CNS Spectrums (2014), **19**, 305–315.
doi:10.1017/S1092852913000990

REVIEW ARTICLE

Risks of neurobehavioral teratogenicity associated with prenatal exposure to valproate monotherapy: a systematic review with regulatory repercussions

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Beyond its formal indications (epilepsy, bipolar disorder, and migraine), valproate sodium (VPA) is widely used in a number of other clinical conditions. Recently, however, the U.S. Food and Drug Administration (FDA) issued a warning regarding a decrease in IQ scores in children prenatally exposed to the drug. For patients with migraine, the pregnancy labeling of VPA will be changed from Category "D" to "X." VPA products will remain in pregnancy category "D" for treating epilepsy and manic episodes associated with bipolar disorder. Thus, this article aims to assess (through a computerized Medline/PubMed search) the neurobehavioral teratogenicity of valproate monotherapy, in order to evaluate alternative regulatory decisions. Reviewed information suggests a detrimental impact of antenatal valproate exposure on the global child neurodevelopment. Affected areas include not just reduced IQ scores, but also behavioral problems and a potential increase in the risk for a future diagnosis of attention-deficit/hyperactivity disorder. An increased risk of developing autism-spectrum disorders has also been reported. Thus, in my opinion, VPA should be assigned definitively to the Category "X," independent of any considerations about its clinical indications, and should be strictly avoided during pregnancy, due to the demonstrated risk of both neurobehavioral and neurocognitive teratogenicity.

Received 17 October 2013; Accepted 21 November 2013; First published online 26 February 2014

Key words: neurobehavioral teratogenicity, pregnancy, valproate.

Introduction

Beyond its formal indications (epilepsy, bipolar disorder, and migraine), valproate sodium (VPA) is widely used in a number of other clinical conditions, such as neuropathic pain, trigeminal neuralgia, and cancer adjuvance.[1] In European countries, VPA use has increased dramatically in psychiatric patients, and even in women of child-bearing age diagnosed with either schizophrenia or bipolar disorder.[2,3] The same trend was observed in the U.S. Indeed, the prevalence of antiepileptic drug (AED) prescriptions among women without epilepsy tripled during the period 1996–2007.[4] Eighty-three percent of VPA prescriptions were issued to fertile women without epilepsy (74% of these women were affected by psychiatric disorders[4]).

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However, scientific evidence reviewed in recent years[5] has consistently shown that taking VPA during pregnancy increases the risk of congenital malformations (structural teratogenicity[6]). Most of the fetal anomalies associated with antenatal VPA use seem to be dose-dependent. However, lower VPA dose may offer benefits in reducing spina bifida and hypospadias; however, a lower dose has not been shown to prevent other types of fetal malformations.[7] The differences in dose susceptibility for malformations could be due to relative sensitivity of different developing systems or to changes in the predominant metabolism shifting with dose and pregnancy.[8] Increased risks for delivering babies that are small for gestational age and with transiently reduced Apgar scores (perinatal teratogenicity[6]) both have also been associated with prenatal VPA exposure.[9]

Moreover, on May 6, 2013, the U.S. Food and Drug Administration (FDA) advised

> … health care professionals and women that the anti-seizure medication VPA and related

products, valproic acid and divalproex sodium, are contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. Based on information from a recent study, there is evidence that these medications can cause decreased IQ scores in children whose mothers took them while pregnant. Stronger warnings about use during pregnancy will be added to the drug labels, and VPA pregnancy category for migraine use will be changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug). With regard to VPA use in pregnant women with epilepsy or bipolar disorder, VPA products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable. VPA products will remain in pregnancy category "D" for treating epilepsy and manic episodes associated with bipolar disorder. With regard to women of childbearing age who are not pregnant, VPA should not be taken for any condition unless the drug is essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking VPA products should use effective birth control.[10]

Nevertheless, since the early 1990s, a growing body of evidence has suggested that antenatal exposure to AEDs, either in mono- or polytherapy, may adversely impact on several aspects of child neurodevelopment[11] (neurobehavioral teratogenicity[6,12]), and not just on IQ scores.[13,14]

Given this background, this article aims to assess the neurobehavioral teratogenicity of VPA in order to evaluate alternative regulatory decisions. The term neurobehavioral teratogenicity identifies the whole spectrum of behavioral and developmental alterations that result from genetic and environmental perturbations of the nervous system during the pre- and perinatal periods.

Methods

A computerized Medline/PubMed search for the period between 1967 (year of VPA first marketing as an antiepileptic drug in France) and November 13, 2013, was conducted using the following filters/details:

- Article type: classic article, clinical trial, multicenter study, journal article, comparative study, randomized controlled trial
- Language: English
- Species: humans
- MeSH terms: ("valproic acid"[MeSH Terms] OR ("valproic"[All Fields] AND "acid"[All Fields]) OR "valproic acid"[All Fields] OR ("sodium"[All Fields] AND "valproate"[All Fields]) OR "sodium valproate"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) AND ("child development"[MeSH Terms] OR ("child"[All Fields] AND "development"[All Fields]) OR "child development"[All Fields])

The search provided 60 articles. The resulting articles were cross-referenced for other relevant articles not identified in the initial search. An extensive noncomputerized review of pertinent journals and textbooks was also performed. All peer-reviewed articles that reported primary data on developmental outcome of infants exposed in utero to VPA monotherapy and born without major or minor congenital anomalies were collected. Twenty-eight additional articles were identified.

Findings

Studies demonstrating VPA-related neurobehavioral teratogenicity

A small case-series study[15] demonstrated that children exposed prenatally to VPA might show poor motor performance and impaired neurological outcome. VPA serum concentrations at birth correlated with the degree of neonatal hyperexcitability and neurological dysfunction when children were re-examined 6 years later. However, mothers were treated with the same AED for different typologies of epilepsy (eg, tonic clonic seizures during pregnancy occurred in 33% of VPA-exposed women, whereas the remaining 67% were diagnosed with other forms of epilepsy). Hence, potential effects of maternal seizure types and frequency on the children's development cannot be ruled out.

To examine the relative risks of additional educational needs in children exposed to antiepileptic drugs, a survey was conducted of women between the ages of 16 and 40 who were registered at the Mersey Regional Epilepsy Clinic in the United Kingdom.[16] The main study findings were that VPA monotherapy during pregnancy might carry particular risks for the development of children exposed in utero. However, 22 of the 56 children who were prenatally exposed to VPA and with developmental problem had mothers with definite idiopathic generalized epilepsies. These genetic disorders could be linked to genetically determined learning disabilities.[16]

To investigate the frequency of neonatal and later childhood morbidity in children exposed to AEDs in

https://doi.org/10.1017/S1092852913000990 Published online by Cambridge University Press

utero, a retrospective population-based study[17] was performed on a population of epileptic mothers from the Grampian region of Scotland. The main study conclusions were that prenatal AED exposure in the setting of maternal epilepsy was associated with developmental delay and later childhood morbidity, in addition to congenital malformation. In particular, analysis of the different drug exposure groups showed that VPA monotherapy, as well as carbamazepine (CBZ) and phenytoin (PHT) monotherapy, were associated with significantly more developmental delay. Speech delay was common following exposure to VPA (29%) or CBZ (22%) monotherapy. Four cases of autism-spectrum disorders were also recorded in VPA-exposed children. Moreover, significantly reduced verbal IQ scores were found by Gaily et al in children exposed to VPA compared with the other study group children and control subjects.[18]

A further research study,[19] whose population was identified through a prospective community-based pregnancy registry covering the whole catchment area of the Kuopio University Hospital (population 250,000 inhabitants) in Finland, also led to worrying results. The increased prevalence of neurocognitive symptoms demonstrated in children exposed to VPA in utero raised further concern about long-term iatrogenic behavioral effects. In this study, the mothers had moderately or well controlled epilepsy during pregnancy. This clinical situation allowed the authors to exclude the potential confounding effect of the frequency of maternal seizures on children's development.

In a second, small, population-based study[19] (performed by the same research team and, presumably, on the same population of patients), all children exposed to VPA were affected by minor, and some of them major, cognitive or neurological problems. The mothers using VPA had a lower IQ and lower level of education compared with other women. In contrast, no statistically significant differences were noted in the frequency of seizures during pregnancy and/or in the consumption of tobacco or alcohol.

A prospective study[21] was carried out in the Kerala Registry of Epilepsy and Pregnancy at a tertiary referral epilepsy center in Trivandrum, Kerala State, India. This registry examines the diverse problems related to pregnancy, delivery, and health status of infants, including late developmental outcome until 6 years of age. Developmental scores of VPA-exposed infants were lower than scores of those exposed to other AEDs. Maternal age, epilepsy type, seizure frequency during pregnancy, and use of folic acid did not influence these results.

Between 1999 and 2004, the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study, an ongoing prospective observational multicenter study in the United States and United Kingdom, enrolled pregnant women with epilepsy who were taking a single antiepileptic agent [CBZ, lamotrigine (LTG), PHT, or VPA]. The primary analysis was a comparison of neurodevelopmental outcomes at the age of 6 years after exposure to different antiepileptic drugs in utero. However, a planned interim analysis of cognitive outcomes in 309 children at 3 years of age was published.[22] At 3 years of age, children who had been exposed to VPA in utero had significantly lower IQ scores than those who had been exposed to LTG. After adjustment for maternal IQ, maternal age, antiepileptic drug dose, gestational age at birth, and maternal preconception use of folate, the mean IQ was 101 for children exposed to LTG, 99 for those exposed to PHT, 98 for those exposed to CBZ, and 92 for those exposed to VPA. The association between VPA use and IQ was dose-dependent. A secondary arm[23] of this study also found that children who were prenatally exposed to VPA demonstrated impaired cognitive fluency and originality compared with children exposed to LTG and CBZ.

The NEAD Study produces results on an ongoing basis. Indeed, in a relatively recent article,[24] effects of fetal AED exposure on motor, adaptive, and emotional/behavioral functioning were examined in children at 3 years of age. A significant, dose-related performance decline in motor functioning was seen for VPA. A significant dose-related performance decline in parental ratings of adaptive functioning was also seen. Further, parents endorsed a significant decline in social skills for VPA that was dose-related. Finally, on the basis of parent ratings of attention span and hyperactivity, children of mothers who took VPA during their pregnancy appeared to be at a significantly greater risk for a future diagnosis of attention-deficit/hyperactivity disorder (ADHD). Epilepsy/seizure type was not found to be a significant outcome predictor. Adverse cognitive effects, dose-dependent, of fetal VPA exposure may persist to 4.5 and 6 years, and are related to performances at earlier ages.[25,26] Recently, the increased likelihood of difficulty with adaptive functioning and ADHD was confirmed.[27]

Further evidence[28] has suggested that both verbal and nonverbal cognitive outcomes were impaired in children exposed in utero to VPA, that such effects were dose-dependent, and that their magnitude was greater for verbal than nonverbal abilities.

Two retrospective studies[29,30] (which were conducted by the same group of researchers and, presumably, on the same population of patients) on children born to mothers with epilepsy settled in regional epilepsy clinics in Liverpool and Manchester, UK, identified VPA as a drug carrying potential risks for developmental delay and cognitive impairment. Results of both studies demonstrated that children exposed to VPA might show specific patterns of impairment for verbal abilities. This effect seemed to be dose-dependent.

https://doi.org/10.1017/S1092852913000990 Published online by Cambridge University Press

The Liverpool and Manchester Neurodevelopment Group produced a further retrospective study,[31] wherein behavioral dysfunction and adaptive behavior functioning were evaluated in children exposed to AEDs in utero who were born to women with epilepsy. The study controlled for maternal IQ, employed standardized questionnaires, and used adequate-sized groups so that any differential drug effects could be identified. The results indicated that children exposed to VPA monotherapy were at higher risk of poorer adaptive behavior and, particularly, poorer daily living skills. A further area of concern was the poor socialization skills of VPA-exposed children, which led to high levels of parental stress.

Even in prospective investigations,[32] children exposed to VPA showed a statistically significant increased risk of delayed early development in comparison to the control children. Linear regression analysis showed a statistically significant effect of drug exposure on the child's overall developmental level that was not accounted for by confounding variables. A dose-dependent relationship was found for VPA exposure, with periconceptual daily doses >900 mg being associated with statistically poorer overall developmental scores. Apart from its prospective design, the strengths of this study include its sample sizes, reliable assessment methodology, and control for confounding variables. Even compared with leviracetam (LEV), VPA showed an increased risk of inducing early neurodevelopmental delay.[33]

Other findings reported by The Liverpool and Manchester Neurodevelopment Group (both in original research or in update of previous information[34,35]) were that children exposed to VPA monotherapy in utero may have a risk of developing autism-spectrum disorders (ASDs) or features of this disorder 10 times higher than that recorded in the general population.[36] At recruitment, each woman provided information on habits and lifestyle issues such as smoking and alcohol use during pregnancy. Seizure type, syndrome diagnosis (symptomatic/cryptogenic focal, idiopathic generalized epilepsy, or not classifiable), and current seizure frequency, as well as AED type and dose were also assessed.

A dose-dependent, negative impact of VPA on verbal intellectual abilities and working memory in school-aged children was also reported.[37] The same research group also demonstrated that fetal exposure to VPA might increase the risk of language impairment.[38]

A study conducted in Northern Ireland[39] found that children with a history of in utero exposure to VPA monotherapy were at increased risk of impaired neurodevelopment when covariates were considered in data analysis. There was no impairment in the neurodevelopment of children exposed in utero to LTG. Fetal VPA exposure was also associated with weakness in working memory.[40]

To confirm or exclude these safety concerns, a population-based study[41] of all children born alive in Denmark from 1996 to 2006 was performed. National registers were used to identify children exposed to VPA during pregnancy and diagnosed with ASDs, Asperger syndrome, atypical autism, and other or unspecified pervasive developmental disorders. Overall, maternal use of VPA during pregnancy was associated with a significantly increased risk (dose-independent) of ASDs in the offspring, even after adjusting for maternal epilepsy. However, no specific analysis was performed on the potential relationship between the studied outcome and maternal VPA use for clinical indications others than epilepsy. Moreover, the estimates were based on the trimester when the women redeemed a prescription and not on when the women actually ingested the tablets; therefore, misclassification of timing of the exposure may have occurred. Nevertheless, the authors found no difference in the risk of ASDs between offspring of women who redeemed prescriptions for VPA early vs later in pregnancy.

In an ongoing prospective study,[42] exposures to monotherapy with several AEDs were associated with adverse outcome within different developmental domains. VPA exposure was associated with adverse gross motor skills at 18 months and language at 36 months. Moreover, the authors reported that children exposed to LTG in utero had a higher risk for adverse scores on autistic traits and language at 36 months. The statistical significance of this effect, however, remains unclear. Confidence intervals of difference parameters containing 0 (as in this case) actually imply that there is no statistically significant difference between the populations.[43] Please see Table 1 for a summary of all studies that demonstrated VPA-related neurobehavioral teratogenicity.

Studies not demonstrating VPA-related neurobehavioral teratogenicity

Just one study failed to demonstrate VPA-effects on neurodevelopmental outcomes (see Table 2).[44]

Discussion

Limitations of reviewed data

The studies that have suggested the detrimental impact of intrauterine VPA exposure on child neurodevelopment are numerous and methodologically well conducted, since most of them are designed in a prospective fashion. However, all of the reviewed studies, although they are supported by standardized instruments widely used for screening cognitive, social, and emotional functions, suffer from some degrees of

https://doi.org/10.1017/S1092852913000990 Published online by Cambridge University Press

TABLE 1. Antenatal VPA monotherapy exposure: neurobehavioral/neurocognitive teratogenicity

Study/study design/N	Maternal diagnosis and VPA dose	Age of children/assessment	Main Results
Koch et al, 1996[15] Case series N = 6	Epilepsy 4.2–30.8, r (mg/kg/body weight)	At birth–72 months Neurological examination	• Hyperexcitability at birth ($p < 0.01$ vs PRI/PHY) • Poor motor performance by 6 years • Impaired neurological outcome by 6 years ($p < 0.05$ vs. PRI/PHT)
Adab et al, 2001[16] Retrospective N = 330	Epilepsy N/A	3 months–23 years Structured questionnaire	• Additional educational needs in VPA-exposed vs CBZ-exposed OR: 3.4, 95% CI, 1.63–7.10
Dean et al, 2002[17] Retrospective N = 47	Epilepsy N/A	21 months Structured interview Standardized assessment	• Developmental delay • Speech disorders $p < 0.05$ vs. non-exposed 4 cases of autism-spectrum disorders in VPA-exposed children
Gaily et al, 2004[18] Prospective N = 13	Epilepsy 950, md	5–15 years Wechsler Preschool and Primary Scale of Intelligence–Revised Wechsler Intelligence Scale for Children-Revised	• Significantly reduced verbal IQ scores were found in children exposed to valproate (mean, 82; 95% CI, 78–87) compared with the other study group children and control subjects
Eriksson et al, 2005[19] Retrospective N = 21	Epilepsy N/A	6–13 years Wechsler Intelligence Test for Children-III NEPSY Developmental neuropsychological assessment	• Prevalence of low intelligence (FIQ < 80): 19% in VPA-exposed Prevalence of exceptionally low intelligence (FIQ < 70): 10% in VPA-exposed $p = 0.016$ vs. CBZ-exposed and non- exposed children
Viinikainen et al, 2006[20] Retrospective N = 28	Epilepsy N/A	>6 years Touwen's test Conners' Teacher Rating Scale	• 62% of VPA-exposed required additional educational support $p = 0.022$ vs CBZ-exposed and non-exposed
Thomas et al, 2008[21] Prospective N = 112	Epilepsy 200–1700 mg, r	15 months Mental Developmental Quotient (MeDQ) Motor Developmental Quotient (MoDQ)	• Statistically significant lower mean MoDQ score in VPA-exposed $p = 0.031$ vs CBZ-exposed
Meador et al, 2009[22] Prospective N = 309	Epilepsy 22–31, r (mg/kg/body weight)	36 months Bayley Scales of Infant Development, Second Edition Differential Ability Scales	• VPA-exposed: IQ score 9 points lower than the score of those exposed to LTG $p = 0.009$, 95%CI 3.1–14.6
McVearry et al, 2009[23] Prospective N = 42	Epilepsy N/A	2, 3, and 4.5 years Torrance Thinking Creatively in Action and Movement	• Cognitive fluency and originality lower inVPA-exposed $p = 0.003$ and 0.004 vs CBZ- and LTG-exposed
Cohen et al, 2011[24] Prospective N = 229	Epilepsy 1070 mg, m (95% CI, 876–1264)	36–45 months, r Bayley Scales of Infant Development, Second Edition Adaptive Behavior Assessment System, Second Edition Behavior Assessment System for Children Parent Stress Index, Third Edition	• BSID-II and ABAS-II scores lower in VPA-exposed than in other AED-exposed $p < 0.0001$

Table 1. Continued

Study/study design/N	Maternal diagnosis and VPA dose	Age of children/assessment	Main Results
Meador et al, 2012[25] Prospective N = 310	Epilepsy 992 mg (95% CI, 833–1150)	4.5 years Differential Ability Scales at ages 3 and 4.5 Bayley Scales of Infant Development at age 2	IQ of VPA-exposed was lower than exposed to other AEDs $P < 0.0001$
Meador et al, 2013[26] Prospective N = 224	Epilepsy 1000 mg, md	6 years Children's Memory Scale Behavior Rating Inventory of Executive Function NEPSY Expressive One-Word Picture Vocabulary Test Developmental Test of Visual Motor Integration	● IQ of VPA-exposed was lower than exposed to other AEDs $p < 0.0001$
Cohen et al, 2013[27] Prospective N = 45	Epilepsy 1058 (860:1256), md	6 years Adaptive Behavior Assessment System, Second Edition Behavior Assessment System for Children	● Increased risks of poor adaptive functioning and ADHD with fetal VPA exposure than with other AED exposure $p < 0.001$
Adab et al, 2004[29] Retrospective N = 42	Epilepsy < 800 >1500 mg, r	6–16 years Wechsler Intelligence Test for Children III Schedule of Growing Skills II	● Significantly lower mean verbal IQ Adab's results: $p = 0.003$ vs CBZ Vinten's results: OR: 3.47, 95% CI: 1.14–10.5 vs non-exposed or CBZ-exposed
Vinten et al, 2005[30] Retrospective N = 41	Epilepsy N/A	6–16 years, r Vineland Adaptive Behavior Scales	● Lowest adjusted mean scores on tasks relating to daily living and socialization in VPA- exposed $p = 0.009$ and 0.006 vs. exposed to other AEDs
Vinten et al, 2009[31] Retrospective N = 242			
Bromley et al, 2010[32] Prospective N = 198	Epilepsy N/A	< 2 years Griffiths Mental Development Scales	● VPA-exposed scored poorer than those non-exposed or CBZ- or LTG-exposed $p < 0.001$
Shallcross et al, 2011[33] Prospective N = 229	Epilepsy N/A	< 24 months Griffiths Mental Development Scale	● LEV-exposed obtained higher developmental scores than VPA-exposed $p < 0.001$
Bromley et al, 2008[34] Prospective N = 51	Epilepsy 600–2500 mg, r	3–6 years, r N/A	● 6.3% of VPA-exposed showed ASDs vs the reported incidence of 6 per 1000 in the general population

Table 1. Continued

Study/study design/N	Maternal diagnosis and VPA dose	Age of children/assessment	Main Results
Bromley et al, 2013[35] Prospective N = 51	Epilepsy N/A	6 years N/A	• VPA-exposed showed an increased risk of neurodevelopmental disorders (6/50, 12.0%; aOR 6.05, 95% CI, 1.65 to 24.53, p = 0.007) compared with control children (4/214; 1.87%). ASDs were the most frequent diagnosis. No significant increase was found among children exposed to CBZ (1/50) or LTG (2/30)
Nadebaum et al, 2011[37] Retrospective N = 23	Epilepsy 964.7 mg, m (651.5 SD)	7.4 years, m (0.6:SD) Wechsler Intelligence Scale for Children, Fourth Edition	• Mean full-scale IQ scores in the VPA- exposed fell significantly below the test mean $p < .05$
Nadebaum et al, 2011[38] Prospective N = 102	Epilepsy N/A	6–8 years, r Clinical Evaluation of Language Fundamentals, Fourth Edition	• VPA-exposed showed poorest core language scores compared to LTG-exposed $p < 0.025$
Cummings et al, 2011[39] Prospective N = 186	Epilepsy N/A	9–60 months, r Bayley Scales of Infant Development or Griffiths Mental Development Scales	• VPA-exposed were at higher risk of impaired neurodevelopment than LTG-exposed $p < 0.001$
Christensen et al, 2013[41] Population-based N = 5437 diagnosed with autism-spectrum disorders	Epilepsy/others N/A	4–14 years, ICD-10	• Absolute risk for the 508 VPA-exposed: 4.42% (95% CI, 2.59%–7.46%) for ASDs (adjusted HR, 2.9 1.7–4.9,95% CI) • Absolute risk of 2.50% (95% CI, 1.3–4.81%) for childhood autism (adjusted HR, 5.2 [95% CI, 2.7–10.0)]
Kantola-Sorsa et al, 2007[40] Prospective N = 13	Epilepsy 950, md	5–15 years NEPSY	• VPA-exposed children obtained lower scores on sentence repetition, as well as on the more demanding part of a test of auditory attention, than other children in the study group
Veiby et al, 2013[42] Prospective N = 41	Epilepsy N/A	18–36 months MoBa Questionnaires Ages and Stages Questionnaire 40-Item Social Communication Questionnaire Modified Checklist for Autism in Toddlers 14-Item Early Screening of Autistic Traits Questionnaire	• VPA-exposure was associated with adverse gross motor skills vs unexposed OR 7.0, 95% CI, 2.4–21

Abbreviations: r: range; m: mean; SD: standard deviation; VPA: valproate sodium; VPA: valproate; LTG: lamotrigine; PHT: phenytoin; CBZ: carbamazepine; PRI: primidone; AEDs: antiepileptic drugs; BSID-II: Bayley Scales of Infant Development, Second Edition; md: median; ABAS-II: Adaptive Behavior Assessment System, Second Edition; N/A: not available, ASDs: autism-spectrum disorders; aOR: adjusted odds ratio; HR: hazard ratio; CI: confidence interval; ICD-10: International Statistical Classification of Diseases, Tenth Revision; Developmental Neuro Psychological Assessment (NEPSY).

TABLE 2. Antenatal VPA monotherapy exposure: lack of neurobehavioral/neurocognitive teratogenicity

Study/study design/N	Maternal diagnosis and VPA dose	Age of children/assessment	Main Results
Veiby et al, 2013[44] Prospective N = 27	Epilepsy N/A	6–18 months At age 6 months, Ages and Stages Questionnaire. Bayley Scales of Infant Development, the Infant Characteristics Questionnaire At age 18 months, Ages and Stages Questionnaire, Modified Checklist for Autism in Toddlers	VPA showed no effects on fine and gross motor control and social

Abbreviation: VPA: valproate sodium.

procedural inadequacy. Indeed, evidence from research and practice in early childhood assessment indicates that issues of technical satisfactoriness are more difficult to address with young children who have short attention spans and go through periods of variable and rapid development.[45,46] The relevant limitations of standardized screening instruments that are routinely used for neurobehavioral evaluation in infants are summarized elsewhere.[47]

Furthermore, the vast majority of the existing data comes from the neurology literature regarding epileptic women, and an exhaustive analysis of potential confounding factors was rarely available. Indeed, although genetic predisposition accounts for most of the variance in offspring ADHD, maternal smoking a remains a significant environmental influence even when other potential confounders are taken into account.[48] Such a potential confounder has not constantly been assessed in the reviewed studies. Maternal smoking, together with other environmental factors (such as paternal age and maternal psychopathology), which, of note, may act independently,[49,50] seem also to represent risks factors for ASDs.

Moreover, one study[29] identified VPA as a drug that carries potential risks for developmental delay and cognitive impairment, but also suggested that frequent tonic-clonic seizures might have similar effects. Also, no clear evidence exists about trimester-specific results: in particular, it remains unclear if VPA effects on the developing brain may occur just for exposure during the first trimester or later as well.

Last but not least, we have to remind readers of the tendency of authors, editors, and pharmaceutical companies to handle the reporting of experimental results that are positive differently from results that are negative or inconclusive, which can lead to a misleading bias in the overall published literature.[51]

Regulatory implications

The reviewed information (despite its own intrinsic limitations) suggests concordantly a devastating impact of antenatal VPA exposure on global child neurodevelopment. Affected neurodevelopmental areas do not merely include those linked to IQ scores. Behavioral problems, such as poor social skills, needs of additional educational support, overall impaired neurodevelopment, and a potential increase in the risk for a future diagnosis of ADHD, all have been associated with antenatal VPA exposure. Such effects were dose-dependent. An increase in the risk of developing ASDs has also been reported. This effect seems to be dose-independent also. Moreover, VPA has been associated "historically" with an increased risk of congenital anomalies, as well as with poor pregnancy and neonatal outcomes.[52,53]

In the light of such considerations, the FDA's choice to assign 2 different pregnancy categories to VPA, depending on the indications for which it is prescribed, seems to be unjustified. It could be hypothesized that the FDA's choice is based on the availability of alternative, effective, and reproductively safer medications for the prophylaxis of migraine. However, propanolol represents actually a relatively safe prophylactic option,[54] and animal studies on flunarizine show no direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or postnatal development.[55] In contrast, available information suggests an increased risk of oral clefts and of growth retardation in infants exposed to topiramate.[56]

In addition, alternative options are also available for epilepsy. The National Institute for Health and Clinical Excellence (NICE) guidelines[57] recommend VPA as a first-choice agent for new-onset absence, generalized tonic-clonic, and myoclonic seizures. However, LTG is also indicated in the first 2 clinical conditions, despite its risk of worsening myoclonic seizures. A suitable alternative to VPA for myoclonic seizures is LEV. Both LTG and LEV seem to be devoid of intrinsic neurobehavioral teratogenicity.[33] It must be stressed that data on the reproductive safety on LEV are limited (in fact there are only 2 registered reports regarding malformations and just 1 regarding neurodevelopment); however, together with such neurodevelopmental data, recent (albeit preliminary) information suggests that either LTG and LEV should be used as drugs of choice over VPA, even at low dose, in women of childbearing age with epilepsy.[58]

https://doi.org/10.1017/S1092852913000990 Published online by Cambridge University Press

Alternative medications, such as lithium, LTG, and atypical antipsychotics, whose reproductive safety remains a matter of concern,[59–61] but until now have not been definitively associated with neurobehavioral teratogenicity,[62] are also available for bipolar mothers.

A second hypothesis that could explain the FDA's decision is that the regulatory agency considers migraine to be a disease less severe than both epilepsy and bipolar disorder. It is true that maternal bipolar disorder is associated with severe consequences in the offspring and can be considered, per se, a teratogen condition,[63] and epilepsy increases not just the risk of congenital birth defects, but also of placental abruption, preeclampsia, premature birth, low birth weight, and failure to progress during labor and delivery.[64] However, migraine should not be considered a benign clinical problem, and especially during pregnancy. Migraine- and headache-related disability are prevalent conditions among pregnant women. Diagnosing and treating migraine and headaches during pregnancy are essential.[65] Despite the fact that there is no evidence that migraine affects the risk of miscarriage, stillbirth, or congenital abnormalities over and above the expected outcome for pregnancy in women without migraine,[66] this condition has actually been associated with an increase in the risk of both preeclampsia and stroke.[67]

Conclusions

Treatment of epilepsy, migraine, and bipolar disorder during pregnancy remains a formidable clinical challenge. Unfortunately, because none of the drugs with clear effectiveness in such clinical conditions are without risks, clinicians cannot hope to identify a "safe choice," but merely a "less harmful" one.[6]

However, it is difficult to understand why reproductive safety data on VPA should be more reassuring for patients with bipolar disorder or epilepsy than for those with migraine. Children born to epileptic or bipolar mothers treated with VPA during pregnancy may actually have the same risk of developing neurodevelopmental impairment, including lower intelligence, ADHD, and ASDs, than those born to mothers with migraine. Moreover, the FDA does not provide any suggestions about what "other medications"[8] should be used in epileptic or bipolar patients.

Therefore, in all these clinical situations, VPA should be strictly avoided during pregnancy, due to the demonstrated risk of neurobehavioral and neurocognitive teratogenicity. Preliminary data (requiring however urgent confirmation) also seem to suggest that VPA may explicate its own neurobehavioral effects, even in the case of late pregnancy exposure.[41] Hence, the drug should be assigned definitively to the Category "X," independent of any considerations about its clinical indications.

Disclosures

Salvatore Gentile does not have anything to disclose.

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