Neurodevelopmental outcomes in children exposed to antiseizure medications

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Disclosure

UCB Women's Health Advisory Board

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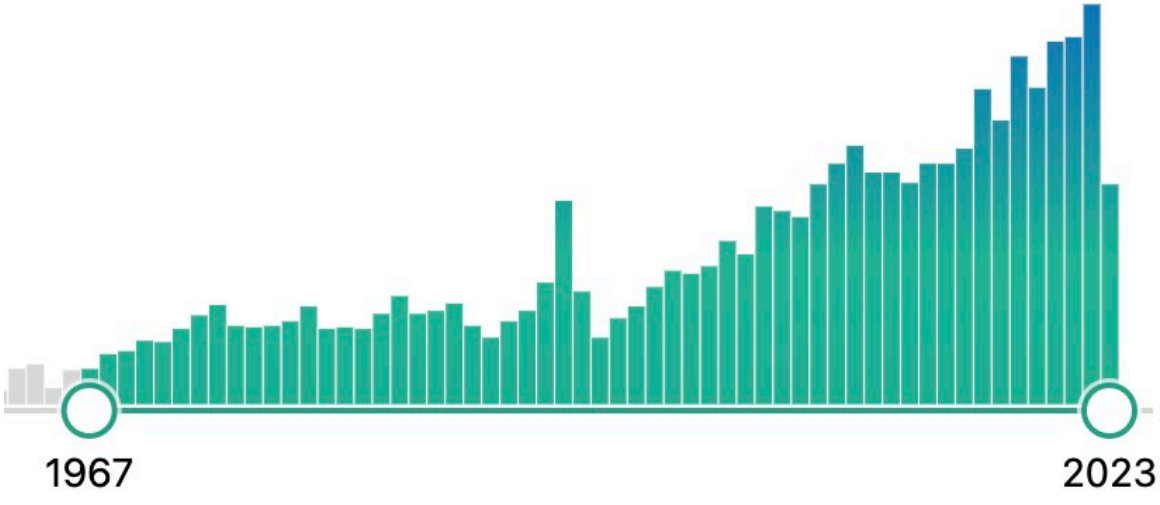
Pregnancy and Epilepsy



Source: Pubmed August 2023. Search ‘Epilepsy and Pregnancy’

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Home > Drug Safety Update

Topiramate (Topamax): start of safety review triggered by a study reporting an increased risk of neurodevelopmental disabilities in children with prenatal exposure

We have initiated a new safety review into topiramate as a result of an observational study reporting an increased risk of neurodevelopmental disabilities in children whose mothers took topiramate during pregnancy. Topiramate is known to be associated with an increased risk of congenital malformations and effects on fetal growth if used during pregnancy. Continue to counsel patients who can become pregnant on the known and emerging risks of topiramate for an unborn baby and on the need to use effective

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EMA review of data on paternal exposure to valproate

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Press release 16/08/2023

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31/05/2018
EMA/375438/2018

New measures to avoid valproate exposure in pregnancy endorsed

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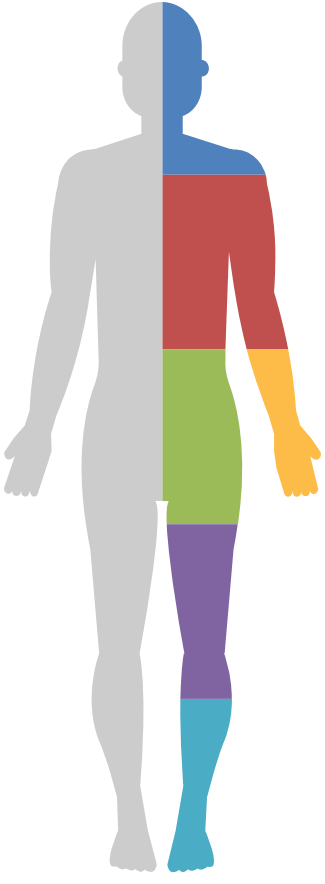

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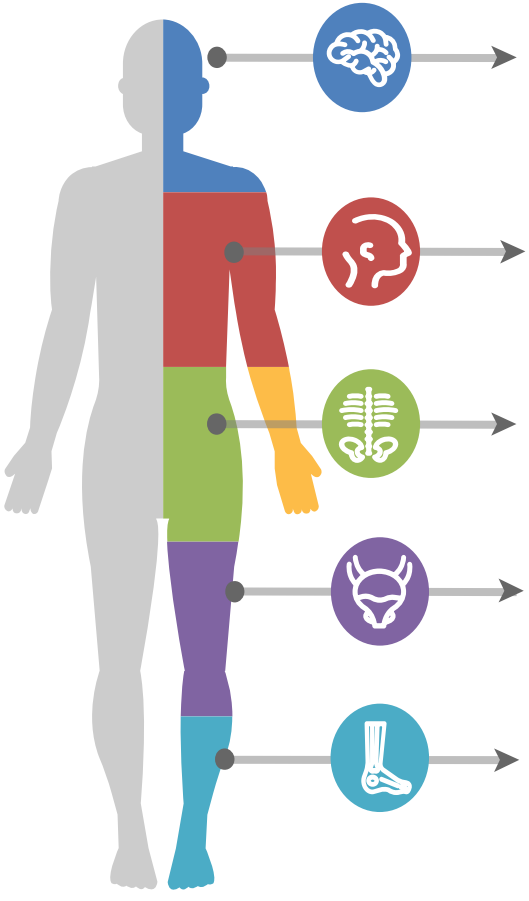
Fetal Valproate Spectrum Disorder



Neurodevelopmental

Poorer cognitive skills (IQ, language, memory, attention & executive functioning)
Increased ASD, ADHD rates

Minor congenital anomalies

Characteristic pattern of facial dysmorphia, ocular

Major congenital anomalies

Skeletal, cardiac, orofacial, limb all at higher rates

Functional difficulties

Organ functioning difficulties, bladder control.

Hypotonia & joint hypermobility

Impact on walking longer distances, long periods of writing

- ICD-11
  - LD2F.03 Fetal Valproate Spectrum Disorders
- Characteristic, recognizable set of symptoms physical and neurodevelopmental difficulties
- Dose associated
- Neurodevelopmental features can be present in isolation
- Social, sensory and executive functioning appear frequently

Clayton-Smith et al 2019, Orphanet Journal of Rare Diseases, Bromley et al 2019 Neurotoxicology and Teratology, Bluett- Duncan et al 2023 In submission.

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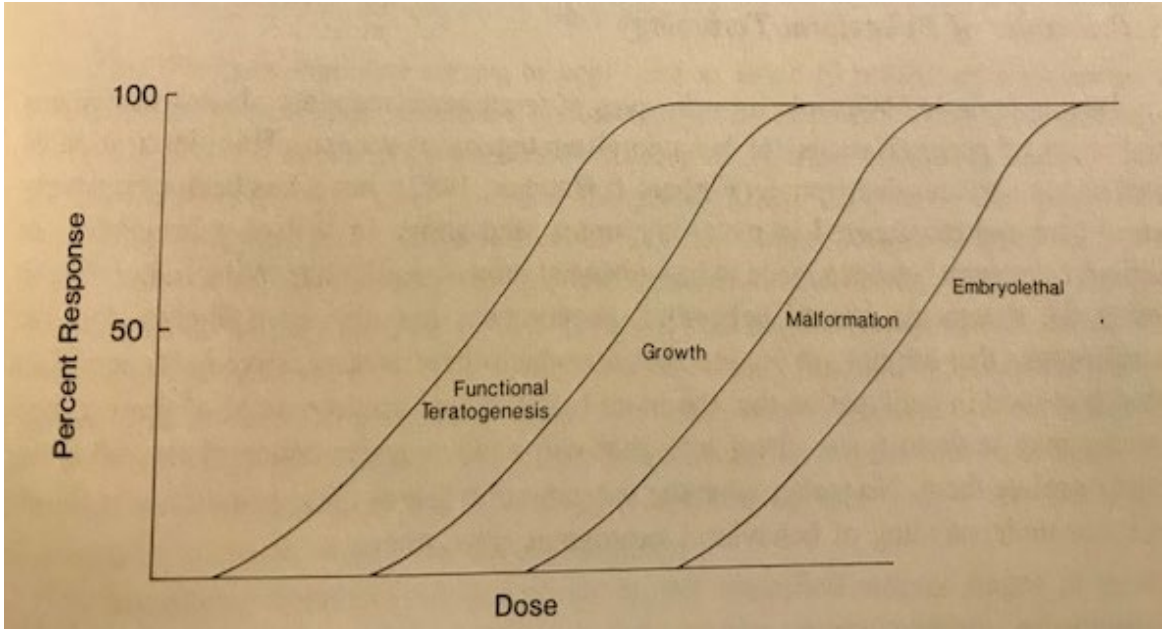
Dose of the exposure



Vorhees 1986 Origins of behavioral teratology. Handbook of behavioral teratology.

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Neurodevelopmental Outcomes

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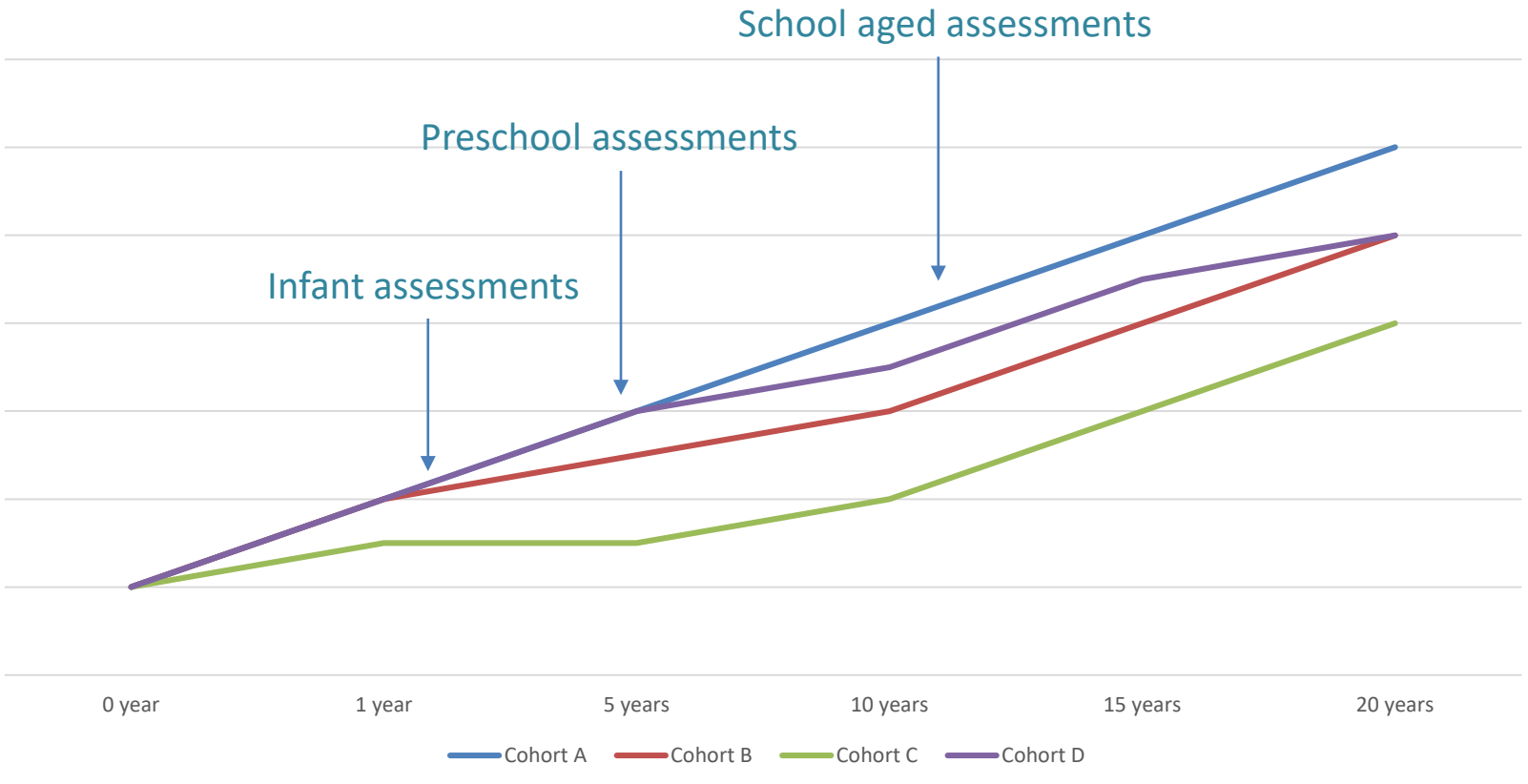
Trajectories



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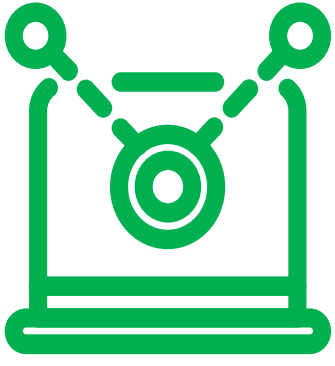
Pregnancy Pharmacovigilance

Hospital Based Studies

Pregnancy Registers

Adverse Event Reporting

Secondary Use Data



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Outcomes in children exposed to antiseizure medications

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Neurodevelopment

- Now known risks to neurodevelopment for certain medications
- MHRA 2021 review concluded deficits in our knowledge about nearly all ASMs.
  - Including the widely used lamotrigine and levetiracetam
  - Evidence is most notably absent for the longer-term child health and neurodevelopmental outcomes

Medical and Healthcare Products Regulatory Agency (MHRA), 2021.

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Valproate

Birth

- Evidence of a dose dependent increased risk of MCA.
- Range of organs affected.

Infancy

- Evidence of early infant developmental milestone disruption vs control children, lamotrigine and levetiracetam exposed.
- 30-40% below average.
- Deviation in developmental seen as young as 24 months.

Pre School

- Poorer cognitive functioning in comparison to children exposed to lamotrigine, carbamazepine and phenytoin.
- Poorer motor functioning, milestone attainment.
- Increased referrals to speech therapy services.

School Age

- Reduced cognitive functioning to children exposed to lamotrigine, carbamazepine and phenytoin.
- Language skills markedly affected.
- Increased rates of autistic spectrum conditions to controls and other ASMs.
- Reduced school attainments, increased risk for education support services.
- Clear evidence of dose dependent effects. Doses over 800-1000mg/d.

Adolescence

- No studies of cognitive functioning (IQ).
- Cumulative risk of increased clinical disorders (ADHD, ASD etc).

Cohen et al Annals of neurology 2023, Bromley et al 2023 Cochrane Library, In Press; Moore et al 2000 Am J Med Genetics; Adab et al 2004 JNNP; Bromley et al 2010 Epilepsia; Bromley et al 2014 Cochrane Library; Shallcross et al 2011 Neurology; Elkær et al 2018 JAMA Neurology; Meador et al 2009 NEJM, Meador et al 2013 JAMA Neurology; Christensen et al 2013 JAMA; Baker et al 2015 Neurology; Huber-Mollema 2020 Journal of Neurology, Bjørk et al JAMA Neurology; Bloitère et al 2020 BMJ Open; Wereberg Dreier et al 2023 JAMA Neurology.

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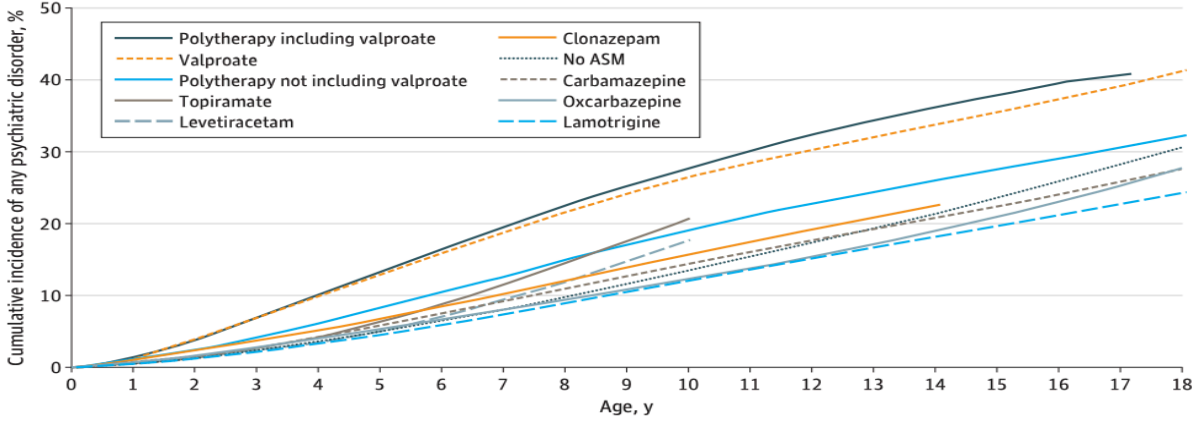
Figure 1. Cumulative Incidence of the Combined Psychiatric End Point According to Prenatal Antiseizure Medication (ASM) Exposure



No. of children followed up																			
No ASM	22 203	20 520	18 676	16 888	15 182	13 397	11 721	10 041	8338	6767	5272	3868	2552	1856	1466	1148	869	620	400
Monotherapies																			
Valproate	1952	1935	1878	1807	1729	1634	1532	1419	1297	1160	1015	853	724	619	542	463	382	306	227
Lamotrigine	5288	4894	4452	4010	3549	3158	2722	2317	1927	1543	1189	847	546	374	279	207	151	88	61
Levetiracetam	1061	947	782	630	510	397	302	230	162	109	62								
Carbamazepine	2665	2608	2504	2397	2276	2144	2001	1846	1693	1499	1336	1139	944	820	733	642	535	428	328
Oxcarbazepine	1460	1446	1369	1293	1216	1133	1060	968	876	806	740	663	569	489	417	347	280	210	147
Topiramate	290	276	262	244	216	191	170	141	115	90	70								
Clonazepam	339	NA	327	320	306	290	274	263	243	218	194	167	136	113	101				
Polytherapies																			
Without valproate	2092	1951	1780	1637	1475	1316	1177	1060	899	785	658	556	446	357	299	253	202	161	110
With valproate	822	800	748	702	662	622	573	535	473	413	372	322	278	240	214	186	154	124	

The cumulative incidence curves are unadjusted. Different lengths of the curves reflect differences in available follow-up data for the ASMs. NA indicates not applicable.

Wereberg Dreier et al 2023 JAMA Neurology

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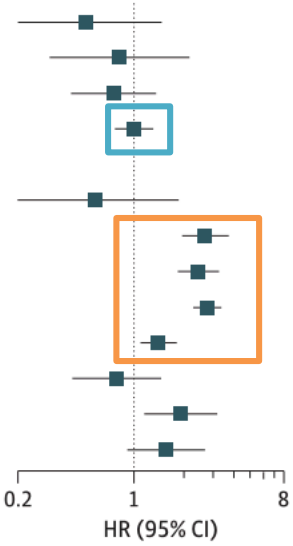
Figure 2. Hazard Ratios (HRs) of Psychiatric Disorders According to Maternal Antiseizure Medication (ASM) Use in Pregnancy for Valproate, Lamotrigine, Levetiracetam, and Carbamazepine Monotherapies

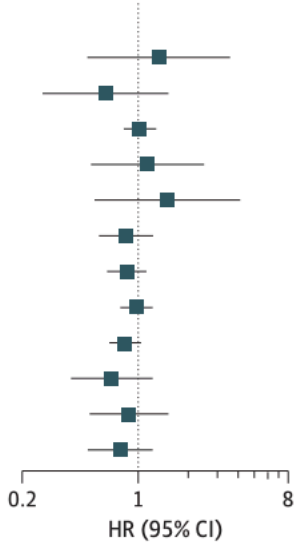
A Valproate monotherapy

Psychiatric disorder	No. of unexposed cases	No. of exposed cases	HR (95% CI)
Substance use disorder	31	5	0.52 (0.18-1.47)
Schizophrenia spectrum disorder	29	8	0.82 (0.31-2.16)
Mood disorder	58	23	0.75 (0.42-1.36)
Anxiety disorder	458	104	1.00 (0.77-1.31)
Eating disorder	37	<5	NA
Personality disorder	24	5	0.59 (0.19-1.86)
Intellectual disability	184	81	2.70 (1.94-3.74)
Autism spectrum disorder	323	93	2.45 (1.84-3.26)
Other developmental disorder	433	274	2.76 (2.27-3.36)
ADHD	528	106	1.41 (1.10-1.81)
ODD/CD	110	15	0.79 (0.43-1.46)
Attachment disorder	97	28	1.91 (1.15-3.18)
Tic disorder	123	22	1.56 (0.91-2.68)



B Lamotrigine monotherapy

No. of exposed cases	HR (95% CI)
<5	NA
5	1.33 (0.49-3.59)
10	0.64 (0.27-1.52)
97	1.01 (0.80-1.27)
10	1.14 (0.52-2.50)
5	1.50 (0.55-4.13)
34	0.85 (0.58-1.24)
64	0.86 (0.65-1.14)
101	0.98 (0.78-1.23)
95	0.83 (0.66-1.04)
14	0.69 (0.39-1.22)
17	0.88 (0.51-1.52)
23	0.78 (0.50-1.23)



Wereberg Dreier et al 2023 JAMA Neurology

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Carbamazepine

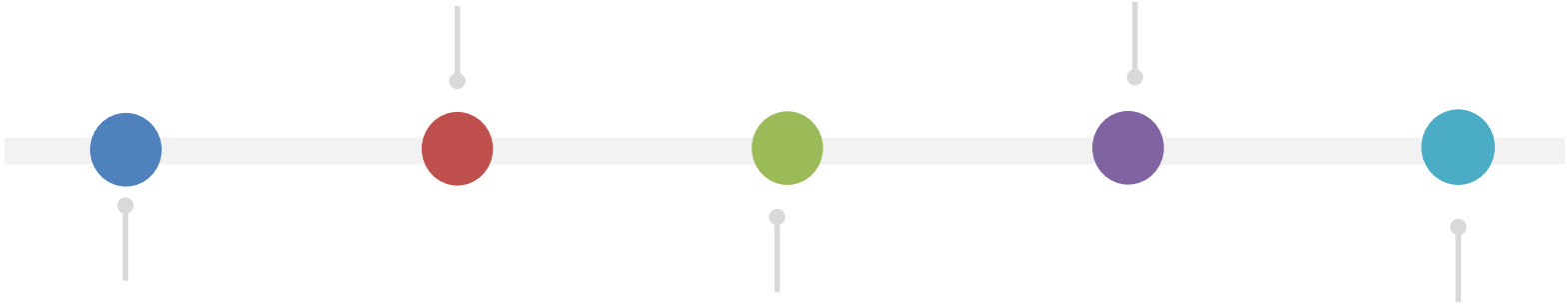
Infancy

- No clear evidence of early infant developmental milestone disruption vs control children.
- Outcomes improved in comparison to children exposed to valproate.

School Age

- Variation in cognitive outcomes in comparison to general population controls.
- Comparable cognitive functioning to children exposed to lamotrigine
- Comparable rates of autistic spectrum conditions to controls
- Comparable school attainments

- No evidence of dose dependent effects, yet cohorts are limited for cognitive outcomes.



Birth

- Evidence of a dose dependent increased risk of MCA.
- Not found in the recent Nordic paper.

Pre School

- Improved cognitive functioning in comparison to children exposed to valproate.
- Comparable cognitive functioning in comparison to lamotrigine.

Adolescence

- No studies of cognitive functioning.
- Cumulative data, suggests no increased clinical disorders (ADHD, ASD etc).
- Possible reduction in certain school attainments.

Cohen et al Annals of neurology 2023, Tomson et al 2018, Lancet Neurology; Bromley et al 2023 Cochrane Library, In Press; Bromley et al 2010 Epilepsia; Bromley et al 2014 Cochrane Library; Scolnik et al 1994; Elkær et al 2018 JAMA Neurology; Meador et al 2009 NEJM, Meador et al 2013 JAMA Neurology; Baker et al 2015 Neurology; Huber- Mollema 2020 Journal of Neurology, Bjørk et al JAMA Neurology; Elkær et al 2018 JAMA Neurology; Bloitère et al 2020 BMJ Open; Wereberg Dreier et al 2023 JAMA Neurology.

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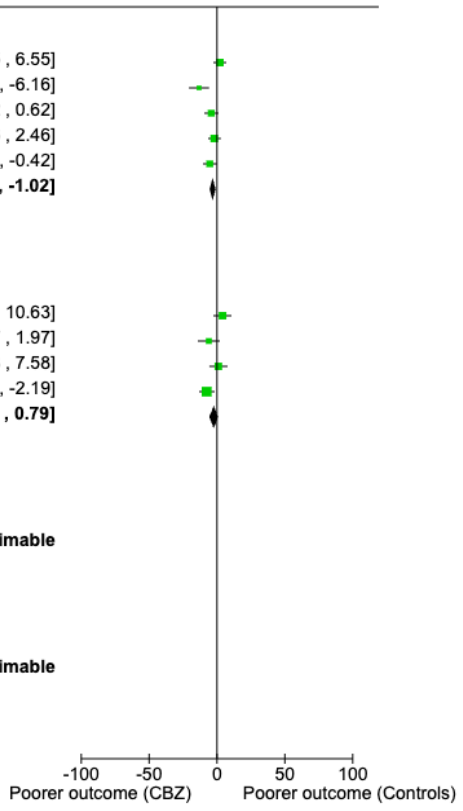
Study or Subgroup	CBZ Mean [IQ points]	CBZ SD [IQ points]	CBZ Total	Controls Mean [IQ points]	Controls SD [IQ points]	Controls Total	Weight	Mean difference IV, Fixed, 95% CI [IQ points]
1.5.1 CBZ vs Women without epilepsy (cohort studies)								
Gaily 2004	99.7	16.6	86	97.6	16.6	141	24.5%	2.10 [-2.35 , 6.55]
Kasradze 2017	88.2	13.7	16	101.4	7.7	50	9.8%	-13.20 [-20.24 , -6.16]
Kerala Register	82.2	13.9	40	86.4	13.4	149	20.9%	-4.20 [-9.02 , 0.62]
Liverpool & Manchester Group	105	15	50	107	12	210	24.4%	-2.00 [-6.46 , 2.46]
NEAD Study	106.2	12.1	61	111.5	12.01	38	20.4%	-5.30 [-10.18 , -0.42]
Subtotal (95% CI)			**253**			**588**	**100.0%**	**-3.23 [-5.43 , -1.02]**
Heterogeneity: Chi² = 14.34, df = 4 (P = 0.006); I² = 72%								
Test for overall effect: Z = 2.87 (P = 0.004)								
1.5.2 CBZ vs Epilepsy, no treatment (cohort studies)								
Gaily 2004	99.7	16.7	86	95.6	18.8	45	24.3%	4.10 [-2.43 , 10.63]
Kerala Register	90.9	19	38	96.9	8.8	11	16.3%	-6.00 [-13.97 , 1.97]
Liverpool & Manchester Group	105	15	50	104	13	25	24.0%	1.00 [-5.58 , 7.58]
North American AED Pregnancy Registry	109.6	12.8	41	117.2	12.2	41	35.4%	-7.60 [-13.01 , -2.19]
Subtotal (95% CI)			**215**			**122**	**100.0%**	**-2.43 [-5.65 , 0.79]**
Heterogeneity: Chi² = 9.16, df = 3 (P = 0.03); I² = 67%								
Test for overall effect: Z = 1.48 (P = 0.14)								
1.5.3 CBZ vs Women without epilepsy (database studies)								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.5.4 CBZ vs Epilepsy, no treatment (database studies)								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%								



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BMJ

RESEARCH

Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study

Janneke Jentink, research fellow and lecturer in pharmacoepidemiology,[1] Helen Dolk, professor of epidemiology and health services research,[2] Maria A Loane, EUROCAT research fellow and lecturer in public health,[2] Joan K Morris, professor of medical statistics,[3] Diana Wellesley, clinical geneticist,[4] Ester Garne, consultant paediatrician and EUROCAT perinatal epidemiologist,[5] Lolkje de Jong-van den Berg, professor in pharmacoepidemiology, [1] for the EUROCAT Antiepileptic Study Working Group

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Lamotrigine

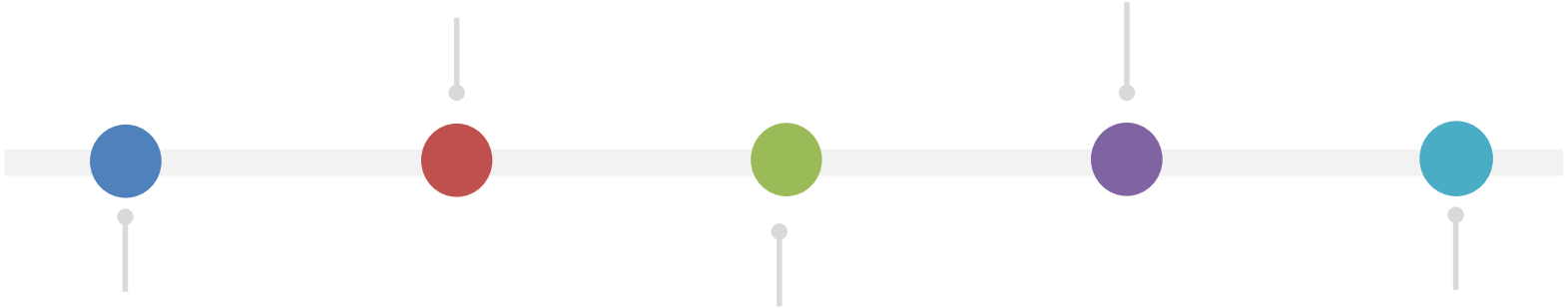
Infancy

- No evidence of poorer milestone attainment from cohort studies vs control children.
- Improved outcomes vs valproate exposure
- No clear dose relationship.
    - Larger numbers needed.

School Age

- More limited comparisons to unexposed groups for cognitive functioning.
- Educational test results comparable to controls.
- Improved cognitive outcomes (incl. IQ) vs children exposed to valproate. Comparable to carbamazepine, levetiracetam.
- Data is too limited to investigate dose associations.

- No increased risk of clinical disorders. But there is evidence of poorer emotional, social functioning, when rated by parents.



Birth

- Evidence from greater than 10,000 pregnancies. No increased rate of major congenital anomaly.
- EURAP finds increased risk with doses over 325mg/d.

Pre School

- Suggestion of poorer language development, but limited, and not seen at older ages.
- No increased risk of diagnosed NDD, referrals to speech therapy.

Adolescence

- Very limited data.
- Comparable language and mathematics vs control children improved vs valproate.
- Cumulative data from different ages, no increased of clinic disorders.
- Limited dose investigations.

MHRA Review 2021, Bromley et al 2023 Cochrane Library, Tomson et al 2018 Lancet Neurology, Meador et al 2009 NEJM, Meador et al 2021 JAMA Neurology, Bromley et al 2010, Bromley et al 2023 Epilepsia, Bloitère et al 2020 BMJ Open , Veiby et al 2013 BMJ Open , Huber- Mollema 2020 Journal of Neurology, Meador et al 2013 Lancet Neurology, Christensen et al 2013 JAMA, Christensen et al 2019 JAMA Open, Richards et al 2019 Epilepsy & Behavior, Veiby et al 2013 Epilepsia, Bromley et al 2023, in preparation, Elkær et al 2018 JAMA Neurology, Bjørjk et al 2022 JAMA Neurology; Wereberg Dreier et al 2023 JAMA Neurology.

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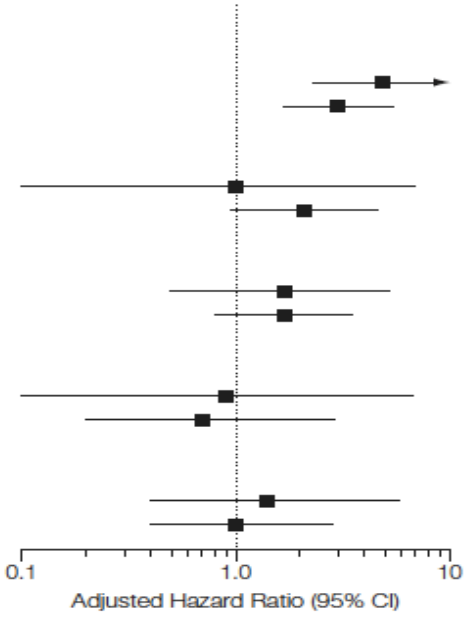
Autistic Spectrum Disorder

Figure 2. Autism Spectrum Disorder and Childhood Autism in Offspring of Mothers Who Used Antiepileptic Drugs as Monotherapy During Pregnancy Compared With Offspring of Women Who Did Not Use the Individual Antiepileptic Drug

	No.		Adjusted Hazard Ratio (95% CI)
	Unexposed	Exposed	
Valproate			
Total	655 107	388	
Childhood autism	2058	7	4.9 (2.3-10.3)
Autism spectrum disorder	5423	12	3.0 (1.7-5.4)
Oxcarbazepine			
Total	655 205	321	
Childhood autism	2064	1	1.0 (0.1-6.9)
Autism spectrum disorder	5427	7	2.1 (0.96-4.6)
Lamotrigine			
Total	654 747	647	
Childhood autism	2062	4	1.7 (0.5-5.2)
Autism spectrum disorder	5426	8	1.7 (0.8-3.5)
Clonazepam			
Total	655 233	269	
Childhood autism	2063	2	0.9 (0.1-6.7)
Autism spectrum disorder	5431	3	0.7 (0.2-2.9)
Carbamazepine			
Total	655 153	386	
Childhood autism	2065	2	1.4 (0.4-5.8)
Autism spectrum disorder	5433	4	1.0 (0.4-2.8)



Christensen et al 2013, JAMA

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Autistic Spectrum Traits

MoBA, Norway

- National study
- 41, 3 year olds exposed to LTG
- Increased parent ratings of traits or symptoms of the spectrum
- Influenced by folate use

Dutch EURAP F/U

- Primary data in 88 LTG exposed
- Higher parental ratings of symptoms of autistic behaviour vs population norms.
- But numbers of clinical diagnoses were low

New Zealand

- Routine data collection including n= 149 LTG monotherapy exposed
- Found higher prevalence of emotional and behavioural difficulties

Veiby et al 2013 Epilepsia; Bjørk et al 2018 JAMA Neurology; Huber- Mollema et al 2020, Richard et al 2019 Epilepsy and Behavior.

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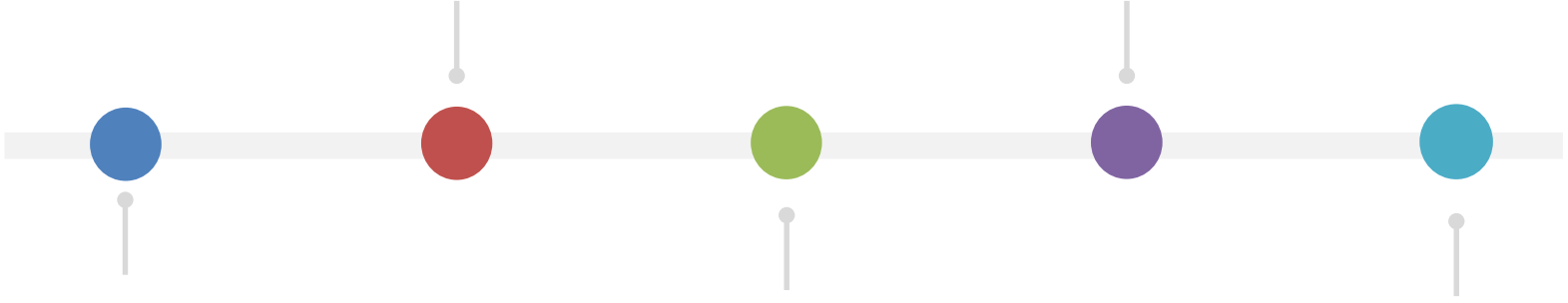
Levetiracetam

Infancy

- No evidence of poorer milestone attainment from cohort studies. Better developmental outcomes vs valproate, consistent with children exposed to lamotrigine.
- No clear dose relationship, but larger numbers needed. MONEAD, potential association with poorer motor development.

School Age

- More limited, particularly vs controls.
- Improved cognitive outcomes (incl. IQ) vs children exposed to valproate.
- Comparable to carbamazepine, lamotrigine.
- Data is too limited to investigate dose associations.



Birth

- Evidence from greater than 1800 pregnancies. No increased rate of major CA.
- No evidence of a dose association or specific anomaly risk.

Pre School

- No risk in comparison to controls.
- No increased risk of diagnosed ASD, NDD, referrals to speech therapy in comparison to lamotrigine.

Adolescence

- No data on cognitive functioning,
- Data pooled from Nordic countries demonstrate an increased risk of anxiety and ADHD.

Shallcross et al 2011 Neurology; Shallcross 2014 Neurology; Bromley et al 2016 Neurology; Meador et al 2021 JAMA Neurology; Bromley et al 2023 Epilepsia, Huber- Mollema 2020 Journal of Neurology, Bloitère et al 2020 BMJ Open; Bjørk et al 2022 JAMA Neurology, Wereberg Dreier et al 2023 JAMA Neurology.

Levetiracetam

MONEAD Study

WWE, treated and not
N= 456

Recruitment by <20 weeks
Demographics, blood ASM levels

Birth: Congenital anomaly, feeding, maternal health and wellbeing

2 years, 3 years 4.5 years and 6 years.

NaME Study

WWE, treated and not
N=401

Recruitment by <20 weeks
Demographics, prescribed dose

Birth: Congenital anomaly, breastfeeding status

12 months, 2 years, 8-9 years.

Meador et al 2021 JAMA Neurology; Bromley et al 2023 Epilepsia.

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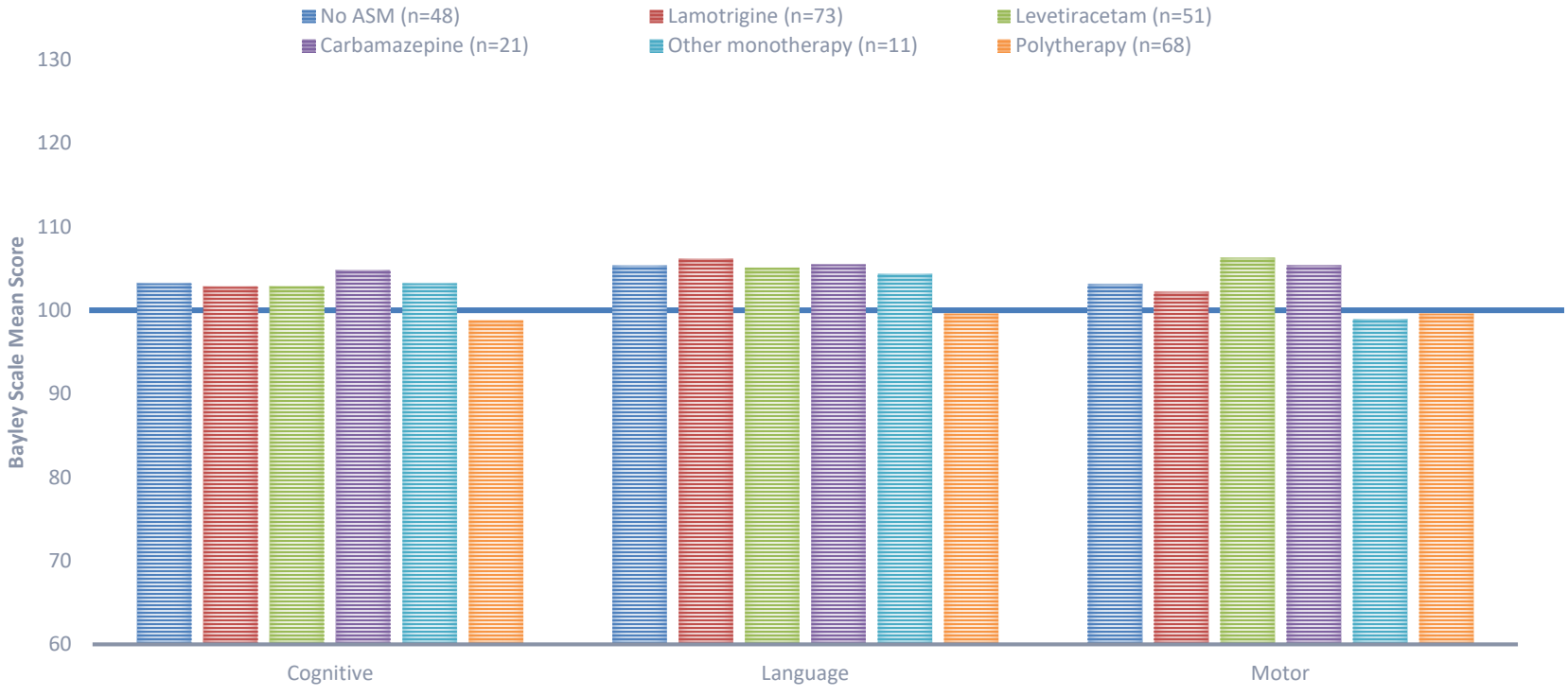
NaME Study

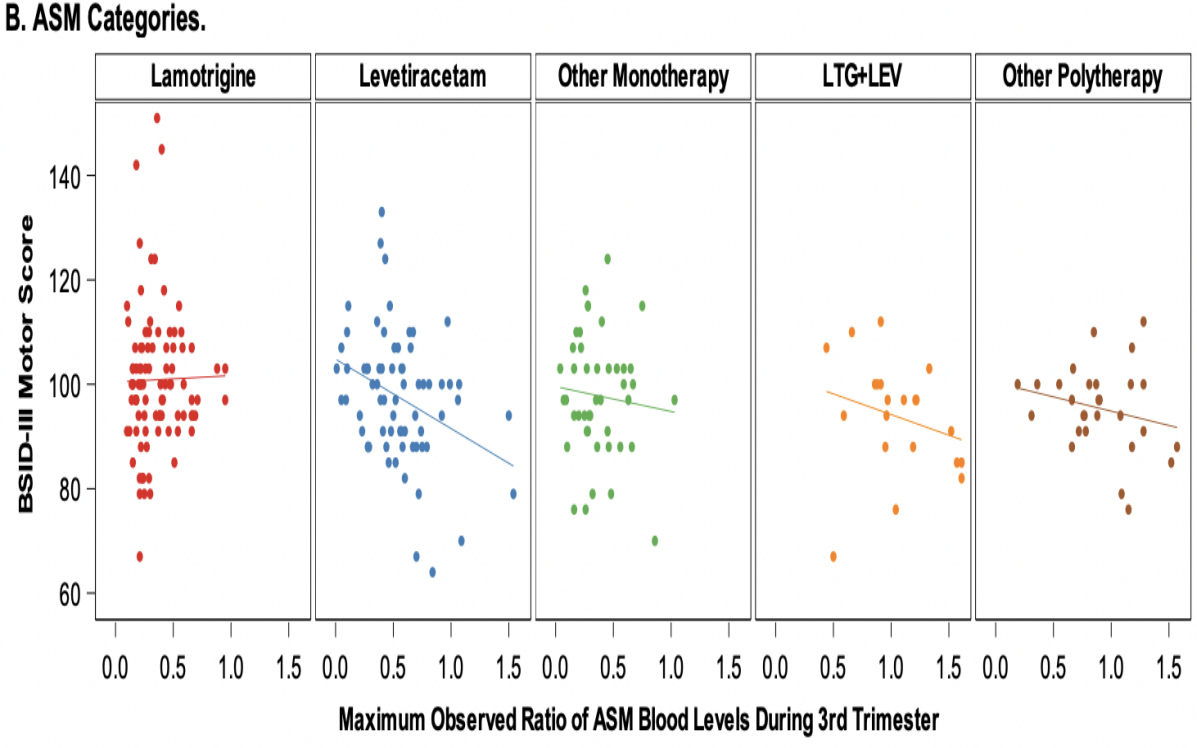
2 YEAR OLD MEAN SCORES*



* Adjusted for maternal IQ and engagement

Bromley et al 2023, Epilepsia.

Levetiracetam



Meador et al 2021 JAMA Neurology, Meador et al 2023 JAMA Neurology.

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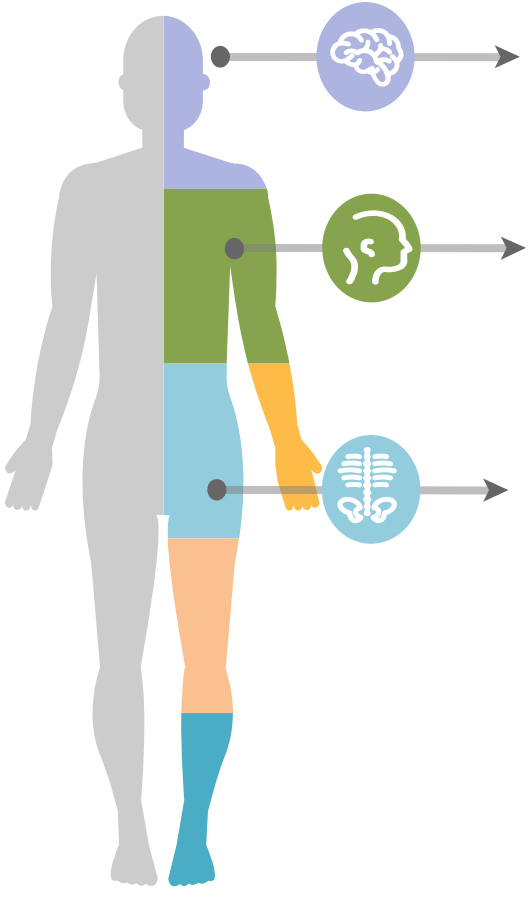
Topiramate Exposure



Neurodevelopmental

Evidence emerging

Major congenital anomalies

Increased risk of orofacial clefts, skeletal and limb anomalies.

Dose dependent.

Fetal Growth

Increased risk of Small for Gestational Age births

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Topiramate (Topamax): start of safety review triggered by a study reporting an increased risk of neurodevelopmental disabilities in children with prenatal exposure

We have initiated a new safety review into topiramate as a result of an observational study reporting an increased risk of neurodevelopmental disabilities in children whose mothers took topiramate during pregnancy. Topiramate is known to be associated with an increased risk of congenital malformations and effects on fetal growth if used during pregnancy. Continue to counsel patients who can become pregnant on the known and emerging risks of topiramate for an unborn baby and on the need to use effective contraception throughout use.

Cohen et al 2022 Annals of Neurology, Bjork et al 2022 JAMA Neurology, Bromley et al 2023 Cochrane Library, In Press

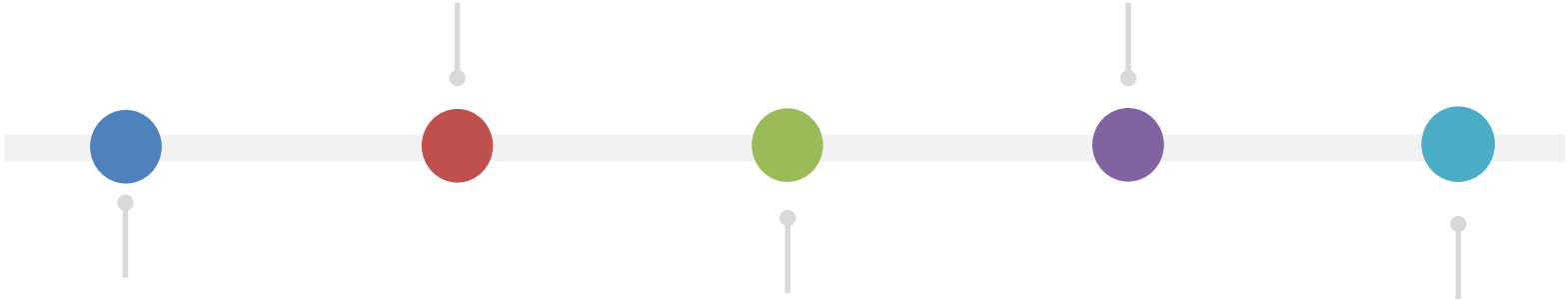
Topiramate

Infancy

- No adequately powered directly assessed cohorts.

School Age

- Two small cohort studies = conflicting results on cognitive measures.
- Pooled Nordic data find increased ID risk and increased risk of ASD at 8 years of age.
- Poorer parent rated, adaptive behaviour.



Birth

- CA prevalence is increased
- Specifically cleft anomalies and skeletal and limb.
- Increased risk of SGA.

Pre School

- No increased risk of speech therapy referrals or NDD diagnosis; (n=477) but this group were young for this type of diagnosis.

Adolescence

- No data
- Updated SCAN AED data suggests ADHD is increased, borderline ASD result.

Cohen et al Annals of neurology 2023; Bromley et al 2023, Cochrane Library, In Press. Hernandez_Diaz et al 2017 Annals of Neurology; Bromley et al 2016 Neurology, Rihtman et al 2009 Reproductive Toxicology, Bech et al 2018 JNNP, Bloitère et al 2020 BMJ Open, Bjørk et al 2022 JAMA Neurology, Knight et al Seizure 2023; Wereberg Dreier et al 2023 JAMA Neurology.

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Topiramate

Table 5
Summary of included topiramate-exposed children with diagnosed ASD.

	Case 1	Case 2	Case 3	Case 4
Demographics/background				
ASM dose, mg/d (high/low)[a]	300 (high)	400 (high)	450 (high)	150 (low)
Family history[b] **of neurodevelopmental conditions, O/P**	O	O	O	O
Family history[b] **of learning difficulties, O/P**	O	O	O	O
Family history[b] **of major malformations, O/P**	O	O	O	O
Birth and health outcomes				
Gestational age at birth, wks	39	42	41	40
Major malformations,[c] **O/P**	O	O	O	O
Birth weight centile	25	25	25	9
Small for gestational age (≤ 10th centile), O/P	O	O	O	P
Long-term health conditions, O/P	O	P	O	O
Hearing/eyesight conditions, O/P	P	O	O	O
Educational outcomes				
Reported learning difficulties, O/P	P	P	P	P
Formal learning support provision in place, O/P	P	P	P	O
Adaptive behaviour outcomes				
Below average[d] **Adaptive Behaviour Composite (ABC) score, O/P**	P	P	P	P
Below average[d] **communication skills (COM), domain standard score, O/P**	P	P	P	P
Below average[d] **daily living skills (DLS), domain standard score, O/P**	P	P	P	O
Below average[d] **socialisation skills (SOC) domain standard score,, O/P**	P	P	P	P

[a] Low dose = <200 mg, high dose = ≥200 mg.
[b] First degree relatives.
[c] Requiring intensive and/or surgical intervention.
[d] Score of ≤85.

Knight et al Seizure 2023

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SCAN AED PROJECT

	N Exposed	N ND	Adjusted hazard ratio (95% confidence interval)[d]
Children of valproate discontinuers	1239	39	1
Valproate exposed children	1468	92	2.01 (1.32-3.04)

Children of topiramate discontinuers	1095	15	1
Topiramate exposed children	679	22	2.29 (1.09-4.82)

eTable 7 Risk of any neurodevelopment disorder (ND)a in the child prenatally exposed to antiseizure medication (ASM)b in monotherapy using women discontinuing ASM before pregnancy as a reference

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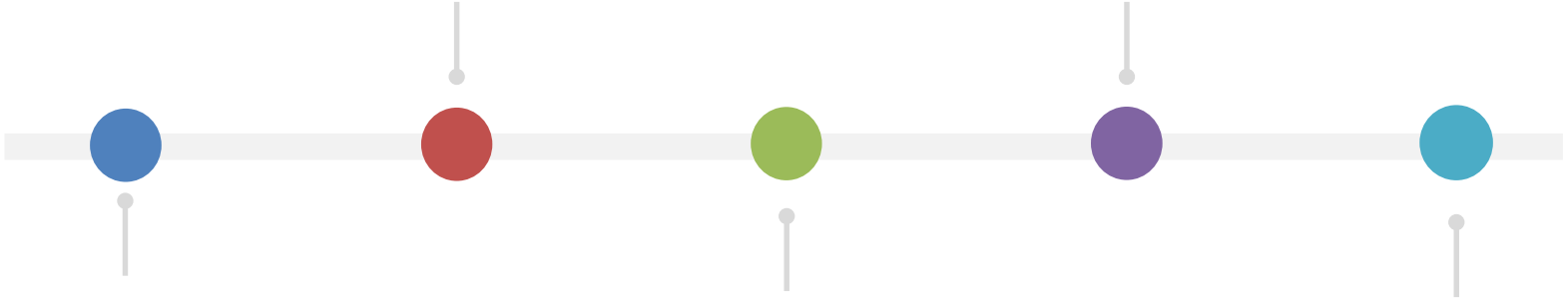
Oxcarbazepine

Infancy

- No increased risk of speech therapy referrals.

School Age

- No blinded, per protocol studies for cognitive outcomes.
- No increased risk of learning disability
- Unclear evidence of increased risk of clinical disorders
- Comparable educational outcomes up to 6th grade.



Birth

- Current data, no increased risk of major congenital anomalies.
  - Data limited for dose

Pre School

- No increased risk found of ASD and other developmental disorders.
  - Poor sensitivity at this age

Adolescence

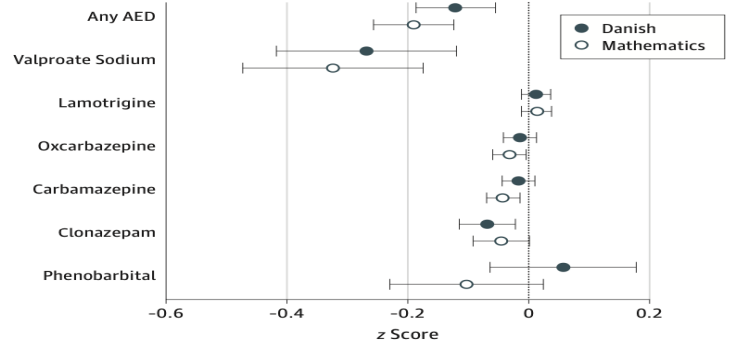
- Cumulative data across ages suggest no risk of clinical disorders, but data limited to Scan AED or associated projects.

Cohen et al Annals of neurology 2023; Bromley et al 2023, Cochrane Library, In Press. Bloitère et al 2020 BMJ Open, Elkær et al 2018 JAMA Neurology, Christensen et al 2013 JAMA; Bjørk et al 2023 JAMA Neurology; Wereberg Dreier et al 2023 JAMA Neurology.

Oxcarbazepine

- Educational outcome data – proxy for brain development and function
- Data linked across Danish national population registers
  - Birth, prescriptions, education
- 1997-2006
- Included children entered for examinations
- 125 OXC exposed
- Income, gender and maternal education adjusted

Figure. *z* Score Difference in Sixth-Grade Danish and Mathematics Tests for Children Prenatally Exposed to Different Monotherapy With Antiepileptic Drugs (AEDs)



Comparison of children receiving AED monotherapy vs unexposed children, including children who completed the sixth-grade Danish test and were exposed to any AED (n = 795), valproate (n = 151), lamotrigine (n = 117), oxcarbazepine (n = 125), clonazepam (n = 101), carbamazepine (n = 182), and phenobarbital (n = 59). The any AED group contains children exposed to monotherapy with 1 of the following drugs: phenobarbital, primidone, clonazepam, carbamazepine, oxcarbazepine, valproate, vigabatrin, lamotrigine, topiramate, gabapentin, clobazam, phenytoin, levetiracetam, or pregabalin. The vertical line represents the reference of unexposed children. The school performance was adjusted for the sex of the child, calendar year, and maternal education and household income at birth. Error bars indicate 95% CI.

Elkær et al 2018 JAMA Neurology

Other ‘newer ASMs’

Brivaracetam
Clonazepam
Eslicarbazepine
Ethosuximide
Gabapentin

- For Lacosamide more data are needed to understand outcomes

Rufinamide
Perampanel
Pregabalin
Tiagabine
Vigabatrin
Zonisamide
Cenobamate

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An absence of evidence of risk, should not be viewed as evidence of safety

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Summary

- Neurodevelopmental outcomes key outcomes for CNS acting medications
- Valproate, phenobarbital and possibly topiramate are associated with poorer outcomes
- Possible emergence of evidence for levetiracetam
- Investigation of higher doses is missing for most
- Timelines remain too long and need improved pregnancy PV strategy
  - Likely to be multi-factorial

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Manchester

- Dr Rebecca Bromley, Paediatric Neuropsychologist
- Prof Jill Clayton-Smith, Clinical Geneticist
- Dr Matthew Bluett-Duncan, Psychologist
- Ms Miffy Rawson, Project Co Ordinator
- Ms Sarah Rushton, Research Practitioner
- Dr Sonia Khanom, Psychologist
- Dr Rajiv Mohanraj, Adult Neurologist
- Prof Marta Garcia Fíanã, Biostatistics

NaME Study

- Collaborating hospitals
- Women and their children

ConcePTION

- Dr Laura Yates, Clinical Geneticist
- Dr David Lewis, Pharmacovigilance lead
- Prof Eugène van Puijenbroek, Professor of Pharmacovigilance
- Dr Saskia Vorstenbosch, Pharmacovigilance Scientist
- Prof Marta Bjørk, Professor of Neurology
- Dr Jonathan Richardson, Clinical Scientists, UKTIS

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- Dr John Craig, Neurologist
- Dr Jim Morrow, Neurologist
- Beth Irwin, Epilepsy Nurse
- Dr Norman Delanty, Neurologist
- Dr Craig Heath, Neurologist

Cochrane Epilepsy Group

- Prof Tony Marson, Neurologist
- Prof Jakob Christensen, Neurologist
- Dr Naghme Adab, Neurologist
- Prof Catrin Tudor Smith, Biostatistics

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Thank you for listening

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