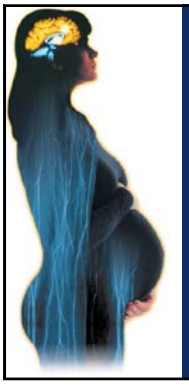


Epilepsy and Pregnancy

Southern Epilepsy and EEG Society

Page B. Pennell, MD
Professor, Harvard Medical School
Director of Research, Division of Epilepsy
Department of Neurology,
Division of Women's Health
Brigham and Women's Hospital
Boston, MA

Magnitude

- 1.3 million women of child-bearing age in US with epilepsy[1]
  - One of the most common disorders requiring daily dosing w/known teratogen
  - Approximately 25,000 AED-exposed babies per year born in US to WWE
- 4.3 million AED prescriptions annually to women of childbearing age
- Prenatal AED exposure rates = 2.19%, with varied maternal dx[3]
  - mental illness (48%), pain disorders (22%), epilepsy (21%)
- Clinical dilemma of minimizing teratogenic effects of AED exposure while maintaining maternal disease control

Pregnancy planning w/optimization of med type, dose, & FA is key

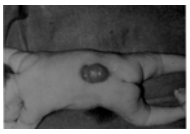
1. Meador KJ, et al. *Neurology*. 2008; 2. Holmes LB, et al. *N Engl J Med*. 2001;344(15):1132-1138.; 3. Bobo WV, et al. *PaediatrPerinatEpidemiol* 2012. 4. Adedinsewo DA, et al., Birth Defects Research (Part A) 2013.

Disclosures

- Commercial Interests: None
- Dr. Pennell has received research support from the Epilepsy Foundation, the Epilepsy Therapy Project, the Milken Family Foundation, Harvard Catalyst and the National Institutes of Health
- Dr. Pennell has received travel support and/or honoraria from the American Epilepsy Society, American Academy of Neurology, International Association of Therapeutic Drug Monitoring and Clinical Toxicology, the National Institutes of Health, and governmental and academic institutions for CME lectures

Spina bifida is a neural tube defect (NTD) involving incomplete formation of the spine

Spina Bifida



Day 17-18 after conception the neural tube starts forming

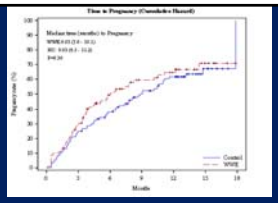
(3 days after the missed menstrual period)

A Precise Balancing Act: Benefits versus Risks of AEDs during Pregnancy

- Teratogenic effects on offspring significant[2]
  - Increased risk for major congenital malformations in offspring of women on AEDs (OR 3.9 (1.29-11.9))
- Neurodevelopmental defects common, with lifelong consequences
- Risk for adverse OB and Neonatal outcomes may also be higher
- Growing evidence that not only *type* of AED but *amount* of AED impacts level of risk

Clinical dilemma of minimizing teratogenic effects of AED exposure while maintaining maternal seizure control

WEPOD Study



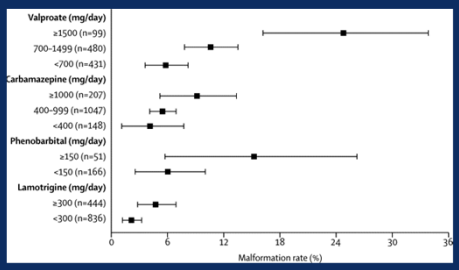
Study of WWE and healthy controls without any diagnoses of infertility or related factors, enrolled <6 months of D/C of contraception:

- Among 89 WWE, 60.7% achieved pregnancy vs. 60.2% for 108 controls.
- Median time to pregnancy was no different between groups (p=0.30)
- Sexual activity & ovulatory rates were similar in WWE and HC.
- 81.5% of pregnancies resulted in live births in both groups.
  - No differences in miscarriage rates.
- A trend for women on EIAEDs being less likely to achieve pregnancy compared to other medications (HR 0.457; 95% CI 0.19-1.08).

Pennell PB, French JA, Harden CL, JAMA Neuro, *in press.*

Pregnancy & Postpartum Care in Women with Epilepsy

EURAP: Number of offspring with MCMs for the four monotherapies at different doses at conception (mg per day), (rate, 95% CI)



Tomson T, et al. *Lancet Neurol* 2011;10(7):609-17.

AED Pregnancy Registries

Prospective studies of anatomical defects and major adverse outcomes

- **EURAP: An international registry of AEDs and pregnancy**
- **North American AED Pregnancy Registry**
- **UK Epilepsy and Pregnancy Registry**
- **Australian Pregnancy Register**
- **Kerala Pregnancy Registry, India**
- **Pharmaceutical company registries**

Treatment of Women

Polytherapy rule: true or not so true?

LTG polytherapy (n=505)
- LTG plus VPA: 9.1% (OR, 5.0; 95% CI, 1.5-14.0)
- LTG plus any other AEDs: 2.9% (OR 1.5; 0.7-3.0)

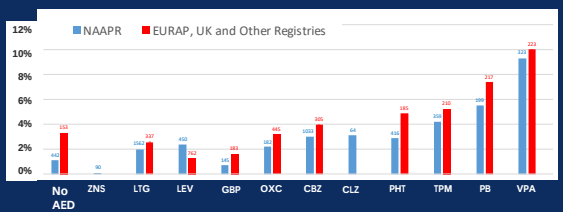
CBZ polytherapy (n=365)
- CBZ plus VPA: 15.4% (OR, 6.2; 95% CI, 2.0-16.5)
- CBZ plus any other AED: 2.5% (OR 0.8; 0.3-1.9)

LEV polytherapy (n=367) (6.5%; CI 4.3-9.6%)
- Highest with CBZ (9.4% (CI 4.4-19.0%))
- High with VPA (6.9% (CI 1.9-22.0%)
- Low with LTG (1.8% (CI 0.5 – 6.2%)

Increased risk for polytherapies may be based on which AEDs are combined

Holmes LB, et al. *Arch Neurol* 2011; Mawhinney E, et al. *Neurology* 2013.

Major Congenital Malformation Rates in NAAPR and EURAP and other registries



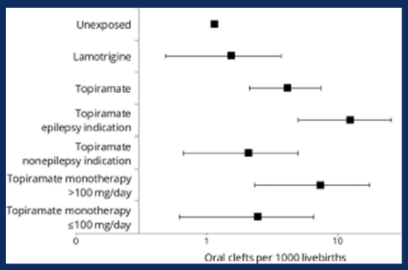
Voinescu PE, Pennell PB, Seminars in Neurology, 2017.

Topiramate Pregnancy Outcomes

- MCM rates reported as 4.2 - 4.9%
- Increased cleft lip/palate risk of 4.1 - 29/1000
- Increased risk for LBW (Israeli Teratogen IS, 2008)
- 17.9% of TPM monoRx infants were SGA (NAAPR)
  - SGA RR = 2.4 (95% CI 1.8-22) compared to LTG
- Dose response relationship reported in Aust PR
- 14.1% MCM in polyRx in Aust PR [RR 4.2 (1.57; 11.05)]
- Commonly prescribed for migraines and weight loss
- 03/04/11: FDA label change to Pregnancy Category D

Hernandez-Diaz S, NAAPR, OBGyn 2014; Mølgaard-Nielsen and Hviid, 2011; Hunt, Morrow, UK Epil Preg Reg, 2006, 2008; Ornoy, Israeli Teratogen IS, 2008; Vajda, Australian Register of AEDs in Pregnancy 2012; Vajda F, Acta Neurol Scan 2014; Hernandez-Diaz, Neurology 2017.

Topiramate and Oral Clefts



Population-based study nested in the US 2000–2010 Medicaid Analytic eXtract

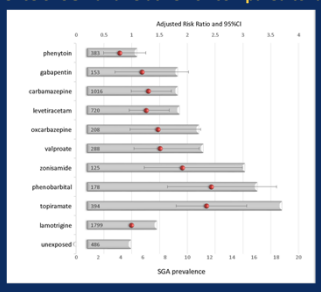
Hernandez-Diaz, Neurology 2017.

2009 AAN/AES PPUpdate on Neurodevelopmental Outcomes

- Cognition is probably *not* reduced in children of untreated WWE.
- CBZ probably does *not* increase poor cognitive outcomes compared to unexposed controls.
- Monotherapy exposure to VPA probably reduces cognitive outcomes, and monotherapy exposure to PHT or PB possibly reduces cognitive outcomes.
- AED polytherapy exposure probably reduces cognitive outcomes as compared to AED monotherapy.

1. Gaily E, et al. *Neurology*. 2004;62(1):28-32. 2. Holmes LB, et al. *Teratology*. 2000;61(3):196-202. 3. Reinisch JM, et al. JAMA. 1995;274(19):1518-1525. 4. Adab N, et al. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1575-1583. 5. Vinten J, et al. *Neurology*. 2005;64(6):949-954. 6. Adab N, et al. *J Neurol Neurosurg Psychiatry*. 2001;70(1):15-21. 7. Harden CL, et al. *Neurology* 2009.

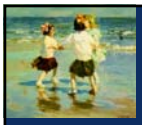
Prevalence of SGA and relative risk compared to lamotrigine



Findings were similar in WWoE on AEDs.

The risk of prematurity was 6.2% for no-AED-WWOE, 9.3% for AED-WWE (RR 1.5, 95%CI: 1.0-2.1) and 10.5% for AED-WWOE (RR 1.5: 1.0-2.4).

Hernandez-Diaz S et al: *Ann Neurol* 2017; 82:457-465.



NEAD STUDY DESIGN

NIH/NINDS #2RO1 NS 38455
NIH/NINDS #1 R01050659
UK Epilepsy Research Foundation #RB219738

- Multicenter prospective, parallel-group observational study with statistical control.
- 309 pregnant mothers with epilepsy enrolled from late 1999 to early 2004 in USA & UK.
- Antiepileptic drug (AED) monotherapy:
  - Carbamazepine (CBZ)
  - Lamotrigine (LTG)
  - Phenytoin (PHT)
  - Valproate (VPA)
- Blinded cognitive assessments: 2, 3, 4.5, & 6 y/o
- Primary outcome: IQ at 6 y/o

Polytherapy, take 2

- Kerala Registry of Epilepsy and Pregnancy
- Dual therapy during TM1, 1998-2013
- Relative Risk to lamotrigine monotherapy
- N=368 (of 1688) pregnancies
- RR of dual therapy to LTG monoRx = 1.6 (p=0.0015)
  - Renal, alimentary, skeletal MCMs more likely than monoRx
  - RR highest for TPM dual therapy= 14.82 (95% CI: 1.88-113.83))
  - Reduction in RR of MCM when TPM or VPA were excluded
- No MCMs with LTG & LEV dual therapy

Keni RR, Thomas SV. *Neurology*, ePub Feb 02, 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 & folate:

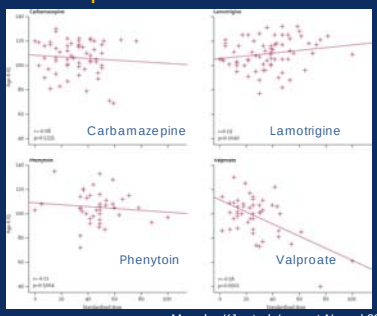
	CBZ	LTG	PHT	VPA
Mean IQ	**105 ***	**108 ***	**108 ***	**97**
Difference	**7**	**10**	**10**	
DCIs	(3:12)	(6:15)	(5:16)	
# Children	93	100	56	62

* Significantly better than VPA.

CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate

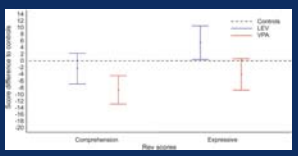
Meador KJ, et al. *Lancet Neurol* 2013;12:244-52.

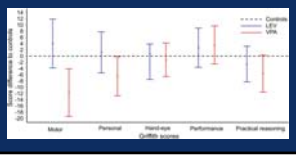
Dose-Dependent Effects in NEAD



Meador KJ, et al. *Lancet N*eurol 2013;12:244-52.

In Utero LEV vs VPA: testing at 3yo

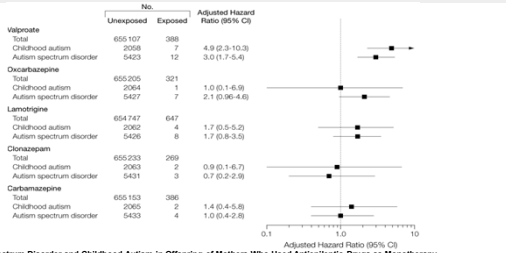




Shallcross R, et al. *Neurology* 2014.

The JAMA Network

From: Christensen J, et al. **Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism**
JAMA. 2013;309(16):1696-1703. doi:10.1001/jama.2013.2270



Autism Spectrum Disorder and Childhood Autism in Offspring of Mothers Who Used Antiepileptic Drugs as Monotherapy

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

Child IQ & Periconceptional Folate

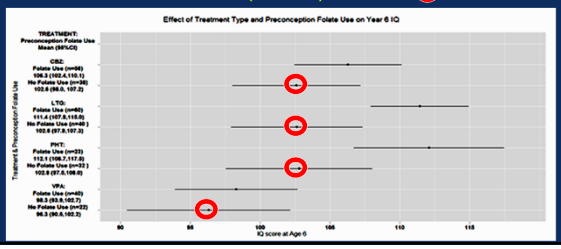
F=11.4, p<.0009

Adjusted Mean IQs (95% CIs):

Folate 108 (106, 111)

No Folate 102 (98, 104)

= No Folate



May 13, 2013: FDA Drug Safety Communication: Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children

- VPA's pregnancy category for migraine use will be changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug).
- With regard to… epilepsy or bipolar disorder, valproate products should only be prescribed if other medications are not effective in treating the condition or are otherwise unacceptable. Valproate products will remain in pregnancy category D for treating epilepsy and manic episodes associated with bipolar disorder.

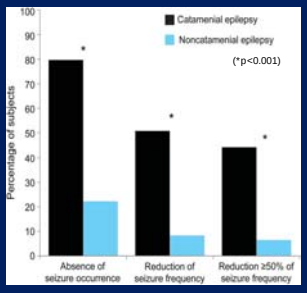
Association of Folic acid Supplementation with risk of Autistic Traits

- Population-based, prospective Norwegian Mother and Child Cohort study
- Children exposed in utero to AED, June 1999-Dec 31, 2008
  - Children 18-36 mos (n=104,946; 335 exposed to AEDs)
- Folic acid 4 weeks prior to and 12 weeks after conception
- MCHAT questionnaire
- Adjustments for maternal health and SES
- AOR = 5.9 (CI 2.2-15.8) at 18 mos and AOR = 7.9 (CI 2.5-24.9) at 36 mos for the AED-no folate group compared to the AED-folate group.
- Folate benefit still present but to lower degree in the WWoE
- Degree of autistic traits inversely associated with folate concentrations (17-19 weeks GA) and folic acid doses.
- 60.4% were on folic acid >0.4 mg per day

Bjork M, Gilhus NE, *JAMA Neurol*, epub 12/28/2017.

Risks of Seizures versus Antiepileptic Drugs

Course of Seizures during Pregnancy



Cagnetti, C. et al. *Neurology* 2014.

Risk of Seizures

Generalized Tonic-Clonic Convulsions

- 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)

Status epilepticus

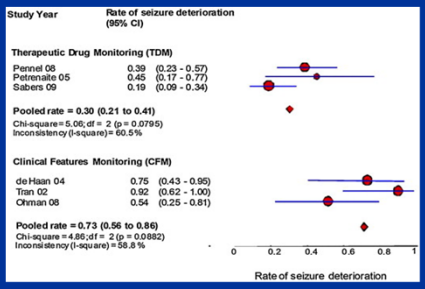
- 30% maternal mortality; 50% infant mortality

Maternal Risks

- Death rate during pregnancy in WWE 10-fold higher (SUDEP)
- 11.5 OR [95% CI, 8.64-15.19]), of death during delivery hospitalization

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; Macdonal SC, et al. JAMA Neurol 2015.

Effects of TDM with LTG in Pregnancy



Pirie DAJ, et al. EJOGRB 2014.

Seizure Frequency Change compared to Non-pregnant baseline

- **Studies report that 20-50% (9-75%) of women have seizure worsening during pregnancy compared to baseline**
- **Depends on several factors:**
  - Baseline seizure frequency, in prior month or 9-12 months
  - Seizure types (Focal > Generalized)
  - AEDs at beginning of pregnancy (LTG, OXC, Polytherapy)
  - Use of Therapeutic Drug Monitoring
  - Patient Adherence
  - Other factors less known: sleep, stress, neurosteroids
  - Varies with GA in pregnancy and peripartum (Thomas SV)

Pennell PB, Ngy 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.

Physiological Changes in Pregnancy: Effects on Drug Disposition

Parameter	Consequences
↑ Total body water; xtc fluid	Altered drug distribution
↑ Fat stores	↓ Elimination of lipid soluble drugs
↑ Cardiac output	↑ Hepatic blood flow; ↑ elimination
↑ Increased RBF; ↑ GFR	↑ Renal clearance of unchanged drug
Altered CYP/UGT activity	Altered systemic absorption &/or hepatic elimination of 50% of drugs
↓ Maternal albumin	Altered free fraction; increased hepatic extraction

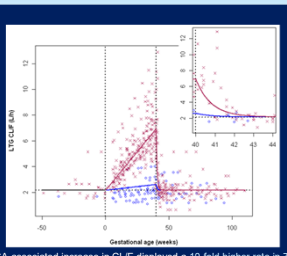
Pennell PB. *Neurology*. 2003;61(6 Suppl 2):S35-42.

Clearance

Daily dose (mg/kg)

AED concentration (mg/L)

Post hoc estimates of LTG CL/F increase during pregnancy
Maroon data points: subjects w/ high rate of increase (population I)
Blue data points: subjects w/ low rate of increase (population II)



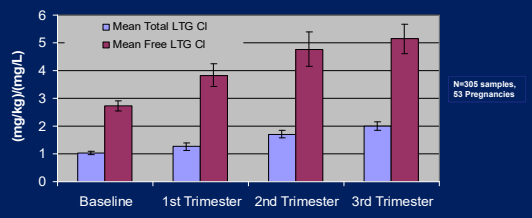
Pop. I: 219% ⬆

Pop II: 21% ⬆

The GA-associated increase in CL/F displayed a 10-fold higher rate in 77% of the women (0.118 L/h per week) compared to 23% (0.0115 L/h per week).

Rolepally Pennell, Birnbaum. *Annals of Clin & Translational Neurology 2014.*

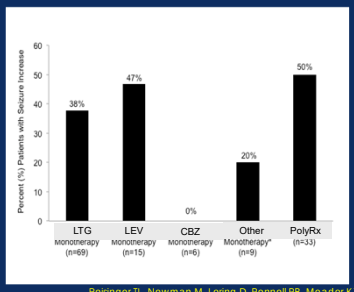
Total and Free LTG Clearance Across Pregnancy



N=305 samples, 53 Pregnancies

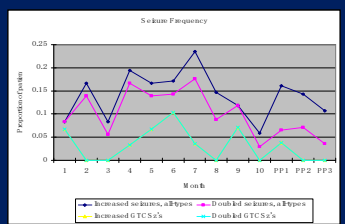
Pennell PB, et al. *Neurology*, 2008. Funded by NIH P50 MH68036.

Clinical impact of Gestational-induced Changes in Clearance



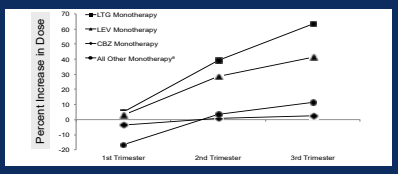
Reisinger TL, Newman M, Loring D, Pennell PB, Meador KJ. Epil & Beh 2013.

Proportion of Patients That Had Worsening of Seizures Above Their Baseline With the Use of TDM



- Ratio to target concentration of 0.65 predicts increased seizure risk
- Empiric taper of LTG over 10 days reduced postpartum toxicity (p<0.05)

Pennell PB, et al. *Neurology 2008*. Supported by NIH P50 MH68036.



Women with epilepsy on a variety of AEDs
Risk for seizures deterioration higher in
a) patients w/ seizures in previous 12 months
b) focal epilepsy

Seizures worsened signifcantly during the 2nd trimester
a) when ABL < 65% from preconception baseline

Reisinger TL, Newman M, Loring D, Pennell PB, Meador KJ. Epil & Beh 2013.

CBZ Clearance and Seizure Stability during Pregnancy

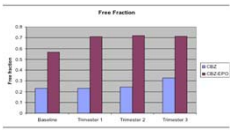
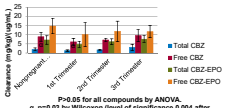


Figure 1. Increase in Free Fraction of CBZ and CBZ-EPO throughout pregnancy (p<0.05)

- RTC <0.65 not correlated with increased SzF for total or free CBZ or CBZ-EPO concentrations

Johnson E, et al. Epilepsy Behav 2014

CBZ Clearance by stage of pregnancy



P>0.05 for all compounds by ANOVA.
α p=0.03 by Wilcoxon (level of significance 0.004 after Bonferroni correction)

Discussion:

- The increase in free fraction of CBZ & CBZ-EPO during pregnancy may help protect against seizure worsening.
- There was no clear relationship between decreased concentrations & increased SzF.
- TDM of CBZ during pregnancy may not be necessary when resources are limited.

Supported by NIH P50 MH68036.

PRELIMINARY DATA FROM SCOR, MONEAD, P-PEP

Breastfeeding

- Consider combination of breast and bottle-feeding to avoid extreme sleep-deprivation
  - *My Suggested Strategy*: Family support to obtain ≥ 4 hours of uninterrupted sleep and ≥ 6 hours total /24 hours
- Theoretical risk to newborn, but exposure is substantially lower than *in utero*

NEAD study and Breastfeeding

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

Meador, et al. *JAMA Pediatrics*, 2014.

MONEAD Study

Maternal Outcomes & Neurodevelopmental Effects of Antiepileptic Drugs

MONEAD

https://web.emmes.com/study/monead/

Funded by NIH/NINDS #2U01-NS038455 and U01-NS050659

20 sites

Postpartum AED 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 AEDs less clear:
  - CyP450 metabolism change to baseline over 3 mos., based on data with PHT
  - Renal excretion returns to baseline over 2-3 weeks

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

MONEAD Study

MONEAD

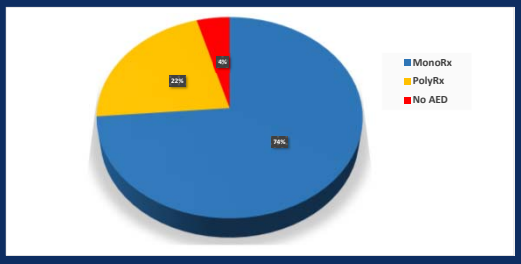
Multiple-PIs:
Kimford Meador, MD (Stanford)
Page B. Pennell, MD (BWH)

Funded by NIH/NINDS,NICHD
#U01-NS038455

- **MATERNAL OUTCOMES:**
  Risks in WWE during pregnancy & postpartum
  - **Seizures**
  - **OB Complications** (e.g., C section)
  - **Depression** (pregnancy & postpartum)
- **OUTCOMES in CHILDREN of WWE:**
  - **Neurodevelopment** (cognitive & behavioral)
  - **Neonatal Outcomes** (e.g., SGA)
  - **Breastfeeding** (effects if WWE taking AED)
- **Pharmacokinetics:** Relation of AED exposure & outcomes
- Supplemental studies include genomics and metabolomics

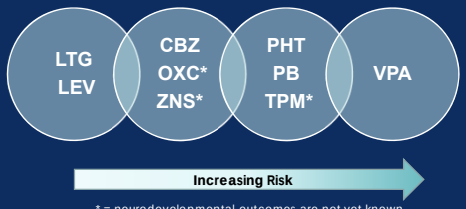
PWWE=Pregnant Women with Epilepsy (n=351) & their children (n=345);
HPW=healthy pregnant women (n=105) & their children (n=106);
NPWWE=Non-Pregnant WWE (n=109)

Number of AEDs in Pregnant Women With Epilepsy



Supported by NIH NINDS, NICHD #U01-NS038455 (Meador, Pennell) and U01-NS050659 (May).

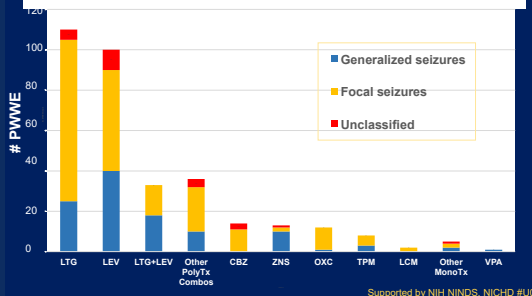
Teratogenic Risk Profiles of Antiepileptic Drugs



Increasing Risk

* = neurodevelopmental outcomes are not yet known

Use of Specific AEDs in PWWE



Supported by NIH NINDS, NICHD #U01-NS038455 (Meador, Pennell) and U01-NS050659 (May).

Collaborators

Kimford Meador, M.D.
Angela Birnbaum, Ph.D.
Ryan May, PhD
Adam Hartman, MD,
Deborah Hirtz, MD
P. Emma Voinescu, MD, PhD
Jacqueline French, MD
Cynthia Harden, MD
Zachary N. Stowe, MD
D. Jeffrey Newport, MD
Limin Peng, PhD
Lewis B. Holmes, MD
Sonia Hernandez-Diaz, MD, PhD
Tom McElrath, MD, PhD
Linda Van Marter, MD, MPH.
Morris Cohen, PhD
David Loring, PhD
Alison Pack, MD, MS

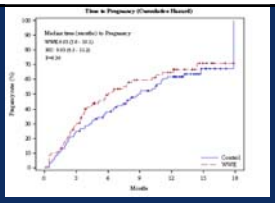
Elizabeth Gerard,MD
Laura Kalayjian, MD
Patricia Penovich, MD
Evan Gedzelman, MD
Jennifer Cavitt, MD
Michael Privitera, MD
David Labiner, MD
Maria Sam, MD
Emily Johnson, MD
Greg Krauss, MD
Naymee Velez-Ruiz, MD
Suzanne Strickland, MD
Jennifer DeWolfe, MD
Paul McCAbe, MD
Greg Barkley, MD
Sean Hwang, MD
Anto Bagic, MD
Enrique Serrano, MD
John Miller, MD

Guiding Principles for AED Management in Pregnancy

- ***Preconception***
  - ✓ Transition to AED with favorable teratogenic profile
  - ✓ Establish individual target concentration
  - ✓ Lower dose as needed, with adjustment after D/C of any contraceptives
- ***Pregnancy***
  - ✓ Monthly AED levels for therapeutic drug monitoring
  - ✓ Adjust dose for seizures, SEs, and to maintain **RTC > 0.65**
- ***Postpartum***
  - ✓ Adjust dose to (slightly above) pc baseline over 2 weeks – 3 months, depending on AED
  - ✓ Educate about newborn care and importance of sleep
  - ✓ Breastfeeding plan when desired
  - ✓ Educate about clinical signs of medication toxicity

Thank you for your attention!

WEPOD Study



Study of WWE and healthy controls without any diagnoses of infertility or related factors, enrolled <6 months of D/C of contraception:

- Among 89 WWE, 60.7% achieved pregnancy vs. 60.2% for 108 controls.
- Median time to pregnancy was no different between groups (p=0.30)
- Sexual activity & ovulatory rates were similar in WWE and HC.
- 81.5% of pregnancies resulted in live births in both groups.
  - No differences in miscarriage rates.
- A trend for women on EIAEDs being less likely to achieve pregnancy compared to other medications (HR 0.457; 95% CI 0.19-1.08).

Pennell PB, French JA, Harden CL, JAMA Neuro, *in press.*