	31 (30:32)	29 (27:32)	28 (27:30)	29 (28:30) [p = 0.20]
Mean dose, ^b mg/day (95% CI)	N/A	772 (665:880)	496 (435:557)	401 (353:448)	1058 (860:1256)	N/A
Standardized dose ^c (95% CI)	36 (33:38)	32 (27:37)	38 (33:43)	49 (42:56)	27 (21:33)	33 (29:37) [p = 0.36]
Gestational age in weeks (95% CI)	39 (39:39)	39 (38:39)	39 (39:40)	39 (38:40)	39 (38:40)	39 (38:39) [p = 0.13]
Preconception folate, n (%)	113 (59)	29 (55)	40 (63)	15 (48)	29 (64)	61 (54) [p = 0.47]
Alcohol use during pregnancy, ^d n (%)	12 (6)	5 (9)	3 (5)	0 (0)	4 (9)	12 (11) [p = 0.19]
Epilepsy types ^e						
Localization-related, n (%)	113 (59)	46 (87)	33 (52)	25 (81)	9 (20)	71 (63) [p = 0.10] ^f
Idiopathic generalized, n (%)	59 (31)	3 (6)	23 (37)	2 (6)	31 (69)	38 (34)
GTCSs, n (%)	20 (10)	4 (8)	7 (11)	4 (13)	5 (11)	4 (4)
Race						
Caucasian	160 (83)	46 (87)	57 (90)	16 (52)	41 (91)	85 (75) [p = 0.26] ^g
Black	6 (3)	2 (4)	0 (0)	3 (10)	1 (2)	8 (7)
Hispanic	17 (9)	3 (6)	2 (3)	11 (35)	1 (2)	14 (12)
Other	9 (5)	2 (4)	4 (6)	1 (3)	2 (4)	6 (5)

Note: N/A = not applicable.

^aMothers of children with missing outcome data [p-value for difference from mothers included in analysis].

^bAverage dose for pregnancy.

^cSee Methods for description of how dosages were standardized.

^dAny alcohol use during pregnancy (yes/no).

^eEpilepsy types: localization-related (includes cryptogenic and symptomatic); idiopathic generalized (includes absence, juvenile myoclonic, genetic, and other idiopathic generalized not otherwise classified); GTCSs = generalized tonic-clonic seizures (unknown if generalized or secondarily generalized).

^f p-Value is from a Fisher's exact test for differences between completers and noncompleters in frequency of seizure type categories.

^g p-Value is from a Fisher's exact test for differences between completers and noncompleters in frequency of race categories.

Table 2

Analysis of covariance results for ABAS-II: General Adaptive Composite score.

Dependent variable	Covariate	Degrees of freedom	Parameter estimate	F-value	p-Value
ABAS-II GAC	AED	3		4.19	0.0068
	Maternal IQ	1	-0.0573	0.72	0.3990
	Standardized dose	1	-0.2001	12.33	0.0006
	Gestational age	1	0.3038	0.37	0.5422
	Preconception folate use	1	2.7670	1.46	0.2288

Table 3

Adjusted age 6 means (95% confidence intervals) for ABAS-II General Adaptive Composite score for each antiepileptic drug (AED).

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
ABAS GAC score ^a	96 (92:100)	100 (97:104)	105 (100:111)	94 (89:98)
p-Value in comparison with the adjusted mean in the valproate group	0.4289	0.0252	0.0014	N/A

^aMean ABAS-II General Adaptive Composite score adjusted for maternal IQ, standardized AED dose, birth gestational age, and preconception folate use.

Table 4

Relationships of pregnancy average standardized dose ABAS-II General Adaptive Composite score, using Pearson correlations (p-values).

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
ABAS	-.09 (p = .5698)	-.14 (p = .2883)	-.41 (p = .0303)	-.55 (.0002)
	n = 46	n = 60	n = 28	n = 41

Table 5A

Summary of ANCOVA models for the 9 BASC clinical scales — parent ratings.

Dependent variable	Covariate	Degrees of freedom	Parameter estimate	F-value	p-Value
Hyperactivity	AED	3		0.71	0.5493
	Standardized dose	1	0.0409	1.34	0.2483
	Preconception folate use	1	-0.3969	0.09	0.7708
	Gestational age	1	0.2215	0.54	0.4649
Aggression	Maternal IQ	1	0.0078	0.04	0.8466
	AED	3		0.12	0.9482
	Standardized dose	1	-0.0109	0.10	0.7494
	Preconception folate use	1	0.5821	0.20	0.6583
Conduct Problems	Gestational age	1	-0.1516	0.27	0.6044
	Maternal IQ	1	-0.0078	0.04	0.8412
	AED	3		0.65	0.5856
	Standardized dose	1	0.0371	1.15	0.2848
Anxiety	Preconception folate use	1	1.6372	1.52	0.2196
	Gestational age	1	0.1165	0.16	0.6939
	Maternal IQ	1	-0.0038	0.01	0.9225
	AED	3		1.09	0.3558
Depression	Standardized dose	1	-0.0318	0.66	0.4186
	Preconception folate use	1	-2.6373	3.05	0.0824
	Gestational age	1	0.173	0.27	0.6069
	Maternal IQ	1	0.0064	0.02	0.8873
Somatization	AED	3		0.21	0.8888
	Standardized dose	1	-0.0157	0.26	0.6109
	Preconception folate use	1	-2.0146	2.88	0.0916
	Gestational age	1	0.1749	0.44	0.5087
Somatization	Maternal IQ	1	-0.0224	0.41	0.5253
	AED	3		0.74	0.5294
	Standardized dose	1	-0.0352	0.83	0.3627
	Preconception folate use	1	-4.7806	10.37	0.0015
Somatization	Gestational age	1	-0.3066	0.86	0.3542

Dependent variable	Covariate	Degrees of freedom	Parameter estimate	F-value	p-Value
Atypicality	Maternal IQ	1	0.0483	1.20	0.2739
	AED	3		2.71	0.0466
	Standardized dose	1	0.0426	1.38	0.2412
	Preconception folate use	1	-3.746	7.23	0.0078
	Gestational age	1	-0.0291	0.01	0.9252
Withdrawal	Maternal IQ	1	-0.0436	1.11	0.2930
	AED	3		1.32	0.2679
	Standardized dose	1	0.0334	0.76	0.3860
	Preconception folate use	1	-1.6207	1.20	0.2744
	Gestational age	1	-0.07	0.05	0.8316
Attention Problems	Maternal IQ	1	-0.0146	0.11	0.7401
	AED	3		3.70	0.0128
	Standardized dose	1	0.0758	3.56	0.0609
	Preconception folate use	1	-1.1012	0.51	0.4772
	Gestational age	1	-0.2135	0.39	0.5353
	Maternal IQ	1	-0.0777	2.87	0.0918

Table 5B
Summary of ANCOVA models for the 9 BASC clinical scales — teacher ratings.

Dependent variable	Covariate	Degrees of freedom	Parameter estimate	F-value	p-Value
Hyperactivity	AED	3		0.26	0.8566
	Standardized dose	1	0.0594	1.15	0.2859
	Preconception folate use	1	-2.7492	1.54	0.2174
	Gestational age	1	-0.2893	0.44	0.5068
Aggression	Maternal IQ	1	-0.0499	0.59	0.4422
	AED	3		0.25	0.8577
	Standardized dose	1	-0.0433	0.85	0.3591
	Preconception folate use	1	-0.5294	0.08	0.7791
Conduct Problems	Gestational age	1	0.2703	0.54	0.4655
	Maternal IQ	1	-0.0175	0.10	0.7511
	AED	3		0.74	0.5306
	Standardized dose	1	-0.0302	0.68	0.4098
Anxiety	Preconception folate use	1	-0.1977	0.02	0.8926
	Gestational age	1	0.0746	0.07	0.7949
	Maternal IQ	1	-0.0017	0.00	0.9677
	AED	3		1.37	0.2572
Depression	Standardized dose	1	-0.0406	1.07	0.3039
	Preconception folate use	1	-3.2255	4.17	0.0434
	Gestational age	1	0.6807	4.88	0.0293
	Maternal IQ	1	-0.0741	2.58	0.1107
Somatization	AED	3		1.87	0.1384
	Standardized dose	1	-0.0165	0.13	0.7151
	Preconception folate use	1	-3.1334	2.98	0.0868
	Gestational age	1	0.526	2.21	0.1396
Somatization	Maternal IQ	1	-0.0211	0.16	0.6901
	AED	3		1.11	0.3472
	Standardized dose	1	0.0702	2.13	0.1472
	Preconception folate use	1	-3.4789	3.23	0.0751
	Gestational age	1	-0.3645	0.94	0.3353

Dependent variable	Covariate	Degrees of freedom	Parameter estimate	F-value	p-Value
Atypicality	Maternal IQ	1	-0.0673	1.44	0.2334
	AED	3		2.36	0.0750
	Standardized dose	1	0.1372	3.64	0.0591
	Preconception folate use	1	-4.0112	1.93	0.1679
	Gestational age	1	-0.3509	0.39	0.5353
Withdrawal	Maternal IQ	1	0.0053	0.00	0.9501
	AED	3		2.56	0.0585
	Standardized dose	1	0.104	4.22	0.0423
	Preconception folate use	1	-2.5395	1.57	0.2127
	Gestational age	1	0.6359	2.56	0.1121
Attention Problems	Maternal IQ	1	-0.0274	0.21	0.6444
	AED	3		1.75	0.1617
	Standardized dose	1	0.0859	2.53	0.1142
	Preconception folate use	1	-3.5154	2.65	0.1063
	Gestational age	1	-0.316	0.56	0.4568
	Maternal IQ	1	-0.0862	1.87	0.1738

Table 6A

Adjusted means^a (95% confidence intervals) for 9 BASC clinical scales for each antiepileptic drug (AED) — parent ratings.

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Hyperactivity	49 (47:52)	48 (46:51)	47 (44:51)	50 (48:53)
Aggression	48 (46:51)	48 (46:50)	47 (44:50)	48 (46:51)
Conduct Problems	48 (46:51)	47 (45:49)	49 (46:52)	47 (44:49)
Anxiety	46 (43:49)	47 (45:50)	50 (46:53)	46 (43:49)
Depression	48 (46:50)	47 (45:49)	47 (44:49)	47 (44:49)
Somatization	48 (46:51)	47 (44:49)	50 (46:53)	47 (44:50)
Atypicality	49 (47:52)	48 (46:50)	47 (43:50)	52 (50:55)
Withdrawal	50 (48:53)	49 (47:52)	46 (42:49)	50 (47:53)
Attention Problems	51 (48:53)	48 (46:51)	45 (42:49)	53 (50:56)

^aMean adjusted for maternal IQ, standardized dose, gestational age at birth, and preconception folate use.

Table 6B

Adjusted means^a (95% confidence intervals) for 9 BASC clinical scales for each antiepileptic drug (AED) — teacher ratings.

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Hyperactivity	49 (46:53)	49 (46:53)	48 (42:53)	51 (46:55)
Aggression	48 (45:51)	50 (46:53)	49 (45:54)	50 (46:53)
Conduct Problems	46 (44:49)	47 (44:49)	50 (46:53)	47 (45:50)
Anxiety	47 (44:49)	48 (46:51)	45 (41:49)	49 (46:52)
Depression	48 (45:50)	49 (46:52)	45 (41:50)	52 (48:55)
Somatization	47 (44:51)	51 (47:54)	47 (42:52)	51 (47:54)
Atypicality	51 (46:56)	49 (44:54)	47 (41:54)	58 (52:63)
Withdrawal	48 (44:51)	48 (44:51)	49 (44:53)	54 (50:58)
Attention Problems	50 (47:53)	49 (45:52)	47 (42:52)	54 (50:58)

^aMean adjusted for maternal IQ, standardized dose, gestational age at birth, and preconception folate use.

Table 7

Percentage of children with ADHD inattentive and combined types by AED group for the parent and teacher BASC subscales.

AED group	Parent BASC			Teacher BASC		
	N	Inattentive type, n (%)	Combined type, n (%)	N	Inattentive type, n (%)	Combined type, n (%)
CBZ	52	7 (13.46)	2 (3.85)	39	2 (5.13)	7 (17.95)
LTG	61	4 (6.56)	3 (4.92)	36	2 (5.56)	5 (13.89)
PHT	31	1 (3.23)	1 (3.23)	19	0 (0.00)	3 (15.79)
VPA	45	6 (13.33)	4 (8.89)	29	6 (20.69)	5 (17.24)
All	189	18 (9.52)	10 (5.29)	123	10 (8.13)	20 (16.26)

Note: See Fig. 2 for comparison to the Centers for Disease Control and Prevention estimate of ADHD in the United States.

Table 8

Percentage of children with either ADHD inattentive or combined type by AED group for the subset of children with both parent and teacher BASC scales completed (n = 108).

AED group	# of subjects	% ADHD	Lower limit of 95% CI	Upper limit of 95% CI	p-Value, test of percentage = 7%
CBZ	32	12.50	3.51	28.99	0.2227
LTG	31	12.90	3.63	29.83	0.1977
PHT	17	5.88	0.15	28.69	0.8567
VPA	28	21.43	8.30	40.95	0.0028