Epilepsy module – evidence profile EPI4: Anti-seizure medications for women of childbearing age

WHO mhGAP guideline update: Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders

2023

World Health Organization

Contents

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, available at: https://www.who.int/publications/i/item/9789240084278

1 Background

Epilepsy is a highly prevalent non-communicable neurological disease, particularly affecting people in low- and middle-income countries (LMICs), where diagnostic and therapeutic resources are scarce. (WHO - epilepsy) It is important to treat people with epilepsy (PWE) independent of their origin, ethnicity, age group or gender. Women and girls with epilepsy (WWE), particularly during childbearing years, are of particular interest owing to the risk of maternal seizures on fetal wellbeing; obstetric complications; maternal mortality (Viala et al., 2015, Allotey et al., 2017); and the potential teratogenicity of some antiseizure medications (ASMs; Veroniki et al., 2017, Weston et al., 2016). Also, given the importance of breastfeeding on the neonatal/infant development and the mother-child relationship, (WHO - breastfeeding) it is important to consider the risks of neonatal exposure to ASMs.

This is an update of the previous recommendation. Notably, there is no evidence to suggest that a given anti-seizure medication is more *effective* in males than females. This question will therefore be informed by EPI3 and here we will concentrate on risks from ASMs that may be specific to females, perhaps especially women and girls of childbearing potential. In particular we seek to ensure that the teratogenic risks of certain ASMs are appropriately highlighted.

2 Methodology

Evidence from recent meta-analyses covering the effectiveness and safety of ASMs (phenobarbital, phenytoin, carbamazepine, valproic acid, lamotrigine, levetiracetam, topiramate, and lacosamide) for WWE at childbearing age are summarized.

Owing to the complexity of randomized control data in this specific population, and depending on data quality, we additionally consider data from systematic reviews of observational studies (cohorts, case-control studies) of WWE taking ASMs, and data from relevant registries.

2.1. PICO question

What is the effectiveness and safety of antiseizure medications (ASMs) in women of childbearing age?

Population (P): Women with epilepsy of childbearing potential (who may become pregnant, and women with epilepsy taking ASMs wishing to breast feed).

Intervention (I): Use of ASMs as monotherapy or polytherapy e.g. phenobarbital, phenytoin, valproate, carbamazepine, lamotrigine, levetiracetam, topiramate, lacosamide

Comparator (C): no treatment; head to head comparisons

Outcomes (O):

- **Critical outcome:** Prenatal ASM exposure and congenital malformations in infant
- **Important outcome:** Clinically important amounts of ASMs secreted in breast milk

2.2. Search strategy

High quality published systematic reviews and meta-analyses were identified by conducting searches in the following bibliographic databases:

- PubMed
- Web of Science
- Embase
- Cochrane reviews
- Global Index Medicus

We designed the search strings by combining the following keywords for 1) epilepsy OR epileptic (*Type of Participants*), 2) childbearing OR breastfeed OR pregnant OR teratogenicity (*Particularity of Participants*) 3) antiseizure medication OR antiepileptic medication OR (phenobarbital OR phenytoin OR carbamazepine OR valproic acid OR valproate OR lamotrigine OR levetiracetam OR topiramate OR lacosamide) (*Types of interventions*), and 4) terms related to systematic reviews and meta-analyses (*Type of studies*).

The search strings for PubMed, Web of Science, and Embase were: ((epilepsy OR epileptic) AND ((antiseizure medication) OR (antiepileptic medication) OR phenobarbital OR phenytoin OR carbamazepine OR valproic acid OR valproate OR lamotrigine OR levetiracetam OR topiramate OR lacosamide) AND (childbearing OR breastfeed OR pregnant OR pregnancy OR teratogenicity) AND (systematic review)).

The search strings for Cochrane reviews and Global Index Medicus were: ((epilepsy OR epileptic) AND (childbearing OR breastfeed OR pregnant OR pregnancy OR teratogenicity))

As we are performing an actualization of available recommendations based on recent data (as suggested by World Health Organization, 2014), the period of the searches covered from 1 January 2012 (last data included

in the currently available recommendation) until 31 July 2022. No restrictions were applied for language or country of publication.

2.3. Data collection and analysis

Records retrieved from the bibliographic databases were assessed for eligibility by screening first their titles and abstracts, then full-text based on the inclusion and exclusion criteria developed a priori.
Studies were included if they:

(i) were systematic reviews of randomised controlled trials (RCTs), or of observational cohort studies or registries data,

(ii) included women with epilepsy (WWE) of childbearing potential, either at conceptional age, pregnant, or breastfeeding,

(iii) evaluated the effectiveness or safety (teratogenicity) of ASM compared to placebo/ treatment as usual

(iv) assessed concertation of ASM in maternal milk and safety.

NB: Studies where women who were taking ASMs for a other condition than epilepsy (for example migraine) were taken into consideration seeing the complexity of acquiring RCT data in pregnant women.

Data from eligible studies were extracted into pre-defined templates that include the general characteristics of the study, country of origin, population, intervention, comparator and outcomes. In case of overlap between studies (i.e. they evaluated the same ASM, in similar target populations, and reported the same outcomes), relevant meta-analysis were selected based on the following criteria: (i) Date of publication/of study (more recent reviews covering a more recent search period) (ii) number of included RCTs/observations, (iii) broadness of the review (covering multiple relevant ASMs compared to pill placebo and/or treatment as usual, with a wide range of outcomes).

Two reviewers (AH and MR) independently assessed the eligibility of the identified studies and performed data extraction. Discrepancies between the reviewers were resolved through discussions with the third reviewer (AS). Each step of the search strategy and its corresponding results were compared between reviewers, regularly discussed and have been carefully documented. The flow of articles throughout the search is presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Excluded articles and the reasons for any exclusions at the full-text screening stage were also reported.

2.4. Selection and coding of identified records

Endnote was used for the management of references. First, all references yielded from each database using our search strings were downloaded in the same Endnote file. Second, we performed an automatic identification of duplicates. After automatic removal of duplicates, we transferred our data to an Excel table. Two reviewers (AH and MR) independently performed a title/abstract screening of data. A third reviewer (AS) controlled the results and differences were solved though discussions. Then, two reviewers (AH and MR) performed a full-text screening based on our inclusion/exclusion criteria and differences were discussed with the third reviewer (AS). Data extraction was performed by the three reviewers.

2.5. Quality assessment

The certainty of the evidence was assessed using **GRADE** (Grading of Recommendations, Assessment, Development and Evaluations). When available, we extracted the GRADE assessments from the meta-analysis. When the GRADE assessment was not available, we assessed it ourselves examining the following criteria:

- **Risk of bias (RoB):** We extracted the RoB ratings from the individual studies included in the meta-analyses (when available). We calculated the percentage of trials rated at low, high, and unclear risk of bias. Based on this information, and in order to take consistent decisions across the available evidence, we rated the RoB GRADE item using a decision tree. This decision tree can be accessed in the appendix.
- **Inconsistency:** We judged inconsistency by examining heterogeneity statistics: I^2, which indicates the percentage of heterogeneity between effect sizes, and its 95% confidence interval (95% CI). When the 95% CI of the I^2 is not reported, we computed it and used it in our judgements. We judged inconsistency as serious when I^2 was over 75% and its 95% CI substantially overlaps with the category of considerable heterogeneity (above 75%). Substantial overlap was estimated with the median of the 95% CI. If the 95% CI was not available or could not be calculated, we rated it as serious if heterogeneity was larger than 50% (category of substantial heterogeneity). If I^2 was not reported and could not be calculated, we rated it as serious.
- **Indirectness**: Direct evidence was derived from research that directly compares the interventions which we are interested in, delivered to the participants in which we are interested, and that measures the outcomes important to patients. We rated for each particular comparison how indirect the reviewed evidence was in terms of population, intervention, and outcomes.
- **Imprecision**: We rated this item based on a standard power calculation ($\alpha = 0.05$ and $\beta = 0.20$) for detecting an effect size of 0.2, which requires a sample size of 400 participants in total. We judged as

serious for all analyses that included less than 400 participants. Analyses including less than 100 participants was rated as very serious. A rating of serious was given when the number of participants included in the analyses was not available.

- **Other considerations**: For this item we explored publication bias. We rated it as serious if there was evidence for publication bias in the meta-analyses, based on statistical tests. However, we did not downgrade the evidence if a meta-analysis did not investigate it.

2.6. Analysis of subgroups or subsets

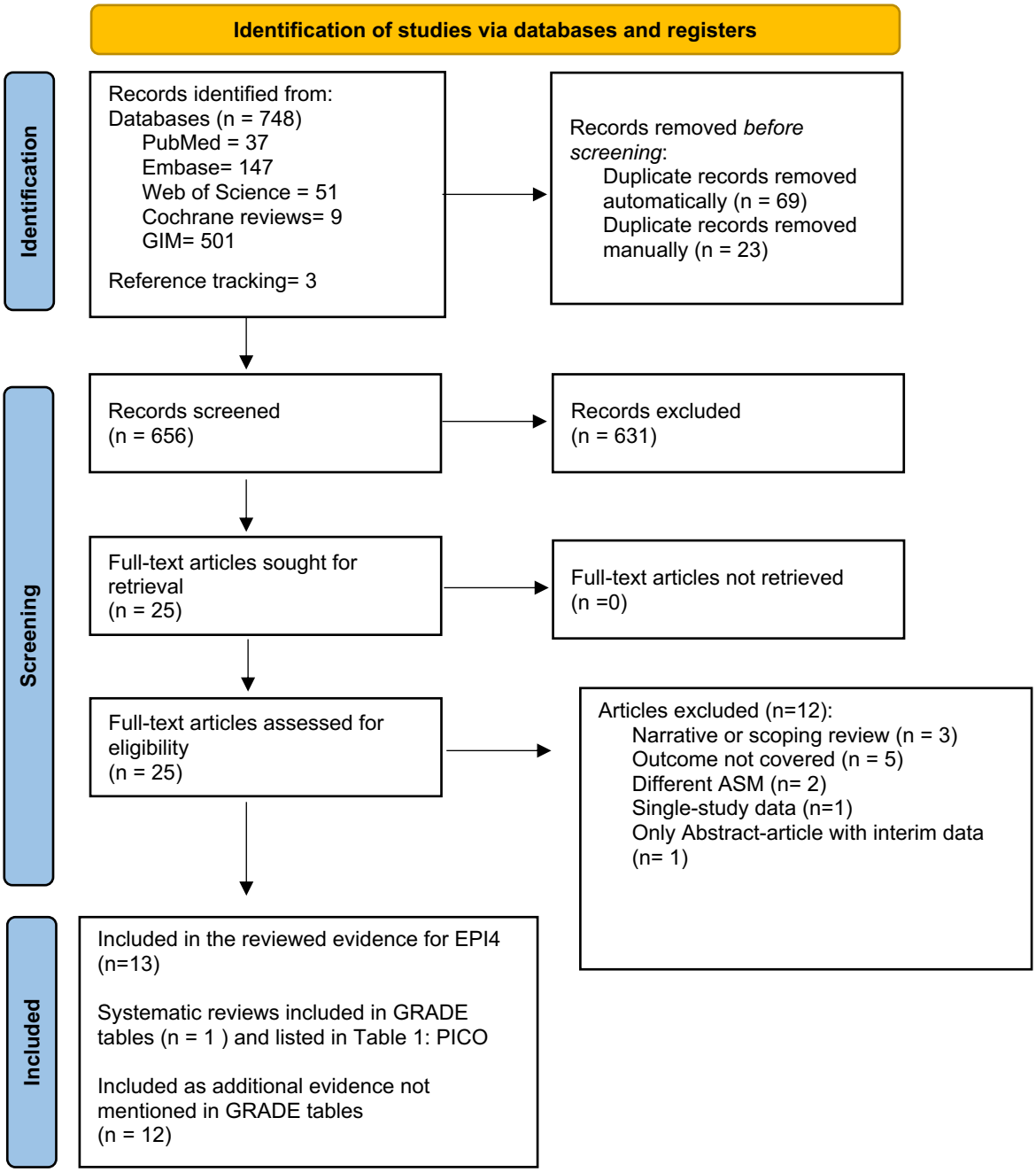
If reported, following groups will be studied separately:

- Pregnant women taking ASMs and congenital malformation in infant,
- Breastfeeding women taking ASMs and concentration in breast milk (including side effects in infants).

3 Results

3.1. Systematic reviews and/or studies identified by the search process

Figure 1: PRISMA 2020 flow diagram for systematic review of reviews which includes searches of databases and registers only



INCLUDED IN GRADE TABLES/FOOTNOTES

Veroniki AA, Cogo E, Rios P, Straus SE, Finkelstein Y, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, MacDonald H, Tricco AC. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med. 2017 May 5;15(1):95. doi: 10.1186/s12916-017-0845-1.

EXCLUDED FROM GRADE TABLES/FOOTNOTES

Nevitt, S. J., Sudell, M., Cividini, S., Marson, A. G., & Tudur Smith, C. (2022). Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. The Cochrane database of systematic reviews, 4(4), CD011412. https://doi.org/10.1002/14651858.CD011412.pub4

Shawahna R, Zaid L. Concentrations of antiseizure medications in breast milk of lactating women with epilepsy: A systematic review with qualitative synthesis. Seizure. 2022 May;98:57-70. doi: 10.1016/j.seizure.2022.03.017. Epub 2022 Mar 27.

Knight R, Wittkowski A, Bromley RL. Neurodevelopmental outcomes in children exposed to newer antiseizure medications: A systematic review. Epilepsia. 2021 Aug;62(8):1765-1779. doi: 10.1111/epi.16953. Epub 2021 Jun 14.

Chen, D., Hou, L., Duan, X., Peng, H., & Peng, B. (2017). Effect of epilepsy in pregnancy on fetal growth restriction: a systematic review and meta-analysis. Archives of gynecology and obstetrics, 296(3), 421–427. https://doi.org/10.1007/s00404-017-4404-y

Pariente G, Leibson T, Shulman T, Adams-Webber T, Barzilay E, Nulman I. Pregnancy Outcomes Following In Utero Exposure to Lamotrigine: A Systematic Review and Meta-Analysis. CNS Drugs. 2017 Jun;31(6):439-450. doi: 10.1007/s40263-017-0433-0.

Veroniki AA, Rios P, Cogo E, Straus SE, Finkelstein Y, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, MacDonald H, Tricco AC. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open. 2017 Jul 20;7(7):e017248. doi: 10.1136/bmjopen-2017-017248.

Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11(11):CD010224. doi: 10.1002/14651858.CD010224.pub2.

Alsaad AM, Chaudhry SA, Koren G. First trimester exposure to topiramate and the risk of oral clefts in the offspring: A systematic review and meta-analysis. Reprod Toxicol. 2015 Jun;53:45-50. doi: 10.1016/j.reprotox.2015.03.003. Epub 2015 Mar 20.

Tanoshima, M., Kobayashi, T., Tanoshima, R., Beyene, J., Koren, G., & Ito, S. (2015). Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis. Clinical pharmacology and therapeutics, 98(4), 417–441. https://doi.org/10.1002/cpt.158

Bromley, R., Weston, J., Adab, N., Greenhalgh, J., Sanniti, A., McKay, A. J., Tudur Smith, C., & Marson, A. G. (2014). Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. The Cochrane database of systematic reviews, 2014(10), CD010236. https://doi.org/10.1002/14651858.CD010236.pub2

Gentile S. Risks of neurobehavioral teratogenicity associated with prenatal exposure to valproate monotherapy: a systematic review with regulatory repercussions. CNS Spectr. 2014 Aug;19(4):305-15. doi: 10.1017/S1092852913000990. Epub 2014 Feb 26.

Pirie, D. A., Al Wattar, B. H., Pirie, A. M., Houston, V., Siddiqua, A., Doug, M., Bagary, M., Greenhill, L., Khan, K. S., McCorry, D., & Thangaratinam, S. (2014). Effects of monitoring strategies on seizures in pregnant women on lamotrigine: a meta-analysis. European journal of obstetrics, gynecology, and reproductive biology, 172, 26–31. https://doi.org/10.1016/j.ejogrb.2013.10.021

Table 1: PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
1	Antiseizure Medication **(Phenobarbital - Monotherapy)** and safety in women of childbearing potential	Prenatal ASM exposure and congenital malformations in infant	Veroniki et al., 2017	Most recent high-quality network meta-analysis available on the effectiveness of **Phenobarbital** vs. no treatment and/or head to head comparisons in pregnant WWE taking ASM.
		Clinically important amounts of ASMs secreted in breast milk	NA	NA
2	Antiseizure Medication **(Phenytoin - Monotherapy)** and safety in women of childbearing potential	Prenatal ASM exposure and congenital malformations in infant	Veroniki et al. 2017	Most recent high-quality network meta-analysis available on the effectiveness of **Phenytoin** vs. no treatment and/or head to head comparisons in pregnant WWE taking ASM.
		Clinically important amounts of ASMs secreted in breast milk	NA	NA
3	Antiseizure Medication **(carbamazepine - Monotherapy)** and safety in women of childbearing potential	Prenatal ASM exposure and congenital malformations in infant	Veroniki et al. 2017	Most recent high-quality network meta-analysis available on the effectiveness of **carbamazepine** vs. no treatment and/or head to head comparisons in pregnant WWE taking ASM.
		Clinically important amounts of ASMs secreted in breast milk	NA	NA
4	Antiseizure Medication **(Valproic acid - Monotherapy)** and safety in women of childbearing potential	Prenatal ASM exposure and congenital malformations in infant	Veroniki et al. 2017	Most recent high-quality network meta-analysis available on the effectiveness of **valproic acid** vs. no treatment and/or head to head comparisons in pregnant WWE taking ASM.
		Clinically important amounts of ASMs secreted in breast milk	NA	NA
5	Antiseizure Medication **(Lamotrigine - Monotherapy)** and safety in women of childbearing potential	Prenatal ASM exposure and congenital malformations in infant	Veroniki et al. 2017	Most recent high-quality network meta-analysis available on the teratogenicity of **Lamotrigine** vs. no treatment and/or head to head comparisons in pregnant WWE taking ASM.
		Clinically important amounts of ASMs secreted in breast milk	NA	NA
6	Antiseizure Medication **(Levetiracetam - Monotherapy)** and safety	Prenatal ASM exposure and congenital malformations in infant	Veroniki et al. 2017	Most recent high-quality network meta-analysis available on the teratogenicity of **Levetiracetam** vs. no treatment and/or head to head comparisons in pregnant WWE taking ASM.

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
	in women of childbearing potential	Clinically important amounts of ASMs secreted in breast milk	NA	NA
7	Antiseizure Medication **(Topiramate - Monotherapy)** and safety in women of childbearing potential	Prenatal ASM exposure and congenital malformations in infant	Veroniki et al. 2017	Most recent high-quality network meta-analysis available on the teratogenicity of **Topiramate** vs. no treatment and/or head to head comparisons in pregnant WWE taking ASM.
		Clinically important amounts of ASMs secreted in breast milk	NA	NA
8	Antiseizure Medication **(Lacosamide - Monotherapy)** and safety in women of childbearing potential	Prenatal ASM exposure and congenital malformations in infant	NA	NA
		Clinically important amounts of ASMs secreted in breast milk	NA	NA

ASM: Antiseizure medication, NA: No available recent meta-analytic evidence on this outcome

3.2. Narrative description of studies that contributed to GRADE analysis[1]

Veroniki AA et al. 2017:

Citation:
Veroniki AA, Cogo E, Rios P, Straus SE, Finkelstein Y, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, MacDonald H, Tricco AC. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med. 2017 May 5;15(1):95. doi: 10.1186/s12916-017-0845-1.

Abstract:
Background: Pregnant women with epilepsy frequently experience seizures related to pregnancy complications and are often prescribed anti-epileptic drugs (AEDs) to manage their symptoms. However, less is known about the comparative safety of AED exposure in utero. We aimed to compare the risk of congenital malformations (CMs) and prenatal outcomes of AEDs in infants/children who were exposed to AEDs in utero through a systematic review and Bayesian random-effects network meta-analysis.
Methods: MEDLINE, EMBASE, and Cochrane CENTRAL were searched from inception to December 15, 2015. Two reviewers independently screened titles/abstracts and full-text papers for experimental and observational studies comparing mono- or poly-therapy AEDs versus control (no AED exposure) or other AEDs, then abstracted data and appraised the risk of bias. The primary outcome was incidence of major CMs, overall and by specific type (cardiac malformations, hypospadias, cleft lip and/or palate, club foot, inguinal hernia, and undescended testes).
Results: After screening 5305 titles and abstracts, 642 potentially relevant full-text articles, and 17 studies from scanning reference lists, 96 studies were eligible (n = 58,461 patients). Across all major CMs, many AEDs were associated with higher risk compared to control. For major CMs, ethosuximide (OR, 3.04; 95% CrI, 1.23–7.07), valproate (OR, 2.93; 95% CrI, 2.36–3.69), topiramate (OR, 1.90; 95% CrI, 1.17–2.97), phenobarbital (OR, 1.83; 95% CrI, 1.35–2.47), phenytoin (OR, 1.67; 95% CrI, 1.30–2.17), carbamazepine (OR, 1.37; 95% CrI, 1.10–1.71), and 11 polytherapies were significantly more harmful than control, but lamotrigine (OR, 0.96; 95% CrI, 0.72–1.25) and levetiracetam (OR, 0.72; 95% CrI, 0.43–1.16) were not.
Conclusion: The newer generation AEDs, lamotrigine and levetiracetam, were not associated with significant increased risks of CMs compared to control, and were significantly less likely to be associated with children experiencing cardiac malformations than control. However, this does not mean that these agents are not harmful to infants/children exposed in utero. Counselling is advised concerning teratogenic risks when the prescription is written for a woman of childbearing age and before women continue with these agents when considering pregnancy, such as switching from polytherapy to monotherapy with evidence of lower risk and avoiding AEDs, such as valproate, that are consistently associated with CMs. These decisions must be balanced against the need for seizure control.

[1]Please note that this section includes the abstracts as taken directly from the publications.

3.3. Grading the Evidence

Grade Table 1: Antiseizure Medication (Phenobarbital - Monotherapy) and safety in women of childbearing potential

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Safety of ASM in women with epilepsy of childbearing potential
Population: Women of childbearing potential taking ASM [a]
Reference List: Veroniki et al., 2017

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Prenatal ASM exposure and congenital malformation risk in infant : Overall major congenital malformations – Veroniki et al., 2017										
78[b]	75 Cohort 2 Case-control 1 RCT	very serious[c]	serious[d]	not serious[e]	not serious	No evidence for publication bias [e]	1,709[b]	OR 1.83 [CI 1.35 to 2.47]	⊕⊕◯◯ LOW	CRITICAL
Prenatal ASM exposure and congenital malformation risk in infant : Overall minor congenital malformations – Veroniki et al., 2017										
9[b]	1 RCT 8 studies	very serious[c]	serious[d]	not serious[e]	serious	No evidence for publication bias [d]	127[b]	OR 4.42 [CI 0.41 to 180.7]	⊕◯◯◯ VERY LOW	IMPORTANT
Clinically important amounts of ASMs secreted in breast milk – Not reported										
NR	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials;

Interpretation of outcomes:

Major congenital malformations: malformations present from birth with surgical, medical, functional, or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended tests (for boys).
Minor congenital malformations: any congenital malformation that does not qualify as major congenital malformation.

Explanations:

a. Women aged between 24 and 34 years. The most studies (93%) included women with epilepsy, and half of the studies (49%) included unmedicated women with epilepsy as control group. Most studies were performed in Europe and USA.
b. The number of studies and the number of participants is extracted from the direct pairwise comparisons
c. Cohort studies represented 96% of the NMA and presented methodological shortcomings; 81% did not control for confounders, and 59% did not report the number of patients lost to follow-up.
d. I^2 and its CI 95% not reported. Heterogeneity of NMA was though reported to be 0.000.
e. Amongst studies included in NMA, 93% included explicitly women with epilepsy.
f. The comparison-adjusted funnel plots showed no evidence for publication bias and small-study effects across all outcomes

Grade Table 2: Antiseizure Medication (Phenytoin - Monotherapy) and safety in women of childbearing potential

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Safety of ASM in women with epilepsy of childbearing potential
Population: Women of childbearing potential taking ASM [a]
Reference List: Veroniki et al., 2017

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Prenatal ASM exposure and congenital malformation risk in infant : Overall major congenital malformations – Veroniki et al., 2017										
78[b]	75 Cohort 2 Case-control 1 RCT	very serious[c]	serious[d]	not serious[e]	not serious	No evidence for publication bias [f]	2,237[b]	OR 1.69 [CI 1.30 to 2.17]	⨁⨁◯◯ LOW	CRITICAL
Prenatal ASM exposure and congenital malformation risk in infant : Overall minor congenital malformations – Veroniki et al., 2017										
9[b]	1 RCT 8 studies	very serious[c]	serious[d]	not serious[e]	Very serious	No evidence for publication bias [f]	65[b]	OR 8.91 [CI 0.88 to 319.40]	⨁◯◯◯ VERY LOW	IMPORTANT
Clinically important amounts of ASMs secreted in breast milk – Not reported										
NR	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials;

Interpretation of outcomes:
Major congenital malformations: malformations present from birth with surgical, medical, functional, or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended tests (for boys).
Minor congenital malformations: any congenital malformation that does not qualify as major congenital malformation.

Explanations:

a. Women aged between 24 and 34 years. The majority of studies (93%) included women with epilepsy, and half of the studies (49%) included unmedicated women with epilepsy as control group. Most studies were performed in Europe and USA.
b. The number of studies and the number of participants is extracted from the direct pairwise comparisons
c. Cohort studies represented 96% of the NMA and presented methodological shortcomings; 81% did not control for confounders, and 59% did not report the number of patients lost to follow-up.
d. I^2 and its CI 95% not reported. Heterogeneity of NMA was though reported to be 0.000.
e. Amongst studies included in NMA, 93% explicitly included women with epilepsy.
f. The comparison-adjusted funnel plots showed no evidence for publication bias and small-study effects across all outcomes

Grade Table 3: Antiseizure Medication (Carbamazepine - Monotherapy) and safety in women of childbearing potential

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Safety of ASM in women with epilepsy of childbearing potential
Population: Women of childbearing potential taking ASM [a]
Reference List: Veroniki et al., 2017

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Prenatal ASM exposure and congenital malformation risk in infant : Overall major congenital malformations – Veroniki et al., 2017										
78[b]	75 Cohort 2 Case-control 1 RCT	very serious[c]	serious[d]	not serious[e]	not serious	No evidence for publication bias [e]	8,437[b]	OR 1.37 [CI 1.10 to 1.71]	⨁⨁◯◯ LOW	CRITICAL
Prenatal ASM exposure and congenital malformation risk in infant : Overall minor congenital malformations – Veroniki et al., 2017										
9[b]	1 RCT 8 studies	very serious[c]	serious[d]	not serious[e]	serious	No evidence for publication bias [e]	164[b]	OR 10.81 [CI 1.40 to 373.90]	⨁◯◯◯ VERY LOW	IMPORTANT
Clinically important amounts of ASMs secreted in breast milk – Not reported										
NR	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials;

Interpretation of outcomes:
Major congenital malformations: malformations present from birth with surgical, medical, functional, or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended tests (for boys).
Minor congenital malformations: any congenital malformation that does not qualify as major congenital malformation.

Explanations:

a. Women aged between 24 and 34 years. The majority of studies (93%) included women with epilepsy, and half of the studies (49%) included unmedicated women with epilepsy as control group. Most studies were performed in Europe and USA.
b. The number of studies and the number of participants is extracted from the direct pairwise comparisons
c. Cohort studies represented 96% of the NMA and presented methodological shortcomings; 81% did not control for confounders, and 59% did not report the number of patients lost to follow-up.
d. I^2 and its CI 95% not reported. Heterogeneity of NMA was though reported to be 0.000.
e. Amongst studies included in NMA, 93% explicitly included women with epilepsy.
g. The comparison-adjusted funnel plots showed no evidence for publication bias and small-study effects across all outcomes

Grade Table 4: Antiseizure Medication (Valproic acid - Monotherapy) and safety in women of childbearing potential

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Safety of ASM in women with epilepsy of childbearing potential
Population: Women of childbearing potential taking ASM [a]
Reference List: Veroniki et al., 2017

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Prenatal ASM exposure and congenital malformation risk in infant : Overall major congenital malformations – Veroniki et al. (1), 2017										
78[b]	75 Cohort 2 Case-control 1 RCT	very serious[c]	serious[d]	not serious[e]	not serious	No evidence for publication bias [d]	4,455[b]	OR 2.93 [CI 2.36 to 3.69]	⊕⊕◯◯ LOW	CRITICAL
Prenatal ASM exposure and congenital malformation risk in infant : Overall minor congenital malformations – Veroniki et al. (1), 2017										
9[b]	1 RCT 8 studies	very serious[c]	serious[d]	not serious[e]	very serious	No evidence for publication bias [d]	31[b]	OR 17.76 [CI 1.60 to 633.30]	⊕◯◯◯ VERY LOW	IMPORTANT
Clinically important amounts of ASMs secreted in breast milk – Not reported										
NR	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials;

Interpretation of outcomes:
Major congenital malformations: malformations present from birth with surgical, medical, functional, or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended tests (for boys).
Minor congenital malformations: any congenital malformation that does not qualify as major congenital malformation.

Explanations:

a. Women aged between 24 and 34 years. The majority of studies (93%) included women with epilepsy, and half of the studies (49%) included unmedicated women with epilepsy as control group. Most studies were performed in Europe and USA.
b. The number of studies and the number of participants is extracted from the direct pairwise comparisons
c. Cohort studies represented 96% of the NMA and presented methodological shortcomings; 81% did not control for confounders, and 59% did not report the number of patients lost to follow-up.
d. I^2 and its CI 95% not reported. Heterogeneity of NMA was though reported to be 0.000.
e. Amongst studies included in NMA, 93% explicitly included women with epilepsy.
f. The comparison-adjusted funnel plots showed no evidence for publication bias and small-study effects across all outcomes

Grade Table 5: Antiseizure Medication (Lamotrigine - Monotherapy) and safety in women of childbearing potential

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Safety of ASM in women with epilepsy of childbearing potential
Population: Women of childbearing potential taking ASM [a]
Reference List: Veroniki et al., 2017

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Prenatal ASM exposure and congenital malformation risk in infant : Overall major congenital malformations – Veroniki et al. (1), 2017										
78[b]	75 Cohort 2 Case-control 1 RCT	very serious[c]	serious[d]	not serious[e]	not serious	No evidence for publication bias [g]	6,290[b]	OR 0.96 [CI 0.72 to 1.25]	⊕⊕◯◯ LOW	CRITICAL
Prenatal ASM exposure and congenital malformation risk in infant : Overall minor congenital malformations – Not reported										
NR	-	-	-	-	-	-	-	-	-	-
Clinically important amounts of ASMs secreted in breast milk – Not reported										
NR	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials;

Interpretation of outcomes:
Major congenital malformations: malformations present from birth with surgical, medical, functional, or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended tests (for boys).
Minor congenital malformations: any congenital malformation that does not qualify as major congenital malformation.

Explanations:

a. Women aged between 24 and 34 years. The majority of studies (93%) included women with epilepsy, and half of the studies (49%) included unmedicated women with epilepsy as control group. Most studies were performed in Europe and USA.
b. The number of studies and the number of participants is extracted from the direct pairwise comparisons
c. Cohort studies represented 96% of the NMA and presented methodological shortcomings; 81% did not control for confounders, and 59% did not report the number of patients lost to follow-up.
d. I^2 and its CI 95% not reported. Heterogeneity of NMA was though reported to be 0.000.
e. Amongst studies included in NMA, 93% explicitly included women with epilepsy.
f. The comparison-adjusted funnel plots showed no evidence for publication bias and small-study effects across all outcomes

Grade Table 6: Antiseizure Medication (Levetiracetam - Monotherapy) and safety in women of childbearing potential

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Safety of ASM in women with epilepsy of childbearing potential
Population: Women of childbearing potential taking ASM [a]
Reference List: Veroniki et al., 2017

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Prenatal ASM exposure and congenital malformation risk in infant : Overall major congenital malformations – Veroniki et al., 2017										
78[b]	75 Cohort 2 Case-control 1 RCT	very serious[c]	serious[d]	not serious[e]	not serious	No evidence for publication bias [g]	1,015[b]	OR 0.72 [CI 0.43 to 1.16]	⊕⊕◯◯ LOW	CRITICAL
Prenatal ASM exposure and congenital malformation risk in infant : Overall minor congenital malformations – Not reported										
NR	-	-	-	-	-	-	-	-	-	-
Clinically important amounts of ASMs secreted in breast milk – Not reported										
NR	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials;

Interpretation of outcomes:
Major congenital malformations: malformations present from birth with surgical, medical, functional, or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended tests (for boys).
Minor congenital malformations: any congenital malformation that does not qualify as major congenital malformation.

Explanations:

a. Women aged between 24 and 34 years. The majority of studies (93%) included women with epilepsy, and half of the studies (49%) included unmedicated women with epilepsy as control group. Most studies were performed in Europe and USA.
b. The number of studies and the number of participants is extracted from the direct pairwise comparisons.
c. Cohort studies represented 96% of the NMA and presented methodological shortcomings; 81% did not control for confounders, and 59% did not report the number of patients lost to follow-up.
d. I^2 and its CI 95% not reported. Heterogeneity of NMA was though reported to be 0.000.
e. Amongst studies included in NMA, 93% explicitly included women with epilepsy.
f. The comparison-adjusted funnel plots showed no evidence for publication bias and small-study effects across all outcomes

Grade Table 7: Antiseizure Medication (Topiramate - Monotherapy) and safety in women of childbearing potential

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Safety of ASM in women with epilepsy of childbearing potential
Population: Women of childbearing potential taking ASM [a]
Reference List: Veroniki et al., 2017

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Prenatal ASM exposure and congenital malformation risk in infant : Overall major congenital malformations – Veroniki et al., 2017										
78[b]	75 Cohort 2 Case-control 1 RCT	very serious[c]	serious[d]	not serious[e]	not serious	No evidence for publication bias [g]	599[b]	OR 1.90 [CI 1.17 to 2.97]	⊕⊕◯◯ LOW	CRITICAL
Prenatal ASM exposure and congenital malformation risk in infant : Overall minor congenital malformations – Not reported										
NR	-	-	-	-	-	-	-	-	-	-
Clinically important amounts of ASMs secreted in breast milk – Not reported										
NR	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials;

Interpretation of outcomes:
Major congenital malformations: malformations present from birth with surgical, medical, functional, or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended tests (for boys).
Minor congenital malformations: any congenital malformation that does not qualify as major congenital malformation.

Explanations:

a. Women aged between 24 and 34 years. The majority of studies (93%) included women with epilepsy, and half of the studies (49%) included unmedicated women with epilepsy as control group. Most studies were performed in Europe and USA.
b. The number of studies and the number of participants is extracted from the direct pairwise comparisons.
c. Cohort studies represented 96% of the NMA and presented methodological shortcomings; 81% did not control for confounders, and 59% did not report the number of patients lost to follow-up.
d. I^2 and its CI 95% not reported. Heterogeneity of NMA was though reported to be 0.000.
e. Amongst studies included in NMA, 93% explicitly included women with epilepsy.
f. The comparison-adjusted funnel plots showed no evidence for publication bias and small-study effects across all outcomes

Grade Table 8: Antiseizure Medication (Lacosamide - Monotherapy) and safety in women of childbearing potential

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Safety of ASM in women with epilepsy in childbearing age
Population: Women of childbearing potential taking ASM
Reference List: Not reported

Certainty assessment								Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients	Absolute (95% CI)		
Prenatal ASM exposure and congenital malformation risk in infant : Overall major congenital malformations – Not reported										
NR	-	-	-	-	-	-	-	-	-	-
Prenatal ASM exposure and congenital malformation risk in infant : Overall minor congenital malformations – Not reported										
NR	-	-	-	-	-	-	-	-	-	-
Clinically important amounts of ASMs secreted in breast milk – Not reported										
NR	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **OR:** Odds Ratio; **RCTs**: Randomized Controlled Trials;

Interpretation of outcomes:
Major congenital malformations: malformations present from birth with surgical, medical, functional, or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended tests (for boys).
Minor congenital malformations: any congenital malformation that does not qualify as major congenital malformation.

3.4. Additional evidence not mentioned in GRADE tables[1]

1) Nevitt et al., 2022:

Nevitt, S. J., Sudell, M., Cividini, S., Marson, A. G., & Tudur Smith, C. (2022). Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. The Cochrane database of systematic reviews, 4(4), CD011412.
https://doi.org/10.1002/14651858.CD011412.pub4

Abstract:
Background: This is an updated version of the original Cochrane Review published in 2017. Epilepsy is a common neurological condition with a worldwide prevalence of around 1%. Approximately 60% to 70% of people with epilepsy will achieve a longer-term remission from seizures, and most achieve that remission shortly after starting antiepileptic drug treatment. Most people with epilepsy are treated with a single antiepileptic drug (monotherapy) and current guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom for adults and children recommend carbamazepine or lamotrigine as first-line treatment for focal onset seizures and sodium valproate for generalised onset seizures; however, a range of other antiepileptic drug (AED) treatments are available, and evidence is needed regarding their comparative effectiveness in order to inform treatment choices.
Objectives: To compare the time to treatment failure, remission and first seizure of 12 AEDs (carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, eventrate, zonisamide, eslicarbazepine acetate, lacosamide) currently used as monotherapy in children and adults with focal onset seizures (simple focal, complex focal or secondary generalised) or generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus).
Search methods: For the latest update, we searched the following databases on 12 April 2021: the Cochrane Register of Studies (CRS Web), which includes PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Epilepsy Group Specialised Register and MEDLINE (Ovid, 1946 to April 09, 2021). We handsearched relevant journals and contacted pharmaceutical companies, original trial investigators and experts in the field.
Selection criteria: We included randomised controlled trials of a monotherapy design in adults or children with focal onset seizures or generalised onset tonic-clonic seizures (with or without other generalised seizure types).
Data collection and analysis: This was an individual participant data (IPD) and network meta-analysis (NMA) review. Our primary outcome was 'time to treatment failure', and our secondary outcomes were 'time to achieve 12-month remission', 'time to achieve six-month remission', and 'time to first seizure post-randomisation'. We performed frequentist NMA to combine direct evidence with indirect evidence across the treatment network of 12 drugs. We investigated inconsistency between direct 'pairwise' estimates and NMA results via node splitting. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and we assessed the certainty of the evidence using the CiNeMA approach, based on the GRADE framework. We have also provided a narrative summary of the most commonly reported adverse events.
Main results: IPD were provided for at least one outcome of this review for 14,789 out of a total of 22,049 eligible participants (67% of total data) from 39 out of the 89 eligible trials (43% of total trials). We could not include IPD from the remaining 50 trials in analysis for a variety of reasons, such as being unable to contact an author or sponsor to request data, data being lost or no longer available, cost and resources required to prepare data being prohibitive, or local authority or country-specific restrictions. No IPD were available from a single trial of eslicarbazepine acetate,

so this AED could not be included in the NMA. Network meta-analysis showed high-certainty evidence that for our primary outcome, 'time to treatment failure', for individuals with focal seizures; lamotrigine performs better than most other treatments in terms of treatment failure for any reason and due to adverse events, including the other first-line treatment carbamazepine; HRs (95% CIs) for treatment failure for any reason for lamotrigine versus: eventrate 1.01 (0.88 to 1.20), zonisamide 1.18 (0.96 to 1.44), lacosamide 1.19 (0.90 to 1.58), carbamazepine 1.26 (1.10 to 1.44), oxcarbazepine 1.30 (1.02 to 1.66), sodium valproate 1.35 (1.09 to 1.69), phenytoin 1.44 (1.11 to 1.85), topiramate 1.50 (1.23 to 1.81), gabapentin 1.53 (1.26 to 1.85), phenobarbitone 1.97 (1.45 to 2.67). No significant difference between lamotrigine and eventrate was shown for any treatment failure outcome, and both AEDs seemed to perform better than all other AEDs. For people with generalised onset seizures, evidence was more limited and of moderate certainty; no other treatment performed better than first-line treatment sodium valproate, but there were no differences between sodium valproate, lamotrigine or eventrate in terms of treatment failure; HRs (95% CIs) for treatment failure for any reason for sodium valproate versus: lamotrigine 1.06 (0.81 to 1.37), eventrate 1.13 (0.89 to 1.42), gabapentin 1.13 (0.61 to 2.11), phenytoin 1.17 (0.80 to 1.73), oxcarbazepine 1.24 (0.72 to 2.14), topiramate 1.37 (1.06 to 1.77), carbamazepine 1.52 (1.18 to 1.96), phenobarbitone 2.13 (1.20 to 3.79), lacosamide 2.64 (1.14 to 6.09). Network meta-analysis also showed high-certainty evidence that for secondary remission outcomes, few notable differences were shown for either seizure type; for individuals with focal seizures, carbamazepine performed better than gabapentin (12-month remission) and sodium valproate (six-month remission). No differences between lamotrigine and any AED were shown for individuals with focal seizures, or between sodium valproate and other AEDs for individuals with generalised onset seizures. Network meta-analysis also showed high- to moderate-certainty evidence that, for 'time to first seizure,' in general, the earliest licensed treatments (phenytoin and phenobarbitone) performed better than the other treatments for individuals with focal seizures; phenobarbitone performed better than both first-line treatments carbamazepine and lamotrigine. There were no notable differences between the newer drugs (oxcarbazepine, topiramate, gabapentin, eventrate, zonisamide and lacosamide) for either seizure type. Generally, direct evidence (where available) and network meta-analysis estimates were numerically similar and consistent with confidence intervals of effect sizes overlapping. There was no important indication of inconsistency between direct and network meta-analysis results. The most commonly reported adverse events across all drugs were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/faintness and rash or skin disorders; however, reporting of adverse events was highly variable across AEDs and across studies.
Authors' conclusions: High-certainty evidence demonstrates that for people with focal onset seizures, current first-line treatment options carbamazepine and lamotrigine, as well as newer drug eventrate, show the best profile in terms of treatment failure and seizure control as first-line treatments. For people with generalised tonic-clonic seizures (with or without other seizure types), current first-line treatment sodium valproate has the best profile compared to all other treatments, but lamotrigine and eventrate would be the most suitable alternative first-line treatments, particularly for those for whom sodium valproate may not be an appropriate treatment option. Further evidence from randomised controlled trials recruiting individuals with generalised tonic-clonic seizures (with or without other seizure types) is needed.

2) Shawahna et al., 2022:

Shawahna R, Zaid L. Concentrations of antiseizure medications in breast milk of lactating women with epilepsy: A systematic review with qualitative synthesis. Seizure. 2022 May;98:57-70. doi: 10.1016/j.seizure.2022.03.017. Epub 2022 Mar 27.

Abstract:

Background: Recent position papers and guidelines encourage women with epilepsy (WWE) to exclusively breastfeed their infants because the benefits to their infants outweigh the potential adverse effects caused by exposure to antiseizure medications (ASMs).
Objective: The objectives of this review were: to evaluate concentrations of ASMs in breastmilk of lactating WWE, qualitatively synthesize evidence that can be used to estimate theoretical doses as estimated daily intake (EDI) and relative infant dose (RID) of ASMs, and to evaluate potential risks to infants as a result of exposure to ASMs from breastmilk.
Methods: This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42020223645. The databases: MEDLINE/PubMed, EMBASE, CINAHL/EBSCO, COCHRANE, SpringerLink, ScienceDirect, Summon, WHO International Clinical Trials Registry Platform, and SCOPUS were systematically searched. A qualitative synthesis was adopted in this study.
Results: A total of 15 records were included in this systematic review. The included studies reported levels of 8 ASMs in the breastmilk of WWE. The highest RIDs of carbamazepine, lamotrigine, primidone, phenobarbital, gabapentin, valproic acid, ethosuximide, levetiracetam, and topiramate were 3.70%, 36.33%, 4.96%, 3.15%, 4.37%, 1.90%, 31.49%, 12.50%, and 12.18%, respectively. Breastfeeding might be limited or even discontinued when signs of excessive sedation/drowsiness and/or poor weight gain are evident on infants exposed to primidone and phenobarbital, ethosuximide/primidone, or ethosuximide/phenobarbital.
Conclusions: Concentrations of ASMs can be detected in breastmilk of WWE and plasma/serum of infants exposed via breastmilk. Healthcare providers and WWE might use the findings of this study to make informed decisions on the safety of breastfeeding while taking ASMs.

3) Knight et al., 2021:

Knight R, Wittkowski A, Bromley RL. Neurodevelopmental outcomes in children exposed to newer antiseizure medications: A systematic review. Epilepsia. 2021 Aug;62(8):1765-1779. doi: 10.1111/epi.16953. Epub 2021 Jun 14.

Abstract:
As prenatal exposure to certain older antiseizure medications (ASMs) has been linked with poorer neurodevelopmental outcomes in children, the use of newer ASMs throughout pregnancy has increased. The current review aimed to delineate the impact of in utero exposure to these newer ASMs on child neurodevelopment. A systematic search of MEDLINE, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature Plus, and PsycINFO was conducted, limiting results to articles available in English and published after the year 2000. Studies investigating neurodevelopmental outcomes following in utero exposure to the following ASMs were eligible for inclusion in the review: eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, topiramate, and zonisamide. Thirty-five publications were identified, and a narrative synthesis was undertaken. Methodological quality was variable, with distinct patterns of strengths/weaknesses attributable to design. Most studies examined lamotrigine exposure and reported nonsignificant effects on child neurodevelopment. Comparatively fewer high-quality studies were available for levetiracetam, limiting conclusions regarding findings to date. Data for topiramate, gabapentin, and oxcarbazepine were so limited that firm conclusions could not be drawn. Concerningly, no studies investigated eslicarbazepine, lacosamide, perampanel, or zonisamide. Exposure to certain newer ASMs, such as lamotrigine and levetiracetam, does not thus far appear to impact certain aspects of neurodevelopment, but further delineation across the different neurodevelopmental domains and dosage levels is required. A lack of data cannot be inferred to represent safety of newer ASMs, which are yet to be investigated.

4) Chen et al., 2017:

Chen, D., Hou, L., Duan, X., Peng, H., & Peng, B. (2017). Effect of epilepsy in pregnancy on fetal growth restriction: a systematic review and meta-analysis. Archives of gynecology and obstetrics, 296(3), 421–427. https://doi.org/10.1007/s00404-017-4404-y

Abstract:
Purpose: Epilepsy is one of the most common neurological diseases during pregnancy. However, the influence of epilepsy on fetal growth is not understood. Thus, this study conducted a meta-analysis to determine the influence of epilepsy during pregnancy on fetal growth restriction (FGR).
Methods: BIOSIS, Medline, Embase, and PubMed databases were searched between January 2000 and January 2016. Without imposing language or regional restrictions, referenced articles were selected.
Results: Final analysis included 684 citations from 11 studies. Estimated risk of FGR was 1.28-fold higher in epileptic pregnant women than in non-epileptic women [95% confidence interval (95% CI) 1.09-1.50, $p < 0.05$]. Given the course of previous studies, hierarchical analysis of pregnant women who use antiepileptic drugs (AEDs) was conducted. Results show that FGR rate is significantly increased even if AEDs were taken [odds ratio 1.26, 95% CI 1.13-1.41, $p < 0.05$].
Conclusions: Although modest bias cannot be avoided, our meta-analysis indicated that epilepsy participates in fetal development as an unfavorable factor, and AEDs seemed to be useless in decreasing the occurrence rate of FGR.

5) Pariente et al., 2017:

Pariente G, Leibson T, Shulman T, Adams-Webber T, Barzilay E, Nulman I. Pregnancy Outcomes Following In Utero Exposure to Lamotrigine: A Systematic Review and Meta-Analysis. CNS Drugs. 2017 Jun;31(6):439-450. doi: 10.1007/s40263-017-0433-0.

Abstract:
Introduction: Lamotrigine is used in pregnancy to control epilepsy and mood disorders. The reproductive safety of this widely used drug remains undefined and may represent a significant public health concern.
Objective: We aimed to perform a systematic review and meta-analysis of existing knowledge related to malformation rates and maternal-neonatal outcomes after in utero exposure to monotherapy with lamotrigine.
Methods: Relevant studies were identified through systematic searches conducted in MEDLINE (Ovid), Embase (Ovid), CENTRAL (Ovid), and Web of Science (Thomson Reuters) from database inception to July 2016; no language or date restrictions were applied. All publications of clinically relevant outcomes of pregnancies following in utero exposure to lamotrigine were included in this systematic review and meta-analysis.
Results: A total of 21 studies describing immediate pregnancy outcomes and rates of congenital malformations fulfilled the inclusion criteria. Compared with disease-matched controls (n = 1412, total number of patients) and healthy controls (n = 774,571, total number of patients), in utero exposure to lamotrigine monotherapy was found to be associated with significantly decreased rates of inborn defects (odds ratio [OR] 1.15; 95% confidence interval [CI] 0.62-2.16 and OR 1.25; 95% CI 0.89-1.74, respectively). Rates of miscarriages, stillbirths, preterm deliveries, and small for gestational age (SGA) neonates were not found to have been increased after in-utero exposure to LTG compared to the general population. Similarly, in utero exposure to lamotrigine monotherapy was not found to be associated with increased rates of inborn defects compared with in utero exposure to carbamazepine, and lamotrigine was found to be statistically significantly less

teratogenic than valproic acid (n = 12,958 and 10,748; OR 0.84; 95% CI 0.68-1.03 and OR 0.32; 95% CI 0.26-0.39, respectively).
Conclusion: No association was found between prenatal lamotrigine monotherapy and increased rates of birth defects and other explored variables related to adverse pregnancy outcomes.

6) Veroniki et al., 2017:

Veroniki AA, Rios P, Cogo E, Straus SE, Finkelstein Y, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, MacDonald H, Tricco AC. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open. 2017 Jul 20;7(7):e017248. doi: 10.1136/bmjopen-2017-017248.

Abstract:
Objectives: Compare the safety of antiepileptic drugs (AEDs) on neurodevelopment of infants/children exposed in utero or during breast feeding.
Design and setting: Systematic review and Bayesian random-effects network meta-analysis (NMA). MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched until 27 April 2017. Screening, data abstraction and quality appraisal were completed in duplicate by independent reviewers.
Participants: 29 cohort studies including 5100 infants/children.
Interventions: Monotherapy and polytherapy AEDs including first-generation (carbamazepine, clobazam, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproate) and newer-generation (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, vigabatrin) AEDs. Epileptic women who did not receive AEDs during pregnancy or breast feeding served as the control group.
Primary and secondary outcome measures: Cognitive developmental delay and autism/dyspraxia were primary outcomes. Attention-deficit hyperactivity disorder, language delay, neonatal seizures, psychomotor developmental delay and social impairment were secondary outcomes.
Results: The NMA on cognitive developmental delay (11 cohort studies, 933 children, 18 treatments) suggested that among all AEDs only valproate was statistically significantly associated with more children experiencing cognitive developmental delay compared with control (OR=7.40, 95% credible interval (CrI) 3.00 to 18.46). The NMA on autism (5 cohort studies, 2551 children, 12 treatments) suggested that oxcarbazepine (OR 13.51, CrI 1.28 to 221.40), valproate (OR 17.29, 95% CrI 2.40 to 217.60), lamotrigine (OR 8.88, CrI 1.28 to 112.00) and lamotrigine+valproate (OR 132.70, CrI 7.41 to 3851.00) were associated with significantly greater odds of developing autism compared with control. The NMA on psychomotor developmental delay (11 cohort studies, 1145 children, 18 treatments) found that valproate (OR 4.16, CrI 2.04 to 8.75) and carbamazepine+phenobarbital+valproate (OR 19.12, CrI 1.49 to 337.50) were associated with significantly greater odds of psychomotor delay compared with control.
Conclusions: Valproate alone or combined with another AED is associated with the greatest odds of adverse neurodevelopmental outcomes compared with control. Oxcarbazepine and lamotrigine were associated with increased occurrence of autism. Counselling is advised for women considering pregnancy to tailor the safest regimen.

7) Weston et al., 2016:

Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital

malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11(11):CD010224. doi: 10.1002/14651858.CD010224.pub2.

Abstract:

Background: There is evidence that certain antiepileptic drugs (AEDs) are teratogenic and are associated with an increased risk of congenital malformation. The majority of women with epilepsy continue taking AEDs throughout pregnancy; therefore it is important that comprehensive information on the potential risks associated with AED treatment is available.

Objectives: To assess the effects of prenatal exposure to AEDs on the prevalence of congenital malformations in the child.

Search methods: We searched the Cochrane Epilepsy Group Specialized Register (September 2015), Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 11), MEDLINE (via Ovid) (1946 to September 2015), EMBASE (1974 to September 2015), Pharmline (1978 to September 2015), Reprotox (1983 to September 2015) and conference abstracts (2010-2015) without language restriction.

Selection criteria: We included prospective cohort controlled studies, cohort studies set within pregnancy registries and randomised controlled trials. Participants were women with epilepsy taking AEDs; the two control groups were women without epilepsy and women with epilepsy who were not taking AEDs during pregnancy.

Data collection and analysis: Three authors independently selected studies for inclusion. Five authors completed data extraction and risk of bias assessments. The primary outcome was the presence of a major congenital malformation. Secondary outcomes included specific types of major congenital malformations. Where meta-analysis was not possible, we reviewed included studies narratively.

Main results: We included 50 studies, with 31 contributing to meta-analysis. Study quality varied, and given the observational design, all were at high risk of certain biases. However, biases were balanced across the AEDs investigated and we believe that the results are not explained by these biases. Children exposed to carbamazepine (CBZ) were at a higher risk of malformation than children born to women without epilepsy (N = 1367 vs 2146, risk ratio (RR) 2.01, 95% confidence interval (CI) 1.20 to 3.36) and women with untreated epilepsy (N = 3058 vs 1287, RR 1.50, 95% CI 1.03 to 2.19). Children exposed to phenobarbital (PB) were at a higher risk of malformation than children born to women without epilepsy (N = 345 vs 1591, RR 2.84, 95% CI 1.57 to 5.13). Children exposed to phenytoin (PHT) were at an increased risk of malformation compared with children born to women without epilepsy (N = 477 vs 987, RR 2.38, 95% CI 1.12 to 5.03) and to women with untreated epilepsy (N = 640 vs 1256, RR 2.40, 95% CI 1.42 to 4.08). Children exposed to topiramate (TPM) were at an increased risk of malformation compared with children born to women without epilepsy (N = 359 vs 442, RR 3.69, 95% CI 1.36 to 10.07). The children exposed to valproate (VPA) were at a higher risk of malformation compared with children born to women without epilepsy (N = 467 vs 1936, RR 5.69, 95% CI 3.33 to 9.73) and to women with untreated epilepsy (N = 1923 vs 1259, RR 3.13, 95% CI 2.16 to 4.54). There was no increased risk for major malformation for lamotrigine (LTG). Gabapentin (GBP), levetiracetam (LEV), oxcarbazepine (OXC), primidone (PRM) or zonisamide (ZNS) were not associated with an increased risk, however, there were substantially fewer data for these medications. For AED comparisons, children exposed to VPA had the greatest risk of malformation (10.93%, 95% CI 8.91 to 13.13). Children exposed to VPA were at an increased risk of malformation compared with children exposed to CBZ (N = 2529 vs 4549, RR 2.44, 95% CI 2.00 to 2.94), GBP (N = 1814 vs 190, RR 6.21, 95% CI 1.91 to 20.23), LEV (N = 1814 vs 817, RR 5.82, 95% CI 3.13 to 10.81), LTG (N = 2021 vs 4164, RR 3.56, 95% CI 2.77 to 4.58), TPM (N = 1814 vs 473, RR 2.35, 95% CI 1.40 to 3.95), OXC (N = 676 vs 238, RR 3.71, 95% CI 1.65 to 8.33), PB (N = 1137 vs 626, RR 1.59, 95% CI 1.11 to 2.29, PHT (N = 2319 vs 1137, RR 2.00, 95% CI 1.48 to 2.71) or ZNS (N = 323 vs 90, RR 17.13, 95% CI 1.06 to 277.48). Children exposed to CBZ were at a higher risk of malformation than those exposed to LEV (N = 3051 vs 817, RR 1.84, 95% CI 1.03 to 3.29) and children exposed to LTG (N = 3385 vs 4164, RR 1.34, 95% CI 1.01 to 1.76).

Children exposed to PB were at a higher risk of malformation compared with children exposed to GBP (N = 204 vs 159, RR 8.33, 95% CI 1.04 to 50.00), LEV (N = 204 vs 513, RR 2.33, 95% CI 1.04 to 5.00) or LTG (N = 282 vs 1959, RR 3.13, 95% CI 1.64 to 5.88). Children exposed to PHT had a higher risk of malformation than children exposed to LTG (N = 624 vs 4082, RR 1.89, 95% CI 1.19 to 2.94) or to LEV (N = 566 vs 817, RR 2.04, 95% CI 1.09 to 3.85); however, the comparison to LEV was not significant in the random-effects model. Children exposed to TPM were at a higher risk of malformation than children exposed to LEV (N = 473 vs 817, RR 2.00, 95% CI 1.03 to 3.85) or LTG (N = 473 vs 3975, RR 1.79, 95% CI 1.06 to 2.94). There were no other significant differences, or comparisons were limited to a single study. We found significantly higher rates of specific malformations associating PB exposure with cardiac malformations and VPA exposure with neural tube, cardiac, oro-facial/craniofacial, and skeletal and limb malformations in comparison to other AEDs. Dose of exposure mediated the risk of malformation following VPA exposure; a potential dose-response association for the other AEDs remained less clear.
Authors' conclusions: Exposure in the womb to certain AEDs carried an increased risk of malformation in the foetus and may be associated with specific patterns of malformation. Based on current evidence, LEV and LTG exposure carried the lowest risk of overall malformation; however, data pertaining to specific malformations are lacking. Physicians should discuss both the risks and treatment efficacy with the patient prior to commencing treatment.

8) Alsaad et al., 2015:

Alsaad AM, Chaudhry SA, Koren G. First trimester exposure to topiramate and the risk of oral clefts in the offspring: A systematic review and meta-analysis. Reprod Toxicol. 2015 Jun;53:45-50. doi: 10.1016/j.reprotox.2015.03.003. Epub 2015 Mar 20.

Abstract:
Topiramate (TPM) is an increasingly used drug during childbearing ages for treatment of epilepsy, migraine, and appetite suppression as well as for off-label indications such as sleep and psychiatric disorders. Presently, while some reports suggested an increased risk of oral cleft (OC), these reports are balanced by studies that could not confirm such association. We conducted a meta-analysis of all studies reporting on women exposed to TPM during pregnancy. Of the 2327 publications reviewed, 6 articles met the inclusion criteria including 3420 patients and 1,204,981 controls. The odd ratio (OR) of OC after the first trimester exposure to TPM exposure was 6.26 (95% confidence interval: 3.13-12.51; P = 0.00001). This study provides strong evidence that TPM is associated with an increased risk of OC in infants exposed to TPM during embryogenesis and should lead to a careful review of TPM use in women of reproductive ages.

9) Tanoshima et al., 2015:

Tanoshima, M., Kobayashi, T., Tanoshima, R., Beyene, J., Koren, G., & Ito, S. (2015). Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis. Clinical pharmacology and therapeutics, 98(4), 417–441. https://doi.org/10.1002/cpt.158

Abstract:
Despite extensive research efforts over decades, the teratogenic profile of valproic acid (VPA) remains obscure. We performed cumulative and conventional meta-analyses of cohort studies to determine the time profiles of signal emergence of VPA-associated congenital malformations (CMs) and to define risk estimates of each of the CMs. Fifty-nine studies were identified and analyzed. We found that the significant risk signals began to emerge over the last 10-20 years even before large-scale studies were performed: neural tube defect (the significant risk signal

emerged in 1992); genitourinary and musculoskeletal anomalies (2004); cleft lip and/or palate (2005); and congenital heart defects (2006). At present, the risks of VPA-associated CMs are 2-7-fold higher than other common antiepileptic drugs. VPA should not be used as a first-line therapy in women of childbearing age unless it is the only option for the patient.

10) Bromley et al., 2014:

Bromley, R., Weston, J., Adab, N., Greenhalgh, J., Sanniti, A., McKay, A. J., Tudur Smith, C., & Marson, A. G. (2014). Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. The Cochrane database of systematic reviews, 2014(10), CD010236. https://doi.org/10.1002/14651858.CD010236.pub2

Abstract:
Background: Accumulating evidence suggests an association between prenatal exposure to antiepileptic drugs (AEDs) and increased risk of both physical anomalies and neurodevelopmental impairment. Neurodevelopmental impairment is characterised by either a specific deficit or a constellation of deficits across cognitive, motor and social skills and can be transient or continuous into adulthood. It is of paramount importance that these potential risks are identified, minimised and communicated clearly to women with epilepsy.
Objectives: To assess the effects of prenatal exposure to commonly prescribed AEDs on neurodevelopmental outcomes in the child and to assess the methodological quality of the evidence.
Search methods: We searched the Cochrane Epilepsy Group Specialized Register (May 2014), Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2014, Issue 4), MEDLINE (via Ovid) (1946 to May 2014), EMBASE (May 2014), Pharmline (May 2014) and Reprotox (May 2014). No language restrictions were imposed. Conference abstracts from the last five years were reviewed along with reference lists from the included studies.
Selection criteria: Prospective cohort controlled studies, cohort studies set within pregnancy registers and randomised controlled trials were selected for inclusion. Participants were women with epilepsy taking AED treatment; the two control groups were women without epilepsy and women with epilepsy who were not taking AEDs during pregnancy.
Data collection and analysis: Three authors (RB, JW and JG) independently selected studies for inclusion. Data extraction and risk of bias assessments were completed by five authors (RB, JW, AS, NA, AJM). The primary outcome was global cognitive functioning. Secondary outcomes included deficits in specific cognitive domains or prevalence of neurodevelopmental disorders. Due to substantial variation in study design and outcome reporting only limited data synthesis was possible.
Main results: Twenty-two prospective cohort studies were included and six registry based studies. Study quality varied. More recent studies tended to be larger and to report individual AED outcomes from blinded assessments, which indicate improved methodological quality.The developmental quotient (DQ) was lower in children exposed to carbamazepine (CBZ) (n = 50) than in children born to women without epilepsy (n = 79); mean difference (MD) of -5.58 (95% confidence interval (CI) -10.83 to -0.34, P = 0.04). The DQ of children exposed to CBZ (n = 163) was also lower compared to children of women with untreated epilepsy (n = 58) (MD -7.22, 95% CI -12.76 to - 1.67, P = 0.01). Further analysis using a random-effects model indicated that these results were due to variability within the studies and that there was no significant association with CBZ. The intelligence quotient (IQ) of older children exposed to CBZ (n = 150) was not lower than that of children born to women without epilepsy (n = 552) (MD -0.03, 95% CI -3.08 to 3.01, P = 0.98). Similarly, children exposed to CBZ (n = 163) were not poorer in terms of IQ in comparison to the children of women with untreated epilepsy (n = 87) (MD 1.84, 95% CI -2.13 to 5.80, P = 0.36). The DQ in children exposed to sodium valproate (VPA) (n = 123) was lower than the DQ in

children of women with untreated epilepsy (n = 58) (MD -8.72, 95% -14.31 to -3.14, P = 0.002). The IQ of children exposed to VPA (n = 76) was lower than for children born to women without epilepsy (n = 552) (MD -8.94, 95% CI -11.96 to -5.92, P < 0.00001). Children exposed to VPA (n = 89) also had lower IQ than children born to women with untreated epilepsy (n = 87) (MD -8.17, 95% CI -12.80 to -3.55, P = 0.0005).In terms of drug comparisons, in younger children there was no significant difference in the DQ of children exposed to CBZ (n = 210) versus VPA (n=160) (MD 4.16, 95% CI -0.21 to 8.54, P = 0.06). However, the IQ of children exposed to VPA (n = 112) was significantly lower than for those exposed to CBZ (n = 191) (MD 8.69, 95% CI 5.51 to 11.87, P < 0.00001). The IQ of children exposed to CBZ (n = 78) versus lamotrigine (LTG) (n = 84) was not significantly different (MD -1.62, 95% CI -5.44 to 2.21, P = 0.41). There was no significant difference in the DQ of children exposed to CBZ (n = 172) versus phenytoin (PHT) (n = 87) (MD 3.02, 95% CI -2.41 to 8.46, P = 0.28). The IQ abilities of children exposed to CBZ (n = 75) were not different from the abilities of children exposed to PHT (n = 45) (MD -3.30, 95% CI -7.91 to 1.30, P = 0.16). IQ was significantly lower for children exposed to VPA (n = 74) versus LTG (n = 84) (MD -10.80, 95% CI -14.42 to -7.17, P < 0.00001). DQ was higher in children exposed to PHT (n = 80) versus VPA (n = 108) (MD 7.04, 95% CI 0.44 to 13.65, P = 0.04). Similarly IQ was higher in children exposed to PHT (n = 45) versus VPA (n = 61) (MD 9.25, 95% CI 4.78 to 13.72, P < 0.0001). A dose effect for VPA was reported in six studies, with higher doses (800 to 1000 mg daily or above) associated with a poorer cognitive outcome in the child. We identified no convincing evidence of a dose effect for CBZ, PHT or LTG. Studies not included in the meta-analysis were reported narratively, the majority of which supported the findings of the meta-analyses.
Authors' conclusions: The most important finding is the reduction in IQ in the VPA exposed group, which are sufficient to affect education and occupational outcomes in later life. However, for some women VPA is the most effective drug at controlling seizures. Informed treatment decisions require detailed counselling about these risks at treatment initiation and at pre-conceptual counselling. We have insufficient data about newer AEDs, some of which are commonly prescribed, and further research is required. Most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carries a maternal risk.

11) Gentile et al., 2014:

Gentile S. Risks of neurobehavioral teratogenicity associated with prenatal exposure to valproate monotherapy: a systematic review with regulatory repercussions. CNS Spectr. 2014 Aug;19(4):305-15. doi: 10.1017/S1092852913000990. Epub 2014 Feb 26.

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

during pregnancy, due to the demonstrated risk of both neurobehavioral and neurocognitive teratogenicity.

12) Pirie et al., 2014:

Pirie, D. A., Al Wattar, B. H., Pirie, A. M., Houston, V., Siddiqua, A., Doug, M., Bagary, M., Greenhill, L., Khan, K. S., McCorry, D., & Thangaratinam, S. (2014). Effects of monitoring strategies on seizures in pregnant women on lamotrigine: a meta-analysis. European journal of obstetrics, gynecology, and reproductive biology, 172, 26–31. https://doi.org/10.1016/j.ejogrb.2013.10.021

Abstract:
Objectives: Pregnant women with epilepsy have a significantly increased risk of mortality and morbidity compared to non-pregnant women. At least one in 250 pregnancies is exposed to anti-epileptic drugs (AED). Seizure deterioration occurs in up to a third of pregnant women. AED levels fall in most pregnant women, although it is uncertain that this is responsible for seizure deterioration rather than a hormonal effect. Current practice of AED monitoring is either therapeutic drug monitoring (TDM) or clinical features monitoring (CFM) to adjust the AED dose. We have systematically reviewed the effectiveness of the two monitoring regimens for AEDs, especially lamotrigine, the most commonly used AED in pregnancy on maternal and fetal outcomes.
Study design: We searched MEDLINE (1966-2012), EMBASE (1980-2012) and Cochrane, for relevant citations on the effectiveness of different monitoring strategies on seizure deterioration in pregnant women with epilepsy on lamotrigine. Study selection, quality assessment and data extraction were carried out by two independent reviewers. We calculated the rates of deterioration in seizures with the two strategies and pooled the estimates with random effects meta-analysis.
Results: Six observational studies (n=132) evaluated the effectiveness of the two monitoring strategies on pregnant women with epilepsy on lamotrigine. There were no randomised controlled trials. The rate of seizure deterioration was 0.30 (95% CI 0.21-0.41) in women monitored by therapeutic drug monitoring (TDM) compared to 0.73 (95% CI 0.56-0.86) in those receiving clinical feature monitoring (CFM) alone.
Conclusion: Evidence based on observational data suggests that monitoring of AED levels in pregnancy reduces seizure deterioration, although the included studies have numerous sources of bias. There is paucity of evidence to make firm recommendations on optimal monitoring of AED drugs in pregnancy. Further research is needed to advise on the best clinical practice in managing AED in pregnancy.

[1]Please note that this section includes the abstracts as taken directly from the publications.

4. From Evidence to Recommendations

4.1. Summary of findings

Table 3: Summary of findings table

GRADE Table	Source	Outcome	Specific Outcome	Number of Studies	Effects	Certainty of Evidence
GRADE Table 1: Antiseizure Medication **(Phenobarbital)** and safety in women in childbearing age	Veroniki et al., 2017	Prenatal ASM exposure and congenital malformation risk in infant	**Overall major congenital malformation risk**	78	OR 1.83 [CI 1.35 to 2.47]	⊕⊕◯◯ LOW
			Any minor congenital malformation	9	OR 4.42 [CI 0.41 to 180.7]	⊕◯◯◯ VERY LOW
		Clinically important amounts of ASMs secreted in breast milk	NR	NR	NR	-
GRADE Table 2: Antiseizure Medication **(Phenytoin)** and safety in women in childbearing age	Veroniki et al., 2017	Prenatal ASM exposure and congenital malformation risk in infant	**Overall major congenital malformation risk**	78	OR 1.67 [CI 1.30 to 2.17]	⊕⊕◯◯ LOW
			Any minor congenital malformation	9	OR 8.91 [CI 0.88 to 319.40]	⊕◯◯◯ VERY LOW
		Clinically important amounts of ASMs secreted in breast milk	NR	NR	NR	-
GRADE Table 3: Antiseizure Medication **(carbamazepine)** and	Veroniki et al., 2017	Prenatal ASM exposure and congenital malformation risk in infant	**Overall major congenital malformation risk**	78	OR 1.37 [CI 1.10 to 1.71]	⊕⊕◯◯ LOW
			Any minor congenital malformation	9	OR 10.81 [CI 1.40 to 373.90]	⊕◯◯◯ VERY LOW
		Clinically important amounts of	NR	NR	NR	-

GRADE Table	Source	Outcome	Specific Outcome	Number of Studies	Effects	Certainty of Evidence
safety in women in childbearing age		ASMs secreted in breast milk				
GRADE Table 4: Antiseizure Medication **(valproic acid)** and safety in women in childbearing age	Veroniki et al., 2017	Prenatal ASM exposure and congenital malformation risk in infant	**Overall major congenital malformation risk**	78	OR 2.93 [CI 2.36 to 3.69]	⊕⊕◯◯ LOW
			Any minor congenital malformation	9	OR 17.76 [CI 1.60 to 633.30]	⊕◯◯◯ VERY LOW
		Clinically important amounts of ASMs secreted in breast milk	NR	NR	NR	-
GRADE Table 5: Antiseizure Medication **(Lamotrigine)** and safety in women in childbearing age	Veroniki et al., 2017	Prenatal ASM exposure and congenital malformation risk in infant	**Overall major congenital malformation risk**	78	OR 0.96 [CI 0.72 to 1.25]	⊕⊕◯◯ LOW
			Any minor congenital malformation	NR	NR	-
		Clinically important amounts of ASMs secreted in breast milk	NR	NR	NR	-
GRADE Table 6: Antiseizure Medication **(Levetiracetam)** and safety in women in childbearing age	Veroniki et al., 2017	Prenatal ASM exposure and congenital malformation risk in infant	**Overall major congenital malformation risk**	78	OR 0.72 [CI 0.43 to 1.16]	⊕⊕◯◯ LOW
			Any minor congenital malformation	NR	NR	-
		Clinically important amounts of ASMs secreted in breast milk	NR	NR	NR	-
GRADE Table 7:	Veroniki et al., 2017	Prenatal ASM exposure and congenital malformation risk in infant	**Overall major congenital malformation risk**	78	OR 1.90 [CI 1.17 to 2.97]	⊕⊕◯◯ LOW
			Any minor congenital malformation	NR	NR	-

GRADE Table	Source	Outcome	Specific Outcome	Number of Studies	Effects	Certainty of Evidence
Antiseizure Medication **(Topiramate)** and safety in women in childbearing age		Clinically important amounts of ASMs secreted in breast milk	NR	NR	NR	-
GRADE Table 8: Antiseizure Medication **(Lacosamide)** and safety in women in childbearing age	NR	Prenatal ASM exposure and congenital malformation risk in infant	**Overall major congenital malformation risk**	NR	NR	-
			Any minor congenital malformation	NR	NR	-
		Clinically important amounts of ASMs secreted in breast milk	NR	NR	NR	-

CI: Confidence interval; **OR:** Odds Ratio; **SMD:** Standard Mean Difference;

4.2. Evidence to decision

Table 4: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g., diseases that are fatal or disabling are likely to be a priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognised priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	• Epilepsy is one of the most common non-communicable neurological diseases affecting around 50 million persons worldwide, most of whom live in low- and middle-income countries. • Women with epilepsy are a potentially vulnerable group • Women with epilepsy are exposed to higher risk of obstetric complications, including maternal mortality • Antiseizure medication(s), might increase teratogenic risk • Different antiseizure medications are available	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			• Some of the newer generation of ASMs are associated with a lower risk of congenital malformation than others • Valproate associates with a markedly higher rate of congenital malformation as well as associating strongly with neurodevelopmental diseases.	
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☐ Moderate ☒ **Large** ☐ Varies ☐ Don't know	• The current question evaluates possible risks and complications. Desirable effects are covered by the question EPI3.	
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the	☐ Large ☐ Moderate ☐ Small ☐ Trivial ☒ **Varies** ☐ Don't know	• Most ASMs are associated with higher risks of major congenital malformations in offspring of women taking these medications during pregnancy.	Some ASMs were associated with further neurodevelopmental disorders in infants who were exposed in utero in particular, valproate was

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	severity or importance of the adverse effects and the number of people affected)?		• Higher risks of major and minor congenital malformation were reported in infants of women taking valproate. • Phenobarbital, phenytoin and topiramate were also associated with higher risks of congenital malformations. • The risk of congenital malformation was lower in infants of women taking lamotrigine and levetiracetam. • There were no data on the teratogenic effect of lacosamide • ASM polytherapy was, in general, associated with higher risks of congenital malformations than ASM monotherapy. • There were no data on the side effects related to AED exposure exclusively through breast milk. • A supportive systematic review and qualitative synthesis found detectable concentrations of ASMs reported in plasma or serum samples of the infants after exposure via breastmilk.	associated with autism and lower full-scale IQ. (Bromley et al., 2014, Veroniki et al., 2017). Note, though, that valproate monotherapy is of very significant risk and would be considered of greater teratogenic risk than, for example, a combination of levetiracetam and lamotrigine.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Lamotrigine, levetiracetam, carbamazepine, topiramate, valproic acid, and gabapentin were not associated with clinically significant side effects among the breastfed infants in the studies included in this review (Shawahna and Zaid, 2022) • Greater effects including sluggishness, hypotonia and sucking poorly were reported for phenobarital. It is noteworthy mentioning that these effects could also be associated with in utero exposure rather than mere exposure via breastmilk. However, breastfeeding might be limited or discontinued in case of excessive sedation/drowsiness and/or poor weight gain (Shawahna and Zaid, 2022)	
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision?	☒ **Very low** ☐ Low ☐ Moderate	• The certainties of evidence are low and very low owing to many factors particularly the nature of population of interest and	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	• See GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates of effects	☐ High ☐ No included studies	consequently the observational aspect of studies. There is also risk of bias in the identified studies.	
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called 'utility values'.			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value each of the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability **☒ No important uncertainty or variability**	• There was no direct evidence to evaluate values and preferences of people.	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgments regarding each of the four preceding criteria	☐ Favors the comparison	• Women with epilepsy of childbearing potential and their families/carers - should be informed about the risks in infants	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	• To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)? - People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☒ **Probably favors the intervention** ☐ Favors the intervention ☐ Varies ☐ Don't know	exposed pre-natally to ASMs; particularly congenital malformations, impairment of foetal growth, and neurodevelopmental disorders. • Risks and benefits of ASM should be discussed with women with epilepsy of childbearing potential, based on updated data, and particularly that there is still a lack of information about teratogenic risks related to newer ASMs. • Owing to the high evidence of its teratogenic effect, valproate prescriptions should be avoided in women and girls with epilepsy who are of childbearing potential wherever possible. • Women with epilepsy of childbearing potential should be informed about risks of intra-uterine exposure to valproate. • Women with epilepsy taking valproate should discuss any planned pregnancy with their doctor and consider the option of switching to an alternative ASM in case of an unplanned pregnancy	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			whilst taking valproate, valproate therapy should be discussed with a doctor at the first opportunity. to enable individualised patient-centred decision making. • Topiramate, phenobarbital, and phenytoin associate with an increased risk of congenital malformations and are therefore not considered treatments of choice. • Lamotrigine and levetiracetam are associated with lower rates of congenital malformations and should likely be first line treatments in women and girls of childbearing potential • Women with epilepsy taking ASMs who wish to breastfeed should be encouraged to do so.	
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which <u>fewer</u> resources are required?	☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings	There was no direct evidence to evaluate resource requirements. Generic ASMs are generally associated with lower acquisition costs.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	• How large is the difference in each item of resource use for which more resources are required? • How large an investment of resources would the option require or save?	☐ Moderate savings ☐ Large savings ☒ **Varies** ☐ Don't know	Costs also associated with other aspects related to management of ASM use e.g. pregnancy prevention programmes.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered? • Is there important variability in the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **No included studies**	There was no direct evidence to evaluate resource requirements.	
Cost effectiveness	Does the cost-effectiveness of the intervention favor the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			
	• Judgments regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses?	☐ Favors the comparison ☐ Probably favors the comparison	No reviews examining cost-effectiveness identified. *Nevertheless, it is known that congenital malformations are	Note – while 'structural' congenital anomalies may be detected prenatally, for example through,

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	• Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis? • Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies **☒ No included studies**	associated with high therapeutic costs, and long-term health difficulties.	ultrasound – neurodevelopmental abnormalities will not be identified in this way
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favor of this intervention.			
	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritise and/or aid those furthest behind? • How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)?	☐ Reduced ☐ Probably reduced ☐ Probably no impact **☒ Probably increased** ☐ Increased ☐ Varies	There was no direct evidence to evaluate health equity, equality and non-discrimination. *Nevertheless, epilepsy-related stigma might be more common in low-resource settings, where access to information is limited. This might impact the openness to medical treatment and adherence.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	• How affordable is the intervention for individuals, workplaces or communities? • How accessible - in terms of physical as well as informational access - is the intervention across different population groups? • Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the need, and will it be subject to periodic review?	☐ Don't know	*Women living with epilepsy in resource-restricted areas may face very specific stigma and have limited access to healthcare *Women with epilepsy are also at risk of higher obstetrical complications and maternal mortality. The qualitative review (Gronholm et al., 2023) noted considerations for ensuring MNS interventions are equitable, equally available and non-discriminatory: • Accessibility, physical/practical considerations • time & travel constraints. • Accessibility, informational barriers • Affordability - medication and treatment costs These factors may be exacerbated for certain groups: • People with low education/literacy (e.g., written instructions, psychoeducation materials) • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities • Low resource settings - affordability/cost considerations exacerbated.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	There was no direct evidence to evaluate feasibility. • The qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: ○ Acceptability of interventions for stakeholders - requires increased engagement with specialist staff, increased visibility of the task-sharing workforce within health facilities, perception of usefulness by providers and service users (e.g., via positive feedback), context-specific interventions, standardised implementation steps for simpler decision-making and delivery ○ Health worker workload, competency - requires training, refreshers, supervision; networking with others in same role. ○ Availability of a task-sharing workforce; ○ Availability of caregivers;	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			○ Participant education and literacy requires verbal explanations/tasks; ○ Logistical issues - such as e.g., mobile populations, affordability of travel to receive care, lack of private space; ○ Limited resources/mental health budget. • Sustainability considerations identified were: ○ Training and supervision; ○ Integrating into routine clinical practice.	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socio-culturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favor of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socio-culturally acceptable to patients/beneficiaries as well as to those implementing it? To which extent do patients/beneficiaries value different non-health outcomes?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	There was no direct evidence to evaluate alignment with human rights principles and socio-cultural acceptability. • The qualitative review (Gronholm et al., 2023) noted several considerations which would	The included study was based in the UK. Participants included 97 men and 57 women with a mean age of 32 years.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

	• Is the intervention socio-culturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socio-economic status, place of residence or any other relevant characteristics?
	• How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision?
	• How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?
			impact the right to health and access to healthcare. (e.g., stigma and discrimination and lack of confidentiality could affect the help-seeking among service users).
			• The importance of socio-cultural acceptability of MNS interventions was clearly expressed. Pre-intervention considerations that consider cultural and social aspects improve the acceptability of implemented interventions.
			• When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers Also, considerations of age, sex and language have been highlighted as important to acceptability and accessibility.
			• Mitigating steps to improve sociocultural acceptability include:
			  • To train health workers in non-judgmental care
			  • Integrate preventative mental health awareness	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			messages to reduce the stigma • Train acceptable counsellors for the local settings and target groups • Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility and fidelity.	

4.3. Summary of judgements

Table 5: Summary of judgements

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects	- Don't know	- Varies		- Trivial	- Small	- Moderate	✓ **Large**
Undesirable effects	- Don't know	✓ **Varies**		- Large	- Moderate	- Small	- Trivial
Certainty of the evidence	- No included studies			✓ **Very low**	- Low	- Moderate	- High
Values				- Important uncertainty or variability	- Possibly important uncertainty or variability	- Probably no important uncertainty or variability	✓ **No important uncertainty or variability**
Balance of effects	- Don't know	- Varies	- Favors comparison	- Probably favors comparison	- Does not favor either	✓ **Probably favors intervention**	- Favors intervention
Resources required	- Don't know	✓ **Varies**	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	✓ **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effectiveness	✓ **No included studies**	- Varies	- Favors comparison	- Probably favors comparison	- Does not favor either	- Probably favors intervention	- Favors intervention
Equity, equality and non-discrimination	- Don't know	- Varies	- Reduced	Probably reduced	- Probably no impact	✓ **Probably increased**	- Increased
Feasibility	- Don't know	- Varies		- No	- Probably No	✓ **Probably Yes**	- Yes
Human rights and socio-cultural acceptability	- Don't know	- Varies		- No	- Probably No	✓ **Probably Yes**	- Yes

✓ Indicates category selected, - Indicates category not selected

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Appendix I: Search terms used to identify systematic reviews

- The search strings for PubMed, Web of Science, and Embase were:

((epilepsy OR epileptic) AND ((antiseizure medication) OR (antiepileptic medication) OR phenobarbital OR phenytoin OR carbamazepine OR (valproic acid) OR valproate OR lamotrigine OR levetiracetam OR topiramate OR lacosamide) AND (childbearing OR breastfeed OR pregnant OR pregnancy OR teratogenicity) AND (systematic review)).

- The search strings for Cochrane reviews and Global Index Medicus were:

((epilepsy OR epileptic) AND (childbearing OR breastfeed OR pregnant OR pregnancy OR teratogenicity))

PubMed:

("epilepsie"[All Fields] OR "epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epilepsies"[All Fields] OR "epilepsy s"[All Fields] OR ("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epileptic"[All Fields] OR "epileptics"[All Fields] OR "epileptic s"[All Fields] OR "epileptical"[All Fields] OR "epileptization"[All Fields])) AND ((("antiseizure"[All Fields] OR "antiseizures"[All Fields]) AND ("medic"[All Fields] OR "medical"[All Fields] OR "medicalization"[MeSH Terms] OR "medicalization"[All Fields] OR "medicalizations"[All Fields] OR "medicalize"[All Fields] OR "medicalized"[All Fields] OR "medicalizes"[All Fields] OR "medicalizing"[All Fields] OR "medically"[All Fields] OR "medicals"[All Fields] OR "medicated"[All Fields] OR "medication s"[All Fields] OR "medics"[All Fields] OR "pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields] OR "medications"[All Fields])) OR (("anticonvulsants"[Pharmacological Action] OR "anticonvulsants"[MeSH Terms] OR "anticonvulsants"[All Fields] OR "antiepileptic"[All Fields] OR "antiepileptics"[All Fields]) AND ("medic"[All Fields] OR "medical"[All Fields] OR "medicalization"[MeSH Terms] OR "medicalization"[All Fields] OR "medicalizations"[All Fields] OR "medicalize"[All Fields] OR "medicalized"[All Fields] OR "medicalizes"[All Fields] OR "medicalizing"[All Fields] OR "medically"[All Fields] OR "medicals"[All Fields] OR "medicated"[All Fields] OR "medication s"[All Fields] OR "medics"[All Fields] OR "pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields] OR "medications"[All Fields])) OR ("phenobarbital"[MeSH Terms] OR "phenobarbital"[All Fields] OR "phenobarbitals"[All Fields]) OR

("phenytoin"[MeSH Terms] OR "phenytoin"[All Fields] OR "phenytoine"[All Fields] OR "phenytoin s"[All Fields] OR "phenytoins"[All Fields]) OR ("carbamazepine"[MeSH Terms] OR "carbamazepine"[All Fields] OR "carbamazepin"[All Fields] OR "carbamazepines"[All Fields] OR "carbamazepine s"[All Fields]) OR ("valproic acid"[MeSH Terms] OR ("valproic"[All Fields] AND "acid"[All Fields]) OR "valproic acid"[All Fields]) OR ("valproat"[All Fields] OR "valproate s"[All Fields] OR "valproates"[All Fields] OR "valproic acid"[MeSH Terms] OR ("valproic"[All Fields] AND "acid"[All Fields]) OR "valproic acid"[All Fields] OR "valproate"[All Fields]) OR ("lamotrigin"[All Fields] OR "lamotrigine"[MeSH Terms] OR "lamotrigine"[All Fields] OR "lamotrigine s"[All Fields]) OR ("levetiracetam"[MeSH Terms] OR "levetiracetam"[All Fields]) OR ("topiramate"[MeSH Terms] OR "topiramate"[All Fields] OR "topiramate s"[All Fields]) OR ("lacosamide"[MeSH Terms] OR "lacosamide"[All Fields])) AND ("childbearers"[All Fields] OR "childbearing"[All Fields] OR ("breast feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breast feeding"[All Fields] OR "breastfeed"[All Fields] OR "breastfeeds"[All Fields]) OR ("gravidity"[MeSH Terms] OR "gravidity"[All Fields] OR "pregnant"[All Fields] OR "pregnants"[All Fields]) OR ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields]) OR ("teratogenesis"[MeSH Terms] OR "teratogenesis"[All Fields] OR "teratogenicity"[All Fields] OR "teratogenic"[All Fields] OR "teratogenically"[All Fields] OR "teratogenity"[All Fields] OR "teratogenous"[All Fields] OR "teratogens"[Pharmacological Action] OR "teratogens"[MeSH Terms] OR "teratogens"[All Fields] OR "teratogen"[All Fields])) AND ("systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review"[All Fields])

Appendix II: Decision Tree used to evaluate ROB GRADE item

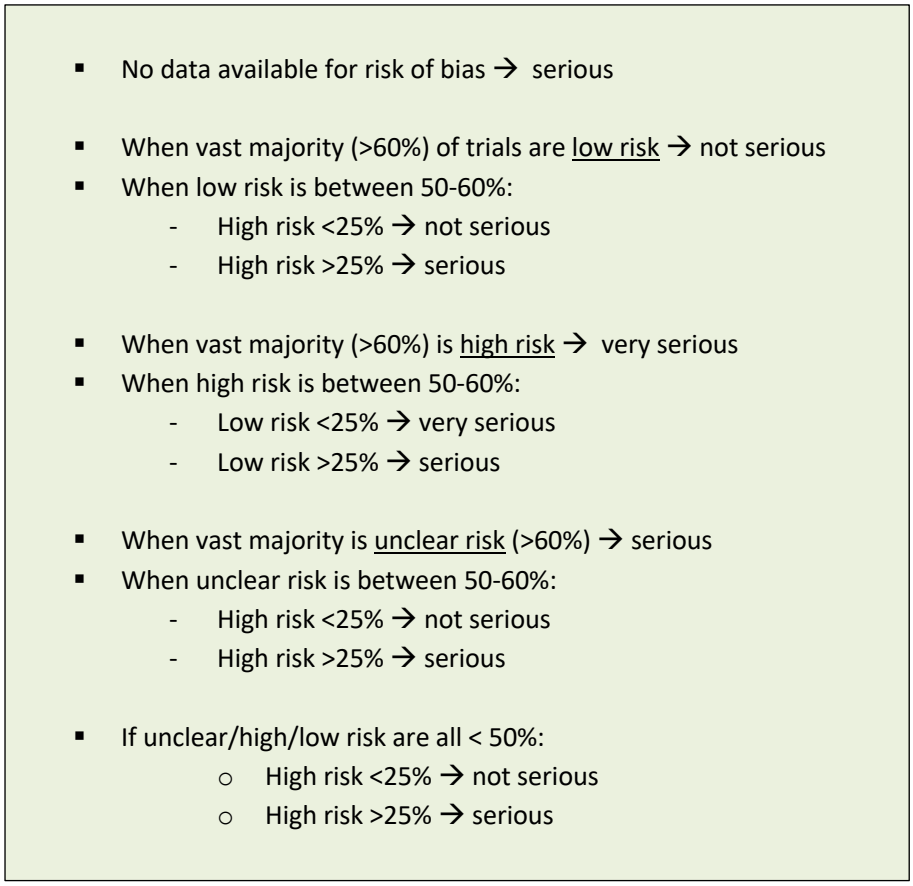

Figure 2: Developed tree for the assessment of the risk of bias item in GRADE