National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults: diagnosis and management

[06] Evidence review: Safety of ASMs in women and girls

NICE guideline

Evidence for recommendations 4.4.1 – 4.4.8 in the NICE guideline

November, 2021

Draft for Consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1. Safety of anti-seizure medications (ASMs) in women and girls

1.1. Review question

What Anti-seizure medications (ASMs) (individually or add-ons) are safe in the treatment of epilepsies in women and girls who are pregnant and already taking ASMs and in those women who are breastfeeding?

1.1.1. Introduction

Antiseizure medications (ASMs) are used to control the frequency and intensity of seizures being experienced by the person with epilepsy. In women and girls who are pregnant and already taking ASMs there are, additional safety concerns related to foetal neurodevelopment for example: poorer levels of ability for skills such as IQ, language and memory as well as structural abnormalities, and risk of other congenital harms to the foetus.

Current practice is guided by the advice provided by the Medicines and Healthcare products Regulatory Agency (MHRA) in their Public Assessment Report entitled: Antiepileptic drugs: review of safety of use during pregnancy.

This review summarises and considers the results of the MHRA report, examining which Anti-seizure medications (ASMs) are safe in the treatment of epilepsy in women and girls who are pregnant and already taking ASMs

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	• Pregnant women and girls of childbearing potential with undergoing treatment for epilepsy (including generalised tonic-clonic (GTC), focal onset seizures, absence seizures, myoclonic seizures, tonic seizures, atonic seizures) • Breastfeeding women and girls undergoing treatment for epilepsy
Interventions	• Pregnant women and girls with epilepsy taking a single Anti-seizure medications of interest • Pregnant women and girls with epilepsy taking a combination of • Breastfeeding women and girls with epilepsy taking a single ASMs of interest • Breastfeeding women and girls with epilepsy taking a combination of ASMs.
Comparisons	• pregnant women and girls with epilepsy taking another ASM of interest (for single ASM and combinations of ASMs as interventions) • pregnant women and girls with epilepsy taking a different combination of ASMs • pregnant women and girls with epilepsy taking no ASM • pregnant women and girls who did not have epilepsy • • breastfeeding women and girls with epilepsy taking another ASM of interest (for single ASMs and combinations of ASMs as interventions) • breastfeeding women and girls with epilepsy taking a different combination of ASMs • breastfeeding women and girls with epilepsy taking no ASMs • breastfeeding women and girls who did not have epilepsy
Outcomes	• Major congenital malformations such as neural tube defects (spina bifida), limb

	defects (club foot), cleft lip and palate, urogenital defects (hypospadias, absent kidneys, abnormal genitalia), cardiac related (congenital heart disease, including ventricular or atrial septal defect) gastric related (oesophageal atresia and gastroschisis), lung related (congenital lung cysts) • Minor (less major) congenital malformations such as missing digit or additional digit, cavernous haemangioma of the skin, or minor versions of congenital heart disease, or spina bifida occulta. • Intellectual quotient (IQ) (Wechsler Intelligence Scale for Children, the Differential Ability Scales) • Development quotient (DQ): (Griffiths and the Bayley Scales) • Other cognitive outcomes: language, memory, attention and executive functioning (Clinical Evaluation of Language Fundamentals, Peabody picture naming. The Children's Memory Scale, Rivermead Memory Test, NEPSY: Neuropsychological Assessment) • Adaptive Behaviour (Vinelands Adaptive Behaviour Scale, the Adaptive Behaviour Assessment System (both have been used in this area) • Neurodevelopmental disorders such as autism, ADHD, dyspraxia
Study design	• Systematic reviews of randomised controlled trials and cohort studies • Randomised controlled trials • Prospective and retrospective cohort studies will be included if adjustments have been made • Published registry databases will be included if adjustments have been made, except when the database includes 5000 plus individuals, in which case no adjustments are needed

1.1.3. Methods and process

The evidence incorporated into this chapter was taken from a report published by the Medicines and Healthcare products Regulatory Agency (MHRA) (2021) Public Assessment Report: Antiepileptic drugs: review of safety of use during pregnancy, found here. It investigates and addresses the safety concerns of ASMs in women and girls who are pregnant. As this is a key aspect of the protocol developed for this evidence review (Table 1), the pragmatic decision to incorporate the MHRA report within this chapter instead of conducting a separate evidence review was taken. However, this does mean that clinical evidence for the safety of ASMs in women who are breastfeeding was not investigated. Instead, this issue will be discussed by the guideline committee, taking into account published information sources such as the Summaries of Product Characteristics (SPCs) and Patient Information Leaflets (PILs). The MHRA report does not provide evidence for all the outcomes listed in the protocol (Table 1). Table 2 lists the protocol outcomes and the MHRA evidence for those outcome and additional outcomes included in MHRA report.

The ROBIS tool for determining risk of bias in systematic reviews was to be used to assess the evidence included in the MHRA report. However, we did not have access to the methods underpinning the MHRA evidence selection and analysis and therefore the ROBIS tool could not be applied.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Table 2: Outcomes listed in evidence review protocol vs MHRA report

Protocol outcomes	MHRA evidence directly/indirectly addressing protocol outcome	Additional outcomes reported by the MHRA report*
Major congenital malformations i.e., neural tube defects (spina bifida), limb defects (club foot), cleft lip and palate, urogenital	Prevalence rate of congenital malformations (no specific information given on type)	Cognitive effects: delayed recognition, visual delayed, developmental delay, behaviour

Protocol outcomes	MHRA evidence directly/indirectly addressing protocol outcome	Additional outcomes reported by the MHRA report*
defects (hypospadias, absent kidneys, abnormal genitalia), cardiac related (congenital heart disease, including ventricular or atrial septal defect) gastric related (oesophageal atresia and gastroschisis), lung related (congenital lung cysts)		disorder Other reproductive toxic effects of prioritised ASMs: foetal loss, pre-term birth, prenatal growth restriction
Minor (less major) congenital malformations i.e. missing digit or additional digit, cavernous haemangioma of the skin, or minor versions of congenital heart disease, or spina bifida occulta.	Prevalence rate of congenital malformations (no specific information given on type)	
Intellectual quotient (IQ) (Wechsler Intelligence Scale for Children, the Differential Ability Scales)	IQ (Wechsler scale, other measures, IQ mean differences reported)	
Development quotient (DQ): (Griffiths and the Bayley Scales)	DQ (Griffiths scale, Bayley scale, other measures, DQ mean differences reported)	
Other cognitive outcomes: language, memory, attention and executive functioning (Clinical Evaluation of Language Fundamentals, Peabody picture naming. The Children's Memory Scale, Rivermead Memory Test, NEPSY: Neuropsychological Assessment)	Effects on development: attention/concentration, languages, verbal immediate, verbal delayed	
Adaptive Behaviour (Vinelands Adaptive Behaviour Scale, the Adaptive Behaviour Assessment System (both have been used in this area)	Specified scales not reported	
Neurodevelopmental disorders such as autism, ADHD, dyspraxia	ADHD and ASD Other neurodevelopmental effects: communication, daily living skills, socialisation, motor skills, languages, mathematics	

**These outcomes were presented in the MHRA report and have been included in the summary of evidence below for completeness, but they were not specified as the outcomes of interest by the guideline committee in the protocol.*

1.1.4. MHRA report conclusions

The MHRA report concludes that Lamotrigine and levetiracetam are the safer ASMs to use during pregnancy. Large amounts of data showed no increased risk of major congenital malformations or other reproductive toxic effects at their usual maintenance doses. There is however contradictory data for an increased risk of major congenital malformations for lamotrigine at higher doses. Furthermore, there was also limited data on the risk of neurodevelopment disorders and delay for both these ASMs, so an increased risk of neurodevelopmental disorders therefore cannot be ruled out.

Carbamazepine, phenobarbital, phenytoin and topiramate have been associated with an increased risk of major congenital malformations during pregnancy. Limited evidence suggests pregabalin may be associated with a slightly increased risk of major congenital malformations. There is uncertainty around the risks for gabapentin, oxcarbazepine, and zonisamide.

There was limited evidence overall on the risk of ASMs on neurodevelopmental disorders. Some limited evidence did show no increase in adverse effects on neurodevelopment and delay of carbamazepine use during pregnancy, however some neurotoxic effects were observed.

Evidence for the risk of ASMs on other reproductive toxic effects show an association of phenobarbital, topiramate, and zonisamide with an increased risk of intrauterine growth retardation (small for gestational age), this is not currently reflected in product information. Non-clinical data for carbamazepine, gabapentin, oxcarbazepine, topiramate, and zonisamide show they can affect fetal growth, but the clinical data are either too limited or report inconsistent findings. Overall, the risks of other reproductive toxic effects with carbamazepine, gabapentin, oxcarbazepine, and pregabalin remain uncertain.

The evidence included in this report could not be assessed for risk of bias and overall quality.

1.1.5. Summary of the effectiveness evidence

The tables below are taken from the Medicines and Healthcare products Regulatory Agency (MHRA) (2021) Public Assessment Report: Antiepileptic drugs: review of safety of use during pregnancy.

1.1.5.1.1. Prevalence rate of congenital malformations

	Carbamazepine	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Pregabalin	Topiramate	Valproate	Zonisamide
Meta-analyses											
Veroniki et al, 2017a	4.14% 8437 exposures	2.43% 329 exposures	2.62% 6290 exposures	1.77% 1015 exposures	2.96% 372 exposures	**5.50%** **1709 exposures**	**6.08%** **2237 exposures**	-	**4.67%** **599 exposures**	**9.07%** **4455 exposures**	-
Weston et al, 2016	**3.71% (95% CI 3.19 to 4.27)** **4.93% (95% CI 3.84 to 6.16)** Random effects modelling* **RR 2.01 (1.20, 3.36)** vs WWOE **RR 1.50 (1.03, 2.19)** vs WWE 4666 exposures	1.47% (95% CI 0.26 to 3.64) RR 0.61 (0.07, 5.18) vs WWOE RR 1.50 (1.16, 0.23, 5.93) vs WWE 190 exposures	2.31% (95% CI 1.87 to 2.78) RR 1.68 (0.78, 3.65) vs WWOE RR 1.07 (.064, 1.77) vs WWE 4195 exposures	1.77% (95% CI 0.98 to 2.79) RR 2.16 (0.76, 6.17) vs WWOE RR 0.32 (0.10, 1.07) vs WWE 817 exposures	2.39% (95% CI 0.85 to 4.68) RR 1.94 (0.53, 7.15) vs WWOE RR 2.75 (0.53, 14.43) vs WWE 238 exposures	7.10% (95% CI 5.36 to 9.08)) **RR 2.84 (1,57, 5.13)** vs WWOE RR 1.95 (0.97, 3.93) vs WWE 709 exposures	**5.38% (95% CI 4.22 to 6.67)** **6.26% (95% CI 4.37 to 8.47)** Random effects modelling **RR 2.38 (1.12, 5.03)** vs WWOE **RR 2.40 (1,42, 4.08)** vs WWE 1279 exposures	-	4.28% (95 % CI 2.65-6.29) **RR 3.69 (1.36, 10.07)** vs WWOE RR 1.99 (0.65, 6.08) vs WWE 473 exposures	9.09% (95% CI 8.02 to 10.23) 10.93% (95% CI 8.91 to 13.13) Random effects modelling* **RR 5.69 (3.33, 9.73)** vs WWOE **RR 3.13 (2.16, 4.54)** vs WWE 2565 exposures	0.28% (95% CI 0.25 to 2.39) RR 0.44 (0.02, 7.93) vs WWOE 90 exposures
Meador et al, 2008	4.62% (95% CI 3.48 to 5.76) CBZ mono 7.10% (95% CI 3.71 to 10.49) CBZ dual 8.57 (95% CI 1.99 to 15.16) CBZ poly 4411 mono 942 dual and 70 poly exposures	-	2.91% (95% CI 2.00 to 3.82) LMT mono 5.59% (95% CI 1.11 to 10.08) LMT dual 1337 mono and 599 dual exposures	-	-	4.91% (95% CI 3.22 to 6.59) PHB mono **9.19% (95% CI 5.88 to 12.50) PHB dual** **14.57% (95% CI 8.81 to 20.33) PHB poly** **945 PHB mono exposures**	7.36% (95% CI 3.60 to 11.11) PHT mono **11.47% (95% CI 6.65 to 16.30) PHT dual** **14.27% (95% CI 8.95 to 19.60) PHT poly** 1198 mono 720 dual and 276 poly exposures	-	-	**10.73% (95% CI 8.16 to 13.29) VPA mono** **9.79% (95% CI 7.57 to 12.02) VPA dual** **25.00% (95% CI 5.97 to 44.03) VPA poly** 2097 mono 694 dual and 20 poly exposures	-
Pregnancy Registries											
UK and Ireland Pregnancy Registry (UKEPR)											
UKEPR † Campbell et al, 2014	2.6% (95% CI 1.9 to 3.5) 1657 exposures		2.3% (95% CI 1.8 to 3.1) 2098 exposures							6.7% (95% CI 5.5 to 8.3) 1220 VPA exposures	

† UKEPR Morrow et al, 2006	2.2% (95% CI 1.4 to 3.4) 927 exposures	3.2% (95% CI 0.6 to 16.2) 31 exposures	3.2% (95% 2.1 to 4.9) 647 exposures	0.0% (95% CI 0.0 to 14.9) 26 exposures			3.7% (95% CI 1.3 to 10.2) 82 exposures		7.1% (95% CI 2.0-22.6) 28 exposures	6.2% (95% CI 4.6 to 8.2) 762 exposures	
† Hunt et al, 2008									4.8% (95% CI 5.6-14.1) 70 TPM mono exposures		
European Pregnancy Registry (EURAP)											
Tomson et al, 2018	**5.5% (95% CI 4.5 to 6.6)** 1957 exposures		2.9% (95% CI 2.3 to 3.7) 2154 exposures	2.8% (95% CI 1.7 to 4.5) 599 exposures	3.0% (95% CI 1.4 to 5.4) 333 exposures	**6.5% (95% CI 4.2 to 9.9)** 294 exposures	6.4% (95% CI 2.8 to 12.2) 125 exposures		3.90% (95% CI 1.5-8.4) 152 exposures	**10.3% (95% CI 8.8 to 12.0** 1381exposures	
North American Antiepileptic Drug Pregnancy Registry (NAAEDPR)											
Published on NAAEDPR website - 2019	2.9% (95% CI 2.0 to 4.0%) 1110 exposures	1.5% (95% CI 0.37 to 3.9) 207 exposures	2.3% (95% CI 1.7 to 2.9) 2179 exposures	2.3% (95% CI 1.5 to 3.4) 1029 exposures	1.9% (95 % CI 0.7 to 4.1%) 265 exposures	5.6% (95% CI 3.0 to 9.6%) 195 exposures	2.6% (95% CI 1.4 to 4.4) 431 exposures	-	5.1% (95% CI 3.4 to 7.4) 489 exposures	9.3% (95% CI 6.5 to 12.7%) 335 exposures	1.2% (95% CI 0.2 to 3.9%) 166 exposures
† Hernandez-Diaz et al, 2012	**3.0% (95% CI 2.1 to 4.2)** 1033 exposures	0.7% (95% 0.02 to 3.8) 145 exposures	2.0% (95% CI 1.4 to 2.8) 1562 exposures	2.4% (95% CI 1.2 to 4.3) 450 exposures	2.2% (95% CI 0.6 to 5.5) 182 exposures	**5.5% (95% CI 2.8 to 9.7)** 199 exposures	2.9% (95% CI 1.5 to 5.0) 416 exposures		**4.2% (95% CI 2.4 to 6.8)** 359 exposures	9.3% **(6.4 to 13.0** 323 exposures	0 malformations 90 exposures
Australian Pregnancy Registry (APR)											
Vajda et al, 2019	5.9% 409 exposures		4.9% 406 exposures	3.6% 139 exposures	5.3% 19 exposures		2.3% 44 exposures		1.9% 53 exposures	**14.8%** **290 exposures**	
† Vajda et al, 2014	5.5% 346 exposure		4.6% 307 exposures	2.4% 82 exposures	5.9% 17 exposures		2.4% 41 exposures		2.4% 42 exposures	**13.8%** **253 exposures**	
Prospective studies											
Patorno et al, 2017 Prospective cohort study								5.9% 477 exposures			
Petersen et al, 2017	3.29% (95% CI 1.66 to 5.82) 334 exposures		2.8% (95% CI 1.35 to 5.09) 357 exposures							6.55% (95% CI 3.71 to 10.57) 229 exposures	
Winterfeld et al, 2016 Prospective cohort study								9.6% 164 total 116 1st trimester (19 mono)			

† Veiby et al, 2014[4]	2.9% 685 exposures		3.4% 833 exposures	1.7% 118 exposures	1.8% 57 exposures	7.4% 27 exposures		3.3% 30 exposures	4.2% 48 exposures	6.3% **333 exposures**	
† Fujii et al, 2013		4.1% 223 exposures									
† Kallen et al, 2013	3.40% 1706 total and 1511 mono exposures	1.40% 143 total and 119 mono exposures	2.77% 1337 total and 1084 mono exposures	0.66% 151 total 57 mono exposures	6.90% 58 total and 40 mono exposures	7.14% 28 total and 17 mono exposures	6.94% 173 total and 140 mono exposures	1.56% 128 total and 111 mono exposures	**5.88% 102 total and 49 mono exposures**	**7.19% 862 total and 697 mono exposures**	14.28% 7 total and 3 mono exposures
† Kaaja et al, 2003	3.96% 363 exposures				11% 9 exposures	4.54% 5 exposures	3.3% 124 exposures			**6.35% 61 exposures**	

*Conducted due to significant variance
† These studies were included in the Weston et al, 2016 and/or the Veroniki et al, 2017a meta-analyses and therefore for the purposes of the public assessment report these data will not be presented separately.

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21.1.5.2. Effects on Cognitive function and risk of neurodevelopmental disorders for prioritised ASMs

3 **Effects on IQ/Cognitive effects**

IQ/ Cognitive Effects

	Carbamazepine	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Topiramate	Valproate
Meta-analyses								
Veroniki et al, 2017b Cognitive Developmental Delay	OR 2.07 (0.82, 5.48) N=238	OR 0.93 (0.09, 5.10) N=43	OR 3.42 (0.65, 16.40)	-	OR 1.36 (0.18, 7.02) N=12	OR 2.55 (0.72, 8.55) N=111	**OR 3.14 (0.45, 16.53)** **N=**	**OR 7.40 (3.00, 18.46)** **N=**
Bromley et al, 2014 IQ mean (SD) Verbal IQ (VIQ) Performance IQ (PIQ)	IQ MD -0.03 (95% CI –3.08 to 3.01) Vs WWOE N=150 MD 1.84 (95% CI -2.13 to 5.80) Vs WWE N=163 Vs general population controls VIQ MD -1.81 (95% CI -4.94 to 1.33 PIQ MD 1.27 (95% CI -1.55 to 4.09) N=136	IQ mean 105.56, SD 12.49 versus control mean 108.71, SD 10.20, P>0.05 N=41 Verbal IQ and Performance IQ also did not significantly differ to control population	-	-	86.2 (SD 11) vs WWOE 93 (SD 14.4) N=41	PHT (n=29) mean 90.3 (95% CI 77 to 103) vs WWE control (n=32) mean 92.3 (95% CI 81 to 103) NS* Cognitive dysfunction OR 1.37 (95% CI 0.38 to 5.0) PHT (n=12)	**mean 96.33 SD 10.37) Vs WWOE mean 111.39 (SD 12.20), P=0.005 N=9**	**MD-8.94 (-11.96, -5.92), P<0.00001, I^2=88% Vs WWOE N=76 MD-8.17 (-12.80, -3.55), P=0.005, I^2=27% Vs WWE VIQ MD-11.39 (-14.68, -8.10), P<0.00001, I^2=0% vs general population N=64 PIQ MD-10.48 (-13.94, -7.02), P<0.00001, I^2=68% N=64**
Banach et al, 2010 Wechsler Scale PIQ Bayley or McCarthy scale FSIQ	Wechsler scale Statistically significantly lower PIQ in CBZ (p<0.002) compared all control group; No statistically significant difference for either VIQ or FSIQ compared to all control group N=151 Bayley or McCarthy scales FSIQ no statistically significant different; CBZ vs control group (98 vs 102, p=0.3) N=83							

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Pregnancy Registries								
Gopinath et al. 2015 Wechsler scale Full Scale IQ Mean (SD)	CBZ mono (40) 82.2 (13.9) vs 80.2 (13.4); p=0.449 CBZ all (76) 77 (15.2) vs 78.5 (1.4); p=0.466	LMT mono (1) 89 vs 80.8 (13.6); p=0.551 LMT all (4) mean 71.3 (17.9) vs 78.1 (14.6); p=0.356			**PB mono (n=22)** **74.5 (14)** **vs** **82.5 (13);** **p=0.013** PB all (n=59) 73.5 (14.4) vs 80 (14.4); p=0.05	PHT mono (n=11) 82.6 (13.5) vs 80.7 (13.7); p=0.656 PHT all (n=39) 74.9 (14.8) vs 78.7 (14.5); p=0.153	-	VPA mono (36) 82.8 (12.4) vs 77 (15.3); p=0.190 VPA all (53) 80.2 (12.7) vs 77 (15.3); p=0.313
Huber-Mollema et a l2020 Wechsler Intelligence Scale Full-Scale IQ (FSIQ) Verbal IQ (VIQ) Performance IQ (PIQ) Processing Speed Index Mean (SD) Individual AED Vs VPA	FSIQ 105.3 (13.7) B 5.6 (SE 3.9) (95% -2.2 to 13.4), P=0.157 **VIQ** **106.2 (14.2)** **B 9.1 (SE 4.0) (95% 1.3 to 17.0), P=0.023** PIQ 102.8 (15.5) B 0.1 (SE 4.3) (95% -8.3 to 8.6), P=0.973 PSI 108.7 (12.1) B 5.1 (SE 4.2) (95% -3.3 to 13.5), P=0.229 N=32	**FSIQ** **109.2 (15.0)** **B 7.5 (SE 3.5) (95% 0.6 to 14.4), P=0.033** **VIQ** **109.7 (15.7)** **B 10.3 (SE 3.5) (95% 3.4 to 17.3), P=0.004** PIQ 106.0 (14.9) B 2.3 (SE 3.8) (95% -5.3 to 9.8), P=0.551 PSI 111.0 (14.4) B 6.3 (SE 3.8) (95% -1.1 to 13.7), P=0.097 N=82	FSIQ 110.8 (14.8) B 7.7 (SE 4.1) (95% --0.4 to 15.8), P=0.064 **VIQ** **114.0 (13.1)** **B 13.4 (SE 4.2) (95% 5.2 to 21.6), P=0.002** PIQ 104.4 (14.8) B -0.6 (SE 4.5) (95% -9.5 to 8.3), P=0.901 PSI 111.2 (16.2) B 4.9 (SE 4.4) (95% -3.9 to 3.6), P=0.275 N=25					FSIQ 103.2 (14.8) VIQ 100.6 (14.9) PIQ 105.3 (17.0) PSI 107.4 (18.6) N=22
Kerala Pregnancy Registry								
Thomas et al, 2007 Full Scale IQ (FSIQ-adaptation of Wechsler Intelligence Scale) Malayalam Language Test (MLT) – local proficiency test for language vs Age Matched Controls	FSIQ 83.6 (30.0); p=0.22 (all) 91.9 (21.7); p=0.86 (mono) MLT 71.5 (22.4); p=0.44 (all) 74.9 (21.0); p=0.87 (mono) N=28 (all) N=14 (mono)	-	-	-	FSIQ 84.9 (20.1); p=0.35 (all) **86.2 (11.0);** **p=0.07 (mono)** MLT 71.8 (14.9); p=0.47 (all) 70.6 (8.5); p=0.146 (mono) N=32 (all) N=14 (mono)	FSIQ 87.6 (19.0); p=0.96 (all) 97.8 (9.9) p=0.43 (mono) MLT 71.1 (15.7); p=0.51 (all) 76.0 (10.7); p=0.92 (mono) N=18 (all) N=5 (mono)	-	FSIQ 87.2 (29.8); p=0.90 (all) 98.5 (13.5); p=0.12 (mono) MLT 73.7 (21.1); p=0.95 (all) 81.5 (11.9); p=0.09 (mono) 19 VPA (all) 12 VPA (mono)

Prospective studies								
Cohen et al, 2019 Standardised mean of 6 years IQ (95% CI) Attention/concentration Verbal immediate Verbal delayed Delayed recognition Visual immediate Visual delayed Learning	**IQ** **106.2 (95% CI 103.1 to 109.3);** **Effect -5.4 (-10.4 to -0.4); p=0.0370** Attention/concentration 101.2 (96.8, 105.5) Effect -3.1 (-8.7, 2.6) Verbal immediate 103.2 (99.4, 107) Effect -1.6 (-6.5, 3.3) Verbal delayed 103.8 (99.5, 108.1) Effect 0 (-5.6, 5.5) Delayed recognition 101.5 (97.8, 105.2) Effect -3.8 (-8.6, 1) Visual immediate 98.6 (95, 102.1) Effect -3.1 (-7.7, 1.5) Visual delayed 103.4 (99.7, 107) Effect 0.2 (-4.5, 4.9) **Learning** **98.4 (94.6, 102.1)** **Effect-5.1 (-10, -0.3)** N=61	IQ 108.4 (95% CI 105.5 to 111.3); Effect -3.2 (-8.1 to -1.8); p=0.2111 **Attention/concentration** **98.2 (94.2, 102.3)** **Effect -6 (-11.5, -0.5)** Verbal immediate 103.1 (99.6, 106.7) Effect -1.7 (-6.5, 3.1) Verbal delayed 103.6 (99.6, 107.6) Effect -0.3 (-5.6, 5.1) Delayed recognition 103.1 (99.7, 106.6) Effect -2.2 (-6.8, 2.5) Visual immediate 100.6 (97.3, 103.9) Effect -1.1 (-5.6, 3.4) Visual delayed 105.3 (101.9, 108.7) Effect -2.2 (-2.4, 6.7) **Learning** **98 (94.5, 101.5)** **Effect-5.5 (-10.2, -0.8)** N=73	-	-	-	IQ 107.4 (95% CI 103.3 to 111.4); Effect -4.2 (-9.8 to 1.4); p=0.1467 Attention/concentration 98 (92.5, 103.6) Effect -6.2 (-12.7, 0.3) Verbal immediate 100.8 (96, 105.6) Effect -4 (-9.7, 1.6) Verbal delayed 99.1 (93.7, 104.5) Effect -4.8 (-11.1, 1.6) **Delayed recognition** **99.3 (94.6, 103.9)** **Effect -6 (-11.5, -0.5)** Visual immediate 97.3 (92.8, 101.8) Effect -4.4 (-9.7, 0.9) Visual delayed 99.4 (94.8, 104.1) Effect -3.7 (-9.1, 1.7) **Learning** **94.7 (89.9, 99.4)** **Effect-8.8 (-14.4, -3.3)** N=39	-	**IQ** **100.8 (95% CI 97.2 to 104.3);** **Effect -10.8 (-16 to -5.6);** **p<0.0001** **Attention/concentration** **94.1 (89.1, 99.1)** **Effect -10.2 (-16.3, -4.1)** **Verbal immediate** **94.5 (90, 98.9)** **Effect -10.4 (-15.8, -5.0)** **Verbal delayed** **92.2 (87.2, 97.3)** **Effect -11.6 (-17.7, -5.5)** **Delayed recognition** **90.4 (86, 94.7)** **Effect -14.9 (-20.2, -9.6)** **Visual immediate** **94.4 (90.3, 98.5)** **Effect -7.3 (-12.3, -2.2)** **Visual delayed** **95.2 (90.9, 99.4)** **Effect -8 (-13.2, -2.8)** **Learning** **90.2 (85.9, 94.6)** **Effect-13.3 (-18.6, -8)** **N=48**
Titze et al, 2008 Wechsler Adult Intelligence Scale (WAIS)					**adjusted total IQ: 98.0 SD11.9 versus control 105.4 SD11.0, p=0.037** **N=14 (3 mono)**			
Scolnik et al, 1994 Global IQ (Bayley or McCarthy Scale) Mean (SE) AED Vs Control	Global IQ 111.5 (19.7) Vs 114.9 (13.3) NS Reynell verbal comprehension 0.72 (1.4) Vs 1.05 (0.81) NS					**Global IQ** **103.1 (25.2)** **Vs 113.4 (13.1)** **Significant difference -10.6 (27.9)** **Reynell verbal comprehension** **0.2 (1.6)** **Vs 1.1 (0.95)** **Significant difference -0.47 (1.2)**		

Others								
Reinisch et al, 1995 Retrospective cohort study Denmark Wechsler Adult Intelligence Scale (WAIS) Verbal IQ (VIQ) Mean (SD) Danish Military Board Intelligence Test BPP scores (IBPP)	-	-	-	-	**WAIS** **VIQ 100.69 (14.94)** **Vs predicted 107.86 (6.38) equal to -7.17 (adjusted SE, 3.99; adjusted t, -1.79; df, 37; P<.04)** **IBPP** **mean difference -4.77; adjusted SE, 1.63; adjusted t, -2.92; df, 85; P<.002).**	-	-	- -
Hanson et al, 1976 WISC full scale IQ at 7 years Mean (SD)						**PHT** **91.7 (17.29)** **Vs** **Control** **96.83 (15.5); t=2,01, p<0.05** **N=83**		
Rihtman et al Israeli Teratogen Information Service IQ tests							Fluid reasoning (p=0.005) Quantitative reasoning (p=0.002) Visual-spatial (p=0.003) Verbal IQ (p=0.017), non-verbal IQ (=0.011) General IQ (p=0.005) 9 TPM exposures	

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IQ/ Cognitive Effects								
	Carbamazepine	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbital**	**Phenytoin**	**Topiramate**	**Valproate**
Meta-analyses								
Veroniki et al, 2017b Cognitive Developmental Delay	OR 2.07 (0.82, 5.48) N=238	OR 0.93 (0.09, 5.10) N=43	OR 3.42 (0.65, 16.40)	-	OR 1.36 (0.18, 7.02) N=12	OR 2.55 (0.72, 8.55) N=111	**OR 3.14 (0.45, 16.53)** **N=**	**OR 7.40 (3.00, 18.46)** **N=**
Bromley et al, 2014 IQ mean (SD) Verbal IQ (VIQ) Performance IQ (PIQ)	IQ MD -0.03 (95% CI –3.08 to 3.01) Vs WWOE N=150 MD 1.84 (95% CI -2.13 to 5.80) Vs WWE N=163 Vs general population controls VIQ MD -1.81 (95% CI -4.94 to 1.33 PIQ MD 1.27 (95% CI -1.55 to 4.09) N=136	IQ mean 105.56, SD 12.49 versus control mean 108.71, SD 10.20, P>0.05 N=41 Verbal IQ and Performance IQ also did not significantly differ to control population	-	-	86.2 (SD 11) vs WWOE 93 (SD 14.4) N=41	PHT (n=29) mean 90.3 (95% CI 77 to 103) vs WWE control (n=32) mean 92.3 (95% CI 81 to 103) NS* Cognitive dysfunction OR 1.37 (95% CI 0.38 to 5.0) PHT (n=12)	**mean 96.33 SD 10.37) Vs WWOE mean 111.39 (SD 12.20), P=0.005 N=9**	**MD-8.94 (-11.96, -5.92), P<0.00001, I^2=88% Vs WWOE N=76 MD-8.17 (-12.80, -3.55), P=0.005, I^2=27% Vs WWE VIQ MD-11.39 (-14.68, -8.10), P<0.00001, I^2=0% vs general population N=64 PIQ MD-10.48 (-13.94, -7.02), P<0.00001, I^2=68% N=64**
Banach et al, 2010 Wechsler Scale PIQ Bayley or McCarthy scale FSIQ	Wechsler scale Statistically significantly lower PIQ in CBZ (p<0.002) compared all control group; No statistically significant difference for either VIQ or FSIQ compared to all control group N=151 Bayley or McCarthy scales FSIQ no statistically significant different; CBZ vs control group (98 vs 102, p=0.3) N=83							

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Pregnancy Registries								
Gopinath et al. 2015 Wechsler scale Full Scale IQ Mean (SD)	CBZ mono (40) 82.2 (13.9) vs 80.2 (13.4); p=0.449 CBZ all (76) 77 (15.2) vs 78.5 (1.4); p=0.466	LMT mono (1) 89 vs 80.8 (13.6); p=0.551 LMT all (4) mean 71.3 (17.9) vs 78.1 (14.6); p=0.356			**PB mono (n=22)** **74.5 (14)** **vs** **82.5 (13);** **p=0.013** PB all (n=59) 73.5 (14.4) vs 80 (14.4); p=0.05	PHT mono (n=11) 82.6 (13.5) vs 80.7 (13.7); p=0.656 PHT all (n=39) 74.9 (14.8) vs 78.7 (14.5); p=0.153	-	VPA mono (36) 82.8 (12.4) vs 77 (15.3); p=0.190 VPA all (53) 80.2 (12.7) vs 77 (15.3); p=0.313
Huber-Mollema et a l2020 Wechsler Intelligence Scale Full-Scale IQ (FSIQ) Verbal IQ (VIQ) Performance IQ (PIQ) Processing Speed Index Mean (SD) Individual AED Vs VPA	FSIQ 105.3 (13.7) B 5.6 (SE 3.9) (95% -2.2 to 13.4), P=0.157 **VIQ** **106.2 (14.2)** **B 9.1 (SE 4.0) (95% 1.3 to 17.0), P=0.023** PIQ 102.8 (15.5) B 0.1 (SE 4.3) (95% -8.3 to 8.6), P=0.973 PSI 108.7 (12.1) B 5.1 (SE 4.2) (95% -3.3 to 13.5), P=0.229 N=32	**FSIQ** **109.2 (15.0)** **B 7.5 (SE 3.5) (95% 0.6 to 14.4), P=0.033** **VIQ** **109.7 (15.7)** **B 10.3 (SE 3.5) (95% 3.4 to 17.3), P=0.004** PIQ 106.0 (14.9) B 2.3 (SE 3.8) (95% -5.3 to 9.8), P=0.551 PSI 111.0 (14.4) B 6.3 (SE 3.8) (95% -1.1 to 13.7), P=0.097 N=82	FSIQ 110.8 (14.8) B 7.7 (SE 4.1) (95% --0.4 to 15.8), P=0.064 **VIQ** **114.0 (13.1)** **B 13.4 (SE 4.2) (95% 5.2 to 21.6), P=0.002** PIQ 104.4 (14.8) B -0.6 (SE 4.5) (95% -9.5 to 8.3), P=0.901 PSI 111.2 (16.2) B 4.9 (SE 4.4) (95% -3.9 to 3.6), P=0.275 N=25					FSIQ 103.2 (14.8) VIQ 100.6 (14.9) PIQ 105.3 (17.0) PSI 107.4 (18.6) N=22
Kerala Pregnancy Registry								
Thomas et al, 2007 Full Scale IQ (FSIQ-adaptation of Wechsler Intelligence Scale) Malayalam Language Test (MLT) – local proficiency test for language vs Age Matched Controls	FSIQ 83.6 (30.0); p=0.22 (all) 91.9 (21.7); p=0.86 (mono) MLT 71.5 (22.4); p=0.44 (all) 74.9 (21.0); p=0.87 (mono) N=28 (all) N=14 (mono)	-	-	-	FSIQ 84.9 (20.1); p=0.35 (all) **86.2 (11.0);** **p=0.07 (mono)** MLT 71.8 (14.9); p=0.47 (all) 70.6 (8.5); p=0.146 (mono) N=32 (all) N=14 (mono)	FSIQ 87.6 (19.0); p=0.96 (all) 97.8 (9.9) p=0.43 (mono) MLT 71.1 (15.7); p=0.51 (all) 76.0 (10.7); p=0.92 (mono) N=18 (all) N=5 (mono)	-	FSIQ 87.2 (29.8); p=0.90 (all) 98.5 (13.5); p=0.12 (mono) MLT 73.7 (21.1); p=0.95 (all) 81.5 (11.9); p=0.09 (mono) 19 VPA (all) 12 VPA (mono)

Prospective studies								
Cohen et al, 2019 Standardised mean of 6 years IQ (95% CI) Attention/concentration Verbal immediate Verbal delayed Delayed recognition Visual immediate Visual delayed Learning	**IQ** **106.2 (95% CI 103.1 to 109.3);** **Effect -5.4 (-10.4 to -0.4); p=0.0370** Attention/concentration 101.2 (96.8, 105.5) Effect -3.1 (-8.7, 2.6) Verbal immediate 103.2 (99.4, 107) Effect -1.6 (-6.5, 3.3) Verbal delayed 103.8 (99.5, 108.1) Effect 0 (-5.6, 5.5) Delayed recognition 101.5 (97.8, 105.2) Effect -3.8 (-8.6, 1) Visual immediate 98.6 (95, 102.1) Effect -3.1 (-7.7, 1.5) Visual delayed 103.4 (99.7, 107) Effect 0.2 (-4.5, 4.9) **Learning** **98.4 (94.6, 102.1)** **Effect-5.1 (-10, -0.3)** N=61	IQ 108.4 (95% CI 105.5 to 111.3); Effect -3.2 (-8.1 to -1.8); p=0.2111 **Attention/concentration** **98.2 (94.2, 102.3)** **Effect -6 (-11.5, -0.5)** Verbal immediate 103.1 (99.6, 106.7) Effect -1.7 (-6.5, 3.1) Verbal delayed 103.6 (99.6, 107.6) Effect -0.3 (-5.6, 5.1) Delayed recognition 103.1 (99.7, 106.6) Effect -2.2 (-6.8, 2.5) Visual immediate 100.6 (97.3, 103.9) Effect -1.1 (-5.6, 3.4) Visual delayed 105.3 (101.9, 108.7) Effect -2.2 (-2.4, 6.7) **Learning** **98 (94.5, 101.5)** **Effect-5.5 (-10.2, -0.8)** N=73	-	-	-	IQ 107.4 (95% CI 103.3 to 111.4); Effect -4.2 (-9.8 to 1.4); p=0.1467 Attention/concentration 98 (92.5, 103.6) Effect -6.2 (-12.7, 0.3) Verbal immediate 100.8 (96, 105.6) Effect -4 (-9.7, 1.6) Verbal delayed 99.1 (93.7, 104.5) Effect -4.8 (-11.1, 1.6) **Delayed recognition** **99.3 (94.6, 103.9)** **Effect -6 (-11.5, -0.5)** Visual immediate 97.3 (92.8, 101.8) Effect -4.4 (-9.7, 0.9) Visual delayed 99.4 (94.8, 104.1) Effect -3.7 (-9.1, 1.7) **Learning** **94.7 (89.9, 99.4)** **Effect-8.8 (-14.4, -3.3)** N=39	-	**IQ** **100.8 (95% CI 97.2 to 104.3);** **Effect -10.8 (-16 to -5.6); p<0.0001** **Attention/concentration** **94.1 (89.1, 99.1)** **Effect -10.2 (-16.3, -4.1)** **Verbal immediate** **94.5 (90, 98.9)** **Effect -10.4 (-15.8, -5.0)** **Verbal delayed** **92.2 (87.2, 97.3)** **Effect -11.6 (-17.7, -5.5)** **Delayed recognition** **90.4 (86, 94.7)** **Effect -14.9 (-20.2, -9.6)** **Visual immediate** **94.4 (90.3, 98.5)** **Effect -7.3 (-12.3, -2.2)** **Visual delayed** **95.2 (90.9, 99.4)** **Effect -8 (-13.2, -2.8)** **Learning** **90.2 (85.9, 94.6)** **Effect-13.3 (-18.6, -8)** **N=48**
Titze et al, 2008 Wechsler Adult Intelligence Scale (WAIS)					**adjusted total IQ: 98.0 SD11.9 versus control 105.4 SD11.0, p=0.037** **N=14 (3 mono)**			

Scolnik et al, 1994 Global IQ (Bayley or McCarthy Scale) Mean (SE) AED Vs Control	Global IQ 111.5 (19.7) Vs 114.9 (13.3) NS Reynell verbal comprehension 0.72 (1.4) Vs 1.05 (0.81) NS					**Global IQ** **103.1 (25.2)** **Vs 113.4 (13.1)** **Significant difference** **-10.6 (27.9)** **Reynell verbal comprehension** **0.2 (1.6)** **Vs 1.1 (0.95)** **Significant difference** **-0.47 (1.2)**		
Others								
Reinisch et al, 1995 Retrospective cohort study Denmark Wechsler Adult Intelligence Scale (WAIS) Verbal IQ (VIQ) Mean (SD) Danish Military Board Intelligence Test BPP scores (IBPP)	-	-	-	-	**WAIS** **VIQ 100.69 (14.94)** **Vs predicted 107.86 (6.38) equal to -7.17 (adjusted SE, 3.99; adjusted t, -1.79; df, 37; P<.04)** **IBPP** **mean difference -4.77; adjusted SE, 1.63; adjusted t, -2.92; df, 85; P<.002).**	-	-	- -
Hanson et al, 1976 WISC full scale IQ at 7 years Mean (SD)						**PHT** **91.7 (17.29)** **Vs** **Control** **96.83 (15.5); t=2,01, p<0.05** **N=83**		
Rihtman et al Israeli Teratogen Information Service IQ tests							Fluid reasoning (p=0.005) Quantitative reasoning (p=0.002) Visual-spatial (p=0.003) Verbal IQ (p=0.017), non-verbal IQ (=0.011) General IQ (p=0.005) 9 TPM exposures	

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21.1.5.3. Effects on Developmental Quotient (DQ)

DQ/ Effects on development							
	Carbamazepine	Lamotrigine	Levetiracetam	Phenobarbital	Phenytoin	Topiramate	Valproate
Meta-analyses							
Veroniki et al, 2017b Language Delay (LD) Psychomotor developmental delay (PDD)	LD OR 4.32 (0.81, 26.93) N=117 PDD OR 1.68 (0.85, 3.41) N=249	LD OR 4.36 (0.68,25.41) N=59 PDD OR1.86 (0.72, 4.76) N=745	PDD OR 0.27 (0.00,4.26)	LD OR 1.06 (0.22,5.08) N=41 PDD OR 0.96 (0.39, 2.29) N=117	PDD OR 2.84 (0.97,7.93) N=83	PDD OR 3.89 (0.41,24.27) N=	**LD** **OR 7.95 (1.50,49.13)** **N=** **PDD** **OR 4.16 (2.04, 8.75)** **N=**
Bromley et 2014 DQ Mean	DQ **MD -5.58 (95% CI -10.83 to -0.34) Vs WWOE** **N=50** **MD -7.22 (95% CI -12.76 to -1.67 Vs WWE** **N=163**	Mean 99 (95% CI 94 to 103) vs general population mean 98.8 (95% CI 96 to 102); P=0.62 N=51	Mean 99.9 (95% CI 97 to 103,) vs WWOE mean 100 (95% CI 99 to 102); P=0.21 N=34 Mean 99 (95% CI 94 to 103,) vs WWE mean 104 (95% CI 101 to 108); P=0.21 N=34	mean 115 (SD not reported) vs general population mean 119 (SD not reported) P=0.372 Mean 90.3 (94, 97) Vs WWE Mean 92.3 (81, 103) N=41	MD -0.12 (95% CI -7.54 to 7.30, P=0.98) vs general population N=20 Mean 90.3 (77, 103) Vs WWE Mean 92.3 (81,103) N=29 Motor development PHT (n=15) mean 98 versus control mean 106 (CIs unclear)	-	**mean 92 (87, 96)** **Vs WWOE** **mean 100 (99, 102);** **P<0.001** **N=42** **Bayley Scales** **MD -8.72 (-14.31, -3.31),** **P=0.002, I^2=0%** **N=123** **Griffiths Mental Development Scale** **mean 92 (87, 96)** **Vs WWE** **mean 104 (101, 108)**
Pregnancy Registries							
Cummings et al, 2011 Bayley Scale of Infant Development Griffiths Mental Development Scale	20.4% evidence of mild or significant developmental delay **CBZ vs control** **Adjusted OR 7.7 (95% 1.4 to 43.1); p<0.01** 49 exposures	2.9% evidence of mild or significant developmental delay LMT vs control Adjusted OR 1.1 (95% 0.1 to 13.7); p<0.01 35 exposure					39.6% evidence of mild or significant developmental delay **VPA vs control** **Adjusted OR 26.1 (95% 4.9 to 139); p<0.001** **58 exposures**

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Shallcross et al, 2011 Griffiths Mental Development Scale Mean (95% CI) Overall DQ Locomotor Personal and Social Hearing and Language Hand and Eye Coordination Performance Overall DQ OR AED vs Control			Overall DQ 99.96 (95% CI 97.16 to 102.76) Locomotor 97.35 (95% CI 93.66 to 98.29) Personal and Social 98.00 (95% CI 93.73 to 102.27) Hearing and Language 100.57 (95% CI 96.89 to 104.24) Hand and Eye Coordination 101.88 (95% CI 97.46 to 106.30) Performance 101.75 (95% CI 98.02 to 105.47) N=51				**Overall DQ** **87.63 (95% CI 82.68 to 93.18)** Locomotor 84.66 (95% CI 78.72 to 90.59) Personal and Social 89.82 (95% CI 83.62 to 96.02) Hearing and Language 90.48 (95% CI 84.29 to 96.66) **Hand and Eye Coordination** **88.21 (95% CI 82.07 to 94.35)** **Performance** **88.88 (95% CI 83.29 to 94.48)**
Birth Registers							
Wide et al, 2002 Griffiths Mental Development Scale Mean (95% CI for the differences of mean score) Total Score Locomotor function Personal and Social Hearing and Language Hand and Eye Coordination Performance Overall DQ	Locomotor function 104 (95% CI -5.1 to 4.7) Personal and Social behaviour 107 (-3.4 to 3.3) Hearing and Speech 105 (-9.6 to 6.7) Hand and Eye Coordination 100 (-6.1 to 3.5) Performance 105 (-8.0 to 2.5) Practical reasoning 101 (-11.1 to 3.1) Total Score 618 (-34.7 to 11.8) N=35				**Locomotor** **98 (95% CI -14.0 to -0.4)** Personal and Social Behaviour 105 (95% CI -8.2 to 2.5) Hearing and speech 111 (95% CI -11.9 to 10.4) Hand and Eye Coordination 101 (95% CI -7.8 to 5.4) Performance 110 (95% CI -8.4 to 11.2) Practical reasoning 97 (-23.0 to 3.5) Total Score 612 (-66.8 to 19.7) N=15	-	

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Prospective studies							
Cohen et al, 2019 Standardised mean of 6 years IQ (95% CI)	**IQ** **106.2 (95% CI 103.1 to 109.3);** **Effect -5.4 (-10.4 to -0.4); p=0.0370** Attention/concentration 101.2 (96.8, 105.5) Effect -3.1 (-8.7, 2.6) Verbal immediate 103.2 (99.4, 107) Effect -1.6 (-6.5, 3.3) Verbal delayed 103.8 (99.5, 108.1) Effect 0 (-5.6, 5.5) Delayed recognition 101.5 (97.8, 105.2) Effect -3.8 (-8.6, 1)	IQ 108.4 (95% CI 105.5 to 111.3); Effect -3.2 (-8.1 to -1.8); p=0.2111 **Attention/concentration** **98.2 (94.2, 102.3)** **Effect -6 (-11.5, -0.5)** Verbal immediate 103.1 (99.6, 106.7) Effect -1.7 (-6.5, 3.1) Verbal delayed 103.6 (99.6, 107.6) Effect -0.3 (-5.6, 5.1) Delayed recognition 103.1 (99.7, 106.6) Effect -2.2 (-6.8, 2.5)	-	-	IQ 107.4 (95% CI 103.3 to 111.4); Effect -4.2 (-9.8 to 1.4); p=0.1467 Attention/concentration 98 (92.5, 103.6) Effect -6.2 (-12.7, 0.3) Verbal immediate 100.8 (96, 105.6) Effect -4 (-9.7, 1.6) Verbal delayed 99.1 (93.7, 104.5) Effect -4.8 (-11.1, 1.6) **Delayed recognition** **99.3 (94.6, 103.9)** **Effect -6 (-11.5, -0.5)**	-	**IQ** **100.8 (95% CI 97.2 to 104.3);** **Effect -10.8 (-16 to -5.6);** **p<0.0001** **Attention/concentration** **94.1 (89.1, 99.1)** **Effect -10.2 (-16.3, -4.1)** **Verbal immediate** **94.5 (90, 98.9)** **Effect -10.4 (-15.8, -5.0)** **Verbal delayed** **92.2 (87.2, 97.3)** **Effect -11.6 (-17.7, -5.5)** **Delayed recognition** **90.4 (86, 94.7)** **Effect -14.9 (-20.2, -9.6)**
	Visual immediate 98.6 (95, 102.1) Effect -3.1 (-7.7, 1.5) Visual delayed 103.4 (99.7, 107) Effect 0.2 (-4.5, 4.9) **Learning** **98.4 (94.6, 102.1)** **Effect-5.1 (-10, -0.3)** N=61	Visual immediate 100.6 (97.3, 103.9) Effect -1.1 (-5.6, 3.4) Visual delayed 105.3 (101.9, 108.7) Effect -2.2 (-2.4, 6.7) **Learning** **98 (94.5, 101.5)** **Effect-5.5 (-10.2, -0.8)** N=73			Visual immediate 97.3 (92.8, 101.8) Effect -4.4 (-9.7, 0.9) Visual delayed 99.4 (94.8, 104.1) Effect -3.7 (-9.1, 1.7) **Learning** **94.7 (89.9, 99.4)** **Effect-8.8 (-14.4, -3.3)** N=39		**Visual immediate** **94.4 (90.3, 98.5)** **Effect -7.3 (-12.3, -2.2)** **Visual delayed** **95.2 (90.9, 99.4)** **Effect -8 (-13.2, -2.8)** **Learning** **90.2 (85.9, 94.6)** **Effect-13.3 (-18.6, -8)** **N=48**
Dean et al, 2002 Developmental delay (DD) Behaviour disorder (BD) N(%)	**DD 15 (22%);** **p<0.05** **BD 10 (14.5%);** **p<0.05** **N=70**	-	-	DD 6 (10%) BD 4 (6.6%) N=25	**DD 8 (33%);** **p<0.05** BD 1 (4.2%) **N=25**		**DD 13 (28%);** **p<0.05** **BD 5 (10.9%);** **p<0.05** **N=47**

Others							
Shankaran et al, 2001 Antenatal exposure to PHB or placebo between 24 to 32 weeks Bayley Scale of development In infant at 18-22 months Mental Development Index (MDI) Psychomotor Development Index (PDI) median (range)				MDI PHB 85 (49-124) Vs Placebo 86 (49-129) PDI PHB 91 (49-121) Vs Placebo 91 (49-134) N=344			

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21.1.5.4. ASD and ADHD

Autistic disorders and Attention Deficit Hyperactivity disorder							
	Carbamazepine	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbital**	**Phenytoin**	**Valproate**
Meta-analyses							
Veroniki et al, 2017b Autism/dyspraxia (A/D) ADHD Vs WWE (untreated)	A/D OR 5.76 (95% CI 0.76 to 73.43) N=182 ADHD OR 2.32 (95% CI 0. 70 to 7.86) N=182	**A/D** **OR 8.88** **(95% CI 1.28 to 112.00)** **N=126** ADHD OR 1.63 (95% CI 0.41 to 6.06) N=105	A/D OR 3.64 (95% CI 0.00 to 222.30) LEV mono	**A/D** **OR 13.51** **(95% CI 1.28 to 221.40)** **OXC mono N=321**	ADHD OR 1.29 (95% CI 0.25,6.21) N=61	A/D OR 7.09 (95% CI 0.02 to 397.70) N=83 ADHD OR 0.63 (95% CI 0.07 to 4.07 N=41	**A/D** **OR 17.29** **(95% CI 2.40 to 217.60)** ADHD OR 2.84 (95% CI 0.82 to 9.99)
Bromley et al, 2014 ASD	Autistic traits (parental rating) OR 3.3 (0.5, 24.8 18 months) OR 2.5 (0.3, 19.1) 36 months N=41	Autistic traits (parental rating) OR 1.5 (0.2, 11.0) 18 months) **OR 5.0 (1.7, 14.4) 36 months** **N=154**	-	**-**	-	-	Autistic traits (parental rating) VPA 0% vs 0.5% control 18 months OR 3.7 (0.5, 28.4) 36 months N=19
Pregnancy Registries							
APR							
Wood et al, 2016 Autism traits (assessed using Childhood Autism Rating Scale)	Elevated CARs score 5.9% N=34	-	-	-			Elevated CARs score 7.7% N=26 (mono) **46.7%** **N=15 (poly)**
Huber-Mollema et a 2019 ASD ADHD diagnosis vs population norms	ADHD 2.8% vs 4.3% p=0.653; ASD 0% vs 1.5% p=0.453 N=37	ADHD 5.7% vs 4.3% p=0.529; **ASD 4.6% vs 1.5% p=0.02** N=88	ADHD 7.1% vs 4.3% p=0.897; ASD 3.6% vs 1.5% p=0.352 N=30				ADHD 3.8% vs 4.3%; p=0.897; **ASD 7.1% vs 1.5%; p<0.01** **N=26**

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Birth Registers							
Veiby et al, 2013 Risk at 36 months Autistic traits (Social Communication Questionnaire) ADHD symptoms Vs children born to WWOE	Autistic traits 3.4% Vs 1.5% OR 2.5 (95% CI 0.3 to 19.1) ADHD symptoms 6.5% Vs 4.0% OR 2.0 (95% CI 0.5 to 8.6) N=31	**Autistic traits** **9.3% Vs 1.5%** **OR 5.0 (95% CI 1.7 to 14.4)** ADHD symptoms 7.0% Vs 4.0% OR 1.5 (95% CI 0.4 to 4.8) N=44	-	-	-	-	Autistic traits 5.6% Vs 1.5% OR 3.7 (95% CI 0.5 to 28.4) ADHD symptoms 5.6% Vs 4.0% OR 1.3 (95% CI 0.2 to 9.9) N=19
Others							
Christensen et al, 2019 ADHD Diagnosis Vs unexposed	7.33% 5.6 (95% CI 3.9 to 7.9) Incidence/1000 PYs aHR 1.23 (95% 0.84 to 1.82) N=423	2.96% 3.4 (95% CI 2.5 to 4.6) Incidence/1000 PYs aHR 0.84 (95% 0.59 to 1.19) N=1383		6.72% 5.5 (95% CI 3.7 to 8.1) Incidence/1000 PYs aHR 1.10 (95% 0.72 to 1.67) N=372			**8.82%** **7.2 (95% CI 5.2 to 9.8)** **Incidence/1000 PYs** **aHR 1.52 (95% 1.05 to 2.19)** **N=431**
Christensen et al, 2013 Autism Spectrum disorder (ASD) Childhood Autism Vs unexposed	ASD 1.04% aHR 1.0 (95% CI 0.4 to 2.8) Childhood Autism 0.52% aHR 1.4 (95% CI 0.4 to 2.8) N=386	- ASD 1.23% aHR 1.7 (95% CI 0.5 to 5.2) Childhood Autism 0.62% aHR 1.7 (95% CI 0.8 to 3.5) N=647	-	ASD 2.18% aHR 2.1 (95% CI 0.96 to 4.6) Childhood Autism 0.31% aHR 1.0 (95% CI 0.1 to 6.9) N=321	-	-	**ASD** **3.09%** **aHR 3.0 (95% CI 1.7 to 5.4)** **Childhood Autism** **1.80%** **aHR 4.9 (95% CI 2.3 to 10.3)** **N=388**

11.1.5.5. Other neurodevelopmental effects

	Carbamazepine	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Topiramate	Valproate
Pregnancy Registries									
Deshmukh et al, 2016 Vineland-II Adaptive Behaviour Scale Frequency of low and moderately low adaptive levels (%): Overall ABC domain Communication Daily Living Skills Socialization Motor Skills	ABC 5.1% CBZ vs LMT OR 1.46 (95% CI 0.24 to 9.03) **CBZ vs VPA** **OR 0.16** **(95% CI 0.03 to 0.92)** Communication 10.2% CBZ vs LMT OR 2.91 (95% CI 0.64 to 13.21) CBZ vs VPA OR 0.68 (95% CI 0.15 to 3.05) Daily Living Skills 5.1% CBZ vs LMT OR 0.64 (95% CI 0.15 to 2.75) CBZ vs VPA OR 0.48 (95% CI 0.09 to 2.66) **Socialization** 5.1% CBZ vs LMT OR 1.54 (95% CI 0.18 to 13.15) **CBZ vs VPA** **OR 0.15** **(95% CI 0.02 to 1.00)** **Motor Skills** 8.2% CBZ vs LMT OR 0.81 (95% CI 0.19 to 3.41) **CBZ vs VPA** **OR 0.20** **(95% CI 0.05 to 0.82)** N=97	-	ABC 2.9% **LMT vs VPA** **OR 0.11** **(95% CI 0.02-0.74)** Communication 7.7% LMT vs VPA OR 0.23 (95% CI 0.04-1.27) **Socialization** **4.8%** **LMT vs VPA** **OR 0.10** **(95% CI 0.01-0.89)** **Motor Skills** **7.7%** **LTG vs VPA** **OR 0.09** **(95% CI 0.02-0.50)** N=104	-	-				

Birth Registers									
Husebye et al. 2020 Prospective cohort study using data from the Norwegian Mother and Child Cohort Study Language impairment at 5 years Language impairment at 8 years AED-exposed children of WWE vs Children of women without epilepsy	Language impairment at 5 years aOR 1.9 (95% CI 0.6-5.6) **Language impairment at 8 years** **aOR 3.8 (95% CI 1.6-9.0)** N=23	-	Language impairment at 5 years aOR 1.0 (95% CI 0.5-2.3) Language impairment at 8 years aOR 1.2 (95% CI 0.6-2.6) N=41	Language impairment at 5 years aOR 1.0 (95% CI 0.2-5.3) Language impairment at 8 years aOR 0.7 (95% CI 0.1-6.0) N=6	-	-	-	Language impairment at 5 years aOR 5.8 (95% CI 0.5-64.0) Language impairment at 8 years aOR 1.1 (95% CI 0.1-10.9) N=4	Language impairment at 5 years aOR 2.2 (95% CI 0.7-7.0) Language impairment at 8 years aOR 2.2 (95% CI 0.7-6.4) N=16
Bech et al, 2018 Learning disabilities in 1st year of compulsory education Vs unexposed controls Or Vs AED exposed	cf Unexposed controls aOR 1.74 (95% CI 0.19 to 16.05) cf AED exposed aOR 0.46 (95% CI 0.06 to 3.79) N=35	cf Unexposed controls aOR 1.22 (95% CI 0.14 to 10.52) cf AED exposed aOR 0.31 (95% CI 0.04 to 2.58) N=29	cf Unexposed aOR 1.81 (95% CI 0.74 to 4.41) cf AED exposed aOR 0.42 (95% CI 0.19 to 0.92) LMT mono 290 exposures	**cf Unexposed aOR 13.17 (95% CI 1.581 to 109.99)** cf AED exposed aOR 5.45 (95% CI 0.78 to 38.02) N=12	cf Unexposed aOR 2.34 (95% CI 0.50 to 10.82) cf AED exposed aOR 0.88 (95% CI 0.24 to 3.27) N=44	**cf Unexposed aOR 57.36 (95% CI 4.63 to 710.21)** **cf AED exposed aOR 12.61 (95% CI 1.98 to 80.15)** N=11		**cf Unexposed aOR 5.82 (95% CI 1.21 to 27.97)** cf AED exposed aOR 2.57 (95% CI 0.67 to 9.89) N=27	**cf Unexposed aOR 5.31 (95% CI 2.03 to 13.93)** **cf AED exposed aOR 4.67 (95% CI 1.73 to 12.59)** **N=55**
Forsberg et al, 2011 Children's School Grade OR Not Passing Exams AED exposed versus	Maths OR 1.60 (95% CI 0.99-2.56) English OR 1.31 (95% CI 0.78-2.18) Swedish OR 1.32 (95% CI 0.81-2.17) Sport						Maths OR1.13 (95%CI 0.81-1.54) English OR1.16 (95%CI 0.81-1.66) Swedish OR1.17 (0.81-1.69) Sport OR 1.00 (95%CI 0.68-1.47)		

Other children born in the same period	OR 1.50 (95% CI 0.93-2.44) N=243						N=316		
Others									
Elkjaer et al, 2018 Performance in national tests Difference in standardised z scores AED vs No AED exposure	Danish 2nd grade -0.01 (-0.05 to 0.03) 4th grade -0.02 (-0.05 to 0.01) 6th grade -0.02 (-0.05 to 0.01) 8th grade -0.03 (-0.07 to 0.01) Mathematics 3rd grade -0.04 (-0.08 to 0.01) **6th grade -0.04 (-0.07 to -0.01)** N=294	-	- Danish 2nd grade -0.01 (-0.02 to 0.01) 4th grade 0.00 (-0.02 to 0.02) 6th grade 0.01 (-0.02 to 0.04) 8th grade 0.02 (-0.03 to 0.07 Mathematics 3rd grade 0.00 (-0.02 to 0.02) 6th grade 0.01 (-0.01 to 0.04) N=396		Danish 2nd grade -0.01 (-0.04 to 0.02) 4th grade -0.01 (-0.04 to 0.02) 6th grade -0.01 (-0.04 to 0.02) 8th grade -0.02 (-0.07 to 0.03) Mathematics 3rd grade -0.01 (-0.04 to 0.02) 6th grade -0.03 (-0.06 to 0.00) N=123				

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21.1.5.6. Other Reproductive Toxic Effects for prioritised ASMs

3 **Fetal loss**

Fetal Loss											
	Carbamazepine	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Pregabalin	Topiramate	Valproate	Zonisamide
Meta-analyses											
Veroniki et al, 2017a	OR 1.25 (0.73,2.36) N=3911	-	OR 1.38 (0.70,2.88) N=2540	OR 2.47 (0.50,10.15) N=28	OR 1.66 (0.50,4.50) N=567	OR 0.90 (0.44,1.93) N=407	OR 1.50 (0.85,2.91) N=618	-	**OR 23.58 (1.18,549.60)** **N=2**	**OR 1.83 (1.04,3.45)** N=2612	-
Pregnancy Registries											
Vajda et al, 2018 Vs WWE unexposed	**4.7%** N=404	-	3.67% N=382	1.55% N=129	5.26% N=19	-	2.38% N=42	-	1.96% N=51	3.17% N=284	-
Kerala Pregnancy Registry											
Trivedi et al, 2018 vs WWE unexposed	**5.8%** **N=465**	-	**8.3%** **N=48**	6.4% N=63	**8.9%** **N=56**	3.6% N=138	7.8% N=129	-	**45.4%** **N=11**	**7.1%** **N=322**	-
Birth Registers											
Bech et al, 2014 Vs WWE unexposed	14.4% N=409	-	13.6% N=1128	-	15.0% N=413	-	-	-	-	**15.8%*** **N=474**	
ǂArtama et al, 2013 Finland Vs WWOE (no AED exposure)	**11.6 (all)** **9.2 (mono)** **24.0 (poly)** N=1292 (all) 1084 (mono)	-	No cases	No cases	11.5 (all) **13.2 (mono)** 6.1 (poly) N=695 (all) 532 (mono)	-	No cases	-	-	10.6 (all) 9.9 (mono) 1.3 (poly) N=944 (all) 706 (mono)	-
Fujii et al, 2013		9.8% N=223 (71epilepsy)									
Others											
Winterfeld et al, 2016 Vs unexposed								15.1% N=139			
ǂOrnoy et al, 2008 Vs non-teratogen exposed women	-	-	-	-	-	-	-	-	**11.3%** N=52		

4 * Increased risk driven by high dose VPA (>750mg/.day)

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Preterm birth

Preterm Birth											
	Carbamazepine	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Pregabalin	Topiramate	Valproate	Zonisamide
Meta-analyses											
Veroniki et al, 2017a	OR 1.10 (0.77,1.56) N=2141	OR 1.93 (0.88,4.05) N=76	OR 1.05 (0.70,1.48) N=3015	OR 0.87 (0.04,8.14) N=93	OR 0.80 (0.5,1.26) N=1045	OR 1.59 (0.87,2.75) N=206	OR 1.03 (0.55,1.82) N=283	-	OR 1.38 (0.73, 2.35) N=408	OR 0.96 (0.65,1.37) N=1694	-
Pregnancy Registries											
ǂHernandez-Diaz et al, 2014	-	-	5.9% N=1581	-	-	-	-	-	10.4% N=347	-	10.2% N=98
Birth Registers											
Margulis et al, 2019 Swedish Mean pregnancy duration days compared with LMT	-1.3 (95 % CI -2.3 to -0.3) use any time N= 1975 **-1.6 (95% CI -2.7 to -0.5) 1st trimester N=1686**	-	ref	-0.5 (95 % CI -2.6 to 1.6) any time N=213 -0.7 (95% CI -2.9 to -1.5) 1st trimester N=184	-	-	-	-1.1 (95 % CI -3.0 to 0.8) any time N=522 -1.8 (95% CI -3.7 to 0.2) 1st trimester N=484	-	-0.0 (95 % CI -1.2 to -1.2) any time N=985 -0.1 (95% CI -1.3 to -1.2) 1st trimester N=845	-
Danielsson et al, 2019	**10.6%** **N=243**	-	5.7% N=437	7.2% N=118	-	-	-	-	-	4.5% N=130	-
Killic et al, 2014	**8.4% (all)** **8.1% (mono)** N=416	12.1% (all) 12.5% (mono) N=91	**9.3% (all)** **9.4% (mono)** **N=1157**	5.6% (all) 3.8% (mono) N=72	6.2% (all) 6.5% (mono) N=405	10.8% (all) 10.4% (mono) N=111	-	22.2% (all) 23.1% (mono) N=18	4.7% (all) 8.5% (mono) N=129	7.6% (all) 6.7% (mono) N=461	0
ǂArtama et al, 2013 Finland	**7.5% (all)** 7.7% (mono) N=1292 N=1084 mono	-	4.3% (all) 4.6% (mono) N=345 N=173 mono	**10.7% (all)** 15.4% (mono) N=56 N=13 mono	4.6% (all) 4.4% (mono) N=695 N=532 mono	-	7.5% (all) 7.7% (mono) N=53 N=26 mono	-	-	5.7% (all) 5.7% (mono) N=944 N=706 mono	-
Fujii et al, 2013		10.5% N=223									
Others											
Mostacci et al, 2017	-	**54.5%** **N=11**	-	-	-	-	-	25% N=16	-	-	-
Winterfeld et al, 2016								9.2% N=119			
Ornoy et al, 2008	-								9.8% N=29		

Prenatal growth restriction

Prenatal Growth Restriction											
	Carbamazepine	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Pregabalin	Topiramate	Valproate	Zonisamide
Meta-analyses											
Veroniki et al, 2017a	OR 1.15 (0.77,1.67) N=2897	OR 1.37 (0.44,3.61) N=70	OR 0.90 (0.56,1.42) N=2882	OR 1.27 (3.04,3.54) N=81	OR 0.99 (0.56, 1.76) N=1002	**OR 1.88 (1.07,3.32)** N=400	OR 0.68 (0.37,1.21) N=519	-	**OR 2.64 (1.41, 4.63)** **N=472**	1.28 (0.86,1.95) N=1622	-
Pregnancy Registries											
North American Hernandez Diaz et al, 2017 Compared with LMT		aRR 1.2 (95% CI 0.7 to 2.0) N=153				**aRR 2.4 (95% CI 1.6 to 3.6)** N=178	aRR 0.8 (95% CI 0.5 to 1.25) N=383		**aRR 2.4 (95% CI 1.8 to 3.1)** N=394		**aRR 1.9 (95% CI 1.2 to 3.0)** N=125
#Hernandez-Diaz et al, 2014 TPM and ZNS compared with LMT and unexposed control group	-	-	6.8% SGA N=1581	-	-	-	-	-	**17.9% SGA** **Mean lower BW of 221g** **Mean lesser birth length of 1cm** N=347	-	**12.2% SGA** **Mean lower BW of 202g** **Mean lesser birth length of 1cm** N=98
Birth Registers											
Margulis et al, 2019 Swedish BW (grams) Microcephaly – Birth Head circumference (cm)	**BW** **-69 (95% CI -112 to -26)** **any time** **-87 (95 % CI -133 to -40) 1st trimester use** N=1988 (any time) N=1699 (1st trimester) **Microcephaly** **-0.3 (95% CI -0.5 to -0.2)** **any time** **-0.4 (95% CI -0.6 to -0.3) 1st trimester** N=1883 (any time) N= 1605 (1st trimester)	-	ref	BW -79 (95% CI -166 to 8) any time -95 (95 % CI -189 to 2) 1st trimester N=215 (any time) N=186 (1st trimester) Microcephaly -0.2 (95% CI -0.5 to 0.0) any time -0.3 (95% CI -0.6 to 0.0) 1st trimester N=206 (any time) N=178 (1st trimester)	-	-	-	BW -83 (95% CI -63 to 3) any time -127 (95 % CI -210 to 44) 1st trimester N=528 (any time) N=489 (1st trimester) Microcephaly -0.0 (95% CI -0.3 to 0.2) any time -0.2 (95% CI -0.4 to -0.1) 1st trimester N=516 (any time) N=480 (1st trimester)	-	BW -27 (95% CI -79 to 24) any time -40 (95 % CI -95 to 14) 1st trimester N=992 any time N=852 1st trimester Microcephaly -0.2 (95% CI -0.3 to 0.0) any time -0.2 (95% CI -0.4 to 0.2) 1st trimester N=931 (any time) N=802 (1st trimester)	
Danielsson et al, 2019 SGA	2.9% N=243	-	1.8% N=437	3.4% N=118	-	-	-	-	-	2.3% N=130	-
#Veiby et al, 2014 SGA BW SGA HC	**SGA BW** **11.9%** **Vs** **9.6%** **aOR 1.37 (95% 1.09 to 1.73)** **SGA HC** **4.6%** **Vs** **2.4%**	-	SGA BW OR1.0 NS (CI not provided) SGA HC OR 1.1 NS (CI not provided) N=983	SGA BW OR0.8 NS (CI not provided) SGA HC OR 0.4 NS (CI not provided) N=188	-	-	-	-	**SGA-BW** **25.0% vs 8.9%** **aOR 3.29 (95% 1.70 to 6.39)** **SGA-HC** **14.9% vs 2.4%** **aOR 7.21 (95% CI 3.23 to 16.1)** **N=90**	SGA BW OR 0.9 NS (CI not provided) SGA HC OR 0.8 NS (CI not provided) N=410	

	aOR 2.05 (95% 1.44 to 2.93) N=704										
Killic et al, 2014 SGA LBW	**SGA** **13.5% (all)** 11.2% (mono) **LBW** **6.5% (all)** **6.6% (mono)** N=416	SGA 12.1% (all) 12.5% (mono) LBW 5.5% (all) 6.9% (mono) N=91	SGA 10.3% (all) 8.9% (mono) LBW **5.8% (all)** 5.5% (mono) N=1157	SGA 15.3% (all) 11.5% (mono) LBW 5.6% (all) 7.7% (mono) N=72	SGA 18.7% (all) 16.0% (mono) LBW **6.2% (all)** 5.5% (mono) N=405	SGA 18.9% (all) 18.8% (mono) LBW 9.9% (all) 9.4% (mono) N=111	SGA 38.5% (all) 20.0% (mono) LBW 7.7% (all) 20.0% (mono) N=13	SGA 27.8% (all) 23.1% (mono) LBW 16.7% (all) 15.4% (mono) N=18	**SGA** **23.3% (all)** 17.0% (mono) LBW 5.4% (all) 6.8% (mono) **N=129**	**SGA** **16.8% (all)** **15.3% (mono)** LBW **8.1% (all)** **6.5% (mono)** **N=461**	
♦Artama et al, 2013 LBW SGA	**LBW** **5.2% (all)** **4.7% (mono)** SGA 2.3% (all) 1.8% (mono) N=1292 (all) 1084 (mono)	-	LBW 4.1% (all) 3.5% (mono) SGA 1.7% (all) 1.2% (mono) N=345 (all) 173 (mono)	**LBW** **10.7% (all)** **15.4% (mono)** SGA 3.6% (all) 0 (mono) N=56 (all) 13 (mono)	LBW 4.4% (all) 3.6% (mono) **SGA** 3.9% (all) **3.4% (mono)** N=695 (all) 532 (mono)	-	LBW 3.8% (all) 3.8% (mono) SGA 0 (all) 0 (mono) N=53 (all) 26 (mono)	-	-	LBW 4.6% (all) 4.0% (mono) SGA 1.9% (all) 1.7% (mono) N=944 (all) 706 (mono)	-
Fujii et al, 2013 IUGR LBW		**IUGR** **3.5%** **Vs** **1.9% control** **LBW 10.5%** **Vs** **4.4% control**									
Almgren et al, 2009 BW adjusted HC	**-0.15 mean SD +/- 0.03** **N=1094**	-0.02 +/- 0.13 N=56	-0.004 +/-0.06 N=308	-	-	-	-0.02 +/- 0.09 N=137	-	-	**-0.10 mean SDs +/- 0.05** N=460	-
Others											
Mostacci et al, 2017 SGA	-	**27%** **N=11**	-	-	-	-	6.3% N=30	-	-		
Winterfeld et al, 2016 Birth Weight g (median, IQR)								3,300 g (3,000 to 3,690) N=119			
♦Ornoy et al, 2008 Birth weight (grams)	-	-	-	-	-	-	-	-	**2932g** **vs** **3300** N=52		

1.1.6. Economic evidence

1.1.6.1. Included studies

No health economic studies were included.

1.1.6.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix B.

1.1.7. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.8. Committee's discussion and interpretation of the evidence

1.1.8.1. The outcomes that matter most

The guideline committee were interested in adverse events for the foetus of a woman taking ASMs. ASM can cause neurodevelopmental and congenital harms to the foetus. As well as structural congenital anomalies (for example cardiac abnormalities, cleft lip, cleft palate and spina bifida), outcomes of particular interest to the committee were neurodevelopment, IQ, language, and memory as ASM exposure during pregnancy has been linked to poorer levels of ability in these areas.

The guideline committee outlined that outcomes could be broadly split into those that associated with structural/physical anomalies and those that associated with an impact on learning and education. The committee agreed that all outcomes were important, and the following were incorporated into the evidence review:

- Major congenital malformations i.e., neural tube defects (spina bifida), limb defects (club foot), cleft lip and palate, urogenital defects (hypospadias, absent kidneys, abnormal genitalia), cardiac related (congenital heart disease, including ventricular or atrial septal defect) gastric related (oesophageal atresia and gastroschisis), lung related (congenital lung cysts)
- Minor (less major) congenital malformations i.e., missing digit or additional digit, cavernous haemangioma of the skin, or minor versions of congenital heart disease, or spina bifida occulta.
- Intellectual quotient (IQ) (Wechsler Intelligence Scale for Children, Differential Ability Scales)
- Development quotient (DQ): (Griffiths and the Bayley Scales)
- Other cognitive outcomes: language, memory, attention and executive functioning (Clinical Evaluation of Language Fundamentals, Peabody picture naming. The Children's Memory Scale, Rivermead Memory Test, NEPSY: Neuropsychological Assessment)
- Adaptive Behaviour (Vinelands Adaptive Behaviour Scale, the Adaptive Behaviour Assessment System (both have been used in this area)
- Neurodevelopmental disorders such as autism, ADHD, dyspraxia

The outcomes reported in the Medicines and Healthcare products Regulatory Agency (2021) Public Assessment Report: 'Antiepileptic drugs: review of safety of use during pregnancy' included many of those specified by the committee, but in general the MHRA report provided less detail, for example, the committee were interested in major

congenital malformations separately from minor malformations, but the MHRA report included a general category of congenital malformations. The following outcomes were included in the MHRA report and thus taken into consideration:

- Prevalence rate of congenital malformations
- IQ (Wechsler scale, other measures, IQ mean differences reported)
- DQ (Griffiths scale, Bayley scale, other measures, DQ mean differences reported)
- Effects on development: attention/concentration, languages, verbal immediate, verbal delayed
- ADHD and ASD
- Other neurodevelopmental effects: communication, daily living skills, socialisation, motor skills, languages, mathematics
- Cognitive effects: delayed recognition, visual delayed, developmental delay, behaviour disorder
- Other reproductive toxic effects of prioritised AEDs: foetal loss, pre-term birth, prenatal growth restriction

1.1.8.2. The quality of the evidence

Risk of bias and overall quality assessments could not be carried out due to the absence of methodological details of the evidence included from the Medicines and Healthcare products Regulatory Agency (2021) Public Assessment Report: 'Antiepileptic drugs: review of safety of use during pregnancy'.

1.1.8.3. Benefits and harms

The committee decided to link the recommendations directly to Medicines and Healthcare products Regulatory Agency (2021) Public Assessment Report: 'Antiepileptic drugs: review of safety of use during pregnancy' guidance. Any future changes to the MHRA guidance would then be incorporated within the NICE recommendations.

The committee agreed that it was important to inform women and girls of the known risks of antiseizure medications to an unborn child, such as malformations, neurodevelopmental impairments and foetal growth restriction. They considered the risks and benefits should be reviewed for individual drugs but acknowledged the uncertainty about risks particularly for newer drugs. The committee agreed that access to the most up-to-date information on potential risks from ASMs was very important for women and girls to help in shared decision-making.

The committee acknowledged that risks from ASMs to the unborn child needed to be balanced against harms to the mother that might occur if, for example, she stopped ASMs suddenly. When taking into consideration the MHRA guidance, the committee wanted to ensure that risks of ASMs to the unborn child were balanced against the risks from seizures to the mother. They considered it important to make a recommendation to ensure that the risks of seizures were well communicated to women and girls to avoid women and girls who wished to conceive, discovered they were pregnant from abruptly stopping their ASM treatment.

While the MHRA recommend lamotrigine and levetiracetam in women who wish to conceive, in the absence of the MHRA report methodology and quality assessments the committee were unable to comment on the clinical conclusions that led to these recommendations. Therefore, the committee wanted to ensure risks of other ASMs, e.g., carbamazepine, were put into context to avoid unnecessary fear and stress in girls and women. The committee noted that there may be many women of childbearing potential who would, for differing reasons, be unable to take only lamotrigine and/or levetiracetam through a pregnancy, for example if they had trialled these medications previously and had experienced adverse events. The committee wanted to support and enable women with epilepsy who wished to conceive to make informed choices based on the best available evidence.

The committee highlighted the particular importance of girls and women who are taking ASMs being given contraception advice prior to becoming sexually active. Ideally women and girls with epilepsy should have access to services specifically geared towards them where they could discuss and review advice for contraception and conception, as well as pregnancy, breastfeeding and caring for children, and menopause, as and when needed. There are for example known interactions between ASMs, hormonal contraception, and hormone replacement therapy. The committee were mindful however of the lack of such service and the need for it to be commissioned.

The committee noted that the MHRA report did not include guidance on breastfeeding whilst taking ASMs. They discussed that the baby would potentially have been exposed to (the same) ASMs in utero, and that the amount of drug in breast milk is extremely small and unlikely to harm to the baby. The committee agreed to bring forward recommendations relating to breastfeeding included in the 2012 Epilepsies guidance as they considered those recommendations still valid and encouraged women and girls to breastfeed. The committee agreed that the advantages of breastfeeding for the baby outweighed the very small risks of ASM exposure through breastmilk adversely affecting the baby.

1.1.9. Recommendations supported by this evidence review

This evidence review supports recommendations 4.4.1 – 4.4.8 in the NICE guideline.

References

1. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

Appendices

Appendix A Review protocols

A.1 Clinical Review protocol for safety of ASMs in women and girls

ID	Field	Content
0.	PROSPERO registration number	Not registered.
1.	Review title	Safety of anti-seizure medications (ASMs) in women and girls
2.	Review question	What ASMs (individually or add-ons) are safe in the treatment of epilepsies in women and girls who are pregnant and already taking ASMs and in those women who are breastfeeding?
3.	Objective	The aim of this review is to determine which ASMs are more likely to cause neurodevelopmental and congenital harm to the foetus. ASM exposure during pregnancy has been linked to poorer levels of ability for skills such as IQ, language and memory as well as structural abnormalities. The safety of ASMs does not change according to the type of epilepsy.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Cochrane Central Register of Controlled Trials (CENTRAL) • MEDLINE & Medline in Process • Embase Searches will be restricted by: • Date: No limit • Human studies

		• English language studies only The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Pregnant women or girls with epilepsy **and** women or girls of childbearing potential with epilepsy Breastfeeding women and girls with epilepsy
6.	Population	Inclusion • Pregnant women and girls of childbearing potential with undergoing treatment for epilepsy (including generalised tonic-clonic (GTC), focal onset seizures, absence seizures, myoclonic seizures, tonic seizures, atonic seizures) • Breastfeeding women and girls undergoing treatment for epilepsy Exclusion • Men • Non-pregnant women (excluding breastfeeding women)
7.	Intervention	Pregnant women and girls with epilepsy taking a single ASM of interest Pregnant women and girls with epilepsy taking a combination of ASMs Breastfeeding women and girls with epilepsy taking a single ASM of interest Breastfeeding women and girls with epilepsy taking a combination of ASMs

		The following ASMs will be considered: Brivaracetam, carbamazepine, clobazam, clonazepam, eslicarbazepine, ethosuximide, f, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital (phenobarbitone), phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproate (sodium valproate/valproic acid), vigabatrin, zonisamide, Each single ASM will be compared with another single ASM Combinations of ASMs will be compared with single ASM from the combination One combination will be compared with another combination No strata
Yes8.	Comparator	• pregnant women and girls with epilepsy taking another ASM of interest (for single ASM and combinations of ASMs as interventions) • pregnant women and girls with epilepsy taking a different combination of ASMs • pregnant women and girls with epilepsy taking no ASM • pregnant women and girls who did not have epilepsy • breastfeeding women and girls with epilepsy taking another ASM of interest (for single ASM and combinations of ASMs as interventions) • breastfeeding women and girls with epilepsy taking a different combination of ASMs • breastfeeding women and girls with epilepsy taking no ASM • breastfeeding women and girls who did not have epilepsy
9.	Types of study to be included	• Systematic reviews of randomised controlled trials and cohort studies • Randomised controlled trials • Prospective and retrospective cohort studies will be included if adjustments have been made • Published registry databases will be included if adjustments have been made, except when the database includes 5000 plus individuals, in which case no adjustments are needed Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
10	Other exclusion criteria	Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias.

11.	Context	Recommendations will apply to those receiving care in any healthcare settings (e.g., community, primary, secondary care)
12.	Primary outcomes	○ Major congenital malformations such as neural tube defects (spina bifida), limb defects (club foot), cleft lip and palate, urogenital defects (hypospadias, absent kidneys, abnormal genitalia), cardiac related (congenital heart disease, including ventricular or atrial septal defect) gastric related (oesophageal atresia and gastroschisis), lung related (congenital lung cysts) ○ Minor (less major) congenital malformations such as missing digit or additional digit, cavernous haemangioma of the skin, or minor versions of congenital heart disease, or spina bifida occulta. ○ Intellectual quotient (IQ) (Wechsler Intelligence Scale for Children, the Differential Ability Scales) ○ Development quotient (DQ): (Griffiths and the Bayley Scales) ○ Other cognitive outcomes: language, memory, attention, and executive functioning (Clinical Evaluation of Language Fundamentals, Peabody picture naming. The Children's Memory Scale, Rivermead Memory Test, NEPSY: Neuropsychological Assessment) ○ Adaptive Behaviour (Vinelands Adaptive Behaviour Scale, the Adaptive Behaviour Assessment System (both have been used in this area) ○ Neurodevelopmental disorders such as autism, ADHD, dyspraxia
13.	Secondary outcomes (important outcomes)	
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion.

		A standardised form will be used to extract data from studies. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer. Information to be extracted from studies includes study type, study dates, location of study, funding, inclusion and exclusion criteria, participant characteristics, details of the interventions, outcomes and times of measurement. All data extraction will be quality assured by a senior reviewer. Draft included and excluded studies tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists • ROBIS tool for systematic reviews • ROBINS-I for non-randomised trials 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. <u>Data Synthesis</u> Hazard ratios (HR) and their corresponding 95% confidence intervals will be extracted from the included studies. Where possible those HR which have adjusted for potentially relevant

		confounders (i.e. age, BMI and ethnicity, parity) will be used. Where possible, pair wise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted, and data will be presented as risk ratios for dichotomous outcomes. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean difference <u>Heterogeneity</u> Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity sub-group analysis will be conducted 1) according to the risk of bias of individual studies 2) by age 3) study location Exact subgroup analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis. <u>Validity</u> The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/	
17.	Analysis of sub-groups	Stratification If data is available, separate analysis will be conducted on: • those with and without learning difficulties	
18.	Type and method of review	☐	Intervention

		☐	Diagnostic
		☒	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	TBC	
22.	Anticipated completion date	August 2021	
23.	Stage of review at time of this submission	An evidence review for this question was not conducted as the 'Medicines and Healthcare products Regulatory Agency (MHRA) (2021) Public Assessment Report: Antiepileptic drugs: review of safety of use during pregnancy' was incorporated into this chapter.	
24.	Named contact	**5a. Named contact** National Guideline Alliance **5b Named contact e-mail** Epilepsies@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Alliance	
25.	Review team members	NGC technical team	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including	

		the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10123/	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Drug safety, women and girls with epilepsy, pregnancy, breastfeeding	
33.	Details of existing review of same topic by same authors	Not applicable	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	

A.2 Economics: Review protocol for safety of ASMs in women and girls

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[1] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitation"' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'.
- Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Search strategy

This literature search strategy was used for the following reviews:

- What AEDs (individually or add-ons) are safe in the treatment of epilepsies in women and girls who are pregnant and already taking AEDs and in those women who are breastfeeding?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[1]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 3: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 August 2020	Randomised controlled trials Systematic review studies Observational studies Exclusions
Embase (OVID)	1974 – 26 August 2020	Randomised controlled trials Systematic review studies Observational studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 8 of 12 CENTRAL to 2020 Issue 8 of 12	None

Medline (Ovid) search terms

1.	exp female/
2.	exp pregnancy/
3.	pregnancy outcome/
4.	exp pregnancy complications/
5.	exp prenatal exposure delayed effects/
6.	postnatal care/
7.	postpartum period/
8.	exp Breast Feeding/
9.	(female* or wom?n or girl or pregnan* or conception or prenatal or pre natal or postnatal or post natal or postpartum or post-partum or conceiv* or breast feed* or breastfeed* or breastfed or breast fed or breast milk or breastmilk or mother* milk or human milk or colostrum).ti,ab.

10.	exp infant newborn/
11.	exp fetal development/
12.	((baby or babies or born or newborn* or infant* or fetal or foetal or fetus or foetus) adj2 (develop* or size or measur* or length)).ti,ab.
13.	exp Birth Weight/
14.	((birth* or baby or babies or born or newborn* or infant*) adj weigh*).ti,ab.
15.	or/1-14
16.	exp Abnormalities, Drug Induced/
17.	exp Congenital abnormalities/
18.	exp Fetal Diseases/
19.	((congenital or birth* or baby or babies or born or newborn* or infant* or fetal or foetal or fetus or foetus or prenatal or pre natal or in utero or intra uterine or intrauterine) adj2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph* or disease*)).ti,ab.
20.	(drug induced adj2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)).ti,ab.
21.	exp teratogens/
22.	teratogen*.ti,ab.
23.	exp Fetal death/
24.	exp Infant mortality/
25.	Maternal mortality/
26.	((maternal* or mother* or birth* or baby or babies or born or newborn* or infant* or fetal or foetal or fetus) adj2 (mortality or death or dies or died)).ti,ab.
27.	exp Intellectual Disability/
28.	((intellectual* or mental*) adj2 (impair* or disab* or retard*)).ti,ab.
29.	neurodevelopment*.ti,ab.
30.	education* need*.ti,ab.
31.	long* term outcome*.ti,ab.
32.	exp Child Development/
33.	child* develop*.ti,ab.
34.	exp Autistic Disorder/
35.	(autism or autistic).ti,ab.
36.	exp Attention Deficit Disorder with Hyperactivity/
37.	((attenti* adj3 deficit*) or adhd or addh or ad hd or ad??hd).ti,ab.
38.	exp Apraxias/
39.	(apraxia* or dyspraxia*).ti,ab.
40.	exp Memory/
41.	memory.ti,ab.
42.	exp Language Disorders/
43.	((language or speech) adj2 (disorder* or problem*)).ti,ab.
44.	exp Executive Function/
45.	executive function*.ti,ab.
46.	(cognitive or cognition or problem* solving).ti,ab.
47.	exp Neuropsychology/
48.	neuropsycholog*.ti,ab.
49.	exp Intelligence Tests/
50.	((intelligen* or development*) adj2 (test* or quotient* or scale*)).ti,ab.
51.	("Griffiths Mental Development Scales" or "Bayley Scales of Infant and Toddler Development").ti,ab.

52.	("vineland adaptive behaviour scales" or "vineland 3").ti,ab.
53.	(IQ or DQ or GMDS or BSID or VABS).ti,ab.
54.	exp Spinal Dysraphism/
55.	(spinal dysraphism or spina bifidia).ti,ab.
56.	Cleft palate/
57.	(cleft adj (lip* or palate*)).ti,ab.
58.	Clubfoot/
59.	(clubfoot or clubfeet or equinovarus or pie torcido).ti,ab.
60.	((foot or feet) adj2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)).ti,ab.
61.	((urogenital or genitourinary or kidney* or bladder or ureter or urethra or testes or ovaries or sex develop*) adj2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)).ti,ab.
62.	(hydronephrosis or hypospadias or cryptorchidism or epispadias or fraser syndrome or fused kidney or hypospadias or nulticystic dysplastic kidney or hereditary nephritis or retrocaval ureter or solitary kidney or urinary fistula).ti,ab.
63.	or/16-62
64.	15 and 63
65.	letter/
66.	editorial/
67.	news/
68.	exp historical article/
69.	Anecdotes as Topic/
70.	comment/
71.	case report/
72.	(letter or comment*).ti.
73.	or/65-72
74.	randomized controlled trial/ or random*.ti,ab.
75.	73 not 74
76.	animals/ not humans/
77.	exp Animals, Laboratory/
78.	exp Animal Experimentation/
79.	exp Models, Animal/
80.	exp Rodentia/
81.	(rat or rats or mouse or mice).ti.
82.	or/75-81
83.	64 not 82
84.	limit 83 to English language
85.	exp epilepsy/
86.	seizures/
87.	exp status epilepticus/
88.	seizures, febrile/
89.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
90.	or/85-89
91.	exp Anticonvulsants/
92.	exp Acetazolamide/
93.	exp Carbamazepine/

94.	exp Chloral hydrate/
95.	exp Clomethiazole/
96.	exp Clonazepam/
97.	exp Clorazepate Dipotassium/
98.	exp Diazepam/
99.	exp Ethosuximide/
100.	exp Levetiracetam/
101.	exp Lorazepam/
102.	exp Mephenytoin/
103.	exp Mephobarbital/
104.	exp Midazolam/
105.	exp Methazolamide/
106.	exp Nitrazepam/
107.	exp Paraldehyde/
108.	exp Pentobarbital/
109.	exp Phenobarbital/
110.	exp Phenytoin/
111.	exp Primidone/
112.	exp Propofol/
113.	exp Temazepam/
114.	exp Thiopental/
115.	exp Topiramate/
116.	exp Trimethadione/
117.	exp Valproic Acid/
118.	exp Vigabatrin/
119.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline).ti,ab.
120.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*).ti,ab.
121.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide).ti,ab.
122.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa

	or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide).ti,ab.
123.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate).ti,ab.
124.	hyperbaric oxygen.ti,ab.
125.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids).ti,ab.
126.	*Adrenal Cortex Hormones/ or *adrenocorticotropic hormone/ or *cosyntropin/
127.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin).ti,ab.
128.	or/91-127
129.	randomized controlled trial.pt.
130.	controlled clinical trial.pt.
131.	randomi#ed.ti,ab.
132.	placebo.ab.
133.	randomly.ti,ab.
134.	Clinical Trials as topic.sh.
135.	trial.ti.
136.	or/129-135
137.	Meta-Analysis/
138.	exp Meta-Analysis as Topic/
139.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
140.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
141.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
142.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
143.	(search* adj4 literature).ab.
144.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
145.	cochrane.jw.
146.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
147.	or/137-146
148.	Epidemiologic studies/
149.	Observational study/
150.	exp Cohort studies/
151.	(cohort adj (study or studies or analys* or data)).ti,ab.
152.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
153.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
154.	Controlled Before-After Studies/
155.	Historically Controlled Study/
156.	Interrupted Time Series Analysis/
157.	(before adj2 after adj2 (study or studies or data)).ti,ab.

158.	exp case control studies/
159.	case control*.ti,ab.
160.	Cross-sectional studies/
161.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
162.	or/148-161
163.	84 and (90 or 128)
164.	163 and (136 or 147 or 162)

1 **Embase (Ovid) search terms**

1.	exp *female/
2.	exp *pregnancy/
3.	*pregnancy outcome/
4.	exp *pregnancy complication/
5.	exp *prenatal exposure/
6.	*postnatal care/
7.	*puerperium/
8.	exp *breast feeding/
9.	(female* or wom?n or girl or pregnan* or conception or prenatal or pre natal or postnatal or post natal or postpartum or post-partum or conceiv* or breast feed* or breastfeed* or breastfed or breast fed or breast milk or breastmilk or mother* milk or human milk or colostrum).ti,ab.
10.	exp *newborn/
11.	exp *fetus development/
12.	((baby or babies or born or newborn* or infant* or fetal or foetal or fetus or foetus) adj2 (develop* or size or measur* or length)).ti,ab.
13.	exp *birth weight/
14.	((birth* or baby or babies or born or newborn* or infant*) adj weigh*).ti,ab.
15.	or/1-14
16.	exp *drug induced malformation/
17.	exp *congenital disorder/
18.	exp *fetus disease/
19.	((congenital or birth* or baby or babies or born or newborn* or infant* or fetal or foetal or fetus or foetus or prenatal or pre natal or in utero or intra uterine or intrauterine) adj2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph* or disease*)).ti,ab.
20.	(drug induced adj2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)).ti,ab.
21.	exp *teratogenic agent/
22.	teratogen*.ti,ab.
23.	exp *fetus death/
24.	exp *infant mortality/
25.	*maternal mortality/
26.	((maternal* or mother* or birth* or baby or babies or born or newborn* or infant* or fetal or foetal or fetus) adj2 (mortality or death or dies or died)).ti,ab.
27.	*intellectual impairment/
28.	((intellectual* or mental*) adj2 (impair* or disab* or retard*)).ti,ab.
29.	neurodevelopment*.ti,ab.
30.	education* need*.ti,ab.
31.	long* term outcome*.ti,ab.
32.	exp *child development/

33.	child* develop*.ti,ab.
34.	exp *autism/
35.	(autism or autistic).ti,ab.
36.	exp *attention deficit disorder/
37.	((attenti* adj3 deficit*) or adhd or addh or ad hd or ad??hd).ti,ab.
38.	exp *apraxia/
39.	(apraxia* or dyspraxia*).ti,ab.
40.	exp *memory/
41.	memory.ti,ab.
42.	exp *language disability/
43.	((language or speech) adj2 (disorder* or problem*)).ti,ab.
44.	exp *executive function/
45.	executive function*.ti,ab.
46.	(cognitive or cognition or problem* solving).ti,ab.
47.	exp *neuropsychology/
48.	neuropsycholog*.ti,ab.
49.	exp *intelligence test/
50.	((intelligen* or development*) adj2 (test* or quotient* or scale*)).ti,ab.
51.	("Griffiths Mental Development Scales" or "Bayley Scales of Infant and Toddler Development").ti,ab.
52.	("vineland adaptive behaviour scales" or "vineland 3").ti,ab.
53.	(IQ or DQ or GMDS or BSID or VABS).ti,ab.
54.	exp *spinal dysraphism/
55.	(spinal dysraphism or spina bifidia).ti,ab.
56.	*cleft palate/
57.	(cleft adj (lip* or palate*)).ti,ab.
58.	*clubfoot/
59.	(clubfoot or clubfeet or equinovarus or pie torcido).ti,ab.
60.	((foot or feet) adj2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)).ti,ab.
61.	((urogenital or genitourinary or kidney* or bladder or ureter or urethra or testes or ovaries or sex develop*) adj2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)).ti,ab.
62.	(hydronephrosis or hypospadias or cryptorchidism or epispadias or fraser syndrome or fused kidney or hypospadias or nulticystic dysplastic kidney or hereditary nephritis or retrocaval ureter or solitary kidney or urinary fistula).ti,ab.
63.	or/16-62
64.	15 and 63
65.	letter.pt. or letter/
66.	note.pt.
67.	editorial.pt.
68.	case report/ or case study/
69.	(letter or comment*).ti.
70.	or/65-69
71.	randomized controlled trial/ or random*.ti,ab.
72.	70 not 71
73.	animal/ not human/
74.	nonhuman/

75.	exp Animal Experiment/
76.	exp Experimental Animal/
77.	animal model/
78.	exp Rodent/
79.	(rat or rats or mouse or mice).ti.
80.	or/72-79
81.	64 not 80
82.	limit 81 to English language
83.	exp epilepsy/
84.	seizure/
85.	epileptic state/
86.	febrile convulsion/
87.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
88.	or/83-87
89.	exp Anticonvulsants/
90.	exp Acetazolamide/
91.	exp Carbamazepine/
92.	exp Chloral hydrate/
93.	exp Clomethiazole/
94.	exp Clonazepam/
95.	exp Clorazepate Dipotassium/
96.	exp Diazepam/
97.	exp Ethosuximide/
98.	exp Lorazepam/
99.	exp Mephenytoin/
100.	exp Mephobarbital/
101.	exp Midazolam/
102.	exp Methazolamide/
103.	exp Nitrazepam/
104.	exp Paraldehyde/
105.	exp Pentobarbital/
106.	exp Phenobarbital/
107.	exp Phenytoin/
108.	exp Primidone/
109.	exp Propofol/
110.	exp Temazepam/
111.	exp Thiopental/
112.	exp Topiramate/
113.	exp Trimethadione/
114.	exp Valproic Acid/
115.	exp Vigabatrin/
116.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or

	Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline).ti,ab.
117.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*).ti,ab.
118.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide).ti,ab.
119.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide).ti,ab.
120.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate).ti,ab.
121.	hyperbaric oxygen.ti,ab.
122.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids).ti,ab.
123.	*Adrenal Cortex Hormones/ or *adrenocorticotropic hormone/ or *cosyntropin/
124.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin).ti,ab.
125.	or/89-124
126.	random*.ti,ab.
127.	factorial*.ti,ab.
128.	(crossover* or cross over*).ti,ab.
129.	((doubl* or singl*) adj blind*).ti,ab.
130.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
131.	crossover procedure/
132.	single blind procedure/
133.	randomized controlled trial/
134.	double blind procedure/
135.	or/126-134
136.	Clinical study/
137.	Observational study/
138.	family study/
139.	longitudinal study/
140.	retrospective study/

141.	prospective study/
142.	cohort analysis/
143.	follow-up/
144.	cohort*.ti,ab.
145.	143 and 144
146.	(cohort adj (study or studies or analys* or data)).ti,ab.
147.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
148.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
149.	(before adj2 after adj2 (study or studies or data)).ti,ab.
150.	or/136-142,145-149
151.	exp case control study/
152.	case control*.ti,ab.
153.	or/151-152
154.	150 or 153
155.	cross-sectional study/
156.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
157.	or/155-156
158.	150 or 157
159.	150 or 153 or 157
160.	systematic review/
161.	meta-analysis/
162.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
163.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
164.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
165.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
166.	(search* adj4 literature).ab.
167.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
168.	cochrane.jw.
169.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
170.	or/160-169
171.	82 and (88 or 125)
172.	171 and (135 or 159 or 170)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Female] explode all trees
#2.	MeSH descriptor: [Pregnancy] explode all trees
#3.	MeSH descriptor: [Pregnancy Outcome] explode all trees
#4.	MeSH descriptor: [Pregnancy Complications] explode all trees
#5.	MeSH descriptor: [Prenatal Exposure Delayed Effects] explode all trees
#6.	MeSH descriptor: [Postnatal Care] explode all trees
#7.	MeSH descriptor: [Postpartum Period] explode all trees
#8.	MeSH descriptor: [Breast Feeding] explode all trees
#9.	(female* or wom?n or girl or pregnan* or conception or prenatal or pre natal or postnatal or post natal or postpartum or post partum or conceiv* or breast feed* or

	breastfeed* or breastfed or breast fed or breast milk or breastmilk or mother* milk or human milk or colostrum):ti,ab
#10.	(or #1-#9)
#11.	MeSH descriptor: [Epilepsy] explode all trees
#12.	MeSH descriptor: [Seizures] this term only
#13.	MeSH descriptor: [Status Epilepticus] explode all trees
#14.	MeSH descriptor: [Seizures, Febrile] this term only
#15.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#16.	(or #11-#15)
#17.	MeSH descriptor: [Abnormalities, Drug-Induced] explode all trees
#18.	MeSH descriptor: [Congenital Abnormalities] explode all trees
#19.	MeSH descriptor: [Fetal Diseases] explode all trees
#20.	((congenital or birth* or baby or babies or born or newborn* or infant* or fetal or foetal or fetus or foetus or prenatal or pre natal or in utero or intra uterine or intrauterine) near/2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph* or disease*)):ti,ab
#21.	(drug induced near/2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)):ti,ab
#22.	MeSH descriptor: [Teratogens] explode all trees
#23.	teratogen*:ti,ab
#24.	MeSH descriptor: [Fetal Death] explode all trees
#25.	MeSH descriptor: [Infant Mortality] explode all trees
#26.	MeSH descriptor: [Maternal Mortality] explode all trees
#27.	((maternal* or mother* or birth* or baby or babies or born or newborn* or infant* or fetal or foetal or fetus) near/2 (mortality or death or dies or died)):ti,ab
#28.	MeSH descriptor: [Intellectual Disability] explode all trees
#29.	((intellectual* or mental*) near/2 (impair* or disab* or retard*)):ti,ab
#30.	neurodevelopment*:ti,ab
#31.	education* need*:ti,ab
#32.	long* term outcome*:ti,ab
#33.	MeSH descriptor: [Child Development] explode all trees
#34.	child* develop*:ti,ab
#35.	MeSH descriptor: [Autistic Disorder] explode all trees
#36.	(autism or autistic):ti,ab
#37.	MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees
#38.	((attenti* near/3 deficit*) or adhd or addh or ad hd or ad??hd):ti,ab
#39.	MeSH descriptor: [Apraxias] explode all trees
#40.	(apraxia* or dyspraxia*):ti,ab
#41.	MeSH descriptor: [Memory] explode all trees
#42.	memory:ti,ab
#43.	MeSH descriptor: [Language Disorders] explode all trees
#44.	((language or speech) near/2 (disorder* or problem*)):ti,ab
#45.	MeSH descriptor: [Executive Function] explode all trees
#46.	executive function*:ti,ab
#47.	(cognitive or cognition or problem* solving):ti,ab
#48.	MeSH descriptor: [Neuropsychology] explode all trees
#49.	neuropsycholog*:ti,ab

#50.	MeSH descriptor: [Intelligence Tests] explode all trees
#51.	((intelligen* or development*) near/2 (test* or quotient* or scale*)):ti,ab
#52.	("Griffiths Mental Development Scales" or "Bayley Scales of Infant and Toddler Development"):ti,ab
#53.	("vineland adaptive behaviour scales" or "vineland 3"):ti,ab
#54.	(IQ or DQ or GMDS or BSID or VABS):ti,ab
#55.	MeSH descriptor: [Spinal Dysraphism] explode all trees
#56.	(spinal dysraphism or spina bifidia):ti,ab
#57.	MeSH descriptor: [Cleft Palate] explode all trees
#58.	(cleft near/1 (lip* or palate*)):ti,ab
#59.	MeSH descriptor: [Clubfoot] explode all trees
#60.	(clubfoot or clubfeet or equinovarus or pie torcido):ti,ab
#61.	((foot or feet) near/2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)):ti,ab
#62.	((urogenital or genitourinary or kidney* or bladder or ureter or urethra or testes or ovaries or sex develop*) near/2 (defec* or deform* or malform* or abnormal* or anomal* or dysmorph*)):ti,ab
#63.	(hydronephrosis or hypospadias or cryptorchidism or epispadias or fraser syndrome or fused kidney or hypospadias or nulticystic dysplastic kidney or hereditary nephritis or retrocaval ureter or solitary kidney or urinary fistula):ti,ab
#64.	(or #17-#63)
#65.	MeSH descriptor: [Anticonvulsants] explode all trees
#66.	MeSH descriptor: [Acetazolamide] explode all trees
#67.	MeSH descriptor: [Carbamazepine] explode all trees
#68.	MeSH descriptor: [Chloral Hydrate] explode all trees
#69.	MeSH descriptor: [Chlormethiazole] explode all trees
#70.	MeSH descriptor: [Clonazepam] explode all trees
#71.	MeSH descriptor: [Clorazepate Dipotassium] explode all trees
#72.	MeSH descriptor: [Diazepam] explode all trees
#73.	MeSH descriptor: [Ethosuximide] explode all trees
#74.	MeSH descriptor: [Lorazepam] explode all trees
#75.	MeSH descriptor: [Mephenytoin] explode all trees
#76.	MeSH descriptor: [Mephobarbital] explode all trees
#77.	MeSH descriptor: [Midazolam] explode all trees
#78.	MeSH descriptor: [Methazolamide] explode all trees
#79.	MeSH descriptor: [Nitrazepam] explode all trees
#80.	MeSH descriptor: [Paraldehyde] explode all trees
#81.	MeSH descriptor: [Pentobarbital] explode all trees
#82.	MeSH descriptor: [Phenobarbital] explode all trees
#83.	MeSH descriptor: [Phenytoin] explode all trees
#84.	MeSH descriptor: [Primidone] explode all trees
#85.	MeSH descriptor: [Propofol] explode all trees
#86.	MeSH descriptor: [Temazepam] explode all trees
#87.	MeSH descriptor: [Thiopental] explode all trees
#88.	MeSH descriptor: [Topiramate] explode all trees
#89.	MeSH descriptor: [Trimethadione] explode all trees
#90.	MeSH descriptor: [Valproic Acid] explode all trees
#91.	MeSH descriptor: [Vigabatrin] explode all trees

#92.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline):ti,ab
#93.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*):ti,ab
#94.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide):ti,ab
#95.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide):ti,ab
#96.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate):ti,ab
#97.	(or #65-#96)
#98.	#10 and #64
#99.	#16 or #97
#100.	#98 and #99

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021	Health economics studies Quality of life studies

Database	Dates searched	Search filter used
	Quality of Life 1946 – 13 May 2021	Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

1 **Medline (Ovid) search terms**

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/

34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

1 **Embase (Ovid) search terms**

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11

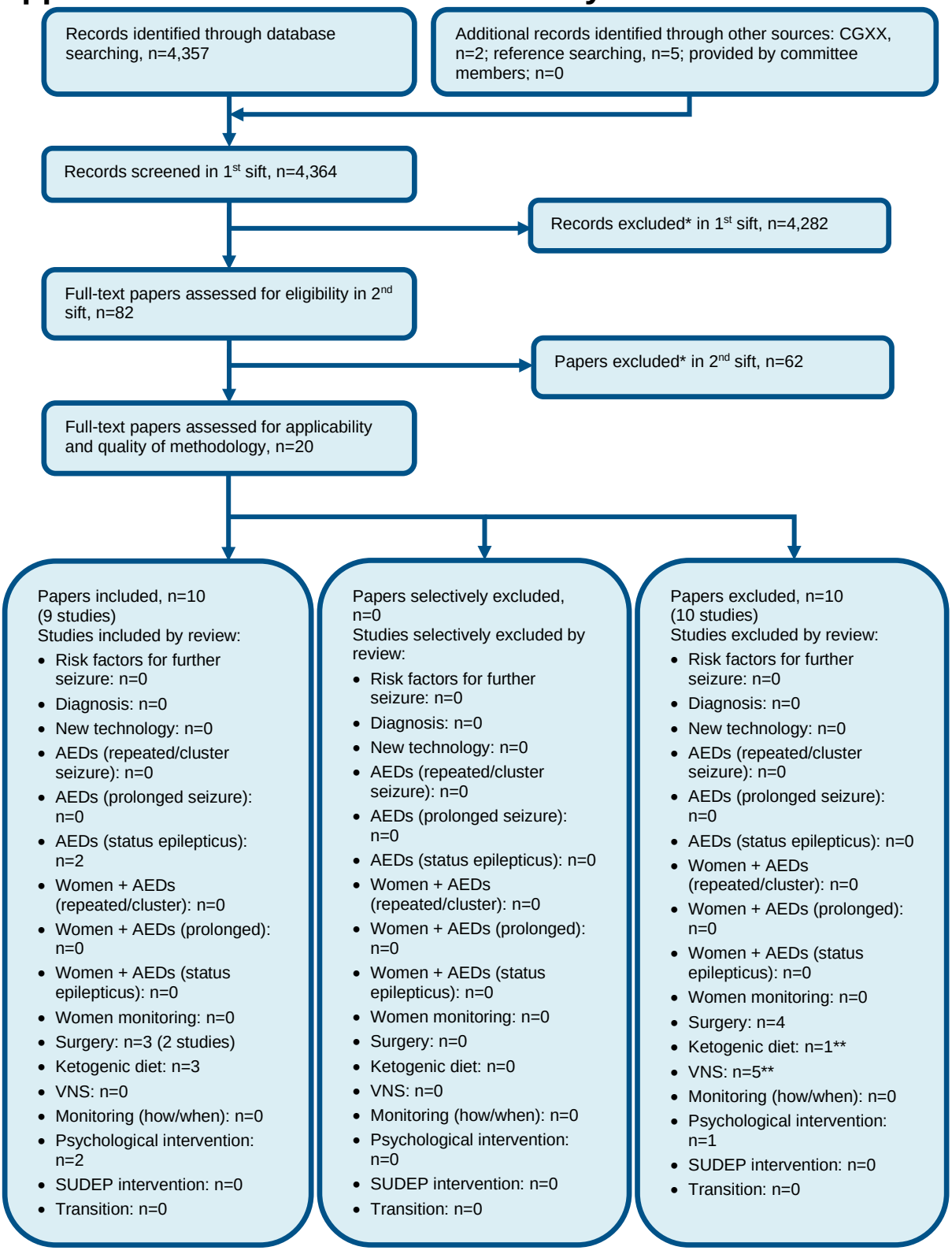
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57

59.	24 and (38 or 58)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

Appendix C Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the number of full text articles assessed for applicability and quality of methodology.

Appendix D Economic evidence tables

Appendix E Health economic model

No original economic modelling was undertaken for this review question.

Appendix F Excluded studies

F.1 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 5: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	