Choosing AEDs in special situations

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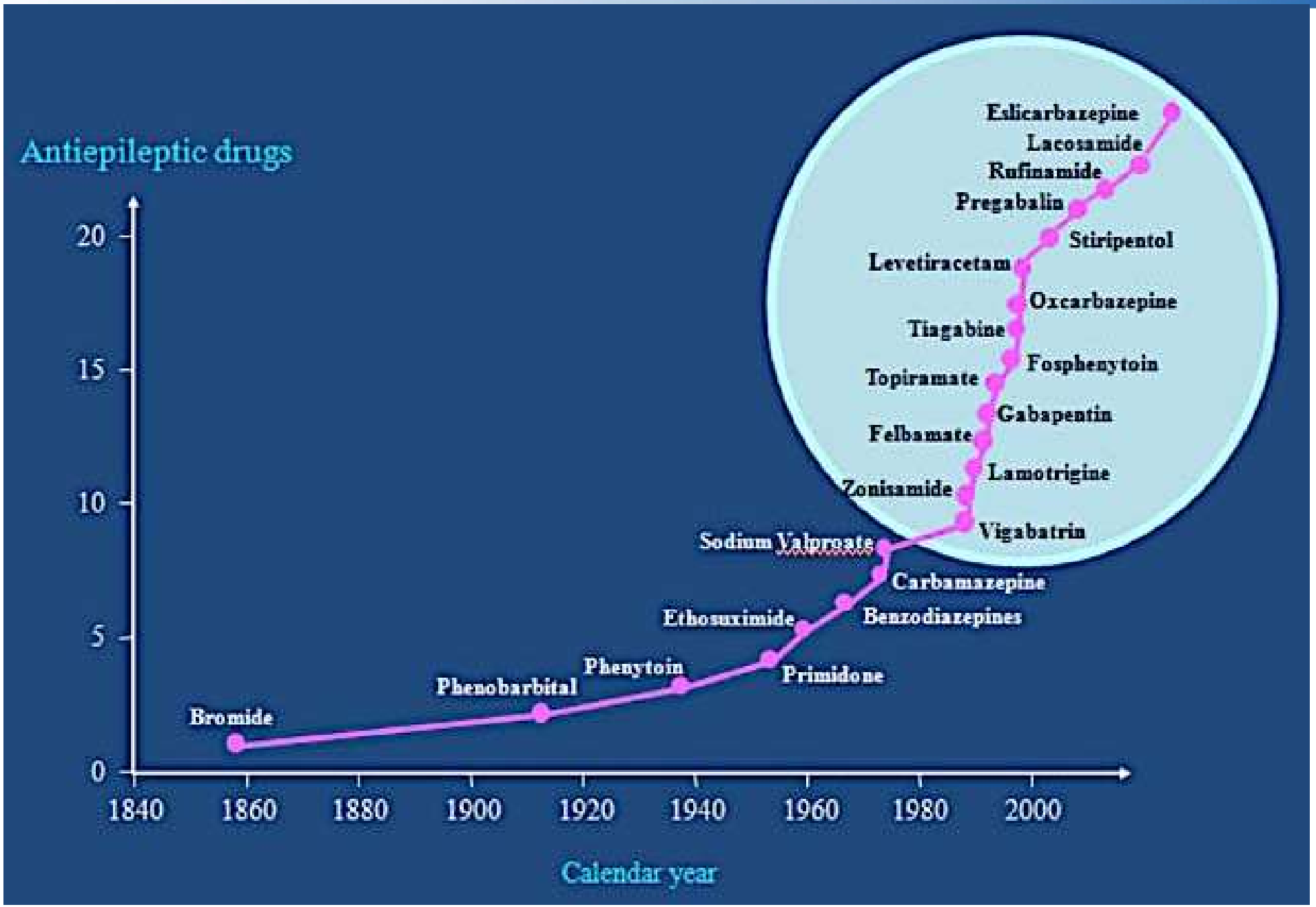
Which medications?

- ลักษณะการชักและประเภทของโรคลมชักของผู้ป่วย
- การบริหารยา
- ผลข้างเคียงของยากันชัก
- Drug interaction กรณีที่ผู้ป่วยได้ยาหลายชนิดพร้อมกัน
- Special situations
  - Reproductive age
  - Elderly
  - Hepatic impairment
  - Renal impairment

Antiepileptic drug development



Special situations

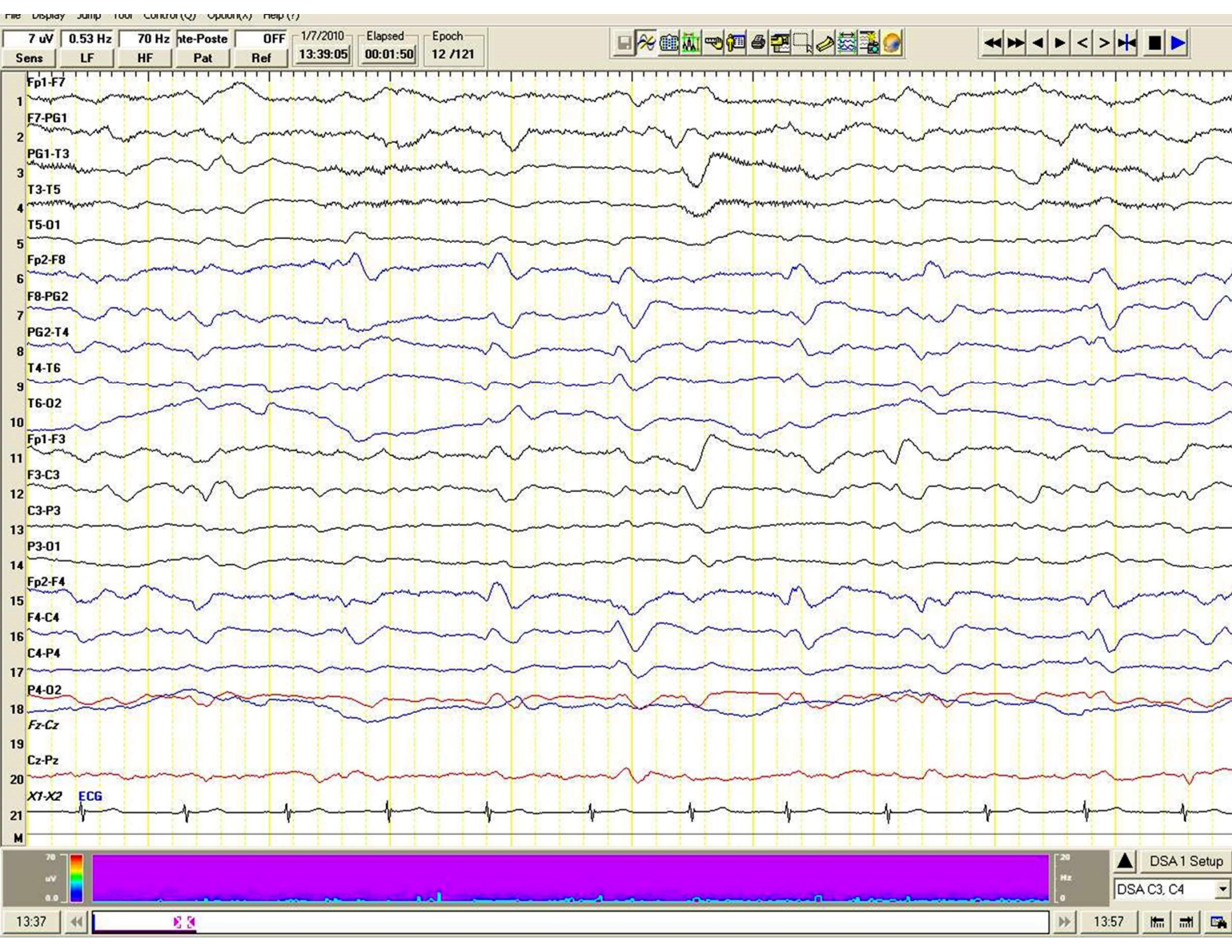
Special situations

- **Hepatic and renal dysfunction**
- **Other medical conditions**
  - Transplant patients
  - HIV infected patients
  - Patients with brain tumor
- **Psychiatric patients**
- **Elderly**
- **Women**

Hepatic and renal dysfunction

Seizures and epilepsy in this condition

- More acute seizures and status epilepticus precipitated by metabolic causes
- Need to differentiate between alteration of consciousness from metabolic encephalopathy and nonconvulsive status epilepticus (Clinically and EEG)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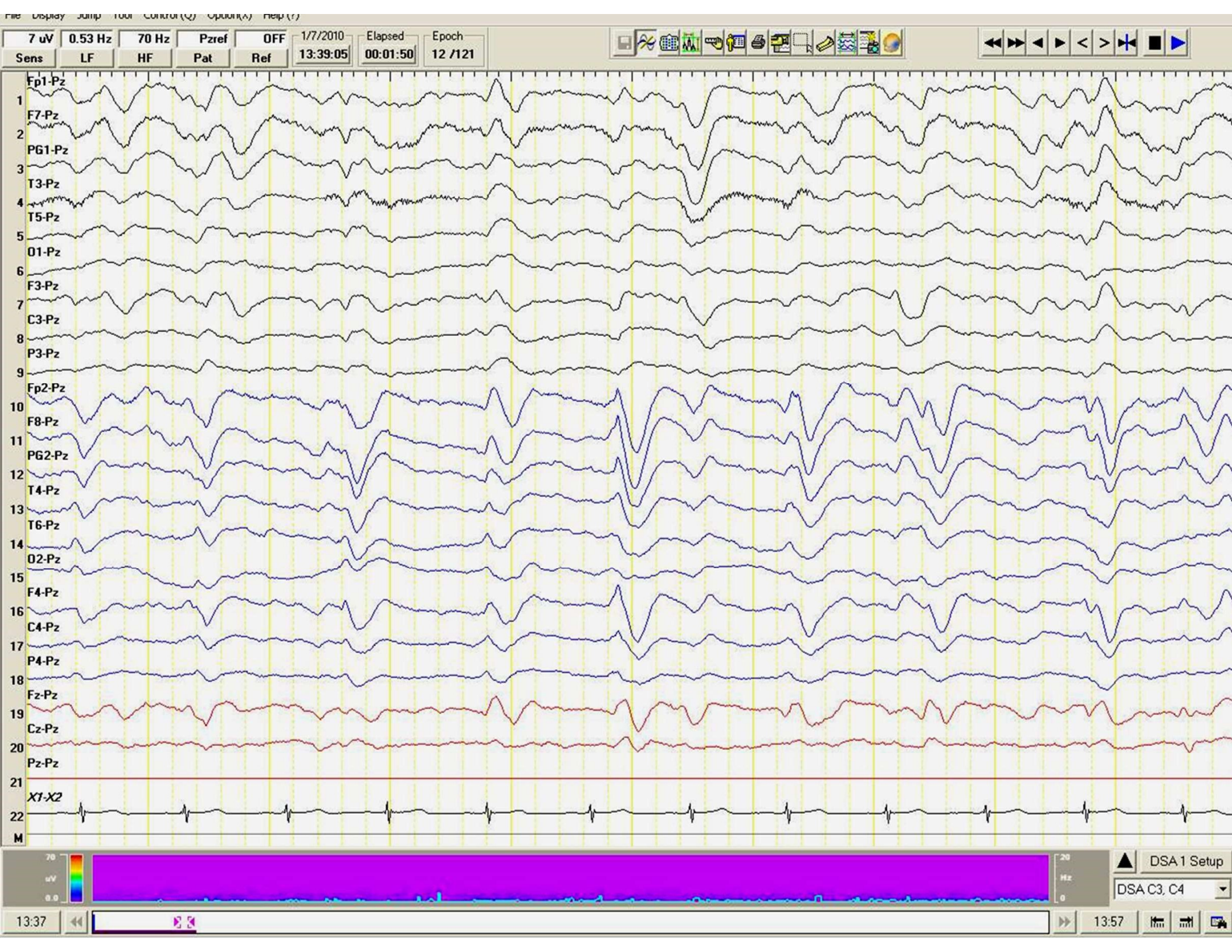
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P4-Pz
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X1-X2
DSA 1 Setup
DSA C3, C4
13:37
13:57

Hepatic dysfunction

Factors affecting hepatic clearance

- The extent of drug binding to the blood component
- Hepatic blood flow
- Hepatic metabolic activity

AED	Protein binding %	T/2	Site of elimination	Remarks
Gabapentin	0	4-6	Renal, 100% Not metabolize	Dose dependent absorption
Lamotrigine	55	15-30	Hepatic, 90% Glucoronidation	Clearance increased by enzyme inducing AEDs, reduced by VPA
Topiramate	9-17	15-23	Renal, 40-70%	Fraction hepatically metabolized, increased by enzyme inducing AEDs
Levetiracetam	0	6-8	Renal, 66%; hydrolysis of acetamide gr, 34%	Metabolism is nonhepatic hydrolysis
Oxcarbazepine	40	4-9	Hepatic, 70% Hepatic conversion to active metabolite	Based upon 10 Hydroxy carbazepine (MHD), the major active metabolite
Zonisamide	40-60	24-60	Hepatic, 70%	Clearance increased by enzyme inducing AEDs
Pregabaline	0	6	Renal Not metabolize	

Effects	Older AEDs	New AEDs
Measurable increased in free fraction with hypoalbuminemia	PHT VPA	-
Metabolism affected by renal disease	PB	GBP, LEV, TPM
Metabolism affected by liver disease	CBZ, PHT, VPA	LTG, ZNS, OXC, TGB

Dosing adjustment for patients with impaired hepatic function

- There is insufficient information available to make recommendations on the necessity of dosage adjustment

Patients with impaired hepatic function

- **Free fractions of diazepam, PHT, and VPA increase as a result of reduced circulating albumin concentrations. Frequent serum determinations of free fractions and gradual dose regulations are required.**

Renal dysfunction

Effects	Older AEDs	New AEDs
Measurable increased in free fraction with hypoalbuminemia	PHT VPA	-
Metabolism affected by renal disease	PB	GBP, LEV, TPM
Metabolism affected by liver disease	CBZ, PHT, VPA	LTG, ZNS, OXC, TGB

Dosing adjustment for patients with impaired renal function

Creatinine clearance (mL/min)	Dosage (mg)
Gabapentin	
>60	400 tid
30-60	300 bid
15-30	300 od
<15	300 every other day
hemodialysis	200-300* supplement
Levetiracetam	
>80	500-1500 bid
50-80	500-1000 bid
30-50	250-750 bid
<30	250-500 bid
hemodialysis ***with supplement dose after HD**	500-1000*q 24 hr then 250-500 mg supplement

Dosing adjustment for patients with impaired renal function

Creatinine clearance (mL/min)	Dosage (mg)
Topiramate	
>70	Normal dosage
10-70	Decrease dosage 50%
<10	Decrease dosage 75%
hemodialysis	Consider supplement

AEDs that can cause renal stone

- Topiramate
- Zonisamide

Using AEDs in patients with other medical conditions

Metabolic pathways of AEDs

CYP 1A2	CYP 2C9	CYP 2C19	CYP 3A4
Carbamazepine*	Phenytoin	Phenytoin*	Carbamazepine
	Phenobarbital	Diazepam	Tiagabine
	Valproate*		Zonisamide
			Ethosuximide
			Felbamate

*Minor metabolic pathway.

Effects on hepatic enzymes

Enzyme inhibitor	Enzyme inducer
Sodium valproate	Phenytoin
	Carbamazepine
	Phenobarbital

Interaction with other drugs

- Interaction between CYP3A4 inhibitors and carbamazepine
- Warfarin
- OCPs
- Psychiatric drugs
- Cardiac drugs
- Chemotherapy and immunosuppressive agents

Commonly used medications that inhibit the CYP3A4 isoenzymes

Erythromycin	Fluvoxamine
Clarithromycin	Nefazodone
Troleandomycin	Sertraline
Cimetidine	Ritonavir
Diltiazem	Indinavir
Verapamil	Nelfinavir
Fluconazole	Omeprazole
Itraconazole	Propoxyphene
Ketoconazole	

Drug interaction with warfarin

- Metabolites through CYP3A4, 2C9
- Phenytoin, phenobarbital and carbamazepine reduce the concentration of warfarin by up to 50-65%
- Phenobarbital and carbamazepine also reduce the anticoagulation effects of warfarin metabolites
- Newer AEDs do not have signinificant interaction with anticoagulant

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Short communication

Interactions between non-vitamin K oral anticoagulants and antiepileptic drugs

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ABSTRACT

Atrial fibrillation (AF) is a frequent cause of stroke. Secondary prophylaxis by oral anticoagulants (OAC) is recommended after stroke in AF-patients. OAC can be achieved by vitamin-K antagonists (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) like dabigatran, rivaroxaban, apixaban or edoxaban. Seizures are frequent after stroke, and antiepileptic drugs (AEDs) are indicated. The review, based on a literature research, aims to give an overview about pharmacokinetic knowledge and clinical data about drug–drug interactions (DDIs) between NOACs and AED.

Carbamazepine, levetiracetam, phenobarbital, phenytoin and valproic acid might decrease the effect of NOACs by inducing P-glycoprotein (P-gp) activity. Carbamazepine, oxcarbazepine, phenytoin, phenobarbital and topiramate might decrease the effect of NOACs by inducing CYP3A4 activity. Controversial data – inhibition as well as induction of CYP3A4 – were found about valproic acid.

The relevance of these DDIs is largely unknown since there are only sporadic case reports available. To increase the knowledge about DDIs between NOACs and AEDs we suggest subgroup analyses addressing effects and safety of VKAs versus NOACs in patients with AF on AEDs, in case they have been included in previously completed or still ongoing trials or registries. This could be easily feasible and would be desirable in view of the large data already accumulated.

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Stollberger C, et al. Epi Res 2016;126:98-101

- Intestinal absorption and renal elimination of NOACs are dependent on the intestinal and renal permeability glycoprotein (P-gp) efflux transporter protein system
- Some NOACs are substrates of the hepatic CYP3A4 enzymes
- Induction of P-gp or CYP3A4 might decrease serum NOAC levels, reduce anticoagulant effects and lead to an increase in embolic risk.

NOAC	P-GP substrate	CYP 3A4 substrate
Dabigatran	Yes	No
Rivaroxaban	Yes	Yes
Apixaban	Yes	Yes
Edoxaban	Yes	Yes

Pharmacokinetic drug interactions mediated by P-gp alone (dabigatran) or in combination with CYP3A4 enzymes (rivaroxaban and apixaban) have been reported

Chin PK, Wright DF, Zhang M, et al. C. Drugs R. D. 2014;14: 113–23.
Hellwig T, Gulseth M. Ann. Pharmacother 2013;47: 1478–87.
Serra W, Li Calz M, Coruzzi P. Clin. Pract 2015; 5: 788

Drug interaction with OCPs

- **AEDs that cause induction of CYP 3A4 increase metabolism of oral contraceptives resulting in failure of contraceptives.**
- **Potent enzyme inducing AEDs:**
  - phenytoin, carbamazepine, primidone, phenobarbital.
- **Less-potent enzyme inducing AEDs:**
  - oxcarbazepine, lamotrigine
  - topiramate >200 mg.

Drug Class	Interactions with AEDs
Antiarrhythmics	Inductor AEDs enhances antiarrhythmics metabolism; phenytoin decreases amiodarone metabolism.
Hypotensive agents	Inductor AEDs enhances beta-blockers and calcium-antagonist metabolism; verapamil and diltiazem inhibit carbamazepine metabolism.
Digoxin	Phenytoin increases digoxin metabolism.
Lipid-lowering drugs	Inductor AEDs enhance lipid-lowering agents metabolism.
Immunosuppressants	Phenytoin, carbamazepine, and barbiturates enhance tacrolimus, sirolimus, and methylprednisolone metabolism.
Antivirals	Inductor AEDs enhance anti-HIV agents metabolism; anti-HIV agents increase carbamazepine, gabapentin, levetiracetam, and lamotrigine levels.
Antibiotics	Carbapenems decrease valproate levels; macrolides increase carbamazepine levels.
Antifungal	Antifungals enhance carbamazepine and phenytoin levels.
Tuberculostatics	Rifampicin enhances phenytoin, carbamazepine, valproate, ethosuximide, and lamotrigine metabolism; isoniazide inhibits it.

Transplant patients

Using AEDs in transplant patients

- CBZ, oxcarbazepine, PB, and PHT may reduce cyclosporine, tacrolimus, and corticosteroid blood levels with a delayed effect of up to 10 days.
- Azathioprine, mycophenolate mofetil, and OKT3 metabolism are not significantly affected by AEDs.

HIV patients

Interaction between ARVs and AEDs

ARV	Protein binding (%)	Metabolism	Potential drugs that may have interaction with AEDs	AEDs that may have interaction with
NRTI	Min- 38	Gluc	↑Zidovudine	VPA
NNRTI	50-90	CYP450		
PI	>99	CYP450	↓Lopinavir/ Ritonavir	PHT

SPECIAL REPORT

Antiepileptic drug selection for people with HIV/AIDS: Evidence-based guidelines from the ILAE and AAN

*†Gretchen L. Birbeck, ‡Jacqueline A. French, §Emilio Perucca, ¶David M. Simpson, #Henry Fraimow, **Jomy M. George, ††Jason F. Okulicz, ‡‡David B. Clifford, §§Houda Hachad, and §§René H. Levy for the Quality Standards subcommittee of the American Academy of Neurology and the ad hoc task force of the Commission on Therapeutic Strategies of the International League Against Epilepsy

Epilepsia, 53(1):207–214, 2012

Recommendations

- AED–ARV administration may be indicated in up to 55% of people taking ARVs.
- Patients receiving phenytoin may require a lopinavir/ritonavir (PI) dosage increase of approximately 50% to maintain unchanged serum concentrations (Level C: one class II study).
- Patients receiving valproic acid may require a zidovudine (NRTI) dosage reduction to maintain unchanged serum zidovudine concentrations (Level C).
- Coadministration of valproic acid and efavirenz (NNRTI) may not require efavirenz dosage adjustment (Level C: one class II study).

Epilepsia, 53(1):207–214, 2012

Recommendations

- It may be important to avoid enzyme inducing AEDs in people on ARV regimens that include protease inhibitors or non nucleoside reverse transcriptase inhibitors because pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure efficacy of the ARV regimen (Level C: one class II study).

Epilepsia, 53(1):207–214, 2012

Brain tumors

Potentials interaction between AEDs and chemotherapy

- Enzyme inducing AEDs have been shown to have effects on levels of chemotherapy that metabolite through CYP 450
- Taxanes, vinca alkaloids, methotrexate, teniposide, and camptothecin analogues such as irinotecan

Vecht CJ, Wagner GL, Wilms EB. Lancet Neurol 2003;2:404–9.

Potentials interaction between AEDs and chemotherapy

- In a study of 716 children with ALL, 40 children who were on enzyme-inducing AEDs had worse event-free survival (hazard ratio 2.67 [95% CI, 1.50 to 4.76]), hematological relapse (3.40 [1.69 to 6.88]) and CNS relapse (2.90 [1.01 to 8.28]).
- These children were found to have a higher clearance of teniposide and methotrexate.

Relling MV, Pui CH, Sandlund JT, et al. Lancet 2000;356:285–90

Potentials interaction between AEDs and chemotherapy

- In a study on glioblastoma multiforme treated with adjuvant CCNU after surgery and radiotherapy, patients receiving enzyme-inducing AEDs (carbamazepine in80% of patients) had a significantly shorter survival,10.8 versus 13.9 months, than patients treated withnon-enzyme-inducing AEDs (valproic acid in 80% of patients)

Oberndorfer S, et al. J Neurooncol 2005;72:255–60

Patients with brain tumors

- Enzyme-inducing AEDS can interfere with the level of concomittent chemotherapy and should be avoided.
- Valproic acid may be considered as a first-line agent, although physicians should be aware of the potentially enhanced toxicity of concomitant agents that share the same P-450 coenzyme metabolic pathway.

Patients with brain tumors

- Newer AEDs that do not metabolite through CYP 450 system also can be used.
- More evidence is still needed.

Treatment with AEDs in the elderly

Issues in treatment of epilepsy in the elderly

- Changes in pharmacokinetics of AEDs in the elderly
- Side effects of the AEDs esp. cognitive side effects
- Osteoporosis
- Drug interaction

Pharmacokinetic changes in the elderly

Lean body mass ↓

Total body water mass ↓

Proportion of fat ↓

Volume distribution of hydrophilic drugs and lipophilic drugs ↓

Serum drug concentrations ↑

Pharmacokinetic changes in the elderly

- Decreased albumin level leads to increased free fraction of drugs in the body.
- Measurement of total serum drug concentration may not reflect the true unbound drug level.
- Reduce hepatic metabolism (evidence is still unclear) and reduce renal excretion with reduction of creatinine clearance

Caution of SE of AEDs in elderly

AEDs	Special precautions
Phenobarbital	Drowsiness, cognitive dysfunction May reduce effects of other drugs (enzyme inducer)
Phenytoin	Reduced metabolism and clearance Reduced protein binding → increased free fraction Increase incidence of adverse effects PHT level may be increased by amiodarone, cimetidine, isoniazid, trazodone May reduce effects of other drugs (enzyme inducer)
Carbamazepine	Increase incidence of adverse effects May reduce effects of other drugs (enzyme inducer) Hyponatremia
Sodium valproate	Drowsiness, parkinsonism Thrombocytopenia
Oxcarbazepine	Increase incidence of adverse effects Hyponatremia
Topiramate	Cognitive side effects at higher dosage (can be avoided by slow titration)

Interaction between AEDs and drugs for dementia

Table 2. Interactions Between Medications for Alzheimer Disease and Antiepileptic Drugs[a]

Alzheimer Medications	PHT	CBZ	PB	BZD	VPA	OXC	LEV	TOP	GBP	LTG	ZNS	PGB
Donepezil (D)	↓	↓	↓	—	—	↓	—	—	—	—	—	—
Galantamine (G)	↓	↓	↓	—	—	↓	—	—	—	—	—	—
Rivastigmine (R)	none	none	none	none	none	none	none	none	none	none	—	none
Tacrine (T)	none	none	none	none	none	none	none	none	none	none	—	none
Memantine (M)	none	none	none	none	none	none	none	none	none	none	—	none

Jenssen S, Schere D. American Journal of Alzheimer's Disease & Other Dementias 2010;25:18-26

Epilepsia, **(*):1–13, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

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Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	1	1	3	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized onset tonic–clonic seizures	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB

AEDs and osteoporosis

- **Epilepsy increases the risk of bone disease.**

- **The relative risk for**
  - osteopenia varies from 1.3 to 3.8
  - osteoporosis from 1.7 to 3.8
  - fractures from 1.7 to 6.1.

Phabphal K, Bone 2009;45:232–7.

- In a study from Thailand
- BMD values were found to be reduced to osteopenic levels in 36% of 123 adult patients with epilepsy and to osteoporotic levels in 4.1%
- Although 20% of the patients had vitamin D deficiency, this was unrelated to low BMD.
- Low body mass index, female gender, and longer duration of treatment were risk factors for bone loss.

Enzyme inducing AEDs

↓

Increased metabolism of vitamin D

↓

Reduced intestinal absorption of calcium

↓

Low serum calcium, secondary hyperparathyroidism,

↓

Decreased BMD

AEDs that have effects on bone health

- **Enzyme inducing AEDs: PHT, CBZ, PB**
- **Less evidence in: VPA**
- **Possible evidence in: TPM, OXC**

Gaitatzis A, Sander JW. CNS Drugs 2013; 27:435–455

All patients: adequate intake of dietary vitamin D and Ca and regular exercise

Institutionalized patients and postmenopausal women: supplement of vitamin D (800 IU) and Ca (1000 mg)

Patients with additional increased risk: supplement of vitamin D (1000–4000 IU) and Ca (1500 mg)

Dual-energy X-ray absorptiometry (DXA) scan 5 years after initiation of antiepileptic drugs (AED) treatment

DXA scan at initiation of AED treatment in postmenopausal women

DXA scan every 2–3 years in high-risk patients (eg. users of valproate or enzyme inducers)

T-scores < −1: supplement of vitamin D (800 IU) and Ca (1000 mg) and weight-bearing exercise

T-scores between −1 and −2.5: supplement of vitamin D (800 IU) and Ca (1000 mg), weight-bearing exercise, new DXA scan repeated after 1–2 years

T-scores < −2.5: referral for the treatment of bone disease, usually with the addition of bisphophanates

Svalheim S, et al. Acta Neurol Scand: 2011; 124 (Suppl. 191): 89–95.

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