



## Behavioral outcomes in children exposed prenatally to lamotrigine, valproate, or carbamazepine



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### ABSTRACT

**Objectives:** To evaluate adaptive behavior outcomes of children prenatally exposed to lamotrigine, valproate, or carbamazepine, and to determine if these outcomes were dose-dependent.

**Methods:** Data were collected from women enrolled in the North American Anti epileptic Drug (AED) Pregnancy Registry who had taken lamotrigine, valproate, or carbamazepine monotherapies throughout pregnancy to suppress seizures. The adaptive behavior of 252 exposed children (including 104 lamotrigine-exposed, 97 carbamazepine-exposed, and 51 valproate-exposed), ages 3- to 6-years-old, was measured using the *Vineland-II Adaptive Behavior Scales*, administered to each mother by telephone. Mean Adaptive Behavior Composite (ABC), domain standard scores for communication, daily living, socialization and motor skills, and adaptive levels were analyzed and correlated with first trimester drug dose.

**Results:** After adjusting for maternal age, education, folate use, cigarette and alcohol exposure, gestational age, and birth weight by propensity score analysis, the mean ABC score for valproate-exposed children was 95.6 (95% CI [91, 101]), versus 100.8 (95% CI [98, 103]) and 103.5 (95% CI [101, 106]) for carbamazepine- and lamotrigine-exposed children, respectively (ANOVA;  $p = 0.017$ ). Significant differences were observed among the three drug groups in the ABC ( $p = 0.017$ ), socialization ( $p = 0.026$ ), and motor ( $p = 0.018$ ) domains, with a trend toward significance in the communication domain ( $p = 0.053$ ). Valproate-exposed children scored lowest and lamotrigine-exposed children scored highest in every category. Valproate-exposed children were most likely to perform at a low or moderately low adaptive level in each category. Higher valproate dose was associated with significantly lower ABC ( $p = 0.020$ ), socialization ( $p = 0.009$ ), and motor ( $p = 0.041$ ) scores before adjusting for confounders. After adjusting for the above variables, increasing VPA dose was associated with decreasing Vineland scores in all domains, but the relationships were not statistically significant. No dose effect was observed for carbamazepine or lamotrigine.

**Conclusions:** Unlike carbamazepine and lamotrigine, prenatal valproate exposure was associated with adaptive behavior impairments with specific deficits in socialization and motor function, along with a relative weakness in communication. Increasing valproate dose was associated with a decline in adaptive functioning. This finding of a linear dose-dependent teratogenic effect suggests that valproate should be avoided at any dose during pregnancy. However, some women with epilepsy controlled only by valproate will decide, in consultation with their provider, that the benefits of continuing valproate during pregnancy outweigh the fetal risks. Faced with difficult choices, clinicians should be supportive as these patients consider their options.

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### 1. Introduction

Fetal exposure to anti-epileptic drugs (AEDs) carries elevated risk for birth defects (Samren et al., 1997; Meador et al., 2006; Dean et al., 2002;

Campbell et al., 2014; Morrow et al., 2006; Artama et al., 2005; Wyszynski et al., 2005; Wide et al., 2004), and may be associated with cognitive dysfunction (Scolnik et al., 1994; Titze et al., 2008; Veiby et al., 2013; Moore et al., 2000). Valproate, especially, has been associated with lower IQ (Titze et al., 2008; Adab et al., 2004; Vinten et al., 2005; Eriksson et al., 2005; Meador et al., 2009, 2013), increased special education needs (Viinikainen et al., 2006), behavioral problems (Dean

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et al., 2002; Viinikainen et al., 2006; Vinten et al., 2009; Cohen et al., 2013), and increased risk of autism spectrum disorder (Christensen et al., 2013; Bromley et al., 2008, 2013; Rasalam et al., 2005), when compared to several other AEDs, namely phenytoin, carbamazepine, and lamotrigine.

Unfortunately, most studies investigating neurodevelopmental outcomes of exposed children have relied on language testing and IQ to assess cognitive function, while adaptive behavior outcomes have been significantly less well-studied. Although IQ tests measure general intelligence, they neither assess functional abilities nor adaptive behaviors required for independent daily living, such as socialization, communication, self-care, and motor skills. Deficits in these areas have significant implications for long-term behavioral outcomes. Impairments in socialization and communication, along with repetitive, stereotyped behaviors, form the basis for diagnosis of autism spectrum disorder (American Psychiatric A et al., 2013).

While studies have suggested that IQ is a strong predictor of adaptive impairments for individuals with cognitive disabilities, research has also shown that the gap between IQ and adaptive skills is greater among higher functioning individuals (Kanne et al., 2011; Klin et al., 2007). In individuals with autism spectrum disorder, severe social deficits have been observed even with relatively high IQ (Kanne et al., 2011; Klin et al., 2007). Thus, using IQ scores alone to evaluate neurodevelopmental outcomes for children exposed to AEDs in utero is not sufficient to identify those individuals with adaptive behavior impairments despite high cognitive potential. As a result, information on the long-term behavioral effects of prenatal AED exposure is lacking, and significant limitations exist for physicians counseling women of childbearing age with epilepsy (WWE). We present a cohort study to evaluate adaptive behavior outcomes among children born to WWE who received one of three AED treatments as monotherapy during pregnancy. The a priori hypotheses were that prenatal exposure to carbamazepine (CBZ), lamotrigine (LTG), or valproate (VPA) monotherapies would be associated with adaptive behavior impairments, and that exposure to higher doses during the first trimester would be associated with lower adaptive behavior levels.

## 2. Methods

### 2.1. Recruitment, inclusion, and exclusion criteria

Recruitment letters were sent by mail to WWE who had prospectively enrolled in the North American AED Pregnancy Registry (“the Registry”) while taking LTG, VPA, or CBZ as monotherapy to suppress seizures throughout pregnancy, and whose exposed children were 3- to 6-years-old. The Registry’s methodology has been described previously (Holmes et al., 2011). Children were excluded if they were exposed to other known teratogens, such as isotretinoin or warfarin, or if the AED was not taken throughout pregnancy. Mothers were excluded if they had mental illness or memory disorders, or if they refused to release medical records.

### 2.2. Study procedures

Mothers were screened by telephone to determine eligibility and collect data on participant characteristics and confounding variables. Data on each enrolled child’s development were then collected from mothers by telephone, using the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) Survey Interview Form, a semi-structured interview designed to assess a child’s self-sufficiency and adaptive functioning in the domains of communication, daily living, socialization, and motor skills (Sparrow et al., 2005). The four domains are further divided into 11 subdomains, as shown in Table 1.

The subdomains yield v-scale scores that sum to yield the four domain composite scores, which are then standardized (mean = 100, SD = 15), and summed to produce the global Adaptive Behavior

**Table 1**

The 4 domains and 11 subdomains that make up the overall Adaptive Behavior Composite scores on the Vineland Adaptive Behavior Scales, Survey Interview Form, Second Edition.

Domain	Subdomain
Communication	Receptive Expressive Written
Daily living skills	Personal Domestic Community
Socialization	Interpersonal relationships Play and leisure time Coping skills
Motor skills	Gross Fine

Composite (ABC) for individuals from birth to 6-years-old. The ABC score provides the overall assessment of an individual’s adaptive functioning. Lower Vineland scores indicate increased impairment in adaptive behavior. Standard scores can be grouped into ranges representing high, moderately high, adequate, moderately low, and low levels of adaptive functioning, based on the scores’ standard deviations from the expected mean, as shown in Table 2.

The *Vineland-II* was standardized based on a national sample of over 3000 individuals selected to match the U.S. Census data. Standard scores and adaptive behavior levels are measured relative to a non-clinical, age-matched reference group. The ABC and domain standard scores were the primary and secondary outcome variables. Adaptive levels and subdomains were then examined for a more nuanced analysis of differences in adaptive functioning among the three exposure groups.

Interviews took 60–90 min to complete, on average, and were conducted by non-blinded research coordinators (UD and RD) at the Massachusetts General Hospital who were trained using the official *Vineland-II* training video and survey manual. Interviews were scored by hand or using the *Vineland-II Survey Forms ASSIST* software.

### 2.3. Statistical analyses

Statistical analyses were completed by a research coordinator (UD) and a biostatistician (EM) at Massachusetts General Hospital’s Biostatistics Center using Statistical Analysis Software, version 9.4. The primary analysis examined baseline characteristics of the study participants, including drug exposure, epilepsy type, seizure frequency during pregnancy, child’s age, mother’s marital status, insurance coverage, maternal age at delivery, maternal education, prenatal vitamin and folate use, cigarette and alcohol exposure, presence of major malformations in the exposed child, gestational age at birth, birth weight, and birth length. Differences in covariates among the three exposure groups were examined using Pearson’s chi-squared tests and one-way ANOVA.

Mean adaptive behavior scores were calculated for the children in each exposure group. One-sample t-tests were used to test whether group means differed from the test normative value of 100. Mean Adaptive Behavior Composite (ABC) scores and domain standard scores were analyzed using one-way ANOVA to identify differences among the three

**Table 2**

Adaptive level descriptions, modified from the *Vineland-II* Instruction Manual (Sparrow et al., 2005). Standard scores are classified into adaptive levels based on their standard deviations from the expected mean of 100.

Adaptive level	Standard deviations from the mean	Standard score range	Percentile rank range
High	2.0 or above	130 and above	98 and above
Moderately high	1.0–2.0	115–129	85–97
Adequate	–1.0–1.0	86–114	16–84
Moderately low	–2.0––1.0	71–85	3–15
Low	–2.0 or below	70 and below	2 and below

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