SPECIAL ARTICLE

Teratogenesis, Perinatal, and Neurodevelopmental Outcomes After In Utero Exposure to Antiseizure Medication

Practice Guideline From the AAN, AES, and SMFM

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Abstract

This practice guideline provides updated evidence-based conclusions and recommendations regarding the effects of antiseizure medications (ASMs) and folic acid supplementation on the prevalence of major congenital malformations (MCMs), adverse perinatal outcomes, and neurodevelopmental outcomes in children born to people with epilepsy of childbearing potential (PWECP). A multidisciplinary panel conducted a systematic review and developed practice recommendations following the process outlined in the 2017 edition of the American Academy of Neurology Clinical Practice Guideline Process Manual. The systematic review includes studies through August 2022. Recommendations are supported by structured rationales that integrate evidence from the systematic review, related evidence, principles of care, and inferences from evidence. The following are some of the major recommendations. When treating PWECP, clinicians should recommend ASMs and doses that optimize both seizure control and fetal outcomes should pregnancy occur, at the earliest possible opportunity preconceptionally. Clinicians must minimize the occurrence of convulsive seizures in PWECP during pregnancy to minimize potential risks to the birth parent and to the fetus. Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures. Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in PWECP when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs. Clinicians must avoid the use of valproic acid in PWECP to minimize the risk of MCMs or neural tube defects (NTDs), if clinically feasible. Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born small for gestational age, if clinically feasible. To reduce the risk of poor neurodevelopmental outcomes, including autism spectrum disorder and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in PWECP, if clinically feasible. Clinicians should prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to decrease the risk of NTDs and possibly improve neurodevelopmental outcomes in the offspring.

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Glossary

AAN = American Academy of Neurology; **aHR** = adjusted hazard ratio; **ASD** = autism spectrum disorder; **ASM** = antiseizure medication; **COI** = conflict of interest; **MCM** = major congenital malformation; **NTD** = neural tube defect; **PD** = prevalence difference; **PR** = prevalence ratio; **PWECP** = people with epilepsy of childbearing potential; **RMD** = raw mean difference; **SGA** = small for gestational age.

Epilepsy is one of the most common neurologic disorders, affecting more than 50 million people worldwide. One in 5 of those affected are people of childbearing potential, based on extrapolations from the proportion of the 2022 US female population aged 15–45 years.[1] Infants born to people with epilepsy are at increased risk of major congenital malformations (MCMs), adverse perinatal outcomes, and adverse neurodevelopmental outcomes.[2] Multiple factors are associated with this risk, including genetic differences, environmental factors, seizure control, and intrauterine exposure to antiseizure medications (ASMs). The role of folic acid supplementation in mitigating these risks is unclear. Optimizing the treatment of epilepsy is necessary to achieve the most favorable outcomes for persons with epilepsy and their offspring.

In 2009, the American Academy of Neurology (AAN) published the guideline "Practice Parameter update: Management issues for women with epilepsy—Focus on pregnancy: Teratogenesis and perinatal outcomes."[3] The authors concluded that treatment with valproic acid carries a higher risk of MCMs in the offspring of women with epilepsy than treatment with carbamazepine, phenytoin, and phenobarbital, especially if taken in polytherapy. The risk associated with other commonly used ASMs, such as levetiracetam or topiramate, was not evaluated because of limited available evidence. The authors concluded that treatment with valproic acid carried the highest risk of adverse cognitive outcomes in the offspring of women with epilepsy as compared with carbamazepine, although the risk of autism spectrum disorder (ASD) was not addressed because this association was not yet reported in the literature. Infants exposed to any ASM in utero had a higher risk of being born small for gestational age (SGA), but there was no evidence of an increased risk of fetal death.

A separate 2009 practice guideline recommended that preconception folic acid supplementation "may be considered to reduce the risk of MCMs," but did not provide further guidance on supplementation dosage.[4] Since 2009, new studies have been published related to the risk of MCMs associated with several ASMs, the association between different ASMs and adverse perinatal or neurodevelopmental outcomes, and the effect of folic acid supplementation.

While the 2009 guidelines described the affected population as "women with epilepsy," this phrasing does not recognize the important difference between biological sex and sociocultural gender. In this update, we refer to the affected population with the gender-neutral language, "people with epilepsy of childbearing potential" (PWECP).

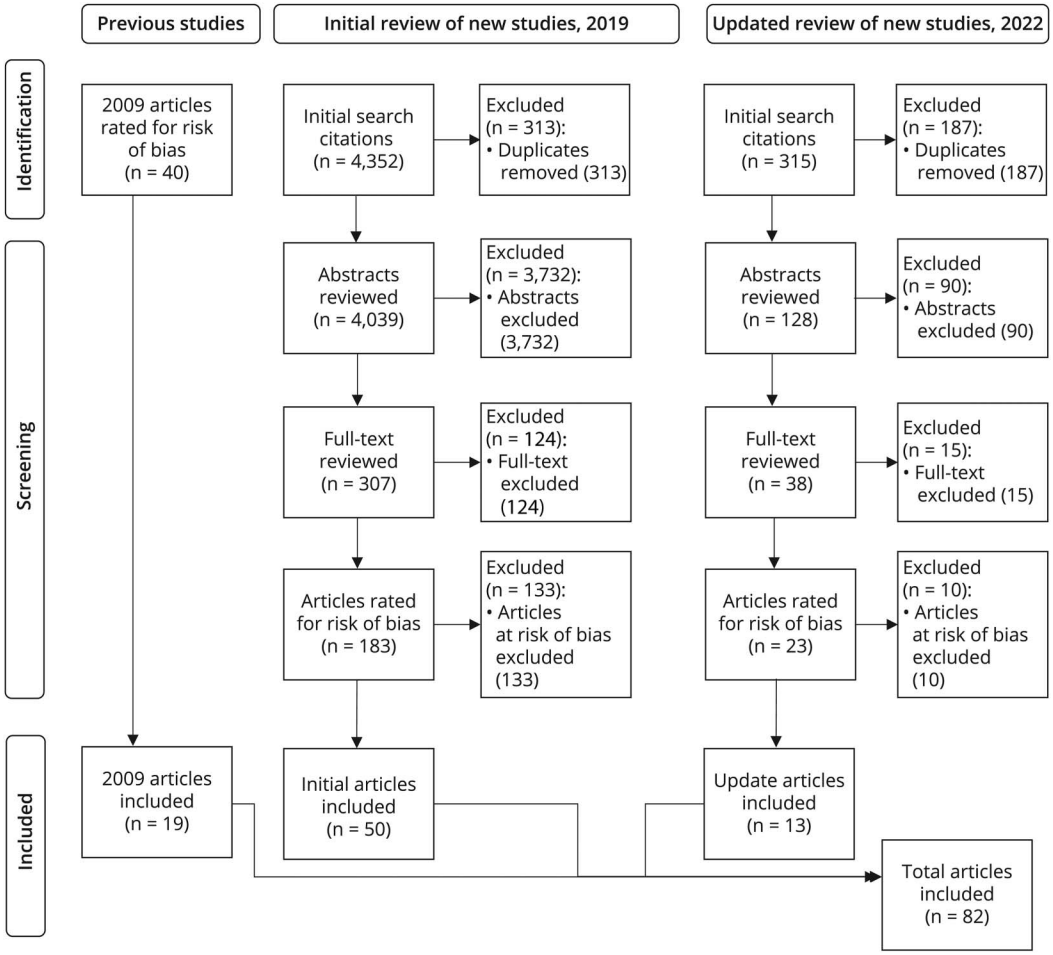
In this practice guideline update, we aim to provide guidance to clinicians when choosing an ASM, in monotherapy or polytherapy, in this patient population. We also aim to clarify the potential role of folic acid supplementation among PWECP. This guideline specifically addresses the following 4 clinical questions:

1. What is the prevalence of MCMs associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high doses vs low-medium doses of ASMs, in children born to PWECP?
2. What is the prevalence of adverse perinatal outcomes associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high doses vs low-medium doses of ASMs, in children born to PWECP?
3. What is the prevalence of adverse neurodevelopmental outcomes associated with intrauterine exposure to specific ASMs, and how does this vary between ASMs in monotherapy vs polytherapy, and at high vs low-medium doses of ASMs, in children born to PWECP?
4. What is the effect of intrauterine exposure to folic acid on the prevalence of MCMs, adverse perinatal outcomes, and neurodevelopmental outcomes, and how does this vary by folic acid dose in children born to PWECP treated with ASMs?

Description of the Analytic Process

The development of this practice guideline followed the 2017 edition of the AAN's guideline development process manual.[5] In March 2018, a multidisciplinary panel was recruited to develop the protocol for this guideline. The authors include content experts, methodologists, Guidelines Subcommittee members, an AAN epilepsy quality measure workgroup representative, physician representatives for the American Epilepsy Society and the Society for Maternal-Fetal Medicine, and patient advocates. In accordance with AAN policy, the current lead developer (A.M.P.), and the majority of the panel, has no conflicts of interest (COIs). Five of the 19 guideline developers (J.F., E.G., K.P., G.S., and T.T.) were determined to have COIs, but each COI was judged to be not significant enough to preclude authorship. These 5 developers were not permitted to review or rate the evidence; they served in an advisory capacity to help with the validation of the key

Figure Study Selection



questions, the scope of the literature search, and the identification of seminal articles. They also participated in the recommendation development process. The full author panel was solely responsible for final decisions about the design, analysis, and reporting of this guideline.

This article is a summary of the key findings of the guideline. The complete guideline, including the literature search strategy, details about evidence classification, and the full systematic review of the evidence, is available in eAppendix 1.

Systematic Review of the Evidence

The panel searched Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, Ovid Embase, CINAHL, the Database of Abstracts of Reviews of Effects, ClinicalTrials.gov, and the US Food and Drug Administration literature databases from June 1, 2007, to February 15, 2019, for relevant peer-reviewed articles that met inclusion criteria. The initial search after duplicates were removed yielded 4,039 articles. Using a systematic process detailed in the AAN's guideline development process manual,[5] 2 review panel members (not the same pair for all articles) independently reviewed the article titles and abstracts for relevance and then reviewed the full text of the articles determined to be relevant (Figure). Disagreements about inclusion were resolved through discussion between the 2 panelists, with a third reviewer included to break ties when necessary. One hundred eighty-three articles were selected and rated for risk of bias by 2 panel members using the AAN criteria for the classification of causation studies. Class I studies have the lowest risk of bias, and Class IV studies have the highest risk of bias. As per predefined exclusion criteria that are laid out in the process manual,[5] the panel excluded articles that were assessed as Class IV (n = 133). This left 50 articles for inclusion. Forty articles included in the 2009 guidelines were reviewed by 2 panel members and 19 were selected for inclusion, for a total of 69 articles.

An updated literature search was completed to identify additional relevant articles published between February 15, 2019, and August 1, 2022. The initial search after duplicates were removed yielded 128 articles. The abstracts and full-text articles were reviewed following the same process as the first literature review, which resulted in 13 articles being added to the systematic review (Figure). The primary findings of the systematic review are summarized in Tables 1–7. Additional data are presented in eTables 1 and 2.

As detailed in the AAN's guideline development process manual, a modified version of the Grading of Recommendations

Table 1 Unadjusted Prevalence of Any MCM by ASM in Monotherapy or Polytherapy

ASM	Mono or polytherapy	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence between monotherapy and polytherapy (95% CI)
Carbamazepine	Monotherapy	9,908	69.6	2 Class I,[6,7] 6 Class II,[8-13] 11 Class III[14-24]	43.7 (35.7–52.6)	−14.9 (−38.1 to 8.3) Low confidence in evidence
	Polytherapy	1,231	59.3	3 Class II,[8,10,12] 5 Class III[17,18,20,25,26]	58.6 (38.8–82.1)	
Clobazam	Monotherapy	64	0	1 Class II[11]	31.3 (0.5–91.9)	−5.8 (−82.4 to 70.8) Very low confidence in evidence, downgraded for imprecision
	Polytherapy	27	0	1 Class II[10]	37.0 (29.2–152.2)	
Clonazepam	Monotherapy	187	26.5	3 Class III[15,18,22]	30.3 (7.4–67.8)	−56.2 (−113.3 to 1.0) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
	Polytherapy	126	0.0	1 Class II,[10] 2 Class III[17,18]	86.4 (44.1–141.1)	
Ethosuximide	Monotherapy	NA	NA	NA	NA	NA
	Polytherapy	35	NA	1 Class II[10]	28.6 (22.4–118.6)	
Gabapentin	Monotherapy	90	0.0	2 Class II[27,28]	30.9 (5.5–76.1)	NA
	Polytherapy	NA	NA	NA	NA	
Lamotrigine	Monotherapy	10,746	49.4	2 Class I,[6,7] 4 Class II,[11-13,27] 8 Class III[15,18,19,22-24,29,30]	30.7 (25.4–36.4)	−13.9 (−26.4 to −1.4) Low confidence in evidence
	Polytherapy	1,421	4.8	1 Class II,[12] 4 Class III[18,25,26,29]	44.6 (34.1–56.5)	
Levetiracetam	Monotherapy	2,248	77.8	1 Class I,[6] 3 Class II,[11,27,31] 6 Class III[18,24,30,32-34]	34.8 (19.5–54.3)	−29.7 (−73.7 to 14.2) Low confidence in evidence, upgraded for magnitude of effect
	Polytherapy	605	67.0	1 Class II,[31] 3 Class III,[18,30,33] 2 Class IV[35,36]	64.5 (30.1–110.8)	
Oxcarbazepine	Monotherapy	1,036	0.0	1 Class I,[6] 2 Class II,[11,27] 2 Class III[18,24]	31.3 (21.6–42.8)	−17.6 (−45.7 to 10.5) Low confidence in evidence
	Polytherapy	262	0.0	1 Class II,[10] 1 Class III[18]	48.9 (26.2–78.2)	
Phenobarbital	Monotherapy	1,116	0.0	1 Class I,[6] 3 Class II,[9-11] 5 Class III[14,18,20,21,24]	60.3 (47.1–75.0)	16.9 (−8.8 to 42.6) Low confidence in evidence
	Polytherapy	341	0.0	1 Class II,[10] 1 Class III[17]	43.4 (24.4–67.5)	
Phenytoin	Monotherapy	1,604	52.3	2 Class I,[6,7] 4 Class II,[9-11,28] 8 Class III[14-17,20-22,24]	51.3 (35.9–69.2)	13.3 (−13.4 to 40.1) Low confidence in evidence
	Polytherapy	318	0.0	1 Class II,[10] 2 Class III[17,26]	38.0 (19.8–61.7)	
Primidone	Monotherapy	99	0.0	3 Class III[14,20,21]	101.5 (50.4–167.7)	NA
	Polytherapy	NA	NA	NA	NA	
Topiramate	Monotherapy	748	0.0	1 Class I,[6] 3 Class II,[11,27,28] 2 Class III[15,18]	44.5 (30.9–60.4)	−26.9 (−110.2 to 56.3) Very low confidence in evidence, downgraded for imprecision
	Polytherapy	42	NA	1 Class III[18]	71.4 (9.3–17.2)	
Valproic acid	Monotherapy	5,658	67.0	2 Class I,[6,7] 5 Class II,[8,10-13] 12 Class III[14,15,17-24,34,37]	96.7 (80.4–114.2)	−5.1 (−32.6 to 22.5) Low confidence in evidence
	Polytherapy	1,262	34.8	4 Class II,[8,10,12,38] 6 Class III[17-20,24,39]	101.7 (81.0–124.5)	
Zonisamide	Monotherapy	116	87.7	1 Class II,[11] 1 Class III[40]	39.2 (11.7–236.1)	−18.9 (−142.3 to 104.4) Very low confidence in evidence, downgraded for imprecision
	Polytherapy	86	0.0	1 Class III[40]	58.1 (16.7–119.3)	

Abbreviations: ASM = antiseizure medication; I^2 = a statistical measure of study heterogeneity; MCM = major congenital malformation; NA = not applicable. No data were available for acetazolamide, brivaracetam, eslicarbazepine acetate, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin.

Assessment, Development and Evaluation process was used to develop conclusions after the analysis of evidence.[5] The evidence was analyzed based on parameters pertaining to risk of bias, consistency, directness, precision, and publication bias, providing transparency of the classification of evidence. As all comparisons included indirect data (comparisons between results reported in

Table 2 Unadjusted Prevalence Differences of Any MCM Across ASMs in Monotherapy

ASM			Carbamazepine	Clobazam	Clonazepam	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Primidone	Topiramate	Valproic acid	Zonisamide
	Prevalence per 1,000		43.7	31.3	30.2	30.9	30.7	34.8	31.3	60.3	51.3	101.5	44.5	96.7	39.2
		95% CI	35.6–52.6	0.5–91.9	7.4–67.8	5.5–76.1	25.4–36.4	19.5–54.3	21.6–42.8	47.1–75.0	35.9–69.2	50.4–167.7	30.9–60.4	80.4–114.2	11.7–236.1
Carbamazepine	43.7	35.6–52.6	X	−12.5 (−58.9 to 34) Low confidence	−13.5 (−44.9 to 17.9) Low confidence	−12.8 (−49.1 to 23.5) Low confidence	**−13 (−23.1 to −2.9)** **Low confidence**	−8.9 (−28.3 to 10.5) Low confidence	−12.4 (−26 to 1.2) Low confidence	**16.6 (0.3 to 32.9)** **Low confidence**	7.6 (−11.1 to 26.3) Low confidence	57.8 (−1.5 to 117.1) Very low confidence	0.8 (−16.2 to 17.8) Low confidence	**53 (34.1–71.9)** **Moderate confidence**	−4.5 (−117 to 108) Very low confidence
Clobazam	31.3	0.5–91.9		X	−1.1 (−55.8 to 53.7) Very Low confidence	−0.4 (−58.1 to 57.4) Very low confidence	−0.6 (−46.6 to 45.5) Low confidence	3.5 (−45.3 to 52.4) Low confidence	0.1 (−46.8 to 46.9) Low confidence	29 (−18.7 to 76.8) Low confidence	20 (−28.6 to 68.7) Low confidence	70.2 (−4.1 to 144.6) Very low confidence	13.2 (−34.8 to 61.3) Low confidence	**65.4 (16.7–114.2)** **Moderate confidence**	8 (−113.2 to 129.1) Very low confidence
Clonazepam	30.2	7.4–67.8			X	0.7 (−45.8 to 47.2) Low confidence	0.5 (−30.2 to 31.2) Low confidence	4.6 (−30.3 to 39.5) Low confidence	1.1 (−30.9 to 33.1) Low confidence	30.1 (−3.2 to 63.4) Low confidence	21.1 (−13.4 to 55.6) Low confidence	**71.3 (5.3–137.3)** **Very low confidence**	14.3 (−19.3 to 47.9) Low confidence	**66.5 (31.9–101.1)** **Moderate confidence**	9 (−107.2 to 125.2) Very low confidence
Gabapentin	30.9	5.5–76.1				X	−0.2 (−35.9 to 35.5) Low confidence	3.9 (−35.5 to 43.3) Low confidence	0.4 (−36.5 to 37.3) Low confidence	29.4 (−8.6 to 67.4) Low confidence	20.4 (−18.6 to 59.4) Low confidence	**70.6 (2.1–139.1)** **Very low confidence**	13.6 (−24.7 to 51.9) Low confidence	**65.8 (26.7–104.9)** **Moderate confidence**	8.3 (−109.3 to 125.9) Very low confidence
Lamotrigine	30.7	25.4–36.4					X	4.1 (−14.1 to 22.3) Low confidence	0.6 (−11.3 to 12.5) Low confidence	**29.6 (14.6–44.6)** **Low confidence**	**20.6 (3.1–38.1)** **Low confidence**	**70.8 (11.9–129.7)** **Very low confidence**	13.8 (−1.9 to 29.5) Low confidence	**66 (48.2–83.8)** **Moderate confidence**	8.5 (−103.8 to 120.8) Very low confidence
Levetiracetam	34.8	19.5–54.3						X	−3.5 (−23.9 to 16.9) Low confidence	**25.5 (3.2–47.8)** **Low confidence**	16.5 (−7.6 to 40.6) Low confidence	**66.7 (5.5–127.9)** **Very low confidence**	9.7 (−13.1 to 32.5) Low confidence	**61.9 (37.6–86.2)** **Moderate confidence**	4.4 (−109.1 to 117.9) Very low confidence
Oxcarbazepine	31.3	21.6–42.8							X	**29 (11.5–46.5)** **Low confidence**	**20 (0.3–39.7)** **Low confidence**	**70.2 (10.6–129.8)** **Very low confidence**	13.2 (−5 to 31.4) Low confidence	**65.4 (45.5–85.3)** **Moderate confidence**	7.9 (−104.8 to 120.6) Very low confidence
Phenobarbital	60.3	47.1–75.0								X	−9 (−30.7 to 12.7) Low confidence	41.2 (−19.1 to 101.5) Very low confidence	−15.8 (−36.1 to 4.5) Low confidence	**36.4 (14.5–58.3)** **Low confidence**	−21.1 (−134.2 to 92) Very low confidence
Phenytoin	51.3	35.9–69.2									X	50.2 (−10.8 to 111.2) Very low confidence	−6.8 (−29 to 15.4) Low confidence	**45.4 (21.7–69.1)** **Low confidence**	−12.1 (−125.5 to 101.3) Very low confidence
Primidone	101.5	50.4–167.7										X	−57 (−117.5 to 3.5) Very low confidence	−4.8 (−65.8 to 56.2) Very low confidence	−62.3 (−188.9 to 64.3) Very low confidence
Topiramate	44.5	30.9–60.4											X	**52.2 (29.8–74.6)** **Moderate confidence**	−5.3 (−118.5 to 107.9) Very low confidence
Valproic acid	96.7	80.4–114.2												X	−57.5 (−171 to 56) Very low confidence

Abbreviations: ASM = antiseizure medication; MCM = major congenital malformation.
Prevalence difference = row − column.
Bold values are statistically significant.

Table 3 Unadjusted Prevalence of Specific MCM, by Individual ASMs in Monotherapy

ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence compared with reference (95% CI)
Brain					
Carbamazepine	1,028	48.5	1 Class II,[12] 1 Class III[18]	1.5 (0.0–6.8)	−24.1 (−104.9 to −3.7) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
Lamotrigine	4,548	0.0	1 Class I,[7] 2 Class II,[12,27] 4 Class III[18,29,41,42]	2.8 (1.5–4.5)	−22.8 (−103.6 to −2.9) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
Phenytoin	56	NA	1 Class I[7]	27.4 (1.3–85.4)	Reference
Valproic acid	616	0.0	1 Class I,[7] 1 Class II,[12] 1 Class III[18]	8.0 (2.5–16.5)	−17.6 (−98.5 to 4.9) Very low confidence in evidence, downgraded for imprecision and not further upgraded for magnitude of effect
Neural tube					
Carbamazepine	3,874	50.0	2 Class II,[11,28] 5 Class III[17,20,22,24,43]	5.6 (2.6–9.7)	−8.7 (−15.1 to −2.3) Moderate confidence in evidence, upgraded for magnitude of effect
Lamotrigine	2,355	43.5	2 Class II,[11,28] 3 Class III[24,41,43]	3.4 (0.4–9.2)	−11.0 (−17.8 to −4.1) Moderate confidence in evidence, upgraded for magnitude of effect
Levetiracetam	556	0.0	1 Class II,[11] 1 Class III[24]	3.1 (0.2–9.3)	−11.3 (−18.3 to −4.2) Moderate confidence in evidence, upgraded for magnitude of effect
Oxcarbazepine	71	0.0	1 Class III[24]	3.5 (3.2 to −30.3)	−10.8 (−25.4 to 3.7) Very low confidence in evidence
Phenobarbital	384	0.0	1 Class II,[11] 2 Class III[20,24]	4.1 (0.2–12.9)	−10.2 (−18.5 to −1.9) Moderate confidence in evidence, upgraded for magnitude of effect
Phenytoin	758	0.0	2 Class II,[11,28] 2 Class III[20,24]	2.0 (0.1–6.4)	−12.3 (−18.5 to −6.1) Moderate confidence in evidence, upgraded for magnitude of effect
Primidone	43	NA	1 Class III[20]	10.6 (2.1–62.1)	−3.7 (−34.2 to 26.8) Very low confidence in evidence, 1 Class III study
Topiramate	359	NA	1 Class II[11]	1.3 (0.2–7.7)	−13.0 (−19.5 to −6.5) Moderate confidence in evidence, upgraded for magnitude of effect
Valproic acid	3,578	31.9	3 Class II,[11,44,45] 5 Class III[17,20,22,24,43]	14.3 (9.5–20.1)	Reference
Cardiac					
Carbamazepine	5,211	70.8	4 Class II,[10-12,28] 6 Class III[17,18,20,22,24,43]	8.5 (4.8–13.2)	−33.4 (−52.7 to −14.1) Moderate confidence in evidence, upgraded for magnitude of effect
Lamotrigine	6,179	87.0	1 Class I,[7] 4 Class II,[11,12,27,28] 5 Class III[18,24,29,41,43]	16.6 (7.8–28.5)	−25.3 (−46.8 to −3.8) Moderate confidence in evidence, upgraded for magnitude of effect
Levetiracetam	556	81.3	1 Class II,[11] 1 Class III[24]	12.5 (0.1–53.4)	−29.4 (−62.0 to 3.2) Low confidence in evidence, upgraded for magnitude of effect
Oxcarbazepine	71	0.0	1 Class III[24]	42.3 (5.4–104.3)	0.4 (−52.6 to 53.3) Very low confidence in evidence
Phenobarbital	432	0.0	2 Class II,[10,11] 2 Class III[20,24]	41.9 (25.1–62.7)	Reference
Phenytoin	955	6.5	1 Class I,[7] 3 Class II,[10,11,28] 2 Class III[20,24]	19.9 (11.6–30.3)	−22.0 (−43.0 to −1.0) Moderate confidence in evidence, upgraded for magnitude of effect

Continued

Table 3 Unadjusted Prevalence of Specific MCM, by Individual ASMs in Monotherapy *(continued)*

ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence compared with reference (95% CI)
Primidone	147	0.0	1 Class II,[10] 2 Class III[17,20]	11.6 (0.8–35.1)	−8.2 (−27.8 to 11.3) Low confidence in evidence, upgraded for magnitude of effect
Topiramate	359	0.0	1 Class II[11]	2.8 (2.1 to −11.9)	−39.1 (−58.5 to −19.6) High confidence in evidence, upgraded twice for magnitude of effect
Valproic acid	2,212	66.2	1 Class I,[7] 5 Class II,[10-12,44,45] 6 Class III[17,18,20,21,24,43]	25.1 (16.9–35.0)	−16.8 (−37.6 to 4.1) Low confidence in evidence
Oral and cleft palate					
Carbamazepine	4,103	27.8	3 Class II,[10,11,28] 5 Class III[17,20,22,43,46]	4.7 (2.5–7.6)	−17.6 (−37.0 to 1.8) Low confidence in evidence
Lamotrigine	8,052	84.4	4 Class II,[11,27,28,47] 4 Class III[29,43,46,48]	4.6 (1.3–9.9)	−17.7 (−37.4 to 2.0) Low confidence in evidence
Levetiracetam	450	0.0	1 Class II[11]	0.0 (0.0–3.8)	−22.3 (−41.6 to −3.0) High confidence in evidence, upgraded twice for large magnitude of effect
Phenobarbital	295	14.3	2 Class II,[10,11] 1 Class III[20]	22.3 (7.1–45.6)	Reference
Phenytoin	904	0.0	3 Class II,[10,11,28] 2 Class III[17,20]	9.7 (4.4–17.2)	−12.6 (−32.8 to 7.7) Low confidence in evidence
Primidone	86	0.4	1 Class II,[10] 1 Class III[20]	16.6 (0.6–54.1)	−5.7 (−38.6 to 27.3) Low confidence in evidence
Topiramate	846	0.0	2 Class II[13,47]	14.1 (7.3–23.1)	−8.2 (−29.0 to 12.6) Low confidence in evidence
Valproic acid	3,636	27.8	4 Class II,[10,11,44,45] 5 Class III[17,20,22,43,46]	8.0 (4.6–12.2)	−14.3 (−34.0 to 5.3) Low confidence in evidence
Urogenital					
Carbamazepine	1,033	NA	1 Class II[11]	1.4 (0.0–4.6)	−11.0 (−17.2 to −4.8) Moderate confidence in evidence, upgraded for magnitude of effect
Lamotrigine	3,203	80.3	1 Class II,[11] 2 Class III[29,41]	2.0 (0.0–8.9)	−10.4 (−17.7 to −3.1) Moderate confidence in evidence, upgraded for magnitude of effect
Levetiracetam	450	0.0	1 Class II[11]	1.0 (0.2–6.1)	−11.4 (−17.9 to −4.9) High confidence in evidence, upgraded twice for very large magnitude of effect
Phenobarbital	199	0.0	1 Class II[11]	7.3 (0.3–23.8)	−5.2 (−18.2 to 7.9) Low confidence in evidence
Phenytoin	416	0.0	1 Class II[11]	1.1 (0.2–6.6)	−11.3 (−17.9 to −4.8) High confidence in evidence, upgraded twice for very large magnitude of effect
Topiramate	359	0.0	1 Class II[11]	7.2 (1.1–18.5)	−5.3 (−15.7 to 5.1) Low confidence in evidence
Valproic acid	1,432	0.0	2 Class II[11,45]	12.4 (7.4–18.8)	Reference
Renal					
Carbamazepine	2,841	3.6	1 Class II,[28] 5 Class III[17,20,22,24,43]	5.5 (3.1–8.7)	−8.2 (−14.5 to −1.9) Moderate confidence in evidence, upgraded for magnitude of effect
Lamotrigine	2,354	41.9	1 Class II,[30] 3 Class III[24,29,43]	6.6 (2.1–13.6)	−7.1 (−15.1 to 0.9) Low confidence in evidence
Levetiracetam	106	0.0	1 Class III[24]	9.4 (7.3–40.1)	−4.3 (−21.6 to 13.1) Very low confidence in evidence

Continued

Table 3 Unadjusted Prevalence of Specific MCM, by Individual ASMs in Monotherapy *(continued)*

ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence compared with reference (95% CI)
Oxcarbazepine	71	0.0	1 Class III[24]	14.1 (10.9–59.5)	0.4 (−24.6 to 24.3) Very low confidence in evidence
Phenobarbital	185	0.0	2 Class III[24,40]	2.5 (0.5–14.8)	−11.2 (−20.3 to −2.1) Moderate confidence in evidence, upgraded for magnitude of effect
Phenytoin	466	0.0	1 Class II,[28] 3 Class III[17,20,24]	8.0 (2.0–18.1)	−5.7 (−15.5 to 4.1) Low confidence in evidence
Primidone	43	0.0	1 Class III[20]	0.0 (0.0–39.6)	−13.7 (−34.3 to 6.9) Very low confidence in evidence
Valproic acid	1,637	0.0	1 Class II,[28] 5 Class III[17,20,22,24,43]	13.7 (8.6–19.9)	Reference

Abbreviations: ASM = antiseizure medication; I^2 = a statistical measure of study heterogeneity; MCM = major congenital malformation; NA = not applicable; RMD = raw mean difference.

different studies) and, at best, classified as Class III evidence to address causation, the initial confidence rating for most conclusions was anchored as low if at least 2 Class III or at least 1 Class I or II studies informed each estimate used in the comparisons. The initial confidence rating was set to very low if one of the contributing estimates was informed by a single Class III study.

In the second step, the classification of evidence was upgraded or downgraded according to criteria specified in the process manual (e.g., upgraded for large magnitude of effect, downgraded for lack of statistical precision).[5] For estimates obtained through indirect comparisons, confidence in the evidence was downgraded for precision when the width of the 95% CI for any prevalence difference (PD) for MCMs or ASD was greater than 100 per 1,000 live births or greater than 300 per 1,000 live births for perinatal outcomes. Confidence was also downgraded for precision when the width of the 95% CI raw mean difference (RMD) for IQ was greater than 20 points. For indirect comparisons, although we present the PD in the synthesis of evidence and conclusions, our assessment of magnitude of effect was based on the corresponding prevalence ratio (PR). Confidence in the evidence was upgraded by 1 level for large magnitude of effect if the calculated PR was greater than 2 or lower than 0.5. Confidence in the evidence was upgraded by 2 levels for very large magnitude of effect if the calculated PR was greater than 10 or lower than 0.1. Confidence in the evidence was upgraded by 1 level for large magnitude of effect for IQ if the RMD was greater than 10 points and by 2 levels if greater than 20 points. For estimates drawn from adjusted PR (relevant to the perinatal and neurodevelopmental outcomes), confidence in evidence was downgraded for precision if the width of the CI was greater than 2. If the confidence in the evidence was very low, it was not upgraded for other factors. Estimates not reaching

Table 4 Global IQ With Exposure to ASM Monotherapy

ASM	Total sample size	I^2	Included studies	Global IQ mean (95% CI)	RMD compared with reference (95% CI)
Carbamazepine	316	86.0	2 Class I,[50,51] 4 Class III[52-55]	100.4 (95.8–105.1)	6.53 (0.39–12.67) Low confidence in evidence
Lamotrigine	129	77.0	1 Class I,[51] 1 Class III[55]	105.8 (100.9–110.6)	11.85 (5.53–18.15) Moderate confidence in evidence, upgraded for magnitude of effect
Levetiracetam	42	NA	1 Class III[56]	99.0 (95.0–103.0)	6.3 (0.9–11.7) Very low confidence in evidence
Phenytoin	76	84.8	1 Class I,[51] 1 Class III[53]	103.2 (93.0–113.4)	9.29 (−1.63 to 20.21) Very low confidence in evidence, downgraded for imprecision
Topiramate	27	NA	1 Class III[56]	100.5 (95.8–105.2)	6.58 (0.37–12.80) Very low confidence in evidence
Valproic acid	173	69.0	2 Class I,[50,51] 2 Class III[53,56]	93.9 (89.1–97.9)	Reference

Abbreviations: ASM = antiseizure medication; I^2 = a statistical measure of study heterogeneity; NA = not applicable; RMD = raw mean difference.

Table 5 Verbal and Non-Verbal IQ With Exposure to ASM Monotherapy

ASM	Total sample size	I^2	Included studies	Mean verbal or non-verbal IQ (95% CI)	RMD compared with reference (95% CI)
Verbal IQ					
Carbamazepine	283	82.0	2 Class I,[50,51] 3 Class III[52,53,55]	98.4 (94.6–102.2)	6.3 (−0.2 to 12.8) Low confidence in evidence
Lamotrigine	103	79.0	1 Class I,[51] 1 Class III[55]	102.4 (96.5–108.2)	10.3 (2.4–18.2) Moderate confidence in evidence[a]
Levetiracetam	42	NA	1 Class III[56]	101.0 (97.7–104.3)	8.9 (2.7–15.1) Very low confidence in evidence
Phenytoin	61	69.2	1 Class I,[51] 1 Class III[53]	103.0 (95.8–110.2)	10.9 (2.0–19.8) Moderate confidence in evidence[a]
Topiramate	27	NA	1 Class III[56]	99.2 (95.2–103.2)	7.1 (0.5–13.7) Very low confidence in evidence
Valproic acid	160	83.0	2 Class I,[50,51] 2 Class III[53,56]	92.1 (86.9–97.4)	Reference
Non-verbal IQ					
Carbamazepine	197	53.9	1 Class I,[51] 2 Class III[52,55]	104.7 (102.2–107.3)	3.6 (0.0–7.1) Low confidence in evidence
Lamotrigine	103	75.5	1 Class I,[51] 1 Class III[55]	105.8 (100.9–110.7)	4.6 (−0.8 to 10.1) Low confidence in evidence
Levetiracetam	42	NA	1 Class III[56]	99.6 (95.5–103.7)	−1.6 (−6.3 to 3.2) Very low confidence in evidence
Phenytoin	40	NA	1 Class I[51]	106.0 (103.1–109.0)	4.8 (0.1–8.7) Low confidence in evidence
Topiramate	27	NA	1 Class III[56]	102.4 (97.1–107.7)	1.2 (−4.6 to 7.1) Very low confidence in evidence
Valproic acid	96	0.0	1 Class I,[51] 1 Class III[56]	101.2 (98.7–103.6)	Reference

Abbreviations: ASM = antiseizure medication; I^2 = a statistical measure of study heterogeneity; NA = not applicable; RMD = raw mean difference.
[a] Items were upgraded for large magnitude of effect.

Table 6 Unadjusted Prevalence of ASD, PDD, or ASD Traits by ASM Monotherapy

ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 of ASD/ASD risk (95% CI)	Difference in prevalence compared with reference (95% CI)
Carbamazepine	4,493	84.9	1 Class II,[57] 4 Class III[49,58-60]	17.1 (6.2–33.1)	−24.9 (−41.5 to −8.2) Moderate confidence, upgraded for large magnitude of effect
Clonazepam	587	51.7	1 Class II,[57] 1 Class III[49]	20.8 (7.5–40.7)	−21.1 (−40.4 to −1.8) Moderate confidence in evidence, upgraded for large magnitude of effect
Lamotrigine	7,568	66.5	1 Class II,[57] 5 Class III[49,58-60]	14.5 (8.6–22.2)	−27.4 (−39.3 to −15.6) Moderate confidence in evidence, upgraded for large magnitude of effect
Levetiracetam	1,226	56.0	2 Class III[49,e1]	11.3 (2.9–25.1)	−30.6 (−45.4 to −15.8) Moderate confidence in evidence, upgraded for large magnitude of effect
Oxcarbazepine	321	NA	1 Class II[57]	23.3 (9.7–42.6)	−18.6 (−37.8 to 0.5) Low confidence in evidence
Valproic acid	3,399	36.7	1 Class II,[57] 4 Class III[49,58,60,e1]	41.9 (32.7–52.3)	Reference

Abbreviations: ASD = autism spectrum disorder; ASM = antiseizure medication; I^2 = a statistical measure of study heterogeneity; NA = not applicable; PDD = pervasive developmental disorder.

Table 7 Unadjusted Prevalence of SGA by ASM Monotherapy

ASM	Total sample size	I^2	Included studies	Prevalence per 1,000 (95% CI)	Difference in prevalence compared with reference (95% CI)
Carbamazepine	3,033	96.3	1 Class II,[e32] 5 Class III[46,e33-e36]	75.7 (31.3–137.5)	−4.4 (−153.9 to 145.0) Low confidence in evidence
Clobazam	30	0.0	1 Class III[e33]	177.1 (64.6–329.9)	96.9 (−95.7 to 289.6) Very low confidence in evidence
Clonazepam	276	NA	2 Class III[e33,e36]	165.4 (123.0–212.7)	85.2 (−61.5 to 231.9) Low confidence in evidence
Gabapentin	225	91.3	2 Class III[e33,e36]	58.5 (0.1–214.2)	−21.7 (−197.7 to 154.3) Low confidence in evidence
Lamotrigine	2,597	98.0	1 Class I,[e37] 1 Class II,[e32] 5 Class III[44,e33–e36]	85.1 (13.6–209.6)	5.0 (−165.7 to 175.6) Low confidence in evidence
Levetiracetam	835	85.2	1 Class I,[e37] 2 Class III[e33,e38]	52.9 (6.8–138.6)	−27.3 (−181.7 to 127.1) Low confidence in evidence
Oxcarbazepine	1,045	96.1	3 Class III[e33,e34,e38]	58.0 (6.8–154.2)	−22.2 (−180.1 to 135.7) Low confidence in evidence
Phenobarbital	274	95.3	2 Class III[e33,e36]	89.3 (0.3–310.0)	9.1 (−199.4 to 217.6) Low confidence in evidence
Phenytoin	464	24.5	3 Class III[e34-e36]	14.4 (2.7–35.1)	−65.8 (−206.3 to 74.8) Low confidence in evidence
Primidone	20	0.0	1 Class III[e33]	166.0 (40.7–352.9)	85.8 (−123.6 to 295.2) Very low confidence in evidence
Topiramate	453	93.6	2 Class III[e33,e38]	80.2 (0.3–279.6)	Reference
Valproic acid	1,829	97.6	1 Class II,[e32] 7 Class III[35,46,e33-e35,e38]	147.1 (53.9–276.0)	66.9 (−111.5 to 245.4) Low confidence in evidence
Zonisamide	125	NA	1 Class III[e36]	20.4 (3.1–52.4)	−59.7 (−201.6 to 82.1) Low confidence in evidence

Abbreviations: ASM = antiseizure medication; I^2 = a statistical measure of study heterogeneity; NA = not applicable; SGA = small for gestational age.

statistical significance were not upgraded for magnitude of effect.

The authors formulated a rationale for each recommendation based on the evidence systematically reviewed and stipulated axiomatic principles of care, related evidence, and inferences. The recommendation development process is described in further detail in the complete guideline (eAppendix 1) and the AAN's guideline development process manual.[5]

Clinical Context

The goal of this guideline is to assist clinicians (e.g., physicians, nurses, and advanced practice providers) in the pharmacologic management of PWECP to limit risk of adverse congenital, perinatal, and neurodevelopmental outcomes. Given the many variables that may confound the outcomes we examined (e.g., genetic conditions, pregnancy conditions, and socioeconomic contexts), we weighted evidence more strongly where analyses could be adjusted for these and other potential confounders (i.e., Class I studies). Demonstration of a dose effect can further support a causal relationship between an exposure and an outcome. Although our preplanned analyses using external comparisons could not reach a level of evidence sufficient to drive recommendations, a statistically and clinically important difference in prevalence of MCMs was found for valproic acid and phenobarbital between high and low-dose exposures (eTable 1). The only Class I study addressing this question from EURAP demonstrated a dose effect for carbamazepine, lamotrigine, phenobarbital, and valproic acid.[6] To reduce the risk of MCMs, it is reasonable practice to use the lowest appropriate dose of ASMs in PWECP, if clinically feasible.

The available evidence on the association between in utero ASM exposure and neurodevelopmental outcomes is rapidly expanding. Although valproic acid exposure shows a strong effect, data from our preplanned analyses on adverse neurodevelopmental outcomes were insufficient to demonstrate an effect; thus, caution in counseling is warranted. While we could not extract sufficient data on topiramate exposure, the SCAN-AED study[49] found even higher prevalences of ASD and intellectual disability with exposure to topiramate than

valproic acid. Their adjusted hazard ratios (aHRs), however, used prevalence in the general population of children as a comparator group (aHRs for ASD and intellectual disability after topiramate exposure were 2.8 [95% CI 1.4–5.7] and 3.5 [95% CI 1.4–8.6], respectively). Further studies are needed to replicate these findings and examine these outcomes across other ASMs.

Folic acid prescribing practices for PWECP are variable.[e2,e3] One much anticipated outcome from the current systematic review was clarification of the optimal folic acid dosage to reduce potential negative effects of ASMs in pregnancy. As discussed, the data do not find that folic acid supplementation reduces the risk of MCMs among PWECP. However, improved neurocognitive outcomes have been observed in offspring of PWECP who received folic acid supplementation before and throughout pregnancy. The analysis does not support a more specific dosage recommendation beyond at least 0.4 mg/d. There is limited evidence from a published analysis of 27,784 children born to people with epilepsy that exposure to periconceptional folic acid ≥1 mg/d was associated with a 0.9% absolute increase in the risk of childhood cancer before age 20 years, resulting in an HR of 2.7 (95% CI 1.2–6.3). Subanalysis restricted to exposure to maternal epilepsy and supplemental folic acid doses <3 mg/d was not significant when compared with maternal epilepsy without a prescription for high-dose folic acid (aHR 2.6, 95% CI 1.0–6.9).[e4] A study of 1,257 mother-child pairs from the general population found that very high maternal serum folic acid concentrations (≥60.3 nmol/L) at birth had a 2.5 times increased risk of ASD (95% CI 1.3–4.6) compared with those with lower folic acid concentrations.[e5] These results are concerning, but the studies have limitations, including their high risk of confounding by indication. The dose chosen should balance demonstrated benefits of supplementation and potential negative consequences of high doses. Future well-designed (preferably randomized) studies are needed to better define optimal folic acid dosing for PWECP.

Practice Recommendations

General

Recommendation 1 Rationale

The overarching goals of care for PWECP are to optimize health outcomes both for individuals and their future offspring. In many cases, in utero ASM exposure may be associated with increased risks to the fetus. There are also risks associated with discontinuing or changing ASMs in PWECP.[53,e6-e8] A shared decision-making process leads to more informed choices, a better understanding of available options, a more accurate risk perception, and improved decision quality grounded in individual values.[e9] This decision-making process may take into account an individual's plans for pregnancy. However, according to the Epilepsy Birth Control Registry of 1,114 PWECP in the United States, more than 65% of pregnancies among PWECP are unintended.[e10,e11] The ASM regimen used for a PWECP when pregnancy is not planned is thus very often the regimen used at the time of conception.

Recommendation 1 Statements

1(A) Clinicians should engage in joint decision-making with PWECP, taking individual preferences into account when selecting ASMs and monitoring their dosing (Level B).

1(B) When treating PWECP, clinicians should recommend ASMs and doses that optimize both seizure control and fetal outcomes should pregnancy occur, at the earliest possible opportunity preconceptionally (e.g., at the time of starting an ASM in a person post-menarche) (Level B).

Recommendation 2 Rationale

The odds of mortality during pregnancy is 5–12 times greater among PWECP as compared with pregnant people without epilepsy, according to an analysis of a Danish cohort of more than 2 million pregnancies and a US cohort of more than 20 million participants.[e12,e13] Among 202 pregnancy-related deaths in the United Kingdom from 2013 to 2015, most of the 13 epilepsy-related deaths were from sudden unexpected death in epilepsy. All participants with prepregnancy data had uncontrolled seizures. Five of the participants who died had stopped taking their ASMs during pregnancy.[e14]

In an analysis of the EURAP study including 1,956 pregnancies among 1,882 participants, there was no statistical association between seizures during pregnancy and spontaneous abortion or stillbirth. However, the 1 stillbirth that occurred soon after a seizure was an episode of convulsive status epilepticus.[e15] The frequency of generalized tonic-clonic seizures or focal-to-bilateral tonic-clonic seizures may also be a risk factor of lower IQ in children born to PWECP.[53]

Valproic acid is one of the most effective ASMs at obtaining adequate seizure control among people with idiopathic generalized epilepsy.[e7,e8] An analysis of the EURAP cohort of PWECP treated with valproic acid at the onset of pregnancy showed that generalized tonic-clonic seizures or focal-to-bilateral tonic-clonic seizures during pregnancy were twice as likely to occur when valproic acid was removed or replaced with another ASM, compared with when it was maintained throughout the pregnancy.[e6]

The serum concentration of most ASMs has a defined therapeutic window for effective seizure control. The serum concentration of some ASMs (in particular, lamotrigine and levetiracetam) decreases during pregnancy. These decreases may occur at any point during the pregnancy.[e16-e18]

There are limited data available on epilepsy-related outcomes during pregnancy among PWECP for numerous ASMs, including but not limited to acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, and vigabatrin.

Recommendation 2 Statements

2A. Clinicians must minimize the occurrence of convulsive seizures (generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures) in PWECP during pregnancy to minimize potential risks to the birth parent (e.g., seizure-related mortality) and to the fetus (Level A).

2B. Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures, even if it is not an optimal choice with regards to the risk to the fetus (e.g., valproic acid) (Level B).

2C. Clinicians should monitor ASM levels in PWECP throughout pregnancy as guided by individual ASM pharmacokinetics and patient clinical presentation (Level B).

2D. Clinicians should adjust the dose of ASMs at their clinical discretion during the pregnancy in response to (1) decreasing serum ASM levels or (2) worsening seizure control (observed or anticipated based on the clinician's judgment and known pharmacokinetics of ASMs in the pregnant state) (Level B).

2E. Clinicians treating PWECP using acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin should counsel their patients that there are limited data on pregnancy-related outcomes for these drugs (Level B).

Antiseizure Medications: Major Congenital Malformations

Recommendation 3 Rationale

The unadjusted birth prevalence of any MCM among children born to people without epilepsy is approximately 2.4%–2.9%.[e19] Of the ASMs with sufficient numbers of exposures to draw reliable conclusions (greater than 1,000 exposures), lamotrigine, levetiracetam, and oxcarbazepine are associated with the lowest unadjusted birth prevalence of any MCM in monotherapy (3.1%, 3.5%, and 3.1%, respectively) among children born to PWECP. Valproic acid exposure is associated with the highest unadjusted birth prevalence (9.7%) of any MCM among children born to PWECP as compared with other ASMs.

Valproic acid is associated with the highest unadjusted birth prevalence of neural tube defects (NTDs) (1.4%) as compared with other ASMs. Phenobarbital is associated with the highest unadjusted birth prevalence of cardiac malformations (4.4%) as compared with other ASMs. Phenobarbital and topiramate are associated with the highest unadjusted birth prevalence of oral and cleft palate (2.2% and 1.4% respectively) compared with other ASMs. Valproic acid is associated with the highest unadjusted birth prevalence of urogenital (1.2%) and renal (1.4%) malformations compared with other ASMs.

A detailed anatomical ultrasound of the fetus can enable earlier diagnosis of MCMs.[e20-e24] Early detection of severe congenital heart defects, especially those requiring surgery in the early postnatal period, has been shown to improve morbidity and mortality in affected newborns.[e25-e28] Detection of MCMs can also inform an early pregnancy termination decision or guide perinatal management, including giving birth in specialized pediatric centers, while a normal ultrasound may offer reassurance to expecting parents. This needs to be balanced with differences in individual preferences.

Recommendation 3 Statements

3A. Clinicians must counsel their patients with epilepsy that the birth prevalence of any MCM in the general population is approximately 2.4%–2.9%, providing a comparison framework for their individual risk (Level A).

3B. Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in PWECP when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs (Level A).

3C. Clinicians must avoid the use of valproic acid in PWECP to minimize the risk of MCMs (composite outcome) or NTDs, if clinically feasible (Level A).

3D. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that the risk of any MCM is the highest with valproic acid as compared with other studied ASMs (Level A).

3E. To reduce the risk of cardiac malformations, clinicians must avoid the use of phenobarbital in PWECP, if clinically feasible (Level A).

3F. To reduce the risk of oral clefts, clinicians should avoid the use of phenobarbital and topiramate in PWECP, if clinically feasible (Level B).

3G. To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid in PWECP, if clinically feasible (Level B).

3H. To enable early detection and timely intervention of MCMs, obstetricians should recommend fetal screening for MCMs (e.g., a detailed anatomical ultrasound, where available) for PWECP who are treated with any ASM during pregnancy (Level B).

3I. To enable early detection and timely intervention of congenital heart defects, obstetricians should recommend screening cardiac investigations of the fetus among PWECP who are treated with phenobarbital during pregnancy (Level B).

Antiseizure Medications: Perinatal Outcomes

Recommendation 4 Rationale

Among children exposed to ASMs in utero and born to PWECP, the prevalence of intrauterine death is highly likely

not to differ across ASMs when used in monotherapy and the prevalence of prematurity is possibly no different across ASMs when used in monotherapy (eTable 2). The risk of intrauterine death is likely higher with polytherapy exposure compared with monotherapy exposure. Fetal growth restriction increases the risk of perinatal morbidity and mortality.[e29,e30] The prevalence of children born SGA is possibly greater after exposure to valproic acid or topiramate compared with lamotrigine. Prenatal identification of fetuses at risk of being born SGA leads to improved perinatal outcomes by informing timely delivery.[e31]

Recommendation 4 Statements

4A. Clinicians should counsel PWECP that the prevalence of intrauterine death does not differ among different ASM exposures in monotherapy (Level B).

4B. Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born SGA, if clinically feasible (Level B).

4C. To enable early identification of fetal growth restriction, obstetricians should recommend screening of fetal growth throughout pregnancy among PWECP who are treated with valproic acid or topiramate (Level B).

Antiseizure Medications: Neurodevelopmental Outcomes

Recommendation 5 Rationale

Among children born to PWECP, in utero exposure to valproic acid is likely associated with a decrease in full scale IQ at age 6 years compared with gabapentin and lamotrigine in monotherapy; valproic acid is possibly associated with a decrease as compared with carbamazepine, levetiracetam, and topiramate in monotherapy; and there is possibly no difference in full scale IQ with valproic acid as compared with phenytoin in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid is likely associated with a decrease in verbal IQ at age 6 years compared with gabapentin, lamotrigine, levetiracetam, and phenytoin in monotherapy, and possibly associated with a decrease as compared with carbamazepine and topiramate in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid is possibly associated with a decrease in non-verbal IQ at age 6 years compared with carbamazepine and phenytoin in monotherapy, but there is possibly no difference as compared with gabapentin, lamotrigine, levetiracetam, and topiramate in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid throughout the pregnancy is possibly associated with an increased risk of ASD and autistic traits compared with other studied ASMs (i.e., carbamazepine, clonazepam, lamotrigine, and levetiracetam) used in monotherapy.

Numerous ASMs have limited available data on neurodevelopmental outcomes. These neurodevelopmental outcomes are determined during both early and later stages of pregnancy.[e39] Early screening for neurodevelopmental disorders in children enables early diagnosis, facilitating access to early interventions where available. Early interventions in children with neurodevelopmental disorders optimize developmental trajectories.

Recommendation 5 Statements

5A. To reduce the risk of poor neurodevelopmental outcomes, including ASD and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in PWECP, if clinically feasible (Level A).

5B. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is likely or possibly associated with a decrease in full scale, verbal, and non-verbal IQ, as compared with other studied ASMs (i.e., carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, and topiramate) (Level A).

5C. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is possibly associated with an increased risk of ASD as compared with other studied ASMs (i.e., carbamazepine, clonazepam, levetiracetam, and lamotrigine) (Level A).

5D. Clinicians should implement age-appropriate developmental screening in children exposed to any ASM in utero born to PWECP (Level B).

Folic Acid

Recommendation 6 Rationale

The optimal dosing and timing of folic acid supplementation are unknown in PWECP. There is likely no demonstrated benefit of folic acid supplementation (at least 0.4 mg/d) specifically for the prevention of MCMs in children born to PWECP. Randomized controlled trials conducted before widespread folic acid fortification of foods in the United States demonstrated a reduction in NTDs among the offspring of the general childbearing population receiving periconceptional multivitamin supplementation.[e40] A systematic review of 14 studies of folic acid supplementation (up to 1 mg/d) among pregnant people in the general population (generally without epilepsy), including 1,053 participants (some being control participants without folic acid supplementation) estimated that folic acid supplementation of 0.2 mg/d (the United States' level of folic acid fortification) would reduce the risk of NTDs by 23%.[e41] This protective effect was greater in pregnant people with an initial low serum folate concentration than in those with higher serum folate concentrations.[e41] Although valproic acid exposure in utero is associated with the highest prevalence of NTDs, the teratogenic causal pathway is not exclusively through the disruption of folic acid metabolism.[e42]

Preconception folic acid supplementation is possibly associated with better neurodevelopmental outcomes among children born to PWECP. Folic acid supplementation of at least 0.4 mg/d is possibly associated with reduced autistic traits at 3 years (OR 7.9, 95% CI 2.5–24.9) and likely associated with a higher global IQ (on average 6 points) at 6 years in children born to PWECP exposed to ASMs in utero. Lower plasma concentrations of folic acid at gestational weeks 17–19 among pregnant people with epilepsy exposed to ASMs is correlated with a higher risk of autistic traits at 3 years. Higher exposure levels of folic acid from diet and supplements is associated with statistically significant increases in IQ at age 6 years; this association is not seen among PWECP who only received dietary folic acid and not periconceptional folic acid supplements. Higher doses of folic acid supplementation result in higher serum concentrations of folic acid.[e43,e44] There is inconclusive evidence for an increased risk of adverse events with folic acid supplementation for the PWECP and the child (e.g., increased occurrence of twins, asthma, masking vitamin B12 deficiency, new or worsening of preexisting neoplasia).[e40,e45,e46] In a recent analysis of 27,784 children born to people with epilepsy, exposure to periconceptional folic acid greater than 1 mg/d was associated with a 0.9% absolute increase in the risk of childhood cancer before age 20 years, resulting in an HR of 2.7 (95% CI 1.2–6.3).[e46] There are potential pharmacokinetic interactions where folic acid can decrease phenytoin serum concentrations.[e47] Adherence to folic acid supplementation is generally poor among PWECP, even during pregnancy.[e48] ASM polytherapy is associated with decreased folic acid adherence among PWECP.[e49] In the United States, where there is no high-dose folic acid formulation, higher doses of folic acid require a large number of tablets, potentially reducing adherence to folic acid supplementation.

Recommendation 6 Statements

6A. Clinicians should prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to decrease the risk of NTDs in the offspring (Level B).

6B. Clinicians must prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to possibly improve neurodevelopmental outcomes such as ASD and global IQ in the offspring (Level A).

6C. Clinicians should counsel PWECP treated with an ASM that adherence to recommended folic acid supplementation preconceptionally and during pregnancy is important to minimize the risk of MCMs and poor neurodevelopmental outcomes (Level B).

Suggestions for Future Research

The findings of this systematic review highlight several knowledge gaps that should be addressed in future research to optimize reproductive outcomes for PWECP. The risks of MCMs and adverse perinatal outcomes for newer and understudied ASMs (e.g., lacosamide, zonisamide, clobazam, and perampanel) require further research. Future guidelines should consider even newer ASMs, such as cenobamate and fenfluramine, which were not included in our search strategy. Longitudinal studies evaluating long-term neurodevelopmental outcomes in children with in utero exposure to ASMs other than valproic acid are necessary to inform ASM choice among PWECP, developmental screening requirements, and resource planning. The risk of MCMs, adverse perinatal outcomes, and adverse neurodevelopmental outcomes in polytherapy is a complex picture that merits further clarification. Importantly, an improved understanding of the pathophysiologic mechanisms underlying teratogenic effects of some ASMs will guide rational development of therapeutic strategies. Clarification of factors affecting the pharmacokinetics and pharmacodynamics of ASM metabolism in PWECP during pregnancy and postpartum will inform dosing regimens. Future studies should work to use more uniform definitions for exposures (e.g., high vs low doses of ASMs) and outcomes, as well as which adjustment variables are included in any multivariable analyses, to facilitate the discovery of important findings and their interpretation.

There is considerable practice variation in the dosing of folic acid supplementation. High-quality studies, including randomized controlled trials where possible, will be required to definitively clarify the optimal dose and timing with respect to conception.

The impact of screening for fetal anomalies and growth restriction on perinatal outcomes needs to be established. Clarification of the impact of socioeconomic status on pregnancy outcomes in PWECP will inform social service priorities. To better clarify the potentially diverse needs of underrepresented groups, future studies should work to include diverse ethnic and racial groups, people from low and middle-income countries, as well as transgender, nonbinary, and intersex PWECP. Altogether, these lines of research will help identify pregnancies at greatest risk of adverse outcomes and inform new, targeted interventions to improve parental, fetal, perinatal, and neurodevelopmental outcomes.

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Conflict of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical, and trustworthy clinical practice guidelines (CPGs) and evidence-based documents. Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this evidence-based document. Management and disclosure of document developer relationships is conducted in compliance with the 2017 AAN process manual section titled, "Implementing the AAN Conflict of Interest Policy for Guidelines and Case Definitions," which can be viewed at aan.com.

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Continued

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