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Behavioral Outcomes in Children Exposed Prenatally to Lamotrigine, Valproate, or Carbamazepine

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Uma Deshmukh
2015

Abstract

BEHAVIORAL OUTCOMES IN CHILDREN EXPOSED PRENATALLY TO LAMOTRIGINE, VALPROATE, OR CARBAMAZEPINE. Uma S. Deshmukh and Lewis B. Holmes. Medical Genetics Unit, Department of Pediatrics, MassGeneral Hospital for Children, Harvard Medical School, Boston, MA. (Sponsored by Abha R. Gupta, Department of Pediatrics, Yale University School of Medicine).

This study aimed to determine if prenatal exposure to carbamazepine (CBZ), lamotrigine (LTG), or valproate (VPA) monotherapies would be associated with adaptive behavior impairments in exposed children, and if these impairments would present in a dose-dependent fashion.

Recruitment letters were mailed to 1,032 women enrolled in the North American Antiepileptic Drug Pregnancy Registry who had taken LTG, VPA, or CBZ as monotherapy throughout pregnancy to suppress seizures. The response rate was 48%. Adaptive behavior of 253 children (104 LTG-exposed, 98 CBZ-exposed, and 51 VPA-exposed), 3- to 6-years-old, was measured using the Vineland-II Adaptive Behavior Scales, administered to each mother by phone. Mean Adaptive Behavior Composite (ABC); domain standard scores for communication, daily living, socialization, and motor skills; and adaptive levels were analyzed across drug groups and correlated with first trimester drug dose. Lower Vineland-II scores indicate greater impairment.

After adjusting for maternal age, education, epilepsy type, prenatal seizures, folate use, cigarette and alcohol exposure, gestational age, and birth weight, the mean ABC score for VPA-exposed children was 95.4 (95% CI [91, 100]), versus 101.1 (95% CI [98, 104]) and 103.5 (95% CI [101, 106]) for CBZ- and LTG-exposed children, respectively (ANOVA; $p=0.016$). Performance among the three groups differed significantly in all domains except daily living, with VPA-exposed children scoring lowest and LTG-exposed children scoring highest in every category. VPA-exposed children were most likely to perform at an adaptive level that was low or moderately low (standard scores ≤ 85) in each category. Generalized linear models showed higher VPA dose to be associated with significantly lower ABC ($p=0.021$), socialization ($p=0.009$), and motor ($p=0.041$) scores, with a trend toward significance in the communication domain ($p=0.055$).

Unlike CBZ and LTG, prenatal VPA exposure was associated with adaptive behavior impairments in a pattern consistent with autistic symptoms. The dose-dependent effect suggests that VPA should be avoided during pregnancy and that VPA-exposed children should be routinely referred for early intervention services.

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Introduction

Background

Antiepileptic drugs (AEDs) have long been used to treat and prevent seizures. In 1910, phenobarbital, which had previously been used only as a sleep agent, was found to have anti-seizure properties and soon became a favored drug for anticonvulsant therapy. Over the next decade, other now commonly used antiepileptics were introduced. In 1940, phenytoin was found to be highly effective for treatment of partial and secondarily generalized seizures. In 1958, clinicians began using ethosuximide to treat absence seizures. Carbamazepine was approved in 1974 for treatment of partial seizures (1). Four years later, valproate was licensed for use in the U.S., initially for treatment of absence seizures. In 1996, it was also approved for the control of complex partial seizures (2).

Until the mid-1990s, the aforementioned agents were considered the drugs of choice for seizure treatment and prophylaxis. While their efficacy is indisputable, concerns have been raised about their toxicities, side effect profiles, and harmful fetal effects. A number of newer drugs have thus been introduced in the market, which have proven to be efficacious with improved tolerability. Furthermore, these newer drugs are associated with reduced toxicity and fetal effects, and do not require frequent monitoring of blood levels as with the more traditional agents, making them more convenient for patients (3). Among these newer agents is lamotrigine, which was approved in 1994 for treatment of partial seizures.

While these antiepileptic drugs have been effective for seizure control and have, indeed, revolutionized the management of epilepsy in the modern age, they are not without risks, particularly for women with epilepsy of reproductive age. There is mounting evidence

that fetal exposure to AEDs carries elevated risk for birth defects (4-12), and may even be associated with cognitive dysfunction (13-16).

Malformation Risks

The first report of birth defects associated with AED exposure (specifically phenytoin) was published in 1963 (17). A little more than a decade later, Hanson and colleagues (7) proposed that phenytoin produced a distinctive constellation of congenital abnormalities affecting multiple systems, including craniofacial anomalies, nail and digit hypoplasia, growth restriction, and developmental delay – a pattern which they named fetal hydantoin syndrome. These early observations inspired multiple subsequent evaluations of children exposed to antiepileptic drugs during pregnancy.

Since the publication of these early reports, many studies have corroborated the initial suggestion that there is increased risk of major congenital malformations among children exposed to AEDs during gestation, with some studies estimating the risk to be elevated two-fold when comparing exposed children with unexposed controls (10). In 1997, Samrén and colleagues analyzed pooled data from five prospective European studies and found a significantly increased risk of major congenital malformations in 192 children exposed to anticonvulsants during gestation compared with 158 unexposed, matched, non-epileptic controls (RR 2.3; 95% CI: 1.2-4.7) (10).

Studies have typically found that the malformation risks associated with AED exposure further increases with polytherapy. In 2002, Dean et al. published a retrospective population-based study investigating the frequency of neonatal and childhood morbidity in

children exposed to a variety of AEDs during gestation. When comparing all exposed children with a non-exposed group, they actually did not find a statistically significant difference in the frequency of major malformations (13.8% vs. 5.3%, $p>0.05$). However, when they compared those exposed to polytherapy with the non-exposed group, the difference in the rates of major malformations met statistical significance (25.5% vs. 5%, $p=0.012$) (6). Similarly, Morrow and colleagues (2006) found the rates of major malformations to be greater among children with polytherapy exposure. They observed that the rate of major malformations among children exposed to polytherapy was 6.0% vs. 3.7% among children exposed to monotherapy, producing an adjusted odds ratio of 1.83 (9).

Aside from these findings of increased risk with polytherapy exposure, most studies have actually been conducted on children exposed to various agents as monotherapy. Through these investigations, it has become clear that the fetal risks are, in fact, specific for each drug. Attention has increasingly focused on valproate as the AED that poses the highest risk of major congenital malformations. Samrén et al. (1997) found that the risk for malformations was greater for children exposed to valproate (RR 4.9; 95% CI: 1.6-15.0) or carbamazepine (RR 4.9; 95% CI: 1.3-18.0), when compared with unexposed controls (10). In their 2006 paper, Morrow et al. reported a malformation rate of 6.2% among children exposed to valproate as monotherapy (9). Meador et al. (2006) reported preliminary results from their ongoing prospective observational study across 25 epilepsy centers in the USA and UK. They found that 20.3% of valproate-exposed pregnancies resulted in adverse outcomes, including major congenital malformations and/or fetal death, resulting in a relative risk of 4.59 (95% CI: 2.07-10.18) for valproate versus other antiepileptic drugs (8).

Data from a number of pregnancy registries around the world have further corroborated evidence that valproate increases the risk for major congenital malformations. The Australian Pregnancy Registry reported a malformation rate of 16.8% among children exposed to valproate monotherapy during gestation, compared to 3.8% for carbamazepine-exposed, 0% for lamotrigine-exposed, and 5.9% for phenytoin-exposed children (RR 5.6; 95% CI: 2.42-12.92) (18). Similarly, both the North American Antiepileptic Drug Pregnancy Registry and the Finnish National Birth Registry found a malformation rate of 10.7% among children exposed to valproate monotherapy during gestation (4, 12). Results from a 15-year observational study from the UK Epilepsy and Pregnancy Register reported a malformation rate of 6.7% (95% CI 5.5% to 8.3%) after valproate monotherapy exposure *in utero*, compared with 2.6% for carbamazepine (95% CI 1.9% to 3.5%) and 2.3% for lamotrigine (95% CI 1.8% to 3.1%) (5).

The congenital malformations commonly seen in AED-exposed children include cardiac, orofacial (including cleft lip/palate), skeletal (including hypoplastic phalanges), genitourinary (especially hypospadias), and neural tube defects (including spina bifida) (19). All of these malformation types have been observed most frequently in valproate-exposed children, when compared to children exposed to either carbamazepine or lamotrigine (5).

Cognitive Impairment and Developmental Delays

In addition to major malformations, several studies have described the potential impact of AED exposure on long-term intellectual development. In 2002, Dean et al. reported results from a retrospective population-based study in Scotland, in which they identified developmental delays in 24% of exposed children, compared with 11% of unexposed

siblings, although this paper did not specify if these were full or half siblings. Another 20% had behavior disorders compared with 5% of unexposed siblings (6).

More recently, in 2013, an ongoing prospective Norwegian study by Veiby et al. reported on developmental outcomes for 333 AED-exposed children at 18 months and 36 months of age, compared to unexposed controls. They found that AED-exposed children at 18 months of age had increased risk of abnormal gross motor skills (7.1% vs. 2.9%; OR 2.0) and autistic traits (3.5% vs. 0.9%; OR 2.7), compared to unexposed children born to nonepileptic parents. At 36 months of age, they found persistent gross motor delays (7.5% vs. 3.3%; OR 2.2), along with increased risk for poor sentence skills (11.2% vs. 4.8%; OR 2.1) and autistic traits (6.0% vs. 1.5%; OR 3.4) (16).

Among the antiepileptic drugs frequently studied, valproate especially has been associated with poor neurodevelopmental outcomes, including developmental delays (20), increased special education needs (21, 22), lower IQ (23-27), behavioral dysfunction (6, 22, 28, 29), and increased risk of autism spectrum disorder (30-32), when compared to other commonly used anticonvulsant drugs. In 1988, an evaluation of 19 VPA-exposed children found that 71% of infants exposed to the drug as monotherapy and 90% of those exposed to polytherapy had developmental delays or neurologic abnormalities (20). This small case series was meant only to characterize the findings in a group of VPA-exposed children and elaborate on the fetal valproate syndrome phenotype, and therefore did not include a comparison group.

Subsequently, however, a number of larger studies have reported similar findings. In 2001, Adab et al. published a retrospective study examining the relative risks of additional educational needs for 400 school-age children exposed to anticonvulsants during pregnancy.

They found that those children exposed to valproate had an odds ratio of 3.4 (95% CI 1.62-7.10) for additional educational needs when compared to unexposed children. The odds ratio for carbamazepine-exposed children was 0.26 (95% CI 0.06-1.15) (21).

Several years later, in 2004, Adab and colleagues conducted another retrospective study, this time measuring the IQ of 249 AED-exposed children between the ages of 6 and 16. The mean verbal IQ score among the 41 children exposed to valproate monotherapy was 7.3 points lower than the mean score of unexposed controls ($p=0.025$) (23). A subsequent paper about the same study population reported that valproate-exposed children also had significantly lower verbal IQ scores when compared to carbamazepine ($p=0.003$), phenytoin ($p=0.002$), and unexposed controls ($p<0.001$) (25).

Also in 2004, Gaily and colleagues evaluated IQ of 182 children born to mothers with epilepsy who had taken either valproate or carbamazepine during pregnancy. They similarly found reduced verbal IQ scores among those exposed to valproate as monotherapy ($n=13$) and polytherapy ($n=17$) *in utero*, when compared to unexposed controls. Carbamazepine-exposed children showed normal patterns of intelligence (24).

While most studies of intelligence among valproate-exposed children have found deficits specifically in verbal IQ, Eriksson and colleagues reported lower full scale IQ (FIQ) in this group as well. They found the prevalence of low intelligence (FIQ<80) and exceptionally low intelligence (FIQ<70) to be 19% (4/21) and 10% (2/21), respectively, among children exposed prenatally to valproate monotherapy (26). Like other previously described studies, this investigation was limited by its small sample size ($N=39$, including only 21 exposed to valproate monotherapy), but it did nonetheless raise concerns about the effects of valproate exposure on overall intelligence.

One of the most compelling recent reports of IQ deficits among valproate-exposed children was published by Meador and colleagues through the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, an observational, prospective study of cognitive performance among children exposed to anticonvulsants during pregnancy. In 2009, the group published results from an IQ evaluation of 309 children at 3 years of age. According to their report, after adjusting for a number of confounders, mean IQ scores of valproate-exposed children (n=60) were 9 points lower than lamotrigine-exposed (n=99), 7 points lower than phenytoin-exposed (n=52), and 6 points lower than carbamazepine-exposed (n=92) children. They further reported a dose-dependent association between valproate exposure and IQ scores (27). While this study included relatively larger sample sizes, it was limited by the lack of a comparison group.

In 2011, Nadebaum et al. conducted an observational study of children exposed to valproate, carbamazepine, and lamotrigine during pregnancy, through the Australian Pregnancy Register for Women with Epilepsy and Allied Disorders. They blindly assessed language skills of 102 children using the CELF-4 (Clinical Evaluation of Language Fundamentals, Fourth Edition), and found that mean CELF-4 scores for children exposed only to valproate monotherapy and polytherapy were significantly below the normal mean. They also reported a negative correlation between first trimester valproate dose and language scores, concluding that valproate exposure increases risk for language impairment in a dose-dependent fashion (33).

Also in 2011, Cummings et al. found developmental delay in 23 of 58 valproate-exposed children through a blinded evaluation of 210 children from 9- to 60-months old, using the Bayley Scales of Infant Development or Griffiths Mental Development Scales. By

comparison, only 10 of 40 carbamazepine-exposed children, 1 of 35 lamotrigine-exposed children, and 2 of 44 unexposed controls met criteria for developmental delay using these measures (34).

Behavioral Outcomes and Autism

In addition to developmental delays, language impairments, and IQ deficits, concerns about behavioral disorders and autism have prompted several studies to further investigate the relationship between prenatal anticonvulsant exposure and disorders on the autism spectrum. In 2005, Rasalam and colleagues examined the frequency of autism and Asperger's syndrome over a 20-year period among 260 children prenatally exposed to antiepileptic drugs. Of those, 26 were reported by parents to have behavioral or social problems and 11 met DSM-IV criteria for autistic disorder. Five out of the 56 (8.9%) valproate-exposed children included in the study had either autism or Asperger's syndrome (32).

In 2008, Bromley et al. published results from a large prospective cohort study in Liverpool and Manchester of 632 live births, including 249 children exposed to anticonvulsant drugs throughout gestation. Their study sample included 64 valproate-exposed, 44 lamotrigine-exposed, 76 carbamazepine-exposed, 51 polytherapy-exposed, 14 exposed to other monotherapies, and 47 unexposed children born to epileptic mothers. Their control group included 336 children born to women without epilepsy. They conducted medical and neuropsychological testing at ages 1, 3, and 6-years to evaluate incidence of autism spectrum disorder (ASD) among children exposed to anticonvulsants during gestation. The overall incidence of ASD was 1.6% (10/632), seven of whom were exposed to

anticonvulsants *in utero*. Significantly, over half (4/7) of the AED-exposed children were exposed to valproate during gestation. Thus 6.3% (4/64) of the valproate-exposed children were found to have a disorder on the autism spectrum (31).

However, Christensen et al. (2013) provided perhaps the strongest evidence to date of the increased absolute risk for autism and related disorders on the autism spectrum after prenatal exposure to valproate. Their large population-based study of all children born alive in Denmark from 1996-2006 (N=655,615), found that valproate exposure (n=508) was associated with an absolute risk of 4.42% (95% CI, 2.59%-7.46%) for autism spectrum disorder and 2.50% (95% CI, 1.30%-4.81%) for childhood autism, compared to 1.53% (95% CI, 1.47%-1.58%) and 0.48% (95% CI, 0.46%-0.51%), respectively, for all children. After narrowing their sample to include only those children born to mothers with epilepsy (N=6584), they found that valproate exposure (n=432) had an absolute risk of 4.15% (95% CI, 2.20%-7.81%) for autism spectrum disorder and 2.95% (95% CI, 1.42%-6.11%) for autism, compared to only 2.44% (95% CI, 1.88%-3.16%) for autism spectrum disorder and 1.02% (95% CI, 0.70%-1.49%) for autism among the unexposed children (30).

In addition to specific autistic traits, concerns have been raised about the general behavioral functioning of children exposed to anticonvulsant drugs *in utero*. A study in 2009 by Vinten and colleagues evaluated adaptive behavior in 242 AED-exposed children over the age of 6 using the Vineland Adaptive Behavior Scales. This cohort included 110 children exposed to AEDs as monotherapy (41 valproate-exposed, 49 carbamazepine-exposed, and 20 phenytoin-exposed); 52 exposed to polytherapy (28 of whom were exposed to valproate); and 80 unexposed children born to epileptic mothers. After controlling for maternal and child IQ, they found that among these groups, children exposed to valproate (as monotherapy or

polytherapy) had the poorest performance on activities of daily living and socialization. On multiple regression analysis, exposure to valproate was found to be a significant predictor of overall adaptive functioning, as well as of scores specifically related to daily living skills. A strength of this study was its concurrent evaluation of maternal and child IQ, and its ability to positively correlate IQ scores with global adaptive behavior scores. However, the study was also limited by its small sample sizes for each exposure group, and the inability to control for many confounding factors that may impact behavioral outcomes. Nonetheless, these findings reinforced concerns about the possible effects of valproate exposure on adaptive functioning, with specific focus being placed on exposed children's socialization and daily living skills (28).

In 2011, Cohen et al. published findings from the NEAD Study after examining motor, adaptive, and emotional and behavioral functioning in 229 children exposed to valproate (n=46), carbamazepine (n=61), lamotrigine (n=76), or phenytoin (n=40) monotherapies during gestation. Motor function was assessed by blinded evaluators using the Motor Scale from the Bayley Scales of Infant Development – Second Edition (BSID-II). Adaptive behavior and emotional/behavioral functioning were measured using the parent rating scales for the Adaptive Behavior Assessment System – Second Edition (ABAS-II) and the Behavior Assessment System for Children (BASC), respectively. They found a significant dose-related decline in motor skills, adaptive functioning, and social skills, and an increased risk for a future diagnosis of ADHD, among the valproate-exposed group. Significant dose-dependent motor deficits, along with a slight decline in adaptive functioning, were also observed among the children exposed to carbamazepine (29).

This review of the literature shows that substantial evidence exists to suggest that, in addition to an increased risk for major congenital malformations, prenatal exposure to valproate may be associated with cognitive impairments and poor adaptive functioning, including autism or autistic traits. The effects of carbamazepine exposure also remain questionable, while lamotrigine, though less well studied, has generally been associated with better outcomes. Despite this preponderance of evidence, however, most studies investigating neurodevelopmental outcomes of exposed children (apart from a few rare exceptions described above) have been relatively small, retrospective, and/or relied on language testing and IQ to assess cognitive function. While IQ tests measure general intelligence, they do not assess functional abilities and 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 and behavioral outcomes. Impairments specifically in socialization and communication, in conjunction with repetitive and stereotyped behaviors, form the basis for diagnosis of autism spectrum disorder (35).

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 (36, 37). In individuals with autism spectrum disorder, severe social deficits have been observed even with relatively high IQ (36, 37). 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.

Those few studies that have examined adaptive functioning in children prenatally exposed to anticonvulsants have used various instruments and screening tools, including the

Ages and Stages Questionnaire (ASQ), the Social Communication Questionnaire (SCQ), the Modified Checklist for Autism in Toddlers (MCHAT), the Early Screening for Autistic Traits (ESAT), the Adaptive Behavior Assessment System – Second Edition (ABAS-II) and the Behavior Assessment System for Children (BASC), among others. Surprisingly, only one study has utilized the Vineland Adaptive Behavior Scales to assess adaptive behaviors in these groups of children, despite the fact that this is one of the most widely used validated instruments for evaluation of adaptive functioning in children with autism spectrum disorders (28, 37, 38). That study, by Vinten and colleagues (2009), was retrospective, included relatively small sample sizes of valproate-exposed and carbamazepine-exposed children, and did not evaluate children exposed to lamotrigine.

As a result, information on the long-term behavioral effects of prenatal AED exposure is still lacking, and significant limitations exist for physicians counseling female epileptic patients of childbearing age. We present a moderately-sized ambidirectional (with both prospective and retrospective phases) cohort study, to evaluate adaptive behavior outcomes using the Vineland Adaptive Behavior Scales – Second Edition (*Vineland-II*) among children born to epileptic women who used carbamazepine, lamotrigine, or valproate as monotherapy during pregnancy.

Statement of Purpose

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.

Only first trimester dose was included in our analysis based on the fact that this is a period of organogenesis, including brain development, during which the embryo is particularly susceptible to teratogenic insults resulting in gross structural abnormalities. Previous reports have shown that early exposure to valproic acid, in particular, is associated with increased risk of major congenital malformations in a dose-response manner (27). Additionally, it was felt that data collected on first trimester drug dose would be most accurate for our data analysis, given that these data were prospectively collected from the mothers when they were in their first trimester of pregnancy during the time of enrollment in the North American AED (antiepileptic drug) Pregnancy Registry, from which our subjects were recruited. Finally, given that dosages are often modified as the pregnancy progresses in order to maintain therapeutic effect, it was felt that data collected on first trimester drug dose would be most stable and thus reliable for analysis.

Methods

Recruitment, Inclusion, and Exclusion Criteria

Recruitment letters were sent by mail to women with epilepsy who had prospectively enrolled in the North American AED Pregnancy Registry (“the Registry”) while taking LTG, VPA, or CBZ to suppress seizures throughout pregnancy, and whose exposed children were 3- to 6-years-old. The Registry’s methodology has been described previously (39).

These three drugs were selected for the study because they were used in adequate numbers by Registry participants at the time of enrollment. Additionally, valproate was specifically selected in light of previously raised concerns about developmental outcomes for children exposed to this drug *in utero*. Lamotrigine was selected because it is a relatively newer agent for which only limited outcomes data are currently available. This study thus aims to fill the gap in knowledge about outcomes for children exposed to lamotrigine, while adding a new dimension to the existing literature for outcomes related to valproate and carbamazepine exposure.

Our study was designed to include children between 3- and 6-years-old because it was felt that most adaptive behavior impairments would be readily evident by the time a child reaches this age range. Additionally, most prior studies investigating cognitive or adaptive behavior outcomes of children following AED exposure have focused on children younger than 3-years-old, with a few evaluating children older than 6-years-old. Thus, information is currently lacking as it may relate to children in this intermediate age range. It was felt that children between 3- and 6-years-old would be old enough to exhibit subtle signs of behavior dysfunction, but would likely not have yet received such extensive treatment or intervention so as to significantly influence our study results. Finally, at the time of

enrollment, it was felt that there would be sufficient numbers of women in the Registry with children within this age range meeting inclusion criteria for our study.

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 stopped or switched AEDs during pregnancy, if they had mental illness or memory disorders, or if they refused to release medical records.

Study Procedures

Mothers were screened by telephone to determine eligibility and collect data on participant characteristics and an array of confounding variables, including those identified in Table 2. Written consent forms and authorization forms to request relevant medical records were sent to qualified subjects. Those medical records were then reviewed for each child and his/her mother to confirm eligibility. Subjects were excluded at each stage of the intake and enrollment process if they were found to be ineligible or if the mothers were non-responsive.

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 consisting of 433 items designed to assess a child's self-sufficiency and adaptive functioning in the domains of communication, daily living, socialization, and motor skills (38). Those four domains are further divided into 11 subdomains, as shown below in Figure 1.

The communication domain evaluates a child's receptive, expressive, and written communication skills. Receptive communication refers to how an individual listens, pays

attention, follows directions, and understands spoken language. Expressive communication refers to what an individual is able to say and how he or she communicates using words or sentences. Written communication skills describe one's ability to read and write (38).

The daily living skills domain assesses personal behaviors, including the ability to feed and dress oneself, and maintain personal hygiene. Additionally, this domain evaluates a child's ability to perform age-appropriate domestic skills and interact in the community (i.e., telling time, operating a telephone, using money to make a purchase, etc.) (38).

The socialization domain measures a child's ability to engage in play and leisure time; cultivate interpersonal relationships and interact with others; and develop various coping skills, including the ability to handle disappointment or disruptions in routine, as well as the ability to show sensitivity or empathy towards others (38).

Finally, the motor skills domain evaluates a child's gross and fine motor function. Gross motor skills describe one's ability to use his or her arms or legs for general, unrefined movement and coordination (i.e., to walk or climb stairs). Fine motor skills refer to the ability to use one's hands or fingers to manipulate objects (i.e., using a pencil to draw) (38).

The subdomains yield v-scale scores that sum to yield the domain composite scores, which are then standardized (mean=100, SD=15) and combined to produce the global Adaptive Behavior Composite (ABC) for individuals from birth through 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 classified 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 1.

Figure 1. Categories measured by the Vineland Adaptive Behavior Scales, Survey Interview Form, Second Edition (*Vineland-II*). The eleven subdomains on the left of the diagram make up the four domains of Communication, Daily Living Skills, Socialization, and Motor Skills, which combine to give the overall Adaptive Behavior Composite.

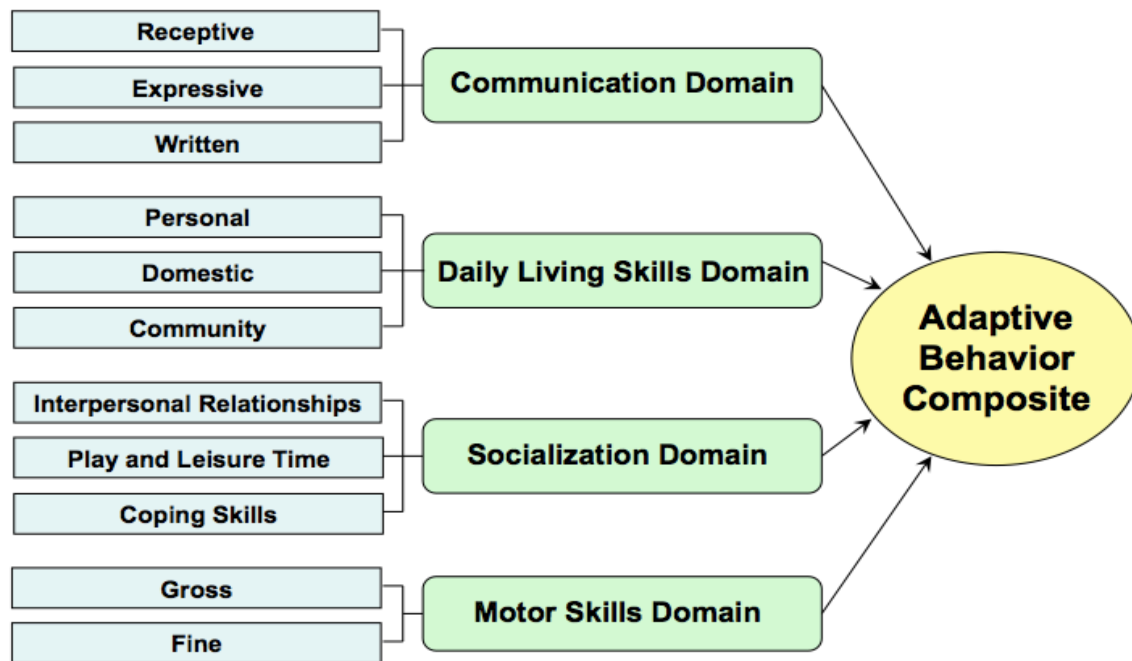


Table 1. Adaptive level descriptions, modified from the *Vineland-II* Instruction Manual (38). Standard scores are classified into adaptive levels based on their standard deviations from the expected mean of 100.

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

The *Vineland-II* was standardized based on a national sample of over 3,000 individuals selected to match 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 of this study. Adaptive levels and subdomains were then examined for a more nuanced analysis of differences in adaptive functioning among the three drug groups.

All research activities, including protocol development, recruitment, screening, enrollment, interviews, interview scoring, database design, data collection, and data management, were completed by the first author (U.S.D.) and another research coordinator (R.D.) at Massachusetts General Hospital who were trained using the official *Vineland-II* training video and survey manual. *Vineland-II* interviews took 60-90 minutes to complete, on average, and were scored by U.S.D and R.D. by hand or using the *Vineland-II Survey Forms ASSIST* software.

Statistical Analyses

Statistical analyses were completed by U.S.D., along with a biostatistician (E.M.) at Massachusetts General Hospital's Biostatistics Center, using Statistical Analysis Software, version 9.4. The primary analysis examined baseline characteristics of the study population and individual 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. Group differences were examined using Pearson's Chi-squared test and one-way

ANOVA for significant associations between exposure and covariates. The Pearson's chi-squared and one-way ANOVA test statistics are reported below and in the accompanying tables.

Mean adaptive behavior scores were calculated for the children in each drug group. One-sample 2-tailed t tests were performed to determine whether group means differed from the test mean of 100. Mean adaptive behavior composite (ABC) scores and domain standard scores were then analyzed using one-way ANOVA to identify differences among the three drug groups. Scores were first compared using unadjusted data. Next, post-hoc subgroup analyses determined whether group differences in adaptive behavior outcomes could be attributed to differences in baseline characteristics. After adjustment for propensity scores from potential confounders including maternal age, education, folate use, cigarette and alcohol exposure, gestational age, and birth weight, differences in ABC and domain standard scores were analyzed using least square means by one-way ANOVA. For measures that differed significantly among the three groups, pairwise differences were analyzed using Tukey post-hoc comparisons. Adaptive levels for each domain and subdomain were then examined for frequency of moderately low or low levels (standard scores ≤ 85 , or ≥ 1 SD from the expected mean of 100) of adaptive functioning in each of the three drug groups.

To examine dose-response relationships, the first trimester drug dose was derived by averaging the dose at the last menstrual period and any changes in dose through the first trimester, as reported by the mother. Standard adaptive behavior scores were correlated with the derived first trimester drug dose using generalized linear models with exposure-dependent dose effects. Significance was set at $p=0.05$ for all analyses.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was reviewed and approved annually by the Partners Human Research Committee, the institutional review board for the Massachusetts General Hospital. All participating women provided informed written consent.

Results

Recruitment Process

Recruitment letters were mailed to 972 women (with 1,032 children) who had enrolled in 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 (mean 4.9 years, SD 1.1 years). Of those contacted, mothers of 495 children (48%) responded, 455 expressed interest, and 346 completed the initial screening to assess eligibility.

Of those that responded to recruitment letters and completed the initial screening, 93 were excluded from the study. The most common reasons for exclusion were that the child was too old (over 6-years-old) by the time of the interview (11.0%); failure to return consent forms (8.1%); inability to schedule an interview (7.8%); loss of interest or inability to meet the time commitment (2.9%); and failure to respond to follow-up calls (1.7%). Three subjects (0.9%) were excluded after discovering through medical records that the children were, in fact, exposed to polytherapy pharmacy during gestation. Other reasons for exclusion included inability to be contacted because the phone number was out of service or mail was returned to sender (0.6%); a mental health disorder was discovered in the mother (0.3%); the anticonvulsant drug was taken for a condition other than a seizure disorder (0.3%); the mother had privacy concerns or other personal reasons for opting out (0.3%); and one child was under 3-years-old during the enrollment period (0.3%). After exclusions, 253 children were eligible to participate in the study, including 98 CBZ-exposed, 104 LTG-exposed, and 51 VPA-exposed children.

Baseline Characteristics

Response rates differed significantly among the LTG (57.1%), VPA (50.7%) and CBZ (41.1%) groups ($\chi^2 = 20.87$; $p < 0.001$). Women were more likely to respond to recruitment letters if they were married ($\chi^2 = 26.64$; $p < 0.001$), had private insurance ($\chi^2 = 18.37$; $p = 0.001$), were 30-34 years-old ($\chi^2 = 36.50$; $p < 0.001$), or had college degrees ($\chi^2 = 48.22$; $p < 0.001$). Data on major malformations (defined as a structural abnormality with surgical, medical, or cosmetic importance, and confirmed by L.B.H. through medical record reviews) were available for 253 children. Mothers of children with major malformations were significantly less likely to respond to recruitment letters ($\chi^2 = 56.96$; $p < 0.001$).

In the recruitment cohort, the three drug groups differed significantly with respect to insurance coverage ($\chi^2 = 21.22$; $p = 0.002$), marital status ($\chi^2 = 29.53$; $p < 0.001$), prenatal folate use ($\chi^2 = 6.49$; $p < 0.039$), cigarette ($\chi^2 = 18.47$; $p = 0.001$) and alcohol exposure ($\chi^2 = 7.86$; $p = 0.020$), epilepsy type ($\chi^2 = 51.36$; $p < 0.001$), seizures during pregnancy ($\chi^2 = 12.57$; $p = 0.002$), presence of major malformations in the exposed child ($\chi^2 = 12.84$; $p = 0.002$), and child's age at the time of interview ($F_{2,250} = 9.59$; $p < 0.001$).

In the final *Vineland* cohort, however, significant differences in maternal education ($\chi^2 = 13.90$; $p = 0.031$), marital status ($\chi^2 = 6.53$; $p = 0.038$), presence of major malformations ($\chi^2 = 7.46$; $p = 0.024$), prenatal folate exposure ($\chi^2 = 7.89$; $p = 0.019$), epilepsy type ($\chi^2 = 43.36$; $p < 0.001$), seizures during pregnancy ($\chi^2 = 17.77$; $p < 0.001$), and child's age at the time of the interview ($F_{2,250} = 9.59$; $p < 0.001$) were observed, while all other group differences disappeared (see Table 2).

Global Adaptive Behavior Composite and Domain Comparisons

Adaptive behavior data were collected for 253 children, including 98 CBZ-exposed, 104 LTG-exposed and 51 VPA-exposed children (see Figure 2). The discrepancy in sample sizes reflects variations in anticonvulsant drug use among the participants enrolled in the North American AED Pregnancy Registry, from which our subjects were recruited. Over the last decade, there has been a steady and precipitous decline in enrollment of VPA cases, presumably secondary to changes in prescribing practices among neurologists who are increasingly aware of the risks associated with VPA use during pregnancy. The decreasing enrollment of VPA cases in the Registry yielded fewer VPA-exposed children who met our inclusion criteria.

Figure 2. Breakdown of the final Vineland cohort, depicting the number of subjects in each drug group included in the final analysis, after exclusion of those who did not meet inclusion criteria.

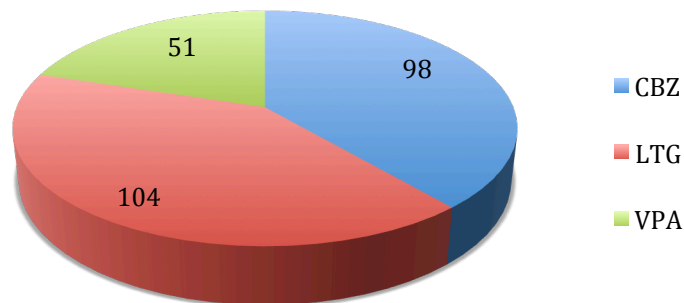


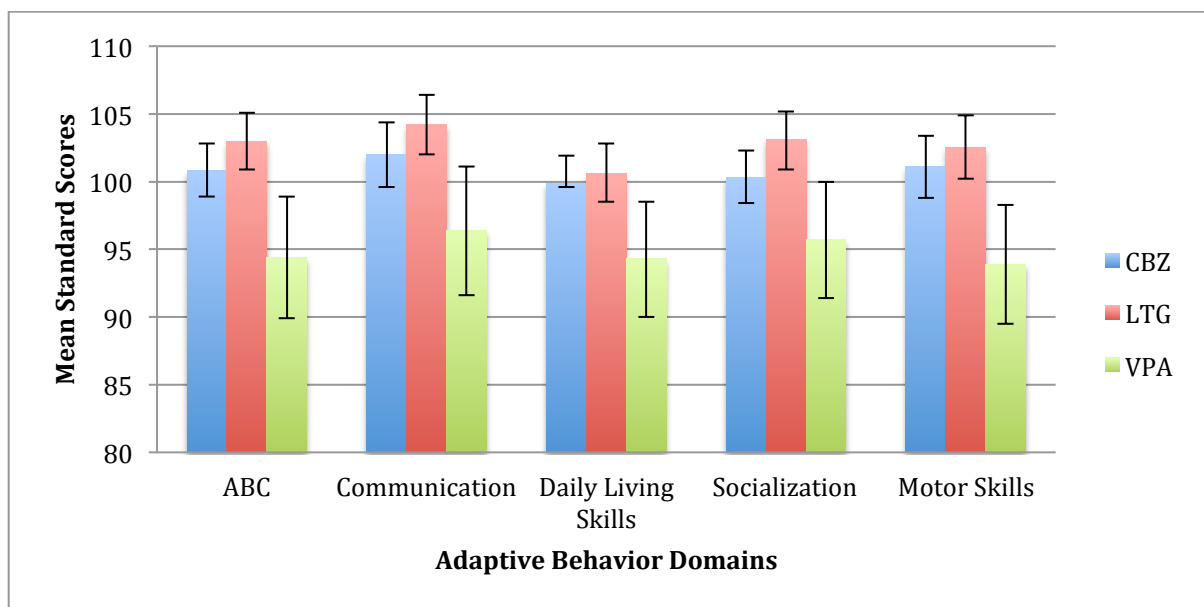
Table 2. Baseline Characteristics of 253 Children and their Mothers By Prenatal AED Exposure. Significant p-values ($p < 0.05$) are indicated in bold print. IGE = Idiopathic Generalized Epilepsy, NCE = Nonclassifiable Epilepsy, NE = Not Epilepsy, PE = Partial Epilepsy.

	CBZ N=98	LTG N=104	VPA N=51	p-value
	<i>% (no.)</i>			
Maternal Education				0.031
High School or Less	2.1% (2)	6.7% (7)	9.8% (5)	
Some College	21.9% (21)	17.3% (18)	23.5% (12)	
College Graduate	38.5% (37)	38.5% (40)	52.9% (27)	
Post-Graduate	37.5% (36)	37.5% (39)	13.7% (7)	
Insurance				0.107
Canadian	7.3% (3)	1.2% (1)	0.0% (0)	
Medicaid	2.4% (1)	1.2% (1)	6.7% (2)	
Private	90.2% (37)	97.6% (81)	93.3% (28)	
Marital Status				0.038
Married	96.1% (49)	95.7% (88)	84.2% (32)	
Unmarried	3.9% (2)	4.3% (4)	15.8% (6)	
Multivitamin Use				0.128
Yes	64.2% (61)	76.0% (79)	76.5% (39)	
No	35.8% (34)	24.0% (25)	23.5% (12)	
Folic Acid Use				0.019
None	30.8% (24)	13.2% (12)	25.6% (11)	
Some	69.2% (54)	86.8% (79)	74.4% (32)	
Cigarette Exposure				0.654
Yes	11.5% (11)	7.7% (8)	7.8% (4)	

	CBZ N=98	LTG N=104	VPA N=51	p-value
No	35.4% (34)	44.2% (46)	45.1% (23)	
Don't remember	53.1% (51)	48.1% (50)	47.1% (24)	
Alcohol Exposure				0.352
Yes	24.0% (23)	23.1% (24)	33.3% (17)	
No	76.0% (73)	76.9% (80)	66.7% (34)	
Major Malformation				0.024
Yes	6.3% (5)	3.3% (3)	15.9% (7)	
No	93.8% (75)	96.7% (89)	84.1% (37)	
Epilepsy Type				<0.001
IGE	5.1% (3)	18.1% (15)	60.0% (21)	
NCE	40.7% (24)	32.5% (27)	25.7% (9)	
NE	1.7% (1)	0.0% (0)	0.0% (0)	
PE	52.5% (31)	49.4% (41)	14.3% (5)	
Prenatal Seizures				<0.001
Yes	15.8% (15)	39.8% (41)	16.3% (8)	
No	84.2% (80)	60.2% (62)	83.7% (41)	
Mean Maternal Age at Delivery (yr)	32.3±5.3	32.1±4.4	31.3±5.0	0.474
Gestational Age (wks)	38.7±2.4	38.5±1.5	38.8±1.6	0.432
Birth Weight (kg)	3.42±0.58	3.34±0.60	3.35±0.61	0.651
Birth Length (cm)	50.8±3.1	50.6±3.4	51.3±2.8	0.443
Interview Age (yrs)	5.3±1.1	4.6±1.1	4.9±1.1	<0.001

The mean ABC and domain standard scores for each drug group are presented graphically in Figure 3. Mean ABC standard scores of CBZ-exposed children (100.8 ± 9.9 ; $t(97)=0.84$, $p=0.401$, 95% CI [99, 103]) were not significantly different from the expected mean of 100. However, the mean scores for LTG-exposed children were significantly higher than expected (103.0 ± 11.0 ; $t(103)=2.76$, $p=0.007$, 95% CI [101, 105]), while those for VPA-exposed children were significantly lower than expected (94.4 ± 16.2 ; $t(50)= -2.47$, $p=0.017$, 95% CI [90, 99]). Group comparisons showed significant differences in the ABC standard scores ($F_{2,250}=5.90$; $p<0.003$) and all domain standard scores (Communication Standard scores ($F_{2,250}=4.47$; $p=0.012$), Daily Living Standard Scores ($F_{2,250}=3.57$; $p<0.030$), Socialization Standard Scores ($F_{2,250}=5.02$; $p<0.007$), and Motor Standard Scores ($F_{2,250}=5.83$; $p<0.003$)) among the three groups, with pairwise comparisons showing VPA-exposed children scoring significantly below LTG-exposed children in all domains, and significantly below CBZ-exposed children in only the ABC, daily living skills, and motor skills domain.

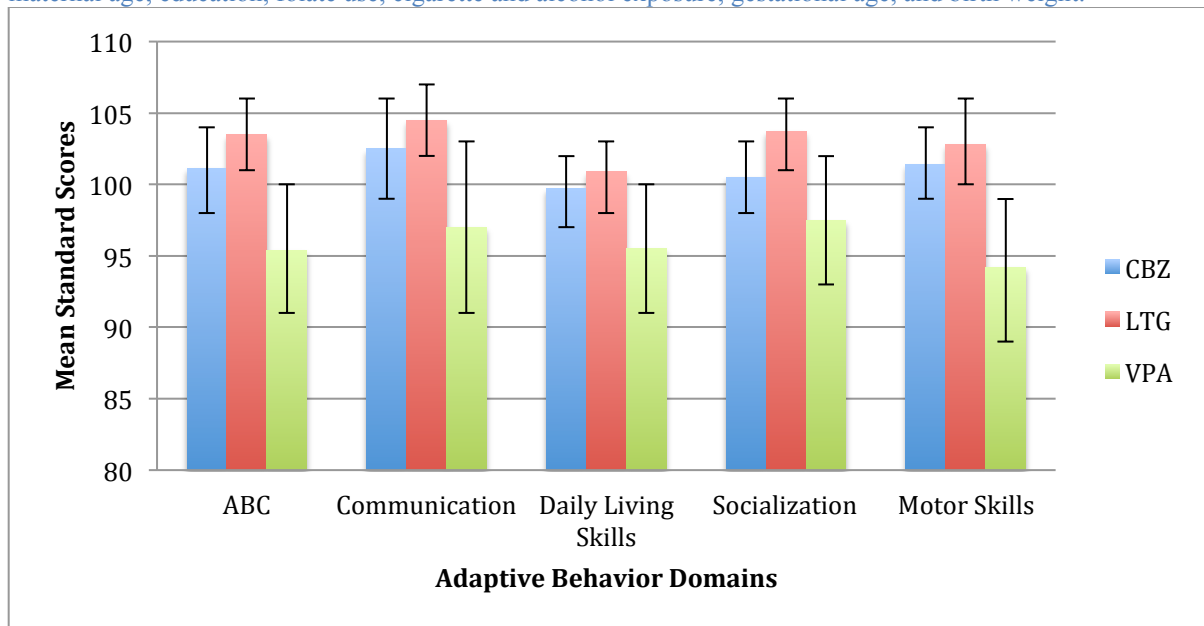
Figure 3. Mean ABC and Domain Standard Scores for each drug group, before adjusting for covariates.



The association of valproate with weaker performance persisted in nearly all domains after adjustment for propensity scores from maternal age, education, folate use, cigarette and alcohol exposure, gestational age, and birth weight (Figure 4). The mean adjusted ABC score for VPA-exposed children was 95.4 (95% CI [91, 100]), versus 101.1 (95% CI [98, 104]) for CBZ-exposed and 103.5 (95% CI [101, 106]) for LTG-exposed children ($F_{2,188}=4.24$; $p=0.016$).

After adjusting for the same propensity scores, significant differences were observed among the three groups in the socialization, communication, and motor domains. In the socialization domain, the mean adjusted standard score for the VPA-exposed group was 97.5 (95% CI [93, 102]), compared to 100.5 (95% CI [98, 103]) and 103.7 (95% CI [101, 106]) for the CBZ-exposed and LTG-exposed groups, respectively ($F_{2,188}=3.72$; $p=0.026$). In the communication domain, VPA-exposed children had a mean adjusted standard score of 97.0 (95% CI [91, 103]), compared to 102.5 (95% CI [99, 106]) and 104.5 (95% CI [102, 107]) for the CBZ-exposed and LTG-exposed groups, respectively ($F_{2,188}=3.05$; $p=0.050$). In the motor domain, the mean adjusted standard score for the VPA-exposed group was 94.2 (95% CI [89, 99]), compared to 101.4 (95% CI [99, 104]) and 102.8 (95% CI [100, 106]) for the CBZ-exposed and LTG-exposed groups, respectively ($F_{2,188}=4.37$; $p=0.014$). Although a similar trend was observed in the domain of daily living, with VPA-exposed children performing lowest and LTG-exposed children performing highest, the cross-group differences were not statistically significant in this category.

Figure 4. Mean ABC and domain standard scores for each drug group after adjusting for propensity scores from maternal age, education, folate use, cigarette and alcohol exposure, gestational age, and birth weight.



Tukey's HSD post-hoc pairwise comparisons showed that, though the mean adjusted adaptive behavior composite (ABC), communication, socialization, and motor standard scores for the VPA group were persistently lower than those for both the LTG and CBZ groups, the differences were statistically significant only when comparing results for the VPA and LTG groups, except in the motor domain, in which VPA-exposed children performed significantly worse than both CBZ- and LTG-exposed children. No significant differences were observed when comparing the CBZ-exposed group with the LTG-exposed group in any measured category.

Adaptive Levels and Subdomain Comparisons

Although the differences among group mean scores met statistical significance as noted above, these mean scores were all within one standard deviation from the expected

mean of 100. This raises the question of whether these differences are meaningful or clinically significant. Indeed, a score within one standard deviation of the expected mean is considered average or adequate, as described above in Table 1. Thus, the group mean scores for the valproate-exposed group, while significantly lower than those of the lamotrigine-exposed group, are not, in and of themselves, indicative of any true clinically significant adaptive behavior impairments.

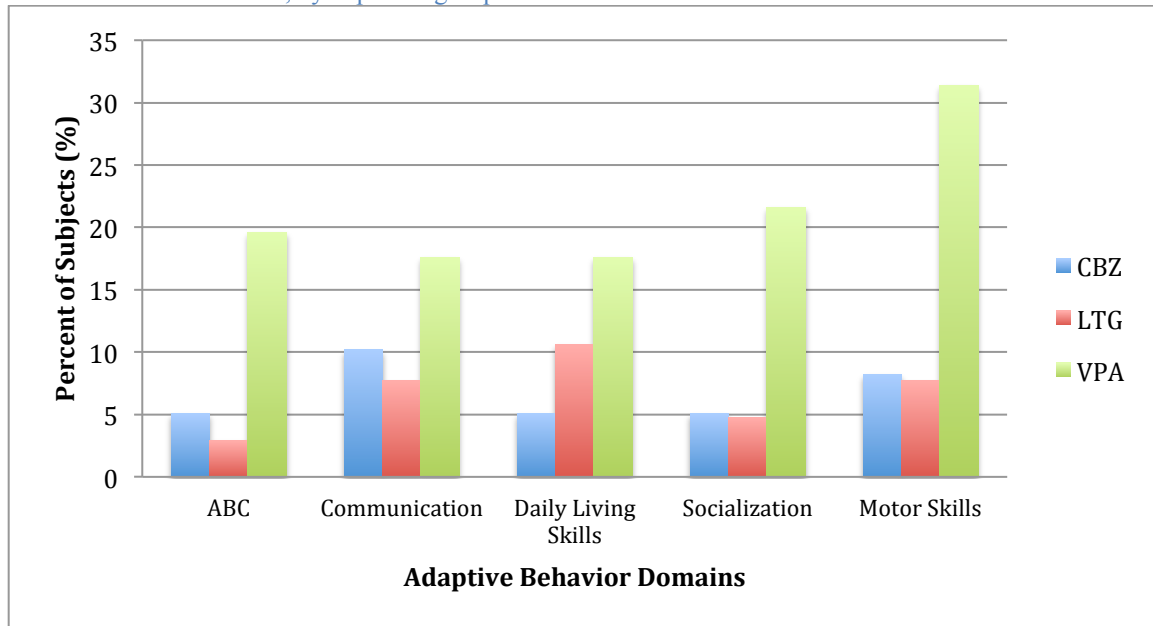
However, it is perhaps more informative to examine the breakdown of the scores for each group by adaptive level, in order to determine if clinically significant differences exist in their frequency distributions. Indeed, such an examination reveals that VPA-exposed children were more likely than the other two groups to perform at an adaptive level that was low or moderately low (standard scores ≤ 85) in each and every category, with significant differences observed in all except the communication domain and the subdomains of written and personal skills. Nearly 22% of VPA-exposed children had low or moderately low performance in the socialization domain, compared with only 5.1% of CBZ-exposed and 4.8% of LTG-exposed children; and over 31% of the VPA-exposed children had low or moderately low motor skills, compared with only 8.2% and 7.7% of CBZ-exposed and LTG-exposed children, respectively. These frequency distributions and accompanying p-values are shown below in Table 3.

Table 3. Frequency of low and moderately low adaptive levels (standard scores ≤ 85) in the overall ABC, domain, and subdomain categories for each drug group. The bolded p-values indicate the categories for which the frequency distributions were significantly different ($p < 0.05$).

	CBZ N=98	LTG N=104	VPA N=51	p-value
	<i>% (no.)</i>			
ABC	5.1% (5)	2.9% (3)	19.6% (10)	<0.001
Communication	10.2% (10)	7.7% (8)	17.6% (9)	0.166
Receptive	11.2% (11)	3.8% (4)	17.6% (9)	0.017
Expressive	6.1% (6)	5.8% (6)	33.3% (17)	<0.001
Written	9.2% (9)	13.5% (14)	19.6% (10)	0.198
Daily Living Skills	5.1% (5)	10.6% (11)	17.6% (9)	0.049
Personal	14.3% (14)	15.4% (16)	27.5% (14)	0.103
Domestic	4.1% (4)	4.8% (5)	15.7% (8)	0.016
Community	6.1% (6)	10.6% (11)	25.5% (13)	0.002
Socialization	5.1% (5)	4.8% (5)	21.6% (11)	<0.001
Interpersonal	9.2% (9)	5.8% (6)	21.6% (11)	0.002
Play	5.1% (5)	3.8% (4)	23.5% (12)	<0.001
Coping	12.2% (12)	12.5% (13)	27.5% (14)	0.029
Motor Skills	8.2% (8)	7.7% (8)	31.4% (16)	<0.001
Gross	13.3% (13)	6.7% (7)	33.3% (17)	<0.001
Fine	10.2% (10)	8.7% (9)	23.5% (12)	0.022

These data are also presented graphically below for the ABC, communication, daily living skills, socialization, and motor skills domains (Figure 5).

Figure 5. Frequency distribution showing the percent of subjects who received standard scores ≤ 85 (equivalent to low and moderately low adaptive levels), in the ABC, Communication, Daily Living Skills, Socialization, and Motor Skills domains, by exposure group.



It is evident from the above data that the VPA-exposed group has a disproportionate number scoring in the low or moderately low range compared to the CBZ-exposed and LTG-exposed groups. These findings suggest that, despite the adequacy of the overall group mean scores, the VPA-exposed group is more likely to possess clinically significant adaptive behavior impairments potentially requiring intervention.

Interestingly, a closer examination of the subdomains also revealed significant differences in the communication subdomains of receptive and expressive communication, while there was no difference in the subdomain of written communication. More specifically, pairwise comparisons revealed that the VPA-exposed group was significantly more likely than the LTG-exposed group to score low or moderately low in the receptive ($p=0.021$) and expressive ($p<0.001$) communication subdomains. The VPA-exposed group was significantly more likely than the CBZ-exposed group to score low or moderately low in

only the expressive subdomain ($p < 0.001$). This suggests that the absence of a significant difference in the overall communication domain is largely explained by the relative strength of the writing skills of the VPA-exposed group despite the weaknesses that this group possesses in the areas of receptive and expressive communication.

The frequency distributions outlined above are also impressive in the sheer proportions of valproate-exposed children falling within the low or moderately low categories for each domain and subdomain. These data reveal that fully 15-33% of VPA-exposed children received standard scores that were greater than one standard deviation below the expected means in every single category.

Dose-Response Relationship

Regression analysis using general linear models with exposure-dependent dose effects identified a significant negative relationship between first trimester VPA drug dose and unadjusted ABC ($t = -2.33$; $p = 0.021$), socialization ($t = -2.64$; $p = 0.009$), and motor standard scores ($t = -2.05$; $p = 0.041$), such that a higher VPA dose was associated with lower scores. There was also a trend toward a significant negative relationship between VPA drug dose and communication standard scores ($t = -1.93$; $p = 0.055$) (Table 4; Figures 6-9).

VPA doses of 1000 mg/day or greater were significantly associated with lower ABC scores ($p < 0.001$) and standard scores across all domains ($p < 0.001 - 0.004$). No dose-response effects were observed for the CBZ and LTG groups.

Table 4. Estimates of exposure-dependent dose effect on Vineland performance in each tested domain (Adaptive Behavior Composite, Communication, Daily Living Skills, Socialization, and Motor Skills) for the three exposure groups. Significant p-values are shown in bold print.

Variable	Measure	Estimate	95% CI		t-value	P-value
			Lower	Upper		
Adaptive Behavior Composite (ABC) Score	CBZ	-0.221	-0.876	0.433	-0.67	0.506
	LTG	-0.081	-1.247	1.085	-0.14	0.891
	VPA	-1.229	-2.268	-0.191	-2.33	0.021
Communication Standard Score	CBZ	-0.139	-0.860	0.582	-0.38	0.705
	LTG	0.331	-0.954	1.615	0.51	0.613
	VPA	-1.120	-2.264	0.024	-1.93	0.055
Daily Living Standard Score	CBZ	0.058	-0.587	0.703	0.18	0.859
	LTG	-0.063	-1.212	1.086	-0.11	0.914
	VPA	-0.865	-1.889	0.158	-1.67	0.097
Socialization Standard Score	CBZ	-0.117	-0.739	0.504	-0.37	0.710
	LTG	-0.255	-1.362	0.852	-0.45	0.651
	VPA	-1.320	-2.306	-0.335	-2.64	0.009
Motor Standard Score	CBZ	-0.386	-1.110	0.337	-1.05	0.294
	LTG	-0.311	-1.600	0.979	-0.47	0.635
	VPA	-1.195	-2.343	-0.047	-2.05	0.041

Figure 6. Relationship between 1st Trimester Dosage and ABC Standard Scores For Each Exposure Group.

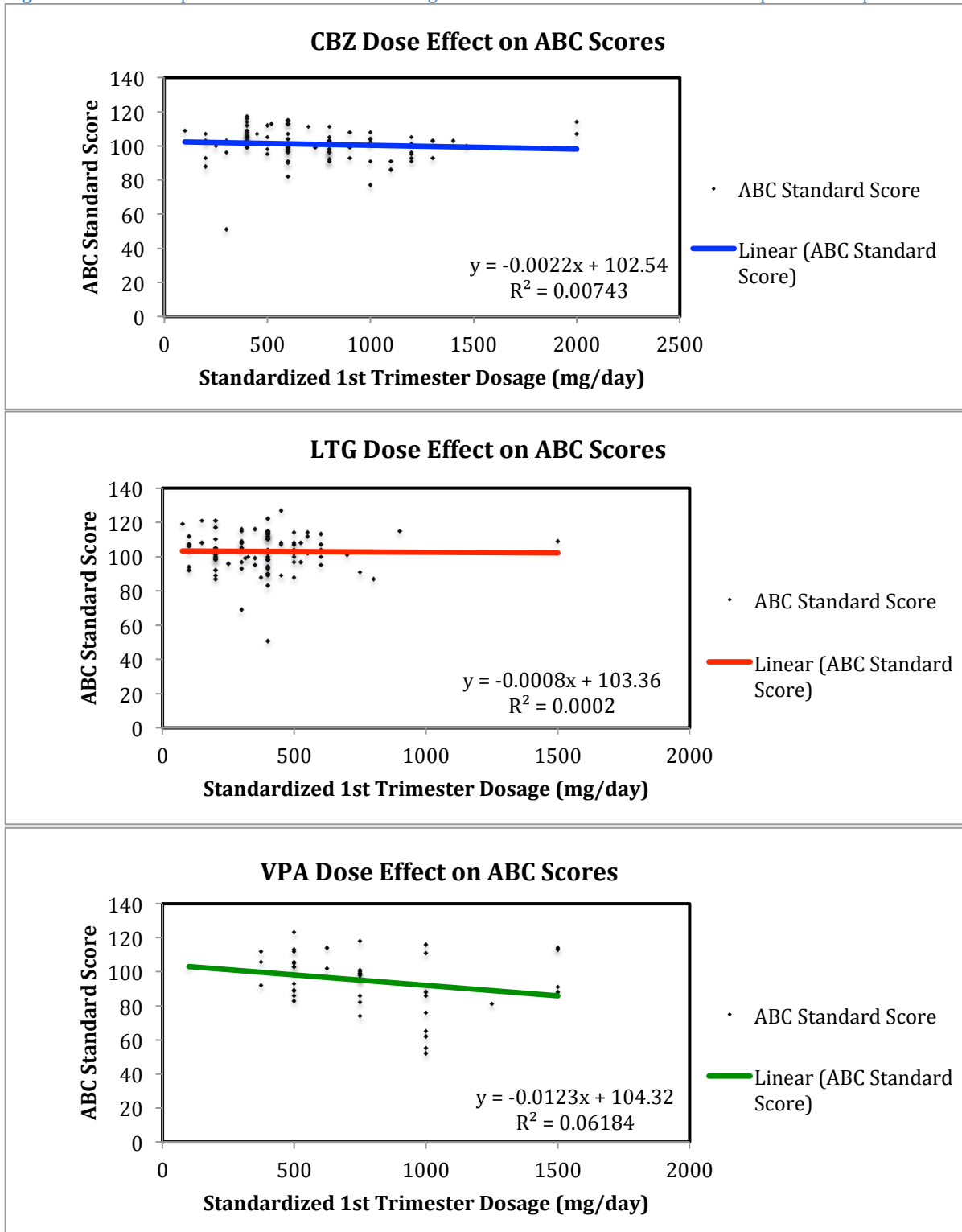


Figure 7. Relationship between 1st Trimester Dosage and Socialization Standard Scores For Each Exposure Group.

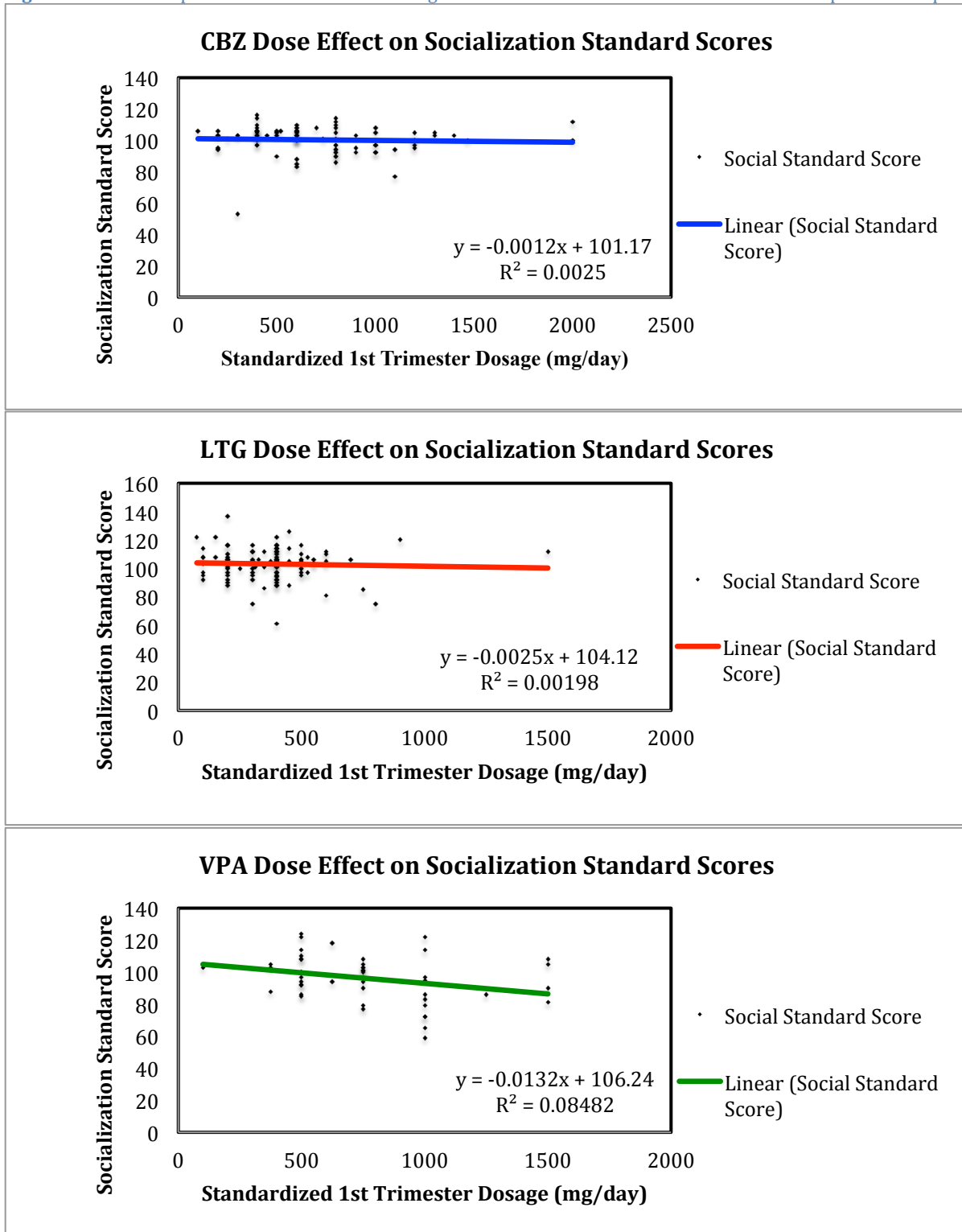


Figure 8. Relationship between 1st Trimester Dosage and Motor Scores For Each Exposure Group.

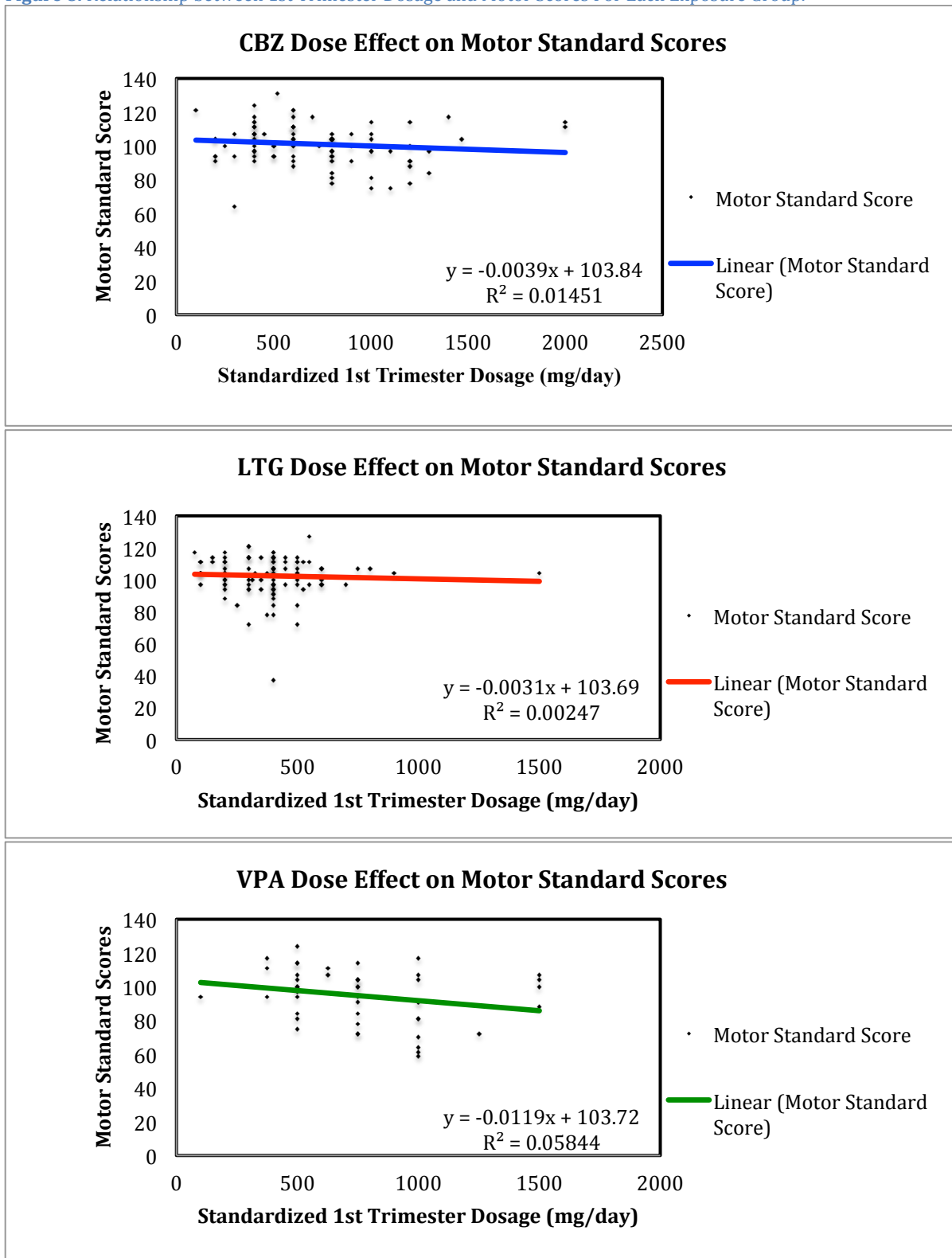
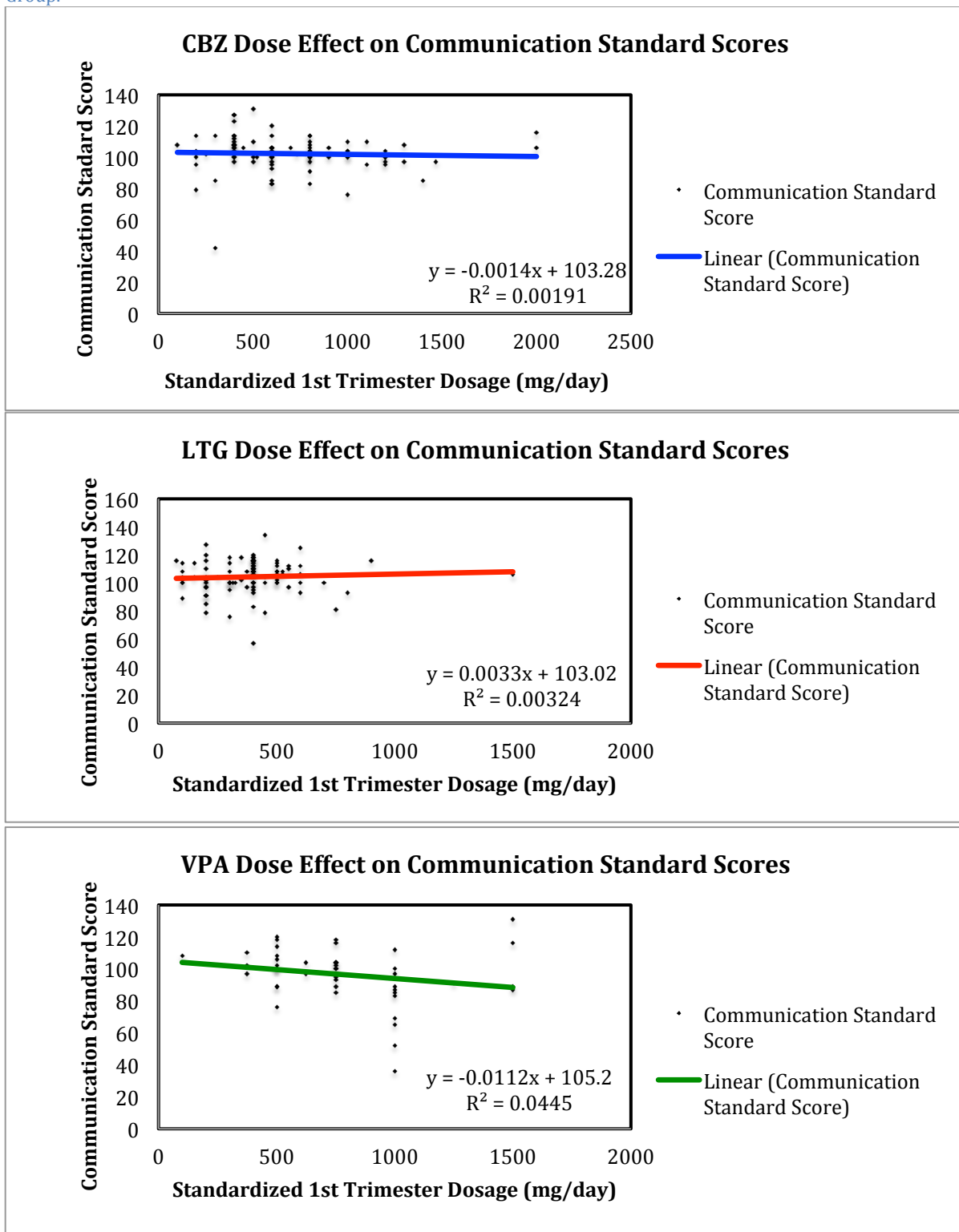


Figure 9. Relationship between 1st Trimester Dosage and Communication Standard Scores For Each Exposure Group.



Discussion

Prenatal exposure to VPA was associated with poorer adaptive behavior outcomes in all of the measured domains, when compared to the test mean and to children exposed to CBZ or LTG. Significant differences in comparison to the LTG-exposed group were noted in the ABC, socialization, communication, and motor domains after adjusting for propensity scores from a variety of potential confounders. While the VPA-exposed group scored the lowest in the domain of daily living, these scores did not differ significantly when compared to the other two drug groups.

The VPA-exposed group was most likely to perform at a low or moderately low adaptive level (standard score ≤ 85 , or ≥ 1 SD below the expected mean) in each and every category, with significant differences in all except the communication domain. Closer examination of the communication subdomain scores revealed that the VPA-exposed group was significantly more likely than the LTG-exposed group to perform at a low or moderately low adaptive level in the subdomains of receptive and expressive communication, making up for these weaknesses with a relative strength in their writing skills. The VPA-exposed group was significantly more likely than the CBZ-exposed group to score low or moderately low in the expressive communication subdomain.

Furthermore, the negative effect of VPA on adaptive behavior outcomes was dose-dependent, such that exposure to higher valproate doses correlated significantly with lower ABC, socialization, and motor scores, with a similar trend toward significance in the communication domain.

Our results are consistent with previous reports that VPA exposure negatively impacts adaptive behavior and cognitive outcomes (20, 21, 23, 26-28, 34, 40). Similar to our findings of weaker performance in the subdomains of receptive and expressive communication, prior studies have identified communication deficits among VPA-exposed children, in the form of reduced verbal IQ and language impairments (23-25, 33). This suggests that valproate exposure may especially impact verbal skills.

Previous investigations also support our findings of poorer socialization (25, 28) and motor skills (41) in VPA-exposed children. While overall mean scores for the VPA-exposed group were within the average range, this group was significantly more likely to perform low or moderately low (with standard scores ≤ 85) in these categories, when compared with children prenatally exposed to either CBZ or LTG. The fact that over 20% of VPA-exposed children had low or moderately low socialization skills, and over 30% of VPA-exposed children had low or moderately low motor skills is alarming, and raises serious concerns for the ability of these VPA-exposed children to perform in school, interact with their peers, develop age-appropriate motor skills, and ultimately function independently in society.

Apart from communication, socialization, and motor skills, Vinten and colleagues (2009) also reported deficits in daily living skills among children exposed to valproate (28). While overall adjusted mean standard scores in the daily living skills domain did not differ significantly among the three exposure groups in our study, the mean daily living score for VPA-exposed children was, indeed, below that of the other two drug groups, and the VPA-exposed group was significantly more likely to score low or moderately low in this category. These findings suggest that additional research is necessary to understand the drug's impact in this domain.

Of particular interest is the combination of socialization and communication (specifically receptive and expressive communication) deficits in the VPA-exposed children, which characterize symptoms commonly associated with autism (38). Previous reports have suggested that VPA exposure is associated with increased risk for autism spectrum disorder, when compared to children exposed to other AEDs or unexposed controls (30-32). Without a thorough neurodevelopmental evaluation of these children, we cannot conclude that VPA is associated with autism based on our study findings. However, the pattern of weaknesses observed in socialization and receptive and expressive communication are, indeed, consistent with autistic traits.

These concerns are further compounded in light of the dose effects we observed for VPA, which are also supported by several previous investigations. Cohen and colleagues (29) found a dose-dependent decline in social and motor skills, as well as in parental ratings of adaptive functioning for children exposed to VPA. Other studies have reported dose-dependent language (33, 42) and IQ effects (27) in VPA-exposed children. Unlike our findings, however, several studies also found dose effects for motor function (29) and lower verbal abilities (42) following prenatal exposure to CBZ. While our results suggest that CBZ poses a relatively low risk for cognitive impairment, and no dose effect was observed for this drug, further research is necessary to examine the impact of the drug at higher doses.

Several studies have also suggested a possible threshold dose of 800 mg (23) - 1000 mg (8-11, 18, 27, 43-46) of VPA daily, beyond which major congenital malformations are more likely to occur. In their research on the cognitive effects of AED exposure, Meador and colleagues (27) noted a dose-response relationship between IQ and VPA consumption and suggested a similar threshold dose. Our findings agree that first trimester VPA doses above

1000 mg/day are associated with a decline in adaptive function across all domains. However, rather than pointing to a specific cut-off below which VPA might be considered safe, our findings importantly reveal an inverse linear relationship between dose and behavioral outcomes. These results indicate that there may be no dose of VPA that can truly be considered safe for fetuses. All women of reproductive age who are taking valproate for seizure prophylaxis should be informed of these risks, and should consequently be counseled about the critical need to switch to another antiepileptic drug before becoming pregnant.

Our study provides a unique evaluation of adaptive behavior outcomes of AED-exposed children, rather than relying on IQ or language tests to measure adaptive function or daily living skills. The use of the *Vineland-II*, a widely recognized, validated instrument for measurement of adaptive behavior, allows consideration of the true functional abilities of these children to live independently within the community, regardless of their intellectual capacity.

This study is also unique in its evaluation of 3- to 6-year-old children, distinguishing it from prior comparable studies that have evaluated younger children up to 3-years-old (27), or older children over 6 years of age (28). Given that deficits in adaptive functioning are likely to become more evident with age, the evaluation of children over 3 years offers greater insight into long-term outcomes of AED exposure. At the same time, the age at diagnosis of autism spectrum disorders typically ranges from 3- to 6-years-old (47), thus making it more likely that older children with impairments will have already been identified, and will have already received early intervention services. This would potentially falsely elevate test scores, and could mask a drug's true impact on adaptive function. Capturing children in this critical age range between 3- and 6-years-old thus allows us to evaluate children at a time

when their impairments are evident but have likely not yet been amply addressed, potentially providing a more accurate measure of an exposed child's baseline adaptive behavior before having received extensive interventions. That being said, our analysis did not control for receipt of previous early intervention services as a potential confounder. This would be important and recommended for a future study.

Our findings are further strengthened by the recruitment of all participants from the hospital-based North American AED Pregnancy Registry. This resource facilitated prospective data collection directly from a large number of U.S. and Canadian mothers with a wide-range of potential confounders, along with retrospective observational data on the adaptive behaviors of their exposed children.

Despite these many strengths, further research is required, including thorough, prospective, blinded neurodevelopmental evaluations of each child, along with inclusion of a control group and a larger study sample, to determine the true prevalence of adaptive behavior impairments and autistic symptoms among AED-exposed children. The dose effect observed in our study should be cautiously interpreted, in the absence of directly observed daily drug compliance during pregnancy, dosage information beyond the first trimester, data on maternal serum drug concentrations, or data on drug metabolism and clearance rates for participating mothers. Gene-mediated differences in the pharmacokinetics of these drugs may also affect metabolism and serum drug concentrations, and should be considered as a potential area for further research. Our study was also limited by the reliance on observational data collected through subjective interviews with the mother; the lack of data on race, ethnicity, and socioeconomic status; and the lack of data collected on family history of neurodevelopmental disorders or delays. A future study should include collection of a

detailed family history, given that a family history of neurodevelopmental delays would be an important potential confounding variable that could alter the interpretation of the results of this study.

Furthermore, although our study controlled for a number of potential confounders, the variations in baseline characteristics and participation rates observed across drug groups suggest a sampling bias commonly encountered in pregnancy registries and prospective studies. However, while one cannot exclude the possibility that mothers who participated in the study were motivated by some underlying concern for their child's development, we can be reassured by the fact that, when compared to the other groups, the LTG-exposed group had both the highest response rate as well as the highest performance in all domains. Additionally, given the high level of education of participating mothers, one might argue that the adaptive behavior scores of the study subjects are in fact higher than we might expect from children of mothers with less education. Similarly, the fact that mothers of children with major malformations were significantly less likely to respond to recruitment letters, suggests that the most severely affected children tended not to participate. Thus, our study sample is likely to be biased towards children with more favorable adaptive behavior outcomes. This raises the possibility that VPA-exposed children may actually fare worse than what we observed in our study.

Despite these limitations, our results contribute to the growing body of literature linking VPA exposure to poor neurodevelopmental outcomes in exposed children, and compel us to advocate for complete avoidance of this drug among women of childbearing age with epilepsy. However, we also recognize that treatment of epilepsy during pregnancy must balance the risk of uncontrolled seizures with the risks associated with fetal exposure to

anticonvulsant drugs. Therefore, at a minimum, women whose epilepsy can only be controlled by valproate should be strictly maintained on the lowest possible dose that is required to suppress seizure activity, and should be candidly advised of the increased risk for adaptive behavior impairments in children exposed to valproate even at lower doses. Finally, in light of these findings, routine referral of valproate-exposed children for evaluation and early intervention services may be of significant benefit and is strongly recommended.

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