IQ at 6 years after in utero exposure to antiepileptic drugs

A controlled cohort study

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ABSTRACT

Objective: To delineate the risk to child IQ associated with frequently prescribed antiepileptic drugs.

Methods: Children born to women with epilepsy (n = 243) and women without epilepsy (n = 287) were recruited during pregnancy and followed prospectively. Of these, 408 were blindly assessed at 6 years of age. Maternal and child demographics were collected and entered into statistical models.

Results: The adjusted mean IQ was 9.7 points lower (95% confidence interval [CI] −4.9 to −14.6; $p < 0.001$) for children exposed to high-dose (>800 mg daily) valproate, with a similar significant effect observed for the verbal, nonverbal, and spatial subscales. Children exposed to high-dose valproate had an 8-fold increased need of educational intervention relative to control children (adjusted relative risk, 95% CI 8.0, 2.5–19.7; $p < 0.001$). Valproate at doses <800 mg daily was not associated with reduced IQ, but was associated with impaired verbal abilities (−5.6, 95% CI −11.1 to −0.1; $p = 0.04$) and a 6-fold increase in educational intervention (95% CI 1.4–18.0; $p = 0.01$). In utero exposure to carbamazepine or lamotrigine did not have a significant effect on IQ, but carbamazepine was associated with reduced verbal abilities (−4.2, 95% CI −0.6 to −7.8; $p = 0.02$) and increased frequency of IQ <85.

Conclusions: Consistent with data from younger cohorts, school-aged children exposed to valproate at maternal doses more than 800 mg daily continue to experience significantly poorer cognitive development than control children or children exposed to lamotrigine and carbamazepine.

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GLOSSARY

AED = antiepileptic drug; **CBZ** = carbamazepine; **CI** = confidence interval; **IGE** = idiopathic generalized epilepsy; **LTG** = lamotrigine; **NEAD** = Neurodevelopmental Effects of Antiepileptic Drugs; **RR** = relative risk; **VPA** = valproic acid; **WWE** = women with epilepsy.

Antiepileptic drugs (AEDs) are associated with teratogenic risk to the development of the fetus, with the prevalence of major congenital malformations differing by treatment type and dose.[1] Determining the association between exposure to AEDs and child cognitive functioning represents a challenge, and a number of different methodologies have been utilized in its investigation including case studies,[2–4] retrospective studies,[5,6] and prospective studies.[7–15] Despite limitations,[16] there is growing evidence that exposure to sodium valproate (VPA) in utero is associated with significantly poorer functioning.[10–12,15,17] Prospective studies consistently document that VPA is associated with an increase in risk of cognitive impairment in young children,[10,12,15] but any longer-term effects are unlikely to be comprehensively documented until the children studied are of school age, when cognitive development is more stable.[10] In a comparison across AED monotherapies, a significantly poorer IQ in school-aged children exposed in utero to

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VPA was found compared with those exposed to carbamazepine (CBZ), lamotrigine (LTG), and phenytoin.[17] However, a comparison against control children was not possible and therefore the effects of CBZ and LTG on school-aged child IQ remain inconclusive. Deficits in IQ have significant educational,[18] health, and economic implications and therefore risks conveyed to the fetus by medications need to be delineated.

Earlier publications from this longitudinal cohort have reported an increased risk of major congenital malformations,[19] significantly lower early cognitive development,[15] and increased rates of autistic spectrum disorder[20] after exposure to VPA.

METHODS This was a prospective observational study with a control group representative of the general population, which aimed to provide critical information on the longer-term impact of in utero exposure to AEDs. Three main groups were recruited: children born to women with epilepsy (WWE) exposed to AEDs, children of WWE not taking AEDs, and control children (table 1). This study had a directional hypothesis: children exposed to VPA would have a significantly lower IQ than control children and children of WWE exposed to other AEDs or to no medication.

Standard protocol approvals, registrations, and patient consents. Ethical approval was obtained from the North West Regional Ethics Committee and individual participating sites. All mothers provided informed written consent for the participation of themselves and their child.

Procedure. WWE were recruited from antenatal clinics at 11 National Health Service hospitals between 2000 and 2004 (table 1). The inclusion criterion was a diagnosis of epilepsy. WWE were excluded from recruitment if they had a severe learning disability or other chronic health condition requiring medication. Because of the neuropsychological measures, families were required to have English as their primary language. Women without epilepsy were recruited from the same antenatal clinics. For each participant with epilepsy, a control of similar age (=/− 5 years), parity, and employment and residing within the same postal area was recruited to ensure comparable groups. The same exclusion criteria applied to the women without epilepsy.

At recruitment, each woman provided information relating to education, occupation, and lifestyle issues such as smoking and alcohol. An epilepsy specialist (G.M.) confirmed seizure type, syndrome (localization-related, idiopathic generalized epilepsy [IGE], or not classifiable), current seizure frequency, and AED. At the time of recruitment, common treatments were VPA, CBZ, and LTG. Other monotherapy treatments (i.e., phenytoin, topiramate, gabapentin, vigabatrin), which were not represented in significant numbers, were included in the "other monotherapy group." Treatment was classed as polytherapy if a second AED (including a benzodiazepine) had been prescribed, even briefly. Seizure frequency was ascertained from the patient and where possible an observer. IQ at 6 years of age was the primary outcome for this longitudinal study, assessed by the Differential Ability Scales.[21] Seeking 80% power at a 95% confidence level to detect a difference of 1.5 SD, it was estimated that 45 children were required in each monotherapy group. To allow for attrition, the recruitment became a minimum of 50 pregnancies in each group. The IQ score is reported along with the subscale scores of verbal, nonverbal, and spatial cognitive abilities.

This study began independently and then later participants with monotherapy AED exposures were invited to participate in the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study. Forty-six percent of the children of the WWE (n = 92) consented to additional enrollment into the NEAD Study and were reported in previous NEAD publications,[10,17] where AED vs AED comparisons were undertaken.

After their sixth birthday, participants were contacted and an appointment arranged at their home, school, or local hospital. The children were assessed by research assistants blinded to the AED exposure or maternal epilepsy status. Information was collected on educational intervention, defined as an educational need ranging from an Individual Educational Plan (a formally agreed set of interventions) through to attendance at a special school. All neuropsychological assessments were double scored. Feedback was provided to the family and where necessary referral to a specialist was arranged. To provide an estimate of the maternal IQ, mothers completed the National Adult Reading Test.[22]

Multiple linear regression and logistic regression analyses were applied to the data where covariates such as maternal epilepsy type, socioeconomic status, maternal IQ, maternal age, gestational age of child at birth, sex, and exposure to seizures, tobacco, or alcohol were considered. The analyses used the inverse probability weighting approach[23] in which the probability of loss to follow-up is estimated from the existing data to account for the influence of missing outcomes. A separate analysis based on the multiple imputation method was applied to consider the robustness of the results, and the results were in agreement. Analysis by high and low dose was undertaken where possible considering dose distribution and numbers. VPA was investigated as 2 groups, with the value determined by previous research[6]: doses >800 mg daily and doses ≤800 mg daily. The polytherapy treatment group that included VPA was too small to undertake this division (mean daily dose 1,114 mg). The underlying model assumptions regarding the statistical properties of the residuals were checked and verified. Two-sided p values of less than 0.05 were regarded as statistically significant. Data were analyzed using the statistical packages MLwiN 2.16 and R 2.11.1. For interpretation purposes, estimates of the adjusted relative risks (RRs) and their 95% confidence intervals (CIs) were derived from the logistic regression analyses (using the adjusted odds ratios, their 95% CIs, and an estimate of the corresponding incidence rates).[24]

RESULTS Five hundred thirty children were enrolled initially of whom 408 (77%) were assessed at 6 years of age (table 1). Differences were found between the demographics of those assessed and those not (maternal IQ $p = 0.01$, socioeconomic status $p = 0.01$, maternal age $p = 0.02$, and nicotine exposure $p = 0.04$).

Children exposed to high-dose VPA (>800 mg daily) had the lowest mean scores (table 1) for IQ and for verbal, nonverbal, and spatial subscales. Exposure to VPA in utero had a negative association with the child's IQ (table 2); an adjusted mean reduction in IQ of 9.7 points was observed for high-dose VPA in comparison to control children. Children exposed to low-dose VPA were not found to have poorer IQ.

Table 1 Demographics and mean child IQ scores (full-scale IQ, verbal, nonverbal, and spatial ability) by treatment group

	Mean child IQ (SD)				Completeness of sampling			Demographics[a]										
								Maternal epilepsy			Seizure exposure			Maternal		Child		
	Full scale	Verbal	Nonverbal	Spatial	Initial,[b] n	Missing, n	Sampled,[a] n (%)	IGE, %	FE, %	UC, %	<20 wk, % yes	>20 wk, % yes	Convulsive,[c] %	Age, y, mean (SD)	IQ, mean (SD)	Age at assessment, mo (SD)	Gestational age, mo (SD)	Sex, % female
Controls	107 (12)	103 (12)	106 (13)	108 (13)	287	77	210 (73)	—	—	—	—	—	—	29.4 (5)	103.4 (12)	73.9 (5)	39.5 (2)	48.1
Epilepsy																		
No medication	104 (13)	99 (12)	104 (14)	105 (13)	34	9	25 (74)	32.0	40.0	28.0	16.0	8.0	4.0	25.9 (5)	96.2 (11)	75.1 (5)	39.9 (1)	28.0
Treatment																		
VPA low, ≤800 mg	98 (11)	94 (14)	98 (9)	101 (14)	25	4	21 (84)	76.2	9.5	14.3	23.8	23.8	28.6	26.4 (5)	93.8 (14)	73.0 (2)	39.6 (2)	28.6
VPA high, >800 mg	93 (12)	90 (10)	96 (15)	96 (16)	34	4	30 (88)	60.0	30.0	10.0	63.3	56.7	50.0	27.1 (7)	97.0 (11)	74.1 (4)	38.5 (2)	33.3
CBZ	105 (15)	98 (15)	108 (14)	106 (16)	59	9	50 (85)	9.8	80.4	9.8	31.4	25.5	19.6	29.4 (5)	99.4 (15)	74.1 (4)	39.3 (2)	51.0
LTG	103 (11)	99 (13)	103 (12)	107 (12)	36	7	29 (81)	23.3	56.7	20.0	40.0	40.0	40.0	27.7 (6)	100.0 (12)	73.7 (4)	39.9 (2)	56.7
Other monotherapy	98 (15)	96 (15)	101 (15)	99 (15)	14	1	13 (93)	28.6	71.4	0.0	42.9	50.0	35.7	29.9 (7)	96.8 (9)	74.0 (3)	40.1 (1)	42.9
Polytherapy																		
With VPA	98 (13)	93 (10)	100 (15)	102 (12)	30	11	19 (63)	35.0	55.0	10.0	52.4	42.9	47.6	25.7 (5)	91.6 (11)	75.4 (6)	38.9 (2)	47.6
Without VPA	103 (13)	99 (12)	105 (16)	103 (17)	11	0	11 (100)	0.0	81.8	18.2	81.8	90.9	81.8	28.8 (6)	94.7 (14)	73.7 (2)	38.8 (2)	45.5

Abbreviations: CBZ = carbamazepine; FE = focal epilepsy; IGE = idiopathic generalized epilepsy; LTG = lamotrigine; UC = unclassified; VPA = valproic acid.

[a] A number of subjects had missing covariates: maternal IQ (24), gestational age (5), socioeconomic status (1), maternal age (1), alcohol (during pregnancy) (2), and smoking (during pregnancy) (2). Three subjects had multiple missing covariates and so are counted as "missing" only once, resulting in a total of 31 subjects with at least one missing covariate.

[b] Figures inclusive of children recruited between 2000 and August 2004 who attended at least one appointment with investigators. Thirty-two children recruited were not aged 6 at study close and are therefore not reported here. An additional 7 cases excluded because of genetic or maternal conditions likely influential on cognitive development (including chromosomal disorders and hydrocephalus).

[c] Percentage of those having seizures that were convulsive, IGE, FE, or UC epilepsy type. The other monotherapy group comprised 8 cases of phenytoin, 1 vigabatrin, 1 oxcarbazepine, 2 gabapentin, and 2 topiramate.

Table 2 Child IQ scores relative to control children and the influence of confounding variables based on the multiple regression analyses (model coefficients, SEs, 95% CIs, and *p* values)

	Full-scale IQ			Verbal			Nonverbal			Spatial		
Explanatory variable/group	Coeff. (SE)	95% CI	*p*	Coeff. (SE)	95% CI	*p*	Coeff. (SE)	95% CI	*p*	Coeff. (SE)	95% CI	*p*
Control	Reference group											
Epilepsy												
No medication	−0.8 (2.5)	−5.6, 4.1	0.76	−1.8 (2.5)	−6.7, 3.1	0.47	1.4 (2.9)	−4.2, 7.0	0.63	−1.9 (3.0)	−7.7, 4.0	0.54
Treatment group												
VPA												
Low, ≤800 mg	−5.0 (2.9)	−10.7, 0.8	0.09	−5.6 (2.8)	−11.1, −0.1	0.04	−5.4 (3.2)	−11.7, 1.0	0.10	−4.2 (3.4)	−10.8, 2.4	0.21
High, >800 mg	−9.7 (2.5)	−14.6, −4.9	<0.001	−9.4 (2.5)	−14.2, −4.6	<0.001	−7.6 (2.8)	−13.1, −2.0	0.007	−9.7 (3.0)	−15.5, −3.9	0.001
CBZ	−0.1 (1.9)	−3.8, 3.6	0.96	−4.2 (1.9)	−7.8, −0.6	0.02	3.0 (2.1)	−1.2, 7.1	0.16	−0.2 (2.2)	−4.6, 4.1	0.92
LTG	−3.0 (2.4)	−7.6, 1.7	0.22	−2.8 (2.4)	−7.5, 1.8	0.23	−2.6 (2.7)	−8.0, 2.8	0.34	−0.7 (2.9)	−6.3, 4.9	0.81
Other mono therapy	−6.6 (3.5)	−13.4, 0.2	0.06	−5.1 (3.5)	−11.9, 1.7	0.14	−3.1 (4.0)	−10.9, 4.7	0.43	−7.5 (4.2)	−15.7, 0.6	0.07
Polytherapy												
With VPA	−6.4 (2.6)	−11.5, −1.2	0.01	−7.3 (2.5)	−12.3, −2.4	0.004	−4.5 (3.0)	−10.4, 1.4	0.14	−4.1 (3.1)	−10.1, 2.0	0.19
Without VPA	−0.3 (3.8)	−7.7, 7.1	0.94	−0.9 (3.7)	−8.2, 6.3	0.80	2.4 (4.4)	−6.2, 11.0	0.58	−2.0 (4.5)	−10.8, 6.8	0.65
Covariates												
Maternal IQ	0.3 (0.1)	0.2, 0.4	<0.001	0.3 (0.1)	0.2, 0.4	<0.001	0.2 (0.1)	0.1, 0.4	<0.001	0.2 (0.1)	0.1, 0.4	<0.001
SES 1 (professional)	Reference status											
SES 2 (skilled employment)	−3.1 (1.6)	−6.2, 0.0	0.05	−5.5 (1.6)	−8.7, −2.4	<0.001	−1.7 (1.8)	(−5.3, 1.9)	0.36	−0.8 (1.9)	−4.5, 3.0	0.69
SES 3 (manual/unemployed)	−4.4 (1.5)	−7.4, −1.5	0.003	−5.2 (1.5)	−8.2, −2.3	<0.001	−3.1 (1.7)	(−6.4, 0.3)	0.08	−3.3 (1.8)	−6.8, 0.2	0.07
Gestational age, wk	0.8 (0.3)	0.1, 1.4	0.02	—	—	—	—	—	—	—	—	—

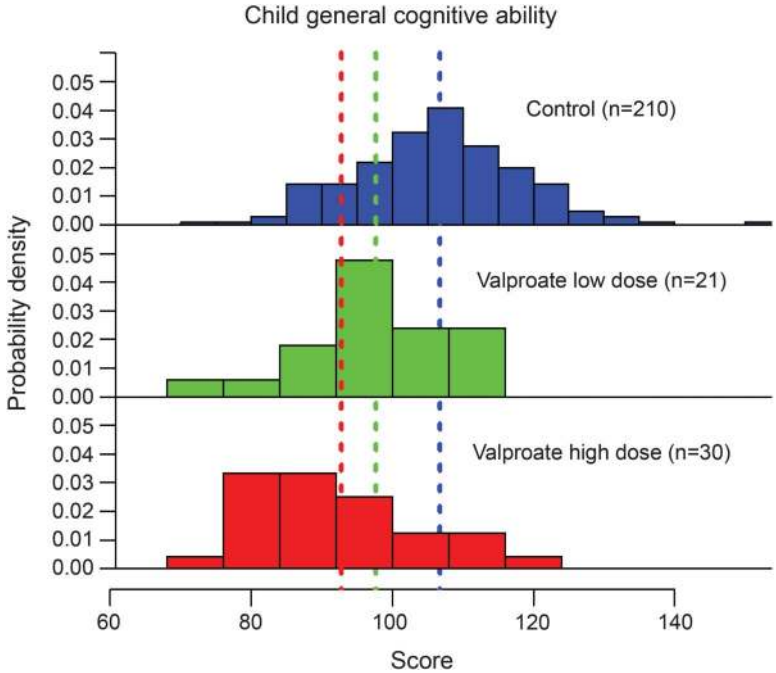
Abbreviations: CBZ = carbamazepine; CI = confidence interval; coeff. = coefficient; LTG = lamotrigine; SE = standard error; SES = socioeconomic status; VPA = valproic acid.
Scores based on the multiple regression analyses (model coefficients, SEs, 95% CIs, and *p* values). Only significant confounders displayed here. Nonsignificant confounding variables: seizure exposure, alcohol exposure, nicotine exposure, age of child at assessment, gestational age at birth, child sex, maternal age, and maternal folate use. Relationship between maternal IQ and child IQ by antiepileptic drug group was as follows: the VPA group $r = 0.20$, control and no medication group $r = 0.35$, CBZ group $r = 0.48$, LTG group $r = 0.38$, other monotherapy group $r = 0.40$, polytherapy with no VPA group $r = 0.45$, and polytherapy with VPA group $r = 0.33$.

The stepwise decrease in IQ relative to control children was consistent with a dose/effect relationship. The influence on IQ of exposure by dose was plotted in distribution graphs (figure 1). Decreases were also noted in verbal, nonverbal, and spatial abilities for high-dose VPA, while low-dose VPA was associated with deficits to a statistically significant level in verbal abilities only (table 2).

High-dose VPA exposure was associated with poorer IQ and nonverbal and spatial abilities in comparison to CBZ and LTG, with verbal abilities additionally being poorer than in those exposed to LTG (table 3). Low-dose VPA (<800 mg/daily) was not associated with poorer abilities compared with the other AED groups, with the exception of nonverbal abilities and CBZ exposure (table 3). Children exposed to both higher and lower doses of VPA were found to require more educational intervention in comparison to control children (table 4).

In a separate logistic regression analysis, child IQ was split into IQ <85 (1 SD poorer than the mean) and >85. The risk of impairment (IQ <85) was 8 times higher in children born to women treated with high doses of VPA than in those born to control women (adjusted RR = 8.6, 95% CI 3.1–18.8; $p < 0.001$). No significant increase in risk of IQ <85 was found for low-dose VPA (adjusted RR = 2.4, 95% CI 0.3–14.0; $p = 0.4$).

Figure 1 **Distribution of IQ scores across the control and valproate-exposed groups**



Because of the small sample size, the histograms in the figure may not look normally distributed, but the medians of the groups were very similar to the highlighted means.

In utero exposure to CBZ did not show an effect on the child's IQ score, the subscales, or nonverbal and spatial abilities. A reduction of 4.2 IQ points in verbal ability was demonstrated in comparison to control children (table 2). In addition, increased RR for scores <85 was found for children exposed to CBZ in utero (adjusted RR = 3.5, 95% CI 1.1–10.2; $p = 0.04$); however, there was no association with increased educational intervention (table 4). No association with dose of CBZ and IQ or its subscales was found.

In utero exposure to LTG was not found to be associated with reduced IQ or verbal, nonverbal, and spatial abilities (table 2). There was no increased rate of below-average performance or need for educational intervention in comparison to control children (table 4). As noted above, LTG-exposed children were superior in their IQ and verbal and spatial abilities in comparison to children exposed to higher-dose VPA (table 3).

Additional analysis confirmed that children born to women treated with polytherapy including VPA showed a mean reduction in 6.4 IQ points relative to children born to control women. No effect was seen in the polytherapy group that did not include VPA (table 2).

Maternal IQ, gestational age, and socioeconomic status were noted to influence IQ scores (table 2). A significant correlation was present between child and maternal IQ for all groups except the children exposed to VPA (figure e-1 on the *Neurology*® Web site at Neurology.org). Thus, the incremental increase in maternal IQ was not associated with the expected incremental increase in child IQ for those exposed to VPA.

The choice of AED was strongly associated with maternal epilepsy type so they cannot be treated as independent variables. However, in separate analyses, variance attributable to differences among AEDs was greater than variance attributable to differences among epilepsy types. When considering the IQ of children born to women with IGE only, those exposed to VPA had a significantly lower mean IQ than those untreated or treated with another AED (figure e-2). The frequency of seizures varied by treatment group (table 1). Regression analysis did not reveal any association between seizures (total or convulsive) and the measures of child cognitive ability, but convulsive seizures were associated with an increased need for additional educational support (table 4). Only 8% of the children born to WWE were exposed to 5 or more generalized seizures. There was no difference in the mean IQ of the children whose mothers took a folate supplement before conception (101.7, 95% CI 98.9–104.5; n = 91) and the children of mothers who did not (99.8, 95% CI 97.4–102.2; n = 108).

Table 3 Child IQ scores after exposure to carbamazepine, lamotrigine, and other monotherapies relative to children exposed to sodium valproate

Treatment group	Full-scale IQ			Verbal			Nonverbal			Spatial		
	VPA low, ≤800 mg	p	VPA high, >800 mg	p	VPA low, ≤800 mg	p	VPA high, >800 mg	p	VPA low, ≤800 mg	p	VPA high, >800 mg	p	VPA low, ≤800 mg	p	VPA high, >800 mg	p
CBZ	4.9 (3.3) [−1.5, 11.3]	0.14	9.7 (2.9) [4.0, 15.3]	<0.001	1.4 (3.1) [−4.7, 7.6]	0.65	5.2 (2.8) [−0.4, 10.8]	0.07	8.3 (3.6) [1.2, 15.4]	0.02	10.5 (3.3) [4.1, 16.9]	0.001	3.9 (3.8) [−3.4, 11.3]	0.30	9.5 (3.4) [2.8, 16.2]	0.006
LTG	2.0 (3.6) [−5.0, 9.0]	0.58	6.8 (3.3) [0.4, 13.2]	0.04	2.8 (3.5) [−4.0, 9.6]	0.42	6.6 (3.2) [0.3, 12.9]	0.04	2.7 (4.0) [−5.1, 10.6]	0.49	5.0 (3.7) [−2.3, 12.2]	0.18	3.5 (4.2) [−4.7, 11.7]	0.40	9.0 (3.9) [1.4, 16.6]	0.02
Other monotherapy	−1.7 (4.4) [−10.2, 6.9]	0.70	3.1 (4.1) [−4.9, 11.1]	0.44	0.6 (4.3) [−7.9, 9.0]	0.90	4.4 (4.1) [−3.6, 12.4]	0.29	2.2 (4.9) [−7.4, 11.9]	0.65	4.4 (4.7) [−4.7, 13.6]	0.34	−3.4 (5.2) [−13.5, 6.7]	0.51	2.2 (4.9) [−7.4, 11.8]	0.66

Abbreviations: CBZ = carbamazepine; LTG = lamotrigine; VPA = valproic acid.
Data are coefficient (standard error) [95% confidence interval]. Statistical comparisons based on the fitted model described in table 2. No adjustments have been made for multiple comparisons.

Children who had signs of poor cognitive development when tested before 2 years of age[15] were now at an increased risk of impaired IQ (<85) (exact McNemar test, $p = 0.04$). Children with a major congenital malformation were also more likely to have an IQ <85 (unadjusted odds ratio 5.9; 95% CI 1.7–20.2; Fisher exact test, $p = 0.01$).

DISCUSSION This is the first prospective study to document the cognitive abilities of a large group of school-aged children who were exposed in utero to AEDs that included VPA, CBZ, and LTG, and were compared with a parallel control group. Retention was high (83%) among the exposed children considering the length and nature of the study and was similar across the AED groups.

The deficits previously reported in young children exposed to VPA from this cohort[15] did not reduce with age and the increased need for educational intervention highlights the real-life implications of the statistical differences in IQ reported here. The association between VPA and IQ was substantial, and high-dose VPA was a more influential predictor of child IQ than expected confounders (i.e., maternal IQ).[25] The dose-related findings here are consistent with reports from this cohort and others pertaining to major congenital malformations[1,19] and cognitive functioning.[6,10,26] The distribution of IQ scores for the children exposed to VPA indicated that the findings cannot simply be accounted for by a small poor-performing group. The finding that polytherapy combinations that included VPA were associated with deficits in IQ while no differences were found for combinations not including VPA replicates that of others[11]; however, the group sizes here were small. Consistent with the findings of others[17] and relevant to treatment decisions, the cognitive abilities of children exposed to LTG or CBZ were higher than those exposed to doses of VPA more than 800 mg daily but not those with exposure to 800 mg daily or less. Reducing the dose of VPA rather than changing to another AED may be a treatment option; however, the effect of lower-dose VPA exposure on verbal abilities and the need for extra educational support merits further exploration.

Research into the cognitive abilities of children exposed to CBZ in utero is conflicting,[5,10,12] with one cohort demonstrating dose-related effects in preschool children,[26] which were not replicated in children at age 6.[17] No effect on mean IQ was found with CBZ in this study, but verbal ability was significantly reduced. The increased frequency of IQ <85 is likely associated with the poorer verbal abilities. There was no association between dose of CBZ and IQ. The results here are in contrast to the only other study in which IQ was blindly measured in an adequately

Table 4 Prevalence of children with additional educational needs in relation to exposure to maternal drug treatment

Group	Total	Educational needs	No educational needs	Incidence rate, %	OR (95% CI)	RR (95% CI)	p
Control	213	5	208	2.3	Reference group		
Epilepsy							
No medication	25	2	23	8.0	4.1 (0.9, 19.8)	3.9 (0.9, 13.7)	0.08
Treatment group							
VPA							
Low, ≤800 mg	21	4	17	19.1	6.6 (1.5, 30.4)	5.9 (1.4, 18.0)	0.01
High, >800 mg	30	11	19	36.7	9.6 (2.6, 35.7)	8.0 (2.5, 19.7)	<0.001
CBZ	50	5	45	10.0	3.2 (0.9, 11.5)	3.0 (0.9, 9.2)	0.07
LTG	30	1	29	3.3	1.0 (0.1, 8.7)	1.0 (0.1, 7.4)	0.99
Other monotherapy	14	5	9	35.7	23.1 (5.4, 98.6)	15.2 (4.9, 29.9)	<0.001

Abbreviations: CBZ = carbamazepine; CI = confidence interval; LTG = lamotrigine; OR = odds ratio; RR = relative risk; VPA = valproic acid.
Prevalence rates, adjusted ORs, and adjusted RRs (including 95% CIs) from the logistic regression model with educational needs as the outcome (event). Two covariates were significantly associated with educational needs: gestational age (OR 0.7, 95% CI 0.6 to 0.8; $p < 0.001$) and convulsive seizures (OR 2.9, 95% CI 1.1 to 7.9; $p = 0.03$).

powered cohort and compared with the IQ of control children,[7] and therefore further research is required to delineate the risks to verbal abilities associated with prenatal exposure to CBZ.

Data pertaining to the cognitive abilities of school-aged children exposed to LTG are limited. Here, the children exposed to LTG in utero did not have significantly lower IQ or specific verbal, nonverbal, or spatial abilities in comparison to control children. The group size was small; however, it is believed that this finding was not attributable solely to the small group size because studies with larger cohorts of younger children have given similar negative results.[12,17] The prescribing of LTG to women of childbearing years is increasing[27]; however, more research is needed, including investigation of a dose relationship with child IQ and investigation of other specific key cognitive abilities, including higher executive functioning.

Preconceptual folate was not found to be influential on outcome and this is inconsistent with the results of the NEAD Study, which showed a higher IQ after starting folate around the time of conception.[17] A failure to find better outcomes with folate supplementation is consistent with the lack of association between folate use and major congenital malformation rate after AED exposure.[28] The reason for this discrepancy is unclear, and further investigation is required to resolve this issue and support current guidelines that recommend at least 0.4 mg of folate daily.[29]

Exposure to seizures in utero has been reported to be associated with reduced cognitive ability,[5] but this has not been replicated by others[7,17] and is not supported by the data here. The numbers of children exposed to frequent convulsive seizures limited the investigation here into the reported association between 5 or more convulsive seizures and child IQ.[5] It is of note that the majority of prospective studies to date have failed to find a significant association between exposure to transient seizures and poorer child IQ[7,14,17]; however, none of these studies undertook rigorous collection of seizure data. The relationship between convulsive seizure exposure and increased educational needs demonstrated here was not through an association with poorer IQ levels, and future research needs to consider both biological and postnatal environmental factors.

AED choice was related to maternal epilepsy type (VPA with IGE and CBZ with localization-related epilepsy); therefore, the association between VPA exposure and child IQ could not be interpreted in complete isolation of maternal IGE. However, when entered separately into the regression models, VPA exposure accounted for more of the variance in child IQ than IGE. Furthermore, analysis of children born to women with only IGE demonstrated a significantly lower group mean for those treated with VPA. Also of note, a correlation between maternal and child IQ was not found in the VPA-exposed group, in contrast to the other treatment and control groups. Animal models add further weight to the teratogenic effect of the drug rather than the maternal factors, with alterations in rat brain morphology and functional behaviors noted after exposure to VPA.[30]

Limitations of this study included the loss to follow-up, but the likelihood of selection bias was reduced by the application of the "inverse probability weighting" method. Even if a more conservative significance level to account for a Bonferroni correction was applied, the results would either remain significant or stay near the

region of significance. Assessment of cognitive development at 6 years of age provides some information about individual potential but cognitive development is far from complete. Follow-up at a later age would provide more comprehensive information on the long-term effects. Strengths of this study include its prospective recruitment and longitudinal follow-up, control over confounding variables, cohort size, and use of standardized measures administered by blinded assessors. Statistical analysis controlled where possible for the influence of confounding variables but replication is required. Finally, an important strength is the utilization of a control group, recruited from the same clinics, without which subtle or lesser deficits could not be detected.

Information regarding the risks and benefits of individual treatments and doses should be routinely presented to women during their potential childbearing years to allow for informed decisions about treatment. Children who are exposed to medications and who show early signs of altered physical development should have their cognitive development closely monitored, allowing for early intervention should it be necessary.

AUTHOR CONTRIBUTIONS

Professor Baker contributed to acquisition of funding, conception and design of the study, analysis and interpretation of data, drafting the article, and final approval. Professor Baker accepts full responsibility for the finished article, had access to any data, and controlled the decision to publish. Dr. Bromley contributed to the conception and design of the study, data collection, study coordination, analysis and interpretation of data, drafting the article, and final approval. Ms. Briggs contributed to data collection, interpretation of data, drafting of the article, and final approval. Dr. Cheyne conducted the data analysis and contributed to the interpretation of data, drafting the article, and final approval. Dr. Cohen contributed to the design of the study, interpretation of data, drafting of the article, and final approval. Dr. García-Fiñana supervised the data analysis and contributed to the interpretation of results, drafting of the article, and final approval. Ms. Gummery contributed to data collection, interpretation of data, drafting of the article, and final approval. Dr. Kneen contributed to data collection, interpretation of data, drafting of the article, and final approval. Professor Loring contributed to the design of the study, interpretation of data, drafting of the article, and final approval. Professor Meador contributed to the acquisition of funding, to the design of the study, interpretation of data, drafting of the article, and final approval. Dr. Shallcross contributed to data collection, interpretation of data, drafting of the article, and final approval. Professor Mawer contributed to the conception and design of the study, study coordination, data collection, analysis and interpretation of data, drafting of the article, and final approval. Professor Clayton-Smith contributed the acquisition of funding, to the conception and design of the study, data collection, study coordination, analysis and interpretation of data, drafting the article, and final approval.

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