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Neurodevelopmental outcomes in children exposed prenatally to levetiracetam

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Abstract

Some old antiseizure medications (ASMs) pose teratogenic risks, including major congenital malformations and neurodevelopmental delay. Therefore, the use of new ASMs in pregnancy is increasing, particularly lamotrigine and levetiracetam. This is likely due to evidence of low risk of anatomical teratogenicity for both lamotrigine and levetiracetam. Regarding neurodevelopmental effects, lamotrigine is the most frequently investigated new ASM with information available for children up to 14 years of age. However, fewer data are available for the effects of levetiracetam on cognitive and behavioral development, with smaller cohorts and shorter follow-up. The aim of the present review was to explicate neurodevelopmental outcomes in children exposed prenatally to levetiracetam to support clinical decision-making. The available data do not indicate an increased risk of abnormal neurodevelopmental outcomes in children exposed prenatally to levetiracetam. Findings demonstrated comparable outcomes for levetiracetam *versus* controls and favorable outcomes for levetiracetam *versus* valproate on global and specific cognitive abilities, and behavioral problems. In addition, the available evidence shows no significant dose-effect association for levetiracetam on neurodevelopmental outcomes. However, this evidence cannot be determined definitively due to the limited numbers of exposures with relatively short follow-up. Therefore, further research is required.

Plain Language Summary

Antiseizure medications (ASMs) are medicines that inhibit the occurrence of seizures. Levetiracetam is a new ASM. Some old ASMs are linked with an increased risk of physical birth abnormalities and adverse effects on the child's brain development. Therefore, the use of new ASMs in pregnancy is increasing, especially lamotrigine and levetiracetam. This is likely due to evidence of low risk of birth abnormalities for both lamotrigine and levetiracetam. Regarding effects on development of the brain, lamotrigine is the most frequently examined new ASM with information available for children up to 14 years of age. However, fewer data are available for the effects of levetiracetam on cognitive and behavioral development. Also, levetiracetam studies were smaller and shorter compared with studies investigating lamotrigine effects. The aim of this article was to review the child's brain development effects after exposure to levetiracetam during pregnancy. The available data do not suggest an increased risk of the child having learning or thinking difficulties. Findings demonstrated comparable outcomes for levetiracetam *versus* controls (i.e. children unexposed to levetiracetam), and favorable outcomes for levetiracetam *versus* valproate. In addition, the available evidence shows no link between the higher dose of levetiracetam and an increased risk of adverse effects on the child's brain development. However, this evidence cannot be determined definitively due to the limited numbers of children exposed to levetiracetam with relatively short duration of follow-up. Therefore, further research is required.

Keywords: antiepileptic drug, antiseizure medication, child development, epilepsy, *in utero* exposure, pregnancy, teratogenicity

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Introduction

Some old antiseizure medications (ASMs) pose teratogenic risks, including major congenital malformations and neurodevelopmental delay.[1–3] Therefore, the use of new ASMs, particularly lamotrigine and levetiracetam, in pregnancy and in women of childbearing age with epilepsy is increasing. In the recent Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study,[4] lamotrigine and levetiracetam were the most frequently prescribed ASMs in monotherapy and also in dual therapy. Likewise, they were the most commonly prescribed ASMs as first-line treatment in women of childbearing potential with epilepsy in a large and recent cohort study.[5] This is likely due to evidence of low risk for major congenital malformations for both lamotrigine and levetiracetam; therefore, they are safer for use during pregnancy than other ASMs. Indeed, findings have consistently demonstrated that *in utero* exposure to lamotrigine or levetiracetam is not associated with increased risk of anatomical teratogenicity.[1,6–10]

Regarding neurodevelopmental effects, lamotrigine is the most frequently investigated new ASM, with information available for children up to 14 years of age. Studies have consistently indicated no negative effects on global or specific cognitive outcomes in children exposed prenatally to lamotrigine,[3,11–15] but data on autism spectrum disorders are less completely consistent.[15–19] However, fewer data are available for *in utero* levetiracetam exposure on the child's cognitive and behavioral development, with smaller cohorts and shorter follow-up. Additional studies on early and later cognition are clearly needed.[20]

There is only one review focusing on new ASMs and neurodevelopment.[21] To date, there has been no review focusing on levetiracetam, which is increasingly used in pregnancy. The aim of the present review was to explicate neurodevelopmental outcomes on children exposed prenatally to levetiracetam to support clinical decision-making.

This work presents a comprehensive general review of all available publications on child neurodevelopment following *in utero* exposure to levetiracetam. Original research, and systematic reviews and meta-analyses investigating cognitive and behavioral outcomes of levetiracetam are reviewed. Two databases were searched: MEDLINE and Web of Science. Search terms related to prenatal exposure, levetiracetam, and child neurodevelopmental outcomes were used. In this article, the word 'significant' is employed for the findings that were statistically significant (i.e. p value < 0.05 or other significance levels). Exposure to levetiracetam was during entire pregnancy in some studies such as Dutch EURAP & Development study.[13,22] Other studies included women at different minimum gestational ages such as 20 weeks in MONEAD Study[23] or 30 days before the end of pregnancy in a population-based study by Blotière *et al.*[15]

Eighteen publications were reviewed and included in this work. Table 1 summarizes characteristics and findings of all included studies investigating cognitive and behavioral outcomes in children exposed prenatally to levetiracetam. This narrative summary of the publications divided into levetiracetam *versus* controls, levetiracetam *versus* valproate, and levetiracetam *versus* other ASMs. Each one is analyzed with respect to the following: global cognitive ability [e.g. intelligence quotient (IQ)/developmental quotient (DQ)], specific cognitive abilities (e.g. language, performance, attention), and behavioral problems [e.g. autistic traits, attention deficit hyperactivity disorder (ADHD)]. In addition, dose-effect and underlying mechanisms of neurodevelopment are discussed. Finally, future research directions are proposed.

Levetiracetam *versus* controls

Developmental quotient and Intelligence quotient

A systematic review and meta-analysis[11] demonstrated that exposure to levetiracetam was not associated with a significant increased risk of cognitive developmental delay in comparison with controls, that is, children of women with untreated epilepsy. Likewise, a prospective study by Videman *et al.*[26] observed comparable general quotient scores of Griffiths Mental Developmental Scale (GMDS) assessed at 7 months of age for levetiracetam-exposed group ($n = 7$) compared with unexposed group ($n = 59$). In addition, the United Kingdom Epilepsy and Pregnancy Register (UKEPR) study[30] evaluated the early neurodevelopmental ability of children aged under 24 months and reported no significant difference in levetiracetam-exposed children ($n = 51$) in comparison with children of women without

Table 1. Summary of studies investigating cognitive and behavioral outcomes in children exposed prenatally to levetiracetam.

Study Country	Design	Outcome measure	Study sample size	LEV (n^a)	Child age at assessment	Key finding	Dose effect for LEV Daily dose in mg	Maternal IQ	Comment
MONEAD Study Meador *et al.*[23] United States	Prospective, observational study Controls = children of women without epilepsy	Language (primary outcome), motor, cognitive, social-emotional, and general adaptive domains by BSID-III	271 exposed to ASMs 90 controls	73 (23 exposed to combination LEV + LTG)	2 years	In the adjusted analysis, no significant difference in LEV-exposed children and children exposed to other ASMs on language score	Significant only for motor domain for LEV monotherapy, but not other domains.	Adjusted in analysis Maternal IQ associated with language domain scores	
Blotière *et al.*[15] France	Population-based cohort study	Diagnosis of neurodevelopmental disorders as defined by ICD-10 codes F70-F98, and visits to a speech therapist	9034 exposed	621	Median 3.7 years, maximum 6 years	No increased risk of poor outcomes measured in LEV-exposed children compared with LTG group (active comparator)	Not investigated for LEV	Not adjusted or investigated	
Dutch EURAP & Development study Huber-Mollema *et al.*[13] Netherlands	Prospective observational study Examiner-blinded to ASM exposure	FSIQ, verbal IQ, performance IQ, and processing speed index by WISC-III-NL. Attention/executive functioning, language ability, memory and learning, fine motor skills and visuospatial skills by NEPSY-II-NL	161 exposed	25	6 or 7 years	LEV-exposed children achieved better scores for all neurocognitive abilities, particularly language[b], compared to VPA group. When adjusting maternal IQ and drug dose, LEV group achieved on average 13.4 points higher on verbal IQ compared with VPA group[b]. No significant difference between LEV and LTG groups	No significant dose effect for LEV	Adjusted in analysis Maternal IQ associated with child outcomes	Part of the cohort was assessed in both studies by Huber-Mollema *et al.*[13] and Huber-Mollema *et al.*[22] but for different outcomes
Dutch EURAP & Development study Huber-Mollema *et al.*[22] Netherlands	Prospective observational study	Child behavioral problems using parent-administered CBCL and SEV	181 exposed	30	6–7 years and 11 months	14% of LEV-exposed children had clinically relevant behavioral problems, lower than VPA (32%) and LTG (16%), and comparable to CBZ (14%) LEV-exposed children had a higher proportion of conduct disorders compared with population norms LEV group had significantly lower social problems, ADHD symptoms and attention problems than those exposed to VPA[b] LEV-exposed children had significantly less "ADHD" attention deficit, but significantly more anxious behavior when compared with LTG-exposed children[b]	No significant relationship between dose of LEV during pregnancy and behavioral outcomes	Maternal IQ not included or investigated Maternal education adjusted in analyses and investigated Significant association between maternal education and child IQ	Part of the cohort was assessed in both studies by Huber-Mollema *et al.*[13] and Huber-Mollema *et al.*[22] but for different outcomes

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Table 1. (Continued)

Study Country	Design	Outcome measure	Study sample size	LEV (n[a])	Child age at assessment	Key finding	Dose effect for LEV Daily dose in mg	Maternal IQ	Comment
MoBa Husebye *et al.*[14] Norway	Prospective, population-based study	Language impairment by parent-reported ASQ and SLAS	346 exposed 388 mothers with epilepsy 113,674 mothers without epilepsy	15 (9 at age 5 and 6 at age 8)	5 and 8 years	Risk of language impairment and language scores at age 5 and 8 years did not differ significantly between LEV group and children of women without epilepsy Children exposed to LEV had lowest language impairment rate at age 5 and 8 years in comparison to VPA, CBZ, LTG, and TPM; no statistical tests were performed Children exposed to LEV had highest language scores at age 5 years in comparison to VPA, CBZ, LTG, and TPM; no statistical tests were performed	No significant association between LEV concentration and language outcomes	Maternal IQ not adjusted but maternal education adjusted in analysis	Part of the cohort was assessed in three studies by Husebye *et al.*,[14] Husebye *et al.*,[24] and Bjørk *et al.*[16] but for different outcomes
MoBa Husebye *et al.*[24] Norway	Prospective, population-based study Controls = children of women without epilepsy	Language delay using parent-reported ASQ	335 exposed 104,222 controls	35 (16 monotherapy)	18 and 36 months	Within folate-supplemented group, LEV had lower language delay proportions in most subdomains than VPA, LTG, TPM, and OXC groups, but higher than CBZ group No language delay in LEV-exposed children in no-supplementation group	No significant correlations between LEV concentrations and language score	–	Part of the cohort was assessed in three studies by Husebye *et al.*,[14] Husebye *et al.*,[24] and Bjørk *et al.*[16] but for different outcomes
MoBa Bjørk *et al.*[16] Norway	Prospective, population-based study Controls = children of women without epilepsy	Autistic traits using parent-reported M-CHAT and SCQ	179 exposed 75,497 controls	12	18–36 months	No significant difference between risk of autistic traits in LEV group compared with controls	No significant correlation between LEV concentration and autistic traits	-	Part of the cohort was assessed in three studies by Husebye *et al.*,[14] Husebye *et al.*,[24] and Bjørk *et al.*[16] but for different outcomes
Videman *et al.*[25] Finland	Prospective observational study Examiner-blinded Controls = children unexposed to ASMs but not clear whether their mothers had epilepsy or were healthy, or mixed cohort	Early processing of emotionally and linguistically relevant sounds using MMN	36 exposed 46 controls	6	Two weeks	No significant differences in LEV group compared with controls or other monotherapies	Not investigated	Not adjusted in analysis Exposed group had significantly lower mean maternal performance IQ than controls	Part of the cohort was assessed in three studies by Videman *et al.*,[25] Videman *et al.*,[26] and Videman *et al.*[27] but for different outcomes

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Table 1. (Continued)

Study Country	Design	Outcome measure	Study sample size	LEV (n^a)	Child age at assessment	Key finding	Dose effect for LEV Daily dose in mg	Maternal IQ	Comment
Videman *et al.*[26] Finland	Prospective observational study Controls = children unexposed to ASMs but not clear whether their mothers had epilepsy or were healthy, or mixed cohort	Neurodevelopmental scores using GMDS and HINE Visual attention and orienting to faces using eye tracking test	56 exposed 62 controls	7	7 months	No significant differences between LEV group and controls in developmental scores and eye-tracker indexes No significant differences in eye-tracker indexes in LEV group compared with CBZ, OXC, LTG or VPA	Correlation not investigated. Mean ± SD (range) 1571 ± 838 (1000–3000)	Maternal IQ did not differ between different ASM groups, or between ASM and control groups	Part of the cohort was assessed in three studies by Videman *et al.*,[25] Videman *et al.*,[26] and Videman *et al.*[27] but for different outcomes
Videman *et al.*[27] Finland	Prospective observational study Controls = children unexposed to ASMs but not clear whether their mothers had epilepsy or were healthy, or mixed cohort	Early neurological status using HNNE and cortical activity using EEG	56 exposed 67 controls	7	41–42 weeks of conceptional age	Significant differences between ASM-exposed group and controls but no comparison for individual ASMs	Not investigated	No significant differences in maternal IQ between exposed and control groups	Part of the cohort was assessed in three studies by Videman *et al.*,[25] Videman *et al.*,[26] and Videman *et al.*[27] but for different outcomes
Richards *et al.*[19] New Zealand	Retrospective population-based study Controls = children unexposed to ASMs but not clear whether their mothers had epilepsy or were healthy, or mixed cohort	Developmental delays and behavioral problems using parent-reported PEDS and SDQ	606 exposed 286,966 controls	10	4 years	One LEV-exposed child was already under specialist care in PEDS evaluation, and one was referred after SDQ evaluation	Not investigated	Not included	LEV group was not statistically analyzed due to small number
Bech *et al.*[28] Denmark	Population-based case–cohort study Controls = mothers received ASMs at any time but not during pregnancy	Diagnosis of learning disabilities (mental retardation, specific neurodevelopmental or emotional/ behavioral conditions, and having special educational needs)	636 exposed 434 controls	12	Median age 6.1 years	LEV group had significant increased risk of learning disability compared with controls[b] No significant differences in risk of learning disability in LEV group compared with GBP, OXC, or TPM groups	No dosage calculations made for LEV	Maternal IQ not adjusted in analysis	
Veroniki *et al.*[11]	Systematic review and network meta-analysis Controls = children of women with untreated epilepsy	Cognitive developmental deficit, autism/ dyspraxia, and psychomotor developmental deficit	29 studies including 5100 children	-	-	Exposure to LEV was not associated with significantly increased risks of cognitive developmental deficit, autism/dyspraxia, or psychomotor developmental deficit compared with controls	-	-	

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Table 1. (Continued)

Study Country	Design	Outcome measure	Study sample size	LEV (*n*[a])	Child age at assessment	Key finding	Dose effect for LEV Daily dose in mg	Maternal IQ	Comment
UKEPR Bromley *et al.*[29] United Kingdom	Cross-sectional observational study Neuropsychological assessments conducted blinded LEV *versus* controls *versus* VPA Controls = children of women with untreated epilepsy	FSIQ, verbal abilities, nonverbal abilities, and processing speed using WISC-IV/ WPPSI-III Memory, and attention and executive skills using NEPSY-II Language using CELF-IV Parental rating of child behavior using BASC-II	130 exposed 55 controls	42	5–9 years 6 years mean age for LEV group	LEV group did not differ significantly from controls in any outcomes measured Better achievement in children exposed to higher doses of LEV compared with those exposed to higher doses of VPA. No significant differences in outcomes at half the median doses of LEV compared with half the median doses of VPA	No significant dose-effect relationship between LEV and poorer outcomes Mean (range) 1725 (200–4000)	Adjusted in analysis Maternal IQ was predictor for FSIQ, verbal abilities, nonverbal abilities, language, memory, and aspects of attention and executive skills	Significant differences in some demographic variables, such as child age at assessment, maternal IQ, educational level, frequency of seizures and preconceptual folate supplements across groups Part of the cohort of Shallcross *et al.*[30] study was reassessed at older ages in Shallcross *et al.*[31] and Bromley *et al.*[29] studies
UKEPR Shallcross *et al.*[31] United Kingdom	Prospective controlled observational study LEV *versus* controls *versus* VPA Controls = children of women without epilepsy	Locomotor, personal and social, hearing and language, eye and hand coordination, and nonverbal performance skills using GMDS subdomains Language development ability using RLDS	97 exposed 131 controls	53	3–4.5 years Mean 42 months	LEV group did not differ significantly from controls in developmental and language abilities LEV group scored significantly higher than VPA group in gross motor skills and comprehension and expressive language abilities[b]	No correlation between dose of LEV and any outcome measure Mean (range) 2,070 (500–5,000)	Adjusted in analysis	Part of the cohort of Shallcross *et al.*[30] study was reassessed at older ages in Shallcross *et al.*[31] and Bromley *et al.*[29] studies
UKEPR Shallcross *et al.*[30] United Kingdom	Prospective controlled observational study Examiner-blinded LEV *versus* controls *versus* VPA Controls = children of women without epilepsy	Early cognitive development (DQ) ability using GMDS Locomotor, personal and social, hearing and language, eye and hand coordination, and nonverbal performance skills using GMDS subdomains	95 exposed 97 controls	51	Under age 24 months	LEV-exposed group did not differ significantly from controls in overall DQ LEV-exposed group achieved significantly higher overall DQ than VPA group[b] LEV group achieved significantly higher scores in all specific cognitive skills of DMDS subdomains compared with VPA group[b] No significant differences in LEV group compared with controls in any specific cognitive abilities	Not investigate for LEV Mean (range) 1700 (250–4000)	Adjusted in linear regression	Small number in VPA group (*n*=44) Part of the cohort of Shallcross *et al.*[30] study was reassessed at older ages in Shallcross *et al.*[31] and Bromley *et al.*[29] studies

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Table 1. (Continued)

Study Country	Design	Outcome measure	Study sample size	LEV (n^a)	Child age at assessment	Key finding	Dose effect for LEV Daily dose in mg	Maternal IQ	Comment
Arkilo *et al.*[32] United States	Cross-sectional observational study	Any neurodevelopmental diagnosis	62 exposed	11	–	No LEV-exposed children had motor development or speech delay compared with 2/24 in LTG, 3/17 in CBZ, and 1/2 in VPA groups	–	–	Pilot study
Bromley *et al.*[3]	Systematic review and meta-analysis LEV *versus* controls *versus* VPA Controls = children of women without epilepsy	DQ using GMDS	28 cohort studies	One study	–	Nonsignificant mean difference (1.09, 95% CI −2.81 to 4.99, $p=0.58$) for LEV compared with controls LEV-exposed group had better global cognitive development compared with VPA with significant mean difference (12.03, 95% CI 6.24 to 17.82, $p<0.0001$)[b]	–		Only one study included[30]

[a]Number of exposures to levetiracetam monotherapy.
[b]Statistically significant (i.e. p value <0.05 or other significance levels).
ADHD, attention deficit hyperactivity disorder; ASMs, antiseizure medications; ASQ, Ages and Stages Questionnaire; BASC-II, Behavior Assessment System for Children, Second Edition; BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CBCL, Child Behavior Checklist; CBZ, carbamazepine; CELF-IV, Clinical Evaluation of Language Fundamentals–Fourth Edition; CI, confidence interval; DQ, developmental quotient; EEG, electroencephalography; FSIQ, full-Scale Intelligence Quotient; GBP, gabapentin; GMDS, Griffiths Mental Development Scales; HINE, Hammersmith Infant Neurological Examination; HNNE, Hammersmith Neonatal Neurological Examination; ICD-10, International Classification of Diseases, 10th Revision; IQ, intelligence quotient; LEV, levetiracetam; LTG, lamotrigine; M-CHAT, Modified Checklist for Autism in Toddlers; MMN, mismatch negativity; MoBa, Mother and Child Cohort Study; MONEAD study, Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs Study; NEPSY-II-NL, Developmental Neuropsychological Assessment, 2nd edition, Netherlands; OXC, oxcarbazepine; PEDS, Parental Evaluation of Development Status; RLDS, Reynell Language Development Scale; SCQ, Social Communication Questionnaire; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire; SEV, Social-Emotional Questionnaire; SLAS, Speech and Language Assessment Scale; TPM, topiramate; UKEPR, United Kingdom Epilepsy and Pregnancy Register; VPA, valproate; WISC-III-NL, Wechsler Intelligence Scale for Children, Third Edition, Netherlands; WISC-IV, Wechsler Intelligence Scale for Children–Fourth Edition; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence–Third Edition.

epilepsy ($n = 97$) in overall DQ of GMDS (mean 99.9 *versus* 98.8, respectively, $p = 0.62$). The UKEPR follow-up study[29] investigated full-scale IQ (FSIQ) at age 5–9 years utilizing the Wechsler Intelligence Scale for Children (WISC-IV), or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) if the children were 5 years old, in children exposed to levetiracetam ($n = 42$) compared with children of mothers with untreated epilepsy ($n = 55$). In this study, a comparable FSIQ in levetiracetam-exposed children compared with controls (mean 99.0 *versus* 99.7, respectively) was observed, and in the adjusted analyses, being exposed to levetiracetam was not associated with poorer outcome on FSIQ ($p = 0.47$).

However, a population-based study by Bech *et al.*[28] observed an increased risk of learning disability in levetiracetam-exposed children compared with unexposed children. However, the levetiracetam-exposed group was small ($n = 12$), and there was no adjustment for important confounding factors in analyses, such as maternal IQ.

Specific cognitive abilities

Language abilities and risk of language impairment did not differ significantly between levetiracetam-exposed children at age 5 ($n = 17$) and 8 years ($n = 6$), and children of mothers without epilepsy in a study by Husebye *et al.*[14] Furthermore, the systematic review and meta-analysis[11] demonstrated that exposure to levetiracetam was not associated with a significant increased risk of psychomotor developmental delay in comparison with controls, i.e. children of women with untreated epilepsy. In addition, Videman *et al.*[26] observed no significant difference in sub-quotient scores (locomotor, personal-social, hearing and language, eye and hand coordination, and performance) of GMDS at age 7 months between the levetiracetam group and the unexposed group. However, the levetiracetam group had higher (but not significantly) eye-tracker indexes than controls. The mean ages of children exposed to levetiracetam and control children in the eye-tracker test were comparable but there was a small number of exposures to levetiracetam ($n = 7$).

In the UKEPR study,[30] the levetiracetam-exposed group did not differ significantly from controls at age under 24 months in any specific cognitive abilities of GDMS: locomotor (mean 97.3 *versus* 95.2, respectively, $p = 0.4$), personal and social (mean 98 *versus* 97.9, respectively, $p = 0.99$), hearing and language (mean 100.5 *versus* 101.2, respectively, $p = 0.79$), hand–eye coordination (mean 101.8 *versus* 97.4, respectively, $p = 0.14$), and performance (mean 101.7 *versus* 101.4, respectively, $p = 92$). Likewise, the UKEPR follow-up study at age 3–4.5 years[31] observed no significant differences in any subdomains of GDMS between levetiracetam-exposed children ($n = 53$) and children of women without epilepsy ($n = 131$): motor scores (mean 110.4 *versus* 110.9, respectively, $p = 0.9$), personal score (mean 116.5 *versus* 119.9, respectively, $p = 0.1$), hand–eye coordination (mean 104.8 *versus* 103.3, respectively, $p = 0.8$), performance score (mean 109.9 *versus* 110.5, respectively, $p = 0.6$), and practical score (mean 113.4 *versus* 113.9, respectively, $p = 0.5$). The study also investigated language development using the Reynell Scales of Infant and Toddler Development (RDLS) at age 3–4.5 years. No significant differences were observed between levetiracetam-exposed children and controls in language comprehension (mean 49.6 *versus* 52.2, respectively, $p = 0.2$). However, levetiracetam-exposed children obtained significantly higher scores in language expression skills compared with controls (mean 52.0 *versus* 46.6, respectively, $p = 0.01$), but after adjusting for confounding variables, the difference was not significant ($p = 0.03$, significance level was $\leqslant 0.007$ after Bonferroni correction).[31] The UKEPR follow-up study at age 5–9 years[29] reported comparable outcomes for levetiracetam-exposed children in comparison with children of mothers with untreated epilepsy in verbal abilities (mean 101.0 *versus* 101.7, respectively), nonverbal abilities (mean 99.6 *versus* 100.8, respectively), and processing speed (mean 94.7 *versus* 97.1, respectively), and when outcomes were adjusted for covariates, being exposed to levetiracetam was not associated with poor outcomes in verbal abilities ($p = 0.51$), nonverbal abilities ($p = 0.72$), or processing speed ($p = 0.51$). Bromley *et al.*[29] evaluated other specific cognitive abilities using the NEPSY-II (Developmental Neuropsychological Assessment) and the Clinical Evaluation of Language Fundamentals (CELF-IV). The adjusted analyses in this study showed that being exposed to levetiracetam was not associated significantly with poorer outcomes in language, memory, attention or executive functioning.

In the recent MONEAD study,[23] a large number of mothers received levetiracetam as monotherapy ($n=70/211$, 33.2%) or in combination with lamotrigine ($n=25/55$, 45%). Language domain score using the Bayley Scales of Infant and Toddler Development (BSID-III) was investigated for children of women with epilepsy ($n=292$) in comparison with healthy women ($n=90$) at 2 years of age. There were no significant differences in language domain score ($p=0.81$) or other domains, including motor ($p=0.25$), cognitive ($p=0.7$), social-emotional ($p=0.15$), and general adaptive (0.86) skills, between children of women with epilepsy and healthy women in the adjusted model. However, there was no subanalysis for levetiracetam monotherapy *versus* controls.

Behavioral problems

Huber-Mollema *et al.*[22] examined child behavioral problems using the parent-administered Child Behavior Checklist (CBCL) and the Social-Emotional Questionnaire (SEV) at age 6–8 years. The study showed that, compared with population norms, there were no differences in ADHD or anxious behavior. However, levetiracetam-exposed children had a higher proportion of conduct disorders. Bjørk *et al.*[16] investigated the parental rating of autistic traits using the Modified Checklist for Autism in Toddlers (M-CHAT) and the Social Communication Questionnaire (SCQ) at 18 and 36 months of age, respectively. No significant difference was reported in the risk of autistic traits between children exposed to levetiracetam ($n=12$) and children of women with no maternal epilepsy at age of 3 years. Likewise, Bromley *et al.*[29] assessed parent-rated child behavior using the Behavior Assessment System for Children (BASC-II) at age 5–9 years and observed that exposure to levetiracetam was not associated significantly with poorer outcomes in behavioral variable compared with children of mothers with untreated epilepsy.

It should be noted that above studies used parental rating of child behaviors and autistic traits, which may be considered a limitation compared with diagnosis and clinical referral assessments. In addition, parent-administered scales may pose risk of biased rating because parents are not blinded to type of medication exposure.[21]

Consistent with the above research, the systematic review and meta-analysis[11] demonstrated that exposure to levetiracetam was not associated with significantly increased risk of autism/dyspraxia compared with controls of women with epilepsy who did not receive ASMs.

Levetiracetam *versus* valproate

Developmental quotient and Intelligence quotient

In the UKEPR study,[30] the levetiracetam-exposed group ($n=51$) achieved significantly higher scores than the valproate group ($n=44$) under the age of 2 years in overall DQ (mean 99.9 *versus* 87.9, respectively, $p<0.001$). Similarly, in the follow-up study,[29] children exposed to levetiracetam had higher unadjusted mean score for FSIQ compared with those exposed to valproate (99 *versus* 95.5, respectively), as well as the rate of below-average (<85) performance for FSIQ was lower in the levetiracetam group (12%, $n=5/42$) than the valproate group (19%, $n=9/47$). Furthermore, children exposed to higher doses of levetiracetam performed better in comparison to children exposed to higher doses of valproate. However, there were no significant differences in outcomes at half the median dose of levetiracetam (750 mg/day) in comparison with half the median dose of valproate (400 mg/day).

A prospective study by Huber-Mollema *et al.*[13] investigated FSIQ measured by WISC-III at age 6–7 years in children exposed to levetiracetam ($n=25$) in comparison with children exposed to valproate ($n=22$) demonstrated that the levetiracetam group had a higher adjusted mean score for FSIQ compared with the valproate group (109.2 *versus* 103.1, respectively). However, when controlling for maternal IQ and drug dose, the difference in FSIQ was not significant ($p=0.054$).

Specific cognitive abilities

Huber-Mollema *et al.*[13] observed better outcomes in levetiracetam-exposed children compared with the valproate group in verbal abilities (mean 114 *versus* 100.6, respectively) and processing speed (mean 111.2 *versus* 107.4, respectively), and comparable outcomes in performance abilities (mean 104.4 *versus* 105.3, respectively)

in unadjusted analysis. When adjusting for maternal IQ and drug dose, children exposed to levetiracetam were on average 13.4 points higher than valproate-exposed children in verbal abilities ($p = 0.002$). There were no significant differences in performance abilities or processing speed. The study also investigated other specific cognitive domains, including attention and executive function, language, memory and learning, fine motor skills, and visuospatial skills by NEPSY-II-NL. Levetiracetam-exposed children achieved better scores in all these neurocognitive abilities compared with the valproate group; the differences were significant in the following subdomains: statue and inhibition naming of attention and executive functioning; and comprehension of instruction and vocabulary of language skills. The authors also noticed that children exposed to levetiracetam were associated with more disharmonic profiles (verbal IQ > performance IQ), opposite to that seen in the valproate group. Nevertheless, the sample size was small, and findings need to be confirmed by further research.

In Shallcross *et al.*[30] study, the levetiracetam group achieved significantly higher scores than the valproate group under the age of 2 years in locomotor skills (mean 97.3 *versus* 84.6, respectively, $p < 0.001$), personal and social skills (mean 98 *versus* 89.8, respectively, $p = 0.03$), hearing and language (mean 100.5 *versus* 90.4, respectively, $p = 0.01$), hand/eye coordination (mean 101.8 *versus* 88.2, respectively, $p < 0.001$), and performance skills (mean 101.7 *versus* 88.8, respectively, $p < 0.00$). Likewise, Shallcross *et al.*[31] found that levetiracetam-exposed children achieved significantly higher scores (on average 15.8 points) than the valproate group at age 3–4.5 years in gross motor skills ($p < 0.001$), 6.4 points higher in comprehension language abilities ($p < 0.005$), and 9.5 points higher in expressive language abilities ($p < 0.001$). But no significant differences were observed in personal and social skills ($p = 0.04$; significance level was $\leqslant 0.007$ after Bonferroni correction), hand/eye coordination ($p = 0.5$), nonverbal performance skills, ($p = 0.8$), or practical reasoning ($p = 0.4$) at this older age assessment.

Although there was no direct comparison between children exposed to levetiracetam *versus* valproate in the study conducted by Husebye *et al.*,[14] the study showed that rate of language impairment for the levetiracetam group was 22% ($n = 2/9$) at age 5% and 17% ($n = 1/6$) at age 8 years, lower than the rates in the valproate group which were 36% ($n = 5/14$) at age 5% and 31% ($n = 5/16$) at age 8. Furthermore, mean language scores at age 5 years were higher for levetiracetam than valproate [Ages and Stages Questionnaire (ASQ) scores of 68 *versus* 64, and Speech and Language Assessment Scale (SLAS) scores of 3.7 *versus* 3.1, respectively].

However, Videman *et al.*[26] found no significant differences in eye-tracker indexes (visual attention and orienting to faces) between levetiracetam and valproate groups.

Behavioral problems

Huber-Mollema *et al.*[22] found that the rate of clinically relevant behavior problems was lower in levetiracetam-exposed children (14%) than in the valproate group (32%). Furthermore, after controlling for key covariates, including maternal behavioral problems, the levetiracetam group ($n = 30$) had significantly fewer social problems ($p = 0.028$), attention problems ($p = 0.013$), ADHD symptoms ($p = 0.03$), and attention deficit ($p = 0.022$) compared with the valproate group ($n = 26$).

Levetiracetam *versus* other antiseizure medications

Developmental quotient and Intelligence quotient

Huber-Mollema *et al.*[13] showed no significant difference in FSIQ between children exposed to levetiracetam ($n = 25$) and lamotrigine ($n = 82$) at age 6–7 years. In the analysis adjusted for maternal IQ, there were comparable mean FSIQ scores between levetiracetam and lamotrigine groups (109.2 *versus* 109.1, respectively).

Bech *et al.*[28] investigated the risk of learning disability with each ASM monotherapy, including levetiracetam ($n = 12$), carbamazepine ($n = 35$), clonazepam ($n = 43$), gabapentin ($n = 29$), lamotrigine ($n = 290$), oxcarbazepine ($n = 44$), phenobarbital ($n = 11$), topiramate ($n = 27$), and valproate ($n = 55$), and found that *in utero* exposure to levetiracetam was not associated with a higher risk [odds ratio: 5.45, 95% confidence interval (CI): 0.78–38.02, $p = 0.087$] compared with other ASMs.

Specific cognitive abilities

Huber-Mollema *et al.*[13] compared neurodevelopmental outcomes in children aged 6–7 years exposed to levetiracetam ($n=25$) and lamotrigine ($n=82$) in an adjusted analysis that controlled for maternal IQ and dose. This study showed no significant differences in verbal abilities, performance abilities, and processing speed, as well as attention and executive function, language, memory and learning, fine motor skills or visuospatial skills, except for visuomotor precision subdomain of fine motor skill in which levetiracetam-exposed children obtained significantly lower scores than lamotrigine-exposed children ($p=0.022$). In the MONEAD study,[23] the 2-year BSID-III language score for levetiracetam monotherapy ($n=73$) did not differ significantly ($p=0.175$) from other ASM monotherapies [lamotrigine ($n=93$), oxcarbazepine ($n=13$), carbamazepine ($n=12$), zonisamide ($n=11$), and topiramate ($n=5$)]. Likewise, no significant differences in eye-tracker indexes (visual attention and orienting to faces) were found between levetiracetam compared to carbamazepine, oxcarbazepine, and lamotrigine.[26]

Behavioral problems

In a large population-based study conducted by Blotière *et al.*,[15] the risk of neurodevelopmental disorder was investigated. Also, the risk of communication-related conditions was evaluated by 'visits to a speech therapist'. The study demonstrated that prenatal exposure to levetiracetam ($n=621$) was not associated with increased risk of any neurodevelopmental outcomes compared with lamotrigine ($n=1627$, active comparator). The results stood after sensitivity analysis. However, the children were followed up to a maximum of 6 years age (average 3.7 years), which allowed detection only of early diagnoses of neurodevelopmental disorders. There are several strengths to this study by Blotière *et al.*:[15] it represents the largest study to date that evaluated neurodevelopmental disorders in levetiracetam-exposed children, the use of lamotrigine as active comparator, and outcomes measured by clinical diagnosis/visits to speech therapy rather than parental reporting.

Other studies have been based on parental reporting of child behaviors. Huber-Mollema *et al.*[22] demonstrated that 14% of levetiracetam-exposed children had clinically relevant behavioral problems, lower than for lamotrigine (16%), and comparable to carbamazepine (14%). In the adjusted analysis, levetiracetam-exposed children ($n=30$) had significantly less 'ADHD' attention deficit ($p=0.026$), but significantly more anxiety problems ($p=0.042$) compared with lamotrigine-exposed children ($n=88$). However, children exposed to levetiracetam or lamotrigine had scores comparable to population norms for parental reports of attention and anxiety behaviors. There were no significant differences in other behavioral outcomes between levetiracetam and lamotrigine. Although there were no direct comparisons or statistical tests performed between children exposed to levetiracetam *versus* other individual ASMs in the study by Husebye *et al.*,[14] the study demonstrated that the rate of language impairment for the levetiracetam group was 22% ($n=2/9$) at age 5% and 17% ($n=1/6$) at age 8 years, lower than the rates for other ASMs (carbamazepine: 35% and 43%, lamotrigine: 23% and 22%, topiramate: 50% and 25% at age 5 and 8 years, respectively). Furthermore, mean language scores at age 5 years were higher for levetiracetam (ASQ score 68, SLAS score 3.7) than for other ASMs (ASQ and SLAS scores for carbamazepine: 56.3 and 3.3, for lamotrigine: 65.3 and 3.4, for topiramate: 64.6 and 3.5, respectively).

Dose effect

All studies found no significant association between dose of levetiracetam,[13,16,22,29,31] or levetiracetam concentration[14,24] and poor neurodevelopmental outcomes. Except in the MONEAD study,[23] higher maximum third-trimester ABLs (antiseizure medication blood level) for levetiracetam monotherapy was significantly associated with lower BSID-III scores for the motor domain (−13.0; 95% CI: −22.1 to −4.0). However, other domains, including language (primary outcome), cognitive, social-emotional, or general adaptive domains, were not associated with third-trimester ratio of ABL for levetiracetam.

Mechanisms of neurodevelopmental effects of antiseizure medications

Several hypotheses may explain why levetiracetam is not associated with increased risk of abnormal neurodevelopmental effects while some other ASMs, such as valproate, have adverse neurodevelopmental effects. The exact underlying neurobiological mechanisms of behavioral and cognitive effects in children exposed prenatally to other ASMs are uncertain.[33,34] However, levetiracetam

is known to have a novel structure and a unique mechanism of action distinct from that of other ASMs. Levetiracetam binds to synaptic vesicle protein SV2A, which modulates vesicle exocytosis and neurotransmitter release.[35,36]

Likewise, research regarding apoptosis in animal studies may explain the neurodevelopmental differences between children exposed to levetiracetam and other ASMs. ASM-induced neuronal apoptosis in animal studies is a possible mechanism implicated in the development of adverse cognitive effects in humans after fetal exposure to ASMs.[37,38] Certain ASMs, including valproate, can induce neuronal apoptosis.[37] Some ASMs do not induce apoptosis in monotherapy but can enhance it when added to another ASM.[39] Levetiracetam does not induce apoptosis in monotherapy or enhance the apoptosis of other ASMs.[38] Furthermore, it has been found that ASMs with proapoptotic action can also impair the physiological maturation of synapses in surviving neurons. However, levetiracetam, an ASM with no proapoptotic action, does not disrupt synaptic development.[40]

Conclusion

The available data do not indicate an increased risk of abnormal neurodevelopmental outcomes in children exposed prenatally to levetiracetam. Findings demonstrated comparable outcomes for levetiracetam *versus* controls and favorable outcomes for levetiracetam *versus* valproate in global and specific cognitive abilities, and behavioral problems. Furthermore, the available research does not indicate any worse effects of levetiracetam on child neurodevelopment compared with lamotrigine. In addition, the available evidence shows no significant dose-effect association of levetiracetam and adverse neurodevelopmental outcomes. However, as concluded by the Medications and Healthcare products Regulatory Agency,[41] this evidence cannot be determined definitively due to the limited number of exposures with relatively short follow-up. Therefore, further research is required.

Future directions

This review proposes several avenues for future research. The duration of follow-up in studies of levetiracetam was up to age 9 years. This is inadequate to establish long-term effects on cognitive and behavioral development beyond childhood.[21,34,42,43] An evaluation in their adolescent years of exposed children is required. In addition, evaluation of dose effects is a key principle in neurobehavioral teratology and is important in supporting real-world clinical decision-making. The recent MONEAD study[23] showed a significant concentration-effect association with motor skills for levetiracetam. However, no other earlier studies found significant dose–response correlations for levetiracetam. Nevertheless, in order to reveal dose effects, adequate sample sizes, utilizing ASM blood levels, are required.[21] Furthermore, most studies compared levetiracetam to unexposed or valproate and were important to show the relative risks. However, valproate now must be avoided in women of childbearing potential.[44] Therefore, direct comparisons between levetiracetam and other new ASMs are needed. There is also a need for investigation of other factors that may affect neurodevelopmental outcomes such as parental IQ, socioeconomic status, folate supplementation, child age and gender, gestational age at birth and breastfeeding. Adjustments for potential confounders are also required.[21,42] Finally, further research is needed for a better understanding of the underlying mechanisms of the neurodevelopmental effects of levetiracetam.

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