



# Gender Issues & Bone Health for People with Epilepsy

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COLUMBIA UNIVERSITY  
MEDICAL CENTER

*Discover. Educate. Care. Lead.*



**Columbia Comprehensive  
Epilepsy Center**

**at New York Presbyterian Hospital**

# Outline

- Reproductive health
- Contraception
- Pregnancy
- Bone Health

# Reproductive Function: Females

- Steroid hormone changes
  - AEDs
    - Enzyme inducing AEDs (eg Dilantin and Tegretol) reduce some reproductive hormones
    - Depakote increases testosterone
  - Epilepsy type
    - Some reproductive hormones lower in females with temporal lobe epilepsy
- “Polycystic ovarian like syndrome”
  - Common in population
  - May be more common in females with epilepsy

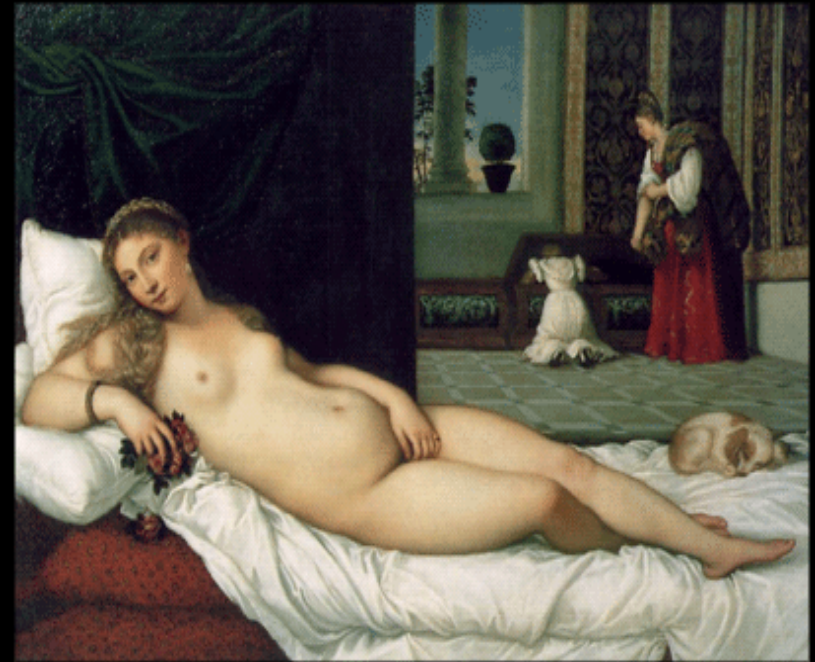


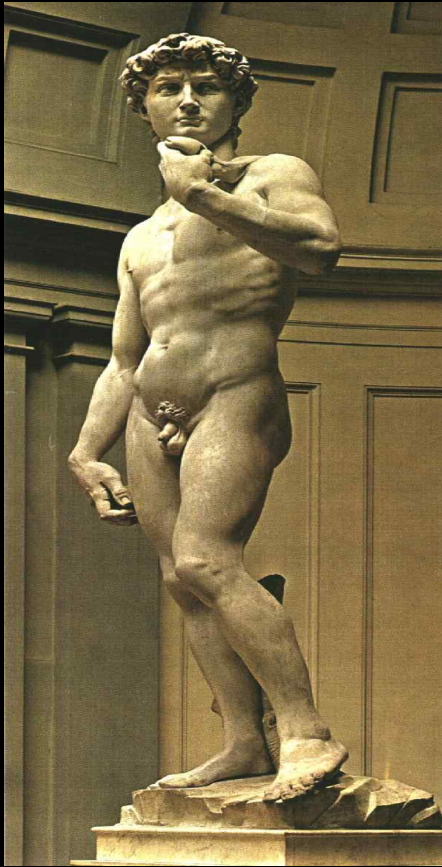
Figure 1

# Polycystic Ovary Syndrome

- Syndrome defined by:
  - Hirsutism, obesity, acne
  - Elevated androgens and LH/FSH ratio
  - Chronic anovulation
  - Insulin resistance
- Polycystic ovaries
- Syndrome associated with:
  - Carbohydrate intolerance
    - Weight gain
  - Elevated LDL and reduced HDL
  - 3× increased risk for endometrial cancer
  - Sleep apnea



# Reproductive Function: Male



- Reduced fertility and virility
- Decreased sexual interest
- Hormonal alterations
  - Lower testosterone and other reproductive hormones: enzyme inducing AEDs eg Dilantin and Tegretol
  - Elevated androgens (testosterone): Depakote
- Effects on sperm quality
  - Lower sperm concentration: Tegretol
  - Morphologically abnormal sperm: Tegretol, Trileptal, Depakote
  - Poor sperm motility: Tegretol, Depakote
- Reduced testicular volume

Herzog et al. *Epilepsia*. 2004 Jul;45(7):764-8. Rattya et al. *Neurology*. 2001 Jan 9;56(1):31-6. Roste et al. *Eur J Neurol*. 2005 Feb;12(2):118-24. Bauer et al. *Neurology*. 2004 Jan 27;62(2):243-6. Isojarvi et al. *Neurology*. 2004 Jan 27;62(2):247-53.

# Contraception

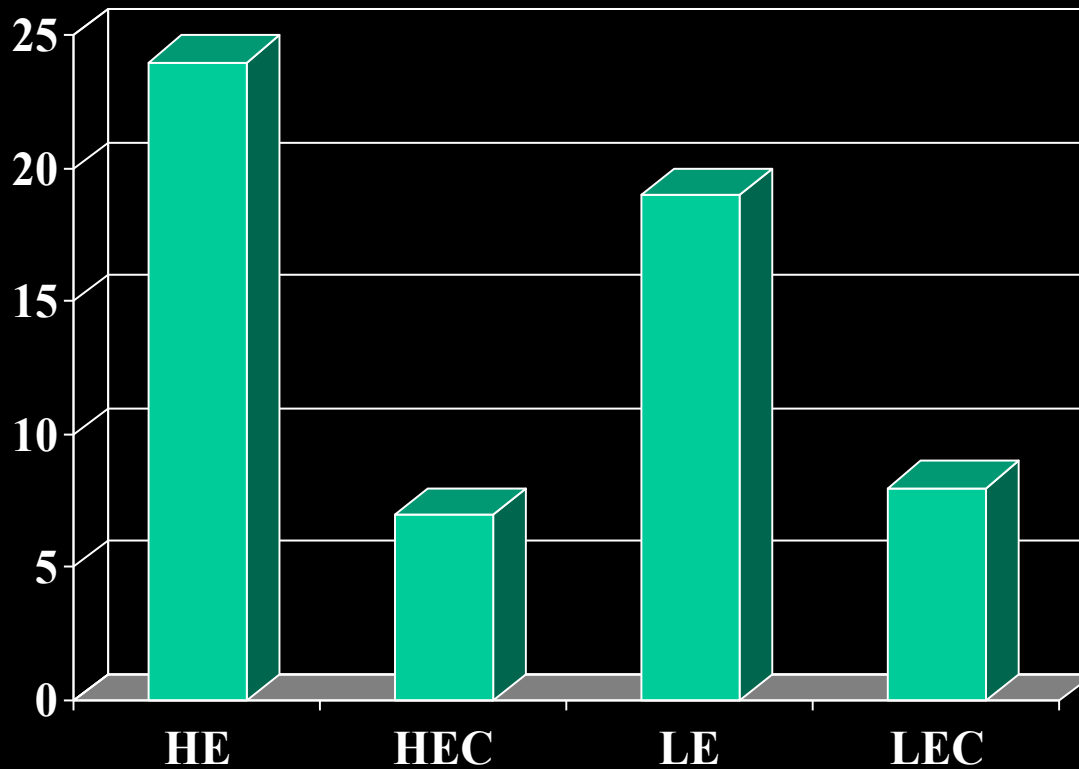
- Family planning important to optimize seizure control and outcome of pregnancy
- Many AEDs decrease the efficacy of hormonal contraception
  - Dilantin, Tegretol, Trileptal, Topamax
  - Women with epilepsy are not aware of this
- Hormonal contraception decreases concentration of LTG





# Use of Contraception *Women with Epilepsy*

n = 58



47% used  
ineffective  
methods

HE: Highly effective; HEC: Highly effective combination; LE: Least effective; LEC: Least effective combination

# Consequences of Contraceptive Failure

- Approximately one-half pregnancies in US unplanned
  - 3 million per year
  - Similar in study of women with epilepsy
- 23% pregnancies terminated by elective abortion
  - Highest among all western developed countries

# AEDs & Hormonal Contraception

## *Recommendations*

- Treat with an AED with no interaction
- If using combined oral contraception, use 50 µg estrogen pill
- Use barrier method in combination
- Use method with no interaction
  - Intrauterine device

# Pregnancy in Women with Epilepsy

- Pre-pregnancy counseling
- Effects of seizures during pregnancy
- Effects of AEDs during pregnancy
- Management
- Neuropsychological outcome of child



# Pre-pregnancy Counseling

- Folic acid
  - AAN recommends at least 0.4mg per day
- Should medication be adjusted before getting pregnant?
  - Consider taper if seizure free for prolonged period of time and at low risk for recurrent seizures
  - **Optimal therapy is drug of choice as monotherapy at lowest possible dose**



# Seizure Frequency During Pregnancy

- Recent studies suggest that most women maintain good seizure control during pregnancy
- Reasons for increased seizure frequency
  - Noncompliance
  - Pharmacokinetic changes
  - Sleep deprivation

# Effects of Seizures During Pregnancy

## *Generalized Tonic-Clonic Seizures*

- Can increase pressure in pregnant uterus
- Trauma if patient falls
- Can induce lactic acidosis
- Fetal bradycardia
- Status epilepticus can result in intrauterine death
  - 36 cases of status epilepticus (12 convulsive)
    - One stillbirth
- No increased risk of MCMs
- One study finds decreased verbal IQ in association with > 5 generalized tonic-clonic seizures in pregnancy

# What are considered MCMs?

- MCMs are structural abnormalities with surgical, medical or cosmetic importance
  - Ventricular septal defect, coarctation of the aorta, tetralogy of Fallot, aortic valve stenosis, hypoplasia of mitral valve
  - Cleft lip and cleft palate
  - Penile hypospadias, imperforate anus, spina bifida
  - Talipes equinovarus (club foot), calcaneovalgus (flexible flat foot) terminal transverse limb defects, hip dysplasia, inguinal hernia (Holmes et al, 2001)

# Is Epilepsy Itself a Risk Factor for MCMs?

## *Probably Not*

- Infants exposed to a single AED
  - 10/233 (4.5%)
- Infants exposed to 2 or more AEDs
  - 8/93 (8.6%)
- Unexposed infants born to mother with a history of a seizure
  - 0/98 (0%)
- Unexposed infants born to women with no history of seizure (Controls)
  - 9/508 (1.8%)

# Effects of AEDs in Pregnancy

## *Major Congenital Malformations*

- Overall 4-6 % have MCMs
  - Risk 2-3 times greater than general population
- Polytherapy associated with higher rates
- Dose dependent effect
  - Particularly with valproate
- Pattern of birth defects seen with some AEDs
  - Neural tube defects with VPA and CBZ

# AED Pregnancy Registries

- Aims of registries
  - To survey the outcomes of a large number of AED-exposed pregnancies, in order to provide accurate information about the magnitude of teratogenic risks
  - Early evidence of any increased risk associated with a new AED
- Different methodology among registries
  - Criteria for enrollment: most enroll prior to any knowledge of pregnancy outcome (1<sup>st</sup> Ultrasound)
  - Timing of malformations: 5 days up to one year
  - Inclusion of information on aborted fetuses

# Pregnancy Registries

- Hospital-based
  - EURAP: An international registry of AEDs and pregnancy
  - North American AED Pregnancy Registry
  - UK Epilepsy and Pregnancy Register
  - Australian Pregnancy Register
- Population-based
  - Swedish register
  - Finnish register
- Pharmaceutical-based
  - Lamotrigine registry

# Malformations Associated with AEDs in Monotherapy

Register	Total Number	Drug			
		VPA	CBZ	LTG	PB
Swedish	1398	9.7% (268)	4.0% (703)	----	----
Finnish	1231	10.6% (263)	2.7% (805)	----	----
UK	3607	6.2% (715)	2.2% (900)	3.2% (647)	----
North American		10.7% (149)	2.5% (873)	2.7% (564)	6.5% (77)
Lamotrigine	802	----	----	2.9% (802)	----
Australian	1052	15.2% (224)	4.9% (243)	5.3% (302)	----

# Levetiracetam in Pregnancy

## UK Register Preliminary Experience

S. Hunt, MRCP; J. Craig, MRCP; A. Russell, MRCP; E. Guthrie, MB; L. Parsons, MD; I. Robertson, MD;  
R. Waddell; B. Irwin; P.J. Morrison, MD; and J. Morrow, MD

- 117 exposures
- MCM: 2.7% (95% CI 0.9 to 7.7)
- All 3 exposed to other AEDs

*Neurology* 2007;28:1876-1878.

# Topiramate in Pregnancy

## UK Register

- 203 pregnancies resulting in 178 live births
- 16 with MCMs
  - 9.0% (95% CI 5.6% to 14.1%)
- 3 MCMs in 70 monotherapy cases
  - 4.8% (95% CI 1.7% to 13.3%)
- 4 with oral clefts
  - 2.2% (95% CI 0.9% to 5.6%)
  - 11 times background rate

# Lamotrigine and Oral Clefts

- North American Registry
  - 684 exposed infants: 2.3% MCM rate identified at birth
  - 5 oral clefts (7.3 per 1000)
  - 10.4 fold increase (95% CI 4.3 to 24.9) when compared to 206,244 unexposed infants
- Other registries
  - 1623 exposed infants
  - 4 with oral clefts (2.5/1000)
  - RR 3.8% (95% CI 1.4-10.0)

# <http://www.massgeneral.org/aed/>



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# Management During Pregnancy

- Work closely with OB
- Screening: AFP, anatomic ultrasound
- Monitor AED concentrations throughout pregnancy
- Vitamin K1 at dose of 10 mg per day beginning at week 36 for those receiving enzyme inducing AEDs

# Pregnancy: AED Concentrations

- AED treatment remained unchanged in 62.7% of the pregnancies
  - Number or dosage of AEDs were more often increased in pregnancies with seizures (OR: 3.6; 2.8 to 4.7)
  - Monotherapy with lamotrigine (OR: 3.8; 2.1 to 6.9)
  - Monotherapy with oxcarbazepine (OR: 3.7; 1.1 to 12.9)
- Highly protein AEDs follow free and total levels
  - (PB – 90%, VPA – 90%, CBZ – 75%)
- Frequent monitoring of lamotrigine
- Oxcarbazepine doses need to be adjusted
- Levetiracetam doses need to be adjusted

# Cognitive Effects of In Utero AEDs

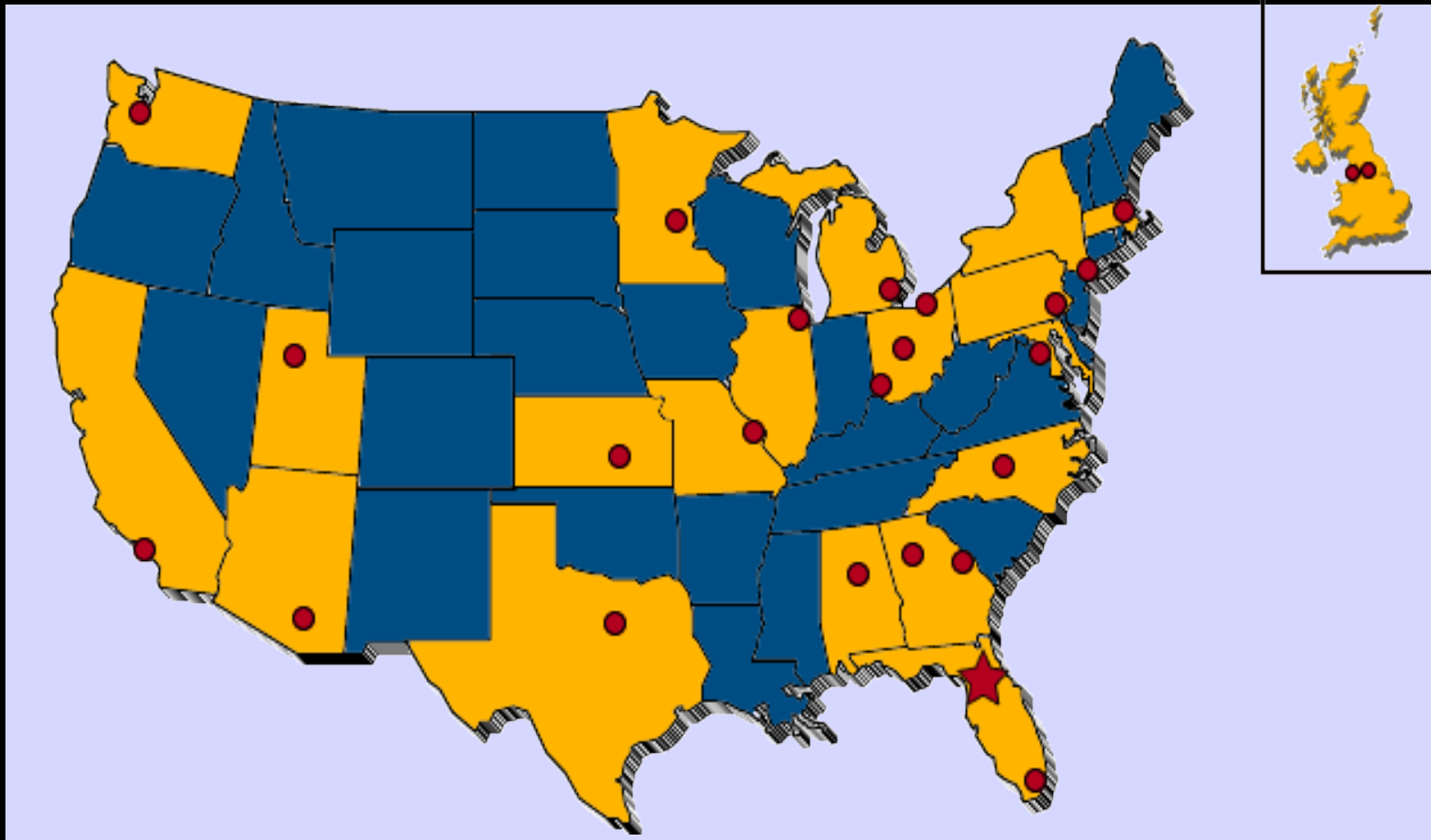
- PB vs general population: 7-point reduction in VIQ
- VPA vs other monotherapy
  - Special education: 30% vs 3%-6%
  - VPA: 10- to 14-point reduction in VIQ
  - VPA: worse development in second cohort <6 y/o
- VPA vs CBZ: 12-point reduction in VIQ

VIQ = verbal IQ.

Reinisch JM, et al. *JAMA*. 1995;274:1518-1525; Adab N, et al. *J Neurol Neurosurg Psychiatry*. 2001;70:15-21; Adab N, et al. *J Neurol Neurosurg Psychiatry*. 2004;75:1575-1583; Gaily E, et al. *Neurology*. 2004;62:28-32.

# NEAD Study

Neurodevelopmental Effects of Antiepileptic Drugs



**25  
sites:  
USA &  
UK**

<http://www.neadstudy.com>

Funded by NIH/NINDS #2R01 NS 38455

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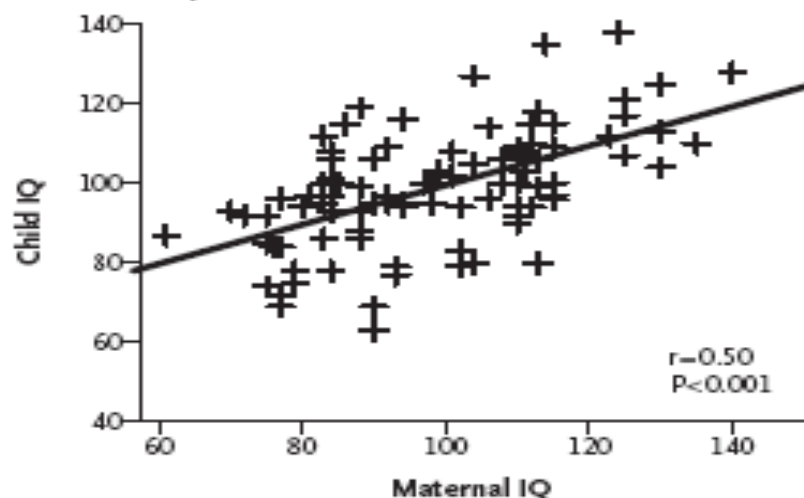
VOL. 360 NO. 16

## Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

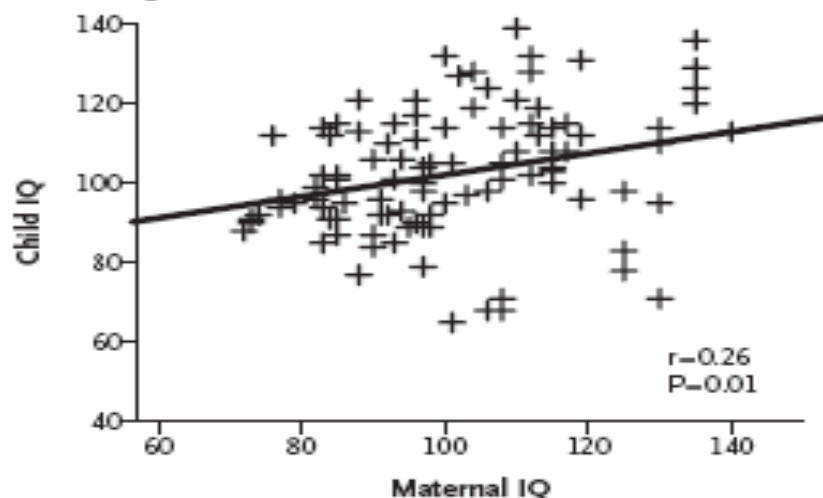
**Table 2.** IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs.\*

Variable	Carbamazepine (N=73)	Lamotrigine (N=84)	Phenytoin (N=48)	Valproate (N=53)
Mean IQ (95% CI)†	98 (95–102)	101 (98–104)	99 (94–104)	92 (88–97)
Mean difference in IQ from valproate group (95% CI)‡	6 (0.6–12.0)	9 (3.1–14.6)	7 (0.2–14.0)	
P value§	0.04	0.009	0.04	

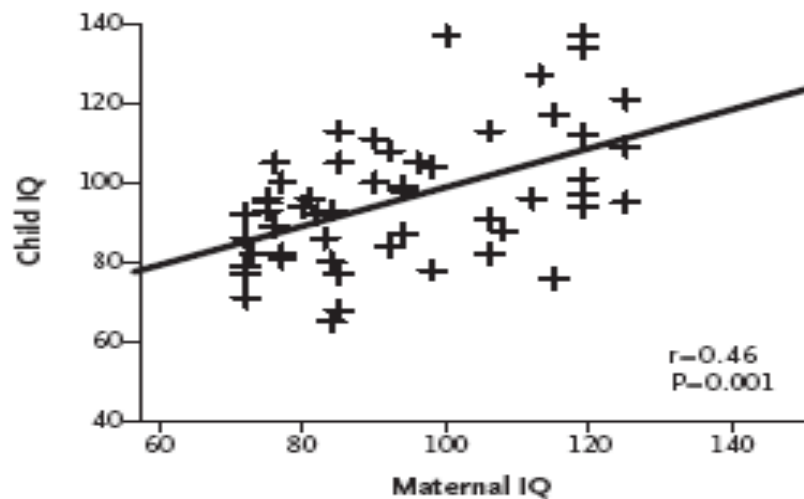
**A Carbamazepine**



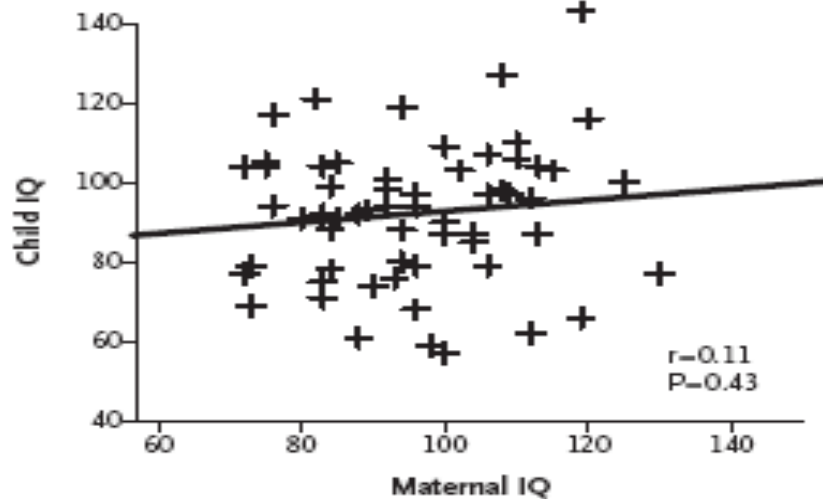
**B Lamotrigine**



**C Phenytoin**



**D Valproate**



**Figure 3. Relationship between Child and Maternal IQ According to Antiepileptic Drug.**

Child IQ at 3 years of age and maternal IQ are significantly correlated for all antiepileptic drugs except valproate. The data are from an intention-to-treat sample of 309 children. IQ was imputed for 77 children.

# In Utero Cognitive Effects

## *Conclusions*

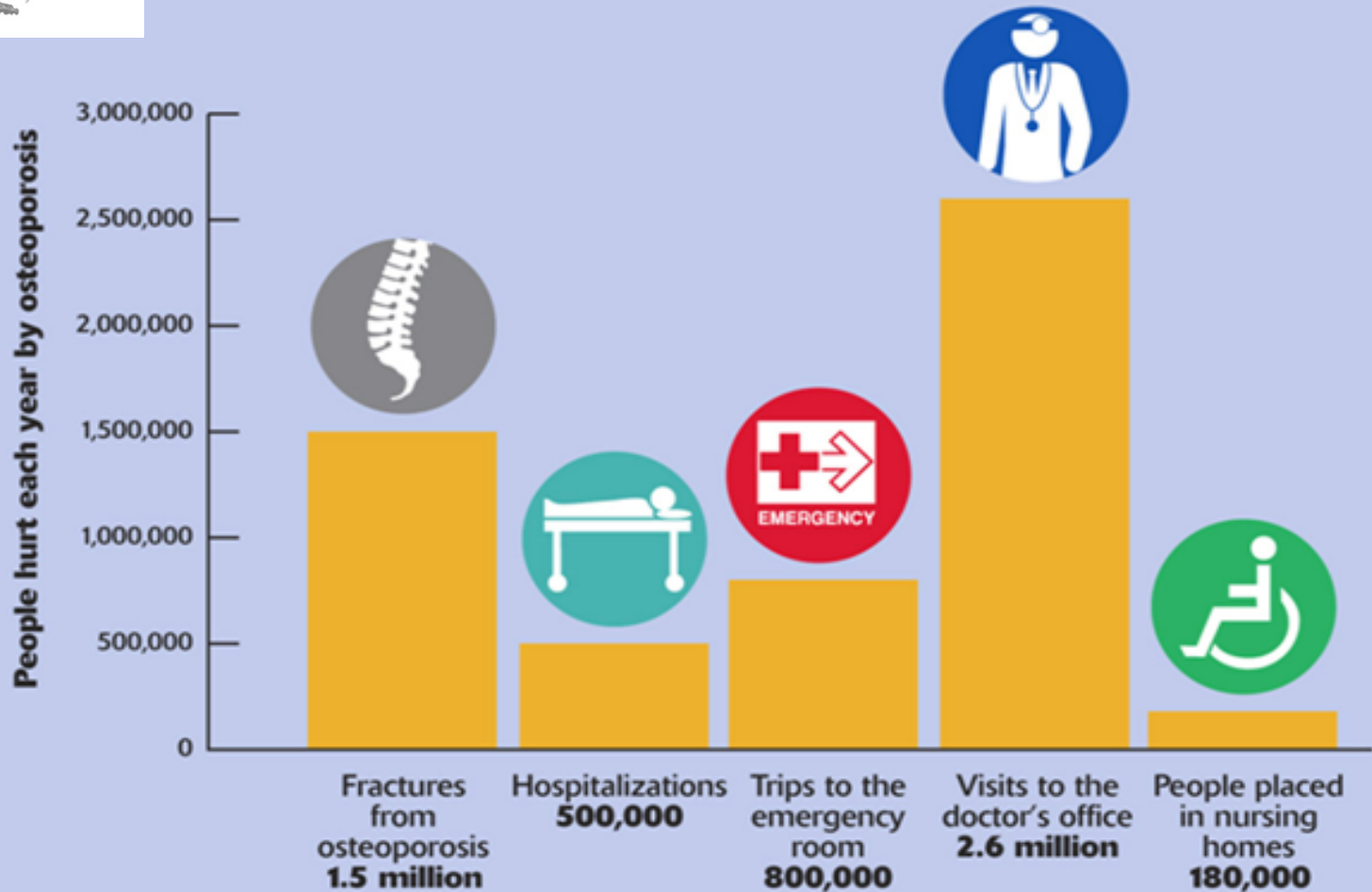
- Results across studies indicate that in utero VPA poses a greater risk for poor behavioral outcomes than other commonly used AEDs
- Further studies are needed to evaluate additional AEDs, determine if the effects are irreversible, and delineate underlying mechanisms

Bone  
*and* Joint  
D E C A D E  
2002 - USA - 2011



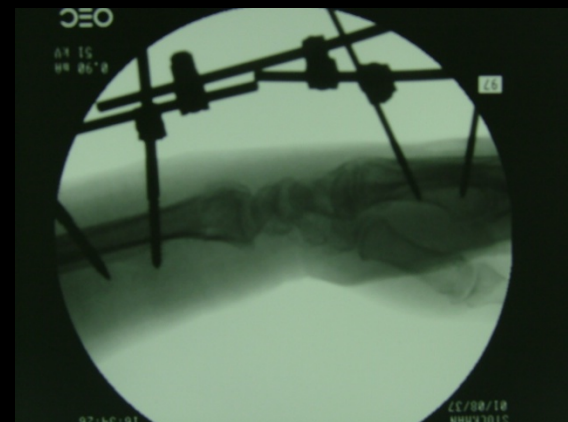
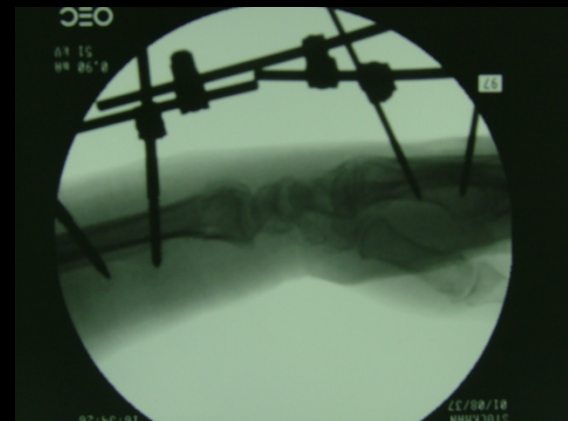
# Bone Health

Poor bone health is common and costly.

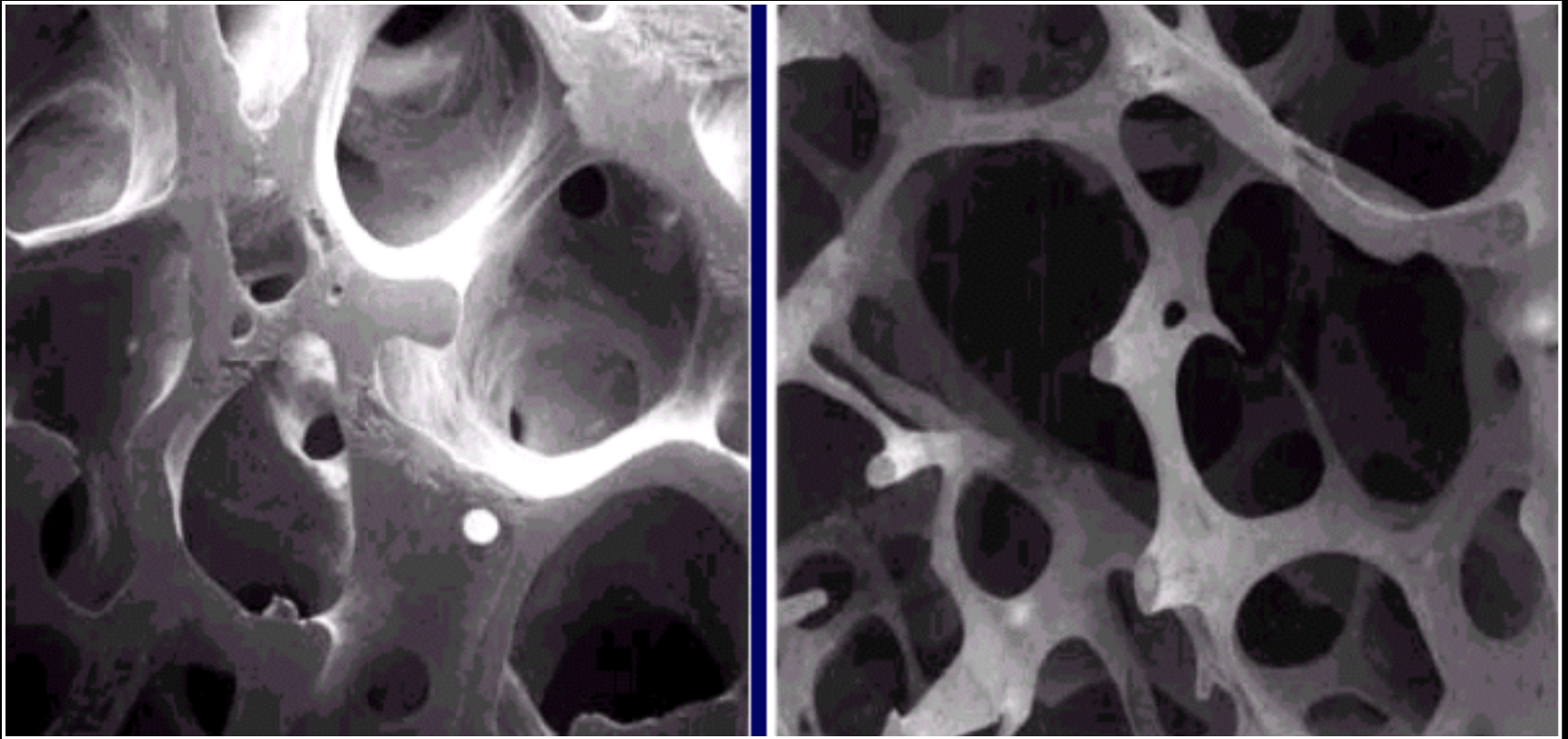


# Fracture

- Risk of fracture
  - Decreased bone mineral density
  - Altered bone quality
  - Propensity to fall
- Increased in persons with epilepsy
  - Effects on bone mineral density
  - Secondary to seizures
  - Poor coordination secondary to side effects



# Normal Bone Versus Osteoporotic Bone

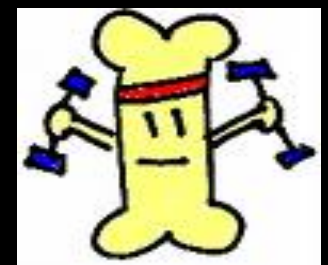




# Bone



- Persons with epilepsy have increases rates of fracture
- Some antiepileptic drugs (AEDs) can result in decreased BMD
- Good bone health practices should be encouraged to create optimal environment for bone development
  - Screening vitamin D
  - DXA scans
  - Avoid AEDs known to negatively affect bone eg Dilantin
  - Weight bearing exercise
  - Recommended daily allowances of calcium and vitamin D



# Conclusion

- Reproductive dysfunction can occur in men and women with epilepsy
- Contraceptive counseling is important for women with epilepsy
- Most women with epilepsy have normal healthy pregnancies
- Speak to your doctor about optimizing the outcome of your pregnancy
- Good bone health practices should be encouraged in men and women with epilepsy

