Practicing Evidence-Based Care for Women with Epilepsy during Pregnancy and Postpartum

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Clinical Neurological Society of America

Disclosures

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Clinical Neurological Society of America

Learning Objectives

At the Conclusion of this Activity, participants will be able to:

1. Identify which antiseizure medications (ASMs) are associated with the lowest rates of major congenital malformations (MCMs) based on recent AAN/AES/SMFM Guidelines

2. Summarize current data about which ASMS have been associated with impaired fetal neurodevelopment

3. Be familiar with treatment strategies to prevent seizure worsening during pregnancy

Clinical Neurological Society of America

Magnitude

- 1.3 million people with epilepsy of childbearing potential (PWECP) in US[1]
- 4.3 million ASM prescriptions annually to people of childbearing potential
- Prenatal ASM exposure rates = 2.2%, with varied maternal dx[3]
  - mental illness (48%), pain disorders (22%), epilepsy (21%)
- Planned pregnancies reduces risks to mother and child
  - Prescriber of ASMs should counsel about ASM – hormonal contraceptive interactions

1. Meador KJ, et al. *Neurology*. 2008; 2. Holmes LB, et al. *N Engl J Med*. 2001;344(15):1132-1138.; 3. Bobo WV, et al. *PaediatrPerinatEpidemiol* 2012. 4. Adedinsewo DA, et al., Birth Defects Research (Part A) 2013.

A Precise Balancing Act in Pregnancy: Maternal Benefits versus Fetal Risks of ASMs

- Teratogenic effects on offspring significant, with increased risk for MCMs
- Neurodevelopmental defects common, with lifelong consequences
- Evidence that not only *type* of ASM but *amount* of ASM impacts level of risk
- For epilepsy, maintain maternal seizure control while minimizing teratogenic effects of ASM exposure

*Use of **evidence-based** approaches is now possible*

1. Holmes LB, et al. *N Engl J Med*. 2001;344(15):1132-1138.. 2012; 2. Adedinsewo DA, et al., Birth Defects Research (Part A) 2013.

Questions and Dilemmas for Management of Epilepsy during Pregnancy

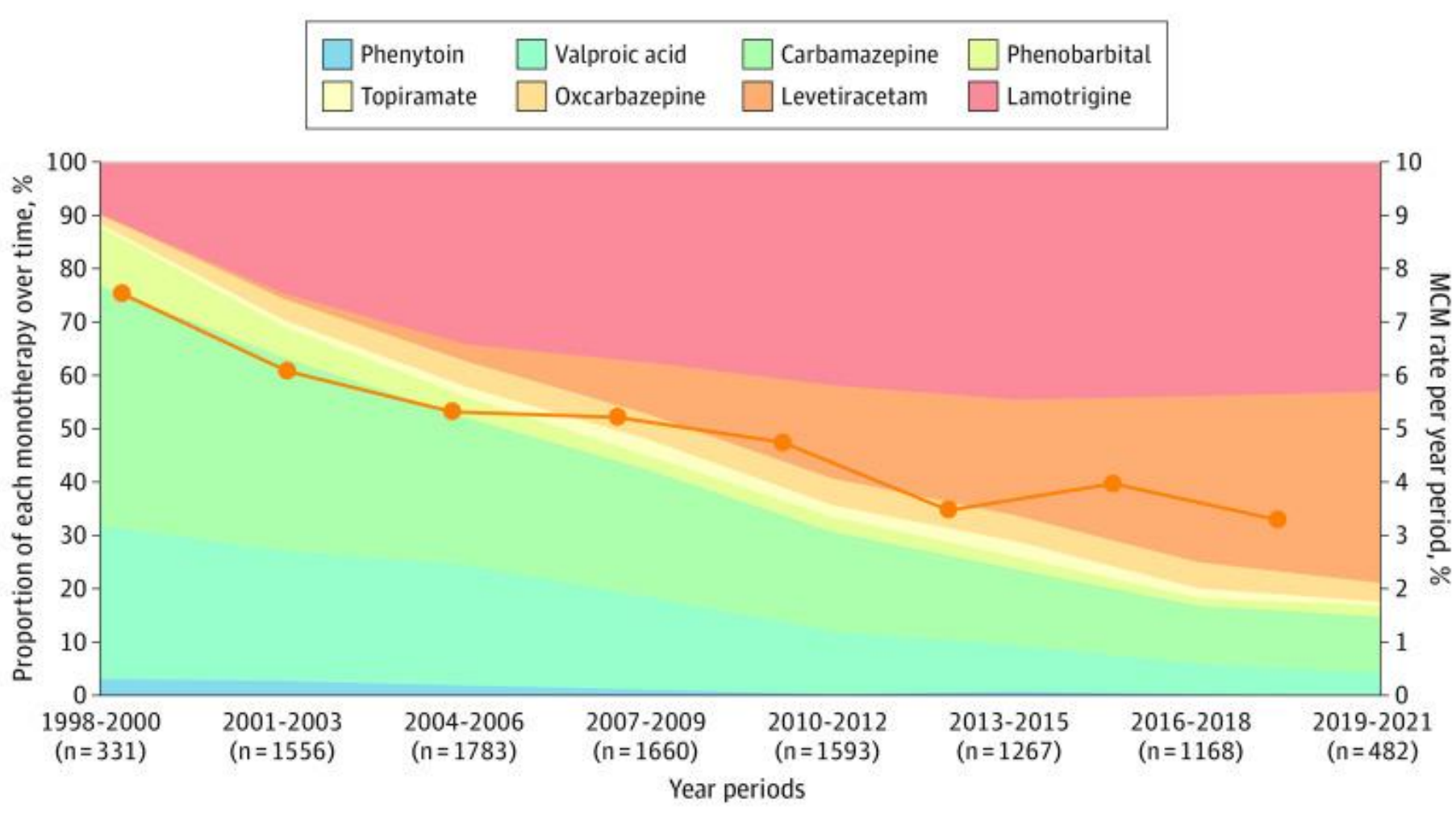
Maternal Outcomes

- Will seizures get worse?
- How should ASMs be managed during pregnancy and postpartum?
- Is there a need for a different delivery plan?
- How to ensure a planned pregnancy, with best vitamin and ASM regimen?

Child Outcomes

- What is the level of risk for MCMs? Does it differ by ASM regimen? By dose?
- What is the risk for abnormal fetal growth? Abnormal brain development?
- What is the harm to the pregnancy/fetus if seizures occur? By type of seizures?
- Are there increased problems in neonatal period?
- Is breastfeeding safe?

EURAP: Proportion of Monotherapies and MCM rates over time (n=9840)



Battino D, Tomson T, Bonizzoni E, et al. Risk of Major Congenital Malformations and Exposure to Antiseizure Medication Monotherapy. *JAMA Neurol*. Published online March 18, 2024. doi:10.1001/jamaneurol.2024.0258

EURAP, updated 2024

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 D, Tomson T, Bonizzoni E, et al. Risk of Major Congenital Malformations and Exposure to Antiseizure Medication Monotherapy. *JAMA Neurol*. Published online March 18, 2024. doi:10.1001/jamaneurol.2024.0258

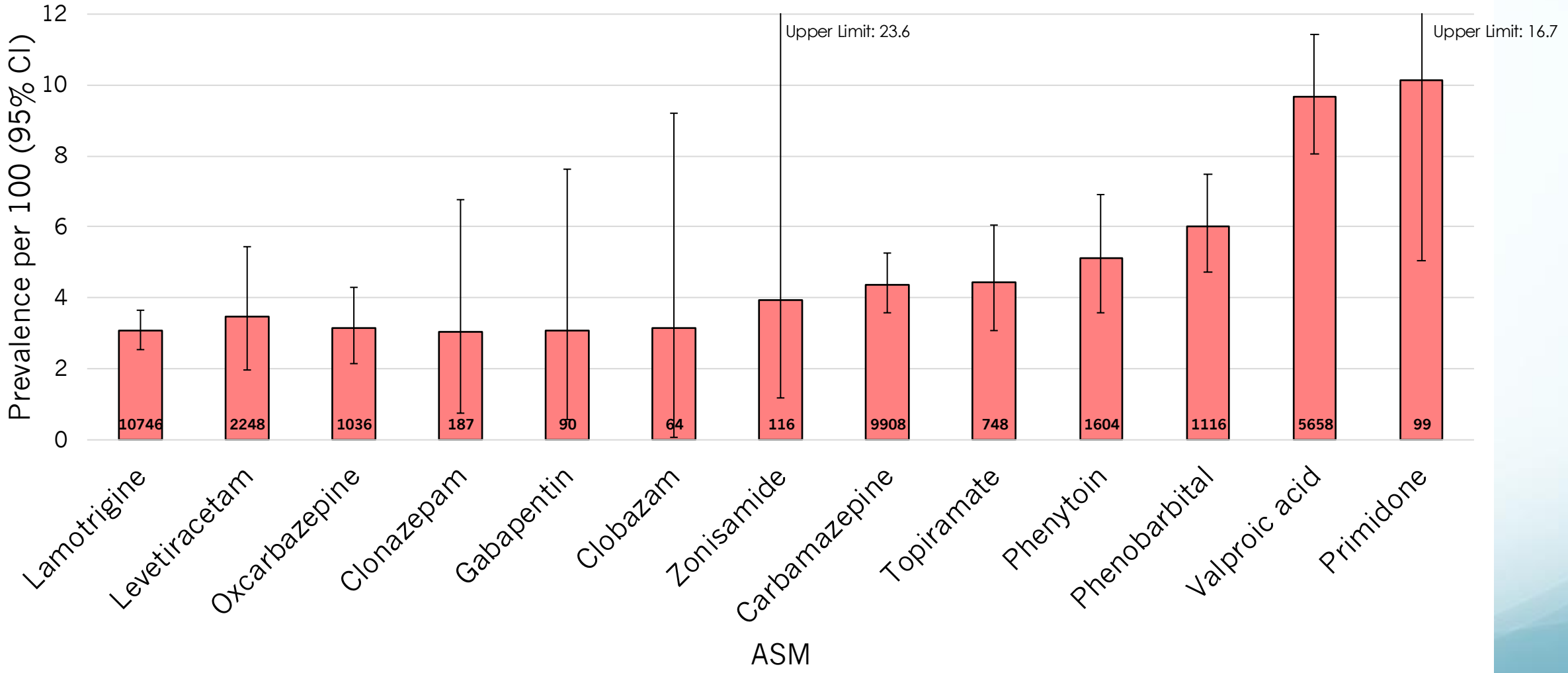
2024 Practice Guideline from AAN, AES, SMFM

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

Pack AM, Oskoui M, Williams Roberson S, Donley DK, French J, Gerard EE, Gloss D, Miller WR, Munger Clary HM, Osmundson SS, McFadden B, Parratt K, Pennell PB, Saade G, Smith DB, Sullivan K, Thomas SV, Tomson T, Dolan O'Brien M, Botchway-Doe K, Silsbee HM, Keezer MR. Teratogenesis, Perinatal, and Neurodevelopmental Outcomes After In Utero Exposure to Antiseizure Medication: Practice Guideline From the AAN, AES, and SMFM. Neurology. 2024 Jun;102(11):e209279. doi: 10.1212/WNL.0000000000209279. Epub 2024 May 15. PMID: 38748979; PMCID: PMC11175651.

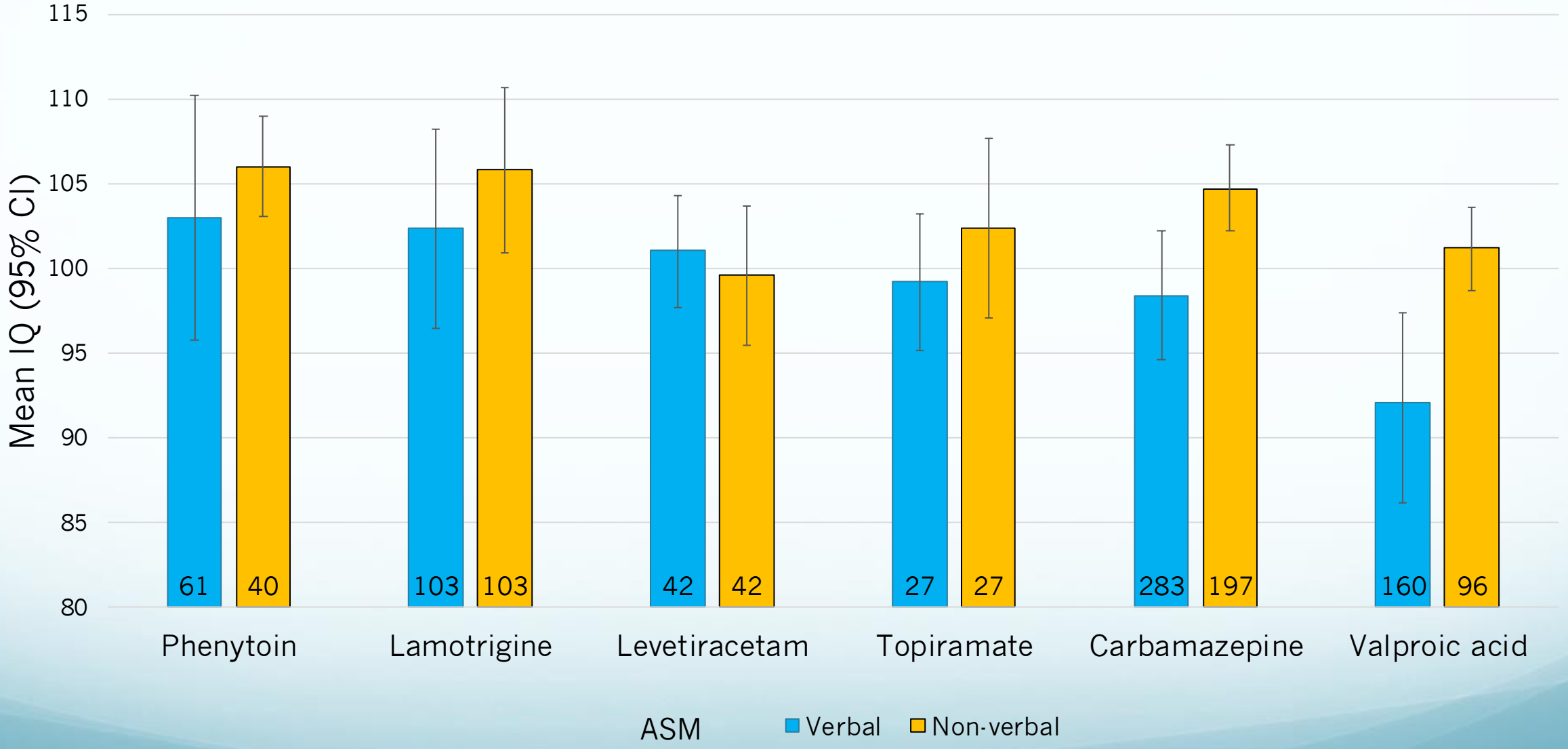
Slides courtesy of Emma Osterhaus, University of Pittsburgh MS3

Prevalence of Any MCM by ASM in Monotherapy

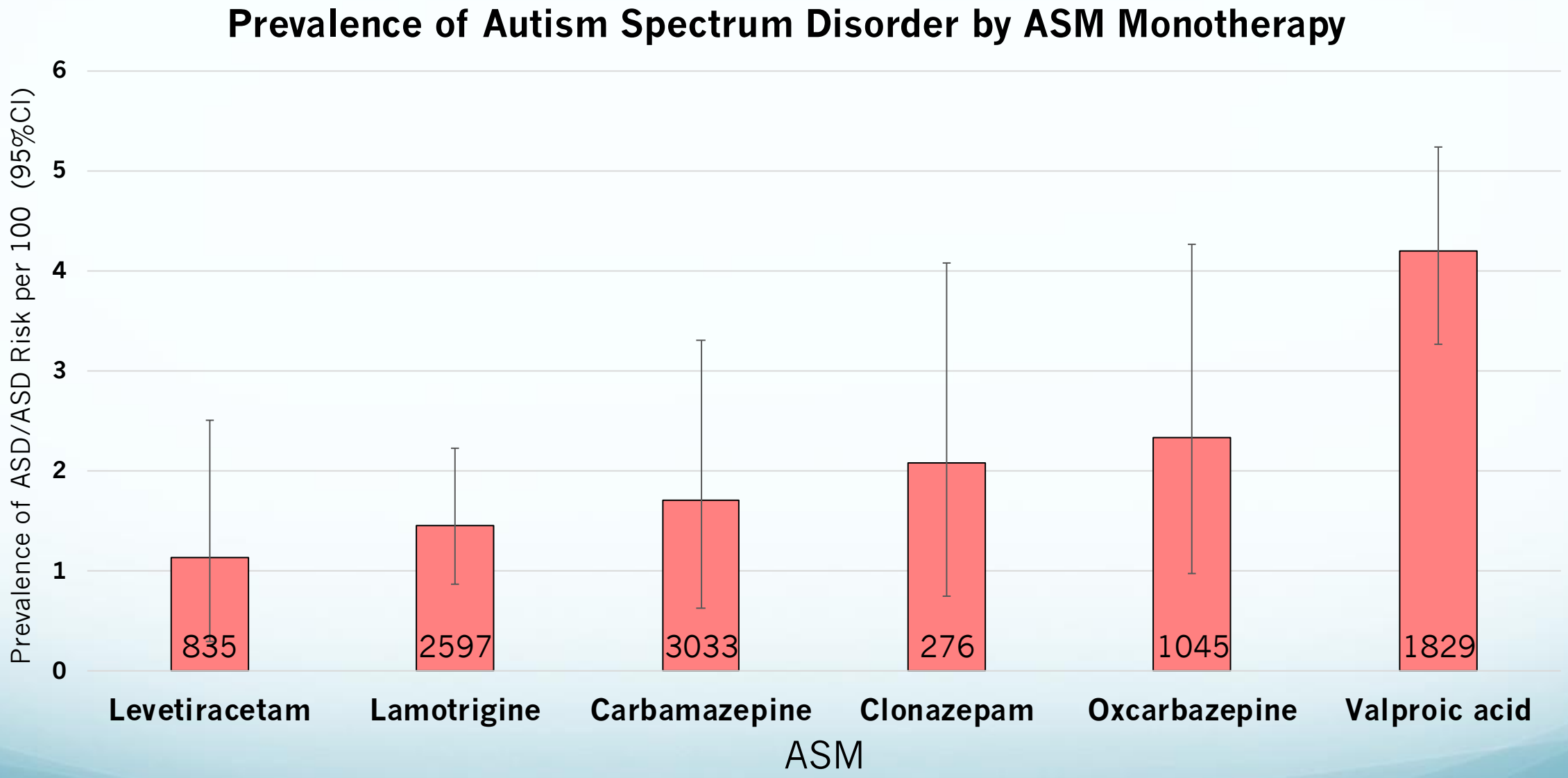


*MCM prevalence in general population is 2.4-2.9%.

Verbal and Non-verbal IQ with Exposure to ASM Monotherapy



Pack, Alison M et al. *Neurology* vol. 102,11 (2024): e209279.


Prevalence of Autism Spectrum Disorder by ASM Monotherapy
Prevalence of ASD/ASD Risk per 100 (95%CI)
6
5
4
3
2
1
0
835
2597
3033
276
1045
1829
Levetiracetam
Lamotrigine
Carbamazepine
Clonazepam
Oxcarbazepine
Valproic acid
ASM

2024 Practice Guideline from AAN, AES, SMFM

Additional Recommendations

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

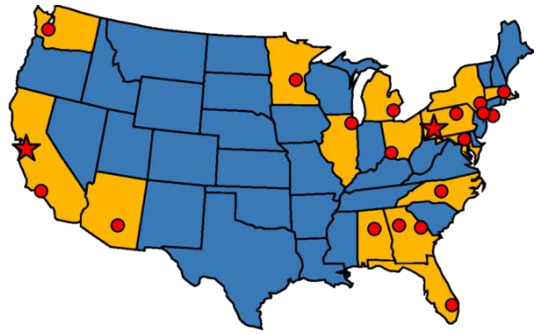
Maternal Outcomes & Neurodevelopmental Effects of Anti-Epileptic Drugs (MONEAD)

Prospective, observational study, across 20 clinical sites

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

Pregnant healthy controls (n=105)

Non-pregnant WWE (n=109)



Maternal Outcomes

- Seizures, OB complications, Depression

Children Outcomes

- Neurodevelopment, Neonatal complications, Breastfeeding

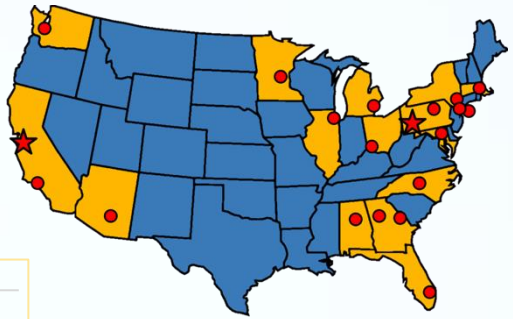
With PK modeling for level of exposure

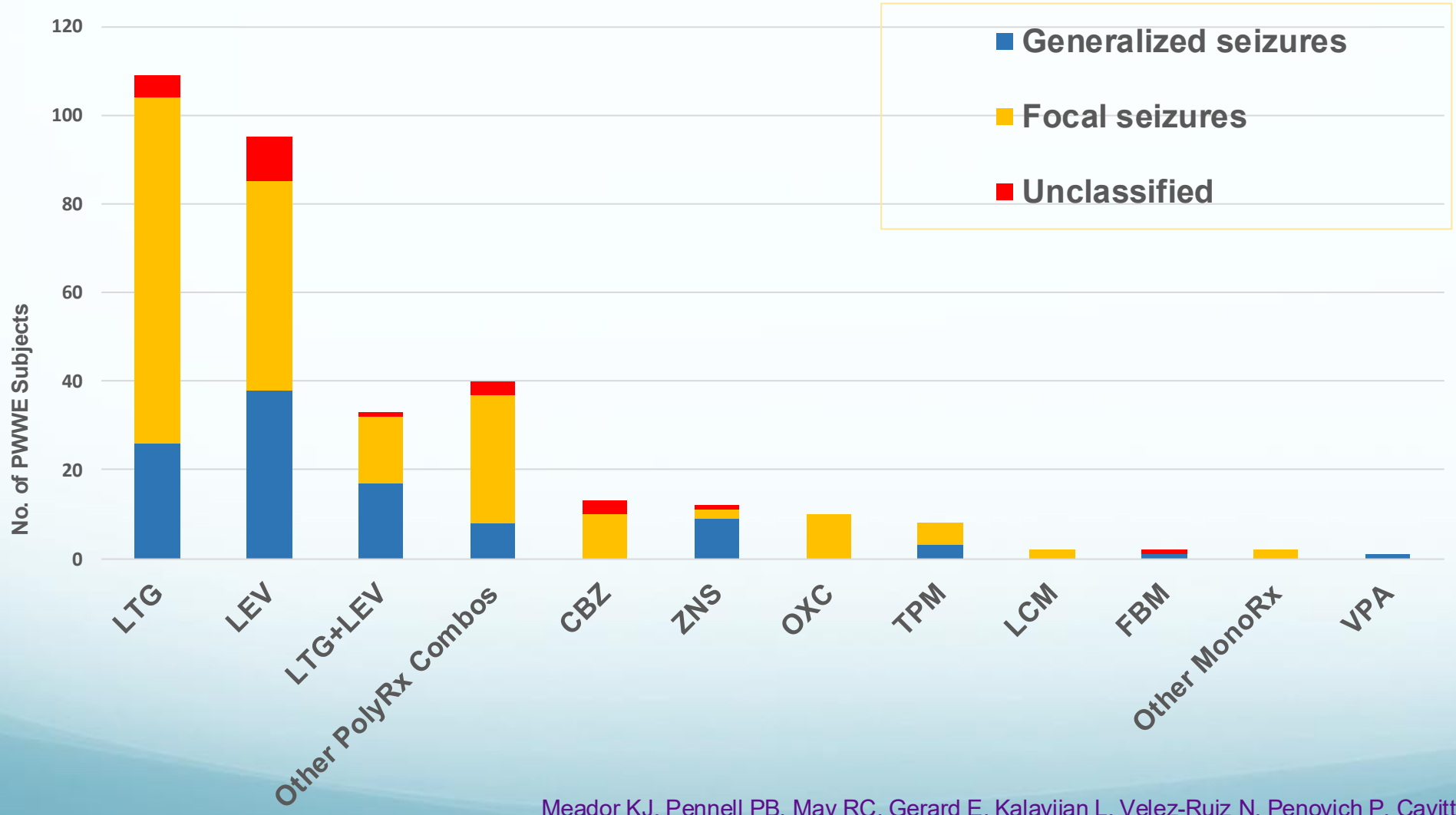
Multiple-PIs:
Kimford Meador, MD (Stanford)
Page B. Pennell, MD (Univ of Pittsburgh)

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)
Pharmacokinetic Core: A. Birnbaum (Univ of Minnesot

Funding: NINIDS and NICHD U01-NS038455, U01-NS050659 and 2U01-NS038455

Prescribing Patterns in PWWE at MONEAD sites

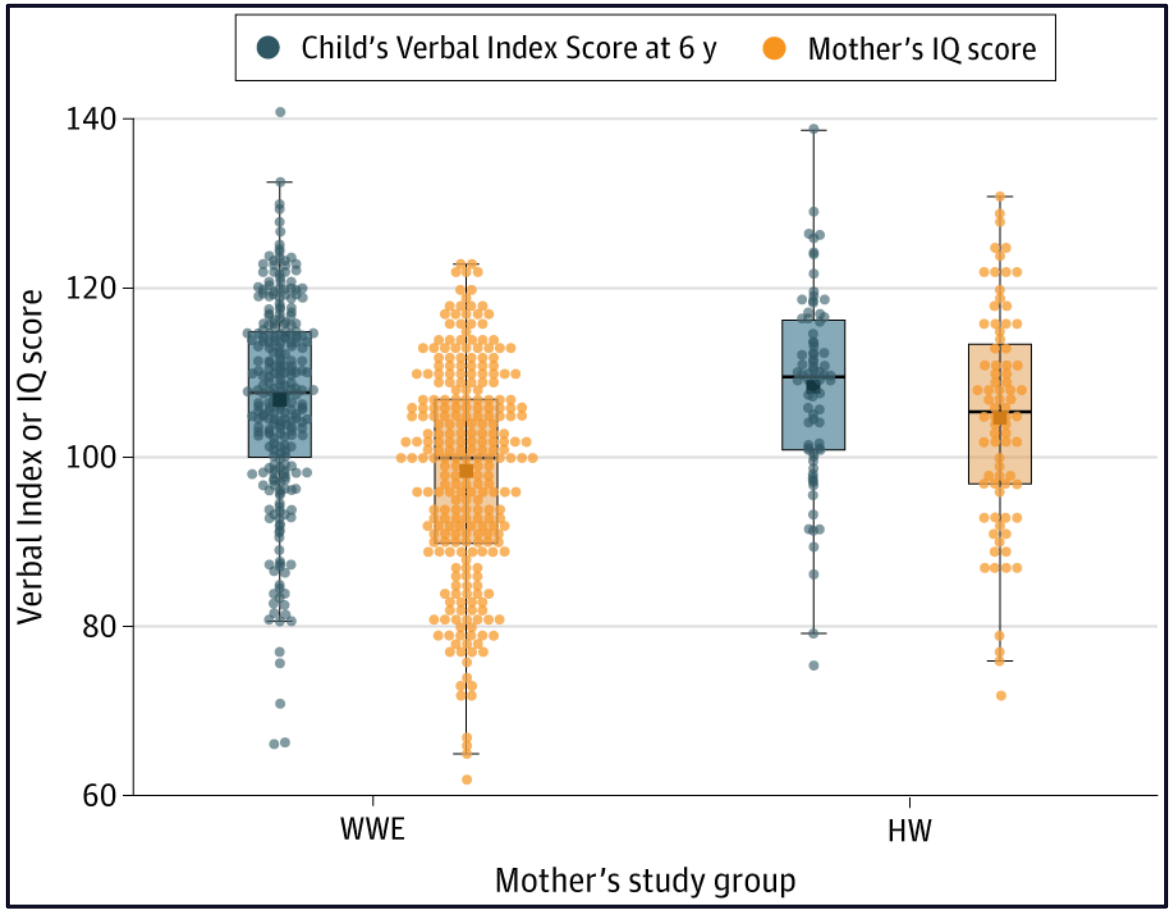




Meador KJ, Pennell PB, May RC, Gerard E, Kalayjian L, Velez-Ruiz N, Penovich P, Cavitt J, French J, Hwang S, Pack A, Sam M, Moore E, Ippolito DM, MONEAD Investigator Group. *Epilepsy & Behavior* 2018.

Verbal Index Scores in 6yo Children of Women with Epilepsy and of Healthy Women

Meador KJ, Cohen MJ, Loring DW, Matthews AG, Brown C, Robalino CP, Carmack A, Birnbaum AK, Voinescu PE, Gerard EE, Kalayjian LA, Gedzelman ER, Hanna J, Cavitt J, Sam M, Hwang S, Pack AM, French JA, Tsai JJ, Taylor C, Pennell PB. JAMA Neurol. 2025;82(1):30-39.
doi:10.1001/jamaneurol.2024.3982



*Significant covariates in the adjusted model: mother's IQ, age, education level, acetaminophen exposure and child's small for gestational age, sex, and ethnicity

Cognitive outcomes at age 3 years in children with fetal exposure to antiseizure medications (MONEAD study) in the USA: a prospective, observational cohort study

*Kimford J Meador, Morris J Cohen, David W Loring, Abigail G Matthews, Carrie Brown, Chelsea P Robalino, Angela K Birnbaum, Paula E Voinescu, Laura A Kalayjian, Elizabeth E Gerard, Evan R Gedzelman, Julie Hanna, Jennifer Cavitt, Maria Sam, Jacqueline A French, Sean Hwang, Alison M Pack, Page B Pennell, for the MONEAD Investigator Group**

Lancet Neurol 2023; 22: 712–22

See Comment page 648

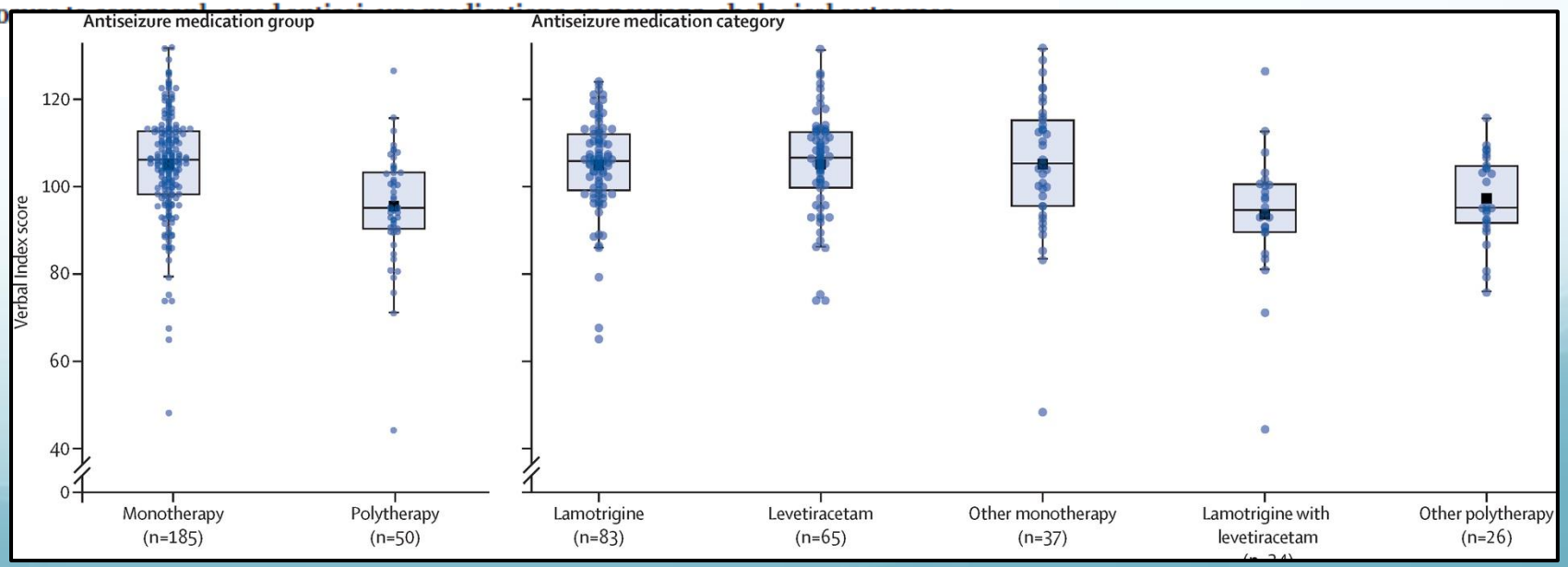
*Members listed in appendix

Stanford University, Palo Alto,

Summary

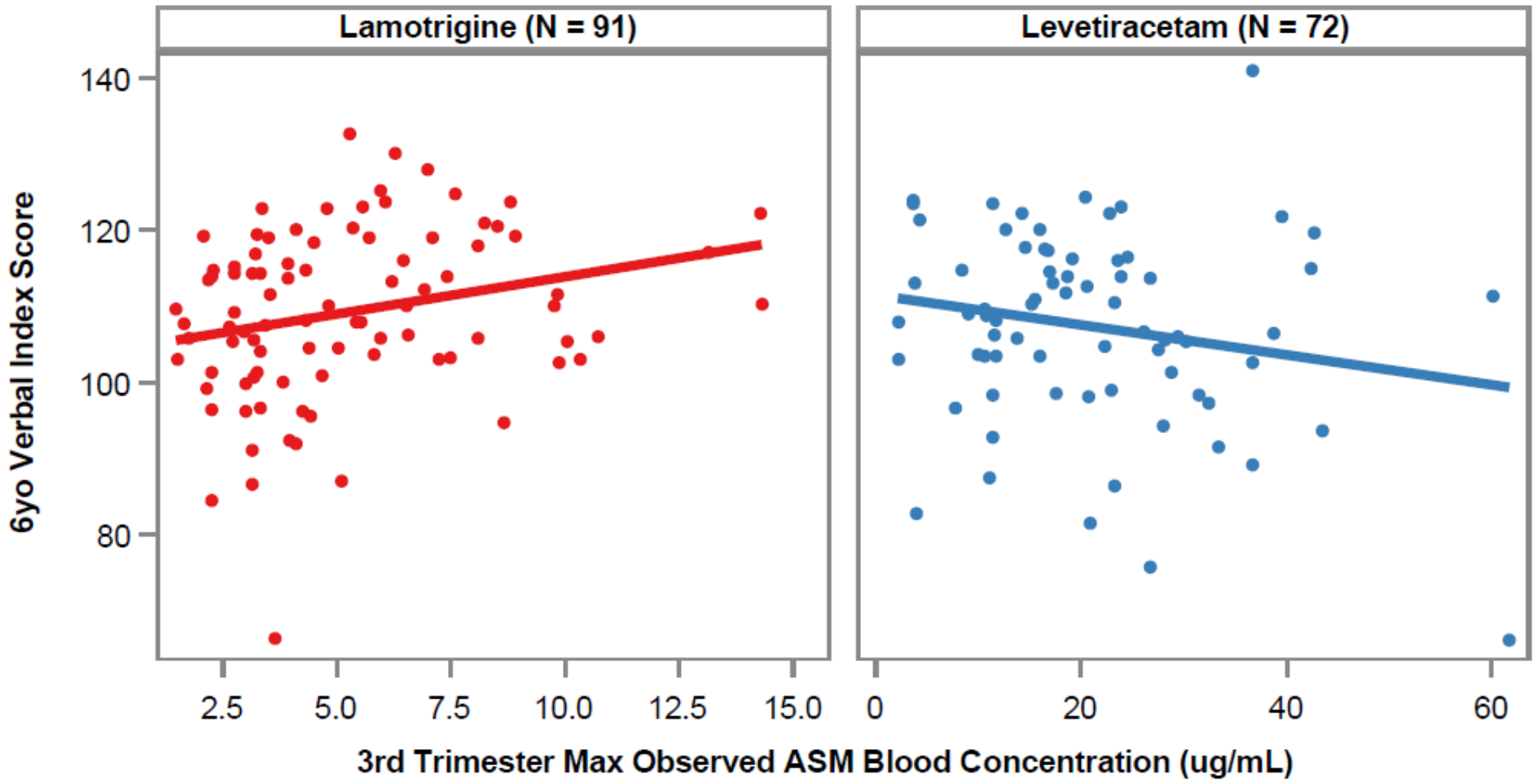
Background The neurodevelopmental effects of fetal exposure to most antiseizure medications are unclear. We aimed to investigate the effects of fetal expo

at age 3 years.



Verbal Index Scores in 6yo Children of Women with Epilepsy by 3rd Trimester ASM Blood Conc.

Meador KJ, Cohen MJ, Loring DW, Matthews AG, Brown C, Robalino CP, Carmack A, Birnbaum AK, Voinescu PE, Gerard EE, Kalayjian LA, Gedzelman ER, Hanna J, Cavitt J, Sam M, Hwang S, Pack AM, French JA, Tsai JJ, Taylor C, Pennell PB. JAMA Neurol. 2025;82(1):30-39. doi:10.1001/jamaneurol.2024.3982



What are the risks of seizures?

- To the woman during pregnancy
- To the developing fetus
- To both mother and child postpartum

How to practice evidence-based medicine to balance the potentially HARMFUL effects of ASMs to the fetus and breastfeeding newborn against the BENEFICAL effects of ASMs for the woman during pregnancy & lactation

Perry Natal, decreased ASM concentrations

Risk of Seizures

Tonic-Clonic Convulsions (Generalized or Focal to Bilateral)

- Maternal & fetal hypoxia & acidosis
- Miscarriage & stillbirths
- Developmental delay (≥5 GTCC in pregnancy)

All seizures: increased OR for LBW, SGA, preterm delivery

- Taiwan birth registry (n=1016 WWE, n=8128 controls)

Elevated Maternal Mortality

Teramo K, et al. *J Perinat Med*. 1979;7(1):3-6; Vinten J, et al. *Neurology* 2005;64(6):949-54; Chen YH, et al. *Arch Neurol* 2009;66(8):979-84; Macdonald SC, et al. JAMA Neurol 2015.

Seizure Frequency Change compared to Non-pregnant Baseline

- Studies reported that 9-75% of women have seizure worsening during pregnancy compared to baseline

- May depend on several factors:
  - Baseline seizure frequency, in prior month or 9-12 months
  - Patient Adherence
  - Other factors less known: sleep, stress, neuroactive steroids
  - Use of Therapeutic Drug Monitoring
  - Ratio to target concentration of 0.65 predicts increased seizure risk

Pennell PB, Neurol 2008; Sabers A, Epilepsia 2009; Petrenaite V, Epi Res 2009; Harden CL, Ngy. 2009; Johnson EL, Epi Beh 2014; Wegner I, Epilepsia 2010; Reisinger TL, et al. Epi Beh 2013; Thomas SV, et al Epilepsia 2012.

Epilepsia, 50(5):1229–1236, 2009
doi: 10.1111/j.1528-1167.2009.02128.x

SPECIAL REPORT

Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency

Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Do WWE have an increased risk of epilepsy-related complications during pregnancy?

Twenty-five articles met inclusion criteria for epilepsy-related complications in pregnant WWE.

Change in seizure frequency

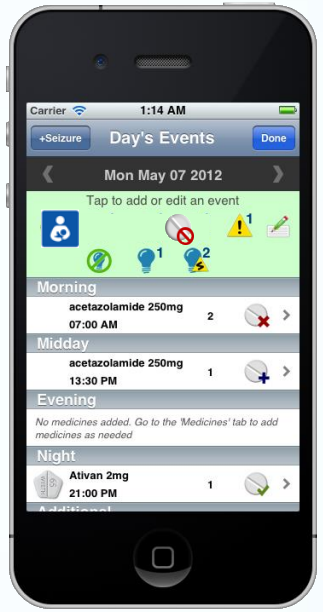
No study compared the change in seizure frequency in pregnant WWE to nonpregnant WWE; therefore, an appropriate "gold standard" comparator group was not available. Hence, all studies were graded Class IV

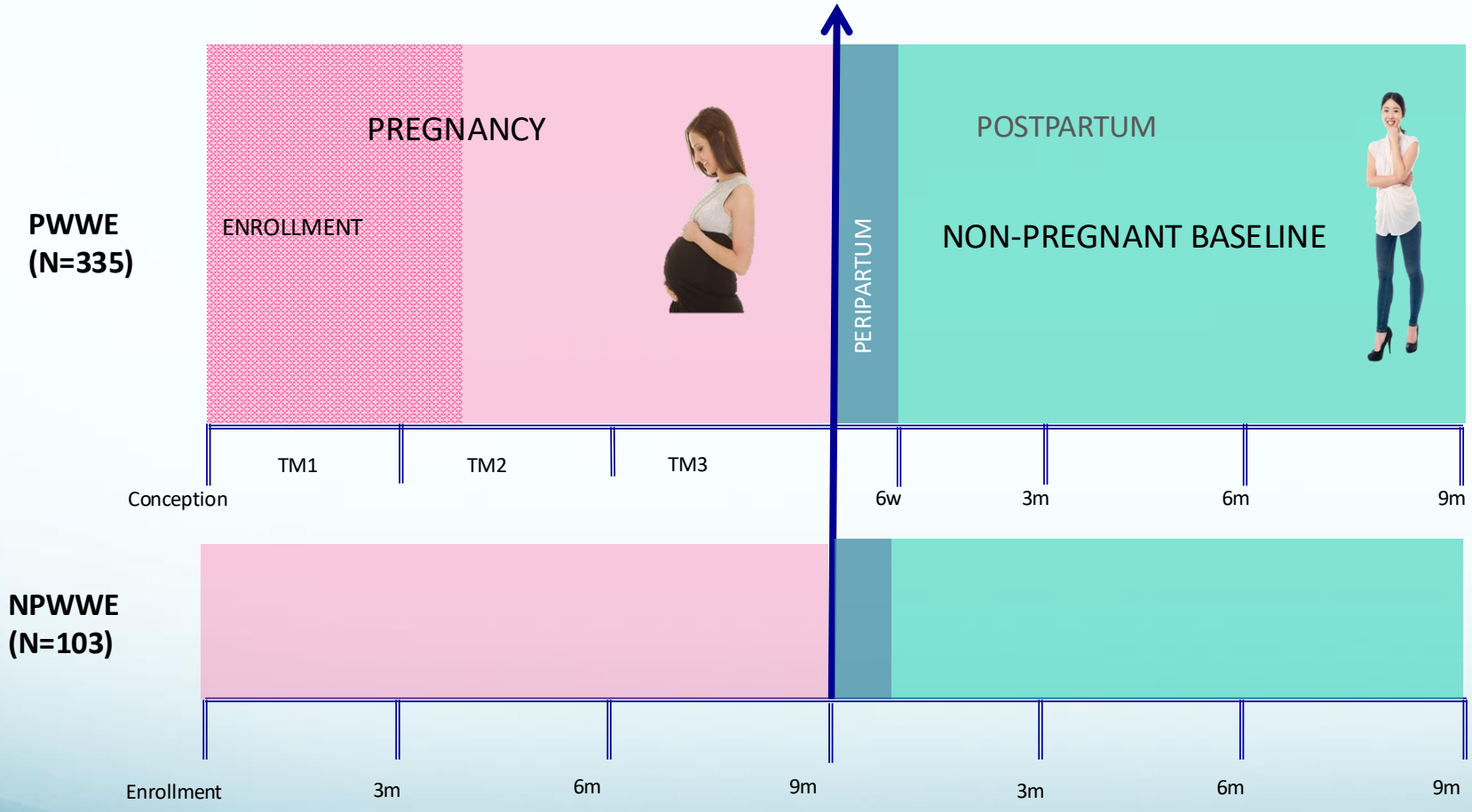
Unfortunately, none of these studies included an appropriate nonpregnant WWE comparator group to provide information on the natural stability of seizure frequency among WWE. Without this information, it is impossible to determine if the changes in seizure frequency observed were related to the pregnancy itself.

Conclusion

There is insufficient evidence to determine the change in seizure frequency in pregnant WWE.

MONEAD Design





NPWWE Balanced on:

Seizure Type
Seizure Frequency
ASMs

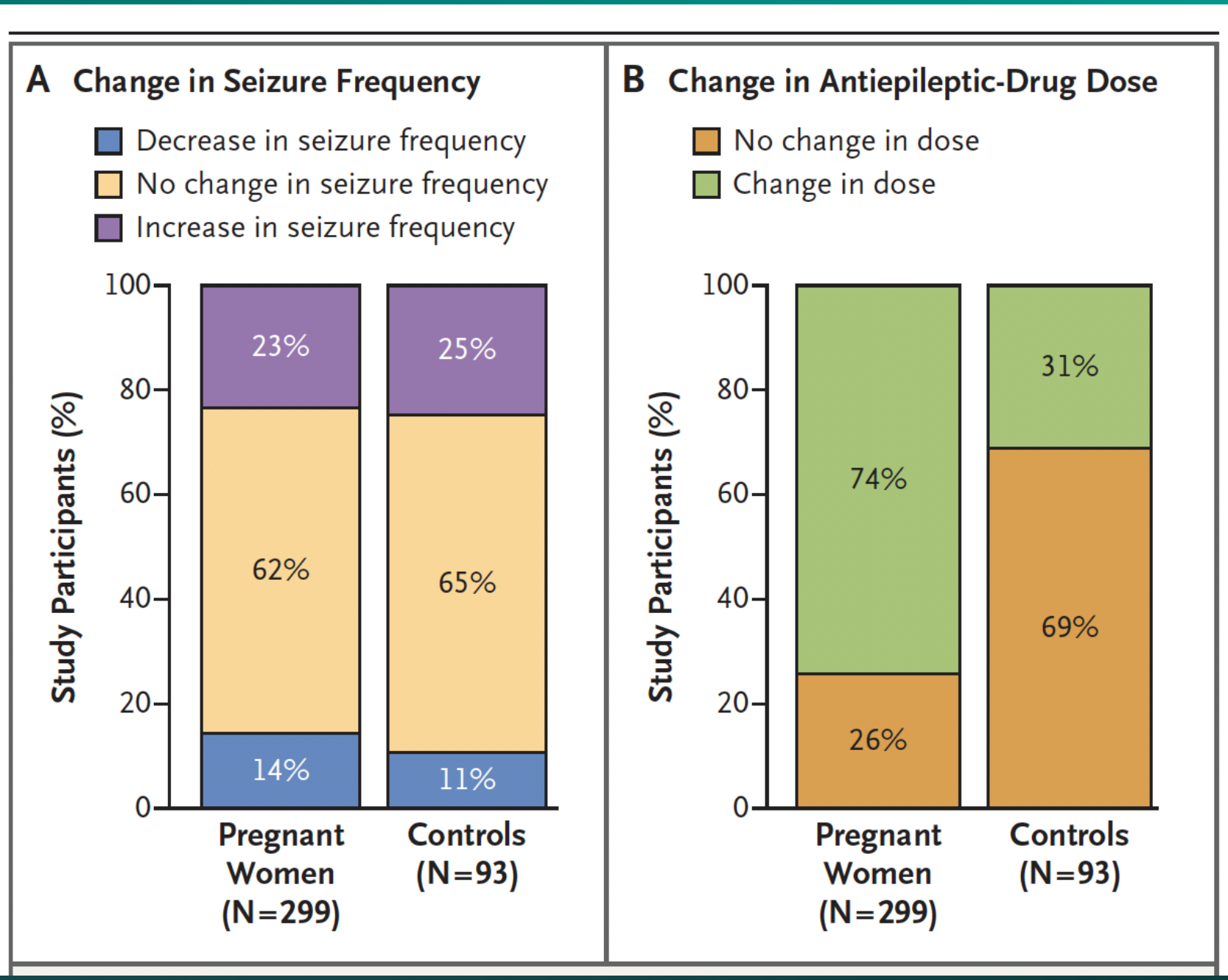
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy

Page B. Pennell, M.D., Jacqueline A. French, M.D., Ryan C. May, Ph.D., Elizabeth Gerard, M.D., Laura Kalayjian, M.D., Patricia Penovich, M.D., Evan Gedzelman, M.D., Jennifer Cavitt, M.D., Sean Hwang, M.D., Alison M. Pack, M.D., Maria Sam, M.D., John W. Miller, M.D., Ph.D., Steffanie H. Wilson, Ph.D., Carrie Brown, M.S., Angela K. Birnbaum, Ph.D., and Kimford J. Meador, M.D., for the MONEAD Study Group*

N ENGL J MED 383;26 NEJM.ORG DECEMBER 24, 2020



*Seizures that Impair Awareness

Risk Factors

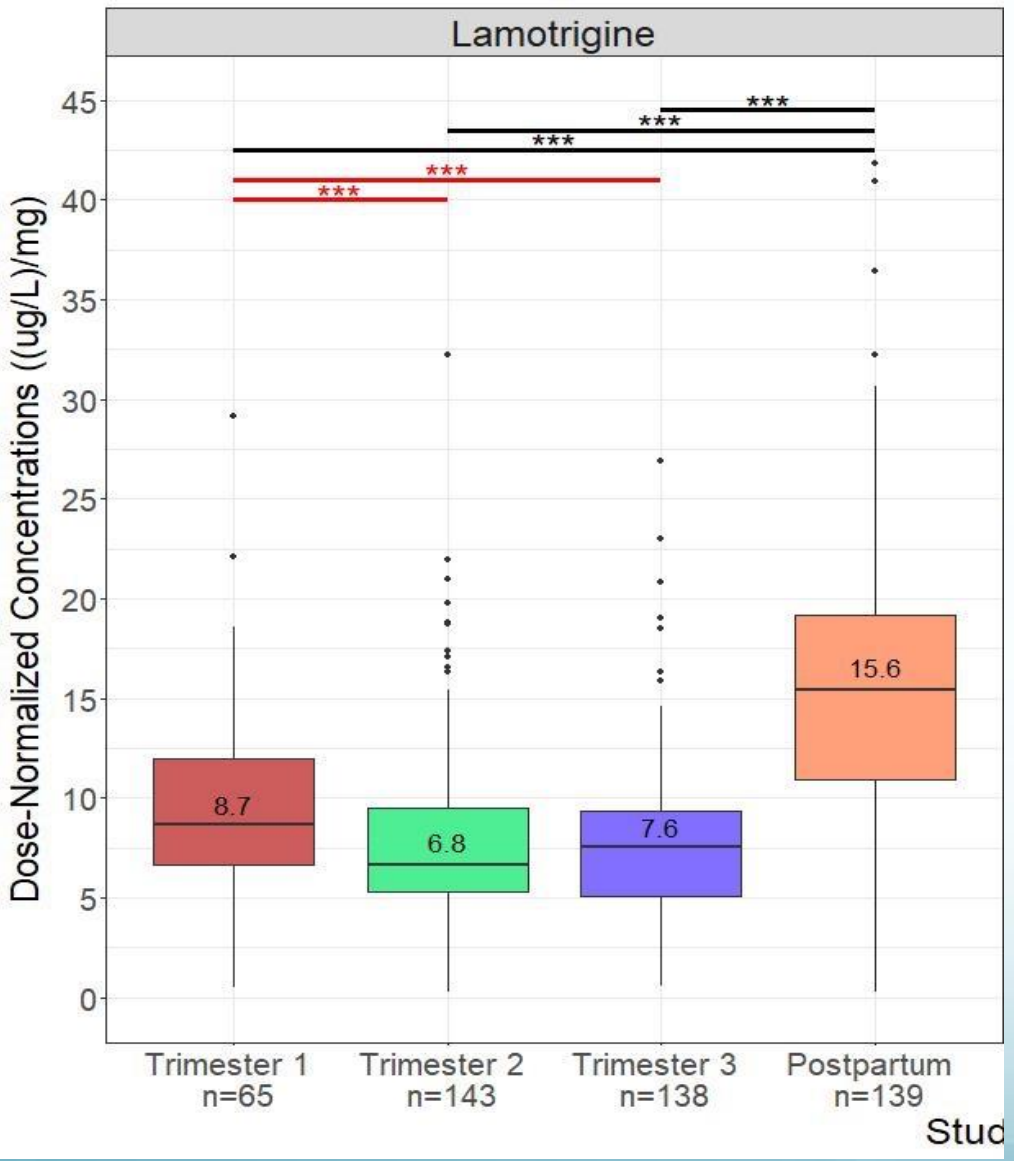
No differences in seizure types, or ASM regimen

Sole risk factor was seizure freedom in 9mos. months pre-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.

Lamotrigine Dose Normalized Concentrations During and After Pregnancy



***significance level p < 0.001

Mean LTG dose normalized concentrations are **significantly different from postpartum**

Mean LTG dose normalized concentrations change **significantly throughout pregnancy**

Box plots show the median and the 25th and 75th percentiles.

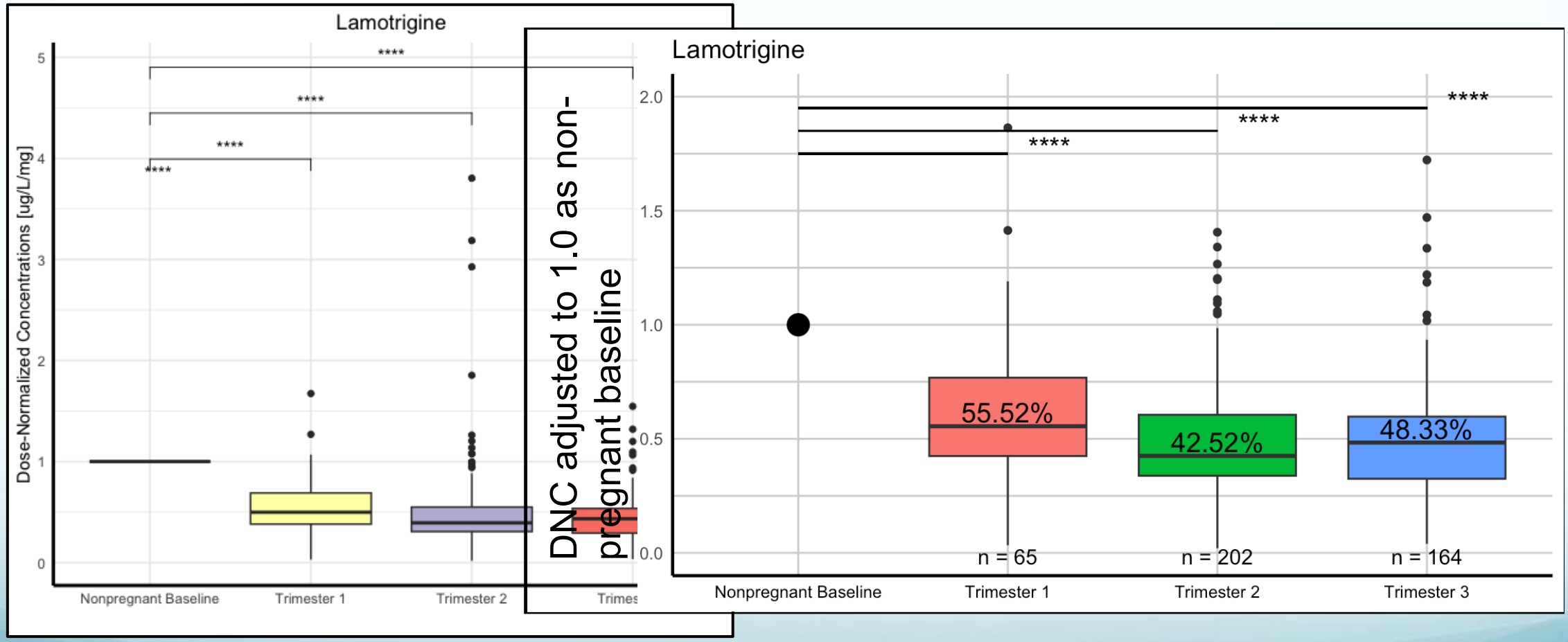
Whiskers represent 1.5 times the interquartile range.

Numbers in the boxplot represent median values of DNC.

Black bars = comparator is postpartum
Red bars = comparator is trimester 1

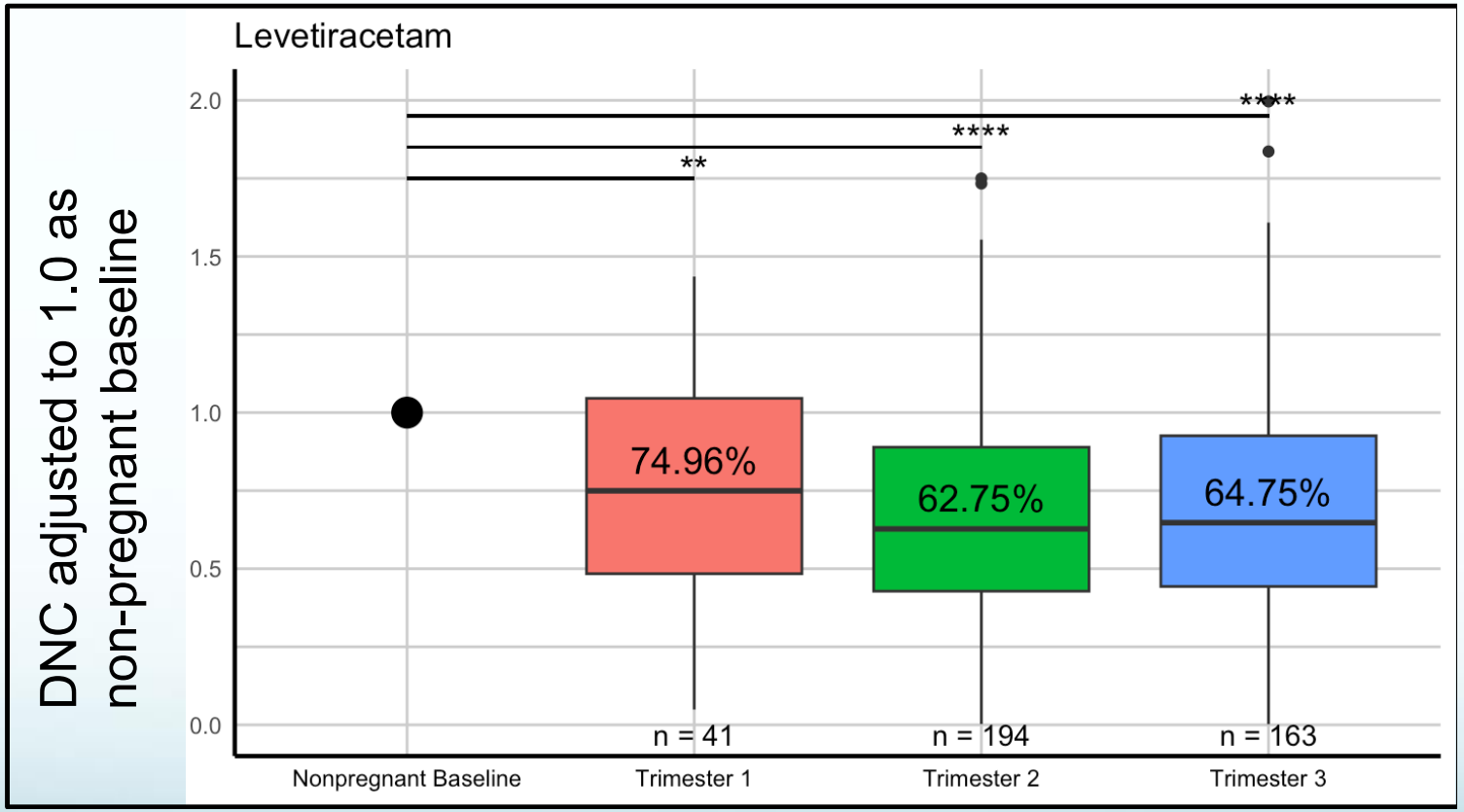
Pennell PB, Karanam A, Meador KJ, et al. JAMA Neurol. 2022. PMID: 35157004.

MONEAD findings: Lamotrigine (n=162) Dose-Normalized Concentrations during Pregnancy



Adapted from Pennell PB, Karanam A, Meador KJ, et al. JAMA Neurol. 2022. PMID: 35157004.

MONEAD findings: Levetiracetam (n=151) Dose-Normalized Concentrations during Pregnancy

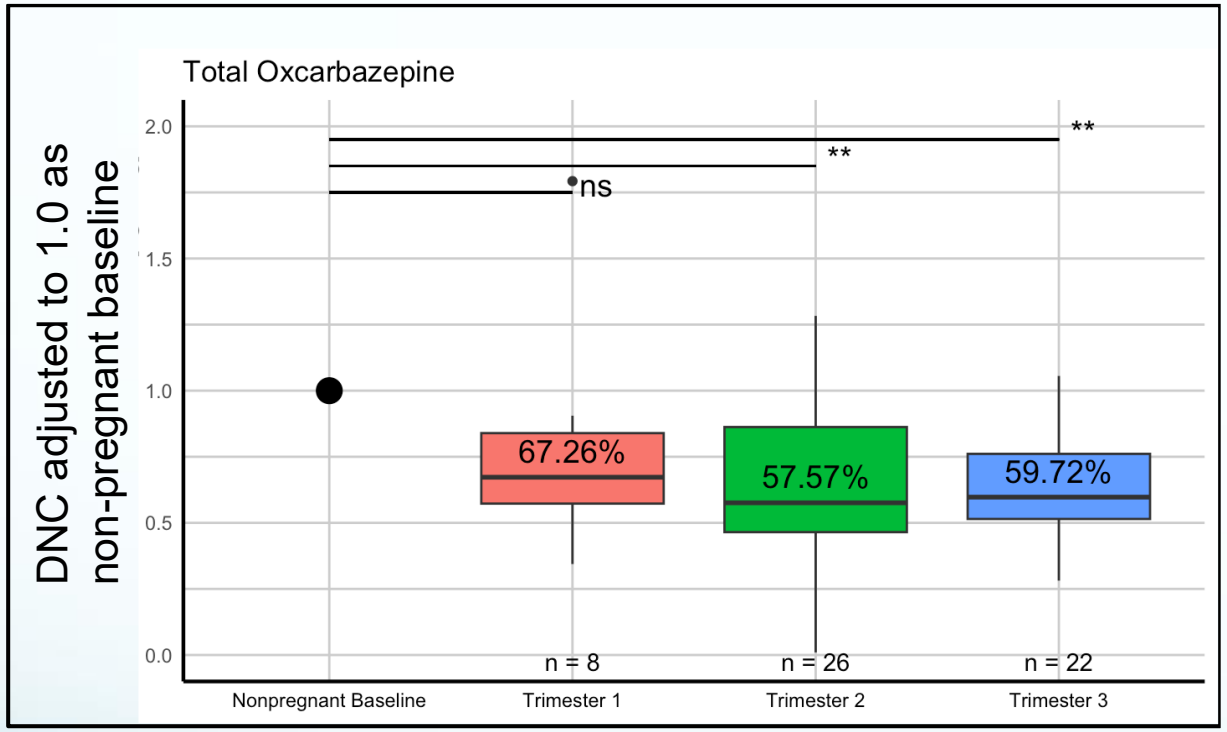


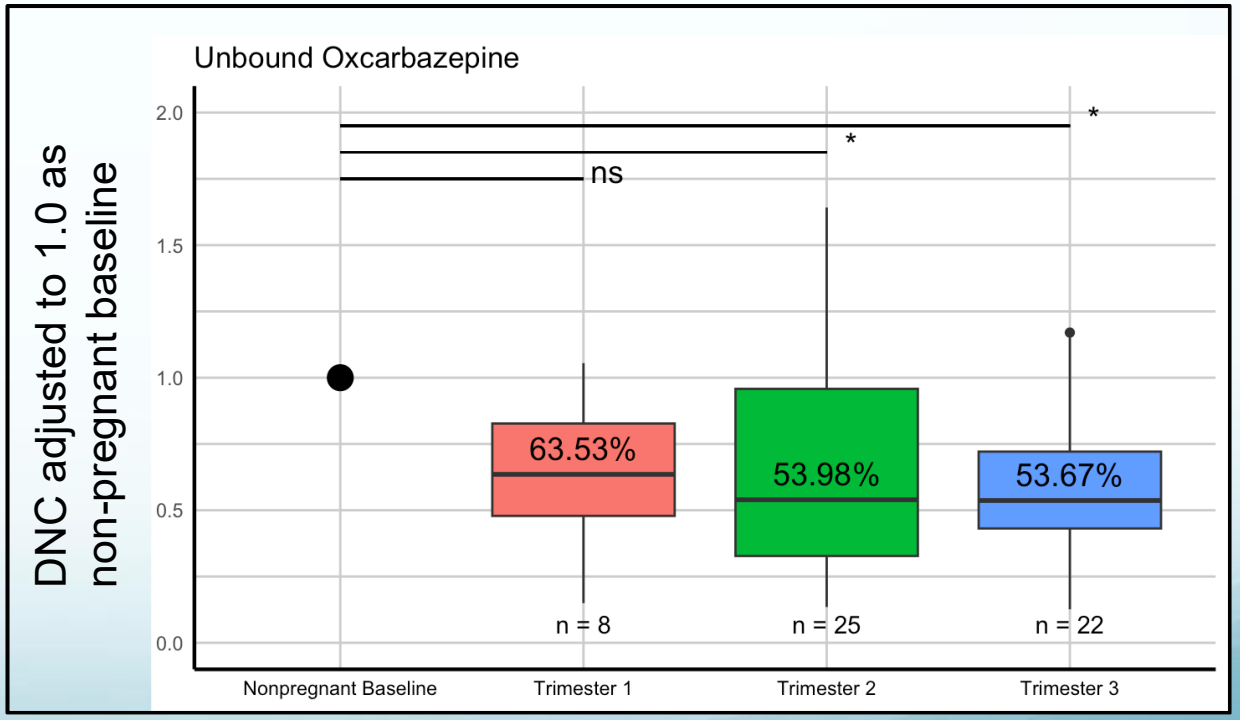
** p < 0.01
*** p < 0.001

Adapted from Pennell PB, Karanam A, Meador KJ, et al. JAMA Neurol. 2022. PMID: 35157004.

Consistent with Voinescu et. al., 2018*

MONEAD findings: Oxcarbazepine (n=20) Dose-Normalized Concentrations during Pregnancy



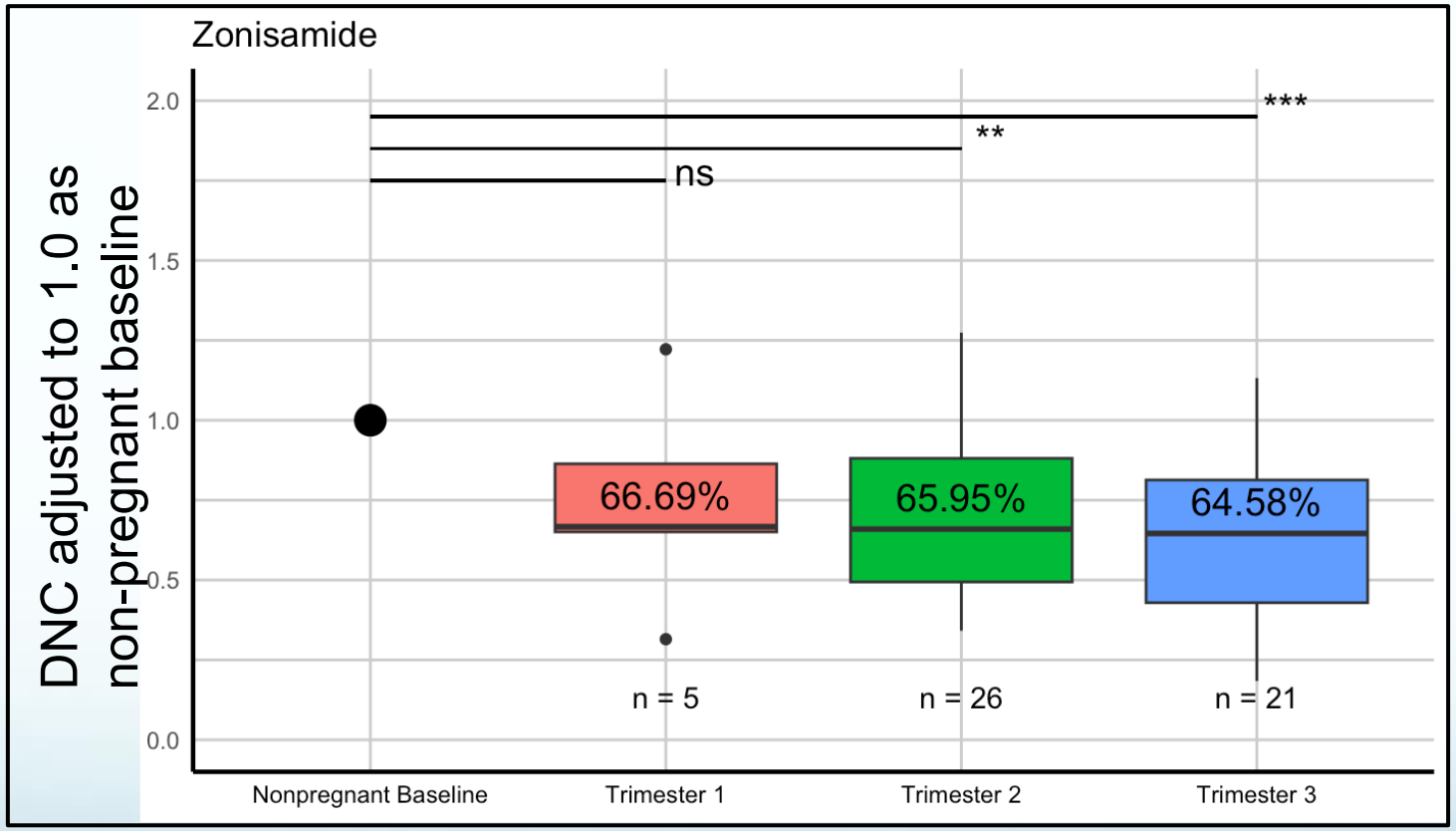


** p < 0.01
*** p < 0.001

Consistent with Voinescu et. al., 2018*

Adapted from Pennell PB, Karanam A, Meador KJ, et al. JAMA Neurol. 2022. PMID: 35157004.

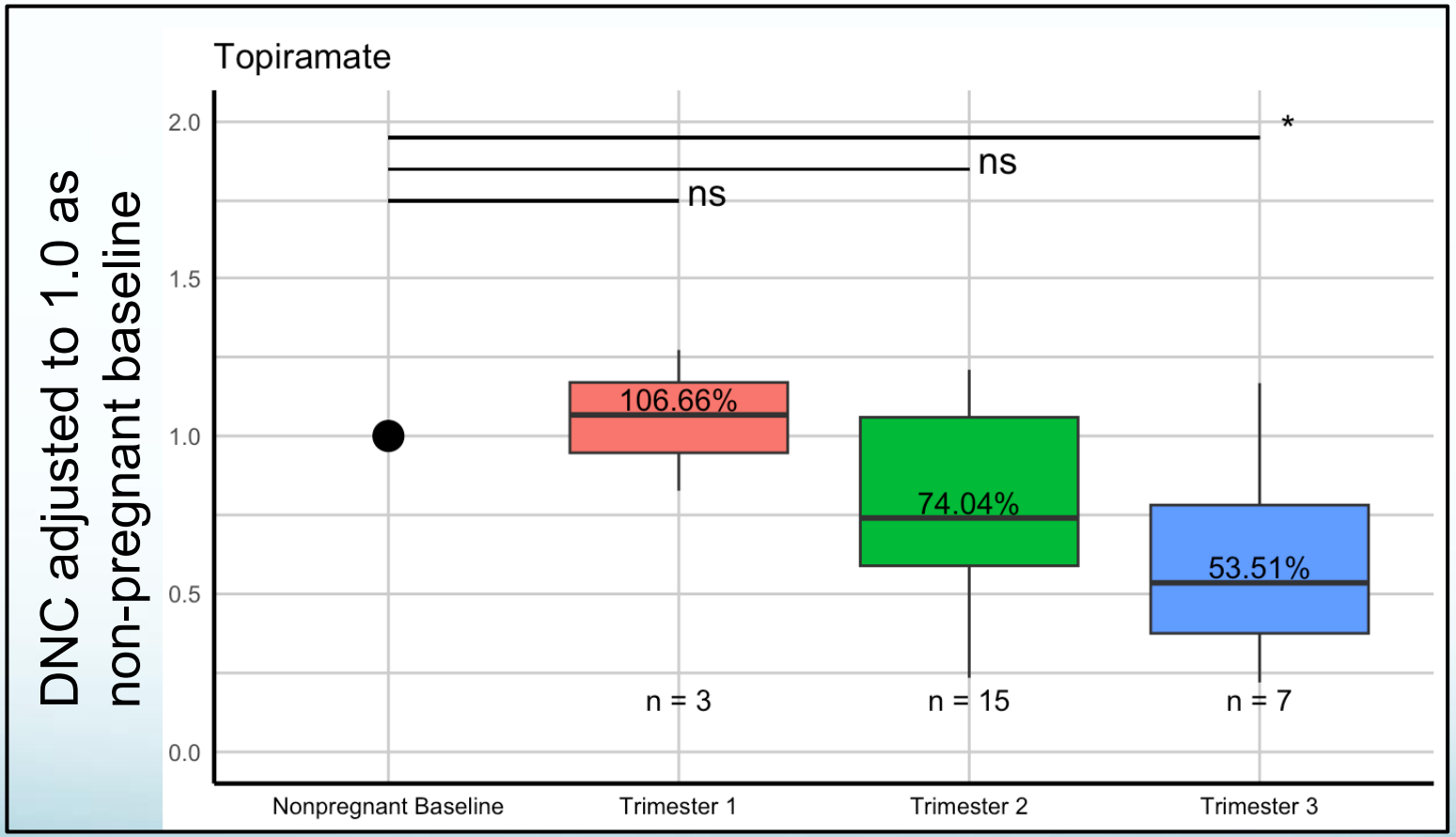
MONEAD findings: Zonisamide (n=22) Dose-Normalized Concentrations during Pregnancy



** p < 0.01
*** p < 0.001

Adapted from Pennell PB, Karanam A, Meador KJ, et al. JAMA Neurol. 2022. PMID: 35157004.

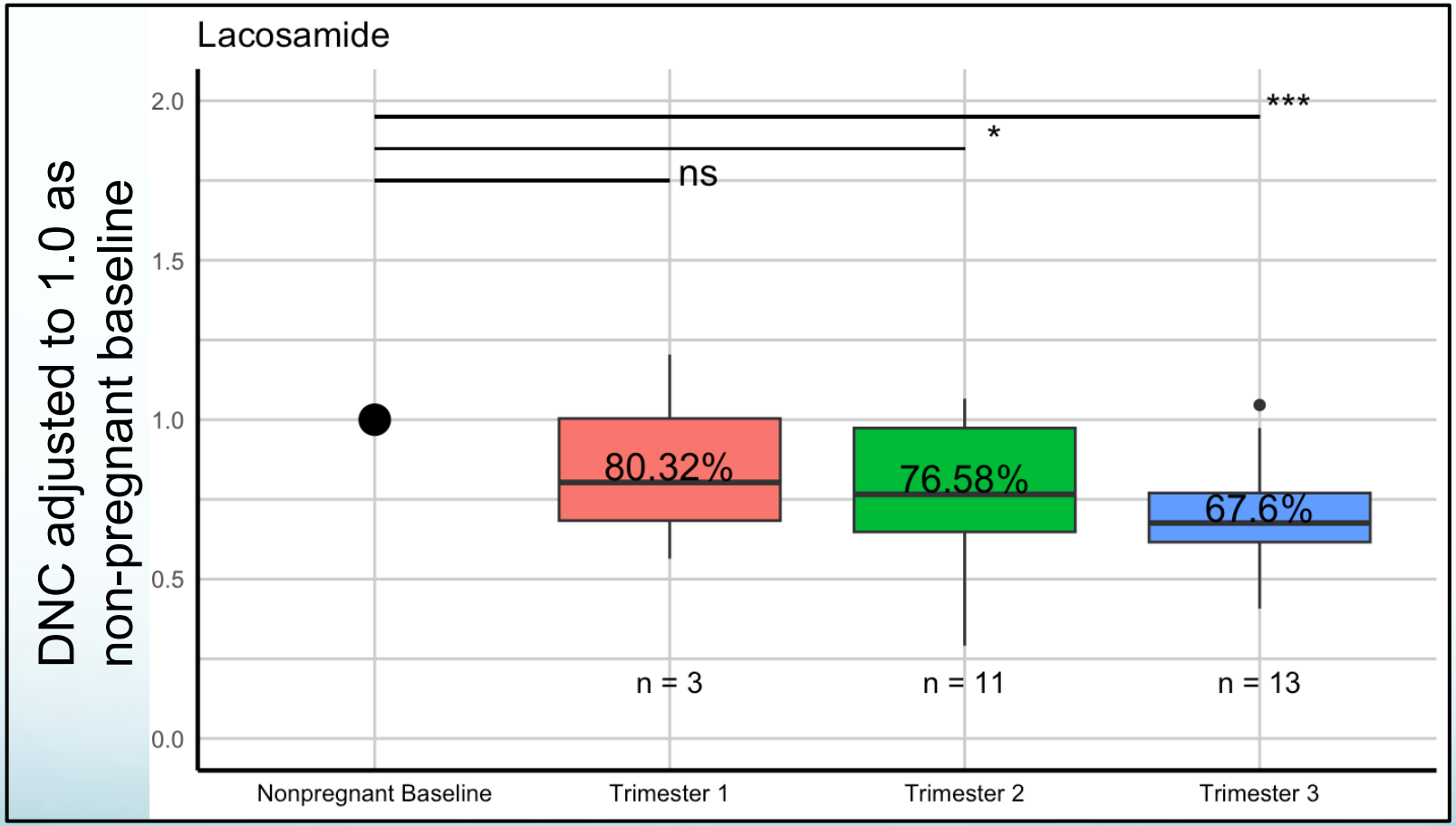
MONEAD findings: Topiramate (n=15) Dose-Normalized Concentrations during Pregnancy



** p < 0.01
*** p < 0.001

Adapted from Pennell PB, Karanam A, Meador KJ, et al. JAMA Neurol. 2022. PMID: 35157004.

MONEAD findings: Lacosamide (n=16) Dose-Normalized Concentrations during Pregnancy



** p < 0.01
*** p < 0.001

Adapted from Pennell PB, Karanam A, Meador KJ, et al. JAMA Neurol. 2022. PMID: 35157004.

Postpartum ASM tapers

- Evidence for empiric taper of LTG over 10 days reduced postpartum toxicity without seizure worsening
  - 4/6 non-adherent vs. 3/21 adherent had pp toxicity (p=0.04)
- Subsequent study demonstrated return to LTG baseline clearance over 2-3 weeks postpartum
- Similar principles can likely be applied to OXC
- Other ASMs less clear, but renal excretion returns to baseline over 2-3 weeks

RESEARCH ARTICLE

Antiseizure Medication Dosing Strategy During Pregnancy and Early Postpartum in Women With Epilepsy in MONEAD

Page B. Pennell,[1] Denise Li,[1] Wesley T. Kerr,[2] Alison M. Pack,[3] Jacqueline French,[4] Elizabeth Gerard,[5] Angela K. Birnbaum,[6] Katherine N. McFarlane,[1] and Kimford J. Meador,[7] for the MONEAD Study Group

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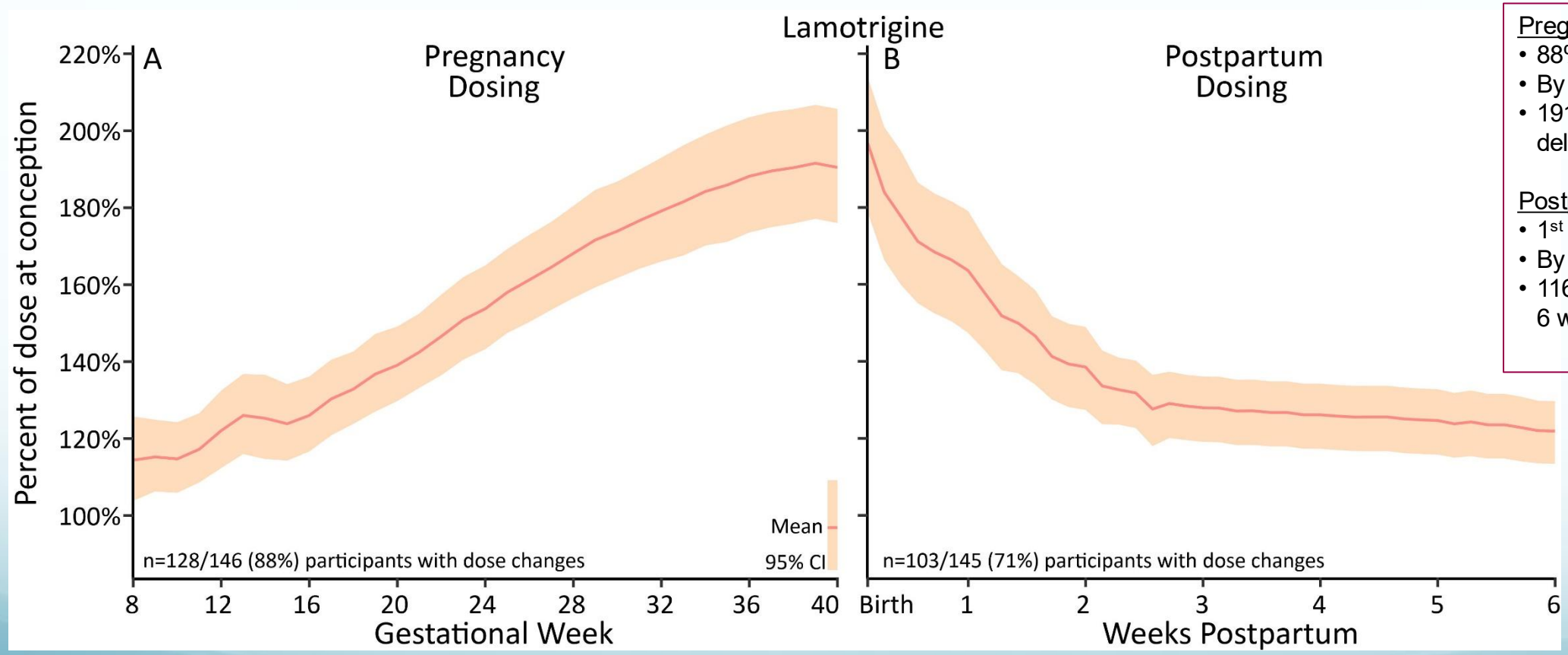
Neurology® 2026;106:e214483. doi:10.1212/WNL.0000000000214483

Ohman, *Epilepsia* 2004; De Haan, *Neurology* 2004; Pennell PB, *Neurology 2008.;* Polepally et al. *Annals Clin & Trans Ngy 2014*.

Lamotrigine Dosing Strategies in MONEAD



Pregnancy
- 88% had doses increased
- By 100mg/day each time
- 191% of conception-dose at delivery

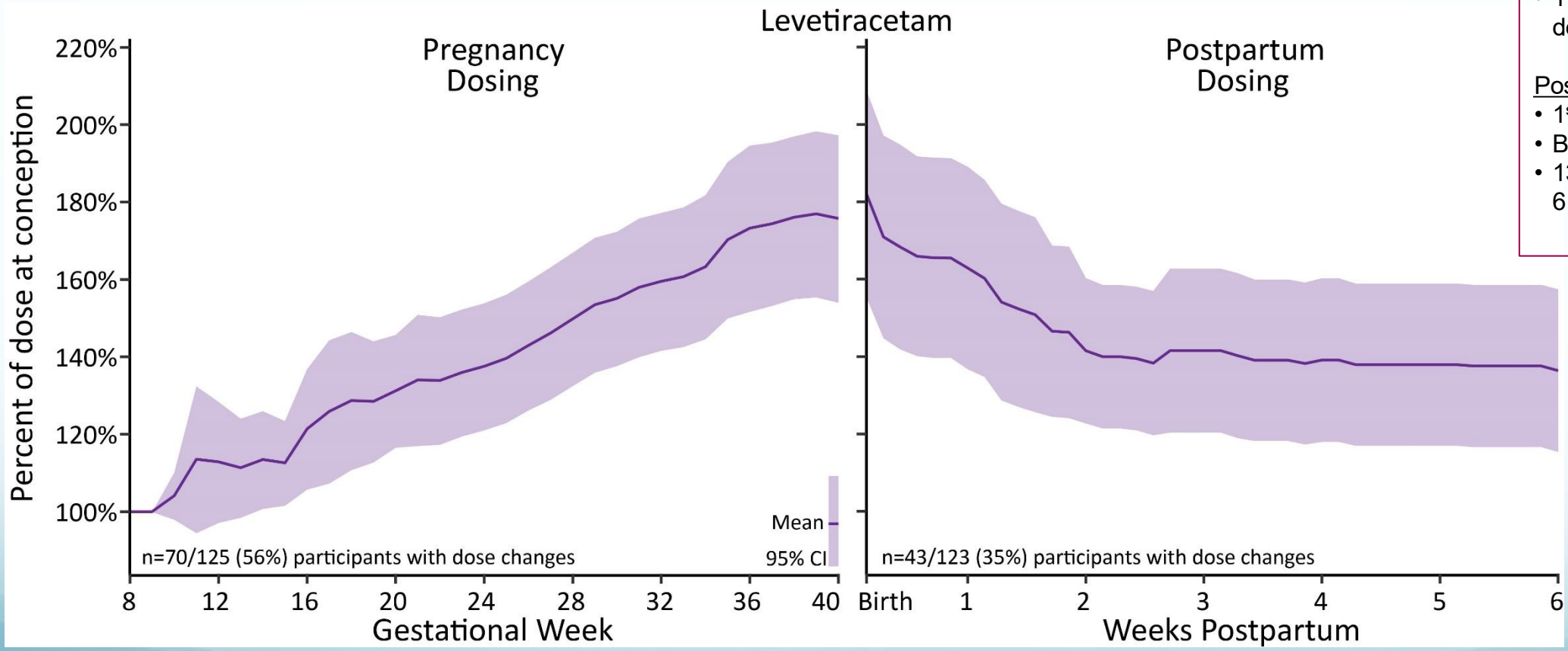
Postpartum
- 1st dose decrease at D2 PP
- By 100mg/day each time
- 116% of conception-dose at 6 weeks PP

Pennell PB, Li D, Kerr WT, Pack AM, French J, Gerard E, Birnbaum AK, McFarlane KN, Meador KJ; MONEAD Study Group. Neurology. 2026 Jan 27;106(2):e214483. doi: 10.1212/WNL.0000000000214483. Epub 2025 Dec 29. PMID: 41461064.

Levetiracetam Dosing Strategies in MONEAD

<u>Pregnancy</u>
- 56% had doses increased
- By 500mg/day each time
- 177% of conception-dose at delivery

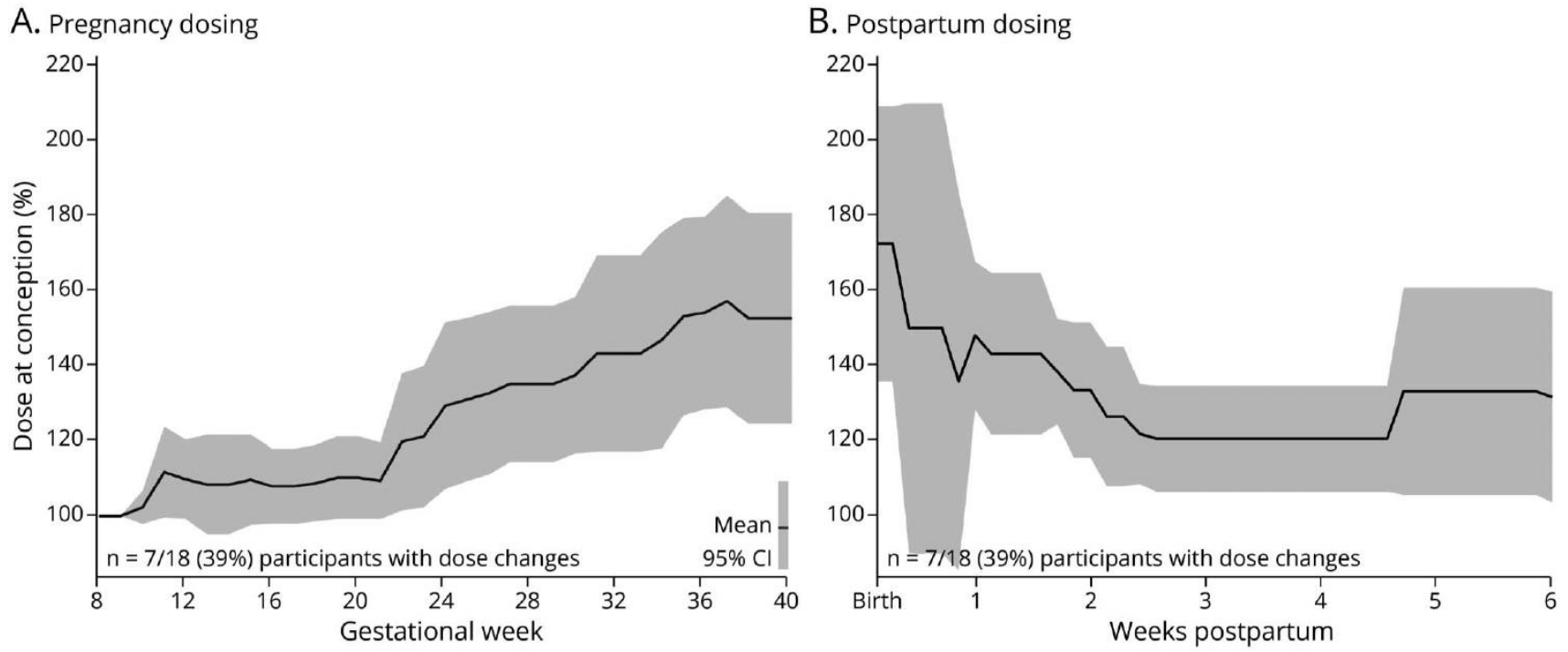
<u>Postpartum</u>
- 1st dose decrease at D3 PP
- By 500mg/day each time
- 136% of conception-dose at 6 weeks PP



Pennell PB, Li D, Kerr WT, Pack AM, French J, Gerard E, Birnbaum AK, McFarlane KN, Meador KJ; MONEAD Study Group. Neurology. 2026 Jan 27;106(2):e214483. doi: 10.1212/WNL.0000000000214483. Epub 2025 Dec 29. PMID: 41461064.

Oxcarbazepine Dosing Strategies in MONEAD

Figure 4 Oxcarbazepine Dosing in Pregnancy and Postpartum



Locally estimated scatterplot smoothing regressions showing the percent of conception dose over time among participants with oxcarbazepine dose changes in pregnancy after enrollment (panel A, 7/18 [39%] participants) and first 6-week postpartum (panel B, 7/18 [39%] participants). The solid line represents the mean, and the gray shading represents the 95% CI. Participants who delivered at or after 34 weeks had their doses at delivery carried forward through gestational week 40 in panel A.

Pregnancy
- 67% had doses increased
- By 300mg/day each time
- 153% of conception-dose at delivery

Postpartum
- 1st dose decrease at D7 PP
- By 300mg/day each time
- 129% of conception-dose at 6 weeks PP

Pennell PB, Li D, Kerr WT, Pack AM, French J, Gerard E, Birnbaum AK, McFarlane KN, Meador KJ; MONEAD Study Group. Neurology. 2026 Jan 27;106(2):e214483. doi: 10.1212/WNL.0000000000214483. Epub 2025 Dec 29. PMID: 41461064.

Breastfeeding in Neurodevelopmental Effects of Anti-Epileptic Drugs study

Theoretical risk to newborn, but exposure is substantially lower than *in utero*

NEAD study and Breastfeeding[1]

- 44% of children were breastfed
- Age 6 yo mean adjusted IQ scores:
  - 4 IQ points higher in the breastfed group for all ASMs
  - 12 IQ points higher in the breastfed group for VPA monotherapy
  - Higher verbal abilities

- Findings supported by other studies, including autistic traits[2]

1. Meador, Baker, Browning, Cohen, Bromley, Clayton-Smith, Kalayjian, Kanner, Liporace, Pennell, Privitera, Loring, NEAD. *JAMA Pediatrics,* 2014.

2. Veiby G, et al., *JAMA Neurol* 2013.

Summary of Review of Evidence

- Increased MCM rates occur with exposure during the 1st Trimester with:
  - Certain ASMs (VPA > PB, PHT, CBZ, TPM)
- Changes in ASM prescribing patterns resulted in lower MCM rates
  - No increase in GTCS or status epilepticus
- In utero VPA exposure throughout the entire pregnancy is associated with:
  - Lower FSIQ and verbal scores
  - Higher rates of educational needs and of autism & ASD
- In utero exposure to some other ASMs appears favorable, but some indication of exposure-dependent effects
- Folic acid beginning periconceptional can lower neurodevelopmental risks
- Clearance of almost all ASMs increases during pregnancy
- Seizure Stability is possible with active management
- Obstetric Outcomes can be similar to healthy pregnant women
- Breastfeeding is safe and should be supported

MONEAD Study Group

supported by NINDS & NICHD (U01-NS038455, U01-NS050659, and 2U01-NS038455)

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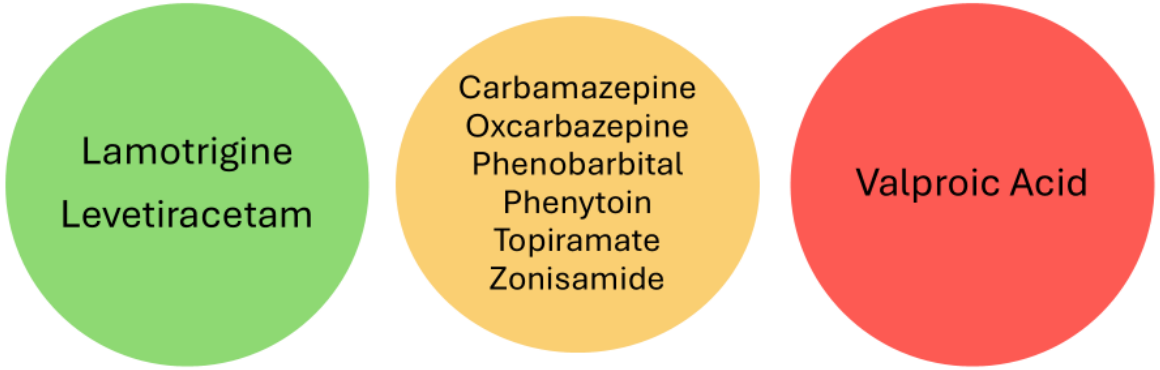
Summary of current data available
*only accounts for 9 of 32 ASMs

Risk of Major Congenital Malformations

For detailed malformations estimates see AAN guidelines (LINK)

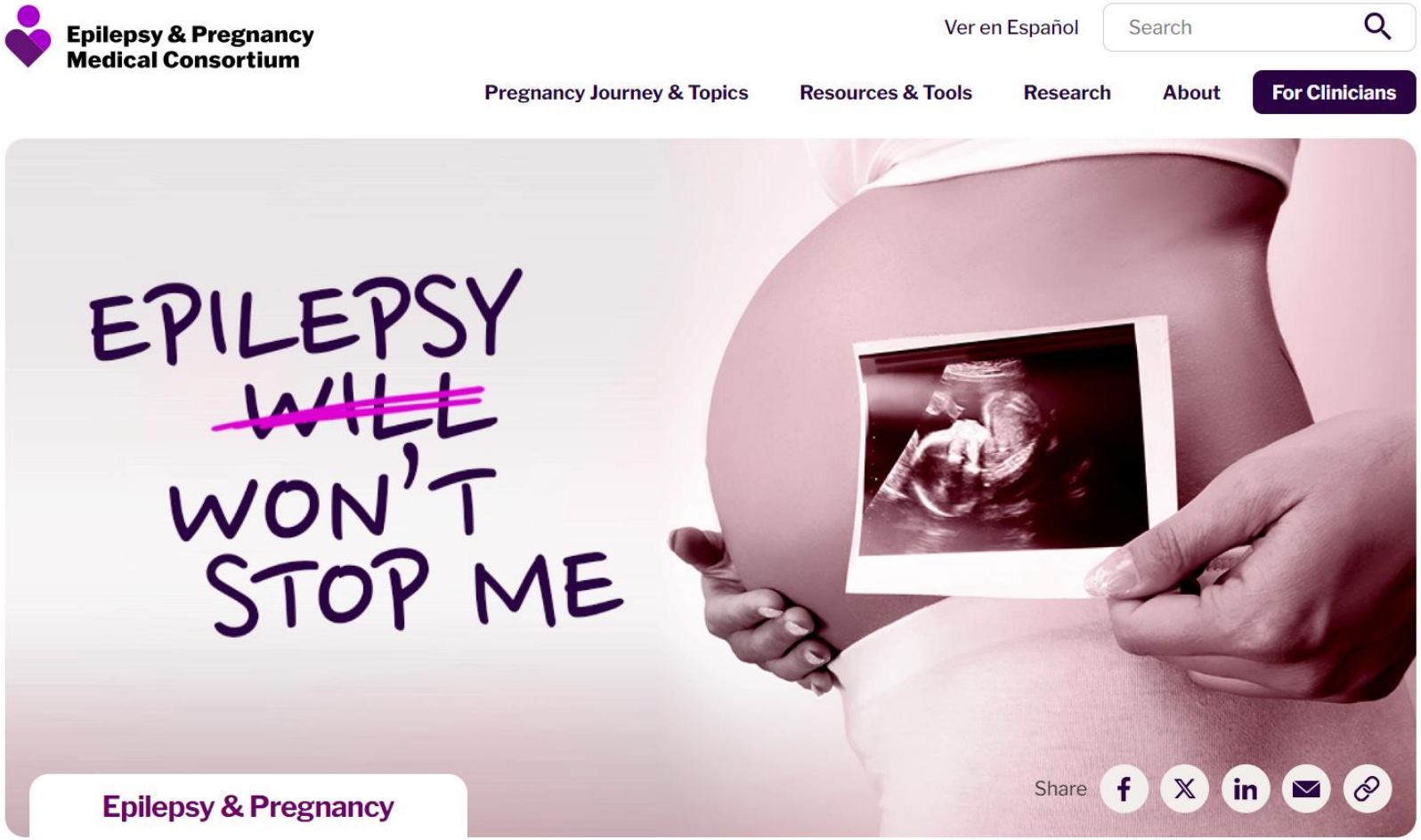
Risk of Adverse Neurodevelopmental Outcomes



Established Low Risk

Mixed data/ Some risk

Established High Risk



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Clinical Neurological Society of America

Questions

Additional updates to slides and other articles to consider

- Fi verify if the graphs with LTG and LEV dose-responses are adjusted for all of the important covariates
- Update reference for the Ngy dosing paper- go through details again, such as mean or median
- Insert information from recent VPA use article that Kim sent