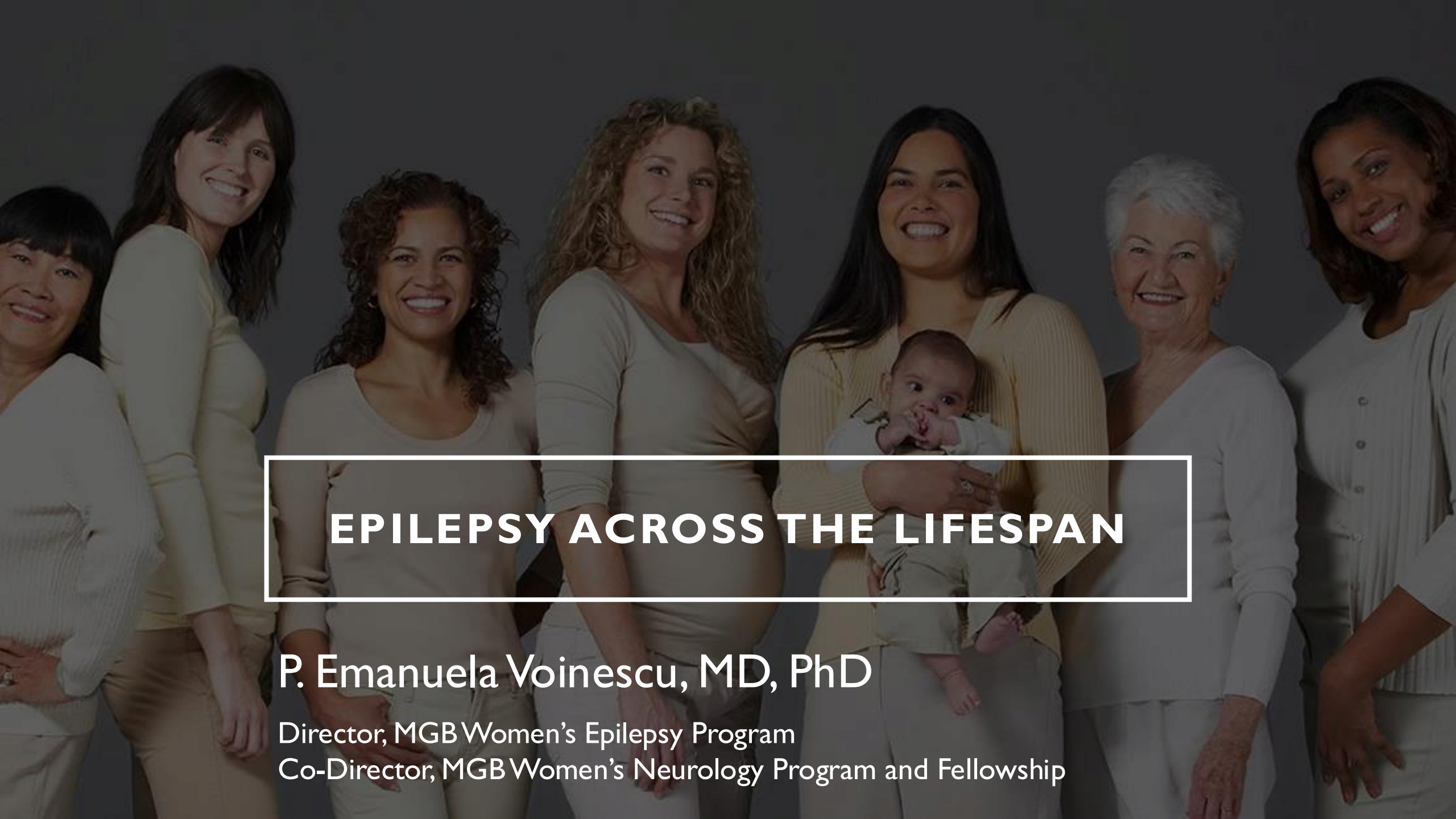


EPILEPSY ACROSS THE LIFESPAN

P. Emanuela Voinescu, MD, PhD

Director, MGB Women's Epilepsy Program
Co-Director, MGB Women's Neurology Program and Fellowship

DISCLOSURES

- Member of the Scientific Advisory Board for the North American AED Pregnancy Registry
- Founder of ECAM (Epilepsy in the Childbearing Ages through Menopause) Consortium
- Honoraria for:
  - PhD Opponent for Håkon Vegrim's PhD thesis defense at University of Bergen, Norway
  - Speaker Honoraria SK Life Science

Personalized Care for Women at Different Biological Stages

Contraception
Catamenial Epilepsy
Fertility
IVF/ART
Pregnancy/Postpartum
Perimenopause
Menopause

NEUROSTEROID PRODUCTION

A. Hypothalamic-pituitary-ovarian axis responsible for distal steroid hormone production.
   i. WWE with TLE: Left – PCOS; R – hypothalamic hypogonadism[1]
   ii. PCOS more frequent in IGE

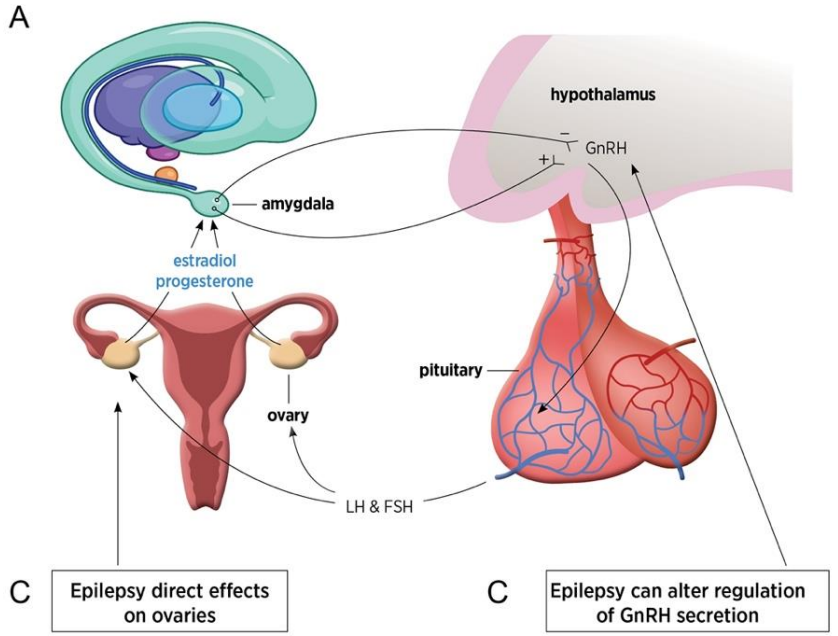
B. Neuronal and glial pathways for local neurosteroid production within the brain.

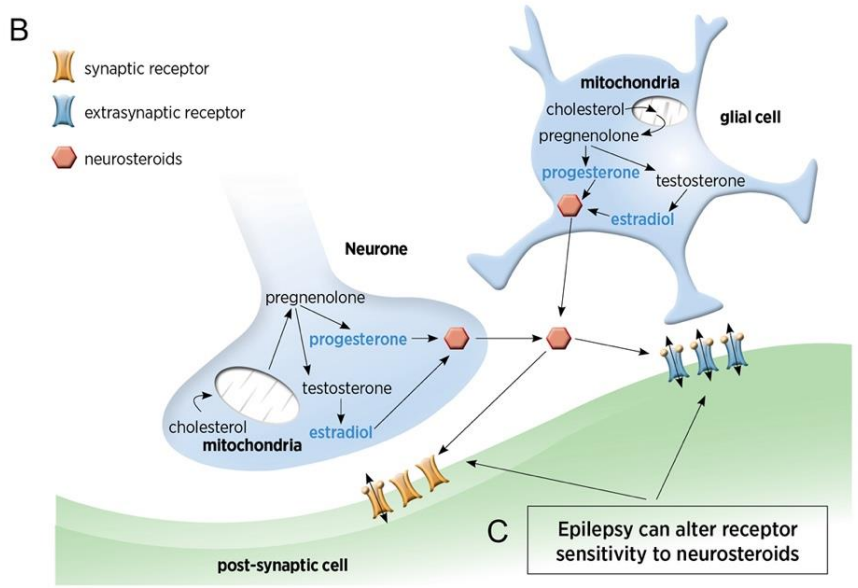
C. The complex inter-relationship between epilepsy and neurosteroids.

   AED effects on female sex steroid hormones
   i. PCOS incidence increased 1.95-fold by VPA compared to other ASMs[2,3]
   ii. VPA had the highest likelihood to cause PCOS (OR 6.86, 95% CI 2.92-24.07), while carbamazepine, oxcarbazepine, and lamotrigine also had a nonsignificant increase (meta-analysis of 16 studies)[4]
   iii. Polytherapy may also increase risk of IVF in women with epilepsy[5]

GnRH- gonadotrophin releasing hormone; LH- luteinizing hormone; FSH- follicle-stimulating hormone.

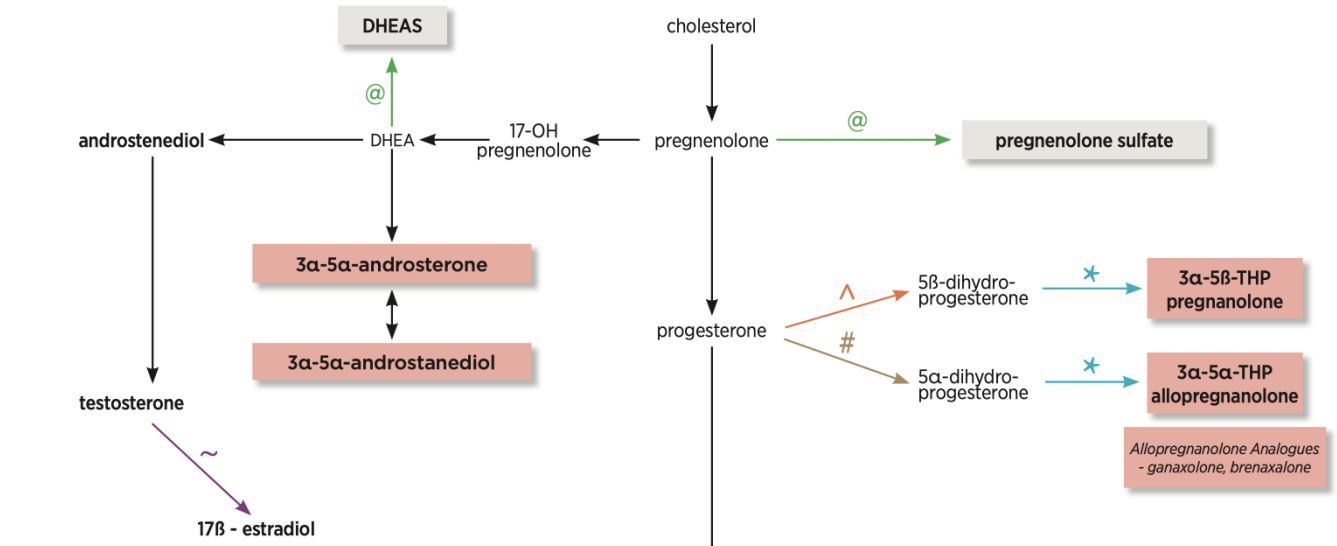
1. Herzog AG. Neurology 1993; 2. Morrell MJ et al. *Ann Neurol* 2008; 3. Xu X et al. *Epilepsy Res* 2011; 4. Guo J et al. *Front Psychiatry* 2023; 5. Sukumaran SC et al. *Neurology* 2010.





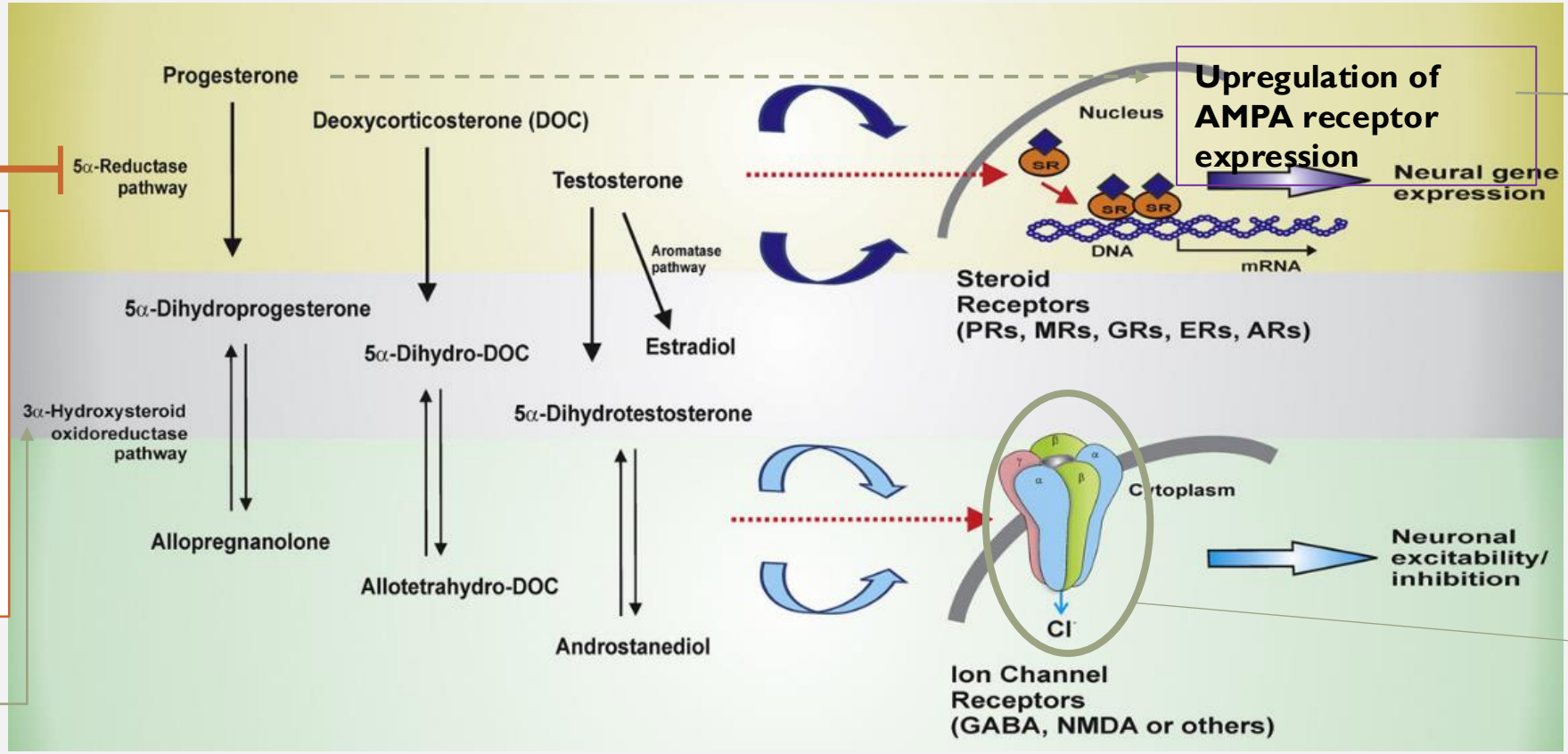
Vadlamudi L and Voinescu PE, *Front Glob Womens Health*. 2024;5:1363470.

NEUROSTEROID PATHWAY AND ENZYMES INVOLVED



Vadlamudi L and Voinescu PE, *Front Glob Womens Health*. 2024;5:1363470.

SEX STEROID HORMONE EFFECT ON NEURONAL EXCITABILITY AND SEIZURE SUSCEPTIBILITY



Upregulation of AMPA receptor expression

→ Seizure exacerbation

Finasteride

- animal model of catamenial epilepsy in which high progesterone (pseudopregnancy) serum concentrations are achieved first, followed by finasteride-induced NAS withdrawal (Reddy and Rogawski, *Epilepsia*, 2001)
- case report of a woman on progesterone therapy developing more seizures when treated with finasteride for male pattern baldness (Herzog and Frye, *Annals of Neurology*, 2003)

Low expression in PCDH19 epilepsy

mutations in GABA-A receptor subunit (α1, α6, β3, γ2 and δ) genes have been involved in the pathophysiology of several idiopathic generalized epilepsies

Modified from Reddy D. *Pharmacology Biochemistry and Behavior* 2017

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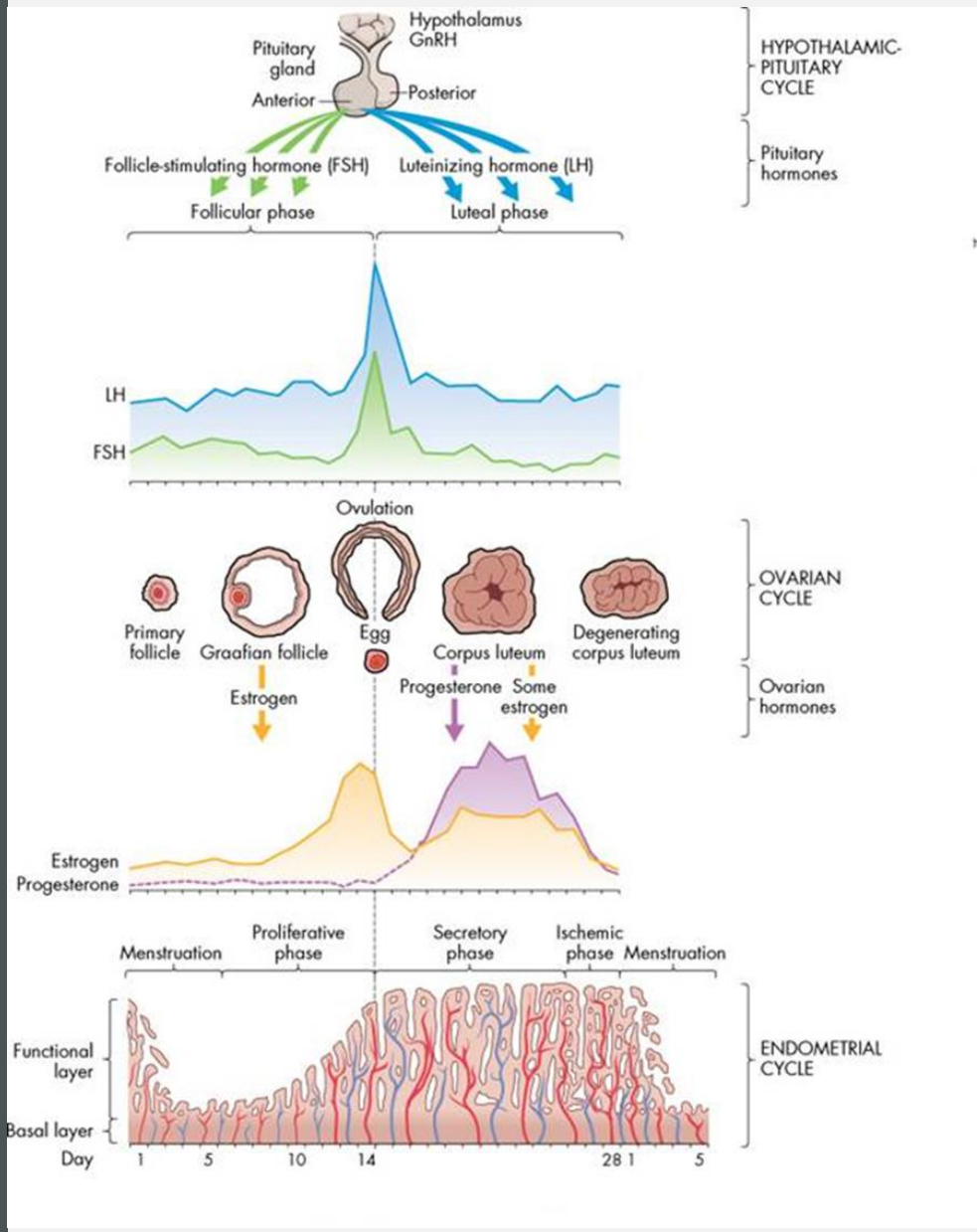
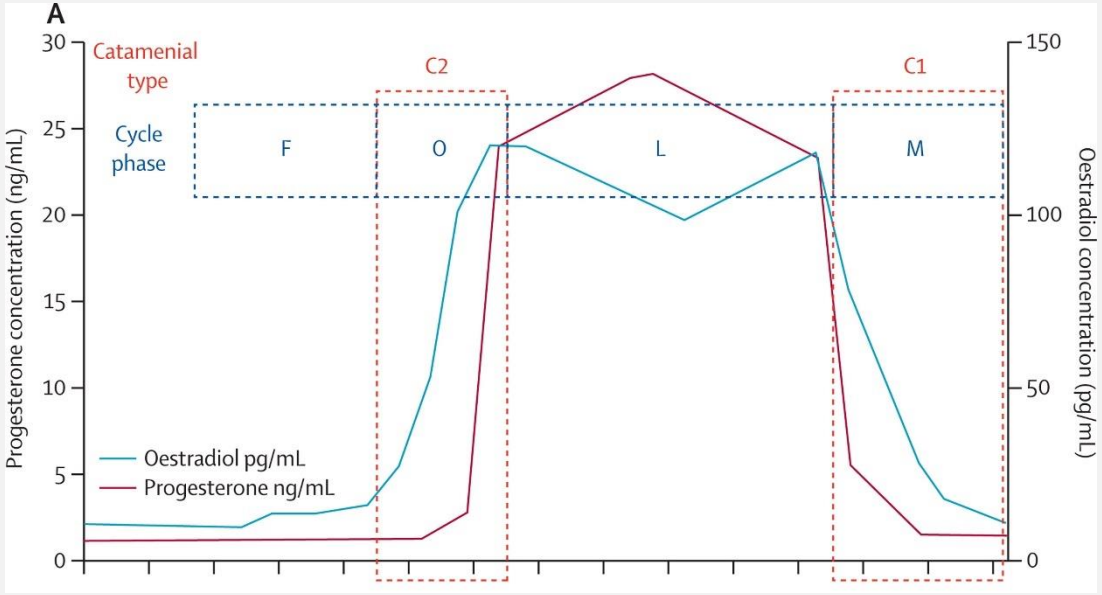
CATAMENIAL EPILEPSY – DEFINITION

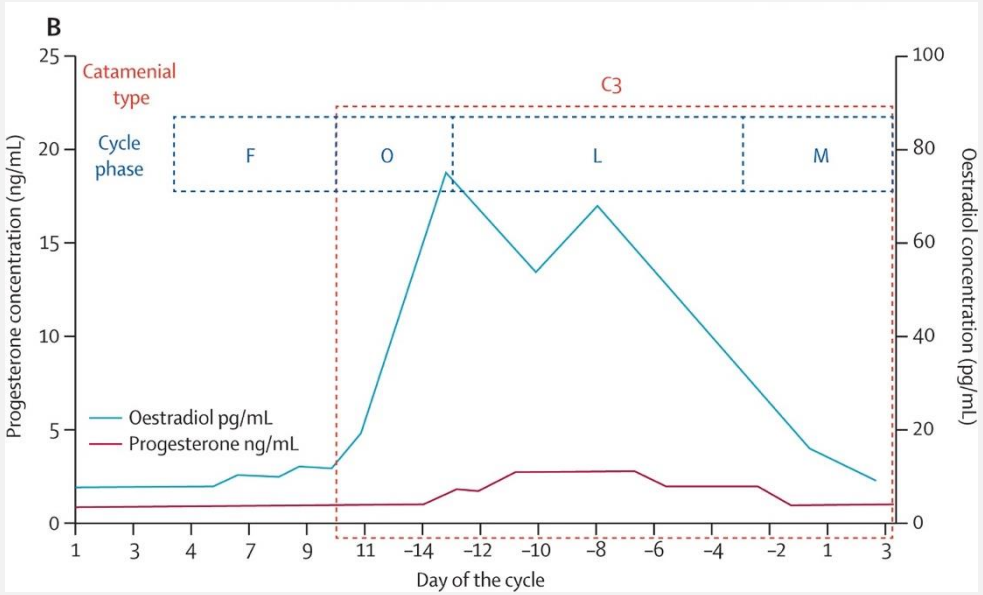
- "Catamenial" (Greek *Katamenios* – monthly) is a seizure exacerbation pattern associated with changes in sex hormone concentrations throughout the menstrual cycle
  - Seizure/Menstruation diary for at least 3 months
  - Two-fold or greater increase during certain phases

"Complex neuroendocrine condition"



CATAMENIAL SEIZURE PATTERN AND BIOLOGICAL BASIS





C2 (Periovulatory)
Estrogen surge

C1 (Perimenstrual)
Progesterone withdrawal

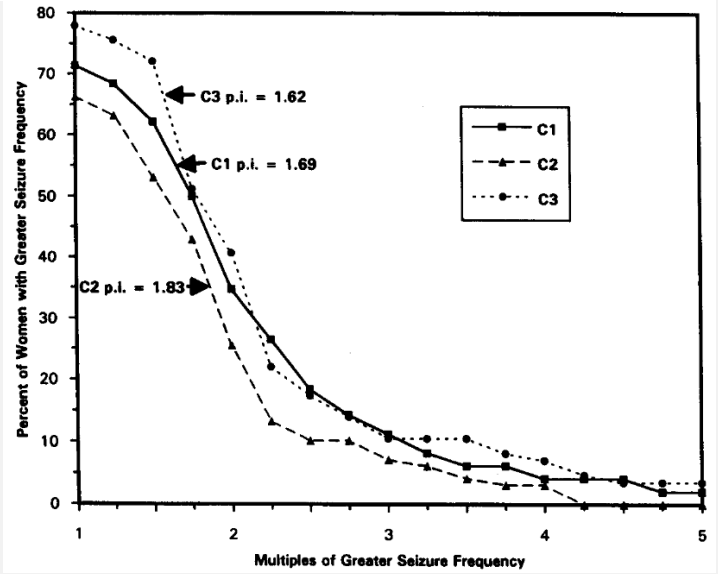
C3 (Anovulatory)
Estrogen surge;
High estrogen:progesterone ratio

Adapted from Herzog AG for Harden CL, Pennell PB, *Lancet Neurology* 2013

CATAMENIAL EPILEPSY - PREVALENCE

184 WWE with intractable focal seizures

Average daily seizure frequency	C1, normal M versus F and L (%)	C2, normal O versus F and L (%)	C3, ILP: M, O and L versus F (%)
>	71.4	68.4	77.9
2×	34.7	25.5	40.7
3×	11.2	7.1	10.5

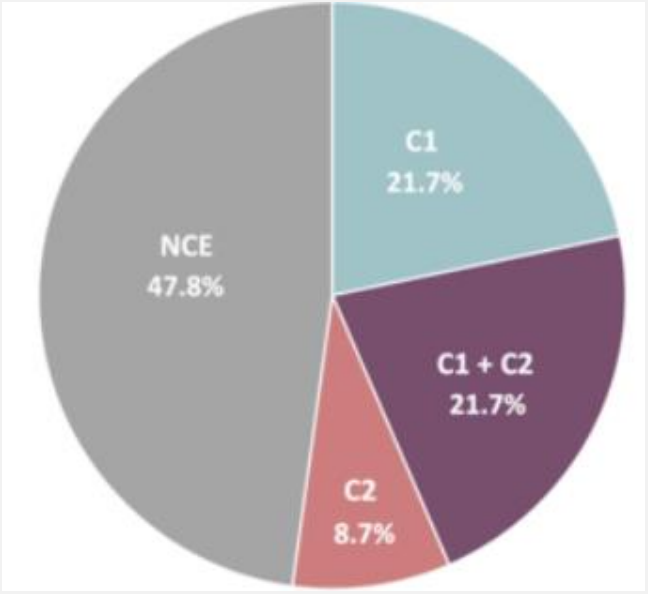


Herzog AG et al. *Epilepsia* 1997

23/89 WWE eligible: ≥1 seizure and ≥1 cycle from WEPOD study

17/23 with focal and 6/23 with generalized epilepsy

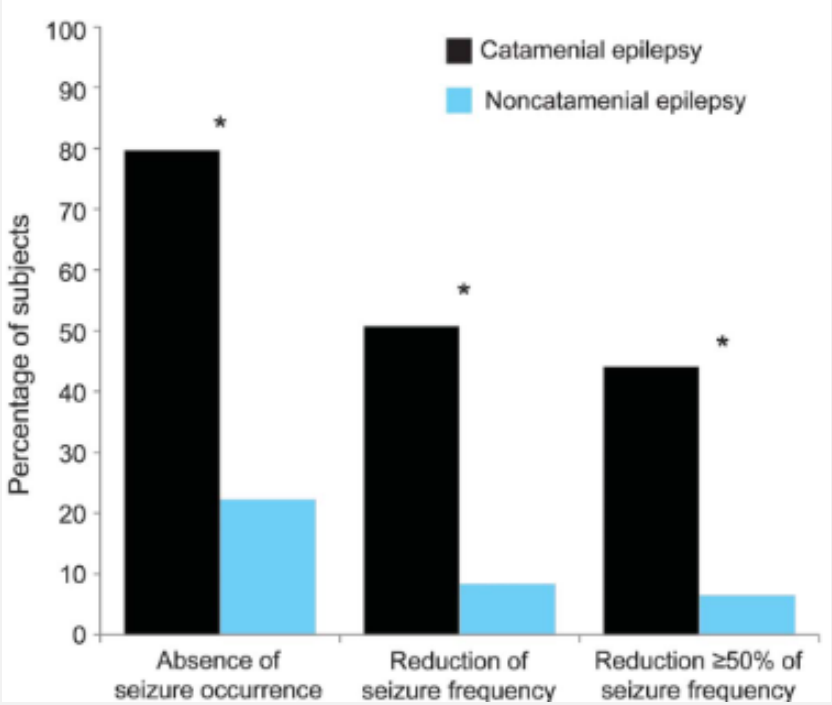
There was no difference in the likelihood of demonstrating a catamenial pattern between those who reported a prior CE and those who did not (p=0.855)



Voinescu PE et al. *Epilepsia* 2023

OTHER CLINICAL OBSERVATIONS

- Perimenarchal seizure onset possibly associated with catamenial epilepsy
- Catamenial seizure exacerbation can occur with any epilepsy type:
  - Focal epilepsy: (L>R?) temporal lobe >> extratemporal or multifocal epilepsy
  - Genetic generalized epilepsies - higher odds of being medically refractory?
- Improved seizure control during pregnancy in a prospective study of women with (n=59) or without (n=215) catamenial epilepsy (only C1 pattern included)[1]
- Catamenial epilepsy may increase the risk of seizure worsening during perimenopause, but decrease during menopause[2]



Cagnetti C et al. *Neurology* 2014

1. Cagnetti C et al. *Neurology* 2014; 2. Harden CL et al. *Epilepsia*. 1999.

NIH PROGESTERONE TRIAL

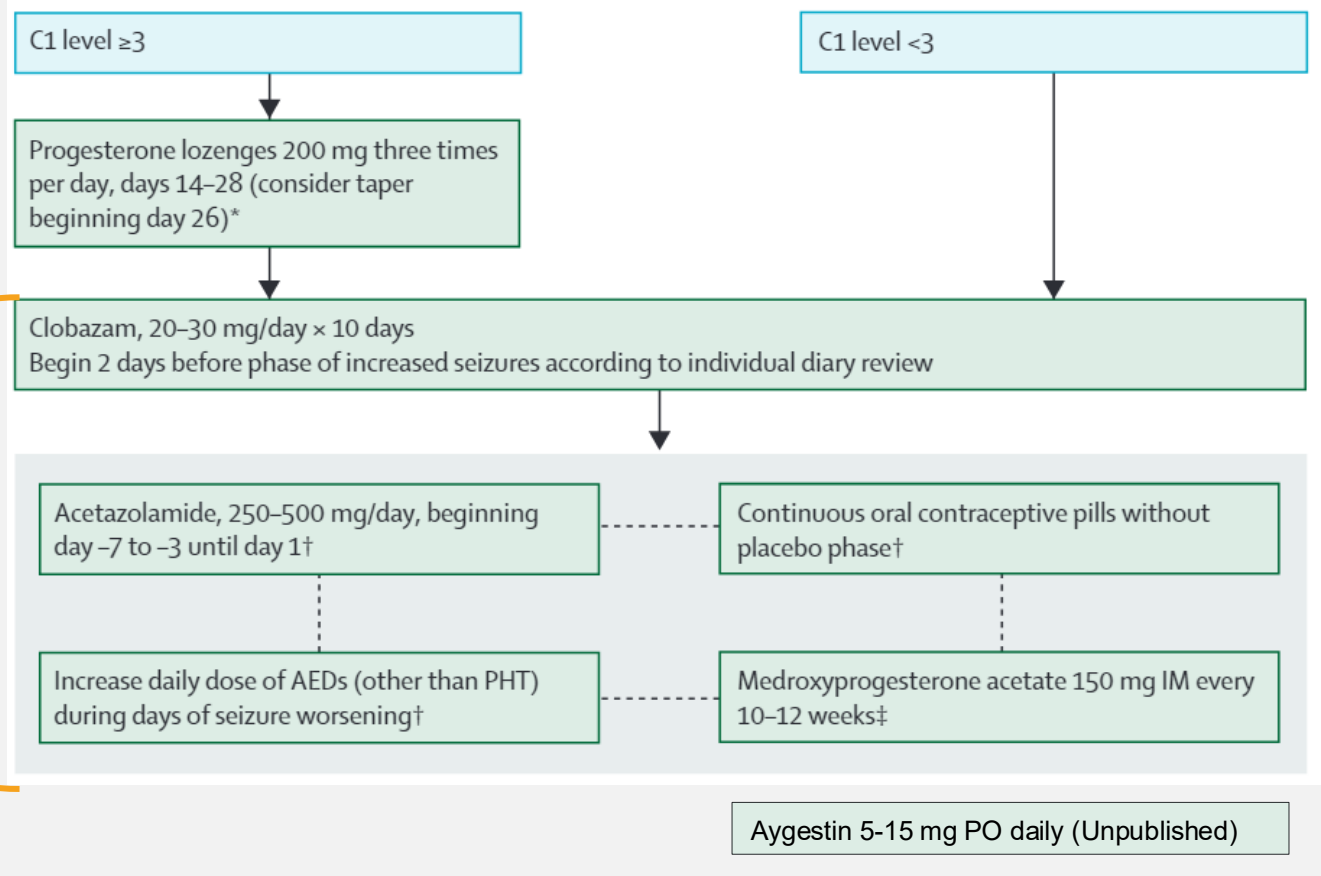
- Cyclic progesterone supplement was not superior to placebo overall, or separately in the noncatamenial or the catamenial cohorts
- Prespecified analyses for predictors of 1) ≥50% progesterone responders & 2) change in ADSF on progesterone found the C1 (perimenstrual) pattern was a significant predictor of responders for progesterone, but not placebo
- A clinically important separation between progesterone and placebo responders (37.8% vs 11.1%; $p<0.037$) was realized among women who had **C1 level ≥3 (21.4%)**
  - There was a significant correlation between AP levels and seizure frequencies from baseline to treatment for this particular subset of subjects, but not for the rest

Herzog AG et al. *Neurology* 2012; Herzog AG et al. *Neurology* 2014

SYNTHETIC NEUROSTEROID (ALLOPREGNANOLONE) CLINICAL TRIALS

- Phase 3 trial of **ganaxolone** for treatment of drug-resistant focal onset seizures in adults did not prove superior to placebo: median percent reduction in seizure frequency from was 21.3% vs 10.2% for the placebo group ($p = 0.15$); ≥50% responder rate was 28.7% vs placebo 22.7% ($p = 0.21$)
  - Yet safety and efficacy was demonstrated for cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (pathogenic variants can alter GABAergic signaling)
- Phase 3 trial of **brexanolone** for super refractory status did not prove superior to placebo for weaning of third-line agents and resolution of status epilepticus: responder rate: 43.9% vs 42.4% ($p = 0.88$)
  - Brexanolone did prove superior to placebo in providing clinically meaningfully, rapid and enduring benefit for postpartum depression, using decrease in HAM-D score as primary outcome (1st study $p = 0.0552$; 2nd $p = 0.0160$)

TREATMENT ALGORITHM FOR CATAMENIAL EPILEPSY



Adjunctive ASMs (Cyclic Buffering)

Any C pattern

Hormonal Manipulation (Suppressing the Cycle)

Aygestin 5-15 mg PO daily (Unpublished)

Adapted from Harden CL & Pennell PB, *Lancet Neurol* 2013.

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REPRODUCTIVE HEALTH AND FERTILITY

- Many studies suggest lower birthrate in WWE – biological or choice?
- USA: state laws allowed forcible sterilization of WWE until 1956[1]
- UK: people with epilepsy were not allowed to marry until 1970[1]
- India: epilepsy was grounds for annulment of marriage until 1999[2]

1. WHO. Epilepsy: social consequences and economic aspects; fact sheet 166. 2001; 2. D'Souza C. Epilepsy and discrimination in India. Neur Asia 2004; 9:53.

Prospective cohort observational study – 3 sites:

Healthy control women (n=108)

Women with epilepsy on ASMs (n=89)

- LTG monotherapy (n=39)
- LEV monotherapy (n=25)
- Strong EI-ASMs mono/polytherapy (n=16)

Results:

*WWE and healthy controls seeking pregnancy had **comparable** ovulatory rates, likelihood and time to achieve pregnancy, pregnancy outcomes*

Pennell PB, et al. *JAMA Neurology* 2018.

Prospective cohort observational study:

No control group

Women with epilepsy (n=375)

- Most frequently used ASMs: carbamazepine, valproate, phenobarbital, phenytoin

Results:

38.4% WWE had infertillity
Important predictors: polytherapy, PB use, older age and lower education

Sukumaran SC, et al. *Neurology* 2010

Kerala Registry of Epilepsy and Pregnancy (1998-2007)

Personalized Care for Women at Different Biological Stages

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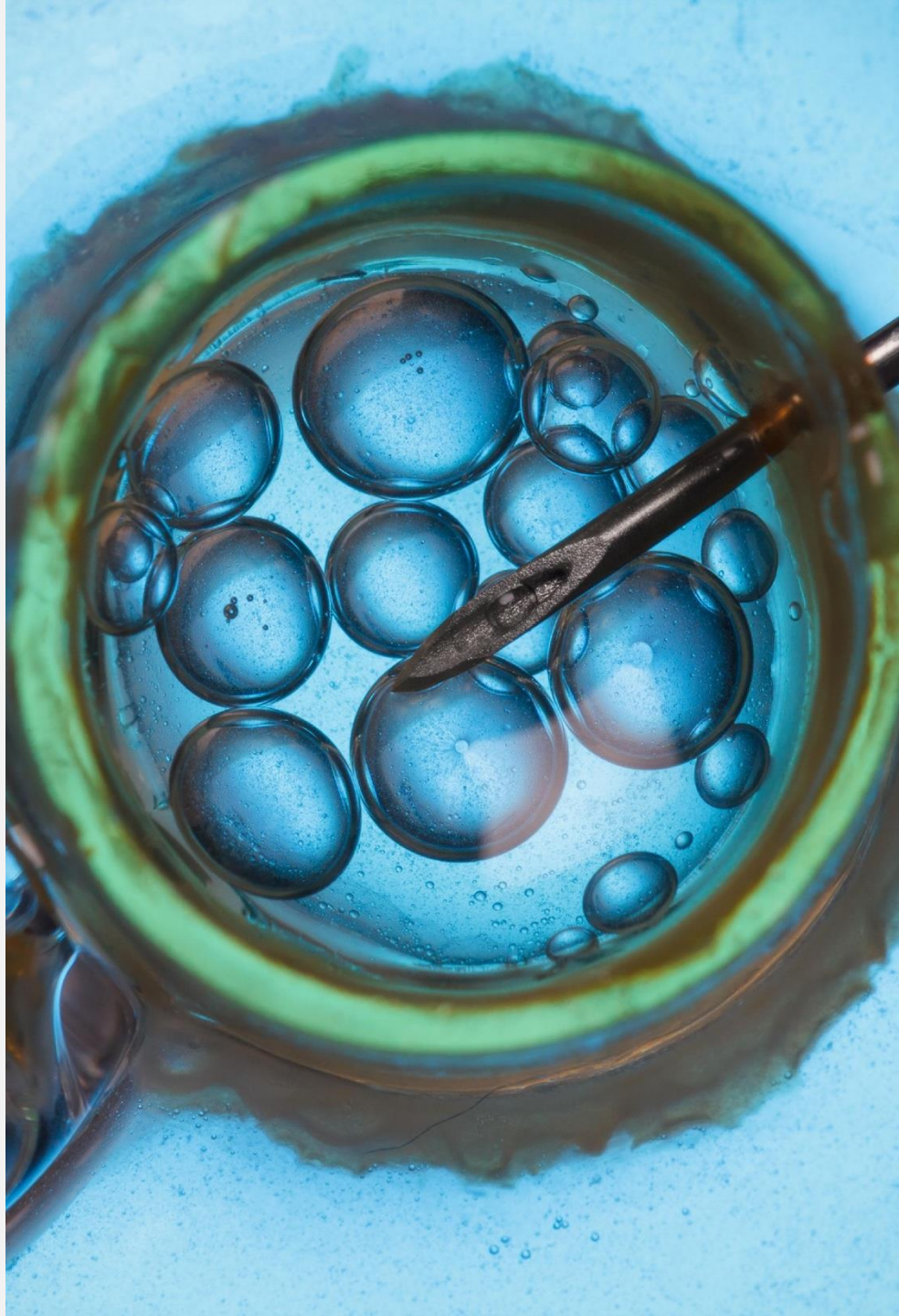
ASSISTED REPRODUCTIVE TECHNOLOGY

- Danish health registries 2006-2017[1]: 260 WWE vs 42,938 WWoE who underwent ART had **similar rates** for: biochemical pregnancy and clinical pregnancy**, live births** (OR 1.03, 95% CI 0.86-1.25), **regardless of ASM** (monotherapy, polytherapy, or EI ASMs)
- 2 WWE who underwent AER: both experienced **seizure worsening**, one with a reduction in lamotrigine serum level during IVF[2]
- 12 WWE, who underwent 29 embryo transfers, resulting in 16 pregnancies and 10 live births, revealed **no increased seizure frequency** associated with fertility treatment and subsequent pregnancy
  - 5 WWE on no ASMs (3/5 with resolved epilepsy); 6 WWE on ASM monotherapy, 1 WWE on ASM polytherapy.
  - 11/12 remained seizure-free throughout fertility treatment.
  - 1/12 (with drug-resistant epilepsy) continued to have seizures throughout fertility treatment and pregnancy without an exacerbation of seizure frequency



1. Larsen MD et al. *Reprod Biomed Online*. 2020;41(6):1015–22. 2. Mostacci B et al. *Seizure*. 2018;61:200–2.
3. Abdulrazaq AA et al. *Epilepsia*. 2023; 2023;64:e207–e213.

Personalized Care for Women at Different Biological Stages

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Perimenopause
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Phase 1 | Preconception Planning

Optimizing outcomes before pregnancy occurs.

ANTISEIZURE MEDICATIONS AND PREGNANCY

Education regarding the risk of ASMs and risk of seizures is important

Establishing a Safe Baseline

AAN Recommendation

Engage in joint decision-making with patients to optimize ASM doses at the earliest possible preconception opportunity.

* Pack AM et al, *Neurology, 2025*

Folic Acid Mandate

Prescribe 1mg daily. Associated with a 5-point higher IQ in offspring, reduced risks for language delay, and reduced risk of autism.

* Voinescu PE, *JAMA Neurol.* 2023; Li Y et al, *Epileptic Disord.* 2025

Optimize the ASM Profile

- Monotherapy is strongly preferred to polytherapy.
- Preferable ASMs: Lamotrigine (LTG), Levetiracetam (LEV).
- Avoid: Valproic Acid (VPA), Phenobarbital (PB), Topiramate (TPM).

Set the Target

Determine the individualized baseline concentration—the ASM concentration on the minimal effective dose.

The Personalized Equation

Risk of Medications:

- Structural teratogenicity
- Cognitive teratogenicity
- Adverse neonatal outcomes

Risk of Optimization:

- Balancing seizure control against side effects when attempting to adjust the Anti-Seizure Medication (ASM) regimen.

Risk of Seizures:

- Risks to both the mother and the fetus.

The Personalized Equation

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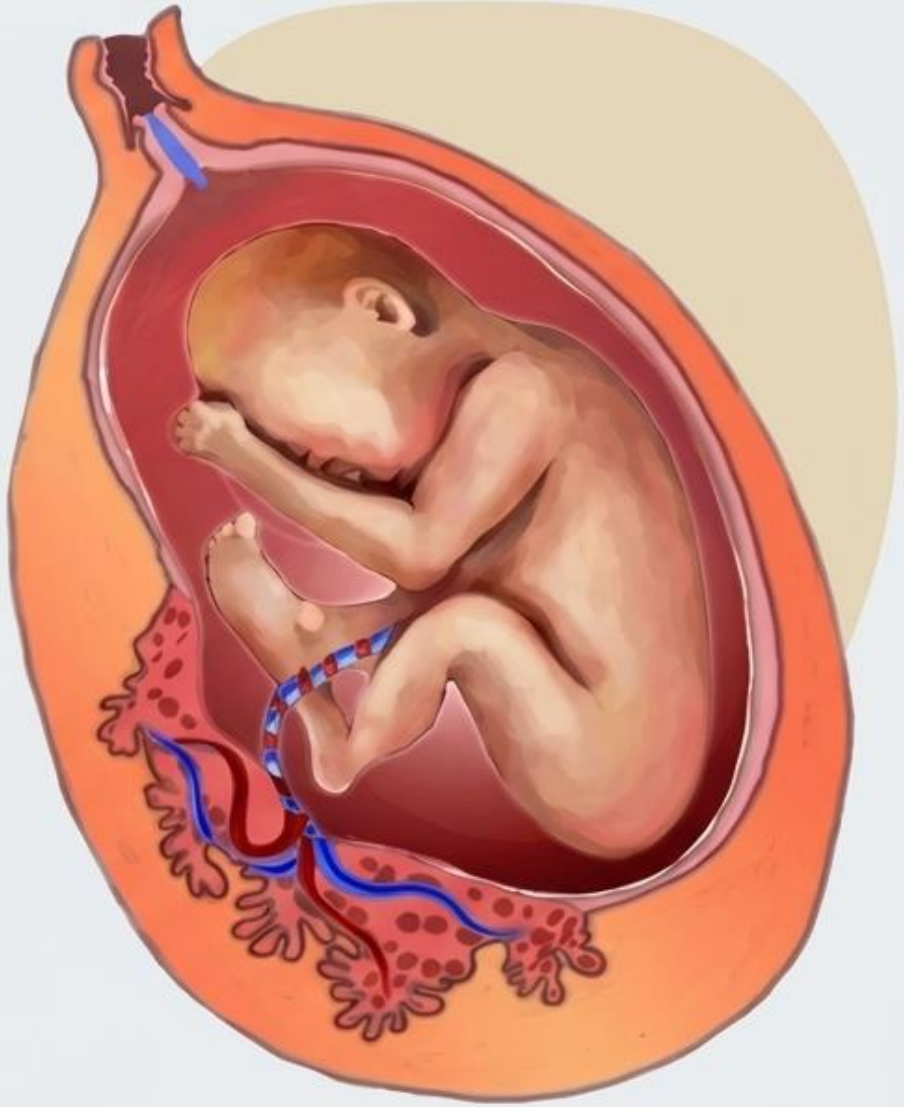
The Risks of Seizures

- **Generalized Tonic-Clonic Convulsions (GTCC)**
  - Cause maternal and fetal hypoxia, acidosis, and fetal bradycardia.
  - Elevate risk of miscarriage and stillbirths.
  - Associated with developmental delay (specifically if >5 GTCCs occur during pregnancy).
- **All Seizure Types**
  - Carry an increased odds ratio (1.3-1.6 fold) for Low Birth Weight (LBW), Small for Gestational Age (SGA), and preterm delivery.
- **AAN Level B Guideline**
  - Once a patient is already pregnant, exercise high caution attempting to remove or replace an ASM that effectively controls GTCCs—even if it is not an optimal fetal choice (e.g., Valproic Acid).



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- Risks to both the mother and the fetus.

SUMMARY OF ASM STRUCTURAL & NEURODEVELOPMENTAL EFFECTS

- Structural teratogenicity may be irreversible by the time the pregnant woman is seen in clinic – Planned pregnancy is key!
- Rate of MCMs with exposure to ASM monotherapy - green with no noticeable impact and red with negative impact on neurodevelopment
  - Low: LTG, LEV, OXC, ZNS, (LCM, GBP)
  - Medium: CBZ, PHT (CLZ)
  - High: TPM, PB, VPA
- Rate of SGA – higher for TPM, PB >ZNS
- Optimize ASM regimen for seizure control and pregnancy outcome:
  - Consider switching to an ASM with a better pregnancy outcome profile
  - Monotherapy preferred to polytherapy
  - Reduce to minimal effective dose
  - If polytherapy is necessary, some ASMs are preferable (LTG, LEV) while some should be avoided (VPA, TPM)

ASM, antiseizure medication; CBZ, carbamazepine; CLZ, clonazepam; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; MCM, major congenital malformations; OXC, oxcarbazepine; SGA, small gestational age; PB, phenobarbital; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

Voinescu PE and Pennell PB. Semin Neurol. 2017;37:611–623.

TIMING OF CERTAIN MCMS

Structural Teratogenicity

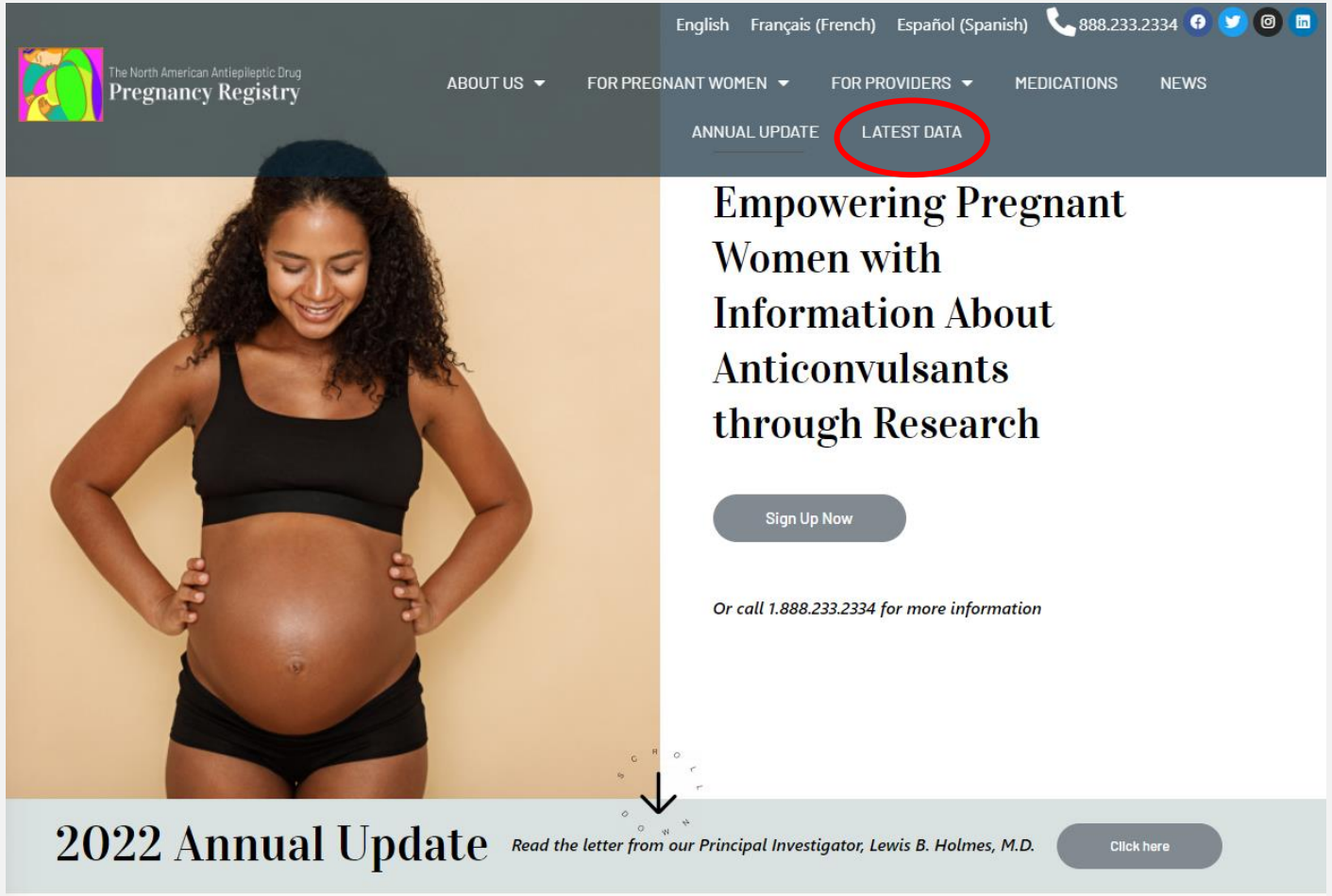
Tissues	Malformations	Postconceptional age
CNS	Neural tube defect	28 d
Heart	Ventricular septal defect	42 d
Face	Cleft lip	36 d
	Cleft maxillary palate	47–70 d
Genitourinary	Hypospadias	84 d

Structural teratogenicity may be irreversible by the time the pregnant woman is seen in clinic!

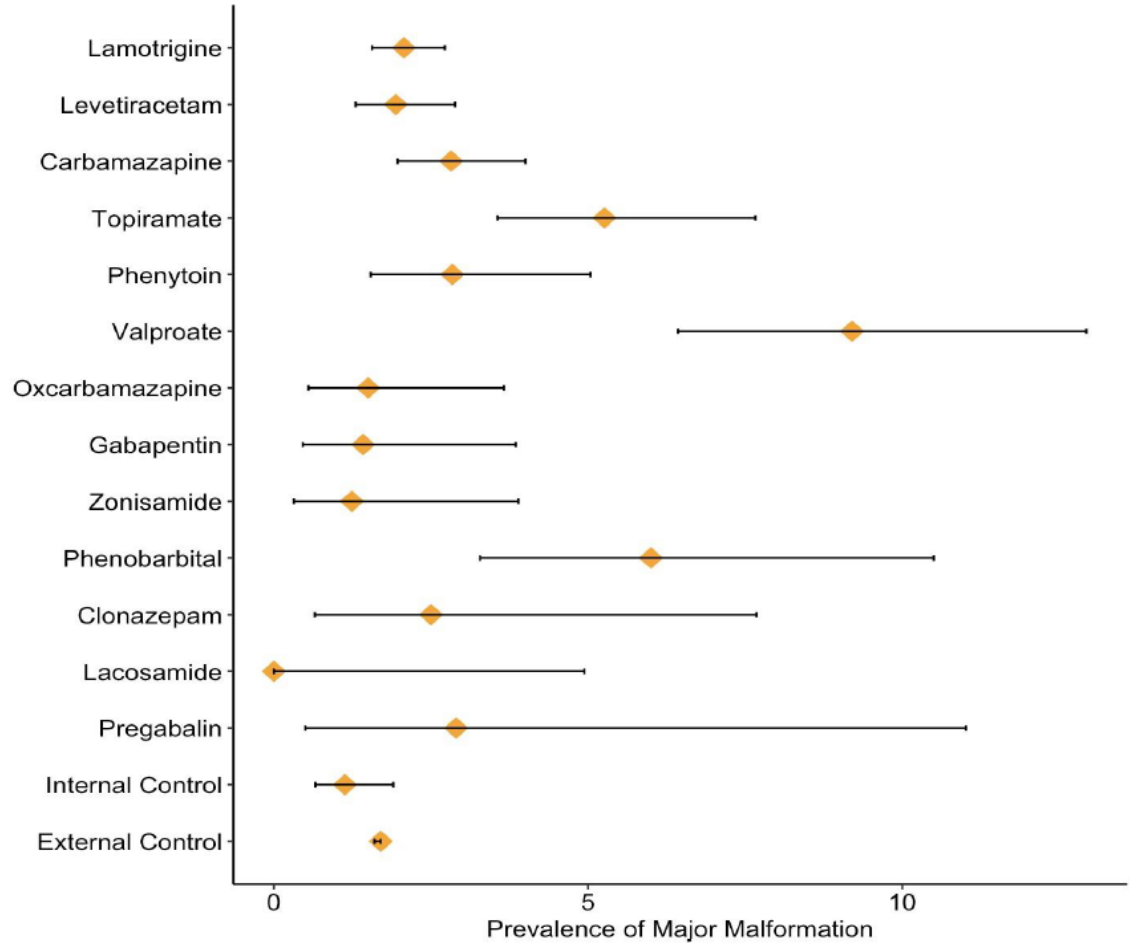
CNS, central nervous system; MCMs, major congenital malformations.

http://www.columbia.edu/itc/hs/medical/humandev/2004/Chpt23-Teratogens.pdf

NAAPR : WWW.AEDPREGNANCYREGISTRY.ORG



Risk of malformations for specific AED in monotherapy 1st trimester and the control groups through 2023



	%	N	95% CI
Lamotrigine	2.07	2514	(1.56, 2.72)
Levetiracetam	1.94	1337	(1.3, 2.88)
Carbamazapine	2.82	1135	(1.97, 4)
Topiramate	5.26	513	(3.56, 7.66)
Phenytoin	2.84	423	(1.54, 5.04)
Valproate	9.2	337	(6.43, 12.93)
Oxcarbamazapine	1.5	334	(0.55, 3.66)
Gabapentin	1.42	281	(0.46, 3.85)
Zonisamide	1.24	241	(0.32, 3.89)
Phenobarbital	6	200	(3.28, 10.5)
Clonazepam	2.5	120	(0.65, 7.68)
Lacosamide	0	93	(0, 4.94)
Pregabalin	2.9	69	(0.5, 11.01)
Internal Control	1.13	1330	(0.66, 1.9)
External Control	1.7	289365	(1.6, 1.7)

ASM, antiseizure medication; NAAPR, North American Antiepileptic Drug Pregnancy Registry; MCM, major congenital malformation.

COMPARATIVE SAFETY OF ASMS DURING PREGNANCY

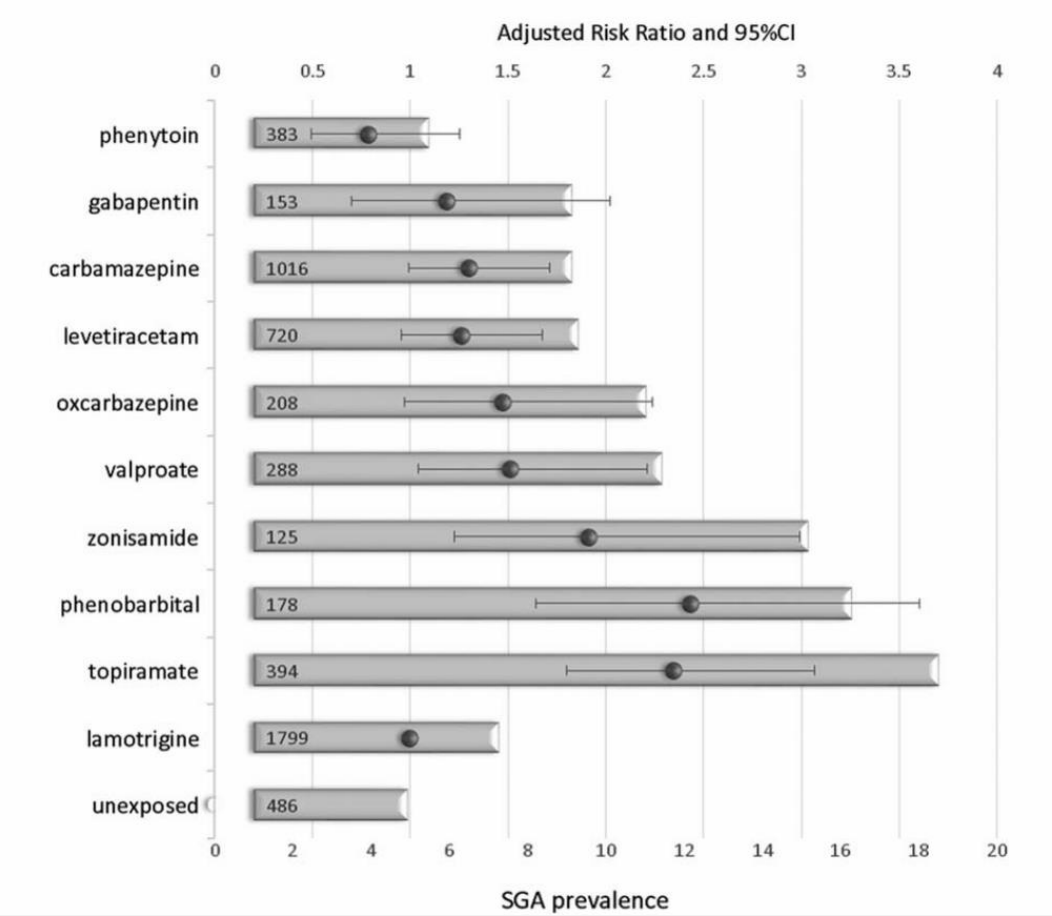
Table 2. Prevalence of Major Congenital Malformations (MCMs) in Offspring Exposed Prenatally to Monotherapy With 1 of 8 Different Antiseizure Medications (ASMs)[a]

ASM treatment (dose range, mg/d)	No. Exposed pregnancies	No. Pregnancies with MCMs	Prevalence of MCMs (95% CI), %	Dose-dependency *P* value
Carbamazepine (25-2400)	2255	121	5.4 (4.5-6.4)	NA
Lamotrigine (5-1300)	3584	110	3.1 (2.5-3.7)	
Levetiracetam (80-5000)	1325	33	2.5 (1.8-3.5)	
Oxcarbazepine (75-4500)	443	13	2.9 (1.7-5.0)	
Phenobarbital (15-300)	338	21	6.2 (4.1-9.3)	
Phenytoin (30-730)	142	9	6.3 (3.4-11.6)	
Topiramate (25-600)	204	10	4.9 (2.7-8.8)	
Valproate (100-3000)	1549	153	9.9 (8.5-11.5)	
Phenobarbital (≤60)	76	2	2.6 (0.3-9.2)	.047
Phenobarbital (>60-≤130)	197	12	6.1 (3.2-10.4)	
Phenobarbital (>130)	65	7	10.8 (4.4-20.9)	
Carbamazepine (≤700)	1506	70	4.6 (3.6-5.8)	.008
Carbamazepine (>700 -≤1000)	541	32	5.9 (4.1-8.2)	
Carbamazepine (>1000)	208	19	9.1 (5.6-13.9)	
Valproate (≤650)	715	43	6.0 (4.4-8.0)	<.001
Valproate (>650-≤1450)	711	79	11.1 (8.9-13.6)	
Valproate (>1450)	123	31	25.2 (17.8-33.8)	

Battino et al, *JAMA Neurology*. 2024.
EURAP, European Registry of Antiepileptic drugs and Pregnancy

NEONATAL OUTCOMES

Small gestational age



AAN – ASMs: Perinatal Outcomes

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).

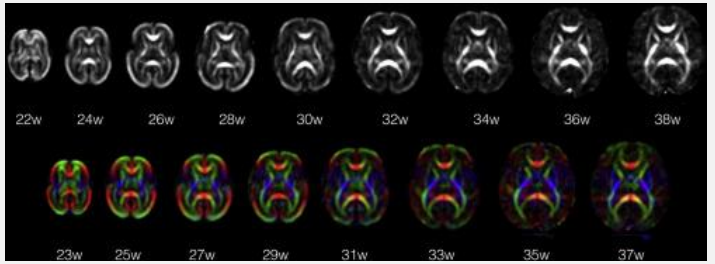
4B. Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born SGA, if clinically feasible (Level B).

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).

Hernandez-Diaz et al. *Ann Neurol*. 2017;82:457–465. 2. Pennel PB et al. *Epilepsy Behav*. 2012;24:449–456.

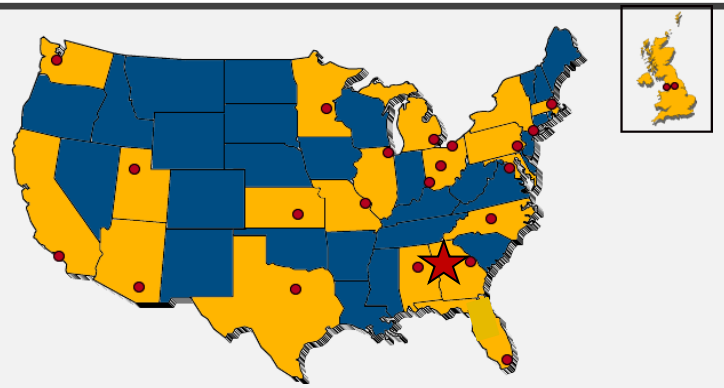
PREGNANCY

Neurodevelopmental Effects



NEAD

NEURODEVELOPMENTAL EFFECTS OF ANTIEPILEPTIC DRUGS



- Pregnant Mothers with Epilepsy-Child Pairs (n=309)
- Antiepileptic drug (AED) monotherapy:
  - Carbamazepine (CBZ)
  - Lamotrigine (LTG)
  - Phenytoin (PHT)
  - Valproate (VPA)

MONEAD

Multiple-PIs:
Kimford Meador, MD (Stanford)
Page B. Pennell, MD (University of Pittsburgh)

Obstetrics Core:
T. McElrath (BWH), M. Druzin (Stanford)

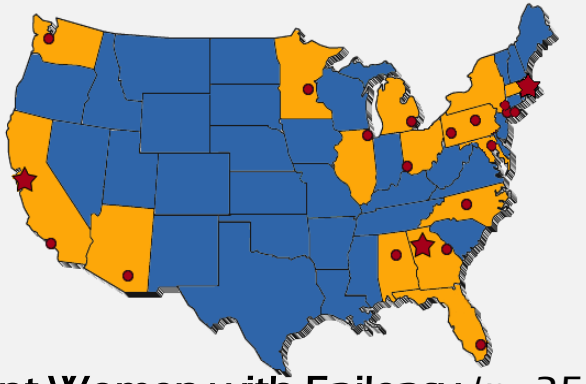
Neonatal Core: L. Van Marter (BWH) Semiology Core: J. French (NYU)
Mood Core: Z. Stowe (U Wisconsin)
OK Core: A. Birnbaum (U Minnesota)

Blinded cognitive assessments: 2, 3, 4.5, & 6 years old
Primary outcome: IQ at 6 years old

Funded by NIH/NINDS,NICHD #U01-NS038455

MONEAD

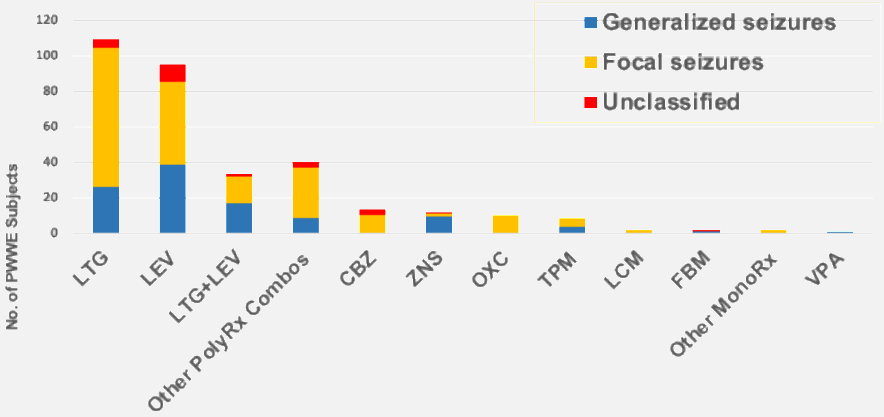
MATERNAL OUTCOMES & NEURODEVELOPMENTAL EFFECTS OF ANTIEPILEPTIC DRUGS



Pregnant Women with Epilepsy (n=355), compared to 2 control groups:

Pregnant healthy controls (n=105)

Non-pregnant WWE (n=109)



Meador KJ, Pennell PB, MONEAD Investigator Group. *Epilepsy & Behavior* 2018.

FETAL EXPOSURE TO VALPROATE ASSOCIATED WITH LOWER IQ AT AGE 6

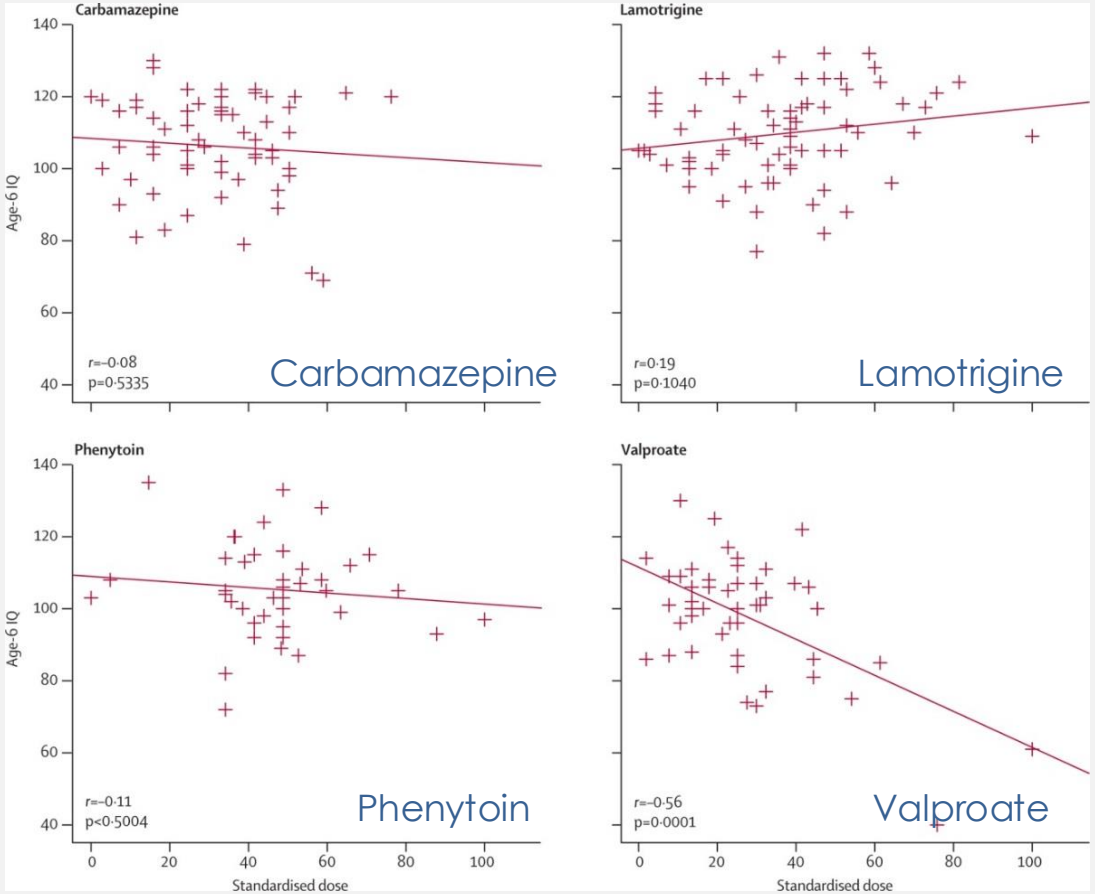
Mean IQs (95% Difference CIs from VPA) adjusted for maternal IQ, AED dose, gestational age and folate

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Total-enrolled				
Participants	94 (30%)	100 (32%)	55 (18%)	62 (20%)
Mean IQ*	105 (102–108)	108 (105–110)	108 (104–112)	97 (94–101)
Difference	7 (3–12)	10 (6–15)	10 (5–16)	NA
p value†	0·0015	0·0003	0·0006	NA
Age-6-completers				
Participants	61 (27%)	74 (33%)	40 (18%)	49 (22%)
Mean IQ*	106 (103–109)	108 (105–111)	109 (105–113)	98 (95–102)
Difference	8 (3–13)	10 (6–15)	11 (5–16)	NA
p value†	0·0010	0·0003	0·0004	NA

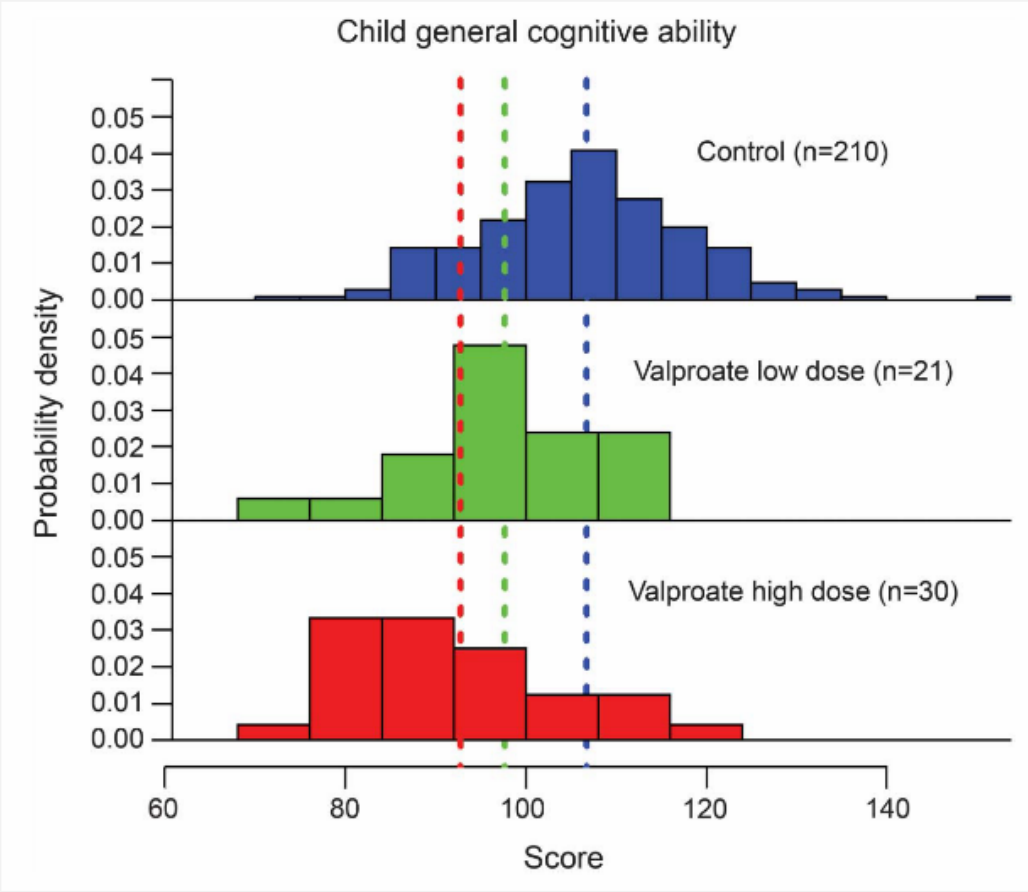
Meador KJ, et al. *Lancet Neurol*. 2013;12:244–252.

DOSE-DEPENDENT IQ DIFFERENCES AMONG VPA-EXPOSED SUBJECT GROUPS

NEAD study[1]



LMNDG study[2]



Colored dashed lines represent the mean IQ for each group.

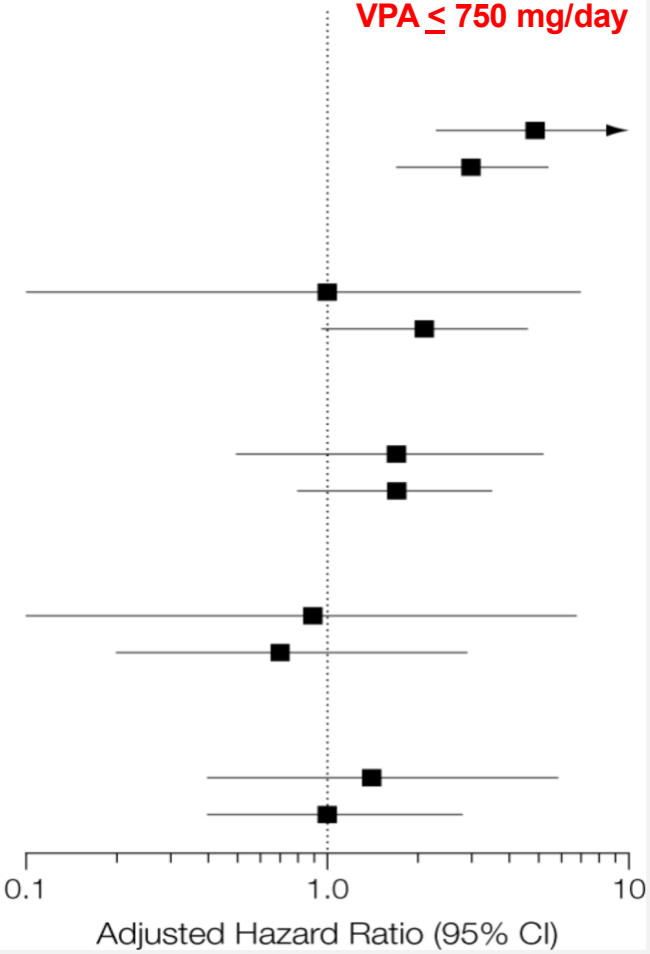
NEAD, Neurodevelopmental Effects of Antiepileptic Drugs. LMNDG, Meador KJ et al. Lancet Neurol 2013;12:244–52

Liverpool and Manchester Neurodevelopmental Group Baker G et al. Neurology 2015;84(4):382–390

RISK OF AUTISM WITH AED MONOTHERAPY

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

***Risks were same for women on VPA ≤ 750 mg/day**



AED, antiepileptic drugs; VPA, valproic acid.

Christensen J, et al. JAMA. 2013;309(16):1696–1703.

FETAL EXPOSURE TO LEVETIRACETAM IS NOT ASSOCIATED WITH A NEGATIVE NEURODEVELOPMENTAL EFFECT

- Neuropsychological assessments were conducted between 5 and 9 years of age
- Adverse cognitive outcomes were not associated with increasing doses of LEV and TPM

Table 2 Unadjusted means, standard errors, and rates below average performance by group for primary cognitive outcomes

	No medication (n = 55)		Gabapentin (n = 14)		Topiramate (n = 27)		Levetiracetam (n = 42)		Valproate (n = 47)	
WISC/WPPSI	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85	Mean (SD)	No. (%) <85
Full-scale IQ	99.7 (13.6)	3 (6)	103.6 (12.9)	1 (8)	100.5 (13.2)	3 (12)	99.0 (13.6)	5 (12)	95.9 (14.1)	9 (19)
Verbal abilities	101.7 (13.0)	4 (7)	105.0 (12.6)	1 (7)	99.2 (11.2)	3 (11)	101.0 (11.2)	1 (2)	93.7 (14.6)	10 (21)
Nonverbal abilities	100.8 (14.6)	6 (11)	104.3 (14.2)	1 (7)	102.4 (14.7)	3 (11)	99.6 (13.8)	7 (17)	101.5 (14.7)	6 (13)
Processing speed	97.1 (12.5)	8 (15)	103.6 (9.7)	0 (0)	100.0 (13.3)	3 (11)	94.7 (12.6)	7 (17)	94.6 (11.9)	8 (17)

LEV, levetiracetam; LTG, lamotrigine; PHT, phenytoin; VPA, valproate; DCI, confidence intervals for difference from VPA.
Bromley RL et al. Neurology. 2016;87(18):1943–1953.

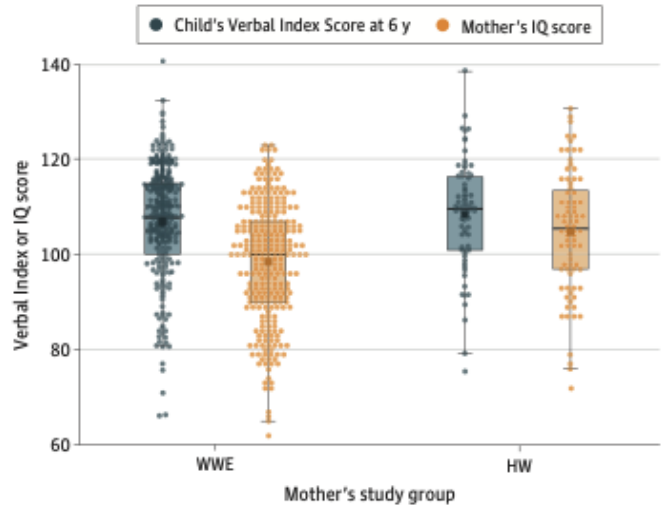
JAMA Neurology | Original Investigation

Neuropsychological Outcomes in 6-Year-Old Children of Women With Epilepsy

A Prospective Nonrandomized Clinical Trial

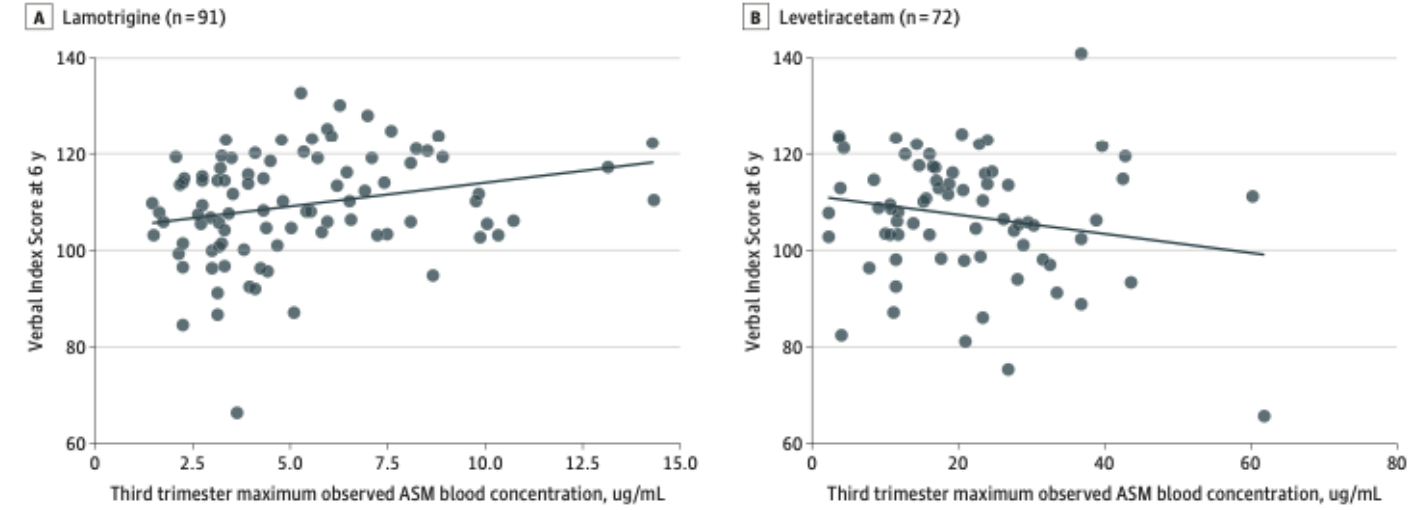
JAMA Neurol. 2025;82(1):30-39. doi:10.1001/jamaneurol.2024.3982
Published online November 25, 2024.

Figure 1. Verbal Index Score in 6-Year-Old Children and Mother's IQ by Mother's Study Group—Children of Women With Epilepsy (WWE) vs Healthy Women (HW) (N = 353)



The bold dot represents the mean, the middle bar is the median, the lower and upper bars of the box represent the 1st and 3rd quartile, respectively, the bottom and top of the whiskers are the most extreme points less than or equal to 1.5 times the IQR, and the dots outside the whiskers are points that are more than ±1.5 times the IQR. Children aged 6 years with imputed Verbal Index Scores excluded from figure.

Figure 2. Scatter Plot of Verbal Index Score in 6-Year-Old Children vs Third-Trimester Maximum Observed Antiseizure Medication (ASM) Blood Concentration for Lamotrigine and Levetiracetam in Children of Women With Epilepsy (WWE) With Third Trimester Blood Concentrations



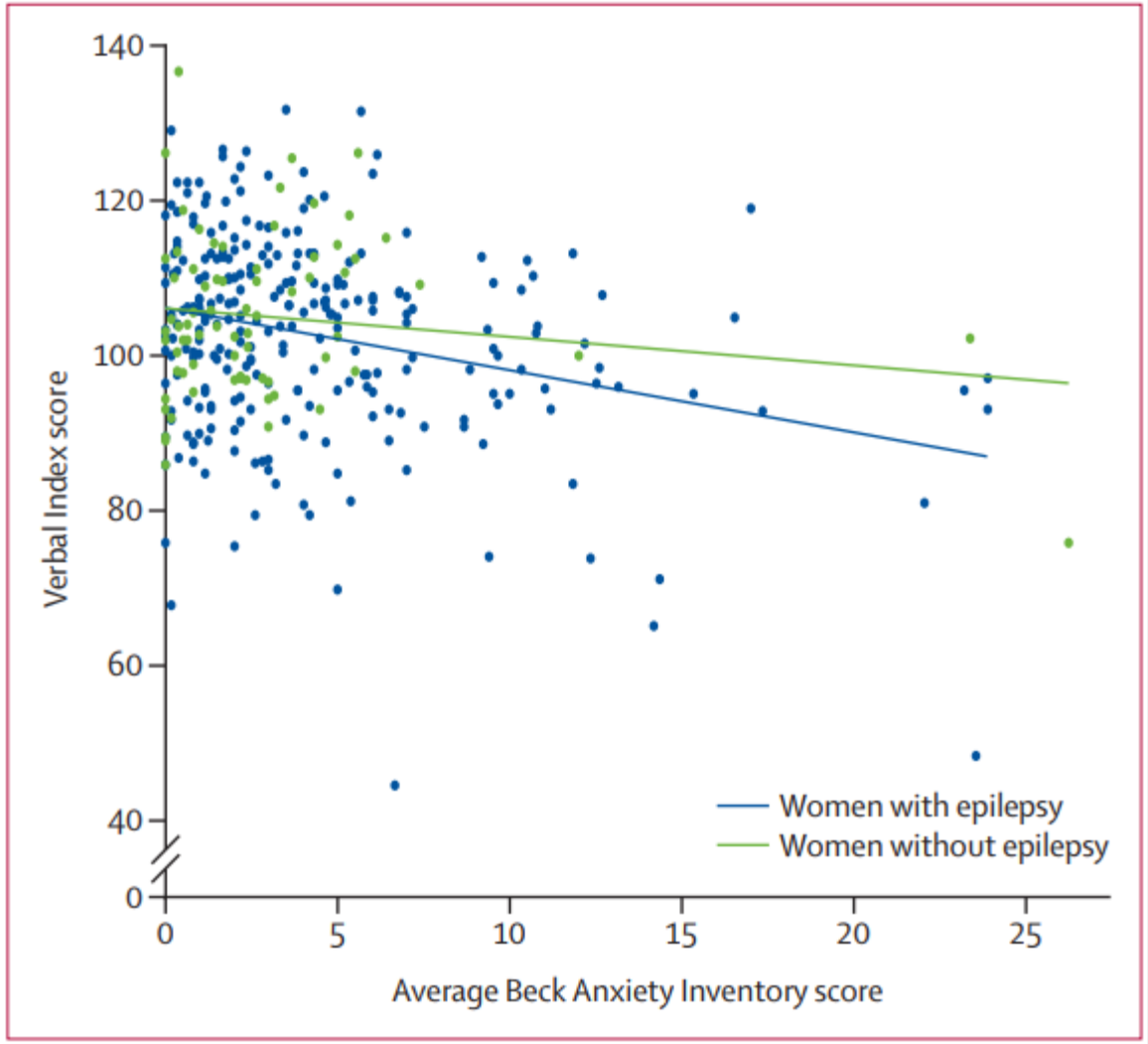


Figure 2: **Scatter plots of Verbal Index scores in children at age 3 years compared with maternal post-birth average Beck Anxiety Inventory scores for children of women with epilepsy and women without epilepsy**

OTHER IMPORTANT RECENT NEURODEVELOPMENTAL STUDIES

JAMA Neurology | Original Investigation

Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability

Marte-Helene Bjørk, MD, PhD; Helga Zoega, PhD; Maarit K. Leinonen, MD, PhD; Jacqueline M. Cohen, PhD; Julie Werenberg Dreier, PhD; Kari Furu, PhD; Nils Erik Gilhus, MD, PhD; Mika Gissler, PhD; Óskar Hálfdánarson, PhD; Jannicke Igland, PhD; Yuelian Sun, PhD; Torbjörn Tomson, MD, PhD; Silje Alvestad, MD, PhD; Jakob Christensen, MD, PhD

IMPORTANCE Women with epilepsy frequently need antiseizure medication (ASM) to prevent seizures in pregnancy. Risk of neurodevelopmental disorders after prenatal exposure to AMSs is uncertain.

OBJECTIVE To determine whether children exposed prenatally to ASMs in monotherapy and duotherapy have increased risk of neurodevelopmental disorders.

DESIGN, SETTING, AND PARTICIPANTS The Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) is a population-based cohort study using health register and social register data from Denmark, Finland, Iceland, Norway, and Sweden (1996-2017; analysis performed February 2022). From 4 702 774 alive-born children with available mother-child identities and maternal prescription data, this study included 4 494 926 participants. Children from a multiple pregnancy or with chromosomal disorders or uncertain pregnancy length were excluded (n = 207 848).

EXPOSURES Prenatal exposure to ASM determined from maternal prescription fills between last menstrual period and birth.

MAIN OUTCOMES AND MEASURES We estimated cumulative incidence at age 8 years in exposed and unexposed children. Cox regression adjusted for potential confounders yielded adjusted hazard ratios (aHRs) with 95% CIs for autism spectrum disorder (ASD), intellectual disability (ID), or any neurodevelopmental disorder (ASD and/or ID).

RESULTS A total of 4 494 926 children were included; 2 306 993 (51.3%) were male, and the median (IQR) age at end of follow-up was 8 (4.0-12.1) years. Among 21 634 unexposed children of mothers with epilepsy, 1.5% had a diagnosis of ASD and 0.8% (numerators were not available because of personal data regulations in Denmark) of ID by age 8 years. In same-aged children of mothers with epilepsy exposed to topiramate and valproate monotherapy, 4.3% and 2.7%, respectively, had ASD, and 3.1% and 2.4% had ID. The aHRs for ASD and ID after topiramate exposure were 2.8 (95% CI, 1.4-5.7) and 3.5 (95% CI, 1.4-8.6), respectively, and after valproate exposure were 2.4 (95% CI, 1.7-3.3) and 2.5 (95% CI, 1.7-3.7). The aHRs were elevated with higher ASM doses compared with children from the general population. The duotherapies levetiracetam with carbamazepine and lamotrigine with topiramate were associated with increased risks of neurodevelopmental disorders in children of women with epilepsy: levetiracetam with carbamazepine: 8-year cumulative incidence, 5.7%; aHR, 3.5; 95% CI, 1.5-8.2; lamotrigine with topiramate: 8-year cumulative incidence, 7.5%; aHR, 2.4; 95% CI, 1.1-4.9. No increased risk was associated with levetiracetam with lamotrigine (8-year cumulative incidence, 1.6%; aHR, 0.9; 95% CI, 0.3-2.5). No consistently increased risks were observed for neurodevelopmental disorders after prenatal exposure to monotherapy with lamotrigine, levetiracetam, carbamazepin, oxcarbazepine, gapapentin, pregabalin, clonazepam, or phenobarbital.

CONCLUSIONS AND RELEVANCE In this cohort study, prenatal exposure to topiramate, valproate, and several duotherapies were associated with increased risks of neurodevelopmental disorders.

Multimedia

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

The NEW ENGLAND JOURNAL of MEDICINE

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Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure

Sonia Hernández-Díaz, M.D., Dr.P.H., Loreen Straub, M.D., Brian T. Bateman, M.D., Yanmin Zhu, Ph.D., Helen Mogun, M.S., Katherine L. Wisner, M.D., Kathryn J. Gray, M.D., Ph.D., Barry Lester, Ph.D., Christopher J. McDougle, M.D., Elyse DiCesare, B.A., Page B. Pennell, M.D., and Krista F. Huybrechts, Ph.D.

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VOL. 390 NO. 12

opiramate,
posure

eman, M.D., Yanmin Zhu, Ph.D.,
., Ph.D., Barry Lester, Ph.D.,
D., and Krista F. Huybrechts, Ph.D.

BACKGROUND

Maternal use of valproate during pregnancy has been associated with an increased risk of neurodevelopmental disorders in children. Although most studies of other antiseizure medications have not shown increased risks of these disorders, there are limited and conflicting data regarding the risk of autism spectrum disorder associated with maternal topiramate use.

METHODS

We identified a population-based cohort of pregnant women and their children within two health care utilization databases in the United States, with data from 2000 through 2020. Exposure to specific antiseizure medications was defined on the basis of prescription fills from gestational week 19 until delivery. Children who had been exposed to topiramate during the second half of pregnancy were compared with those unexposed to any antiseizure medication during pregnancy with respect to the risk of autism spectrum disorder. Valproate was used as a positive control, and lamotrigine was used as a negative control.

RESULTS

The estimated cumulative incidence of autism spectrum disorder at 8 years of age was 1.9% for the full population of children who had not been exposed to antiseizure medication (4,199,796 children). With restriction to children born to mothers with epilepsy, the incidence was 4.2% with no exposure to antiseizure medication (8815 children), 6.2% with exposure to topiramate (1030 children), 10.5% with exposure to valproate (800 children), and 4.1% with exposure to lamotrigine (4205 children). Propensity score–adjusted hazard ratios in a comparison with no exposure to antiseizure medication were 0.96 (95% confidence interval [CI], 0.56 to 1.65) for exposure to topiramate, 2.67 (95% CI, 1.69 to 4.20) for exposure to valproate, and 1.00 (95% CI, 0.69 to 1.46) for exposure to lamotrigine.

CONCLUSIONS

The incidence of autism spectrum disorder was higher among children prenatally exposed to the studied antiseizure medications than in the general population. However, after adjustment for indication and other confounders, the association was substantially attenuated for topiramate and lamotrigine, whereas an increased risk remained for valproate. (Funded by the National Institute of Mental Health.)

AAN – ASMS: NEURODEVELOPMENTAL OUTCOMES

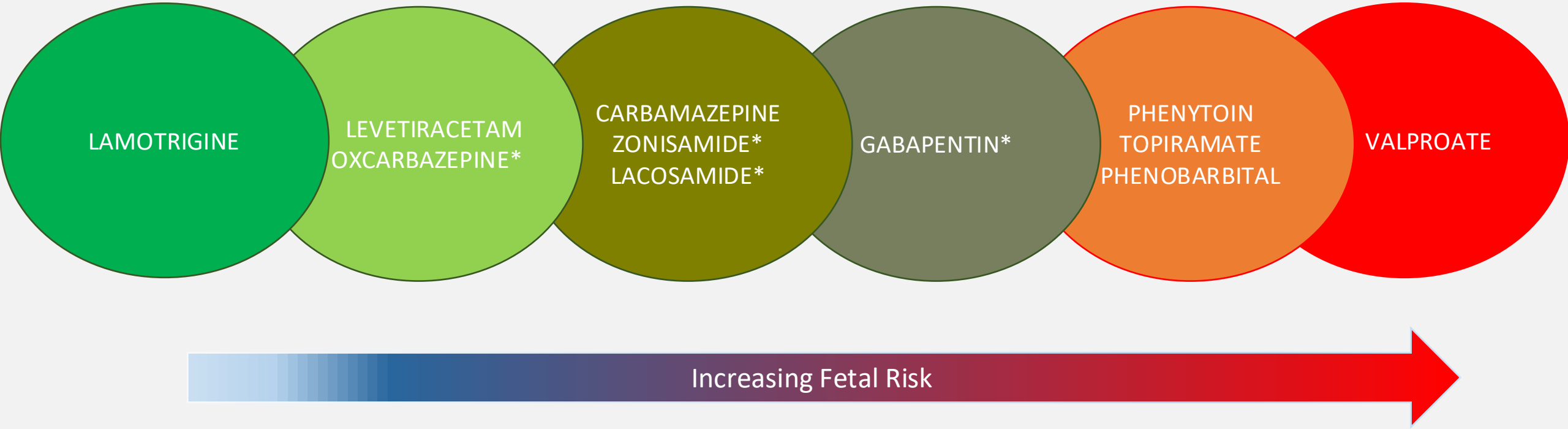
5A. To reduce the risk of poor neurodevelopmental outcomes, including ASD and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in PWECP, if clinically feasible (Level A).

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).

MY CURRENT PREFERENTIAL SELECTION OF ASMS FOR WWE OF CHILDBEARING AGE

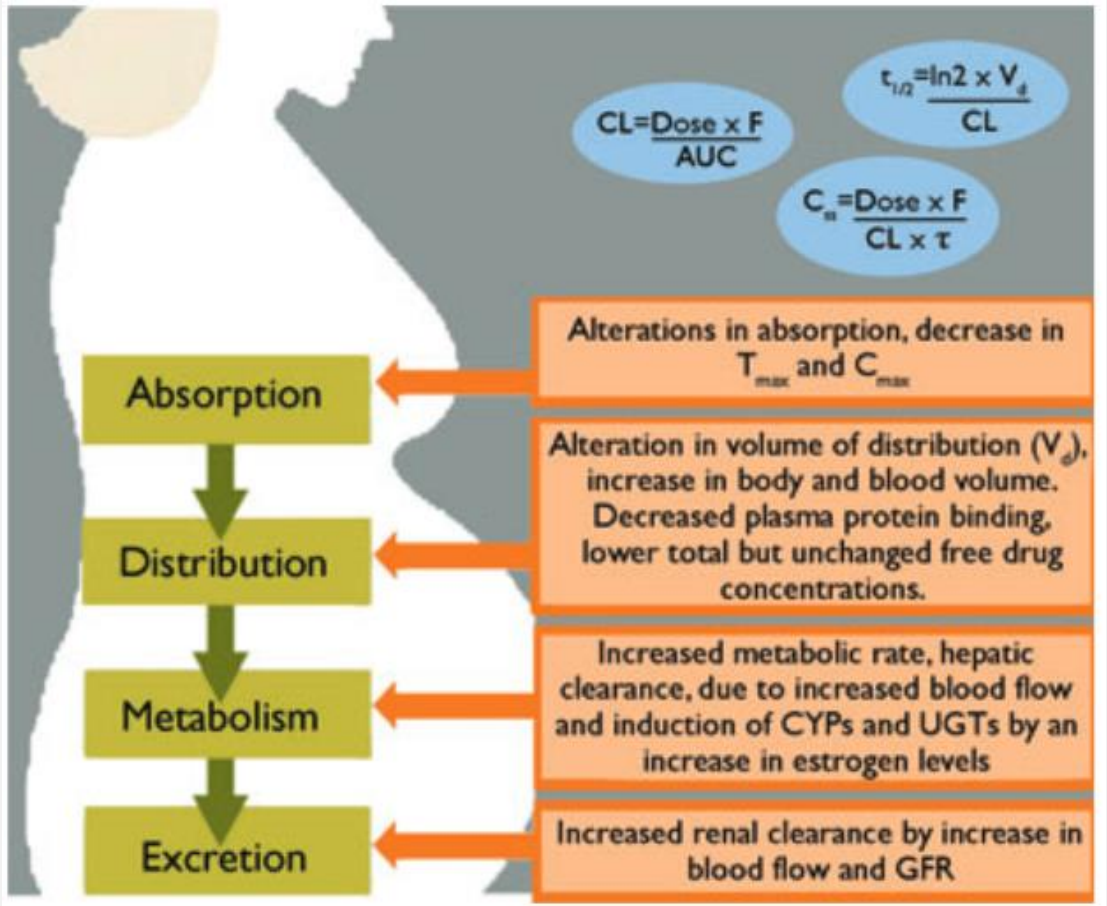


Phase 2 | Navigating Pregnancy

Managing physiological shifts and protecting the fetus.

PREGNANCY - POSTPARTUM

- Pharmacokinetic considerations



Tomson et al. *Epilepsia* 2013 ILAE

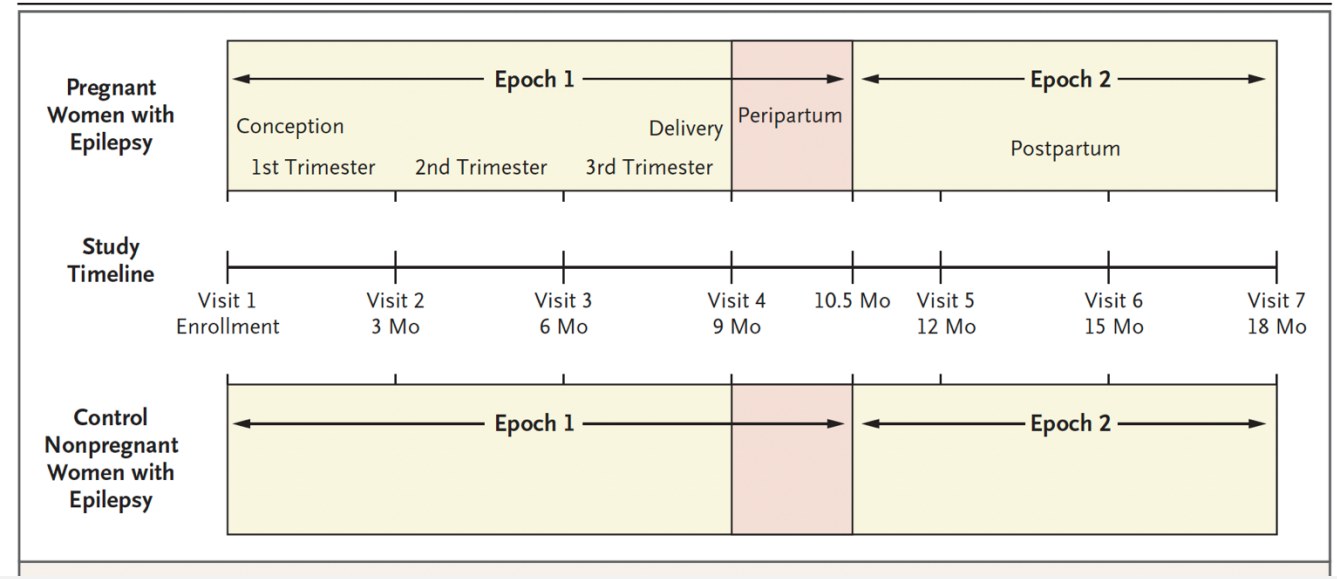
DIRECTION OF PHARMACOKINETIC CHANGES FOR ANTISEIZURE MEDICATIONS DURING PREGNANCY

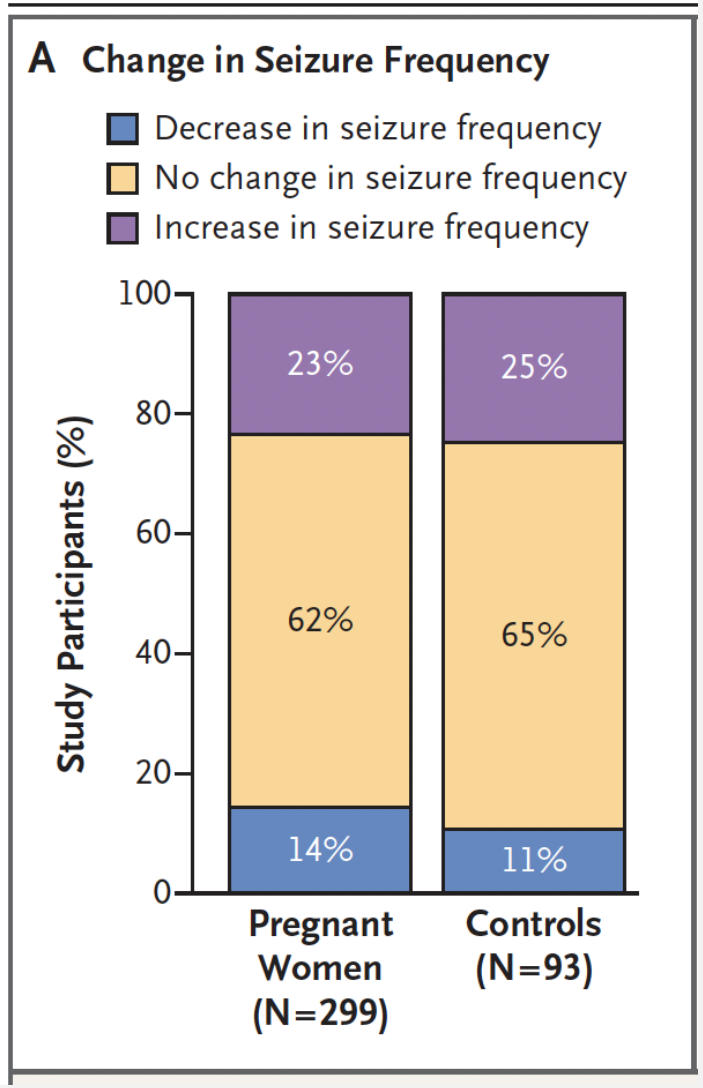
ASM	Concentration	Clearance	Timing of Peak Clearance
Carbamazepine	No change	No change	N/A
Carbamazepine -Epoxide	No change	No change	N/A
Lacosamide	Decrease	Increase	N/A
Levetiracetam	Decrease	Increase	1st trimester
Lamotrigine	Decrease	Increase	3rd trimester
Phenytoin	Decrease	Increase	3rd trimester
Phenobarbital	Decrease	Increase	N/A
Oxcarbazepine	Decrease	Increase	2nd/3rd trimester
Topiramate	Decrease	Increase	2nd/3rd trimester
Valproate	Decrease	No change	N/A
Zonisamide	Decrease	Increase	3rd trimester

Adapted from Lemley RL and Voinescu PE. Queenan's Management of High-Risk Pregnancy: An Evidence-Based Approach, 7th edition

CHANGE IN FREQUENCY OF SEIZURES THAT IMPAIR AWARENESS IN PREGNANT WOMEN VS. CONTROL WOMEN WITH EPILEPSY

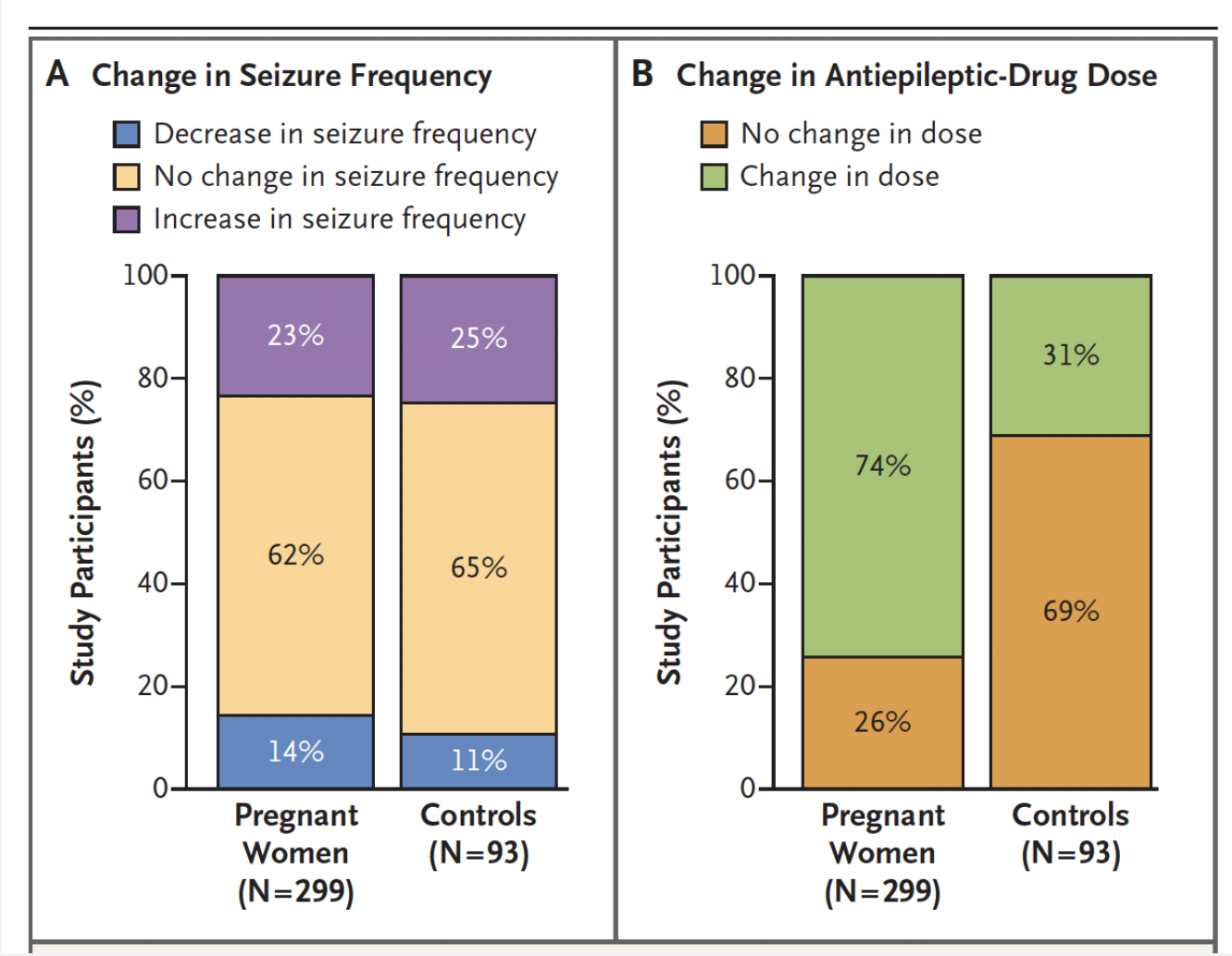
MONEAD Study Design for Seizure Outcomes





Pennell PB et al. Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy. *N Engl J Med.* 2020 Dec 24;383(26):2547-2556.

CHANGE IN FREQUENCY OF SEIZURES THAT IMPAIR AWARENESS IN PREGNANT WOMEN VS. CONTROL WOMEN WITH EPILEPSY



Pennell PB, French JA, May RC, et al. N Engl J Med. 2020 Dec 24;383(26):2547-2556.

Pharmacokinetic Realities and OB Partnership

- **The Clearance Challenge:** The magnitude and time course of pregnancy-related **pharmacokinetic changes** vary significantly by ASM.
- **The Danger Zone:** A **decrease** of more than 35% from the preconception baseline is associated with a significant **increase** in seizure frequency.
- **Strategic Mitigation:** Extended-release formulations and twice (or more) per day dosing are preferred to minimize fluctuations.

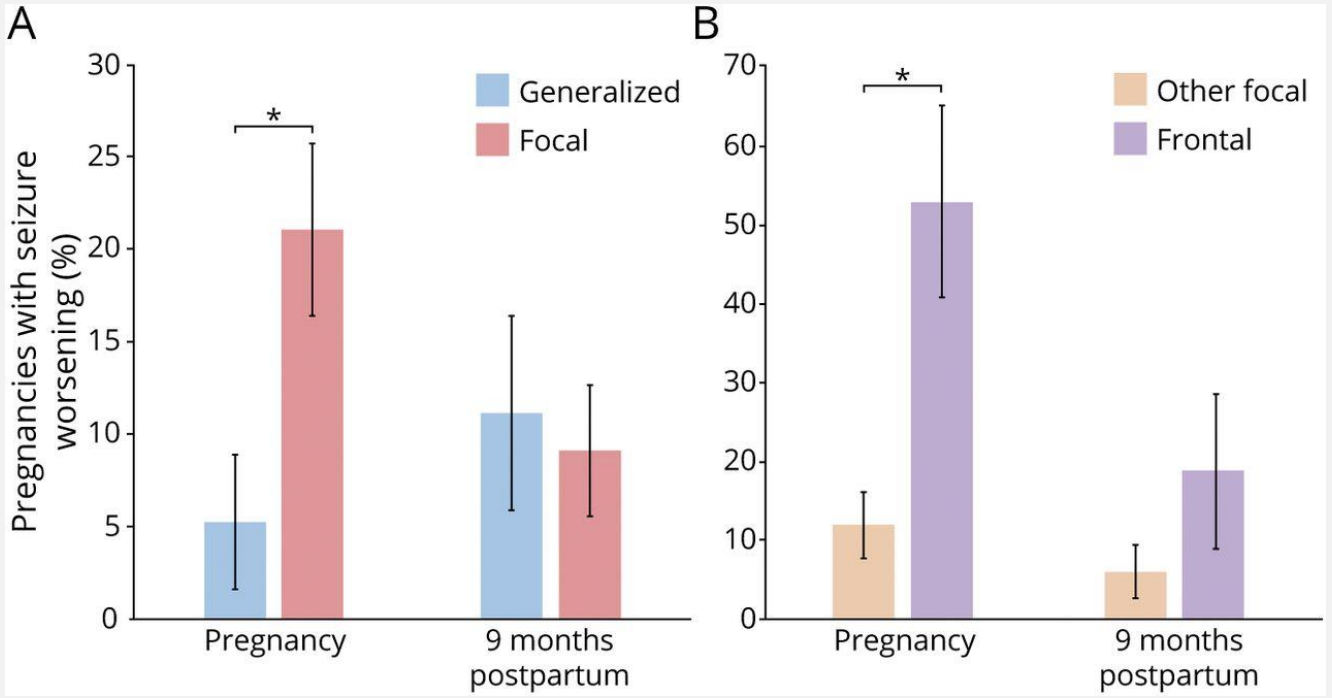
The Critical Partnership: The Obstetrician is a vital partner. Coordinate with them to facilitate monthly blood draws to accurately track ASM serum concentrations against the established preconception baseline.

RISK FACTORS FOR WORSENING OF SEIZURES WITH IMPAIRED AWARENESS DURING PREGNANCY AND PERIPARTUM

- Evaluated in 23% of PWWE with increased seizures with impaired awareness (incl. GTCS)
- No differences in seizure types, ASM regimen or type
- Sole risk factor was seizure freedom in 9 months prior to conception:
  - Adjusted OR = 0.26, 95% CI [0.14, 0.46], p<0.001).

Pennell PB, French JA, May RC, et al.. Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy. N Engl J Med. 2020 Dec 24;383(26):2547-2556.

Variations in Seizure Frequency during Pregnancy and Postpartum by Epilepsy Type

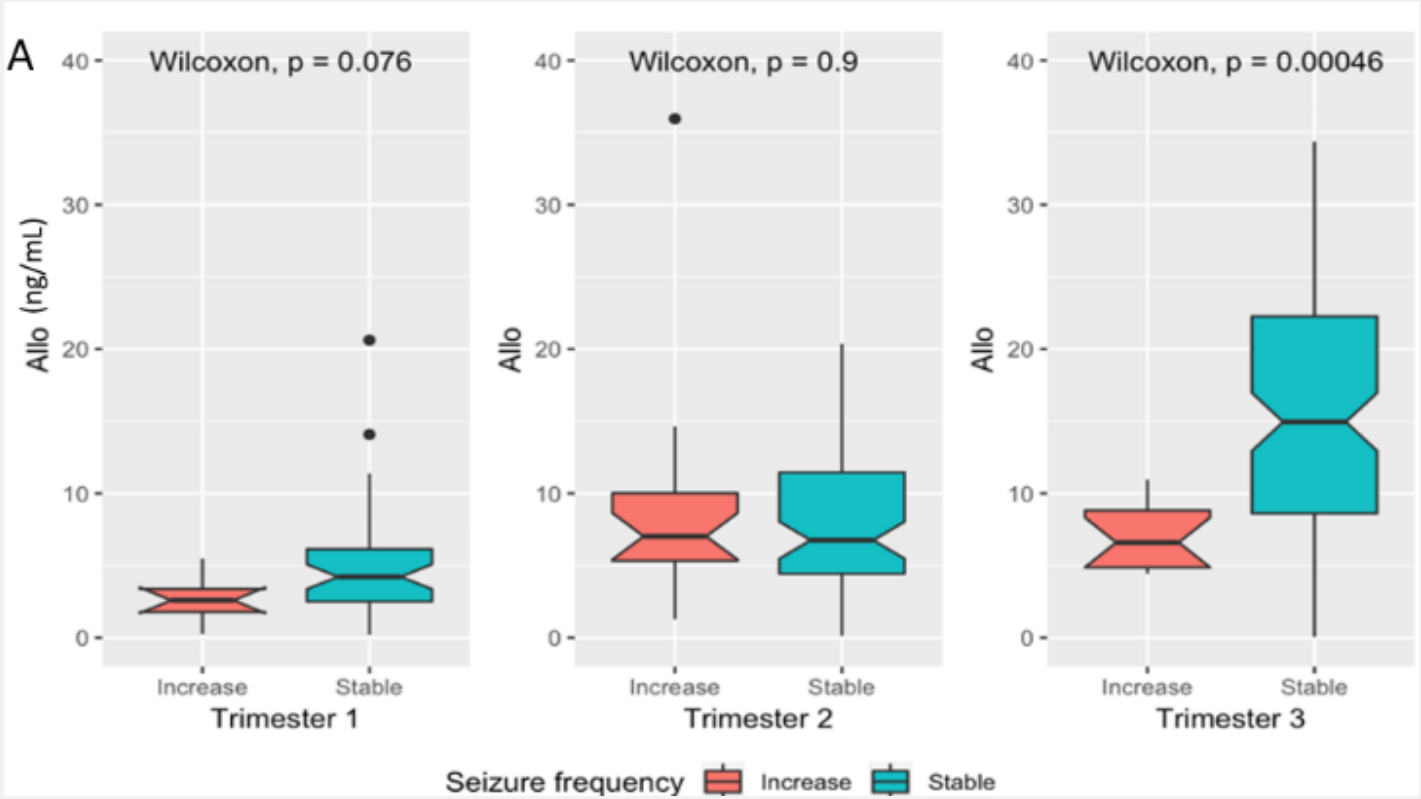


- 99 patients contributing 114 pregnancies
- **Increased** seizure frequency during pregnancies of women with :
  - ❖ **focal** vs generalized epilepsy: 21.1% vs 5.3%, **OR 4.70**; 95% CI (1.00, 22.00); p = 0.0497
  - ❖ **frontal** lobe vs other focal epilepsy: **OR 8.00**; 95 % CI (2.19, 29.21); p = 0.0017
  - ❖ **polytherapy** vs monotherapy: **OR = 8.36**, 95% CI = (2.07, 33.84), p = 0.0029 - regardless of the medication or epilepsy type
  - ❖ **Lack** vs presence of **preconception seizure freedom**: **OR = 6.418**; p = 0.0076

Voinescu PE et al. *Neurology* Feb 2022, 98 (8) e802-e807

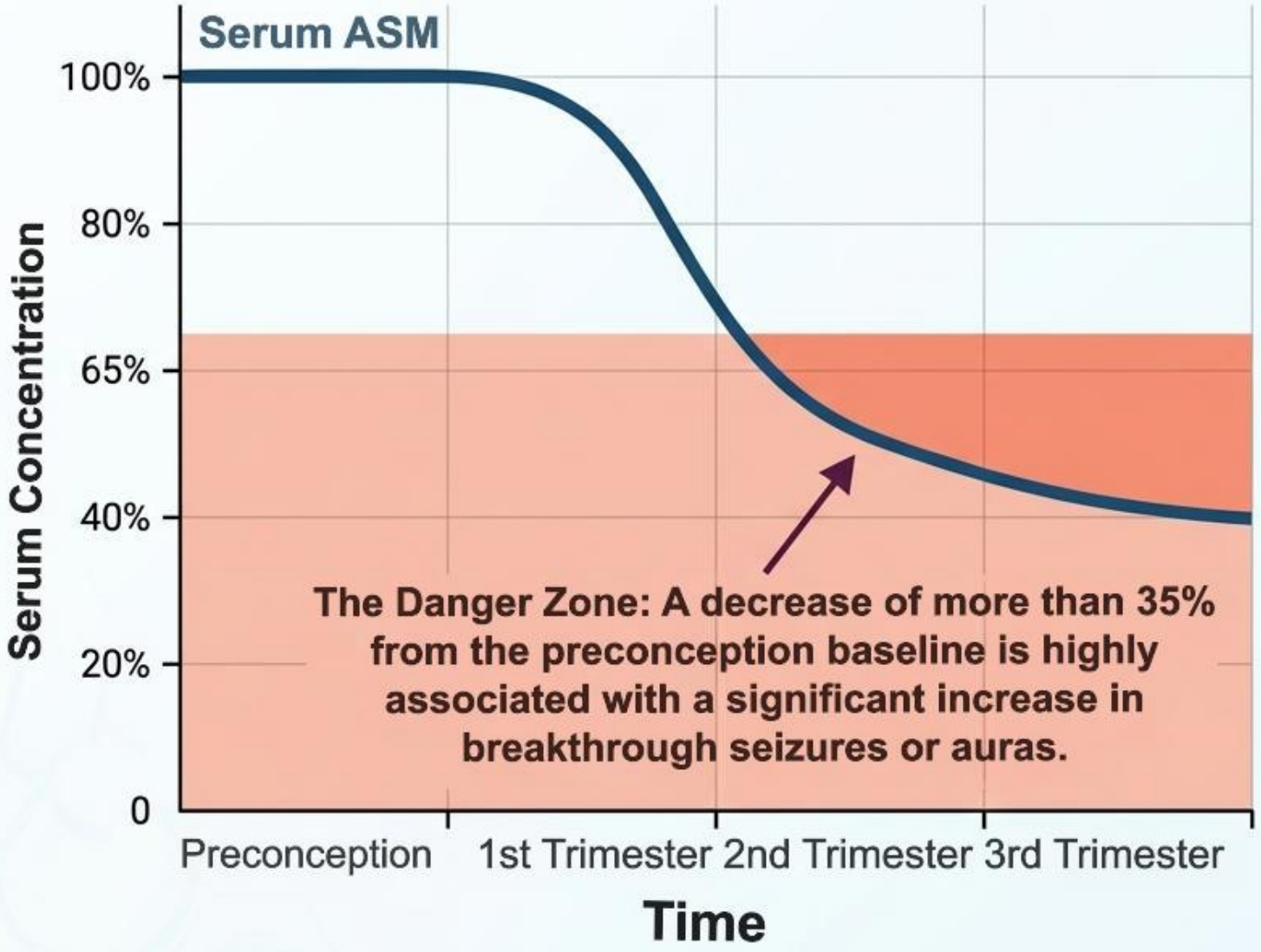
PREGNANT WOMEN WITH INCREASED SEIZURE FREQUENCY HAVE LOWER ALLOPREGNANOLONE CONCENTRATIONS

- 83 pregnancies included
  - 28 had increased seizure frequency during at least one trimester (15, 18 and 10, respectively) compared to preconception seizure frequency
- Allopregnanolone concentrations were lower in the 3rd trimester ($p < 0.001$), with a similar trend in the 1st ($p = 0.08$)
- ALLO concentrations lower than of 11.22 ng/mL during 3rd trimester are indicative of a higher risk of seizures



Voinescu PE et al. *Epilepsy Res.* 2021 Sep 25;177:106778.

The Clearance Challenge: Why Breakthrough Seizures Occur

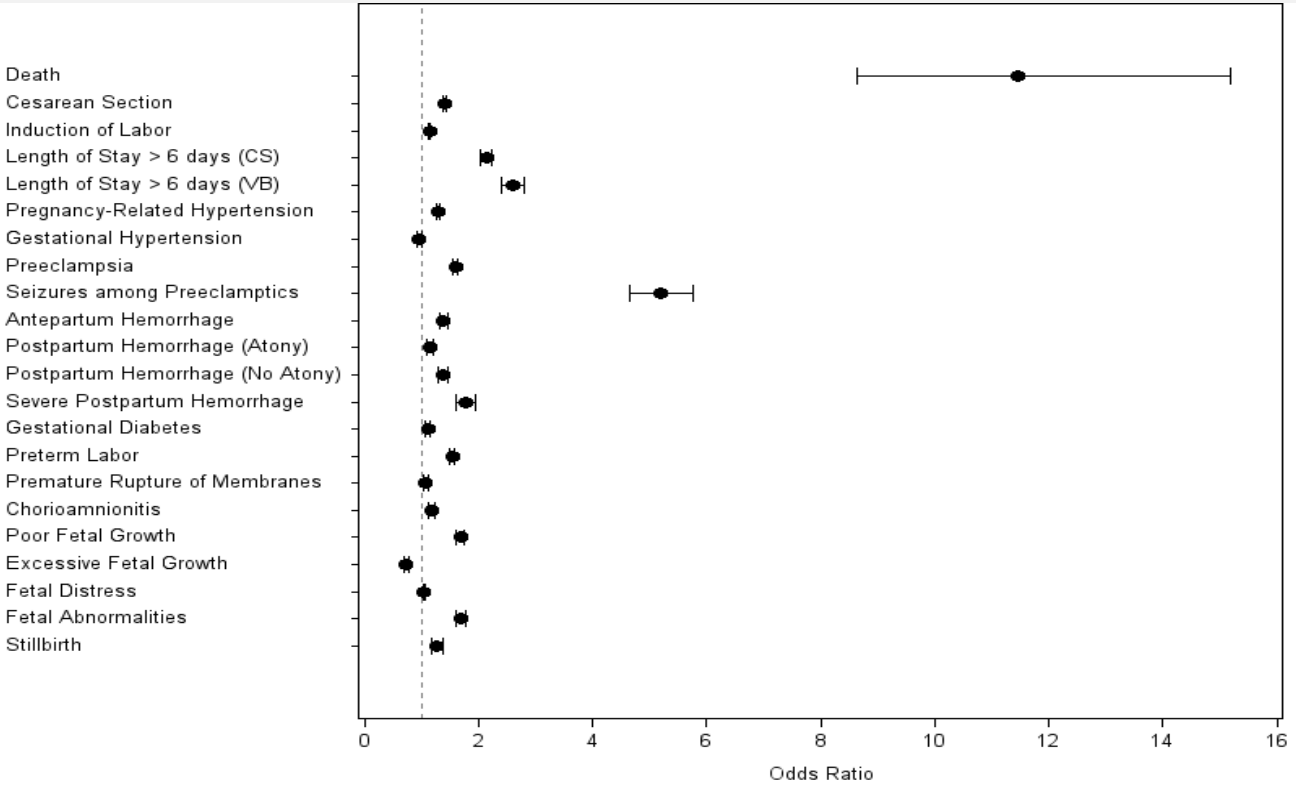


Pharmacokinetic Shifts: Pregnancy hypermetabolism causes massive clearance increases for Lamotrigine (peaks 3rd tri), Levetiracetam (peaks 1st tri), and Oxcarbazepine; concentrations plummet.

The Biological Co-Conspirator: Frontal lobe seizure onset and Allopregnanolone (inhibitory neurosteroid) concentrations lower than 11.22 ng/ml in the 3rd trimester are independently indicative of a higher seizure risk.

Maternal Outcomes

Nationwide Inpatient Sample - Retrospective Study



MacDonald SC et al. *JAMA Neurology.* 2015

MONEAD Study

Key Points

- Unlabored cesarean rates higher among women with epilepsy.
- Provider preference may influence delivery mode among women with epilepsy.
- Type and amount of antiepileptic drug was not associated with mode of delivery.

McElrath TF et al. *Am J Perinatol.* 2022

- ScanAED: WWE had a 23% higher risk of life-threatening complications and approximately 4-fold higher risk of death and in pregnancy and the postpartum period

  Razaz N et al. *JAMA Neurology.* 2024

- UK and Ireland: 2nd most common indirect cause of maternal death; SUDEP may be the leading cause (10 times higher risk of sudden death during pregnancy)

  Knight M et al. MBRRACE-UK
  Edey S et al. *Epilepsia* 2014

- Meta-analysis: WWE have a 5 times higher odds of maternal death

  Mazzone PP et al. *JAMA Neurol.* 2023

Phase 3 | The Postpartum Transition

Navigating recovery, breastfeeding, and dose de-escalation.

Labor Protocols & Breastmilk Penetration

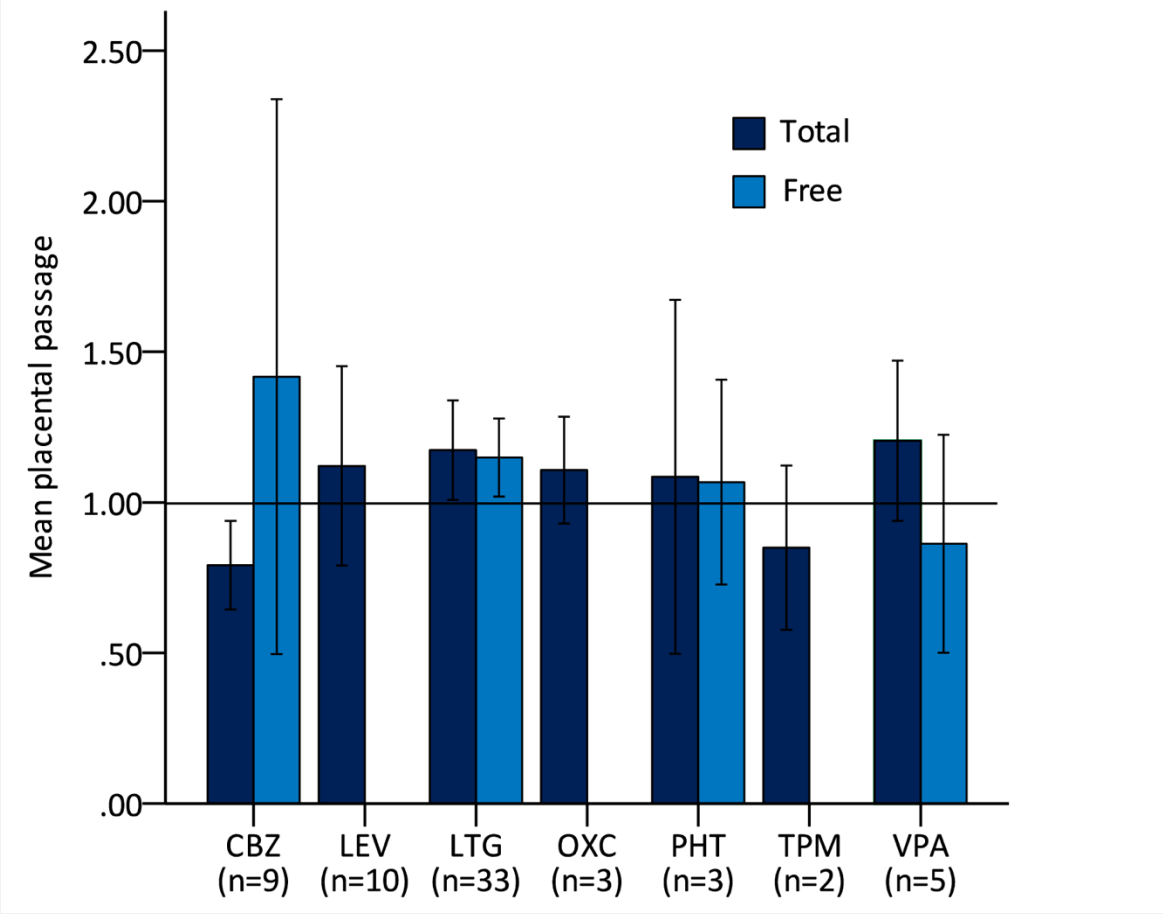
Labor & Delivery:

- Epidural anesthesia is recommended to reduce physical stressors.
- Have IV AEDs/Lorazepam immediately available for acute control.

Breastfeeding (MONEAD Data):

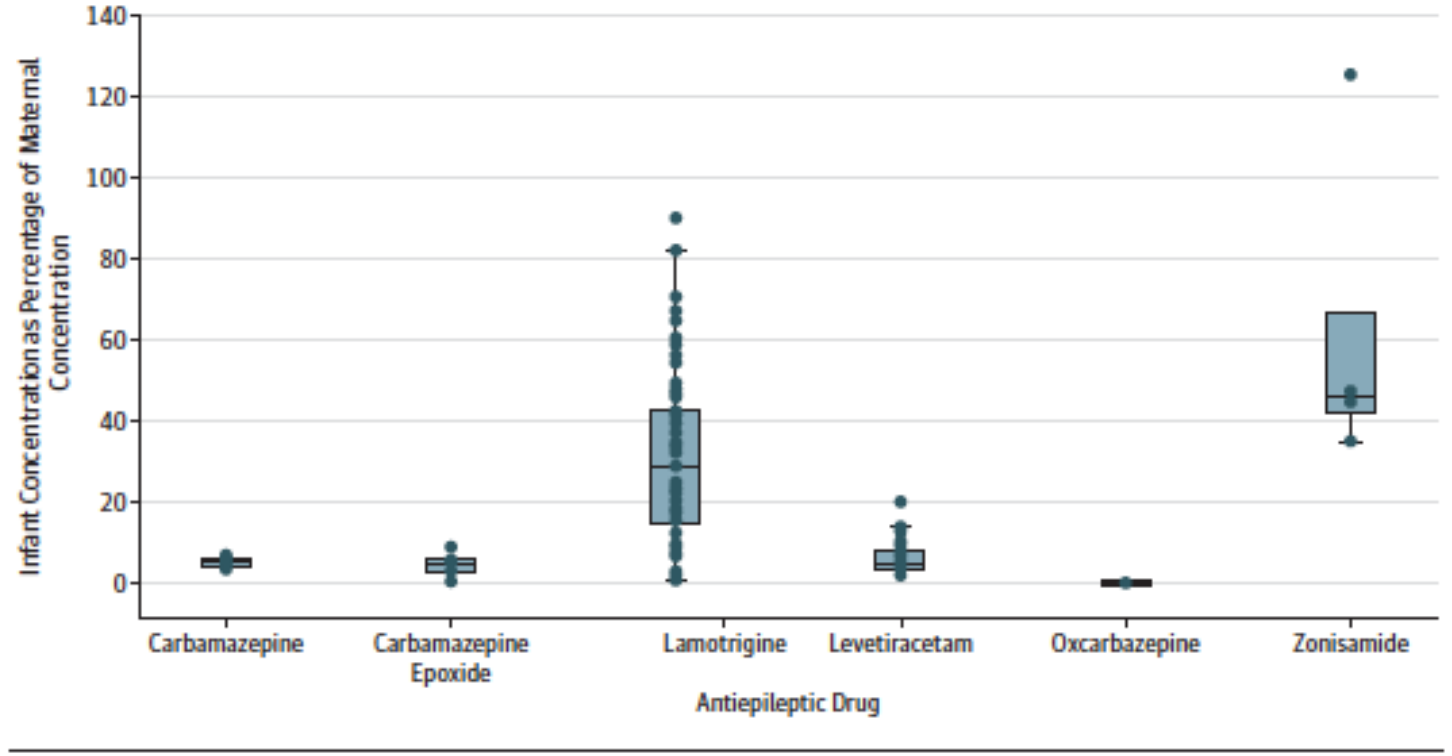
- Exposure via breastmilk is significantly lower than in utero exposure.
  - **High Penetration ASMs:** LEV, LTG, TPM, PRM, GBP.
  - **Low Penetration ASMs:** VPA, PB, PHT, CBZ.

MEAN PLACENTAL PASSAGE OF ASMS
(UMBILICAL CORD/MATERNAL BLOOD VENOUS SAMPLES)



Bank, Stowe, Newport, Pennell, *Epilepsia* 2017.

PERCENTAGE OF INFANT TO MOTHER PLASMA CONCENTRATIONS



Box plots represent 25%ile and 75%ile.

40 /54 infants exposed to LEV were < LLoQ.

Birnbaum A, MONEAD, *JAMA Neuro*, Dec 30, 2019.

NEURODEVELOPMENTAL EFFECTS OF ASMS THROUGH BREASTMILK

- NEAD study and breastfeeding: Age 6 year-old cognitive outcomes
  - 44% of children were breastfed
  - Mean adjusted IQ scores:
    - 4 IQ points higher in the BF group
    - Higher verbal abilities

NEAD, neurodevelopmental effects of antiepileptic drugs
Meador, et al. *JAMA Pediatr.* 2014;168(8):729–736.

Maternal Vulnerability in the Fourth Trimester

Seizure provokers and the necessity of tapers.

The Primary Provoker

Severe sleep deprivation drastically increases the peripartum risk for breakthrough seizures. Protecting maternal sleep is a clinical priority.

Pharmacokinetic Reversal

Clearance rates drop rapidly postpartum. Highly individualized ASM tapering is required to prevent maternal toxicity.

Psychiatric Load

Women with epilepsy face a compounded risk of postpartum depression. Psychiatric needs and screening cannot be neglected.

Personalized Care for Women at Different Biological Stages

Contraception
Catamenial Epilepsy
Fertility
IVF/ART
Pregnancy/Postpartum
Perimenopause
Menopause

AGENDA

- The intersection of sex hormones and neurosteroids with epilepsy
  - The effect of epilepsy on the timing of cessation of reproductive cycling
  - The effect of perimenopause and menopause on seizure frequency
    - Fluctuations in the endogenous neurosteroid concentrations
    - Considerations regarding menopausal hormonal therapy
  - Pharmacokinetic changes during transition to menopause
- The effect of epilepsy on known menopausal comorbidities

THE EFFECT OF EPILEPSY ON MENOPAUSE

Premature ovarian failure with early menopause in WWE is thought to be triggered by hypothalamic–pituitary–gonadal axis dysfunction, to which seizures likely contribute

- WWE have more than a three-fold increase in the risk of premature ovarian failure[1]:
  - 14% of women with epilepsy (n=50) versus 4% of healthy control had premature ovarian failure – mean age 39.6
  - the only clinical factor correlated with a higher risk was catamenial seizure exacerbation ($p<0.02$)
- Seizure frequency or lifetime number

of seizures is associated with the timing

of cessation of reproductive cycling ($p=0.014$)[2]

Table 3 *Menopausal age based on number of lifetime seizures*

No. lifetime seizures	Mean ± SD age at last menses, y	95% CI
1–49, n = 17	49.8 ± 4.0	47.7–51.9
50–245, n = 22	47.6 ± 4.6	45.6–49.6
246–882, n = 23	46.6 ± 3.4	45.1–48.0

$p = 0.048$.

1. Klein P, et al.. *Epilepsia* 2001;42(12):1584–1589 2. Harden CL, et al. *Neurology* 2003;61(04):451–455

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  - the only clinical factor correlated with a higher risk was catamenial seizure exacerbation ($p<0.02$)
- Seizure frequency or lifetime number of seizures is associated with the timing of cessation of reproductive cycling[2]
  - Survey of 68 women age ≥45 from 4 urban epilepsy centers 2001-2002
  - negative correlation leading to an average difference of ~3 years between patients with low vs high seizure frequency

Do all type of seizures contribute? Do ASMs play any role?

1. Klein P, et al.. *Epilepsia* 2001;42(12):1584–1589 2. Harden CL, et al. *Neurology* 2003;61(04):451–455

THE EFFECT OF MENOPAUSE AND PERIMENOPAUSE ON THE COURSE OF EPILEPSY

- Questionnaire study of women with epilepsy currently in menopause and perimenopause (n=42)[1]
  - History of catamenial seizure pattern associated with a decrease in seizures at menopause ($p = 0.013$), but an increase in seizures at perimenopause ($p = 0.02$)

Note: Around half of people with epilepsy have a catamenial pattern, while about two thirds of people with epilepsy have seizure worsening at perimenopause

What is the true overalp between catamenial epilepsy and perimenopausal seizure worsening? Are some epilepsy types more likely to be associated with worsening seizure frequency?

1. Harden CL et al. *Epilepsia*. 1999;40(10):1402–7; 2.

EXOGENOUS SEX HORMONES – MENOPAUSAL HORMONE THERAPY (MHT)

THE EFFECT OF MENOPAUSE AND PERIMENOPAUSE ON THE COURSE OF EPILEPSY

- Randomized, double-blind, placebo-controlled trial of the effect of HRT on seizure frequency in postmenopausal women with epilepsy[1]
  - CEE/MPA is associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy (n=21)
  - CEE/MPA may decrease lamotrigine levels

1. Harden CL et al. *Epilepsia*. 2006;47(9):1447–51

SHOULD WE DENY MENOPAUSAL HORMONE THERAPY TO PEOPLE WITH EPILEPSY?

The 2022 North American Menopause Society position statement, acknowledged that the risks of hormone therapy differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used

- for women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is favorable for treatment of bothersome symptoms and prevention of bone loss.

SHOULD WE DENY MENOPAUSAL HORMONE THERAPY TO PEOPLE WITH EPILEPSY?

- There are currently many MHT options that were not tested for their effect on seizure control at menopause and a recent systematic review did not find a clear increase in seizure frequency with its use in humans or animals[1]
- Hormonal supplementation to suppress endogenous hormonal fluctuations is used as an additional strategy for catamenial epilepsy; could some MHT serve the same role at menopause?
- ASM with hepatic enzyme-inducing properties increase neurosteroid metabolism and reduce their circulating concentrations, which may be relevant when considering MHT options.

Are there some MHT safer for people with epilepsy?
Could some perhaps help with seizure worsening at perimenopause?

1. Carvalho V et al. *Eur J Neurol*. 2023;30(9):2884–98.

DECREASED CLEARANCE IN THE ELDERLY

- No rigorous studies, but estimated to be 20-40%
- Physiological decline with age applicable to all genders
  - Decreased in renal excretion rate
  - Decreased hepatic metabolism
  - Decrease in serum albumin
- Sex steroid hormones influence the clearance mechanisms for most ASMs and a large body of evidence in this direction comes from studies during pregnancy; there are likely clearance changes at perimenopause and menopause, but no studies to demonstrate them

Should we follow perimenopausal patient with therapeutic drug monitoring? Should we consider adjusting the ASM doses with MHT?

LAMOTRIGINE AND SEX STEROID HORMONES

- Lamotrigine (LTG) is is metabolized predominantly via glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) 1A4 and 2B7
- UGT1A4 is inducible by estrogens and LTG serum concentrations often fall by 50–60% when combined with hormonal contraceptives that contain ethinyl estradiol and during pregnancy
- Reversely, women stabilized on lamotrigine treatment who enter menopause might need to reduce their dosage to avoid dose-related adverse effects[1].
  - Samples from 507 women and 302 men taking LTG; increasing clearance as a function of bioavailability (Cl/F) over age 18, a maximum Cl/F at 36 years LTG and a gradual decrease of Cl/F towards older age[1]
  - D/C ratios were available for 752 men and 1115 women on LTG; LTG D/C ratios seemed to decline in women 51–55 years of age, and were in this age group significantly lower among women than among men ($P < 0.05$)[2]

Should lamotrigine concentrations be monitored in the perimenopausal years?

1. Wegner I et al. *Epilepsy & Behavior* 29 (2013) 217–221; 2. Tomson T et al. *Epilepsy & Behavior* 19 (2010) 86-88

HORMONE REPLACEMENT THERAPY WITH ESTROGENS MAY REDUCE LAMOTRIGINE SERUM CONCENTRATIONS

79 HRT users (dose range 1–4 mg/day)

200 EE users (dose range 20–40 lg/day)

158 and 400 matching controls, respectively

Both EE users and HRT users had significantly lower mean LTG CDRs than their respective matched controls.

Reimers A. *Epilepsia*, 58(1):e6–e9, 2017

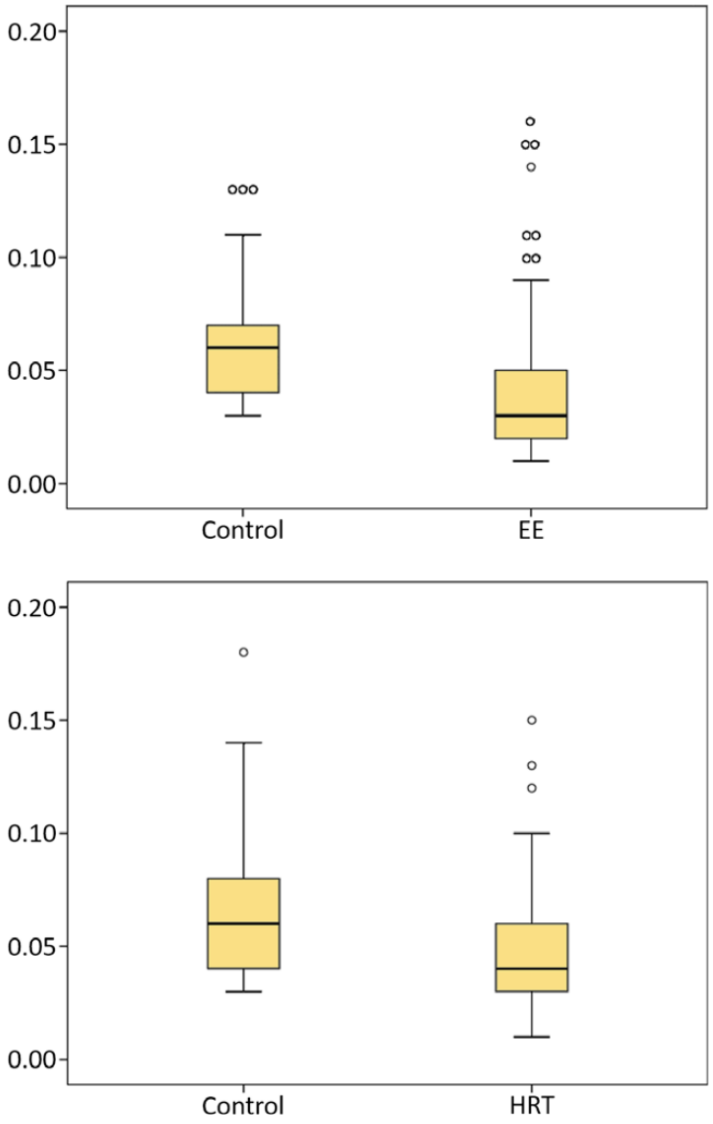


Figure 1.
Box plots showing the median, range, upper, and lower quartiles of the lamotrigine concentration-to-dose ratios. Circles denote outliers. EE, ethinyl estradiol; HRT, hormone replacement therapy with estrogens.

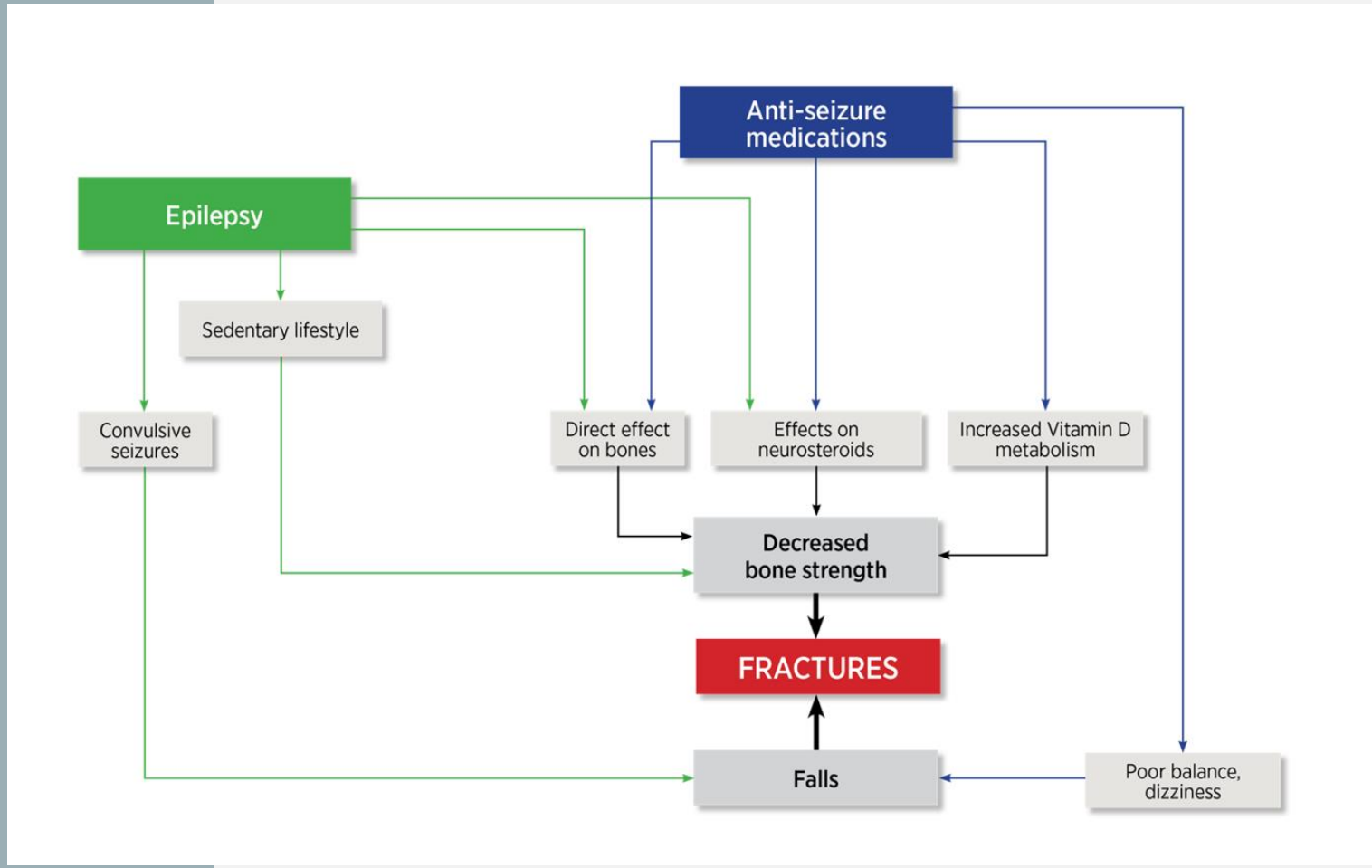
BONE HEALTH

The lack of ovarian-derived estrogen due to menopause leads to an accelerated loss of bone mass density

There is a 2-6 times increased risk of fracture in epilepsy, which increases by 4-6 % every year of anti-seizure medication (ASM) use

- ASM can also affect bone acquisition and turnover
- ASM can also reduce vitamin D levels

Sedentary lifestyle is also more common in epilepsy, as well as a higher frequency of smoking, alcohol, less likely to exercise and less sunlight exposure

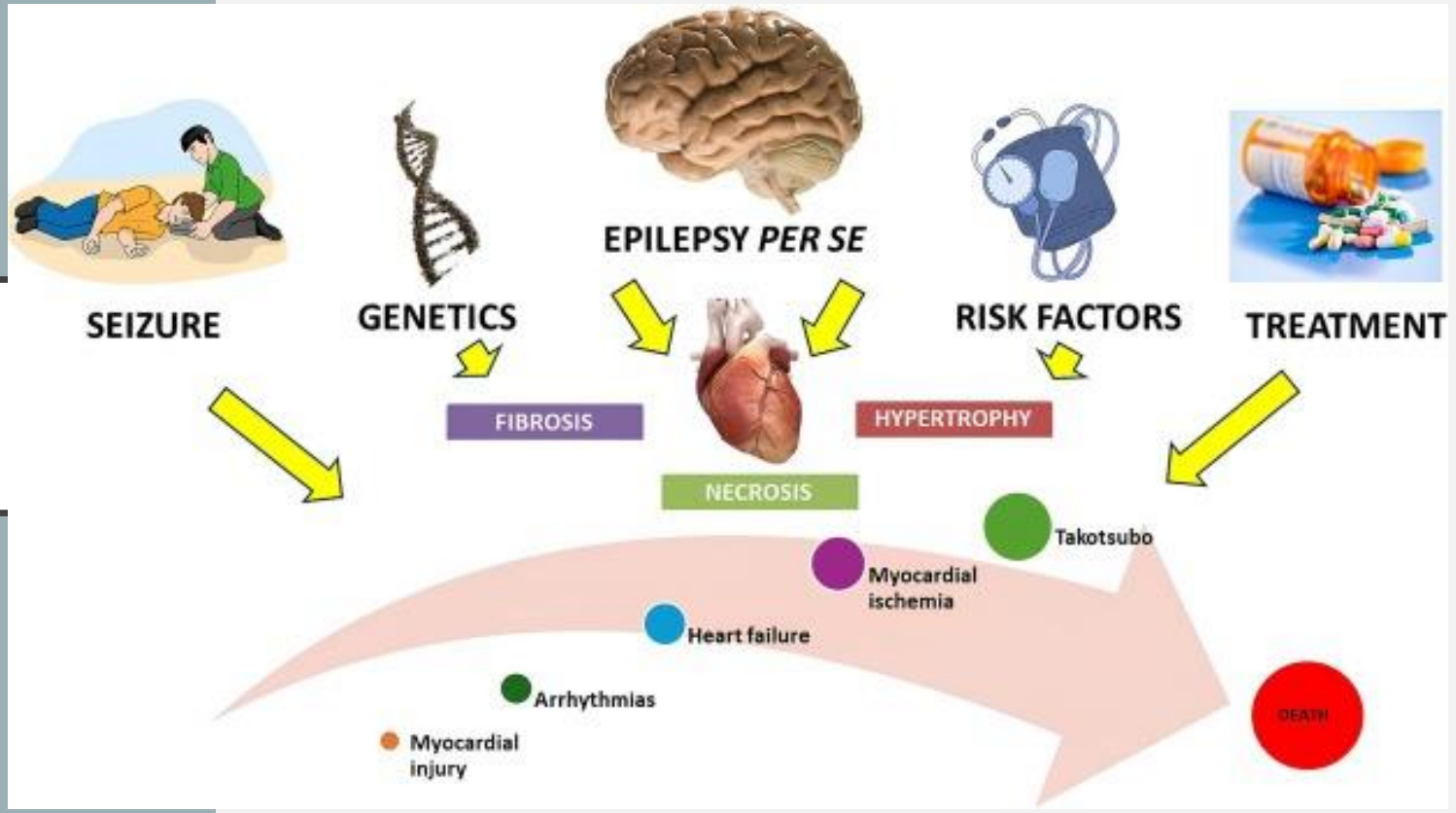


Curtesy Lata Vadlamudi, University of Brisbane

Diemar SS et al. *Epilepsy Behav.* 2019 Nov;100(Pt A):106511; Josephson CB *JAMA Neurol.* 2023;80(8):843–850.

METABOLIC AND CARDIOVASCULAR HEALTH

myocardial infarction, heart failure, and sudden death

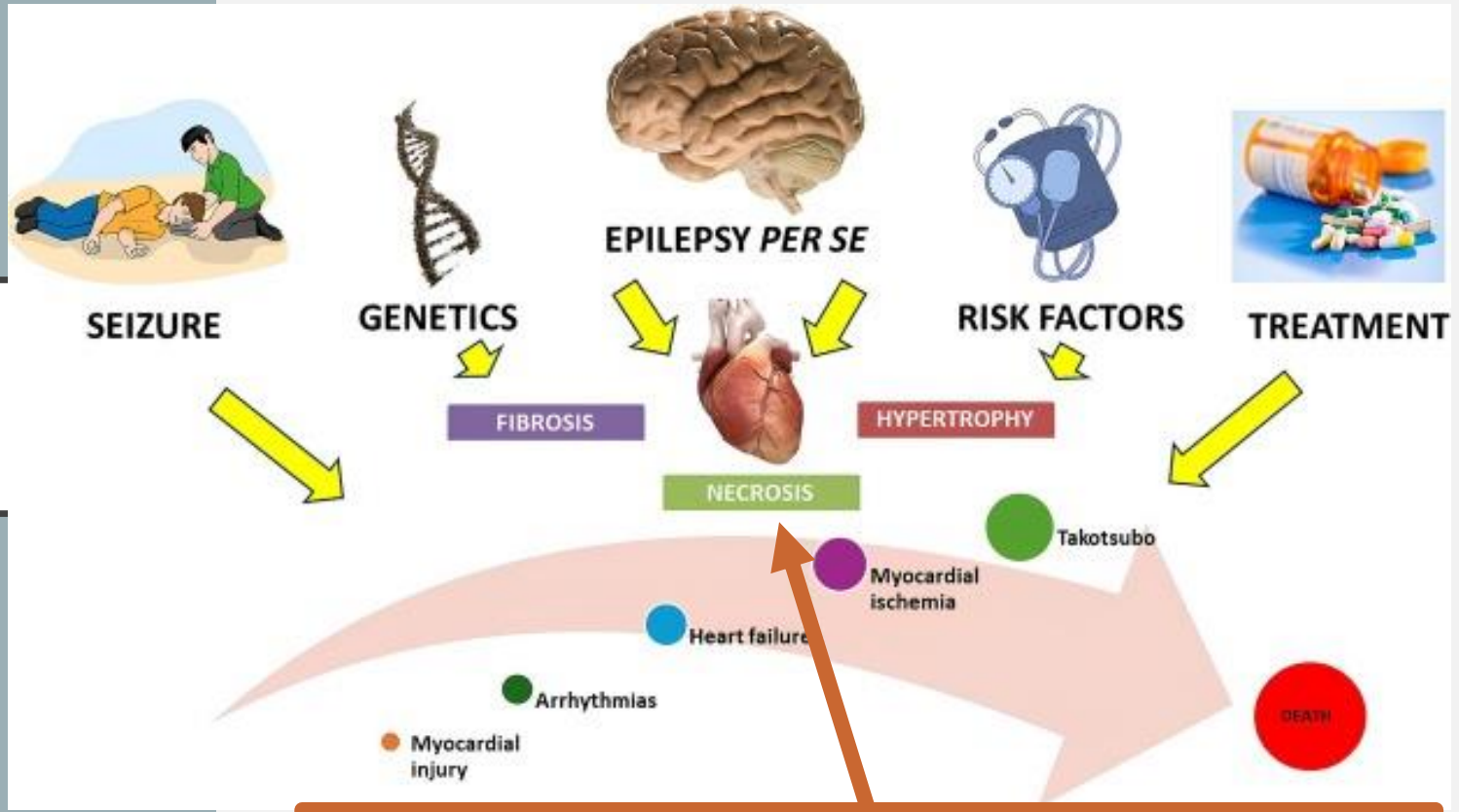


Loureiro Fialho G et al. *Epilepsy Behav Rep*. 2024 Apr 18;26:100668

METABOLIC AND CARDIOVASCULAR HEALTH

Epilepsy is correlate with arrhythmias, myocardial infarction, heart failure, and sudden death

An earlier onset of menopause increases the risk of non-fatal CV events prior to the age of 60 and CVD mortality



Early Menopause

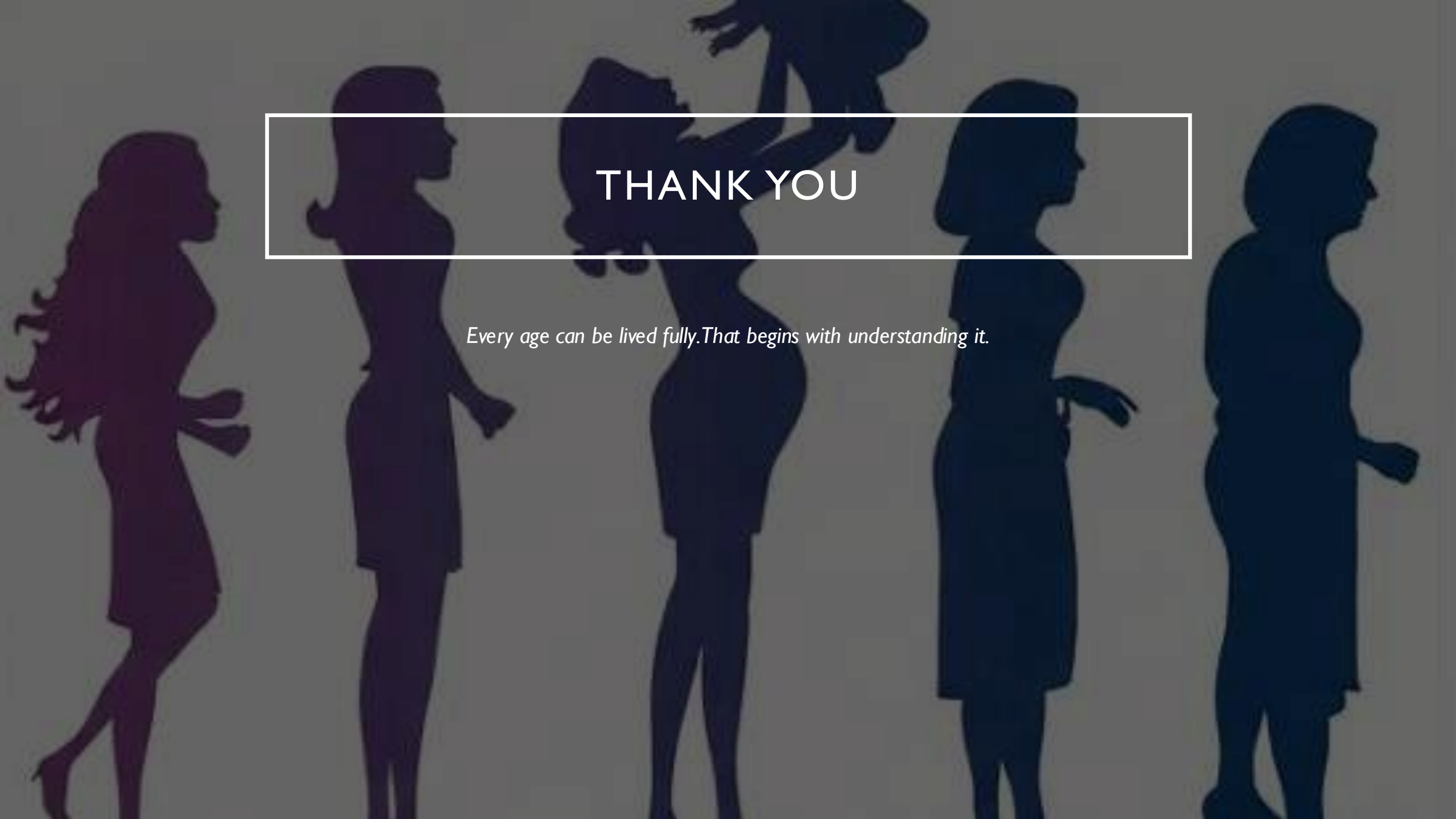
Zhu D et al. *Lancet Public Health*. 2019 Nov;4(11):e553-e564.

UROGENITAL AND SEXUAL PROBLEMS

Genitourinary syndrome of menopause (GSM) is a constellation of symptoms affecting the lower urinary track, vulva, and vagina due to estrogen deficient state of menopause. Symptoms may include nocturia, recurrent urinary tract infections, vulvovaginal atrophy, vaginal dryness, vaginal atrophy, dysuria/dyspareunia, sexual arousal or orgasm disorders .

- Present in up to 50% of menopausal women
- 30% of women will report severe sexual dysfunction and 70% sexual problems
- People with epilepsy have a six time higher rate of reported sexual problems compared to healthy controls
- Females adherence to antiseizure medications improved seizure control and was associate improved sexual function

Portman DJ and Gass ML *Menopause*. 2014 Oct;21(10):1063-8.



THANK YOU

Every age can be lived fully.That begins with understanding it.

ADDITIONAL SLIDES

PATIENT JP
- GENERALIZED EPILEPSY

Date of Blood Draw	Gestational Age Weeks (calculated)	AED 1 Name	AED 1: Formulation	AED 1: Total Daily Dose	AED 1: Total Level	AED 1: Free Level	AED 1: Lower Target Range, Total Level	AED 1: Upper Target Range, Total Level	AED 1: Time Post Dose
1/18/19	-199	Lamotrigine	ER	500	7		6.5	9	
9/1/21	-62.29	Lamotrigine	ER	500	8.1		6.5	9	19
10/3/22	-5.57	Lamotrigine	ER	500	6.3		6.5	9	23
12/14/22	4.71	Lamotrigine	ER	500	6		6.5	9	0.5
1/13/23	9	Lamotrigine	ER	550	6.4		6.5	9	7
2/25/23	15.14	Lamotrigine	ER	550	2.9		6.5	9	5.5
4/6/23	20.86	Lamotrigine	ER	650	4.2		6.5	9	0.5
5/12/23	26	Lamotrigine	ER	750	3.9		6.5	9	1
6/15/23	30.86	Lamotrigine	ER	850	6.5		6.5	9	3
7/18/23	35.57	Lamotrigine	ER	900	5.1		6.5	9	0.75
9/27/23		Lamotrigine	ER	1000	8.9		6.5	9	

POSTPARTUM TAPER EXAMPLES

Current Keppra ER dose: 1500 mg in AM and 2000 mg in PM
Plan:

Keppra ER dosing:	AM	PM
Birth – Postpartum Day 7:	1500 mg	2000 mg
Days 8-14:	1500 mg	1500 mg
Day 15 and continue:	1000 mg	1500 mg

Current Lamotrigine ER dose: 450 mg in AM and 400 mg in PM
Plan:

Lamotrigine ER dosing:	AM	PM
Birth - Postpartum Day 3:	450 mg	400 mg
Days 4-7:	350 mg	400 mg
Days 8-11:	350 mg	300 mg
Days 12-15:	250 mg	300 mg
Days 16 and continue:	250 mg	200 mg