# Matching antiepileptic medications with epilepsy patients

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## Which medications?

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

## Traditional antiepileptic drugs

- Phenobarbital
- Phenytoin
- Carbamazepine
- Sodium valproate
- Benzodiazepine

## New antiepileptic drugs

- Felbamate (1993)
- Gabapentin (1993)
- Lamotrigine (1994)
- Topiramate (1996)
- Tiagabine (1997)
- Levetiracetam (1999)
- Oxcarbazepine (2000)
- Zonisamide (2000)
- Pregabalin (2005)
- Vigabatrin

## Seizure types and epilepsy syndrome

## Spectrum of traditional AEDs

| ชนิดของอาการชัก | Traditional AEDs |
|---|---|
| Absence | Sodium valproate |
| Myoclonic, atonic | Sodium valproate |
| Generalized tonic clonic | Phenobarbital<br>Phenytoin<br>Carbamazepine<br>Sodium valproate |

## Spectrum of traditional AEDs

| ชนิดของอาการชัก | Traditional AEDs |
|---|---|
| Partial | Phenobarbital<br>Phenytoin<br>Carbamazepine<br>Sodium valproate |
| Infantile spasm | Vigabatrin |

## Spectrum of new AEDs

| Type of seizure | FBM | VGB | TGB | GBP | OXC | LTG | TPM | LEV | PGB | ZNS |
|---|---|---|---|---|---|---|---|---|---|---|
| Partial | + | + | + | + | + | + | + | + | + | + |
| Second generalize | + | + | + | + | + | + | + | + | + | + |
| Tonic clonic | ?+ | ?+ | ? | ?+ | + | + | + | + | ? | + |
| Absence | ?+ | - | - | - | - | + | ? | ?+ | ? | ?+ |
| Myoclonic | ? | - | ? | - | - | +* | + | + | ? | + |
| Lennox Gastaut | + | ? | ? | ? | - | + | + | ? | ? | ? |
| Infantile spasm | ? | + | ?+ | ? | - | ?+ | ?+ | ? | ? | ?+ |

*Hitiris N, Brodie MJ. Curr Opin Neurol 2006;19:175-80*

## Aggravation of seizures by AEDs

| | CBZ | OXC | PHT | LTG | VPA | GBP | VGB | BDZ |
|---|---|---|---|---|---|---|---|---|
| Absence | +++ | + | +++ | | | + | ++ | |
| Myoclonic | +++ | + | +++ | + | | + | + | |
| JME | ++ | + | ++ | + | | | | |
| LGS/MAE | ++ | + | ++ | + | | + | ++ | ++ |
| BECTS | + | | | + | + | | | |
| LKS/ ESES | + | | + | | | | | |
| ULD | | | + | | | | | |

| ชนิดของอาการชัก | Traditional AEDs | New AEDs |
|---|---|---|
| Absence | Sodium valproate | Lamotrigine<br>Clonazepam |
| Myoclonic, atonic | Sodium valproate | Lamotrigine<br>Topiramate<br>Clonazepam |
| Generalized tonic clonic | Phenobarbital<br>Phenytoin<br>Carbamazepine<br>Sodium valproate | Lamotrigine<br>Topiramate<br>Oxcarbazepine<br>Levitiracetam<br>Gabapentin<br>Clonazepam |

| ชนิดของอาการชัก | Traditional AEDs | New AEDs |
|---|---|---|
| Partial | Phenobarbital<br>Phenytoin<br>Carbamazepine<br>Sodium valproate | Lamotrigine<br>Topiramate<br>Oxcarbazepine<br>Levitiracetam<br>Gabapentin<br>Clonazepam<br>Clobazam |
| Infantile spasm | Vigabatrin | Sodium valproate<br>Topiramate<br>Clonazepam<br>Clobazam |

## Drug administration

Pharmacologic properties of old AEDs

| AEDs | Dosage in children | Dosage in adults | Half life (hrs) |
|---|---|---|---|
| Phenytoin | 4-8 mg/kg/d | 300 mg/d | 20-30 |
| Carbamazepine | 10-20 mg/ kg/d | 400-600 mg bid | 10-20 |
| Sodium valproate | 30-60 mg/ kg/d | 1000-1500 mg/d | 8-12 |
| Phenobarbital | 2-5 mg/kg/d | 120-250 mg/d | 96 |
| Clonazepam | | 0.5 mg bid | 18-50 |

Pharmacologic properties of the new AEDs

## Absorbtion

- Most of the new AEDs are rapidly absorbed with high bioavailability
- Gabapentin absorbtion is dose dependent

| AED | Protein binding % | T/2 | Site of elimination | Remarks |
|---|---|---|---|---|
| Gabapentin | 0 | 4-6 | Renal, 100%<br>Not metabolize | Dose dependent absorption |
| Lamotrigine | 55 | 15-30 | Hepatic, 90%<br>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%<br>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<br>Not metabolize | |

## New AEDs starting dose and titration

## Dosing table in adults

| Drugs | Starting dose (mg/d)<br>Rate of ↑ | Common dose (mg/d) | Maintenance range (mg/d) | Dosing interval |
|---|---|---|---|---|
| **Gabapentin** | **300-400**<br>**(300mg/d)** | **2400** | **1800-3600** | **tid** |
| **Lamotrigine** | **12.5-25*** | **200-400** | **100-400** | **OD-bid** |
| **Levetiracetam** | **500**<br>**(500mg/wk)** | **2000-3000** | **1000-4000** | **bid** |
| **Oxcarbazepine** | **150-300**<br>**(300 mg/wk)** | **900-1800** | **900-2400** | **Bid-tid** |
| **Topiramate** | **25-50** | **200-400** | **100-1000** | **bid** |
| **Zonisamide** | **100** | **400** | **400-600** | **OD-bid** |
| **Pregabalin** | **150** | **300** | **150-600** | **Bid-tid** |

## Dosing schedule for lamotrigine

| | MonoRx | Titrate | With Valproate | Titrate | With other AEDs | Titrate |
|---|---|---|---|---|---|---|
| **Adult** | | | | | | |
| Wk 1-2 | 25 mg OD | | 12.5 mg OD/AD | Slow | 50 mg OD | |
| Wk 3-4 | 25 mg bid | 25mg/wk | 25 mg OD | Slow | 50 mg bid | 50mg/wk |
| Maintenance | 50-100 mg bid | | 50-100 mg bid | | 100-200 mg bid | |
| **Children** | | | | | | |
| Wk 1-2 | 0.5 mg/kg | | 0.15 mg/kg | | 0.6 mg/kg | |
| Wk 3-4 | 1 mg/kg | 0.5 mg/kg/2wk | 0.3 mg/kg | 0.1-0.3 mg/kg/2wk | 1.2 mg/kg | 1-2 mg/kg/2wk |
| Maintenance | 2-8 mg/kg | | 1-5 mg/kg | | 5-15 mg/kg | |

## Dosing schedule for topiramate

- Monotherapy
- 25 mg bid x 1 wk
- Increase 50 mg/d qwk until 100mg/d then increase 100 mg/d qwk
- Adjunctive therapy
- 25 mg qd-bid 1 wk
- Increase 25-50 mg/d qwk

## Side effects of AEDs

## Side effects of old AEDs

| AEDs | Common side effects | Serious side effects |
|---|---|---|
| Phenytoin | Nystagmus, ataxia, drowsiness, gum hypertrophy | Rash, Steven Johnson syndrome, elevated LFT |
| Carbamazepine | Nystagmus, ataxia, drowsiness | Rash, Steven Johnson syndrome, elevated LFT, leukopenia, hyponatremia |
| Sodium valproate | Drowsiness, tremor, alopecia, weight gain | Thrombocytopenia, elevated LFT, fulminant hepatic failure (rare) |
| Phenobarbital | Drowsiness, mental slowness, behavioral disorder | Rash, Steven Johnson syndrome, elevated LFT |
| Clonazepam | Drowsiness, mental slowness | |

## Side effects of new AEDs

| Drugs | Potentially serious adverse events | Nonserious adverse events |
|---|---|---|
| Gabapentin | None | Weight gain, peripheral edema, behavioral changes |
| Lamotrigine | Rash, including Stevens Johnson and TENS, hypersensitivity reactions | Tics, insomnia |
| Levetiracetam | None | Irritability/ behavior changes |
| Oxcarbazepine | Hyponatremia (elderly), rash | None |
| Tiagabine | Stupor or spike wave stupor | Weakness |
| Topiramate | Renal calculi, open angle glaucoma, anhidrosis | Weight loss, language dysfunction,paresthesia |
| Zonisamide | Rash, renal calculi, anhidrosis | Irritability, weight loss |
| Pregabalin | None | Dizziness and somnolence, myoclonus |

## Risk for rash from AEDs

| High Risk | Low Risk |
|---|---|
| Phenytoin | Valproate |
| Phenobarbital | Topiramate |
| Primidone | Gabapentin |
| Carbamazepine | Tiagabine |
| Oxcarbazepine | Levetiracetam |
| Lamotrigine | |
| Zonisamide | |

## AEDs hypersensitivity syndrome

| Manifestation | Incidence (%) |
|---|---|
| Fever | 100 |
| Skin rash | 87 |
| Hepatitis | 51 |
| Eosinophilia | 30 |
| Blood dyscrasia | 23 |
| Nephritis | 11 |
| Lung involvement | 9 |
| Atypical lymphocytosis | 6 |

## AEDs hypersensitivity syndrome

- Incidence:
  - Phenytoin 2.3-4.5/10,000
  - Carbamazepine 1-4.1/10,000
  - Lamotrigine ?
- Delayed type hypersensitivity
- Occurs 2-8 weeks after starting AEDs
- Occurs with older aromatic AEDs
- Cross reactivity between PHT, PB and CBZ is quite high (up to 70-80% on testing)

## Weight issues from AEDs

| Weight Gain | Weight Neutral | Weight Loss |
|---|---|---|
| Valproate | Lamotrigine | Topiramate |
| Gabapentin | Levetiracetam (?) | Zonisamide |
| Carbamazepine | Phenytoin | Felbamate |
| Tiagabine (?) | | |
| Vigabatrin | | |

## Cognitive and behavioral side effects

| | Cognitive | Behavioral |
|---|---|---|
| **Conventional AEDs** | | |
| Carbamazepine | + | 0 |
| Phenobarbital | ++ | ++ |
| Phenytoin | + | 0 |
| Na Valproate | + | 0 |
| **New AEDs** | | |
| Gabapentin | 0 | 0 |
| Lamotrigine | 0 | 0 |
| Levetiracetam | 0 | + |
| Oxcarbazepine | +? | 0 |
| Topiramate | + (reduced by slow titration) | +? |
| Zonisamide | 0 | +? |
| Pregabalin | 0 | 0 |

## AEDs and osteoporosis

- Enzyme inducing AEDs may interfere with metabolism of vitamin D, therefore can cause increased incidence of osteoporosis with long term use.

## Common drug-drug interaction

## 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.

## Between AEDs

- Enzyme inducing AEDs (PHT, PB, CBZ) VS other AEDs
  - Reduce all AEDs level esp. sodium valproate and lamotrigine

**Effects of enzyme inducing drugs on the concentration and clearance of concurrent AEDs**

| Effect on Concurrent AED Serum Concentration | Approximate Change in AED Clearance |
|---|---|
| ↓ Ethosuximide | ↑ 20–50% |
| ↓ Valproate | ↑ Two- to fourfold |
| ↓ Lamotrigine | ↑ Two- to fourfold |
| ↓ Topiramate | ↑ 40–50% |
| ↓ Tiagabine | ↑ Two- to fourfold |
| ↓ Felbamate | ↑ 50% |
| ↓ Zonisamide | ↑ 30–50% |
| ↓ Oxcarbazepine | ↑ 25–40% |
| Levetiracetam | No change |

## Between AEDs

- Enzyme inhibitors
- Sodium valproate→ ↑↑↑ lamotrigine
- Topiramate, oxcarbazepine→ ↑ phenytoin

## Main inhibitory interaction of AEDs

| Newly Introduced Drug | Effect on Serum Concentration of Concurrent AEDs | Metabolic Pathway/ Enzymes Inhibited |
|---|---|---|
| Valproate | ↑ Phenobarbital (15–40%) | N-glucosidation, p-hydroxylation |
| | ↑ Lamotrigine (40–60%) | Glucuronidation |
| | ↑ Carbamazepine epoxide* | Epoxide hydrolase |
| | ↑ Felbamate (15–20%) | |
| Felbamate | ↑ Phenytoin** (30–100%) | 2C19 |
| | ↑ Carbamazepine epoxide* (40–50%) | |
| | ↑ Valproate (30–50%) | Beta-oxidation |
| | ↑ Phenobarbital (40–50%) | 2C19 |
| Topiramate | ↑ Phenytoin** (25%) | 2C19 |
| Oxcarbazepine | ↑ Phenytoin** (20–30%) | 2C19 |

*Carbamazepine levels will not reflect this increase as the epoxide is not measured routinely.
**Effect may be enhanced by the nonlinear (saturable) elimination kinetics of phenytoin.

## Lamotrigine

- Pregnancy, hormonal contraception can significantly lower lamotrigine level
- Therapeutic drug monitoring may be necessary during pregnancy
- **Valproate is a potent inhibitor of UGT dependent metabolism of lamotrigine and can significantly prolong lamotrigine half-life
- UGTs enzyme inducer AEDs (CBZ, PHT, PB) can increased metabolism of lamotrigine

## 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

## 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 interaction with OCPs

- Oral contraceptives should contain >50 micrograms of estrogen in the combination and external methods to prevent insufficient protection.

## Interaction with cardiac drugs

- Phenytoin → ↑ amiodarone level
  ↓ digoxin level
- Enzyme inducers
  → ↓ calcium channel blocker level
  ↓ beta blocker level
- Verapamil and diltiazem inhibits carbamazepine metabolism

## Interaction with immunosuppresive agents

- 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.

## Interaction with 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.

| 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. |

## Advantage of new AEDs

- Give clinician more choices of antiepileptic medications especially more choices of broad spectrum AEDs
- Better tolerability?
- Better pharmacokinetic properties
- Low protein binding
- Most of the new AEDs are not strong hepatic enzyme inducers→ fewer drug interaction
- Fewer serious adverse events?

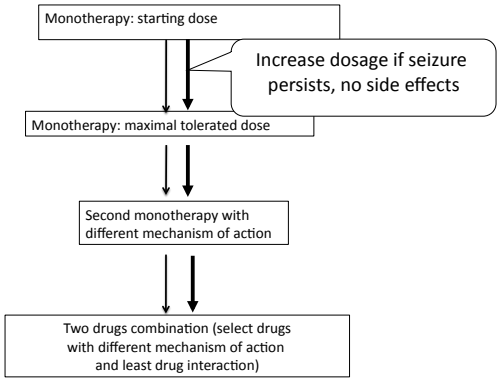
## Disadvantage of new AEDs

- Cost effectiveness
- Availability

| | Tab | Cost/day | Cost/month |
|---|---|---|---|
| Conventional AEDs | | | |
| Carbamazepine<br>Tegretol tab (200)<br>Tegretol CR (200)<br>Tegretol CR (400) | <br>6.28<br>6.66<br>14.76 | 30-60 | 900-1800 |
| Phenobarbital<br>Phenobarbital (30)<br>Phenobarbital (60) | <br>0.30<br>0.41 | 1-2 | 30-60 |
| Phenytoin<br>Phenytoin (50)<br>Dilantin cap (100) | <br>0.97<br>2.87 | 9 | 270 |
| Na Valproate<br>Depakine (200)<br>Depakine chrono (500) | <br>6.45<br>15.99 | 32-64 | 960-1920 |

| | Tab | Cost/day | Cost/month |
|---|---|---|---|
| New AEDs | | | |
| Gabapentin<br>Neurontin (100)<br>Neurontin (300)<br>Neurontin (400) | <br>17.42<br>32.00<br>38.00 | 128-384 | 3840-11520 |
| Lamotrigine<br>Lamictal (25)<br>Lamictal (100) | <br>15.37<br>41.00 | 82-164 | 2460-4920 |
| Topiramate<br>Topamax (25)<br>Topamax (50)<br>Topamax (100) | <br>17.42<br>27.67<br>47.15 | 94-189 | 2829-5658 |
| Oxcarbazepine | | 60-120 | 1800-3600 |
| Levetiracetam | | 90-270 | 2700-8100 |

How to adjust the medications?

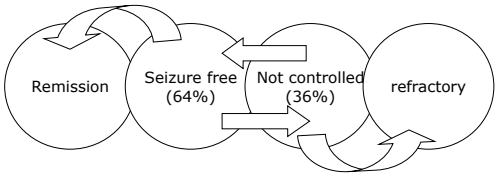



## How to adjust the medications?

- ก่อนจะพิจารณาเปลี่ยนหรือปรับยาในแต่ละขั้นตอนต้องคำนึงถึงสิ่งต่อไปนี้เสมอ
  - Is the diagnosis correct?
  - ยากันชักที่เลือกใช้เหมาะสมกับชนิดของการชักของผู้ป่วยหรือไม่?
  - Compliance
  - Avoid precipitating factors
  - Drug interaction

Prognosis in epilepsy patients

## Natural history of treated epilepsy




1. There seem to be two class of patient :easy versus difficult to control de novo
2. Patient with difficult to control epilepsy commonly have underlying cerebral pathology and higher number (>20) of seizure prior to treatment

## Special situations

## Special situations

- Pregnancy and lactation
- Elderly
- Hepatic dysfunction
- Renal dysfunction
- Transplant patients
- HIV infected patients
- Endocrine disorder
- Patients with brain tumor
- Psychiatric patients

## Pregnancy

## Epilepsy and pregnancy

- ไม่มียากันชักตัวใดที่ปลอดภัยต่อเด็กในครรภ์มากกว่าตัวอื่นอย่างแท้จริง

## Malformation Risks of AEDs in Pregnancy

- No AED 2-3%
- Monotherapy 3.7%-6%
- Polytherapy 6.1%-15%

## AED Specific Malformation Rates in Pregnancy

- Carbamazepine 2.1% to 4%
- Gabapentin 3.7%
- Lamotrigine 2.9% to 3.5%
- Phenytoin 4.1% to 6.8
- Valproic acid 6.1% 10.7%
- Topiramate ?
- Levetiracetam ?

UK Epilepsy and pregnancy Registry JNNP 2005
Swedish Medical Birth Registry Acta Paediatr 2004;93:174
International lamotrigine Registry
North America Antiepileptic Drug Pregnancy Registry

## Epilepsy and pregnancy

- ควรวางแผนล่วงหน้าก่อนการตั้งครรภ์เนื่องจาก
  - ในกรณีที่มารดาไม่มีอาการชักนานเกิน 2 ปีอาจพิจารณาหยุดยากันชักได้
  - ในกรณีที่คุมอาการชักได้ดี และมารดารับประทานยากันชักมากกว่า 1 ชนิดอาจพิจารณาลดขนาดยาหรือลดยาเหลือ 1 ชนิด เพื่อลดโอกาสการเกิดผลข้างเคียงต่อทารกในครรภ์

## Epilepsy and pregnancy

- ในขณะที่ผู้ป่วยตั้งครรภ์ไม่ควรปรับหรือเปลี่ยนยากันชัก เนื่องจากโอกาสที่จะเกิดอันตรายต่อมารดาและทารกในครรภ์หากผู้ป่วยเกิดการชักมีมากกว่าโอกาสการเกิดผลข้างเคียงต่อทารกในครรภ์
- ในผู้ป่วยที่ได้รับ enzyme inducing AEDs ควรได้รับ oral vitamin K supplement 10 mg/d 2-3 สัปดาห์ก่อนคลอด

## Epilepsy and pregnancy

- ในผู้หญิงวัยเจริญพันธ์ควรได้รับ folic acid supplementation ในขนาด 4-5 mg/d ซึ่งจากการศึกษาที่ผ่านมา อาจช่วยลดโอกาสการเกิด neural tube defects ได้

## Epilepsy and lactation

- ยากันชักส่วนมากไม่ได้ excrete ออกมาในน้ำนมมากนัก จึงมีผลน้อยต่อเด็ก นอกจาก phenobarbital ซึ่งอาจจะมีผลทำให้เด็กง่วงซึมได้

## Contraception in epilepsy patients

- 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.

## Contraception in epilepsy patients

- AEDs that are non-enzyme inducing have no effect on oral contraceptives.
- Non-enzyme inducing AEDs:
  - levetiracetam, gabapentin, tiagabine, valproic acid, zonisamide, pregabalin, vigabatrin, topiramate ≤200 mg.

## Contraception in epilepsy patients

- Oral contraceptives should contain >50 micrograms of estrogen in the combination and external methods to prevent insufficient protection.

## Hepatic dysfunction

| Effects | Older AEDs | New AEDs |
|---|---|---|
| Measurable increased in free fraction with hypoalbuminemia | PHT<br>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.

## Patients with impaired hepatic function

- Caution should be taken if VPA is used inpatients with liver disease.
- Hepatic dysfunction is less of a concern with PB, gabapentin, levetiracetam, topiramate, and zonisamide.

## Renal dysfunction

| Effects | Older AEDs | New AEDs |
|---|---|---|
| Measurable increased in free fraction with hypoalbuminemia | PHT<br>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 | 500-1000*q 24 hr then 250-500 mg supplement |

***with supplement dose after HD**

## 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 |

***with supplement dose after HD**