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Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioral Functioning at Age 3 Years

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Keywords

antiepileptic drugs; child development; behavioral neurology; epilepsy; pregnancy

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, some AEDs, including clonazepam, diazepam, phenobarbital, phenytoin, vigabatrin, and valproate can produce widespread neuronal apoptosis in the immature rat brain similar to alcohol [3-9]. The effect is dose dependent, occurs at therapeutically relevant blood levels, and requires only relatively brief exposure (single injection). The effect 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, some AEDs

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have been associated with reduced cognitive abilities (e.g., IQ) in children exposed *in utero* [10-12]. In a follow-up study [13] fetal valproate exposure was shown to significantly impair verbal as well as nonverbal abilities while carbamazepine significantly impacted only verbal abilities. Further, a dose dependent relationship was present for both lower verbal and non-verbal abilities with valproate and for lower verbal abilities with carbamazepine. In this report, we examine the effects of fetal AED exposure on motor, adaptive and emotional/behavioral functioning at 3 years of age in children of women with epilepsy.

2. Methods

2.1 Design

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study is a prospective observational study examining possible cognitive and behavioral teratogenesis of AEDs. We enrolled pregnant women with epilepsy who were on one of four AED monotherapies (i.e., carbamazepine, lamotrigine, phenytoin, or valproate) from October 1999 through February 2004 across 25 epilepsy centers in the USA and UK. These children are being followed to 6 years of age. We recently reported on IQ outcomes in these children at 3 years of age [12]. In a follow-up study we reported on verbal and nonverbal functioning in these same children [13]. In this paper we report on the motor, adaptive and emotional/behavioral outcomes at 3 years of age and examine dose-dependent effects.

2.2 Participants

Consent from participants was obtained according to the Declaration of Helsinki. IRBs at each center approved the study, and written informed consent was obtained prior to enrollment. Pregnant women with epilepsy on carbamazepine, lamotrigine, phenytoin, or valproate monotherapy were enrolled. These four AED monotherapies were the most frequently employed during the enrollment time period. Other AEDs were not included because of insufficient numbers. Polytherapy was not included because of its association with poorer outcomes [14,15]. A non-exposed control group was not included at the direction of an NIH review panel. Mothers with IQ below 70 were excluded to avoid floor effects and because maternal IQ is the major predictor of child IQ in population studies [16]. Other exclusion criteria included positive syphilis or HIV serology, progressive cerebral disease, other major disease (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, seizure/epilepsy types and frequency, AED dosages, compliance, socioeconomic status [17], 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, enrollment and birth gestational age, 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) [18] in 267 mothers, Wechsler Abbreviated Scale of Intelligence (WASI) [19] in 20, and National Adult Reading Test (NART) [20] in 17. To allow for comparisons across AEDs, the dosages were standardized. Average AED dose during pregnancy was standardized relative to ranges observed within each group by the following calculation: $100 \times (\text{observed dose} - \text{minimum dose}) \div \text{range of doses}$.

Motor outcomes were evaluated by assessors (blinded to AED) using the Motor Scale from the Bayley Scales of Infant Development - Second Edition (BSID – II) [21]. In order to assess adaptive functioning, the child's mother/father and preschool teacher/daycare worker (if child was attending) were asked to complete the Adaptive Behavior Assessment System – Second Edition (ABAS – II) [22]. Emotional/behavioral functioning was measured by having the child's mother/father and preschool teacher/daycare worker complete the Behavior Assessment System for Children (BASC) [23]. Due to the small number of children who were attending preschool/daycare only 46 teacher BASC forms and 50 teacher ABAS-II forms were completed and returned. As a result, it was decided to analyze the parent rating scales only. Finally, 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) [24]. The motor assessment and rating scale completion was conducted when the child was 36-45 months/old.

Training and monitoring of the neuropsychological evaluations were conducted to assure quality and consistency across sites. As part of the training, workshops were conducted for all neuropsychological test batteries annually. In addition, each assessor was required to identify errors and provide 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 (non-study child) with record forms to the Neuropsychology 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 229 children with complete motor, adaptive and/or emotional/behavioral assessment at 3 years/old. Outcome data were missing for 82 of the originally enrolled children. Multivariate regression models were used to examine group differences, adjusting for covariates. The *a priori* hypothesis for each dependent variable was that the specific AED, dose, and maternal IQ were important covariates, and thus these were included as predictors in a linear model with child motor performance, adaptive and emotional/behavioral ratings as outcomes. Other covariates were added individually to the model and covariates were included in a final model if found to be significant ($p < .05$), and if they did not exhibit collinearity with existing predictors. The effects of multiple additional covariates were also examined, which included: maternal age, race/ethnicity (Caucasian, African American, Hispanic/Latino, Other), alcohol use during pregnancy (yes/no), preconception folate use, gestational age at birth, epilepsy/seizure types, seizure frequency during pregnancy, education, employment, socioeconomic status, US/UK site, tobacco use during pregnancy, birth weight, unwanted pregnancy, breastfeeding, prior pregnancy birth defects and complications, present pregnancy complications, and AED compliance.

The dependent variables were the Motor Index score (Standard Score; mean = 100, standard deviation = 15) from the BSID – II, the General Adaptive Composite score (Standard Score; mean = 100, standard deviation = 15) from the ABAS – II, the individual Scale scores (T Score; mean = 50, standard deviation = 10) from the BASC, and the percentile scores from the Parent and Child Domains from the PSI – III.

Multivariate regression models were adjusted for AED group and other covariates found to be significant predictors in the linear model at the 0.05 level of significance. Secondary analyses examined the following: 1) relative relationships of AED exposures to child motor performance, adaptive and emotional/behavioral ratings; and 2) relationship of the significant covariates within each model to AED exposure. Analyses were performed at the NEAD Data and Statistical Center using SAS 9.2.

3. Results

The primary analysis included 223 mothers and 229 children (6 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 82 mothers of children who were excluded from the analysis due to missing data. Mothers who were excluded from analysis do not differ statistically on any of these characteristics from those who were included in the analysis. The statistical results for performance on the Motor Index of the BSID-II and the General Adaptive Composite score from the ABAS – II are presented in Table 2.

3.1 Motor functioning

A summary of the analysis of covariance models is given in Table 2 and indicates that the adjusted mean performance scores of the four AED groups on the BSID-II Motor Index did not significantly differ. Adjusted age 3 mean Index scores along with 95% confidence intervals (CIs) for each AED group are listed in Table 3. Maternal IQ, standardized AED dose, gestational age at delivery and site location (US vs. UK) were significantly related to performance on the BSID-II Motor Index. Partial Pearson correlations for maternal IQ and pregnancy average AED dose are listed in Table 4 and scatter plots of the dose dependent effects are depicted in Figure 1. Analysis of Table 4 indicates that higher maternal IQ was associated with higher Motor Index scores in the children whose mothers took phenytoin during pregnancy. A similar trend exists for lamotrigine. Dose dependent effects, when controlling for maternal IQ, were seen for valproate and carbamazepine which indicate that higher average dosages of both of these AEDs were associated with lower Motor Index scores. Finally, prematurity (<37 weeks) appeared to be associated with lower Motor Index scores; however, further inspection of group membership revealed that the number of preterm children in all of the AED groups was extremely small (n's ranging from 2 in the valproate group to 6 in the carbamazepine group) making further analysis of AED group membership suspect. In addition, a t-test comparing Motor Index performance of premature children vs term children was not significant ($p = 0.14$).

3.2 Adaptive Functioning

Results of analysis of covariance models depicted in Table 2 indicate that the adjusted mean performance ratings of the four AED groups on the ABAS-II (General Adaptive Composite score) did not significantly differ. Adjusted age 3 mean Composite scores along with 95% confidence intervals (CIs) for each AED group are listed in Table 3. Standardized AED dose and maternal education beyond high school were significantly related to performance ratings on the ABAS-II. Partial Pearson correlations for standardized AED dose are presented in Table 4 and scatter plots of the dose dependent effects are depicted in Figure 1. Significant dose dependent effects, when controlling for maternal IQ, were seen for valproate and marginally significant effects were seen for carbamazepine 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. Since maternal education beyond high school is a categorical variable a Chi-Square test was performed to further delineate the relationship of this covariate to adaptive functioning. Results indicate that adaptive ratings were significantly higher ($p < .001$) in children whose mothers received education beyond high school. The adjusted mean score for children of mothers who were educated beyond high school was 98.6 (95% CI = 96.4:100.9) vs. 90.6 (95% CI = 86.7:94.6) for the children of mothers with a high school education or less.

3.3 Emotional/behavioral Functioning

Results of the analysis of covariance models for the 10 BASC Scales in Table 5 indicate that the adjusted mean performance ratings of the four AED groups across the 10 BASC Scales did not significantly differ. Adjusted age 3 mean BASC Scale scores along with 95% confidence intervals (CIs) for each AED group are listed in Table 6. Further analysis in Table 5 indicates that gestational age is associated with parent ratings on the Somatization Scale. Specifically, follow-up Chi-Square tests indicate that parents of preterm (<37 weeks) children endorsed significantly ($p = 0.01$) more somatic/medical complaints than parents of full-term children. In addition, ratings on the Social Skills Scale were associated with standardized AED dose. Follow-up Partial Pearson correlation revealed a dose dependent effect for valproate ($r = -0.46$; $p = .002$) which indicated that parents reported increasing problems with their child's social skills with higher average doses of Valproate during pregnancy.

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/percent of children with at risk parent ratings on the Inattention Scale of the BASC (inattentive type) and at risk ratings on both the Inattention 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). The frequency/percent in each AED group 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 [25]. This figure was based upon parental endorsement of ADHD in their children 3-17 years of age. Paired t-test analysis indicated that only the valproate group (23.3%; $p = .02$) had a significantly greater percent of children at risk for ADHD than the national CDC estimate (see Figure 2).

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/percent of children with at risk parent ratings on the Parent and Child Domains from the PSI-III were calculated for each AED group. At risk scores were defined as being greater than the 90th percentile. Fisher's exact testing indicated no significant group differences for the Parent Domain ($p = .07$) or the Child Domain ($p = .24$).

4. Discussion

The NEAD Study is an ongoing prospective observational multicenter study in the USA and UK, which has enrolled pregnant women with epilepsy on AED monotherapy from 1999 to 2004. The study seeks to determine if differential long-term neurodevelopmental effects exist across four commonly used AEDs (carbamazepine, lamotrigine, phenytoin, or valproate). In this report, we examined the effects of fetal AED exposure on motor, adaptive and emotional/behavioral functioning at 3 years of age 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 low average to average range for motor functioning, adaptive functioning, and parental ratings of emotional/behavioral functioning, a significant dose related performance decline in motor functioning was seen for both valproate and carbamazepine. A significant dose related performance decline in parental ratings of adaptive functioning was also seen for valproate with a marginal performance decline evident for carbamazepine. Further, parents endorsed a significant decline in social skills for valproate that was dose related. Finally, based upon parent ratings of attention span and hyperactivity, children of mothers who took valproate during their pregnancy may be at a significantly greater risk for a future diagnosis of ADHD.

These results present the first evidence that motor and adaptive functioning outcomes may be reduced in children exposed *in utero* to higher dosages of valproate and carbamazepine compared to lamotrigine, and phenytoin. In addition, the finding of an increased risk of a future diagnosis of ADHD in children whose mothers took valproate during their pregnancy supports prior studies demonstrating that children exposed to valproate *in utero* may be at increase risk for behavioral abnormalities as well [26-28].

The strengths of our study include its prospective design, blinded cognitive assessments using standardized measures, and detailed monitoring of multiple potential confounding factors. However, caution is advised due to study limitations which include a relatively small sample size, loss of enrolled subjects to analysis, lack of randomization, lack of AED blood levels, absence of an unexposed control group during pregnancy, and the relatively young age of the children at this planned interim analysis. Because the NEAD study is not a randomized trial, it is possible that confounding factors related to baseline characteristics may have affected the results. For example, while epilepsy/seizure type was not found to be a significant outcome predictor, data on additional factors which could influence medication choice, such as medication cost, and whether or not the mother had previously failed another AED prior to being placed on the medication taken during her pregnancy, were not collected and studied as part of this investigation.

Based upon these findings, a raised index of suspicion should translate into more careful follow-up and evaluation of these children with appropriate referral for interventional therapies when indicated. Additional research is needed to confirm these findings, examine risks of other AEDs, define the risks associated with AEDs in the neonate for treatment of seizures, and to understand the underlying mechanisms of adverse AED effects on the immature brain.

Appendix

NEAD Study Group

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Research Highlights

- Children exposed in utero to higher dosages of valproate have lower motor/adaptive functioning
- Children exposed in utero to higher dosages of carbamazepine have lower motor/adaptive functioning
- Children exposed in utero to valproate may be at Increased risk for ADHD

Figure 1. Scatter plots of BSID-II Motor Index and ABAS-II General Adaptive Composite scores vs. standardized dose for each Antiepileptic Drug (AED) during pregnancy.

Figure 2.

Percent 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 [25].

Table 1

Demographics and IQ results for mothers of children included in analyses (complete data on BSID, GAC, and/or one or more of the subscales of the BASC)

Antiepileptic Drug	All (mothers included in analysis)	Carbamazepine	Lamotrigine	Phenytoin	Valproate	Mothers of children with missing outcome data [p-value for difference from mothers included in analysis]
Mothers (n)	223	61	76	40	46	82
Mean Maternal IQs (95% CI)	98 (96:100)	99 (95:103)	101 (98:105)	93 (88:99)	95 (91:100)	97 (94:101) [P=0.70]
Mean Maternal Ages (95% CI)	30 (29:31)	30 (29:32)	31 (30:32)	30 (28:32)	29 (27:31)	29 (28:30) [P=0.13]
Mean Dose ^A mg/day (95% CI)	N/A	771 (667:875)	473 (417:529)	402 (361:442)	1070 (876:1264)	N/A
Standardized Dose ^B (95% CI)	35 (33:38)	32 (27:36)	36 (31:41)	49 (43:55)	27 (22:33)	33 (28:37) [P=0.29]
Gestational Age weeks (95% CI)	39 (39:39)	38 (38:39)	39 (39:40)	38 (37:39)	39 (39:40)	39 (39:40) [P=0.23]
Preconception Folate n (%)	128 (57)	34 (56)	45 (59)	18 (45)	31 (67)	46 (56) [P=0.84]
Alcohol use during pregnancy n (%)	17 (8)	6 (10)	6 (9)	2 (5)	4 (9)	7 (9) [P=0.79]
Epilepsy Types ^D						
Localization Related n (%)	131 (59)	52 (85)	40 (53)	29 (73)	10 (22)	53 (65) [P=0.35]
Idiopathic Generalized n (%)	73 (33)	5 (8)	28 (37)	7 (18)	33 (72)	24 (29) [P=0.56]
GTCS n (%)	19 (9)	4 (7)	8 (11)	4 (10)	3 (7)	5 (6) [P=0.49]
Race						
Caucasian	182 (82)	49 (80)	67 (88)	25 (63)	41 (89)	63 (77) [P=0.35]
Black	9 (4)	4 (7)	1 (1)	3 (8)	1 (2)	5 (6) [P=0.45]
Hispanic	19 (9)	4 (7)	3 (4)	11 (27)	1 (2)	12 (15) [P=0.12]
Other	13 (6)	4 (7)	5 (7)	1 (2)	3 (7)	2 (2) [P=0.22]

^A Average dose for pregnancy.

D Epilepsy types: Localization Related (includes cryptogenic and symptomatic); Idiopathic Generalized (includes absence, juvenile myoclonic, genetic, and other idiopathic generalized not otherwise classified); GTCS = generalized tonic clonic seizures (unknown if generalized or secondary generalized).

B See Methods for description of how dosages were standardized.

C Any alcohol use during pregnancy (yes/no)

Table 2

Analysis of Covariance Results

Dependent Variable	Covariate	Estimate [95% Confidence Interval]	F-value	p-value
BSID – II Motor Index	AED Group (4 groups)	--	1.74	0.1608
	Maternal IQ	0.14 [0.01:0.27]	4.73	0.0310
	Standardized Dose	-0.24 [-0.35:-0.13]	19.26	<.0001
	Gestational Age	1.34 [0.49:2.18]	9.67	0.0022
	Site in UK	-6.39 [-11.35:-1.42]	6.45	0.0120
ABAS – II General Adaptive Composite	AED Group (4 groups)	--	1.59	0.1941
	Standardized Dose	-0.21 [-0.32:-0.11]	17.47	<.0001
	Education Beyond HS	7.63 [2.96:12.31]	10.36	0.0015

Table 3

Adjusted age 3 means (95% Confidence Intervals) for BSID – II Motor Index and ABAS – II General Adaptive Composite for each antiepileptic drug (AED).

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
BSID Motor^A	92.0 (89:96)	91 (88:95)	95 (90:100)	87 (83:92)
ABAS GAC^B	97 (93: 101)	97 (93:100)	100 (95:105)	93 (89:97)

^A Mean BSID – II Motor Index adjusted for maternal IQ, standardized dose, gestational age at birth, and site location (US/UK).

^B Mean ABAS – II General Adaptive Composite adjusted for standardized dose and maternal education beyond high school (yes/no).

Table 4

a. Relationships of pregnancy average standardized dose to BSID – II Motor Index and to ABAS – II General Adaptive Composite, using Partial Pearson correlations (p-values), controlling for maternal IQ.

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
BSID	-.47 (p=.0005) n=51	-.17 (p=.1954) n=62	.16 (p=.4030) n=32	-.60 (p<.0001) n=38
ABAS	-.26 (p=.0577) n=55	-.22 (p=.0688) n=72	-.05 (p=.7804) n=37	-.54 (p=.0002) n=44
b. Relationships of maternal IQ to BSID – II Motor Index and to ABAS – II General Adaptive Composite using Pearson correlations (p-values)				
	Carbamazepine	Lamotrigine	Phenytoin	Valproate
BSID	.17 (p=.2329) n=51	.23 (p=.0665) n=62	.41 (p=.0189) n=32	.17 (p=.3178) n=38
ABAS	.31 (p=.0188) n=55	-.07 (p=.5833) n=72	.30 (p=.0728) n=37	-.03 (p=.8235) n=44

Table 5

Summary of ANCOVA Models for the 10 BASC Subscales

Dependent Variable	Covariate	F Value	P-value
Hyperactivity	AED Group (4 groups)	1.16	0.3274
	Maternal IQ	0.36	0.5476
	Standardized Dose	0.07	0.7886
	Maternal Age	0.02	0.8815
	Gestational Age	0.53	0.4687
	Preconception Folate Use	2.07	0.1521
Aggression	AED Group (4 groups)	1.32	0.2683
	Maternal IQ	0.00	0.9820
	Standardized Dose	0.48	0.4914
	Maternal Age	2.22	0.1374
	Gestational Age	1.22	0.2699
	Preconception Folate Use	0.28	0.5956
Anxiety	AED Group (4 groups)	2.25	0.0833
	Maternal IQ	0.14	0.7123
	Standardized Dose	0.90	0.3427
	Maternal Age	0.36	0.5493
	Gestational Age	0.02	0.8979
	Preconception Folate Use	0.19	0.6601
Depression	AED Group (4 groups)	0.46	0.7126
	Maternal IQ	0.05	0.8176
	Standardized Dose	0.41	0.5234
	Maternal Age	1.02	0.3126
	Gestational Age	0.18	0.6702
	Preconception Folate Use	1.19	0.2768
Somatization	AED Group (4 groups)	0.03	0.9918
	Maternal IQ	0.08	0.7764
	Standardized Dose	0.03	0.8574
	Maternal Age	0.01	0.9183
	Gestational Age	8.96	0.0031
	Preconception Folate Use	2.46	0.1187
Atypicality	AED Group (4 groups)	1.84	0.1411
	Maternal IQ	1.69	0.1949
	Standardized Dose	0.37	0.5453
	Maternal Age	0.98	0.3235
	Gestational Age	0.19	0.6636
	Preconception Folate Use	0.97	0.3249
Withdrawal	AED Group (4 groups)	0.12	0.9511

Dependent Variable	Covariate	F Value	P-value
	Maternal IQ	0.23	0.6330
	Standardized Dose	0.01	0.9210
	Maternal Age	1.18	0.2792
	Gestational Age	1.62	0.2040
	Preconception Folate Use	1.93	0.1667
Attention Problems	AED Group (4 groups)	1.03	0.3816
	Maternal IQ	0.39	0.5307
	Standardized Dose	3.13	0.0784
	Maternal Age	1.18	0.2779
	Gestational Age	0.32	0.5728
	Preconception Folate Use	1.50	0.2227
Adaptability	AED Group (4 groups)	1.00	0.3947
	Maternal IQ	0.54	0.4641
	Standardized Dose	0.03	0.8569
	Maternal Age	4.90	0.0279
	Gestational Age	0.04	0.8460
	Preconception Folate Use	0.05	0.8273
Social Skills	AED Group (4 groups)	1.68	0.1715
	Maternal IQ	3.28	0.0715
	Standardized Dose	9.26	0.0027
	Maternal Age	0.67	0.4131
	Gestational Age	0.03	0.8699
	Preconception Folate Use	0.80	0.3711

Table 6

Adjusted means (95% Confidence Intervals) for 10 BASC subscales for each antiepileptic drug (AED).

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Hyperactivity	48 (46:51)	48 (46:50)	52 (48:55)	49 (46:52)
Aggression	47 (44: 49)	47 (45:50)	49 (46:52)	45 (42:47)
Anxiety	47 (45:50)	47 (45:49)	50 (47:53)	45 (42:48)
Depression	47 (45:50)	47 (45:49)	49 (45:52)	46 (43:49)
Somatization	48 (46:51)	48 (46:50)	49 (46:52)	49 (46:51)
Atypicality	48 (46:51)	49 (47:51)	51 (48:54)	52 (49:55)
Withdrawal	51 (48:53)	50 (48:52)	50 (47:54)	49 (46:53)
Attention Problems	51 (47:54)	49 (46:51)	50 (46:54)	53 (49:56)
Adaptability	51 (48:54)	52 (49:55)	48 (44:52)	52 (48:55)
Social Skills	49 (46:51)	51 (49:54)	51 (47:55)	47 (44:50)

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