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Anatomical, behavioral, and cognitive teratogenicity associated with valproic acid: a systematic review

Kyle Valentino[1,2,3], Kayla M. Teopiz[1], Angela T.H. Kwan[1,4], Gia Han Le[1,3,6], Sabrina Wong[1,2,3], Joshua D. Rosenblat[2,5], Rodrigo B. Mansur[2,5], Heidi K.Y. Lo[7] and Roger S. McIntyre[5]

[1]Brain and Cognition Discovery Foundation, Toronto, ON, Canada; [2]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada; [3]Mood Disorder Psychopharmacology Unit, University Health Network, Toronto, ON, Canada; [4]Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada; [5]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [6]Institute of Medical Science, University of Toronto, Toronto, ON, Canada and [7]Department of Psychiatry, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong

Review

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Corresponding author:
Roger S. McIntyre;
Email: roger.mcintyre@bcdf.org

Abstract

Background. Recent guidance from UK health authorities strongly cautions against the use of valproic acid (VPA) in persons under 55 because of reevaluated risk of teratogenicity.
Objective. To summarize the extant literature documenting VPA-associated anatomical, behavioral, and cognitive teratogenicity.
Method. Pubmed, Medline, Cochrane Library, PsychInfo, Embase, Scopus, Web of Science, and Google Scholar were searched in accordance with PRISMA guidelines. Collected data covered study design, participant characteristics, anatomical, behavioral, or cognitive effects, and folic acid outcomes.
Results. 122 studies were identified meeting inclusion comprised of studies evaluating anatomical ($n = 67$), behavioral ($n = 28$), and cognitive ($n = 47$) teratogenicity. Twenty studies were identified reporting on the risk mitigation effects of folic acid supplementation. Prenatal VPA exposure is associated with anatomical teratogenicity including major congenital malformations (odds ratio [OR] 2.47–9.30; $p < 0.005$). Behavioral teratogenicity including autism (OR 1.70–4.38), impaired motor development (OR 7.0), and ADHD (OR 1.39) are also significantly associated with VPA exposure. VPA was associated with intellectual disability and low IQ (hazard ratio [HR] 2.4–4.48, verbal intelligence: Spearman's $\rho = -0.436$, respectively). Teratogenic effects were dose-dependent across all domains and were significant when compared with controls and other antiepileptic drugs (eg, carbamazepine, lamotrigine, and levetiracetam). Folic acid supplementation does not significantly reduce the hazard associated with VPA.
Conclusions. VPA is significantly associated with anatomical, behavioral, and cognitive teratogenicity. Folic acid supplementation does not abrogate the risk of teratogenicity associated with VPA exposure. Available evidence supports recommendations to reduce VPA exposure in women of reproductive age.

Introduction

Valproic acid (VPA) is an antiepileptic drug (AED) frequently prescribed for the treatment of bipolar disorder, epilepsy, and migraine.[1] In 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) provided guidance to healthcare practitioners that VPA should not be prescribed in the treatment of male or female patients under 55 unless agreed upon by independent consultants before its teratogenic risk.[2] The MHRA opined that the teratogenic risks warranted the proscriptive recommendation. The teratogenic effects of VPA are well documented,[3,4] including major congenital malformations (MCMs) (eg, neural tube defects [NTD], cardiac malformations, and limb malformations),[5] behavioral disturbance (eg, autism spectrum disorder [ASD] and neurodevelopmental disorder [NDD]),[6,7] and cognitive abnormalities (eg, intellectual disability [ID] and lower IQ).[8–10]

Recommendations from the US Preventive Services Task Force (USPSTF), Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) are that women should receive 0.4 mg/daily starting 1–2 months before planned pregnancy up until 12 weeks of pregnancy to prevent anatomical teratogenicity (ie, NTD).[11–13] Notwithstanding the hazard-mitigating effects of folic acid in the general population, its effect on mitigating or abrogating the hazard of teratogenicity in women exposed to VPA has not been convincingly established.[14,15]

Herein, we systematically review and comprehensively estimate anatomical, behavioral, and cognitive teratogenicity hazards associated with prenatal/early gestation VPA exposure as well as

the hazard-mitigating effect of folic acid supplementation. Although this topic has been reviewed elsewhere,[16–18] given the seriousness of this topic, there is an ongoing need for a real-time up-to-date summary of this particular literature. Hence, the overarching aim is to provide an up-to-date risk assessment of VPA to inform algorithmic recommendations for treatment and treatment selection for bipolar disorder, epilepsy, and migraine.

Methods

Data sources and search strategy

This review was conducted based on the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] A systematic search was conducted on PubMed, Medline, Cochrane Library, PsycInfo, Embase, Scopus, and Web of Science from inception to June 10, 2024. A manual search on Google Scholar was also performed. The search string can be found in eTable1.

Study selection

Study screening and selection were conducted independently by two reviewers (KV and KT). Titles and abstracts were screened for relevance. We sought articles reporting data relevant to any primary outcome (ie, Anatomical, Behavioral, or Cognitive), as defined in Table 1. Studies were eligible for inclusion if they: (1) followed a cross-sectional, case–control, or cohort study design; (2) assessed either the anatomical, behavioral, or cognitive effects of in utero VPA exposure or the effect of folic acid supplementation in reducing VPA-associated teratogenicity, and (3) utilized validated scales for measurement. Studies were excluded if they: (1) were not written in English; (2) were not peer-reviewed; (3) did not have full-text availability.

Data extraction

Published summary data from included articles were independently extracted by KV and KT using a piloted data extraction form, and then corroborated. Discrepancies were resolved through discussion with all additional authors. Information to be extracted was determined a priori and included: (1) year of publication, (2) country/region of the population studied, (3) study design, (4) sample size, (5) sample characteristics, (6) assessment tools, and (7) data relevant to the primary outcome(s). Full statistics are reported where relevant.

Table 1. Definition of primary outcomes

Primary outcome	Definition
Anatomical teratogenicity	Structural or functional anomalies that occur during intrauterine life, determined via clinical diagnosis
Behavioral teratogenicity	Adverse neurodevelopmental delay or behavioral outcome determined via any validated tool for behavior/neurodevelopment (eg, CARS, M-CHAT), or clinical diagnosis of a relevant disorder (eg, Autism, ADHD)
Cognitive teratogenicity	Cognitive impairment determined by any validated tool for cognitive performance (eg, GMDS, WISC-IV), or clinical diagnosis

Quality assessment

The Newcastle–Ottawa Scale (NOS) was applied to assess cohort, case–control, and cross-sectional studies.[20] Studies where the design was unclear were assessed using the cohort NOS. Cohort studies were penalized if they failed to include a non-exposed cohort, in addition to other items tested. All component studies were independently rated by KV and KT and results were corroborated, with discrepancies resolved via discussion with all additional authors. All applied NOSs can be found in eTables 2–4.

Results

Search results

The literature search yielded 795 studies. Following the removal of duplicates and screening of titles and abstracts, 188 studies were eligible for full-text screening against the eligibility criteria. Following the full-text screening, 41 studies were further excluded before full-text unavailability. Details of study selection are provided in Figure 1. In total, 122 studies were included.

Study characteristics

Study characteristics and findings are summarized in eTable 5. Sample sizes ranged from 31 to 4 494 926, and included 27 238 488 participants. Maternal age ranged from 12 to 55 years of age. The age of sampled offspring ranged from neonates to 39 years of age. Based on reported numbers, females made up 48.7% of the total offspring. Reported follow-up periods ranged from 1 month to 6 years for anatomical studies, 2 years to 22 years for behavioral studies, 7 months to 16 years for cognitive studies, and 3 months to 8 years for folic acid studies. There were 82 prospective cohort studies, 20 retrospective cohort studies, 9 prospective case–control studies, 5 retrospective case–control studies, and 6 cross-sectional studies. Exactly 67 studied anatomical outcomes associated with prenatal VPA exposure, 28 studied behavioral outcomes, 47 studied cognitive outcomes, and 20 studied folic acid. Measurement tools can be found in eTable 6.

Quality appraisal

Quality appraisal results are presented in eTables 7–9. Awarded stars varied from 5 to 9. In general, the studies received a moderate rating. The mean score for case–control studies was 7.1/9, the mean score for cross-sectional studies was 6.7/8, and the mean score for the cohort studies was 6.4/9. Common methodological limitations were an insufficient adjustment for age and sex as baseline covariates as well as whether the outcome of interest (eg, anatomical teratogenicity) was present before VPA exposure.[21–33]

Anatomical teratogenicity

We identified 67 studies that reported anatomical events associated with VPA use. Reported diagnoses include MCMs and congenital anomalies (CAs) (eg, impaired hearing and low birth weight).

The odds ratio (OR) for MCMs and CAs ranged from 2.47 to 9.30 ($p < 0.005$).[21,22] The OR for MCM and CA without including neural tube defect (NTD) ranged from 4.86 to 5.71 ($p = 0.008$).[23,34] Specific MCMs reported include but were not limited to, hypospadias, cleft lip, polydactyly, kidney, gastrointestinal tract, limb defects, and congenital heart defects.[5,24,25] Dosage/blood levels

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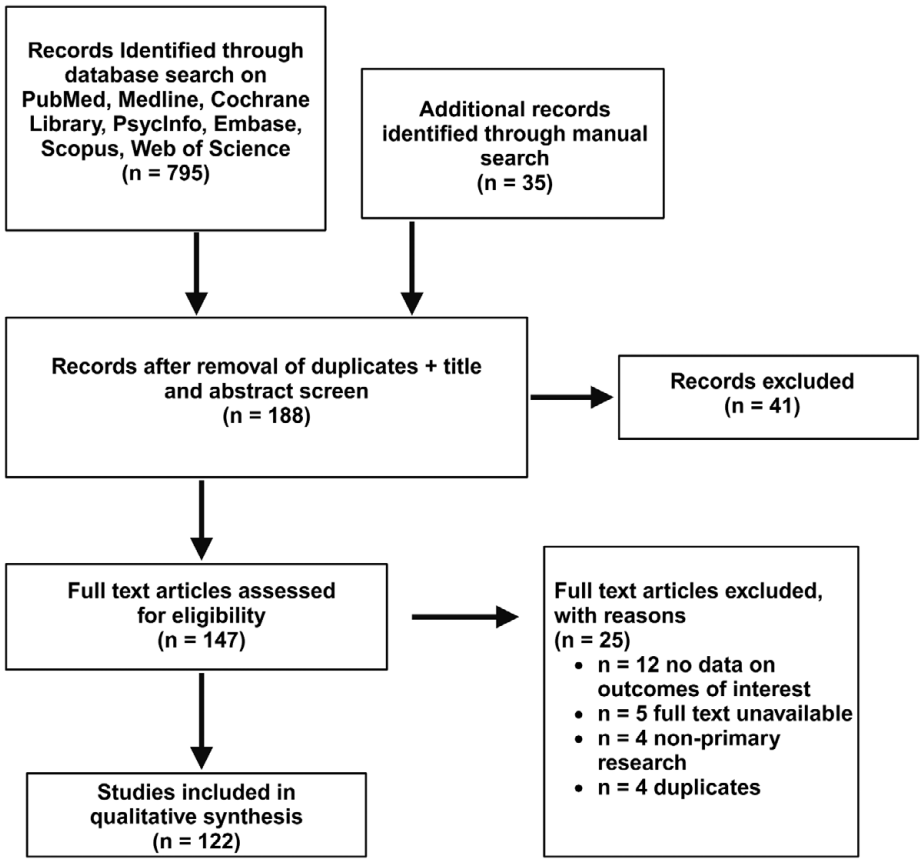

Figure 1. Study selection flow diagram.

were shown as a baseline covariate, where an increased dose was associated with elevated odds of developing MCMs ($p < 0.01$) (Unreported maternal levels),[26,27] and maternal VPA blood level was correlated with malformation occurrence (regression coefficient = 0.052, $p = 0.005$).[28] Reducing VPA dose was also associated with reduced hazard, however, at the risk of reduced pre-pregnancy seizure control.[29,33] Results were consistent when comparing prenatal VPA exposure to AED unexposed controls or children exposed to a different AED (eg, carbamazepine [CBZ], lamotrigine [LTG], and clonazepam [CZP]).[25,26] Differences between VPA monotherapy and polytherapy including VPA were inconclusive.

Independent of MCMs, prenatal VPA exposure was significantly associated with hearing impairments (adjusted OR [aOR] 6.88),[30] low birth weight (OR 3.141, Kappa: 0.147 [$p < 0.001$], χ^2: 14.623 [$p < 0.001$])[35], and poorer Apgar scores ($p = 0.0015$) (the clinical state of a newborn based on five physical signs).[35]

Neural tube defects

Neural tube defects (NTDs) were assessed in eight studies. The ORs for NTD ranged from 3.9 to 19.4[5,36] and were significant when compared with CBZ (OR 4.45; 95% CI [1.45, 13.69], $p = 0.009$) and LTG (OR 11.29; 95% CI [2.54, 50.12], $p = 0.0002$).[31] Dose was positively correlated with spina bifida (+0.0010, $p < 0.01$).[32] It was reported in a single study that the mean VPA dose during the first trimester was higher in mothers whose offspring had spina bifida (2000 ± 707 vs 1257 ± 918 mg/day) ($p < 0.05$).[30] A separate observed an aOR of 19.4 for spina bifida (95% CI 8.6, 43.5).[5]

Behavioral teratogenicity

We identified 28 studies meeting our eligibility criteria that reported on behavioral alterations associated with VPA exposure. Reported outcomes include autism, attention-deficit/hyperactivity disorder (ADHD), poor motor skills, and neurodevelopmental delay.[37–39] Hazard ratios (HR) for autism ranged from 1.70 to 4.38 when compared with unexposed controls,[6,37] with higher doses tending to yield a higher OR.[37] The OR for ADHD associated with VPA ranged from 1.39 to 1.77 when compared with unexposed controls.[35,37] When compared with LTG, CBZ, and CZP, the ORs for ADHD were 2.16, 1.79, and 1.96, respectively.[35] Ceasing VPA use before pregnancy was associated with a reduced, but not eliminated, risk of ADHD (aHR 1.66).[38] Exposure to VPA during the 2nd or 3rd trimester only was associated with a reduced risk of autism (HR 3.44 to HR 1.94).[40]

The scales used to measure motor development and functioning varied across the included studies. A singular study reported an OR of 7.0 ($p < 0.05$) using the Ages and Stages Questionnaire (ASQ).[39] A separate study reported that relative to non-AED exposed controls, VPA-exposed children scored −11.7 points (Standard Error [SE]: 3.9, [95% CI −19.4, −4.1] $p = 0.003$) lower on gross motor development, and −15.8 points (SE: 4.4, $p < 0.001$) lower relative to levetiracetam (LEV) exposed children.[41] VPA dose was also inversely correlated with motor development (Pearson MoDQ correlation: −0.239, $p = 0.042$; BSID-II Motor Index and VPA correlation: −0.60 [$p < 0.0001$]).[42,43]

Similarly, prenatal VPA exposure was associated with poorer adaptive function and behavioral development. ORs for neurodevelopmental delay ranged from 2.44 to 26.1 relative to controls.[40,43]

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A dose-dependent effect was observed relative to LTG and CBZ.[44] A dose-related decline was also observed for adaptive functioning ($p = 0.0252$).[45] Additionally, the mean adaptive behavior composite for VPA-exposed children was significantly lower than CBZ- and LTG-exposed children (ANOVA; $p = 0.017$).[46]

Poor language development was also associated with VPA exposure. One study reported an adverse development in sentence skills (OR 3.4; 95% CI [1.0, 12.0] $p < 0.05$).[39] A separate study reported an expressive language score to be on average −9.5 points ($p < 0.001$) below levetiracetam (LEV) exposed children and poorer language comprehension relative to non-AED exposed controls by −8.7 points ($p < 0.001$).[41] VPA plasma concentrations were also correlated with a poor language score ($r = -0.50$, $p = 0.04$),[47] and an ASQ communication score (Spearman's rho: −0.77, $p = 0.02$).[48]

Cognitive teratogenicity

We identified 47 studies reporting on cognitive teratogenicity associated with VPA exposure. Outcomes included poorer IQ and cognitive impairment, poorer performance on standardized tests, and increased risk for mental disorders and learning disabilities.

IQ scores for VPA-exposed children were significantly lower than non-VPA-exposed ($p = 0.007$),[49,50] including CBZ-, LTG-, and LEV-exposed children.[51] Multivariate analysis demonstrated VPA exposure to be predictive for full-scale IQ (FSIQ) (β, − 12.04; $p = 0.006$).[52] When evaluating discrete domains of intelligence, verbal IQ (VIQ) was associated with poorer outcomes. Specifically, a singular study reported a significant negative correlation between dysmorphic face features and verbal intelligence (Spearman's $\rho = -0.436$, $p = 0.007$).[49] A separate observed a significant relationship between VPA dose and verbal comprehension ($r = -0.265$, $p = 0.046$).[53] Another reported impaired verbal abilities with VPA doses at <800 mg daily (VIQ: −5.6, $p = 0.04$).[50] Additional affected cognitive domains include attention ($r = -0.38$, $p = 0.0075$),[54] memory (free recall, $r = -0.402$, $p = 0.006$; recognition, $r = -0.292$, $p = .038$),[55] language (Pearson correlation: −0.48, $p = 0.001$),[56] executive function ($r = -0{\cdot}42$, $p = 0{\cdot}0004$),[57] perceptual–motor function ($r = -0.46$, $p = 0.02$),[58] and socialization (relative to LTG and CBZ) ($p = 0.026$).[8]

Hazard ratios (HR) for intellectual disability (ID) ranged from 2.40 to 4.48.[7,40] HR for mental retardation was reported to be 5.1 relative to unexposed controls.[59] Further tests also showed that general memory ($p = 0.0434$),[57] working memory ($p \leq 0.031$),[59] inhibition ($p = 0.069$),[51] and internalization skills ($p = 0.05$),[60] were negatively affected by prenatal VPA exposure relative to either AED-unexposed children or exposure to other AEDs (CBZ, LEV, and LTG).

Prenatal VPA exposure was also associated with poorer performance on academic and standardized tests. Relative to anti-seizure medication (ASM) unexposed children, VPA exposure was associated with lower 6th- and 8th-grade math and Danish scores.[9,61] Ranging from a −0.33 to −0.13 difference in *Z* score for Danish, and −0.33 to −0.08 for math. Results were similar when compared with lamotrigine.

A final affected cognitive outcome associated with in utero VPA exposure was mental disorders (HR 1.85),[62] including Tic Disorder (HR 1.56), Attachment Disorder (HR 1.91), and Neuropsychiatric Developmental Delay (NDD) (OR 2.535, Kappa 0.099, χ^2: 5.158).[62,63]

Risk-mitigating effects of folic acid supplementation

We identified 20 studies that sought to determine the teratogenic risk-mitigating effects of folic acid supplementation in persons prescribed VPA, 3 of which evaluated the folic acid prevention effects in persons receiving VPA monotherapy. Results pooling VPA and other AEDs were included.

Pooled results suggest that folic acid supplementation is not proven effective in reducing VPA- or AED-associated malformations. With respect to major congenital malformations and folic acid supplementation, a singular study reported an aOR of 1.75 with high dose folic acid (≥ 5 mg daily) and 1.94 with low dose folic acid (< 5 mg daily), starting at least 4 weeks before conception (periconceptionally).[64] The aforementioned finding indicating no hazard mitigating effects has been replicated, in other studies of different methodologies.[65,66] In contrast, some studies do suggest that folic acid may be effective in protecting against adverse cognitive and behavioral outcomes. For example, it was reported that periconceptional folic acid supplementation was associated with less impaired language function (no dose specification) (OR 0.4, $p < 0.05$).[48] A separate analysis found that the absence of periconceptional folic acid supplementation was associated with an increased risk of autism in AED-exposed women (aOR 5.9), with higher doses of folic acid decreasing risk ($\beta = -0.5$; $p < 0.001$) (Low dose = 0.4 mg/daily, high dose = 5.0 mg/daily).[67] It was additionally reported that the hazard for AED-associated language delay was reduced in women prescribed folic acid periconceptionally when compared with women receiving AEDs and not prescribed folic acid (≥ 0.4 mg folic acid daily, OR 3.9, $p < 0.001$ to OR 1.7, $p = 0.01$).[47]

Studies separately evaluating VPA monotherapy reported that folic acid supplementation does not significantly reduce the risk for anatomic and cognitive teratogencity.[31,57,68] For example, periconceptual folic acid supplementation (dose not specified) had no significant risk-mitigating effect on the risk for MCM ($p = 0.23$) and NTD ($p = 0.78$).[32,65] Moreover, periconceptual folic acid did not protect against VPA-associated impairment in childhood IQ.[54]

Discussion

A highly replicated finding is that VPA as monotherapy or in combination with other AEDs is highly associated with all three subtypes of teratogenicity evaluated herein. Moreover, available evidence does not support the hypothesis that folic acid supplementation abrogates or significantly mitigates the risk for anatomical teratogenicity associated with any AED including VPA.[31,64] The absence of compelling risk-mitigating effects contrasts with findings in the general population wherein the USPSTF has a Grade A recommendation for folic acid (0.4–0.8 mg 1 month prior and up to 2–3 months post conception).[11] Notwithstanding, preliminary evidence suggests that folic acid supplementation may attenuate the risk for behavioral and/or cognitive teratogenicity.[48,67] Possibly through the neurotrophic effects of maternal folic acid.[69] Our findings accord with published reviews and meta-analyses that have also reported on teratogenic hazards associated with VPA and the absence of an evidence-based mitigation study.[16–18]

Our analysis, to our knowledge, is the most updated synthesis of the risk of teratogenicity associated with VPA and the impact of folic acid supplementation. Notwithstanding, despite the calls to decrease the exposure of VPA in reproductive-aged women and some evidence of a downward trajectory of usage, overall rates of rates of usage continue to be considerable.[70] Population-level literacy on the hazards of VPA with respect to teratogenicity is highly inadequate insofar as it was reported in a European sample that the majority of women were not familiar with hazards associated with VPA.[71] Along with inadequate population awareness of

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the hazard, as most persons prescribed VPA by healthcare providers are not routinely informed of this risk.[72]

There are many methodological limitations that affect inferences and interpretations of our findings. Firstly, the preponderance of the data reporting on anatomical teratogenicity utilizes observational designs of pregnancy registries and pharmacovigilance databases. Additionally, most studies reported herein evaluated prenatal VPA exposure in women with epilepsy and not in women living with other disorders (eg, bipolar disorder). Moreover, there is limited data with respect to posology or plasma levels of VPA and its association with teratogenicity. Also, most studies we identified evaluated the teratogenicity risk of VPA as part of a polytherapy regimen. However, we did not observe any lines of evidence suggesting that commonly prescribed co-agents necessarily accounted for the reported hazardous effects.

Conclusion

VPA is associated with anatomical, behavioral, and cognitive teratogenicity. Folic acid supplementation, although beneficial in the general population to mitigate the risk of congenital malformation, has not been shown to mitigate the risk of anatomical malformation specifically associated with VPA exposure. Available evidence supports limited and judicious use in reproductive-age women. Future research should determine the effects of VPA administration in males.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924002311.

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