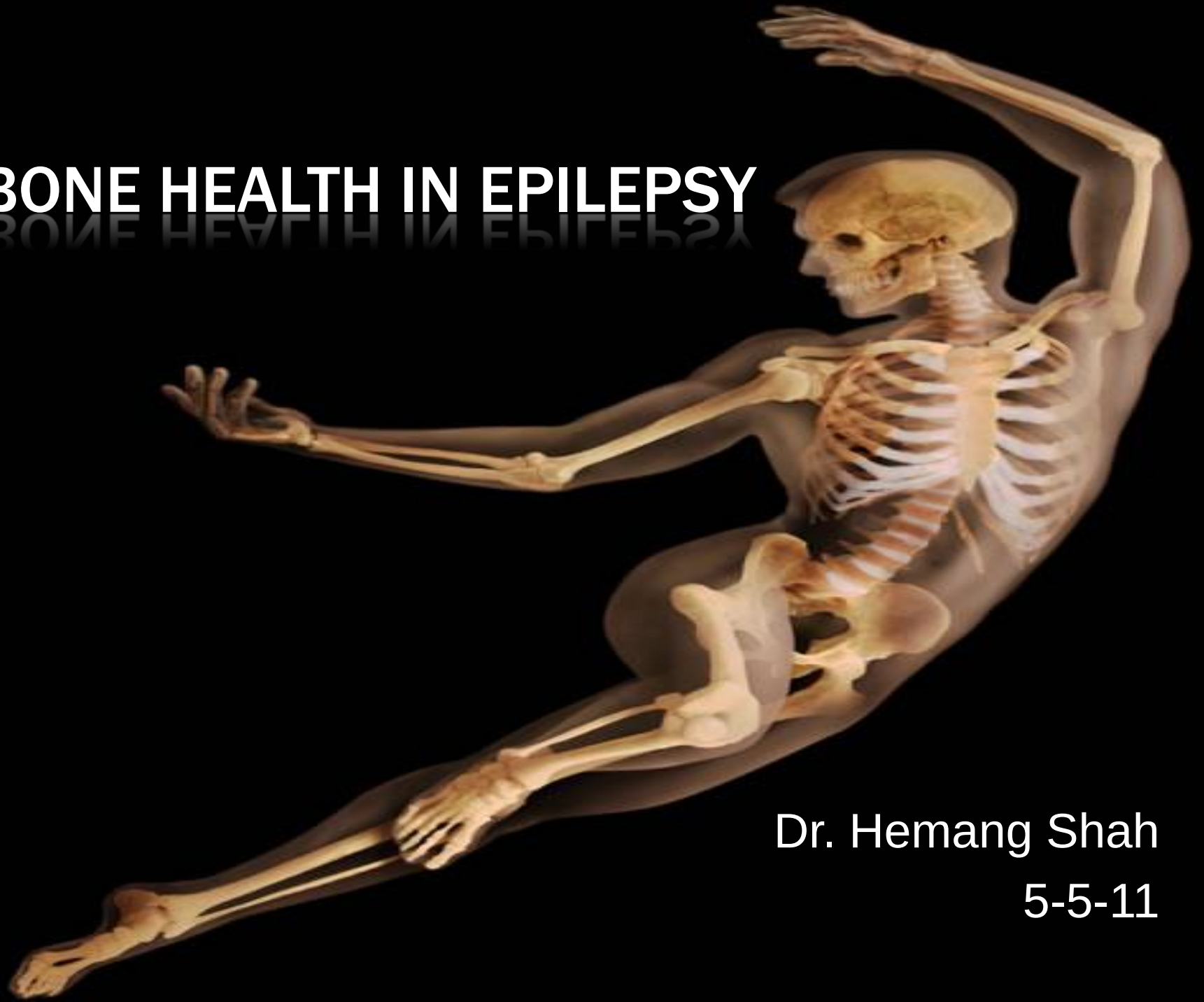
BONE HEALTH IN EPILEPSY

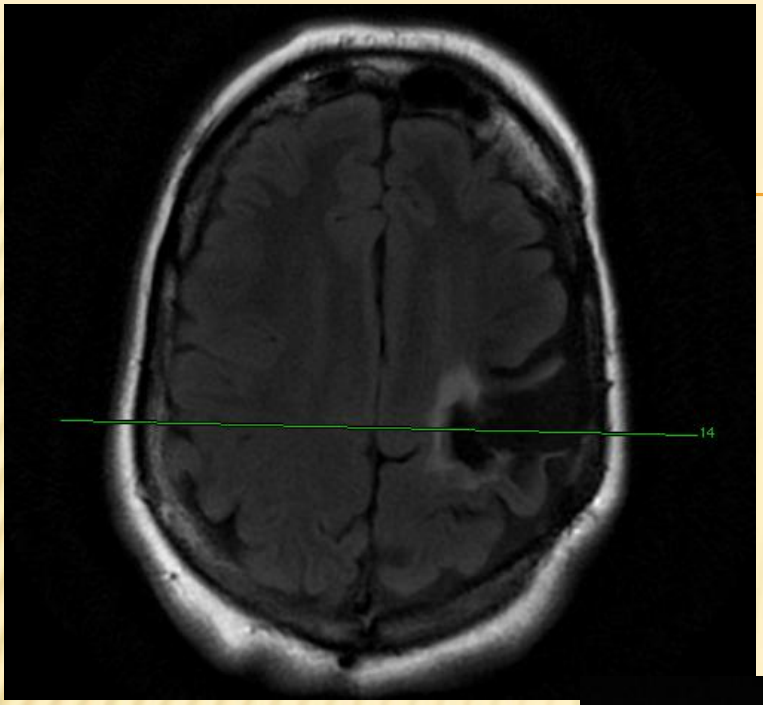


Dr. Hemang Shah

5-5-11

PATIENT HISTORY

- LG is 32 yo LH WF with seizure onset 10.
- Epilepsy surgery (left frontal segmental resection) for Rasmussen's encephalitis
- Current AEDs:
  - Oxcarbazepine 900 bid
  - Lacosamide 200 bid
  - Felbamate 600-1200-1200-600
  - Phenytoin 100 am -300 pm +/- 25 QOD
  - Rituximab 375 mg/m2 Q month
  - Previous meds – CBZ, GBP, PB, VPA, TPX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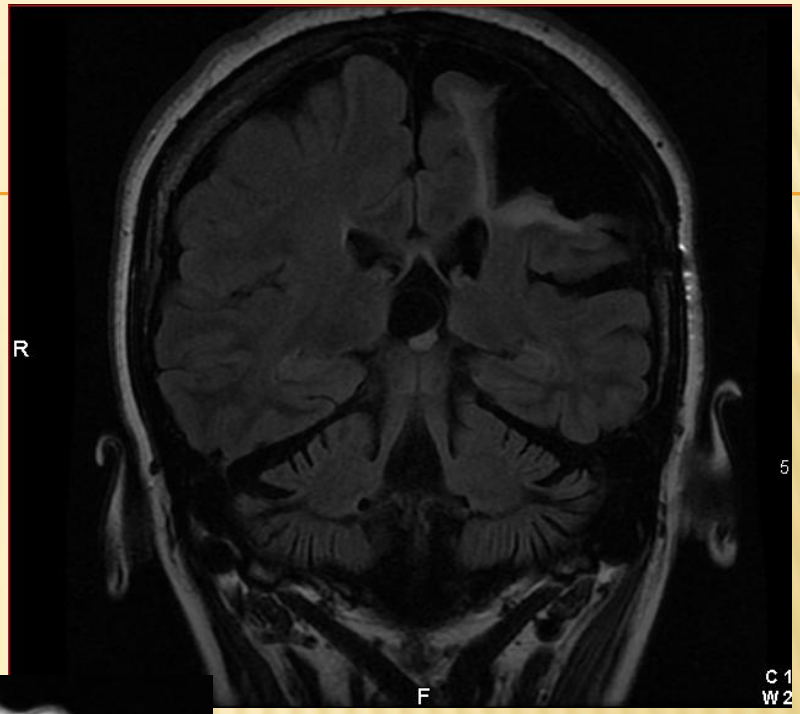
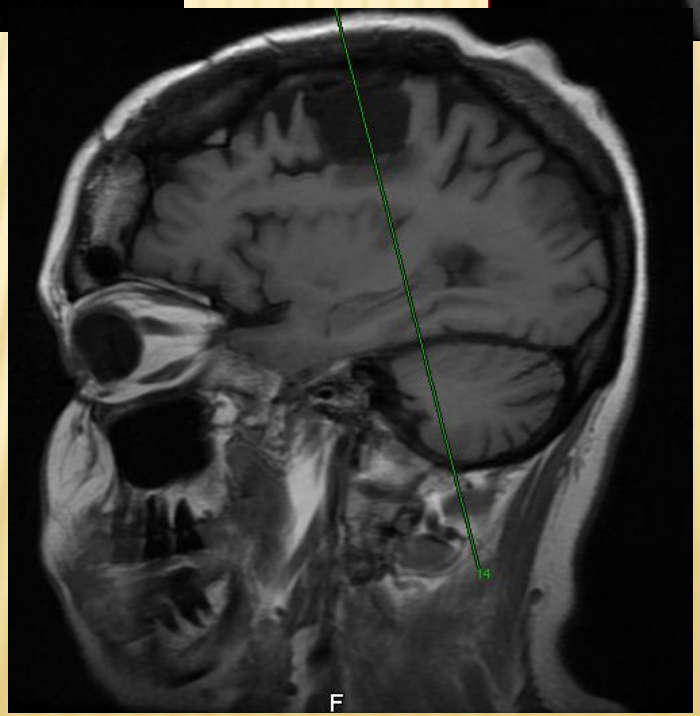

R
F
5
C 1
W 2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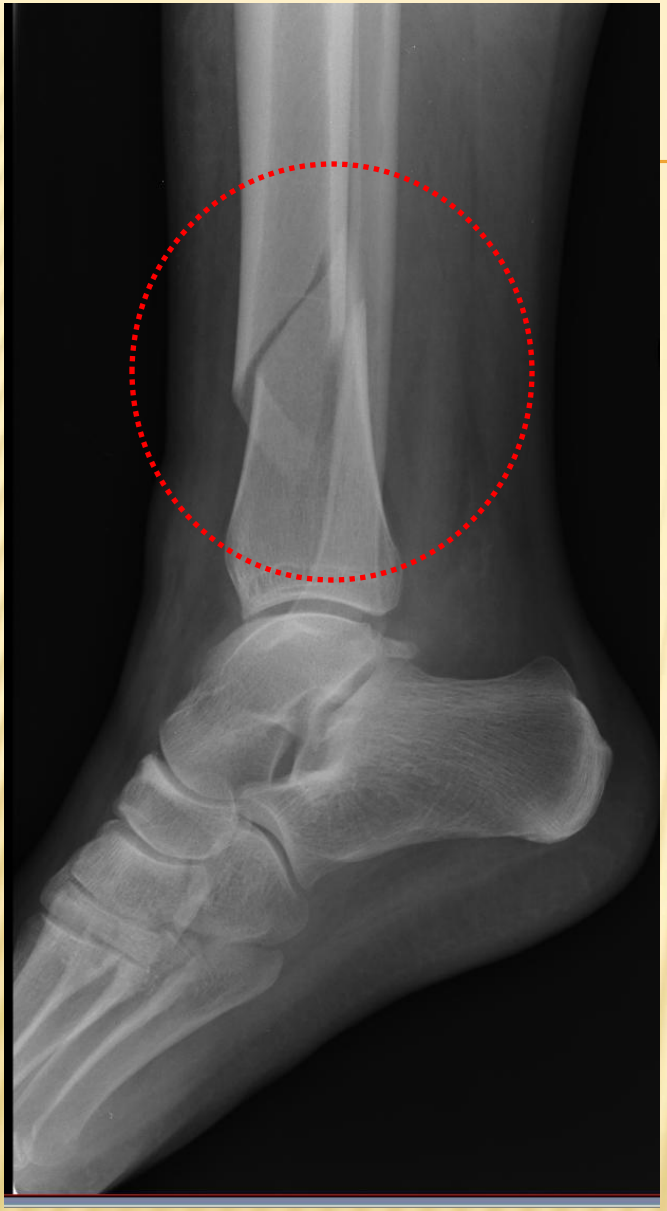
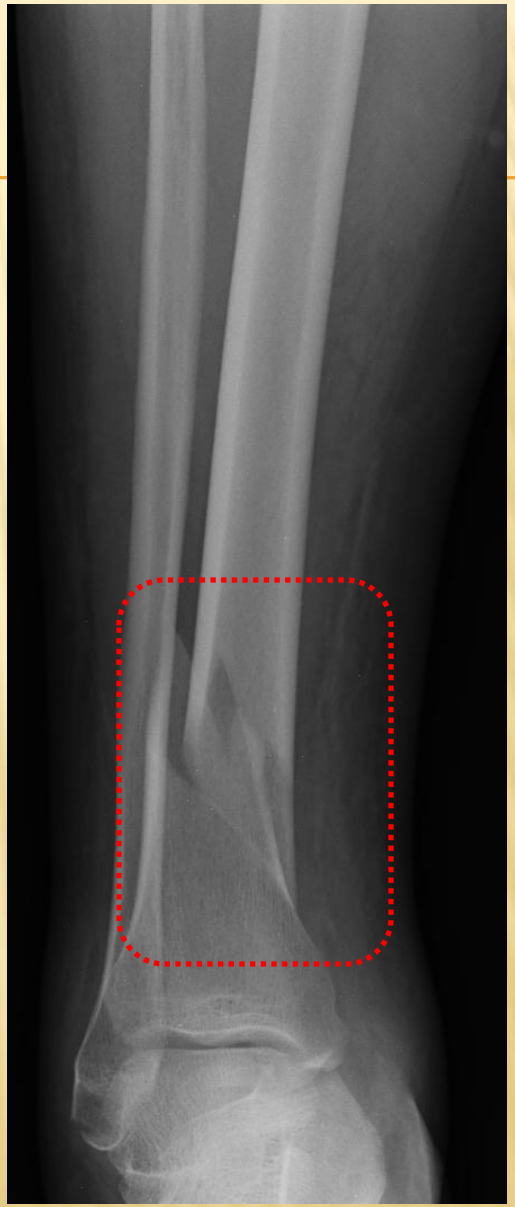


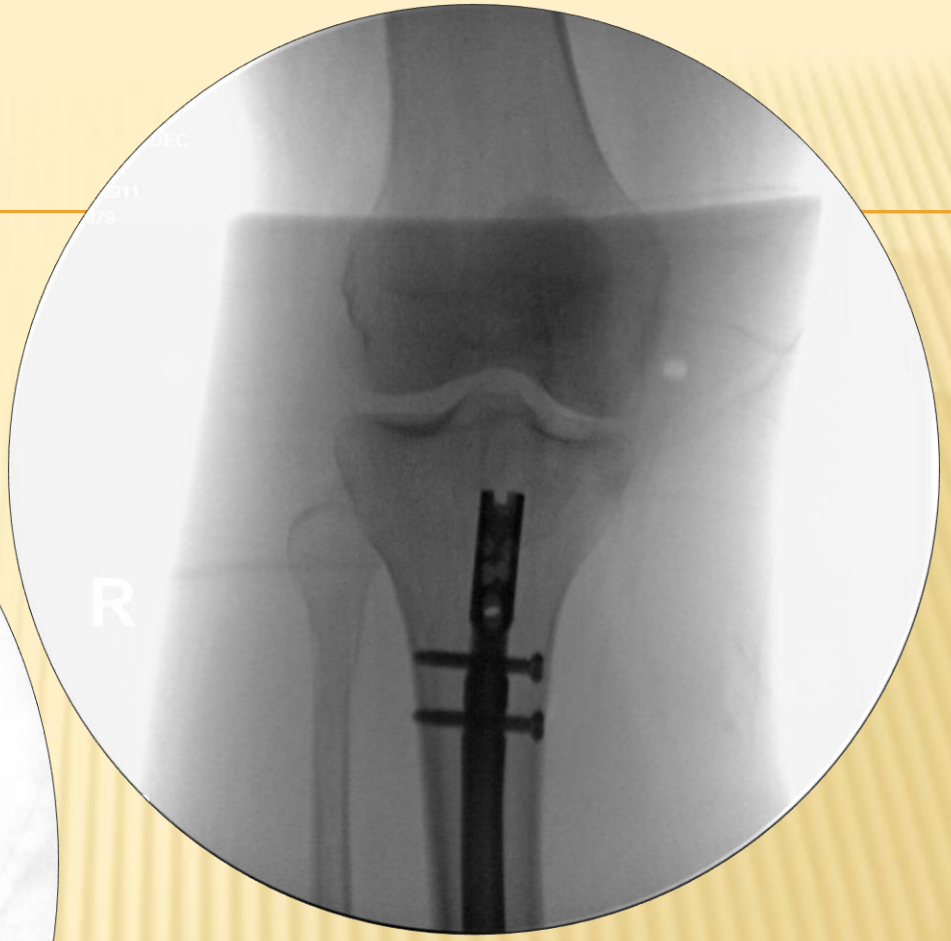
9-29-10 spiral fracture of Rt. distal Tibia

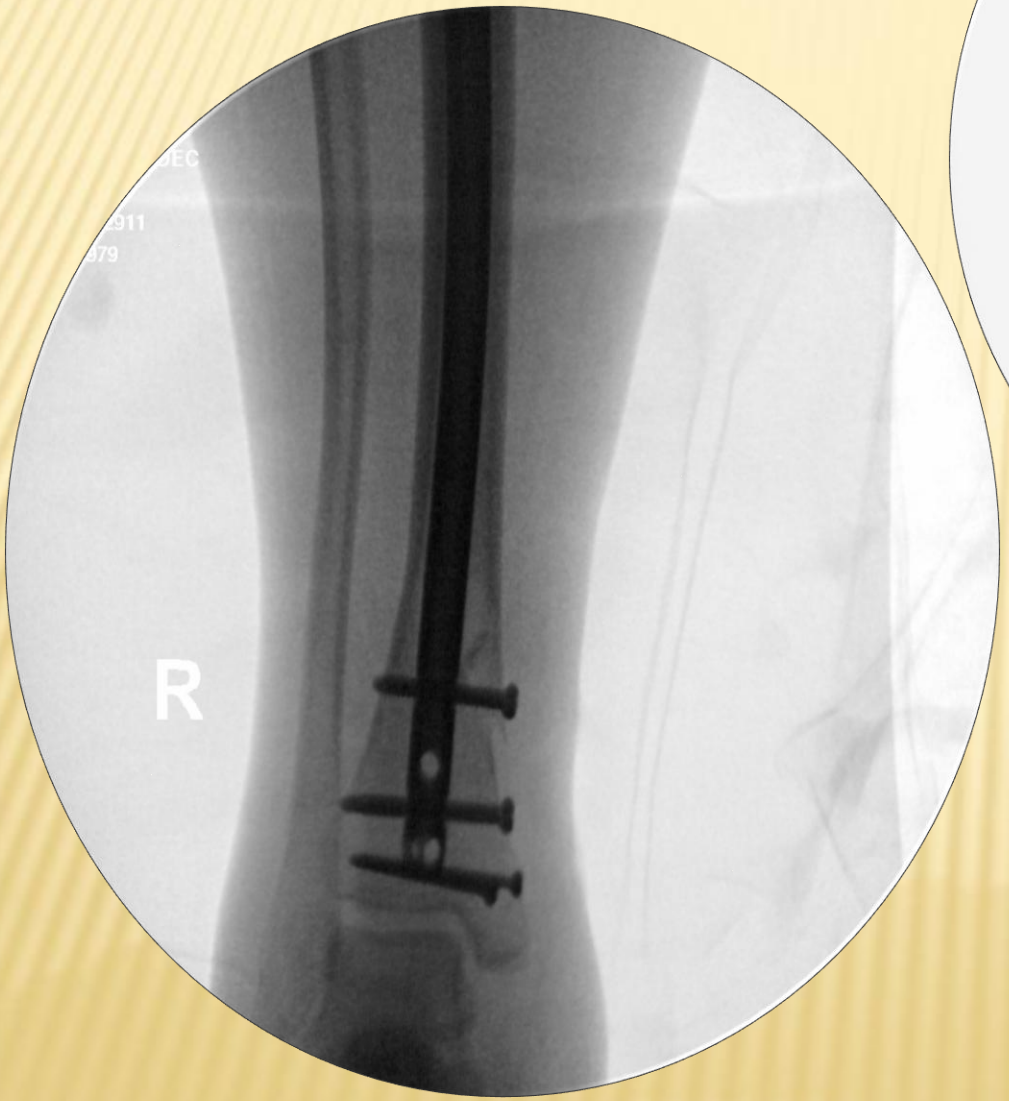


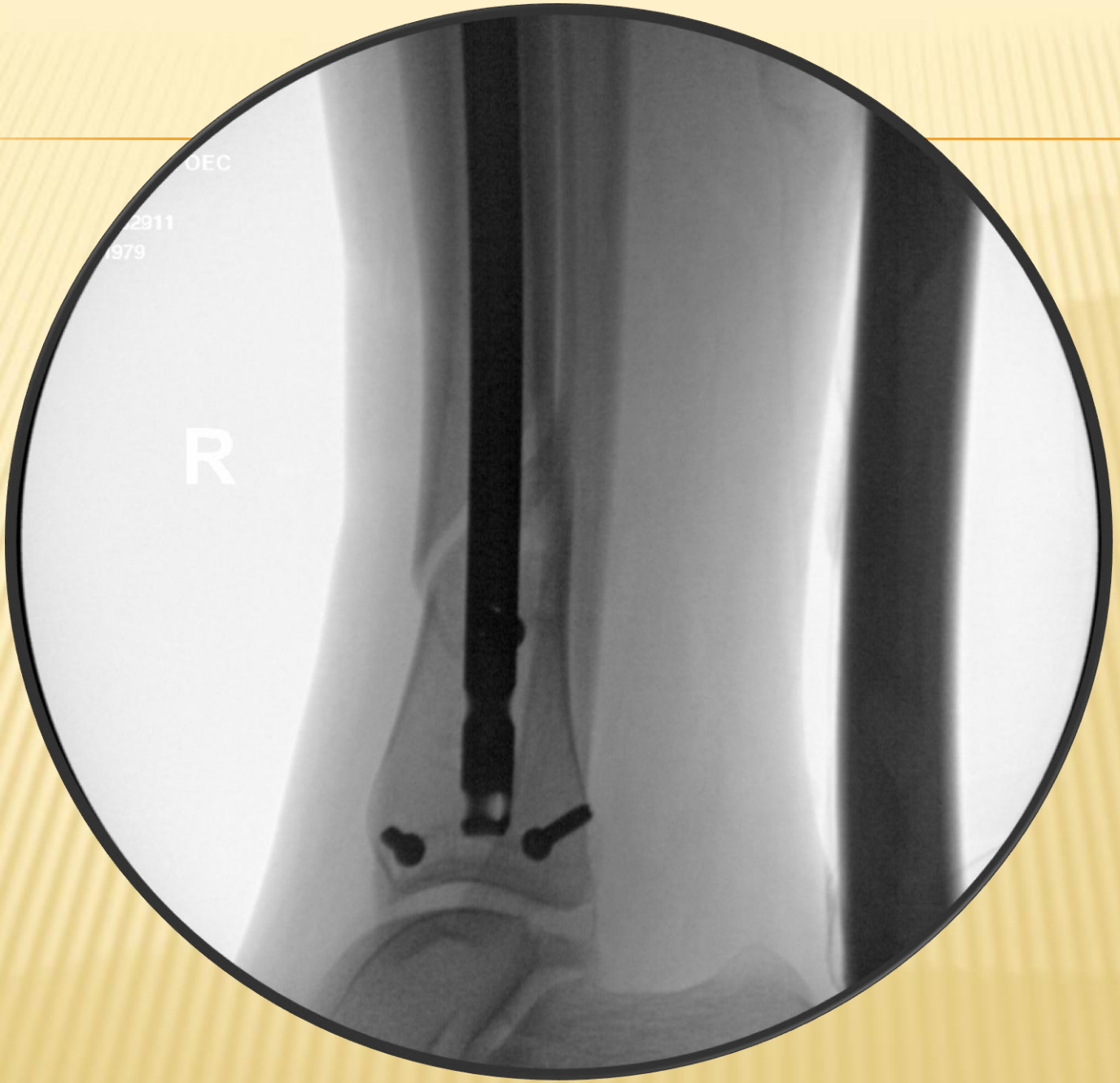
10-1-10: Comminuted fracture of the distal tibia reduced and stabilized.

Intramedullary rod

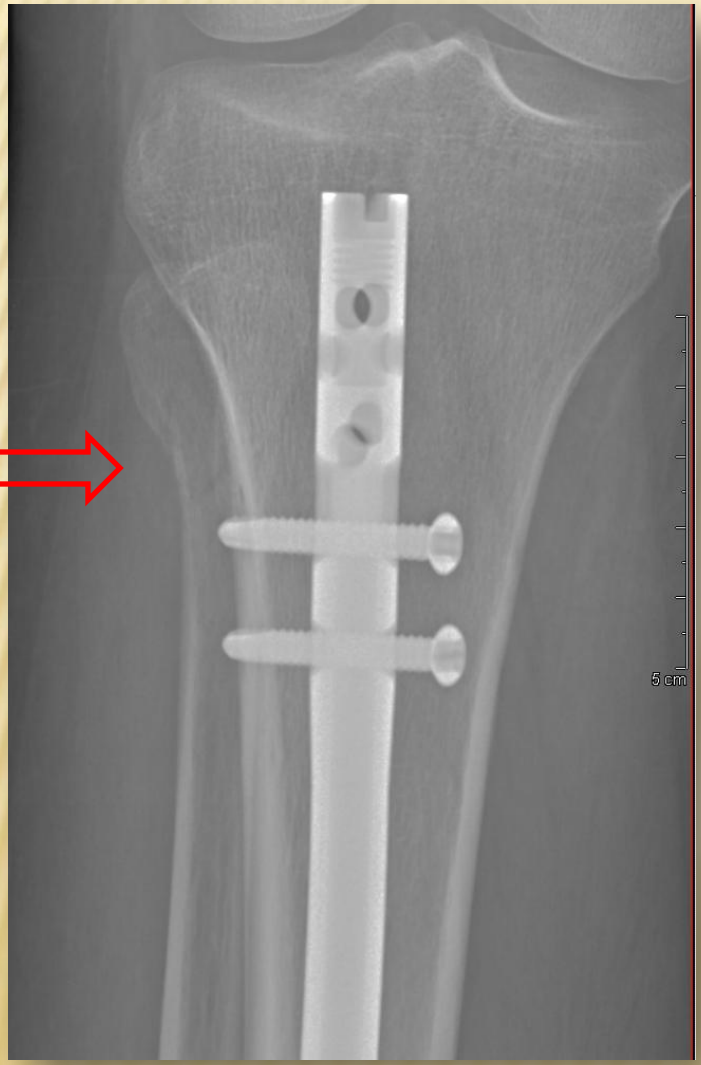
Cross screws

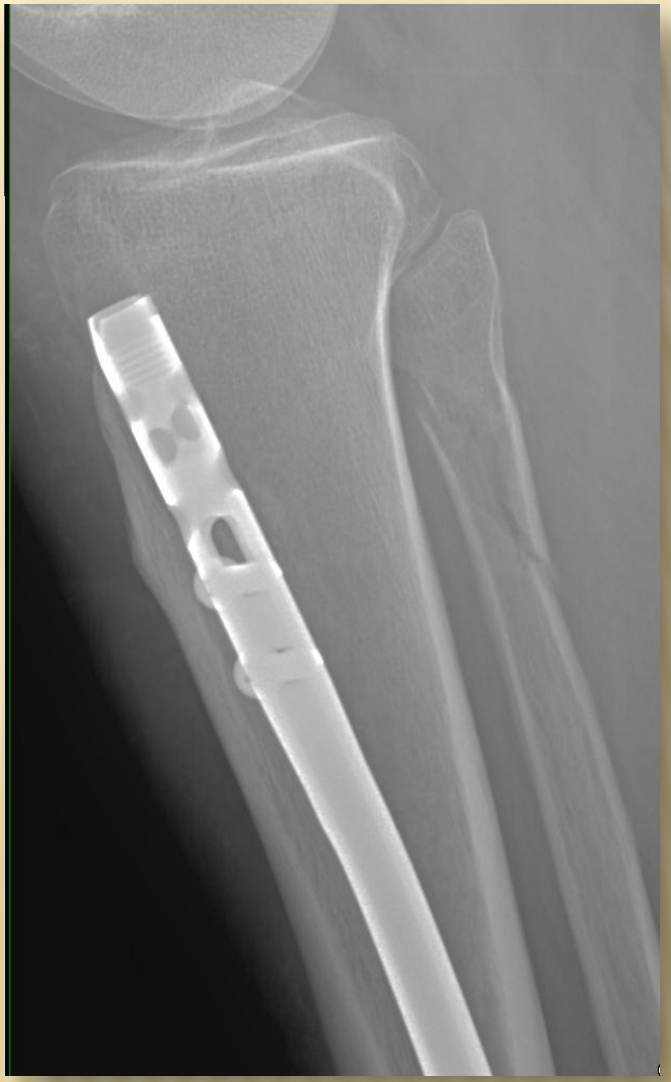





OEC
2911
979
R

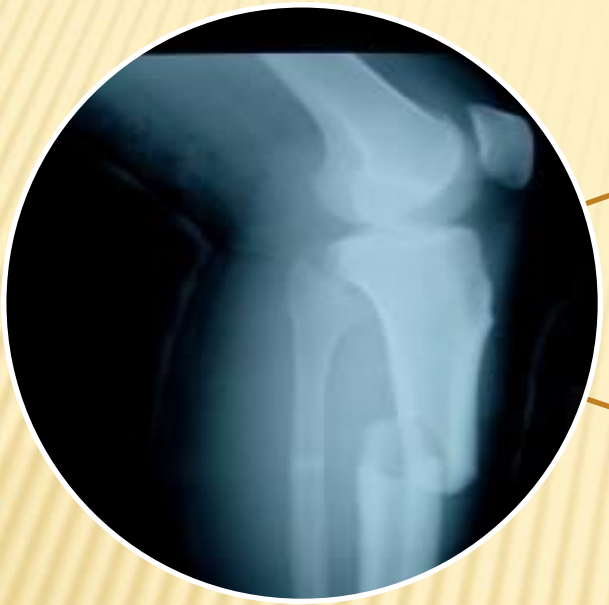
10-19-2010: Right proximal fibular fracture





ELEPHANT IN THE ROOM?

LIFE TIME RISK OF FRACTURE*



Men

Women

U.S. Department of Health and Human Services. Bone health and osteoporosis: a report of the surgeon general. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General; 2004

EPIDEMIOLOGY

- Fractures are 2 and 6 times more common in persons with epilepsy than in the general population.*

Persson HB, Alberts KA, Farahmand BY, Tomson T. Risk of extremity fractures in adult outpatients with epilepsy. Epilepsia 2002;43(7):768-772.

Epilepsia, **46**(2):304–310, 2005
Blackwell Publishing, Inc.

Incidence of Fractures among Epilepsy Patients: A Population-based Retrospective Cohort Study in the General Practice Research Database

*Patrick C. Souverein, †David J. Webb, †Hans Petri, †John Weil, ‡Tjeerd P. Van Staa, and *Toine Egberts

*Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; †GlaxoSmithKline, WorldWide Epidemiology, New Frontiers Science Park, Harlow, and ‡Medical Research Council, Environmental Epidemiology Unit, Southampton University Hospital, Southampton, England

TABLE 1. *Characteristics of the epilepsy (n = 40,485) and control cohort (n = 80,970)*

Characteristic	Epilepsy cohort (n = 40,485)		Reference cohort (n = 80,970)	
	No.	(%)	No.	(%)
Age (median)	39.1 yrs		34.1 yrs	
Age (years)				
< 20	7,695	(19.0)	20,745	(25.6)
20–49	18,185	(44.9)	36,105	(44.6)
≥50	14,605	(36.1)	24,120	(29.8)
Gender				
Male	20,252	(50.0)	38,224	(47.2)
Female	20,233	(50.0)	42,746	(52.8)
Median duration of follow-up	3.0 yrs	3.3 yrs		
History of fractures before cohort entry	4,749	(11.7)	6,162	(7.6)
Diagnosis of epilepsy before practice up to standard	23,791	(58.8)		
Type of epilepsy *				
Nonspecific	36,153	(89.3)		
Partial epilepsy	1,379	(3.4)		
- Temporal lobe epilepsy	976	(2.4)		
- Jacksonian Seizure	370	(0.9)		
- Other/unspecified partial epilepsy	33	(0.1)		
Generalized epilepsy	2,631	(6.5)		
- Absence (petit mal)	1,059	(2.6)		
- Tonic-clonic (grand mal)	1,509	(3.7)		
- Other/unspecified generalized epilepsy	63	(0.2)		
Status epilepticus	322	(0.8)		

*First diagnosis of epilepsy after the start of GPRD qiuality up to date; if patients had a diagnosis of epilepsy prior to the start of GPRD follow-up only, the type of epilepsy was classified as nonspecific.

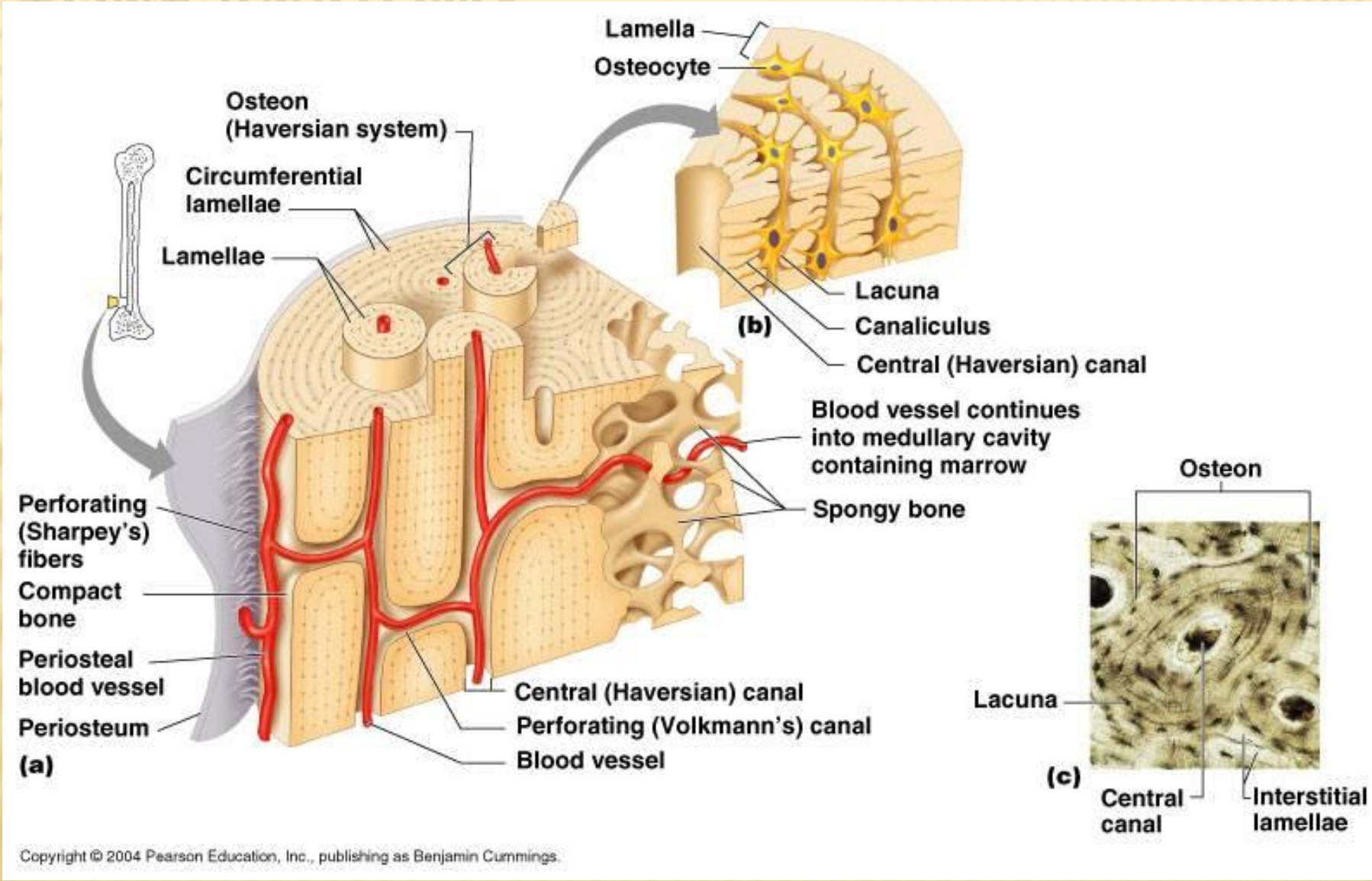
TABLE 2. *Incidence rates of fractures in the epilepsy and reference cohort*

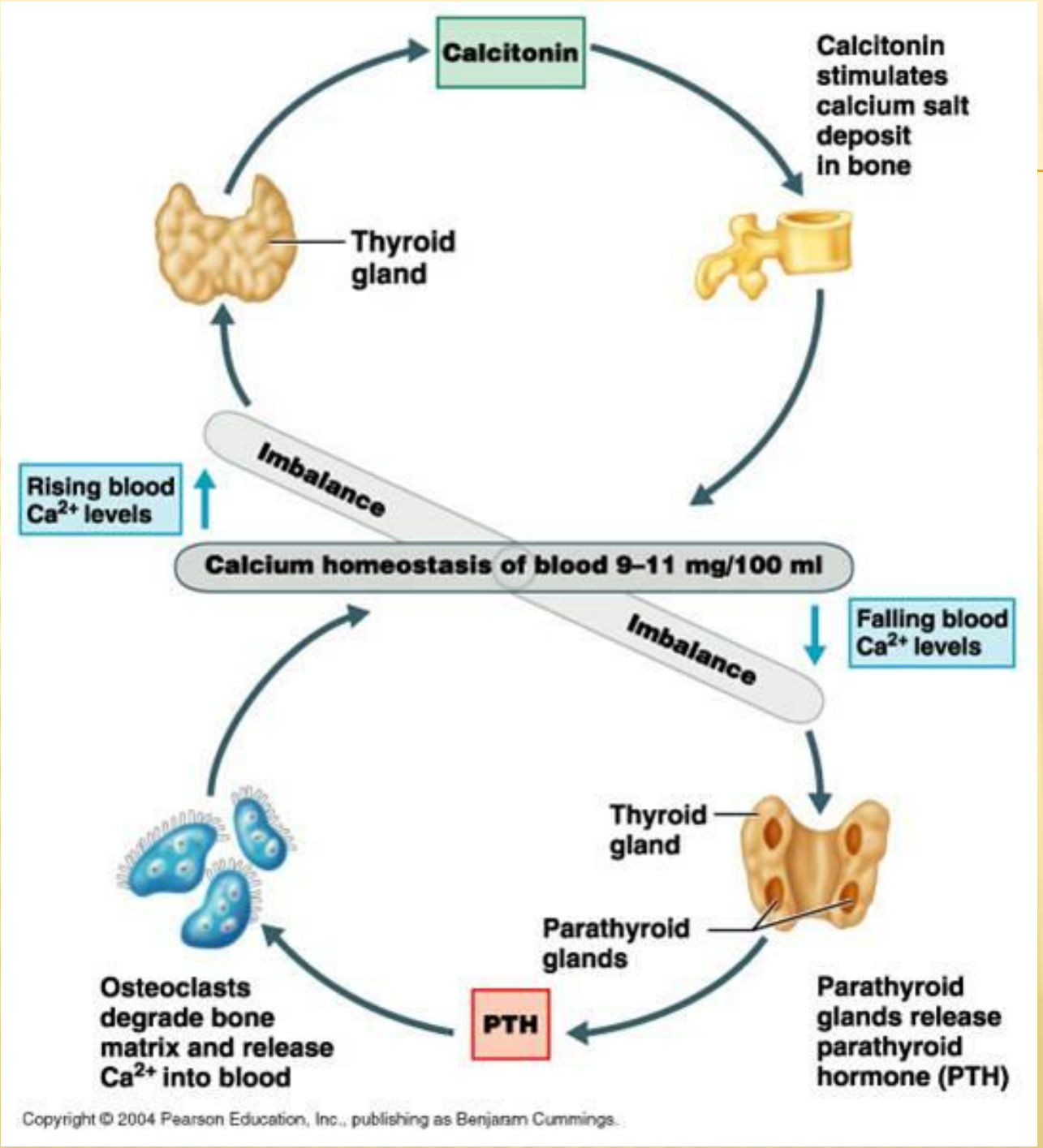
Type of fracture	Number of fractures	Person-years	Rate/10,000 person-years	Crude IRR (95% CI)	Adjusted IRR(95% CI)
Any fracture					
Control	3,940	319,142	123.5	1.00 (Reference)	1.00 (Reference)
Epilepsy	3,478	143,754	241.9	1.96 (1.87–2.05)	1.89 (1.81–1.98)
Hip/femur fracture					
Control	301	319,142	9.4	1.00 (Reference)	1.00 (Reference)
Epilepsy	436	143,754	30.3	3.22 (2.78–3.72)	2.79 (2.41–3.24)
Hand or radius/ulna fracture					
Control	1,445	319,142	45.3	1.00 (Reference)	1.00 (Reference)
Epilepsy	1,101	143,754	76.7	1.69 (1.56–1.83)	1.70 (1.57–1.84)
Tibia, fibula, ankle or foot fracture					
Control	749	319,142	23.5	1.00 (Reference)	1.00 (Reference)
Epilepsy	640	143,754	44.5	1.90 (1.71–2.11)	1.89 (1.70–2.10)
Other fractures					
Control	1,491	319,142	46.7	1.00 (Reference)	1.00 (Reference)
Epilepsy	1,351	143,754	94.0	2.01 (1.87–2.17)	1.94 (1.80–2.09)

IRR, Incidence rate ratio, CI; Confidence interval,
*Adjusted for age and sex.
Patients can have multiple fractures sites.

The study was funded by GlaxoSmithKline, UK

BONE ANATOMY



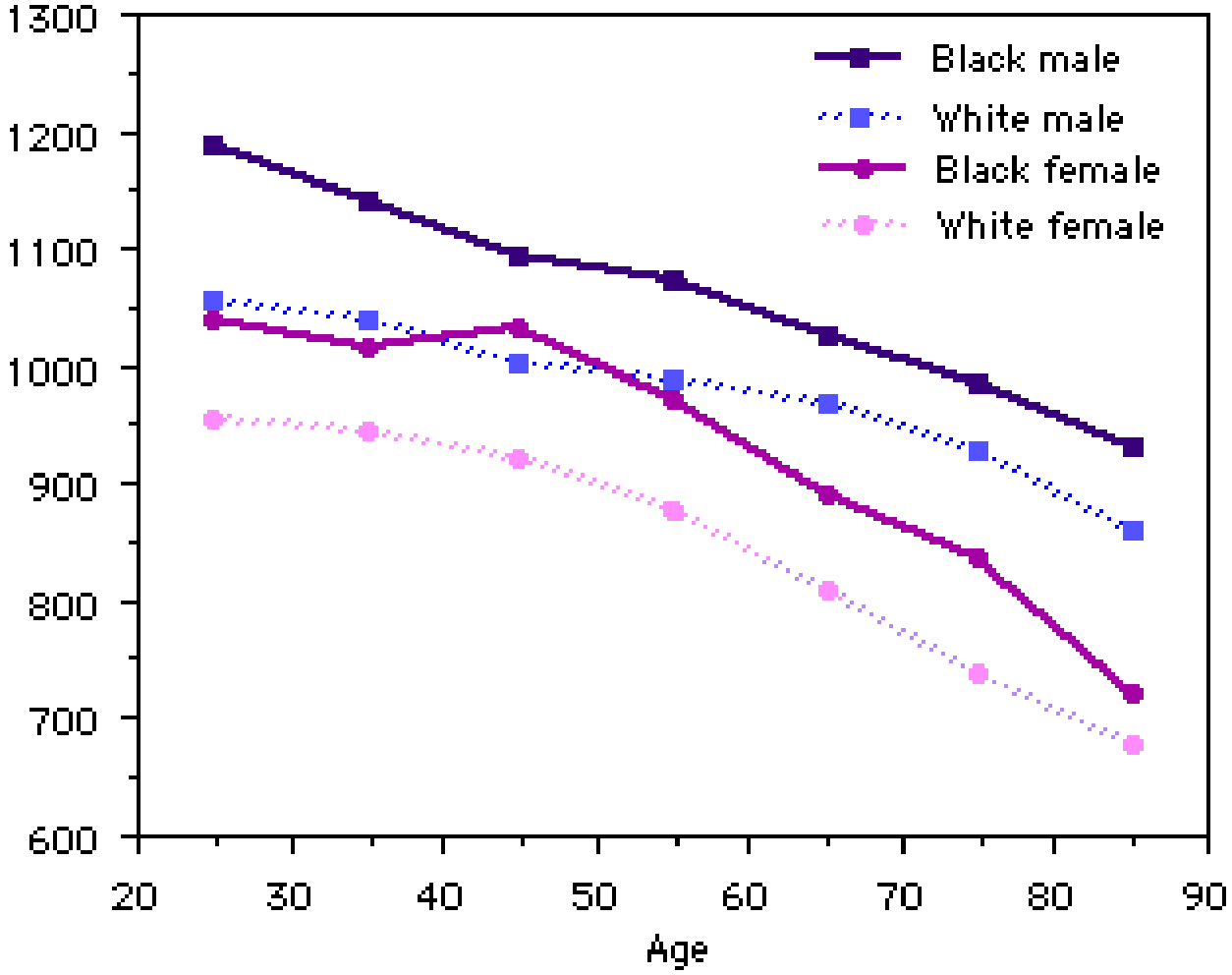


CALCIUM HOMEOSTASIS

VITAMIN D

INCREASED RISK OF FRACTURE

BONE MINERAL DENSITY (BMD)



http://courses.washington.edu/bonephys/opbmd.html

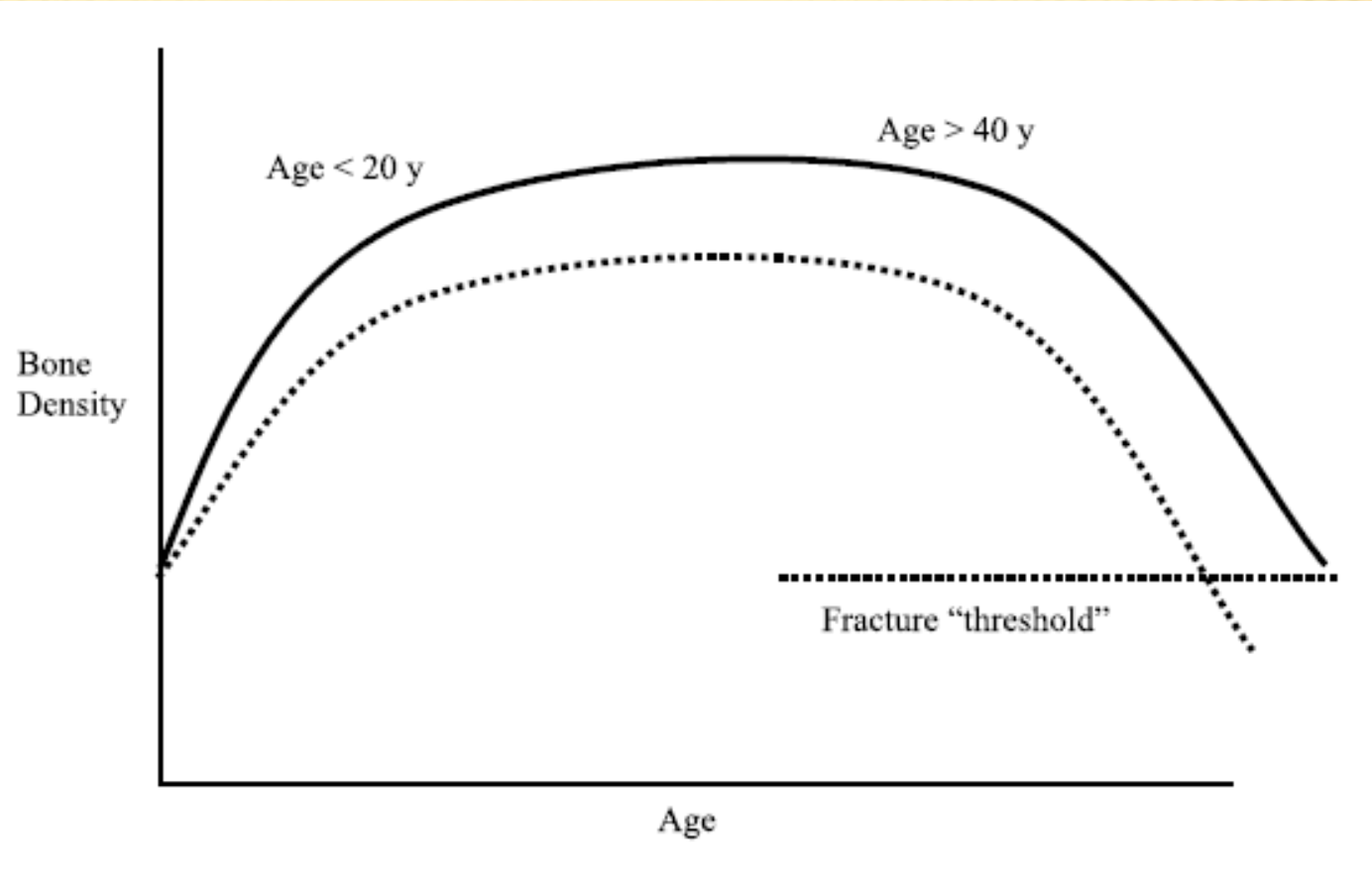
BMD

- Peak at 2-3 decade.
- BMD accumulation and maintenance occur as a function of the coupling of bone resorption and formation.
- Osteoclasts - bone resorption
- Osteoblasts – bone formation
- Osteopenia and osteoporosis are gradations of the same pathology

SECONDARY OSTEOPOROSIS

- Gastrointestinal malabsorption
- Vitamin D and/or calcium deficiency
- Hyperthyroidism
- Hyperparathyroidism
- Cushing's syndrome
- Rheumatoid arthritis and other inflammatory conditions
- Alcoholism
- Renal disease
- Liver disease
- Osteogenesis imperfecta
- Marfan's syndrome
- Homocystinuria
- *Absence of stress*
- *Smoking*
- Glucocorticosteroids
- Immunosuppressants (cyclosporine)
- Antiepileptic drugs
- GnRH agonists
- Heparin
- Cancer chemotherapy
- Depot medroxyprogesterone acetate
- Excess thyroid hormone
- Diuretics
- Metoclopramide
- Methotrexate
- Antiretroviral therapy for HIV

EARLY AED EXPOSURE



Solid curve represents normal bone mineralization.
Dotted curve represents bone mineralization with AED.

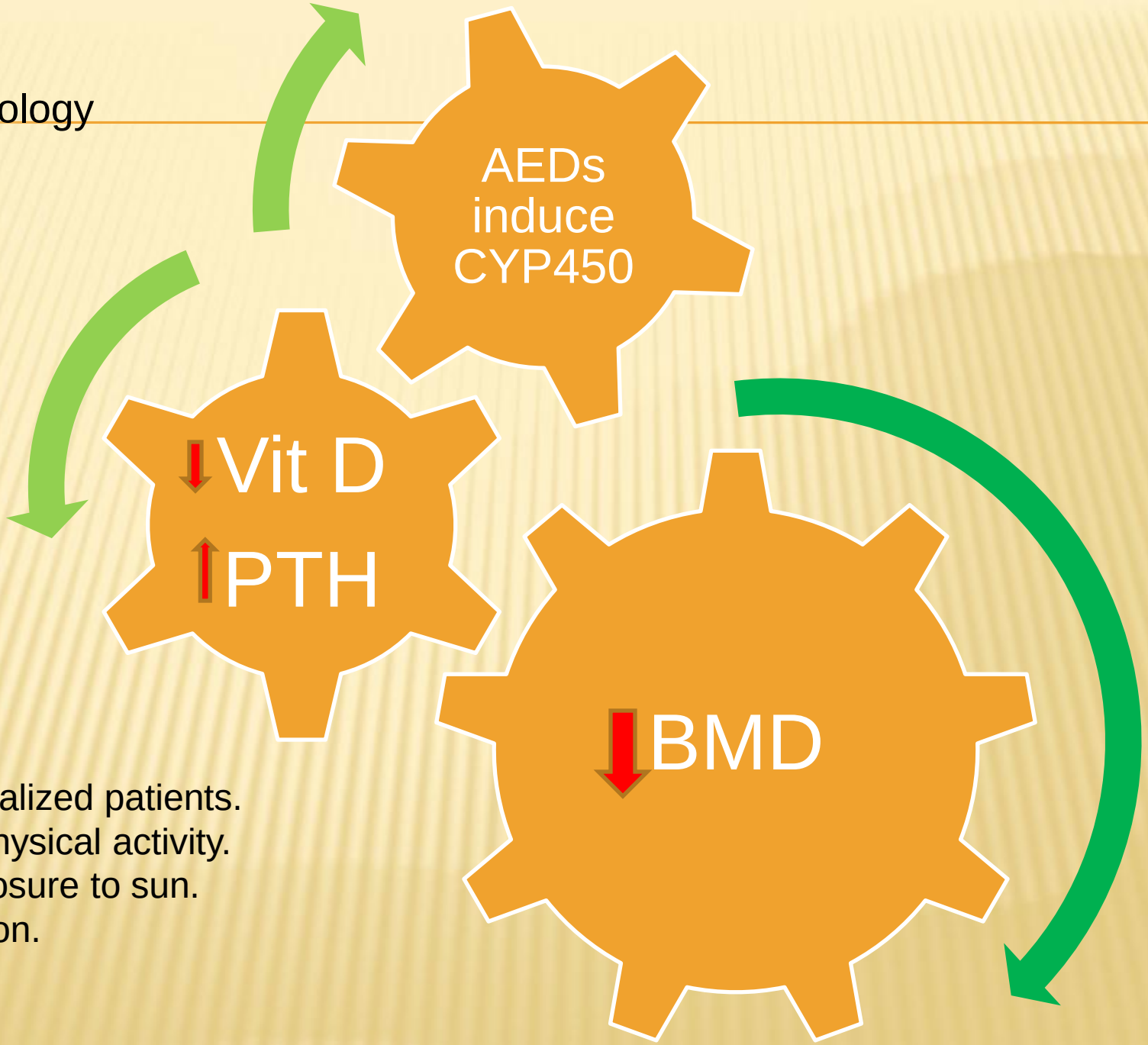
PHENOBARBITAL, PRIMIDONE, AND PHENYTOIN

- Phenytoin, primidone, and phenobarbital contribute to osteomalacia and rickets*
- Cross-sectional studies in children have shown that up to 50% of those treated with the classic AEDs experienced changes in serum markers that were suggestive of osteomalacia.
- Cultured neonatal mouse calvaria treated with phenytoin showed increased bone resorption.

* *Hahn TJ, Scharp CR, Halstead LR, Haddad JG, Karl DM, Avioli LV. Parathyroid hormone status and renal responsiveness in familial hypophosphatemic rickets. J Clin Endocrinol Metab1975;41:926–37*

** *Takahashi A, Onodera K, Shinoda H, Mayanagi H. Phenytoin and its metabolite, 5-(4-hydroxyphenyl)-5-phenylhydantoin, show bone resorption in cultured neonatal mouse calvaria. Jpn J Pharmacol 2000*

Presumed Pathophysiology



Problems:

- Institutionalized patients.
- Lack of physical activity.
- Poor exposure to sun.
- Malnutrition.

CARBAMAZEPINE AND VALPROATE

- Carbamazepine is an enzyme inducer.
- Effect of carbamazepine and valproate on bone mineral density. J Pediatr 1995
- Effect of antiepileptic drugs on bone density in ambulatory patients. Neurology 2002

Effect of carbamazepine and valproate on bone mineral density

Raj D. Sheth, MD, Carl A. Wesolowski, MD, J. C. Jacob, MD, Sharon Penney, RN, Gerald R. Hobbs, PhD, Jack E. Riggs, MD, and John B. Bodensteiner, MD

From the Departments of Pediatrics, Neurology, Community Medicine, Computer Sciences and Statistics, and Medicine, West Virginia University Health Sciences Center, Morgantown, and the Departments of Nuclear Medicine, Pediatrics, and Neurology, Health Sciences Centre, Memorial University of Newfoundland, St. John's, Newfoundland, Canada

Objective: **To examine the effect of carbamazepine and valproate monotherapy on bone mineral density in children.**
Methods: **Axial (second, third, and fourth lumbar vertebrae) and appendicular (distal third of radius) bone mineral density was measured by dual-energy x-ray absorptiometry in 27 healthy children and 26 children with uncomplicated idiopathic epilepsy treated with either carbamazepine (n = 13) or valproate (n = 13)**

CARBAMAZEPINE ON BONE MINERAL DENSITY

Table. Clinical features of control subjects and study subjects

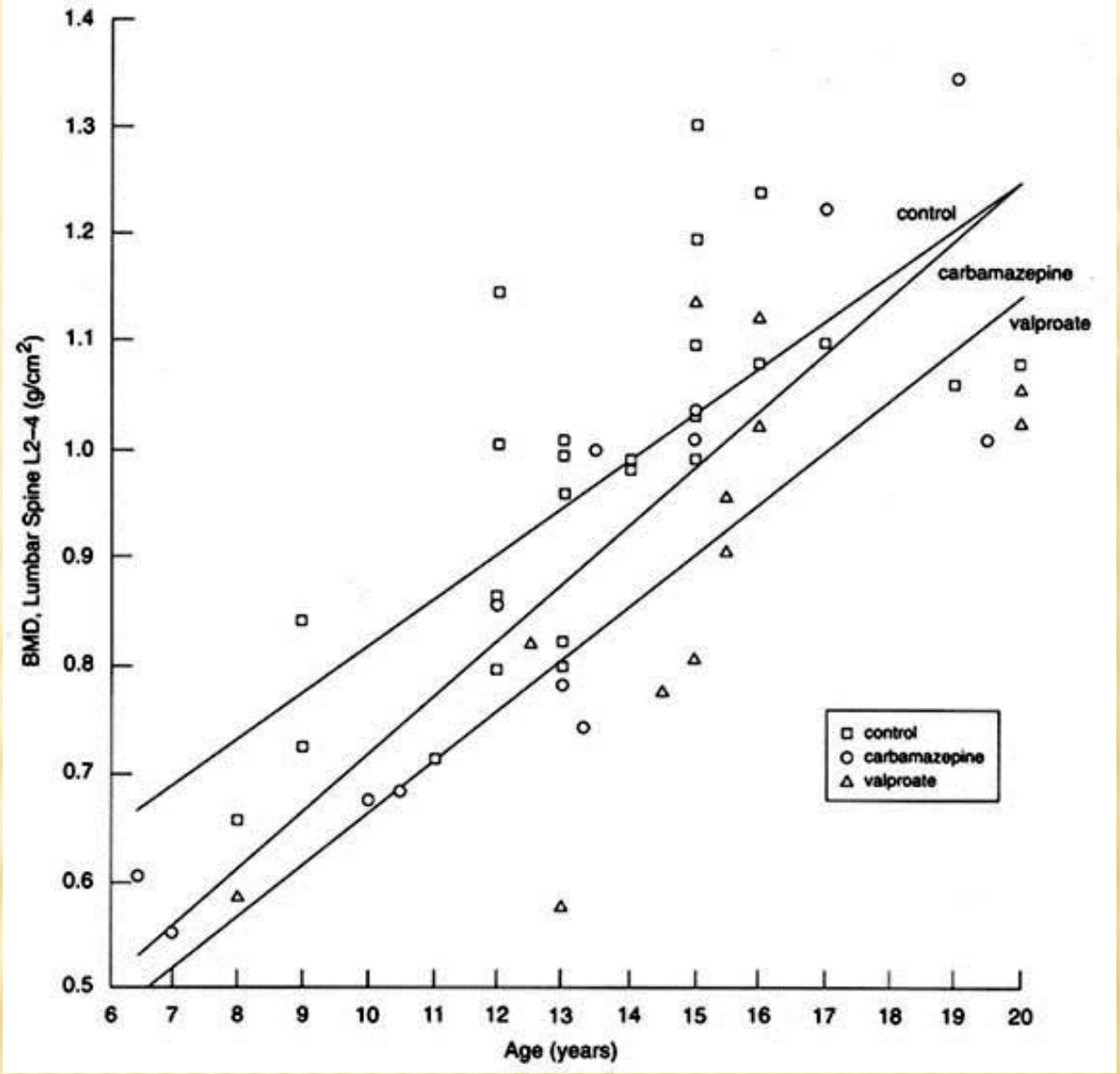
	Control subjects (n = 27)	Study subjects	
		Carbamazepine (n = 13)	
Mean age (yr)	13.4 ± 2.8 (8-20)	13.2 ± 4.1 (6.5-19.5)	
Boys/girls	15/12	3/10	
Calcium intake (mg/day)	642 ± 202	693 ± 140	
Mean dose (mg/kg/day)	—	6.88 ± 2 (4.3-10.9)	
Mean serum trough level (μg/ml)	—	6.88 ± 2 (4.3-10.9)	
Mean duration of therapy (yr)	—	3.9 ± 2.3 (1.5-9)	

Mean values are mean ± SD. Values in parentheses are ranges.

- Subjects – Benign Rolendic Epilepsy, Seizure free for 6 months.
- Control – siblings, cousins. Age- and sex-matched, from a similar social class, and had similar physical activity and dietary calcium intake

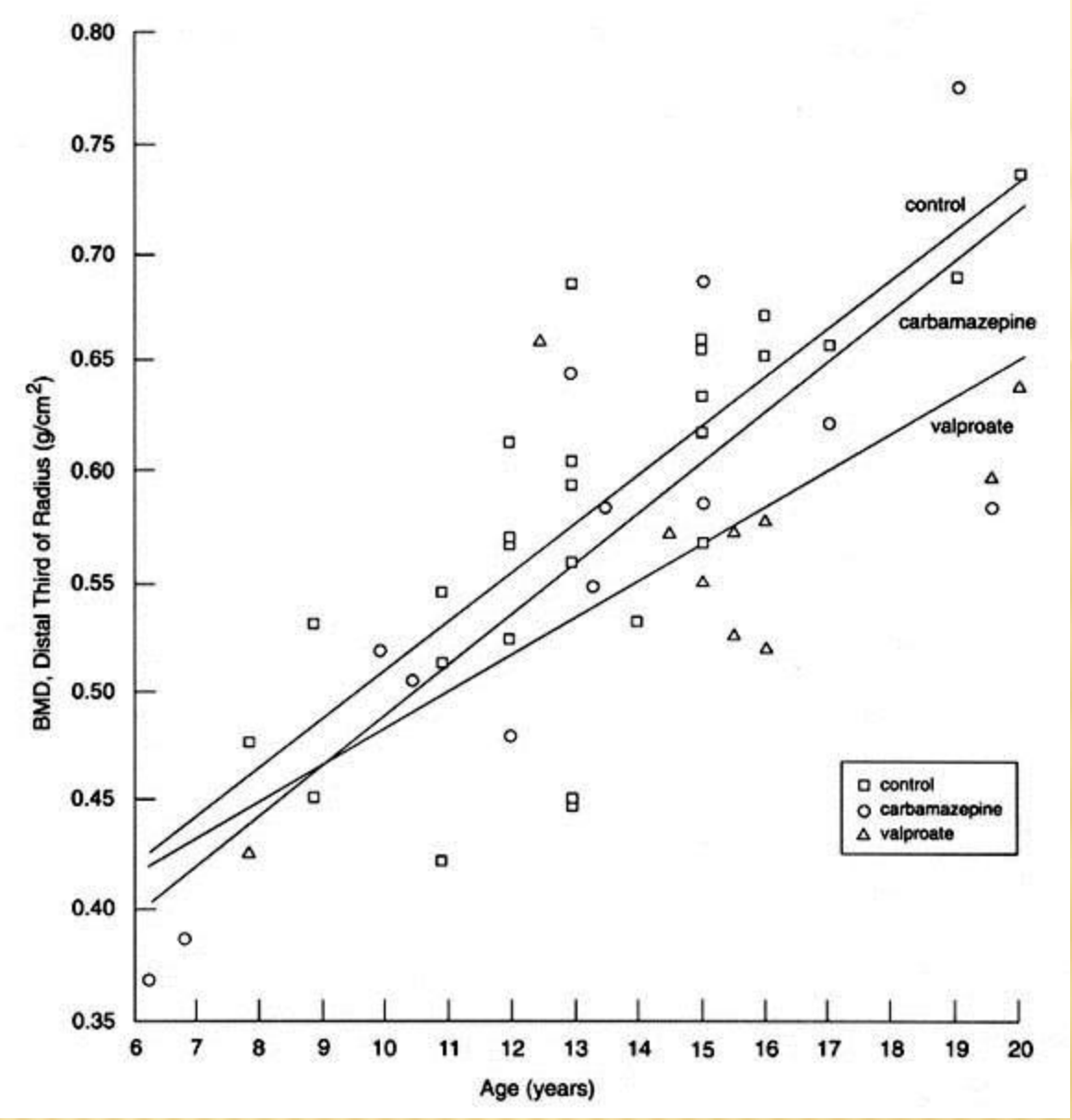
Fig. 2. Linear regression analysis with individual data points of mean bone mineral density of L-2 to L-4 plotted against age.

CBZ 8% lower BMD than control (P > 0:05).



Control (slope = 0.044; standard error of the slope 0.009 and $r^2 = 0.52$)
CBZ (slope = 0.054; standard error of the slope 0.008 and $r^2 = 0.86$)

Fig. 1 Linear regression analysis with individual data points of mean BMD at the distal third of the radius plotted against age.



Control (slope = 0.023; standard error of the slope 0.003 and r^2 = 0.64)
CBZ (slope = 0.024; standard error of the slope 0.005 and r^2= 0.72)

VALPROATE ON BONE MINERAL DENSITY

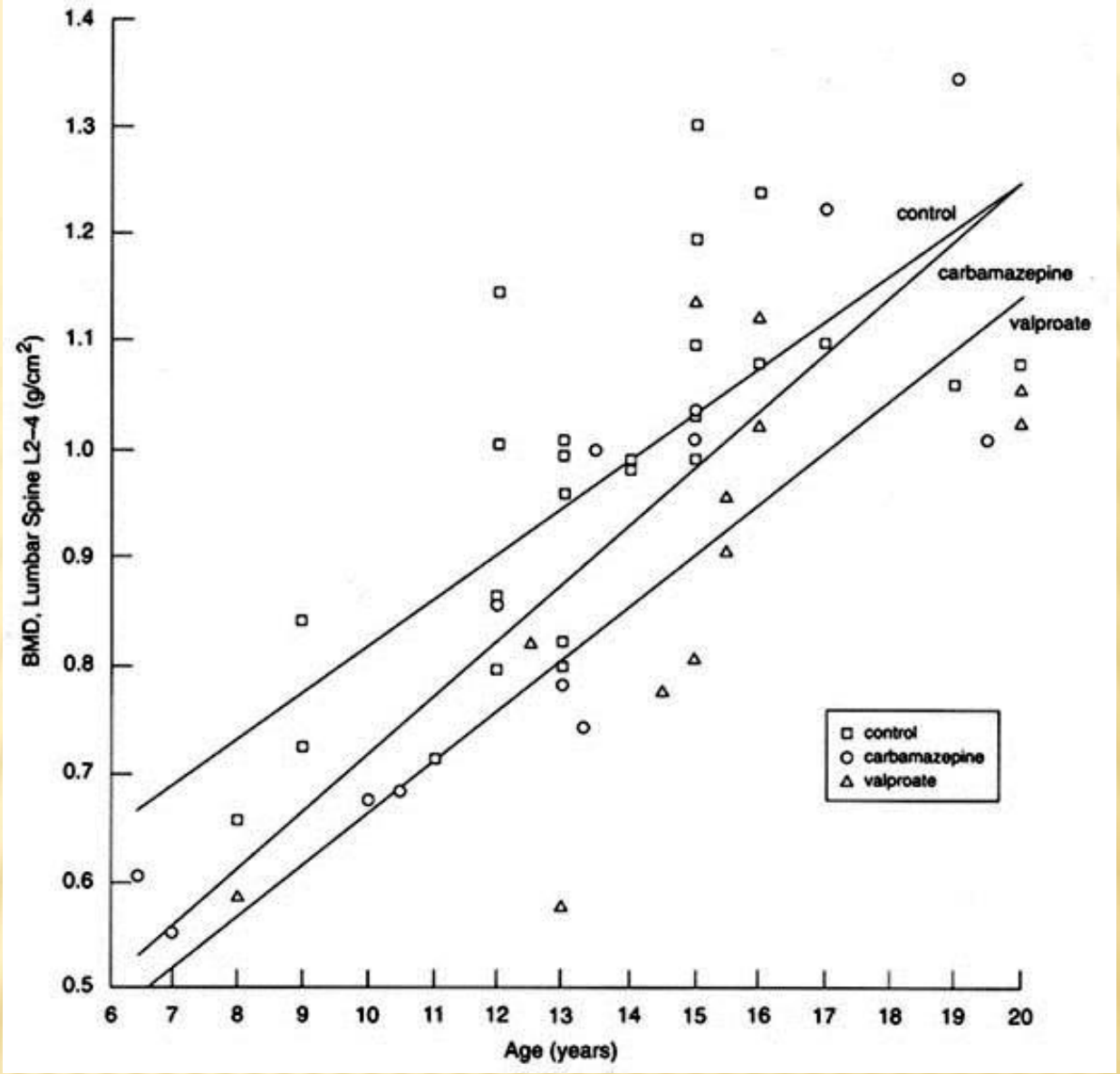
Table. Clinical features of control subjects and study subjects

	Control subjects (n = 27)	Study subjects: Valproate (n = 13)
Mean age (yr)	13.4 ± 2.8 (8-20)	15.4 ± 3.3 (8-20)
Boys/girls	15/12	6/7
Calcium intake (mg/day)	642 ± 202	740 ± 262
Mean dose (mg/kg/day)	—	72.04 ± 35.6 (23-106)
Mean serum trough level (μg/ml)	—	72.04 ± 35.6 (23-106)
Mean duration of therapy (yr)	—	3.1 ± 1.7 (1.5-7)

Mean values are mean ± SD. Values in parentheses are ranges.

- Subjects – JME or absence epilepsy, Seizure free for 6 months.
- Control – siblings, cousins. Age- and sex-matched, from a similar social class, and had similar physical activity and dietary calcium intake

Fig. 2. Linear regression analysis with individual data points of mean bone mineral density of L-2 to L-4 plotted against age.



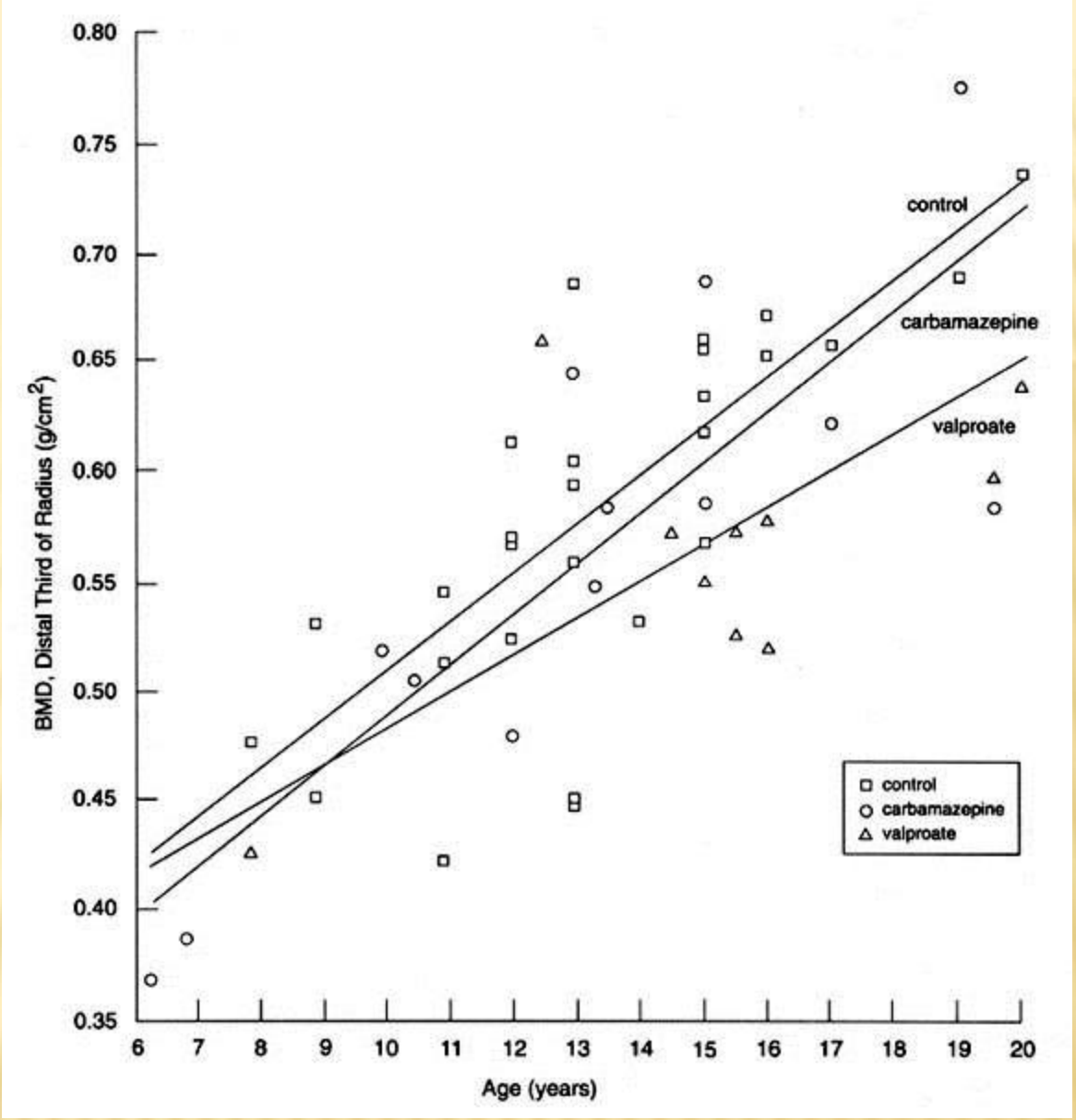
VPA associated with 14% reduction in BMD in lumbar spine ($P < 0:05$)

Control (slope = 0.044; standard error of the slope 0.009 and $r^2 = 0.52$)

VPA (slope = 0.048; standard error of the slope 0.012 and $r^2 = 0.61$)

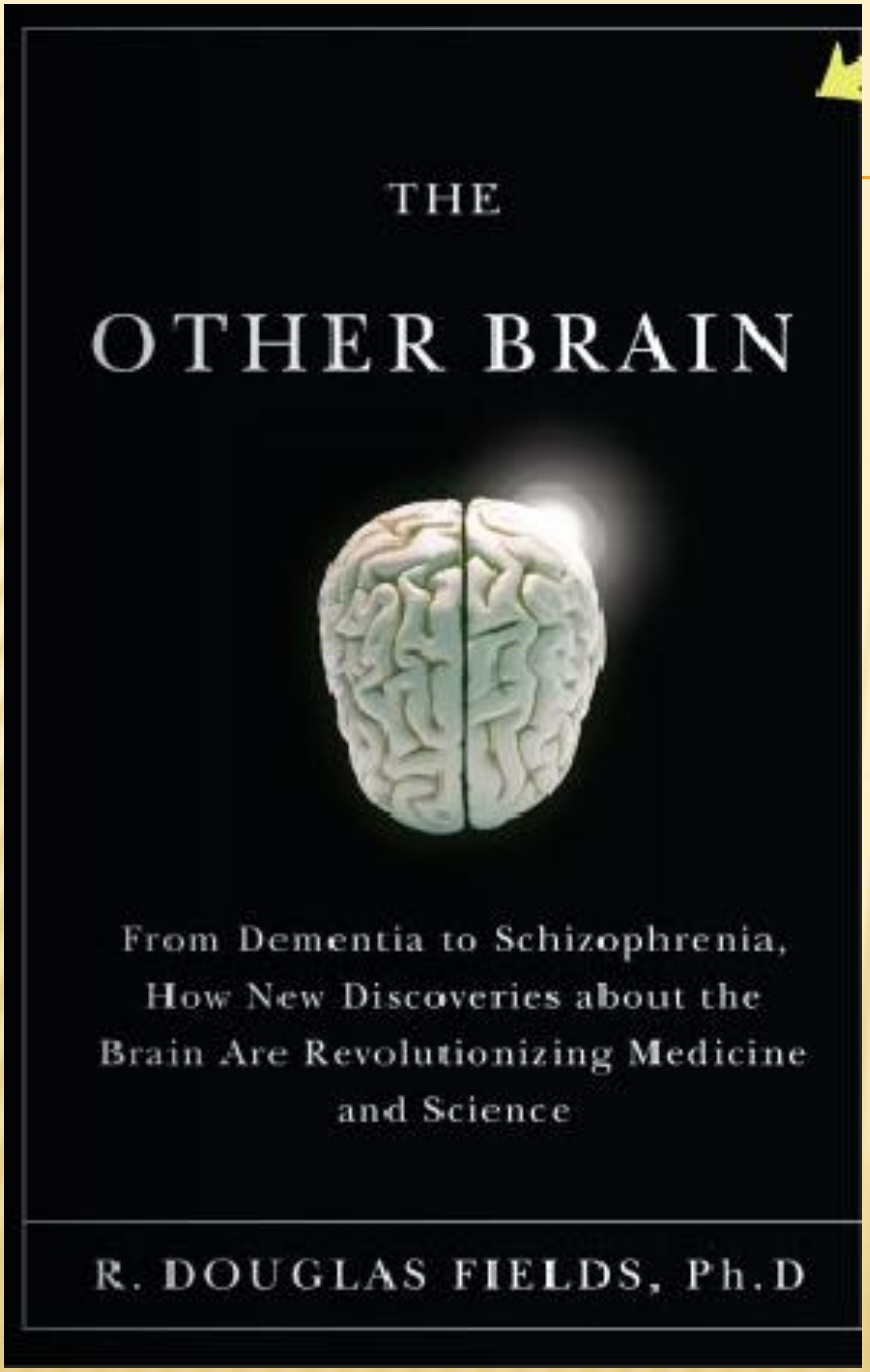
Fig. 1 Linear regression analysis with individual data points of mean BMD at the distal third of the radius plotted against age.

VPA associated with 10% reduction in BMD in distal radius.



Control (slope = 0.023; standard error of the slope 0.003 and $r^2 = 0.64$)

VPA (slope = 0.017; standard error of the slope 0.006 and $r^2 = 0.45$)



BOOK SUGGESTION: THE OTHER BRAIN

Effect of antiepileptic drugs on bone density in ambulatory patients

G. Farhat, MPH; B. Yamout, MD; M.A. Mikati, MD; S. Demirjian, MD, MPH; R. Sawaya, MD; and G. El-Hajj Fuleihan, MD, MPH

Abstract—*Background:* Long-term antiepileptic drug (AED) use causes multiple abnormalities in calcium and bone metabolism that have been most extensively described in institutionalized patients. The objective is to determine the effect of AED on vitamin D levels and bone density in ambulatory patients and to compare the effects of enzyme-inducing and -noninducing AED and of single vs multiple therapy on bone density. *Methods:* A cross-sectional evaluation was conducted of 71 patients (42 adults and 29 children/adolescents) on anticonvulsant therapy for at least 6 months who presented to neurologists at a tertiary referral center. Bone mineral density (BMD) as well as serum 25 hydroxy–vitamin D (25-OHD) levels were measured. A detailed questionnaire assessing calcium intake as well as previous and current intake of antiepileptic medications was administered to all patients. *Results:* Over 50% of adults and children/adolescents had low 25-OHD levels, but this finding did not correlate with BMD. Antiepileptic therapy decreased BMD in adults. Generalized seizures, duration of epilepsy, and polypharmacy were significant determinants of BMD, more so at skeletal sites enriched in cortical bone. Subjects on enzyme-inducing drugs such as phenytoin, phenobarbital, carbamazepine, and primidone tended to have lower BMD than those on noninducers such as valproic acid, lamotrigine, clonazepam, gabapentin, topamirate, and ethosuximide. *Conclusion:* Epilepsy and its therapy, including the newer drugs, are risk factors for low bone density, irrespective of vitamin D levels. Skeletal monitoring with the institution of appropriate therapy is indicated in patients on chronic antiepileptic therapy.

NEUROLOGY 2002;58:1348–1353

Chronic therapy with antiepileptic drugs (AED) causes abnormalities in calcium metabolism, including hypocalcemia, hypophosphatemia, elevated levically assessed the impact of age, multiplicity, and type of AED on vitamin D levels and BMD in ambulatory patients.

Table 1 *Baseline characteristics of study subjects*

Variables	All subjects (n = 71)	Adults (n = 42)	Children (n = 29)
Sex, F/M	34/37	22/20	12/17
Age, y	24.1 ± 14.4	33.0 ± 12.2	11.3 ± 3.8
Body mass index, kg/m^2	23 ± 5	26 ± 4	19 ± 5
Total calcium intake, mg/d, (N = 65)	620 ± 496	541 ± 468	732 ± 521
Duration of therapy, y	7 ± 8	9 ± 10	5 ± 4
25Hydroxy–vitamin D, ng/mL (n = 62)	17 ± 13	15 ± 11	20 ± 14
Type of seizures, n (%)			
Generalized		17 (42)	19 (66)
Focal		24 (58)	10 (34)
Type of therapy, n (%)			
Enzyme inducers		32 (76)	18 (62)
Nonenzyme inducers		10 (24)	11 (38)
Mode of therapy, n (%)			
Single		23 (55)	15 (52)
Multiple		19 (45)	14 (48)
Osteoporosis, n (%)*			
Spine and/or hip		1 (2)	NA
Osteopenia, n (%)*			
Spine and/or hip		25 (59)	NA

Table 1 . Baseline characteristics of study subjects.

Results are expressed as mean +/- SD unless otherwise indicated.* Defined per the World Health Organization operational definition (i.e.) bone mineral density T score <-2.5 for osteoporosis and a bone mineral density T score between -1 and -2.5 for osteopenia.

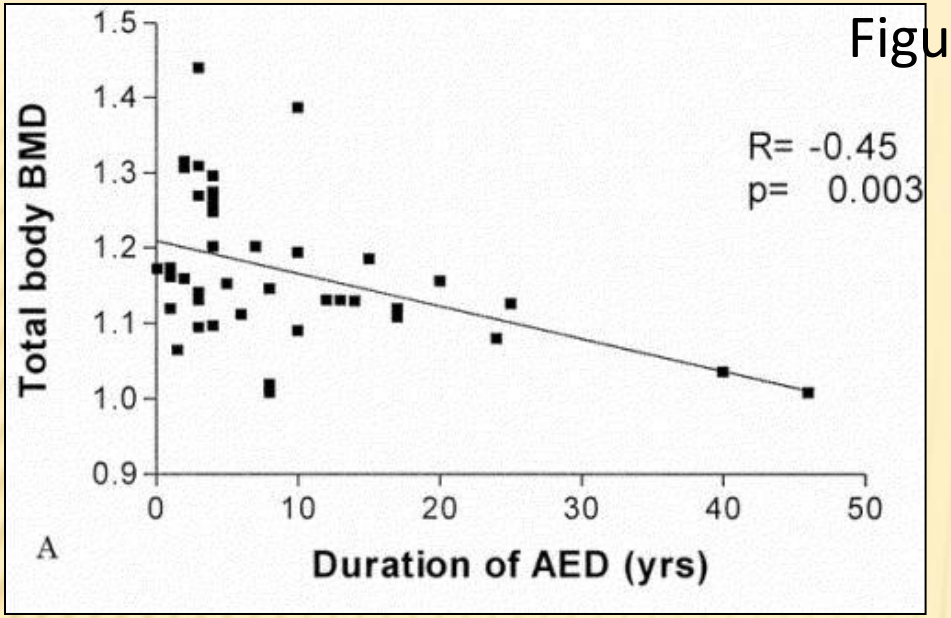
Table 2 *Baseline bone mineral density (BMD) for all study subjects*

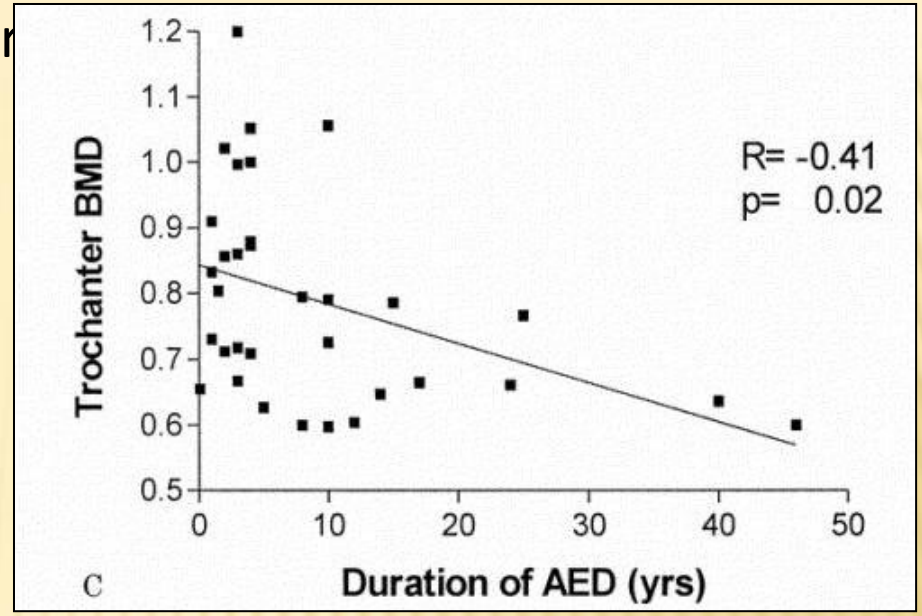
Site of bone mass	Adults (n = 42)	Children (n = 29)
Lumbar spine BMD, g/cm^2	1.14 ± 0.16	0.82 ± 0.27
Z score	−0.43 ± 1.15*	−0.42 ± 1.80
T score	−0.50 ± 1.20*	
Hip BMD, g/cm^2	0.95 ± 0.13	NA
Z score	−0.65 ± 0.78*	
T score	−0.69 ± 0.98*	
Femoral neck BMD, g/cm^2	0.92 ± 0.15	NA
Z score	−0.57 ± 0.96*	
T score	−0.71 ± 1.11*	
Trochanter BMD, g/cm^2	0.79 ± 0.16	NA
Z score	−0.72 ± 0.94*	
T score	−0.75 ± 1.06*	
Total body BMD, g/cm^2	1.17 ± 0.10	0.97 ± 0.14
Z score	−0.11 ± 0.83	0.47 ± 1.22
T score	−0.11 ± 0.99	
Total body BMC, g	2,690 ± 487	1,533 ± 807

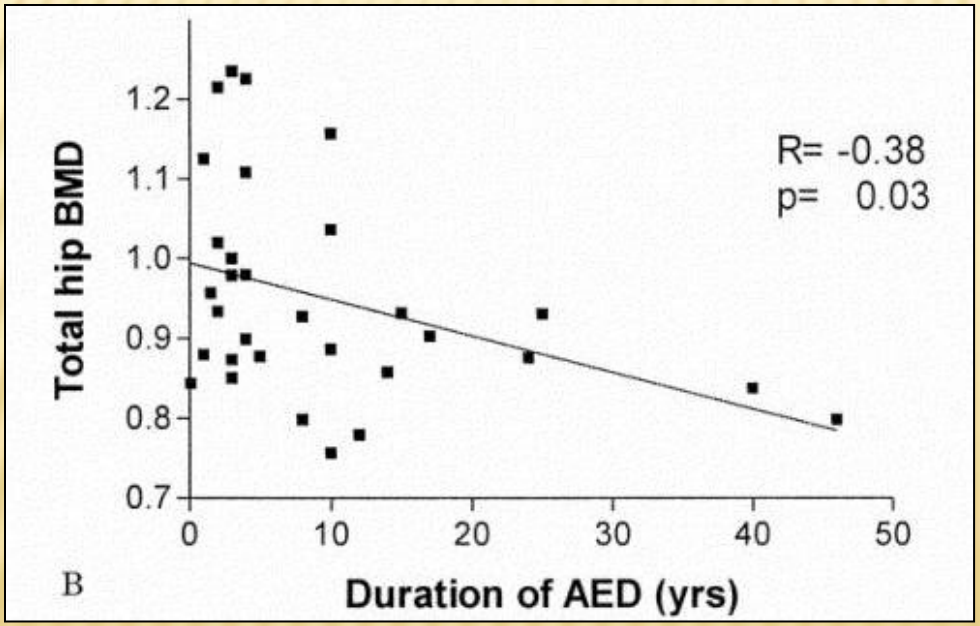
Table 2 . Baseline bone mineral density (BMD) for all study subjects.

Results are expressed as mean +/- SD.*p Z <0 denotes a mean BMD that is lower than that of age-matched controls, and a T score <0 denotes a mean BMD that is less than that of young adults (age range: 20-29 years) as provided by densitometer's database.NA = not available in densitometer's software; BMC = bone mineral content.

Figur







Correlation between duration of antiepileptic drug (AED) and bone mineral density (BMD) at the total body (A), total hip (B), and trochanter (C) in adult patients.

Table 3

Table 3 Serum 25 hydroxy-vitamin D (25-OHD) levels and bone mineral density (BMD) in adult patients taking single or multiple therapy

Variable	All adults	Single therapy (n = 23)	Multiple therapy (n = 19)	*p* Value
Duration of therapy, y	9 ± 10	6 ± 6	13 ± 12	0.01
25-OHD, ng/mL	15 ± 11	11 ± 7	20 ± 13	0.02
Lumbar spine BMD, g/cm^2		1.14 ± 0.19	1.15 ± 0.13	NS
Hip BMD, g/cm^2		1.00 ± 0.13	0.90 ± 0.12	0.03
Femoral neck BMD, g/cm^2		0.95 ± 0.17	0.89 ± 0.12	NS
Trochanter BMD, g/cm^2		0.85 ± 0.16	0.71 ± 0.11	0.01
Total body BMD, g/cm^2		1.19 ± 0.09	1.14 ± 0.10	NS
Total body BMC, g		2,815 ± 474	2,539 ± 471	NS

Values are expressed as mean ± SD.

Table 3 . Serum 25 hydroxy-vitamin D (25-OHD) levels and bone mineral density (BMD) in adult patients taking single or multiple therapy. Values are expressed as mean +/- SD. BMC = bone mineral content; NS = not significant.

Table 4

Table 4 Serum 25 hydroxy-vitamin D (25-OHD) levels and bone mineral density (BMD) in children/adolescents taking enzyme-inducing or -noninducing antiepileptic therapy

Variable	All children	Nonenzyme inducing (n = 18)	Enzyme inducing (n = 11)	*p* Value
Duration of therapy, y	5 ± 4	3 ± 3	6 ± 4	0.05
25-OHD, ng/mL	20 ± 14	22 ± 18	18 ± 11	NS
Lumbar spine BMD, g/cm^2		0.79 ± 0.31	0.84 ± 0.24	NS
Total body BMD, g/cm^2		0.93 ± 0.15	0.99 ± 0.14	NS
Total body BMC, g		1,302 ± 724	1,692 ± 845	NS

Values are expressed as mean ± SD.

Table 4 . Serum 25 hydroxy-vitamin D (25-OHD) levels and bone mineral density (BMD) in children/adolescents taking enzyme-inducing or -noninducing antiepileptic therapyValues are expressed as mean +/- SD.BMC = bone mineral content; NS = not significant.

INFERENCE

- BMD was reduced and that the reduction was not correlated with vitamin D levels.
- Mean (SD) 25-hydroxyvitamin D levels were lower for the enzyme inducing AEDs (18 +/- 11 ng/mL) compared with non-enzyme- inducing AEDs (22 +/- 18 ng/mL).
- Enzyme-inducing AEDs were used for 6 +/- 4 years and non-enzyme-inducing AEDs for 3 +/- 3 years.
- Duration of therapy was the strongest predictor of lowered BMD for both enzyme-inducing and non-enzyme-inducing AEDs.
- Total body bone mineral content was lower in the patients taking non-enzyme-inducing AEDs (1302 +/- 724 g) than in those taking enzyme-inducing AEDs (1692 +/- 845 g),

VALPROATE AND FRACTURES

- Pavlakis et al. reported on four girls treated with valproate for between 1 and 6 years who sustained multiple fractures without obvious derangement in serum markers of osteomalacia.
- A 13-year-old girl with epilepsy resulting from head trauma sustained in a motor vehicle accident, had 20 fractures between 5 and 9 years of age.
- She was treated with valproate monotherapy and had normal serum levels of parathyroid hormone, calcium, vitamin D, and alkaline phosphatase. Valproate levels were below 100 mg/L.
- After discontinuation no further fractures for 4 years of follow-up.

Pavlakis SG, Chusid RL, Roye DP, Nordli DR. Valproate therapy: predisposition to bone fracture. Pediatr Neurol 1998;19:143–4.

Why Valproate is worse than enzyme inducing AEDs?

PATHOPHYSIOLOGY

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The Effects of Valproate, Carbamazepine, and Oxcarbazepine on Growth and Sexual Maturation in Girls With Epilepsy

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From the Departments of * Neurology, ‡ Pediatrics, and § Radiology, University of Oulu, Oulu, Finland.

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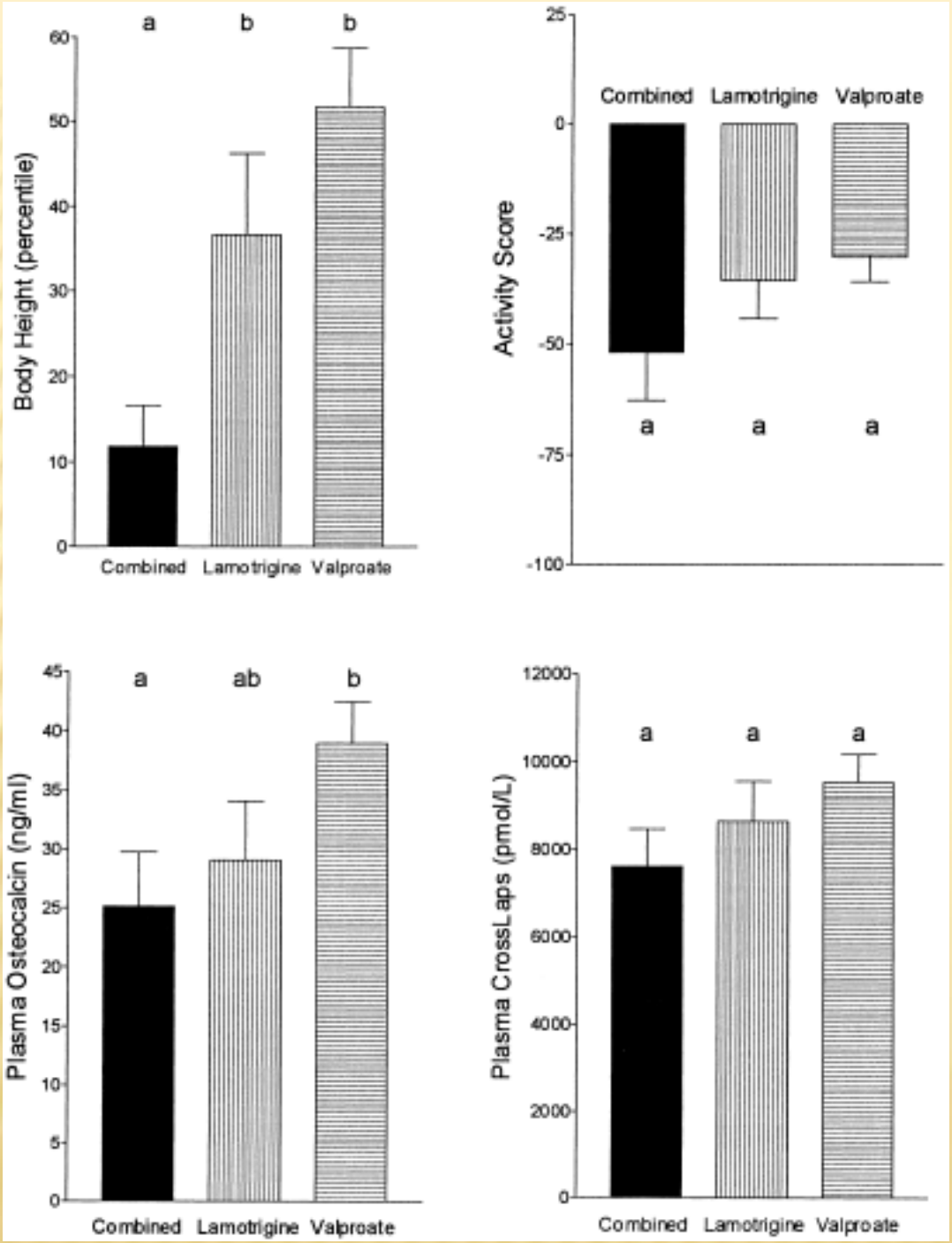
The effect of valproate cannot be readily explained by vitamin D metabolism, since this agent is not an inducer of the CYP450 system.

Effects of valproate on bone may occur as a result of this agents effect on insulin-like growth factor I.

LAMOTRIGINE

- Treatment with valproate or lamotrigine for more than 2 years was associated with short stature, low bone mass, and reduced bone formation.
- The major predictor of lowered bone mass was physical inactivity

Guo CY, Ronen GM, Atkinson SA. Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. Epilepsia 2001;42:1141–7.



Comparison in body height (upper left),

activity score (upper right),

plasma osteocalcin (lower left),

CrossLaps (lower right)

between children with epilepsy treated with valproate (VPA) alone, lamotrigine (LTG) alone, or a combined therapy of VPA and LTG.

The bars represent means, and the whiskers represent standard errors.

LEVETIRACETAM

- Can't find human studies.
- We can look at effect of LEV on rat bone mass, structure and metabolism.*
- Female rats received PHT (50mg/kg), VPA (300mg/kg), or LEV (50 and 150mg/kg) for 90 days.
- Dissected femurs were analyzed using
  - dual energy x-ray absorptiometry (DXA),
  - three-point cantilever bending,
  - histomorphological evaluation,
  - Serum levels of biochemical bone turnover markers were monitored using immunoassay quantification

* *Nissen-Meyer, L. S. H., Svalheim, S., Taubøll, E., Reppe, S., Lekva, T., Solberg, L. B., Melhus, G., Reinholt, F. P., Gjerstad, L. and Jemtland, R. (2007), Levetiracetam, Phenytoin, and Valproate Act Differently on Rat Bone Mass, Structure, and Metabolism. Epilepsia, 48: 1850–1860.*

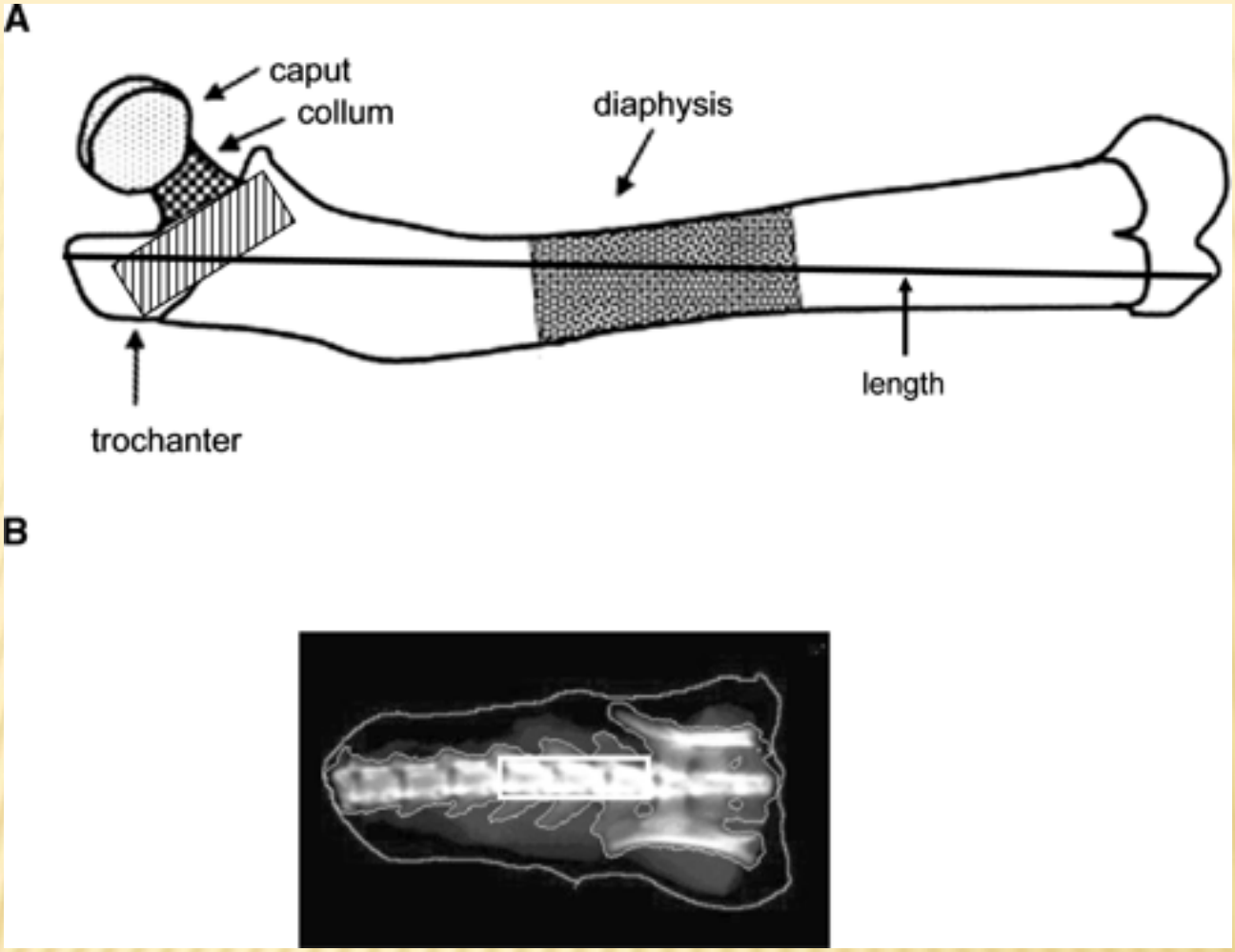


Figure 1.
(A) Diagram of rat femur showing the regions of interest (ROIs) investigated by DXA, that is, femoral neck, trochanter, and diaphysis. The straight line from trochanter to the lateral condyle represents the location where bone length was measured.
(B) DXA of lumbal columna with the ROI L3–L5 shown (white rectangle).

RESULTS

- PHT and VPA reduced BMD and content (BMC) in bone, whereas LEV did not.
- VPA induced increased bone turnover, whereas modest changes were observed for PHT.
- Interestingly, low-dose LEV was associated with reduced biomechanical strength of the femoral neck (mainly trabecular bone).
- In addition, low-dose LEV treatment resulted in significantly reduced levels of serum osteocalcin, a marker of bone formation.
- Histomorphological analyses indicated increased retention of cartilage remnants at the growth plate metaphysis of rats treated with low-dose LEV vs. controls.

GABAPENTIN

- There is no study that has examined the relationship between bone metabolism and GBP monotherapy.
- However, there are three papers [5], [19] and [21] that have studied a group of adult epileptic patients treated with different AEDs, including GBP. From their data, there was evidence that long-term GBP therapy may cause bone loss at the hip and lumbar spine.
- More recently, Ensrud et al. [123] confirmed, in a prospective study, that this AED can cause a significant hip bone loss in older men, suggesting that GBP is not free from this important adverse effect.
- To date, no changes in biochemical parameters of bone metabolism have been associated with GBP treatment.

OXCARBAZEPINE

- OXC and its active metabolite, monohydroxy derivative (MHD) are not well studied.
- Babayigit et al. [16] measured BMD and determined the changes in biochemical markers of bone mineralization in 14 patients with idiopathic epilepsy who had received OXC for more than 1 year. They showed that patients had decreased BMD and increased serum alkaline phosphatase concentrations compared with controls.
- OXC monotherapy induced significant reductions in 25OHD, with a pattern of changes in other bone biomarkers suggestive of secondary hyperparathyroidism such as higher PTH and bALP. *(?Limited enzyme inducer)*

Table 1
Main effects of classic and new AEDs on bone and calcium metabolism.

Drug	BMD	25-OHD	Ca/P	PTH	Bone turnover
Classic AEDs					
Benzodiazepines	↓	↓	N	N	↑bALP ↑OC ↑ICTP ↑NTx
Carbamazepine	↓	↓	N	↑	↑bALP ↑OC ↑ICTP ↑NTx
Phenytoin	↓	↓	↓	↑	↑bALP ↑NTx
Phenobarbital	↓	↓	N	–	↑bALP ↑ICTP
Primidone	↓	↓	N	–	–
Valproic acid	↓	N	N	N	↑ALP ↑OC
New AEDs					
Gabapentin	↓	–	–	–	–
Lamotrigine	N	N	N	?	N
Levetiracetam	N	N	N	–	?
Oxcarbazepine	↓	↓	N	↑	↑bALP
Zonisamide[a]	↓	–	–	–	↑PYD

[a] Results from animal studies.

Bone and calcium metabolism and antiepileptic drugs. *Verrotti A, Coppola G, Parisi P, Mohn A, Chiarelli F. Clin Neurol Neurosurg. 2010 Jan;112(1):1-10. Epub 2009 Nov 12. Review.*

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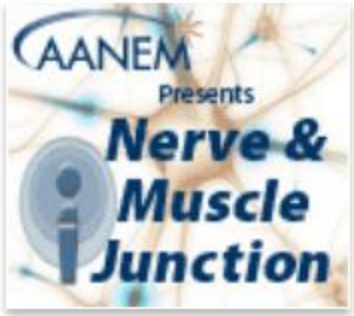

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SUGGESTION OF PODCAST

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SUMMARIES

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AED related bone loss

PREVENTION & TREATMENT

INTRODUCTION

- Most affected patients have increased bone remodeling rather than decreased mineralization.
- Milder cases may show high bone turnover without significant loss of cortical or trabecular bone.
- Intermediate severity may exhibit the characteristic features of a high-turnover osteopenia/osteoporosis.
- Severe bone disease may manifest the features of an osteomalacic disorder

TREATMENT WILL DEPEND ON SEVERIATY

Fracture

Osteomalacia

Osteoporosis

Osteopenia

Increased turnover

Stay Active

FINAL WORDS

- Prophylactic vitamin D 2000 IU/day – at initiation of AED.
- A calcium intake of 600–1000 mg/day.
- Osteopenic/osteoporosis, 2000–4000 IU/day vitamin D.
- Osteomalacia, 5000–15,000 IU/day Vitamin D
- Conventional treatment with bisphosphonates when vitamin D is inadequate.
- Routine use of bisphsphonates – not recommended.

PROPHYLAXIS

- Barden et al. reported that institutionalized adults treated with anticonvulsants were relatively protected from bone loss if supplied with a daily vitamin supplement containing at least 400 IU of vitamin D
- Pathophysiology not understood but likely multifactorial.
- Economic impact of pathological bone fractures far exceeds the cost of a vitamin D supplement, and complications of therapy at doses of <2000 IU/day are negligible.
- Do we need a biomarker – which guides, patient selection?

* *Bone mineral status measured by direct photon absorptiometry in institutionalized adults receiving long-term anticonvulsant therapy and multivitamin supplementation. Calc. Tiss. Int.* ***31*** *(1980),*

PROPHYLAXIS IN SPECIAL SITUATION

- Multiple or high-dose anticonvulsants or the patient is institutionalized or has limited outdoor activity, selection of a higher dose of vitamin D (up to 2000 IU/day).
- Bone loss due to newer AEDs might be “unresponsive” to Vit D.
- Monitoring: serum calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D, and PTH, as well as DEXA.

MONITORING OF OSTEOPENIA/OSTEOPOROSIS

- Serum: hypocalcemia, hypophosphatemia, low 25-hydroxyvitamin D, increased alkaline phosphatase, inreased PTH, increased osteocalcin
- Urine: Urinary calcium,
- DEXA: decreased density

TREATMENT OF OSTEOPENIA/OSTEOPOROSIS

- Vitamin D in doses as high as 2000–4000 IU.* (this will normalize labs)
- Monitoring of response is essential.
- Might need to consider bisphosphonates.

* *N. Collins, J. Maher, M. Cole, M. Baker and N. Callaghan, A prospective study to evaluate the dose of vitamin D required to correct low 25-hydroxyvitamin D levels, calcium and alkaline phosphatase in patients at risk of developing antiepileptic drug-induced osteomalacia. Q. J. Med.* ***78*** *(1991),*

TREATMENT OF OSTEOMALACIA

- Majority of patients will respond to low dose Vit D, but few will not.
- Lab work similar to vitamin D-deficiency osteomalacia.
- Biopsy is gold standard for diagnosis. (excessively unmineralized osteoid)
- Vitamin D between 5000 and 15,000 IU/day for 3–4 weeks are appropriate for management of rickets/osteomalacia. (till Vit D level > 30 ng/mL)
- Optimize dietary calcium intake

Other “minor” issues

FOLIC ACID AND GINGIVAL HYPERTROPHY

Folic acid supplementation prevents phenytoin-induced gingival overgrowth in children

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ABSTRACT

Objective: Gingival overgrowth is an important adverse effect of phenytoin (PHT) therapy, occurring in about half of the patients. This study aimed to evaluate the effect of oral folic acid supplementation (0.5 mg/day) for the prevention of PHT-induced gingival overgrowth (PIGO) in children with epilepsy aged 6–15 years on PHT monotherapy for 6 months.

Methods: This was a randomized, double-blind, placebo-controlled trial conducted at a tertiary level hospital from May 2008 to June 2009. Children aged 6–15 years started on PHT monotherapy within last 1 month were eligible for inclusion. Preexisting gingival overgrowth, use of other folic acid antagonists, and macrocytic anemia were exclusion criteria. Trial subjects were randomized to receive either folic acid or placebo. The primary outcome measure was incidence of any degree of gingival overgrowth after 6 months of PHT monotherapy. The trial was registered with clinicaltrials.gov (NCT00781196).

Results: A total of 120 children were recruited, 62 and 58, respectively, in folic acid and placebo arms. The 2 arms were comparable at baseline. Twenty-one percent of patients in the folic acid arm developed PIGO, as compared with 88% receiving placebo ($p < 0.001$). Absolute risk reduction of PIGO by folic acid was 67% (95% confidence interval 54%–80%), and relative risk reduction was 0.76.

Conclusions: Oral folic acid was found to decrease the incidence of PIGO in children on PHT monotherapy, in a statistically significant and clinically relevant manner.

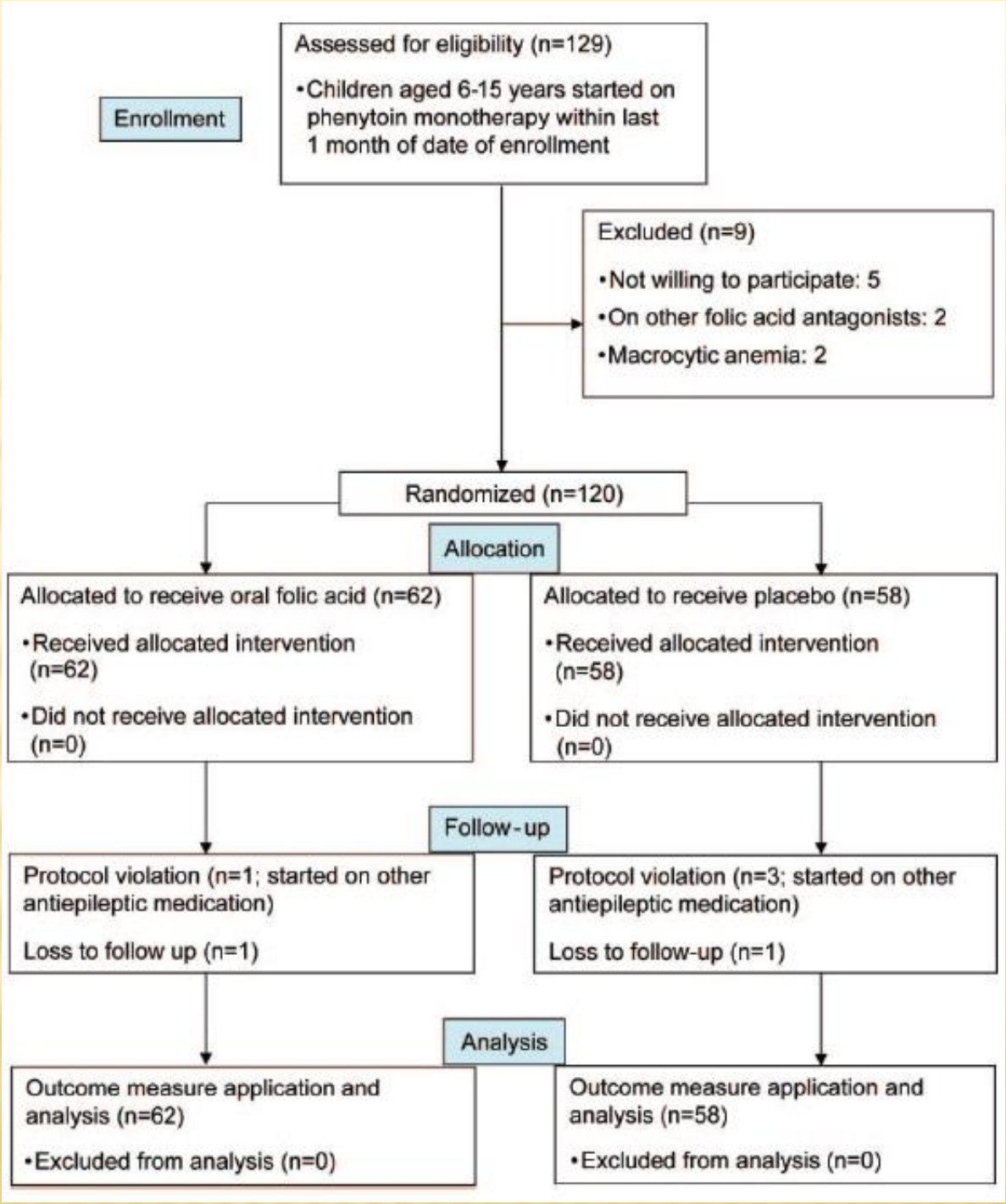
Enrollment
Assessed for eligibility (n=129)
•Children aged 6-15 years started on phenytoin monotherapy within last 1 month of date of enrollment
Excluded (n=9)
•Not willing to participate: 5
•On other folic acid antagonists: 2
•Macrocytic anemia: 2
Randomized (n=120)
Allocation
Allocated to receive oral folic acid (n=62)
•Received allocated intervention (n=62)
•Did not receive allocated intervention (n=0)
Allocated to receive placebo (n=58)
•Received allocated intervention (n=58)
•Did not receive allocated intervention (n=0)
Follow-up
Protocol violation (n=1; started on other antiepileptic medication)
Loss to follow up (n=1)
Protocol violation (n=3; started on other antiepileptic medication)
Loss to follow-up (n=1)
Analysis
Outcome measure application and analysis (n=62)
•Excluded from analysis (n=0)
Outcome measure application and analysis (n=58)
•Excluded from analysis (n=0)

Table 1 Baseline and end-of-trial comparisons between folic acid and placebo arms

	Folic acid	Placebo	*p* Value
Total enrolled	62	58	
Age, y, mean ± SD	8.7 ± 2.3	8.8 ± 2.2	0.839
Time from PHT start to enrollment, d, mean ± SD	10 ± 4.3	11 ± 4.6	0.218
M/F	37/25	29/29	0.287
Baseline plaque index, 0:1:2	22:30:10	22:24:12	0.699
PHT dose, mg/kg/day, mean ± SD	5.7 ± 0.8	6.0 ± 1.1	0.088
Protocol violations and loss to follow-up (%)	4 (6.5)	2 (3.5)	0.744
No. of patients requiring dose modification (%)	26 (41.9)	23 (39.7)	0.800
PHT dose, mg/kg/day, mean ± SD	6.8 ± 0.9	7.0 ± 1.0	0.319
PHT level, μg/mL, mean ± SD	13.7 ± 6.1 (n = 54)	13.2 ± 5.1 (n = 46)	0.323

Table 2 Gingival overgrowth in folic acid and placebo arms at the end of study period

	Folic acid, n (%)	Placebo, n (%)	Effect size (95% confidence interval)	Relative risk (95% confidence interval)	*p* Value
Any degree of gingival overgrowth	13/62 (21.0)	51/58 (87.9)	66.96 (53.808-80.112)	4.198 (2.571-6.856)	<0.001
Gingival overgrowth ≥ grade II	2/62 (3.2)	8/58 (13.8)	10.56 (0.655-20.465)	4.281 (0.949-19.316)	0.036

Table 3 Relationship of gingival overgrowth with phenytoin dose and serum levels in folic acid and placebo arms

Subgroup	GO	No GO	*p* Value
Folic acid group, n	13	49	
Dose, mg/kg/day, mean ± SD	6.1 ± 1.2	5.76 ± 0.8	0.216
Levels, μg/mL, mean ± SD (n)	15.0 ± 3.7 (11)	13.5 ± 2.5 (43)	0.108
Placebo group, n	51	7	
Dose, mg/kg/day, mean ± SD	6.0 ± 1.0	5.5 ± 0.7	0.221
Levels, μg/mL, mean ± SD (n)	13.4 ± 2.8 (41)	10.7 ± 1.0 (5)	0.040

WHY DO I CARE – EPILEPSY IS NOT MAJOR PART OF MY PRACTICE

- AEDs are used for
  - Migraine
  - Chronic pain
  - Psychiatric illness (bipolar – VPA, LTG)
  - Movement disorder (ET – primidone)
  - Obesity (TPX – not FDA approved)