# Anticonvulsants for epilepsy and pain

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건국의대

## Issues to Cover

- AED는 언제 시작하나요?
  - Clinical definition of epilepsy
- 어떤 AED 를 쓰나요?
  - Characteristics of individual AED
- AED 의 복합치료
- AEDs in pain control
- Summary

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# AED는 언제 시작하나요?

Clinical definition of epilepsy

Any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring > 24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

Fisher RS et al, epilepsia 2014

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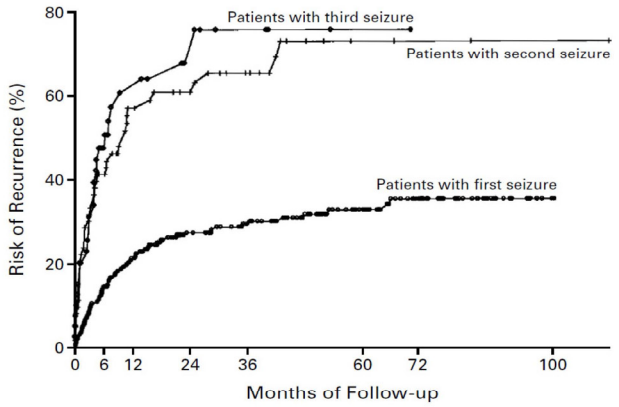
# Risk of Seizure Recurrence

At least two unprovoked (or reflex) seizures occurring > 24 h apart




Hauser WA et al., NEJM 1988

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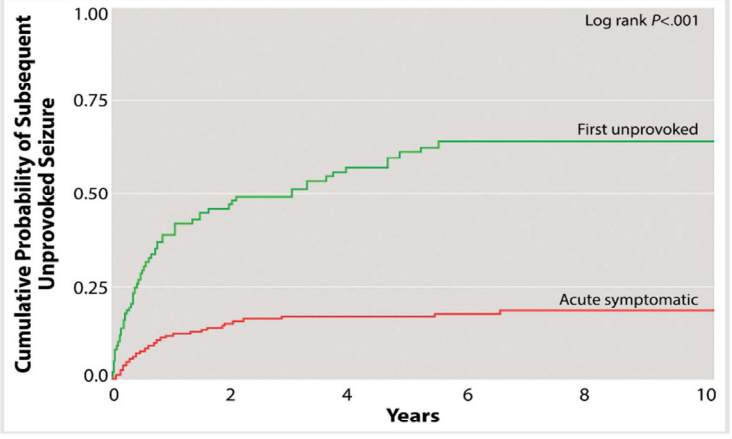


Hesdorffer DC et al., Epilepsia 2009

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# Risk of Seizure Recurrence

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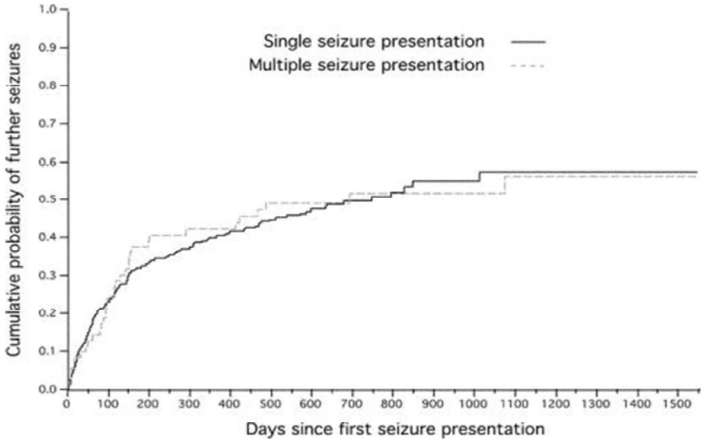


Kho LK DC et al., Neurology 2006

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# Clinical Definition of Epilepsy

Any of the following conditions

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# Risk of Seizure Recurrence

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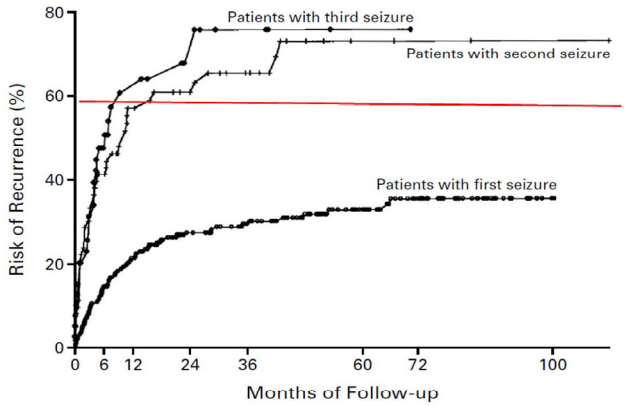


Hauser WA et al., NEJM 1988

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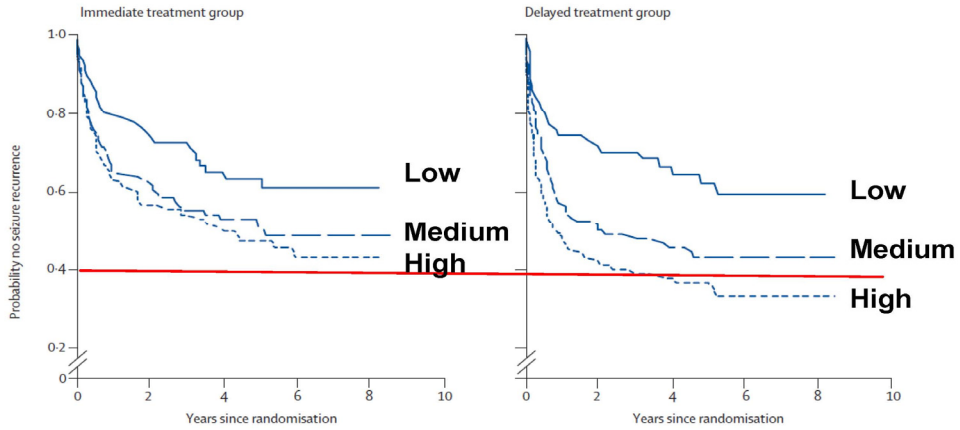
# From the MESS Study




Medium risk
Two or three seizures or **neurological abnormality or abnormal EEG**

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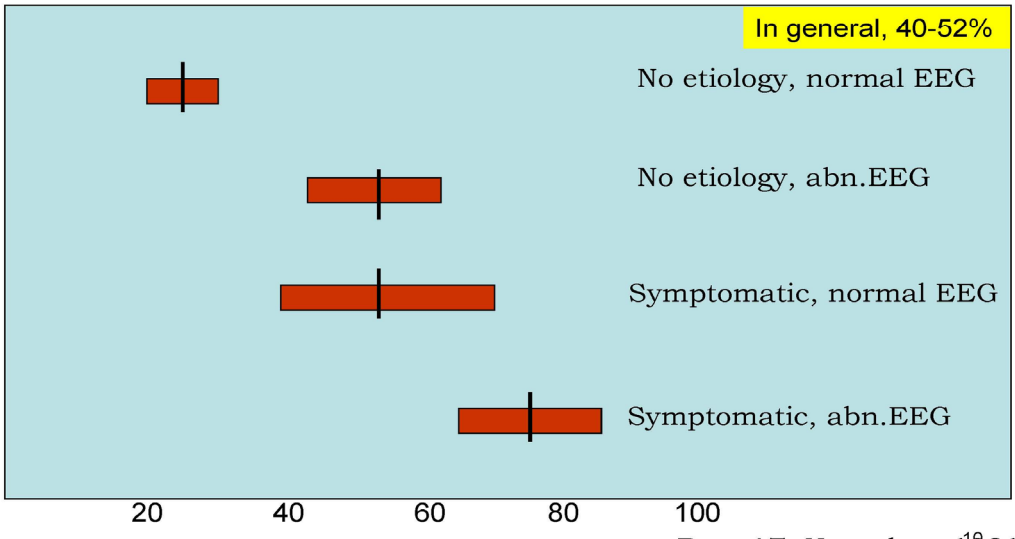
Kim LG et al., Lancet Neurol 2006

# Recurrence Following a First Seizure




Berg AT, Neurology 1991

## Introduction of New AEDs

| | | | |
|---|---|---|---|
| 1857 | Bromides | 1989 | Vigabatrin, Zonisamide |
| 1912 | Phenobarbital | 1993 | Felbamate, Gabapentin |
| 1938 | Phenytoin | 1995 | Lamotrigine |
| 1952 | Acetazolamide | 1996 | Topiramate |
| 1954 | Primidone | 1997 | Tiagabine |
| 1960 | Ethosuximide | 1998 | Oxcarbazepine |
| 1961 | Diazepam & other BZDs | 2000 | Levetiracetam |
| 1970s | Carbamazepine<br>Valproate | 2005 | Pregabalin |
| | | 2007 | Stiripentol, Rufinamide<br>(as orphan drug) |
| | | 2008 | Lacosamide |
| | | 2009 | Eslicarbazepine |
| | | 2011 | Retigabine |
| | | 2012 | Perampanel |

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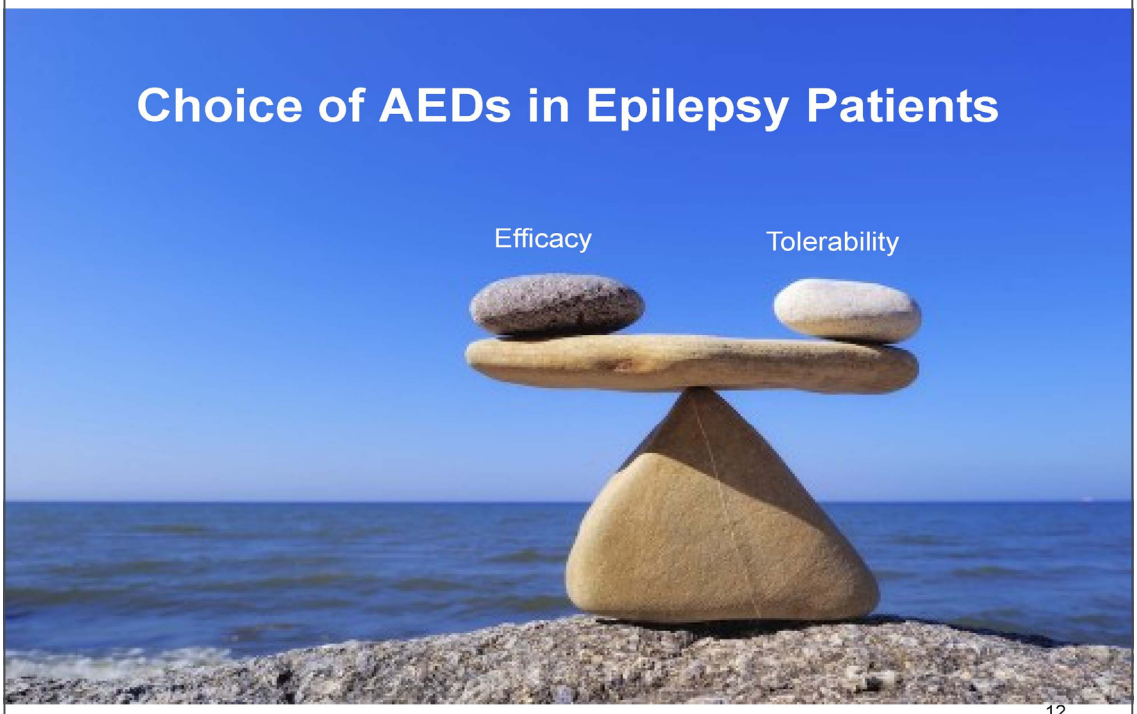
## Choice of AEDs in Epilepsy Patients

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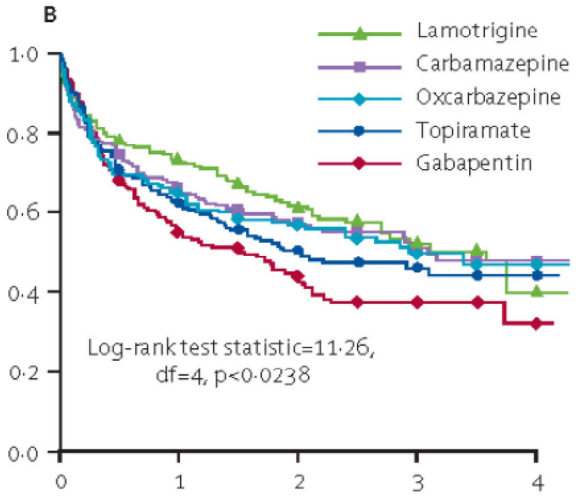
# Comparison of New AEDs vs CBZ; SANAD Study




Marson AG et al., Lancet 2007

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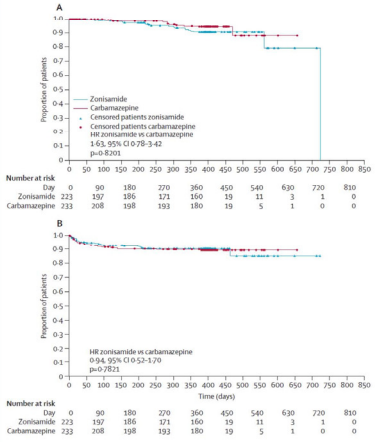
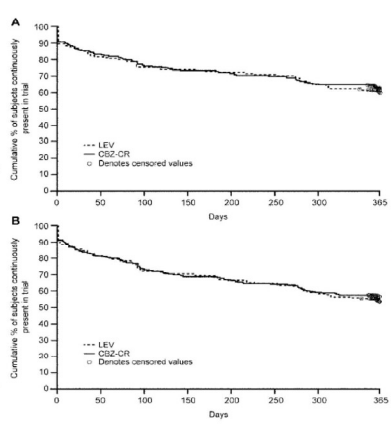
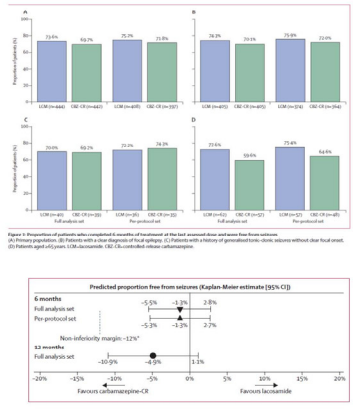
# Comparison of Initial Monotherapy




CBM vs ZNS
Baulac M et al., 2012




CBM vs LEV
Brodie MJ et al., 2007




CBM vs LCM
Mintzer S et al., 2017

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## Considerations in Choice of AEDs

| AED-specific | Patient-specific | Nation-specific |
|---|---|---|
| Sz or epilepsy syndrome | Genetic background | AED availability |
| Specific efficacy/effectiveness | Gender | AED cost |
| Dose-dependent adverse effects | Age | |
| Idiosyncratic reactions | Co-medications | |
| Chronic toxicities | Co-morbidities | |
| Teratogenicity | Insurance coverage | |
| Carcinogenicity | Relative wealth | |
| Pharmacokinetics | Ability to swallow pills/tablets | |
| Interaction potential | | |
| Formulations | | |

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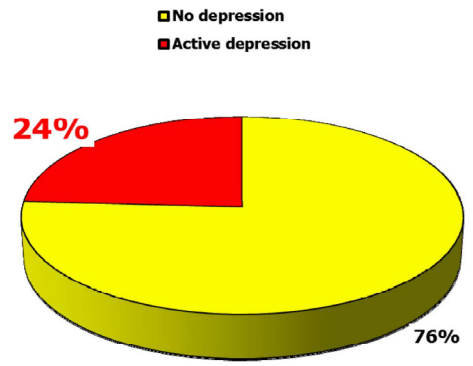
## Depression in Epilepsy Patients


* 1,098 pts with newly diagnosed epilepsy (med. f/u 7.5 yrs) (Brodie et al., 2012) - the probability of seizure freedom with successive antiepileptic drug regimens




* Prevalence of active depression by meta-analysis of nine population-based researches (Fiest et al., 2013)

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## Depression and Choice of AEDs

- Lamotrigine
  - Effective for **acute bipolar depression**
  - Effective for **treatment resistant mood disorders**

Calabrese JR et al. *J Clin Psychiatry*
Frye MA et al. *J Clin Psychopharmacol 2000;20:607–14*

  - Effective for **rapid cycling disease**

Calabrese JR et al. *J Clin Psychiatry* 2000;61:841–50

- Depression and behavioral & psychiatric problems are more commonly observed with LEV, PB, TPM, VGB, ZNS

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## Considerations in Elderly

- The first generation of AEDs (DPH, PB, BDZ)
  - May alter or delay functional outcome in elderly patients

Goldstein LB, 1995

- Drug interaction with old AEDs
  - Hepatic inducers: PB, DPH, CBM
  - Hepatic inhibitors: VPA
- Metabolic consequences such as atherosclerosis, osteoporosis: DPH, PB, CBM, VPA
- High protein binding: DPH, BDZ, VPA, PB

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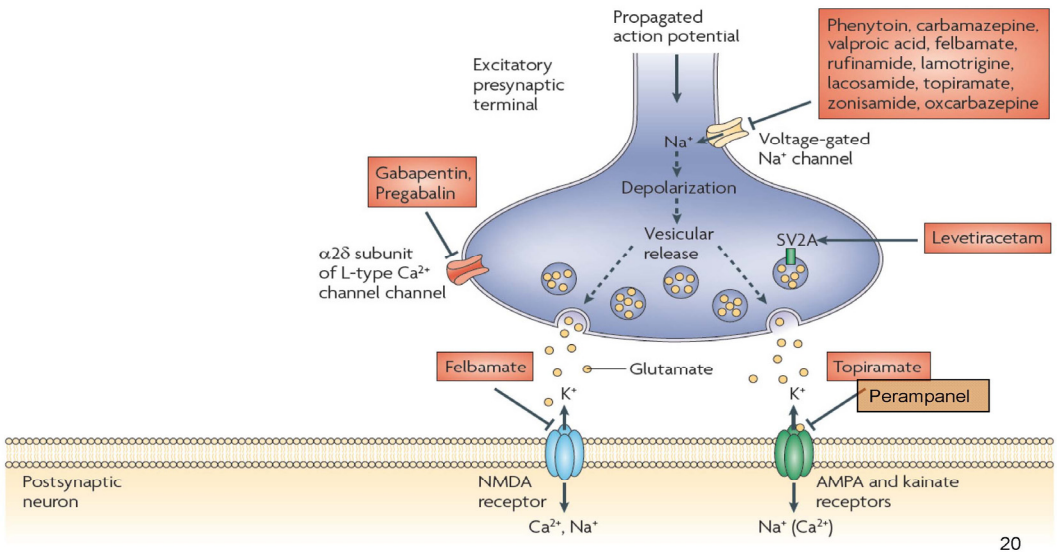
# Classification of Adverse Effects

| | Description | Examples | Prevention | Management |
|---|---|---|---|---|
| Type A | Related to the known mechanism of action of the drug; common (1–10%) or very common (>10%); acute; dependent on dose or serum concentration; predictable; reversible | Drowsiness, lethargy, tiredness, fatigue, insomnia; dizziness, unsteadiness, vertigo, imbalance, ataxia, diplopia, tremor; cognitive impairment; irritability, aggressive behaviour, depression; gastrointestinal symptoms; hyponatraemia; paresthesias | Select an antiepileptic drug with a profile of tolerability suitable to the characteristics and preferences of the patient; start at low doses; up-titrate gradually; target the lowest effective maintenance dose | Reduce dose; modify the dosing scheme; discontinue antiepileptic drug if measures to prevent or ameliorate toxicity are ineffective |
| Type B | Related to the individual vulnerability (immunological, genetic, or other mechanism); uncommon (0·1–1%) or rare (<0·1%); develop during the first few weeks of treatment; unpredictable; high morbidity and mortality; reversible | Skin rashes, severe mucocutaneous reactions (drug rash with eosinophilia and systemic symptoms, toxic epidermal necrolysis, Stevens-Johnson syndrome); aplastic anaemia, agranulocytosis; hepatotoxic effects, pancreatitis; angle closure glaucoma; aseptic meningitis | Avoid (or use very cautiously) specific antiepileptic drugs in high-risk groups; start at low doses; up-titrate gradually | Discontinue antiepileptic drug promptly; symptomatic or supportive management; substitute antiepileptic drug with least risk for cross-reactivity reactions or worsening of underlying condition |
| Type C | Related to the cumulative dose of the drug; common (1–10%); chronic; mostly reversible | Decreased bone mineral density; weight gain, weight loss; folate deficiency; connective tissue disorders; hirsutism, gingival hypertrophy; alopecia; visual field loss | Select an antiepileptic drug with a tolerability profile suitable to the characteristics and preferences of the patient | Symptomatic or replacement treatment (eg, calcium, vitamin D, folic acid) as needed; discontinuation of antiepileptic drug if required |
| Type D | Related to prenatal exposure to the drug (eg, teratogenesis) or carcinogenesis; uncommon (0·1–1%); delayed; dose dependent; irreversible | Birth defects; neurodevelopmental delay in the offspring; pseudolymphoma | If possible, avoid valproate, phenobarbital, and polytherapy in women of childbearing potential; aim at low-risk monotherapies at the lowest effective dose before pregnancy; avoid discontinuation or major treatment changes during pregnancy | .. |
| Type E | Adverse drug interactions; common (1–10%); predictable; reversible | Increased risk of skin rash after adding lamotrigine to valproate; reduced seizure control after adding the combined contraceptive pill to lamotrigine; reduced effectiveness of warfarin after adding carbamazepine; increased risk for CNS neurotoxicity after combination of sodium-channel-blocking antiepileptic drugs | Avoid unnecessary polytherapy; choose concurrent drugs with low potential for adverse drug interactions | Adjust doses according to clinical response and, if necessary, drug concentrations in serum |

*Table 3*: Adverse effects of antiepileptic drugs based on a modified version of the WHO classification

# Proposed mechanisms of action of currently available AEDs at excitatory synapses

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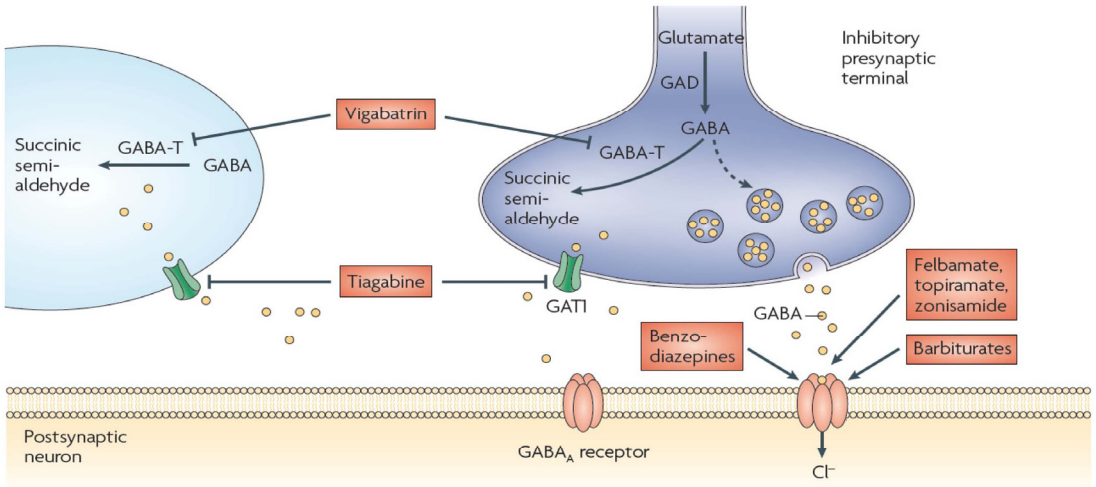
## Proposed mechanisms of action of currently available AEDs at inhibitory synapses

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Bialer M, White HS, et al. 2010

## Classifications of AEDs

- Sodium Channel Blockers
  - Phenytoin, fosphenytoin
  - Carbamazepine, oxcarbazepine, (eslicarbazepine)
  - Lamotringine
  - Lacosamide
- Multiple Mechanisms
  - Valproic acid
  - Topiramate, zonisamide
- SV2A
  - Levetiracetam
  - (Brivaracetam)
- AMPA antagonist
  - Perampanel
- GABA Channel
  - Phenobarbital
- Calcium Channel Blockers
  - Gabapentin
  - Pregabalin

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## Sodium Channel Blockers

- 공통적인 특징
  - Focal seizure 에 효과적, generalized seizure 악화 가능
    - (CBM, OXC >> LTG, DPH > LCM)
  - Dose-dependent CNS adverse effects
    - Dizziness, ataxia, diplopia etc
  - Sodium channel blocker 조합은 비효율적

- 개별 특징
  - DPH: zero-order kinetics => 혈중 농도 예측 어려움
  - OXC > CBM: hyponatremia especially in the elderly
  - Drug eruption: LTG >> CBM, OXC, DPH > LCM
  - DPH, CBM, (PB) > OXC: metabolism induction

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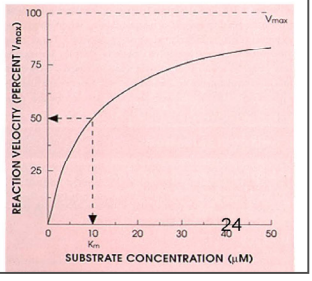
## Phenytoin

- 장점
  - 강력한 효과
  - 대부분의 경련 타입 치료에 효과적 (일부 myoclonic seizure 악화)
  - 주사 혹은 경구 부하 요법이 가능하고, 유지용량으로 바로 사용가능

- 단점
  - 장기간 사용했을 때 gingival hyperplaisa, hirsutism, peripheral neuropathy, cerebellar atrophy
  - Zero-order kinetics: 약물 농도 예측이 어려움

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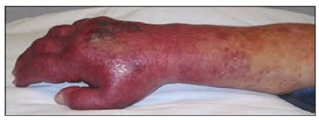
## Fosphenytoin



- Phenytoin 정맥주사
  - Highly alkaline
  - 부정맥, 저혈압
    - Propylene glycol in the formulation
  - Thrombophlebitis and pain when extravasation

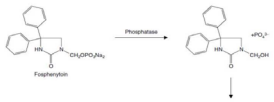


Fig. 1. Pathways involved in the metabolism of fosphenytoin to phenytoin.

- Fosphenytoin 정맥주사
  - A phosphate ester prodrug of DPH with high water solubility
  - Less alkaline pH of 8.8 without propylene glycol or ethanol
  - Well-tolerate of infusion rate up to 150mg/min of DPH-equivalent in healthy volunteer

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## Carbamazepine and Oxcarbazepine

- 장점
  - Focal seizure 의 drug of choice
- 단점
  - Absence seizure, myoclonic seizure 악화
  - Metabolism induction: CBM > OXC
  - Hyponatremia: OXC > CBM

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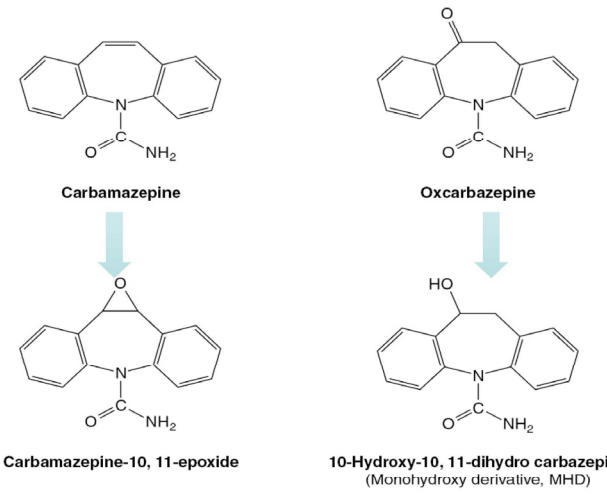
## CBM vs OXC and Eslicarbazepine




Eslicarbazepine: S-isomer of OXC, long half-life, less hyponatremia

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## Lamotrigine

- 장점
  - CBM 과 효과가 비슷하지만 CNS adverse effect 가 적다.
  - Generalized seizure 에도 효과
- 단점
  - Myoclonic seizure 를 간혹 악화 시킴
  - Skin eruption: slow titration
- Drug interaction
  - VPA 와 사용시 용량 절반, inducer 와 사용시 doubling

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# Lacosamide


- 장점
  - 부작용이 다른 SCB 에 비해 적다
  - Generalized seizure 에 효과적일 수 있다.
  - Status epilepticus 에 효과가 있다 (IV form)

- 단점
  - 장기 사용 후 evidence 는 검증이 필요하다.

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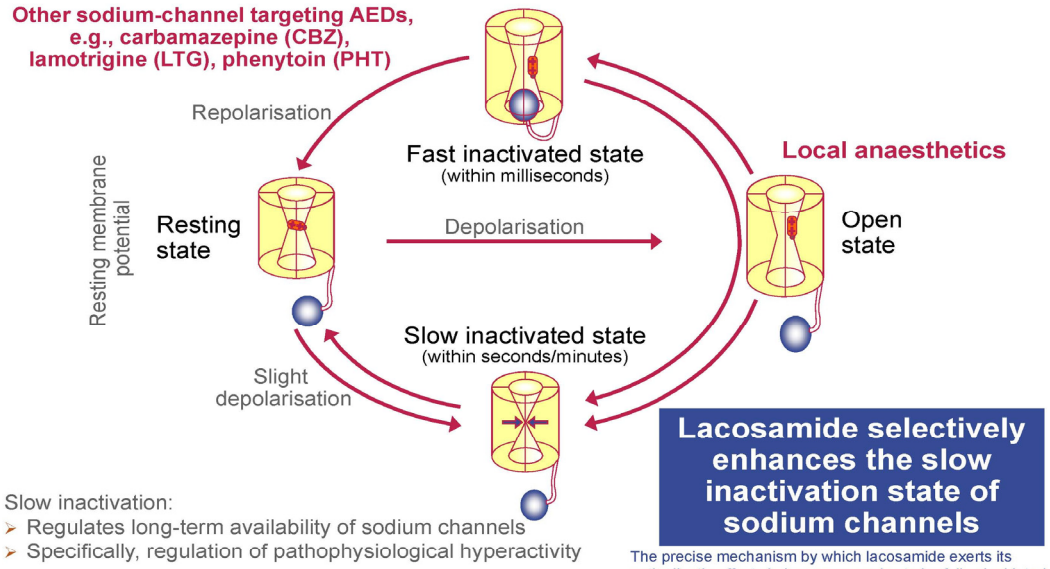
## Voltage-gated Sodium Channels
### A different mode of action

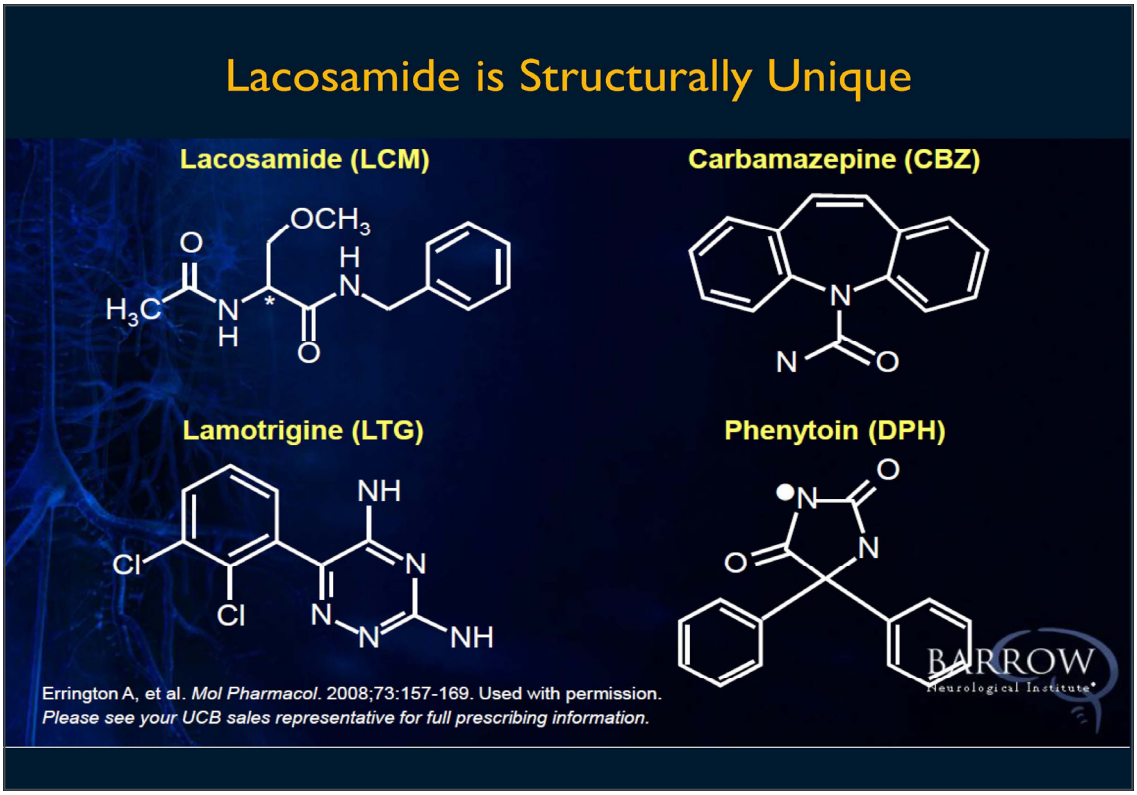



Slow inactivation:
- Regulates long-term availability of sodium channels
- Specifically, regulation of pathophysiological hyperactivity

**Lacosamide selectively enhances the slow inactivation state of sodium channels**

The precise mechanism by which lacosamide exerts its antiepileptic effects in humans remains to be fully elucidated

Adapted from Beydoun et al. Expert Rev Neurother 2009;9(1):33–42;
Errington et al. Mol Pharmacol 2008;73(1):157–169




## AEDs with Multiple Mechanisms

- 공통적인 특징
  - Focal seizure and generalized seizure 에 모두 효과적
  - 처음부터 high dose 사용이 가능 (ZNS: rash)
  - Weight change
- 개별 특징
  - VPA: long-term 사용시 여러 부작용
  - TPM: 인지 기능 장애
  - ZNS: 인지 기능 장애, 발진

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## Valproate

- 장점
  - Drug of choice in generalized seizure
  - Focal seizure 에도 효과적
- 단점
  - 체중증가, 진전, hair loss, thrombocytopenia
  - Polycystic ovarian syndrome, teratogenicity
  - High protein binding
  - Metabolism inhibitor

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## Topiramate and Zonisamide

- 장점
  - Focal seizure, generalized seizure 에 모두 효과적
  - Weight loss
- 단점
  - Tingling (carbonic anhydrase inhibitor)
  - 인지장애 (topiramate), skin eruption (zonisamide)

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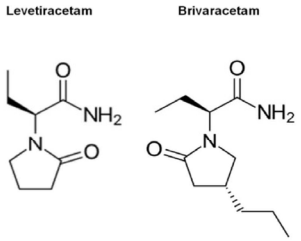
## Levitracetam and Brivaracetam




- 특징
  - Binds to synaptic vesicle protein2A (SV2A)
  - 모든 경련 양상에 잘 듣는다.
  - 90% 이상 renal excretion
- 단점
  - Somnolence, dizziness, agitation, nervousness
- Brivaracetam
  - N-propyl analogue of LEV
  - 15-30 fold higher affinity to SV2A
  - No dose reduction in renal impairment

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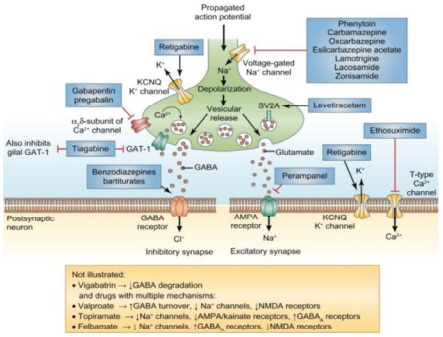
## Perampanel

- 장점
  - AMPA Rc antagonist
  - 뇌전증 중첩증, rational polytherapy 유리
  - 긴 반감기 (105시간)
  - Focal & generalized seizure 효과
- 단점
  - Dizziness (자기 전 복용)
  - Slow titration
  - 장기 안전성 미확립

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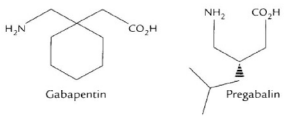
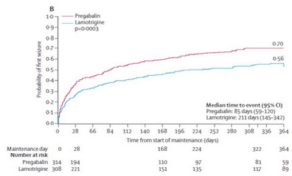
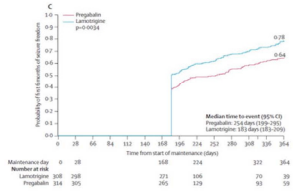
# Gabapentin and Pregabalin



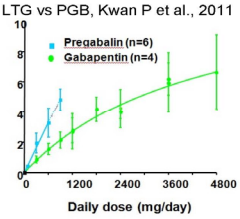

- 장점
  - Anxiety, insomnia, neuropathic pain 에 도움
  - Add-on therapy 로 synergy (calcium channel)

- 단점
  - Monotherapy 로는 효과가 적다
  - 반감기가 짧아서 하루에 2, 3 회 복용
  - Weight gain
  - Generalized seizure 악화시킬 수 있다.
  - 주로 신장배설
  - 혈중 농도 예측이 어렵다 (GBP)





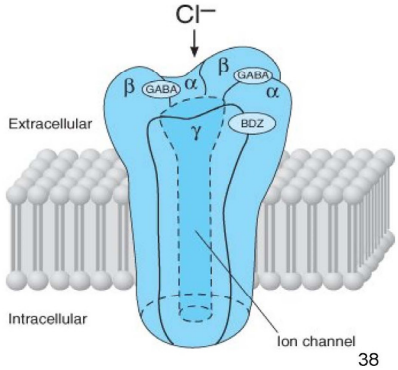
LTG vs PGB, Kwan P et al., 2011




# Phenobarbital

- 특징
  - Chloride channel opening 을 길게해서 GABG 작용 증가
  - 모든 경련에 효과적

- 단점
  - Metabolism induction
  - 긴 반감기
  - Withdrawal seizure
  - Cognitive adverse effect
  - Suicide ideation

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# Classification of AEDs

| | Partial Seizure | Generalized Seizure |
|---|---|---|
| Old AED | Phenytoin<br>Carbamazepine | Valproic acid<br>Phenobarbital |
| New AED | Oxcarbazepine<br>Pregabalin<br>Gabapentin | Lamotrigine<br>Lacosamide<br>Levetiracetam<br>Topiramate<br>Zonisamide<br>Perampanel |

Na blocker (CBM, OXC), L type Ca blocker (GBP, PGB); generalized seizure 악화
LTG (Na blocker); generalized seizure 에 효과, 가끔 myoclonic jerk 악화
VPA; generalized > partial
Metabolic encephalopathy (uremic, 혹은 drug induced )는 generalized 의 양상

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# AED의 복합치료

- 어떤 combination 이 ideal 한가?
  - 20개의 AED=> 190 duotherapy, 1,140 triple therapy
  - Not all combinations are equal!
- Ideal combination
  - No pharmacokinetic interaction
    - Metabolism induction in CBM, Pb, DPH
    - Metebolism inhibition by VPA
    - 예측 가능, 혈중 농도 측정
  - Positive (or synergistic) pharmacodynamic interaction

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# Pharmacodynamic Interaction

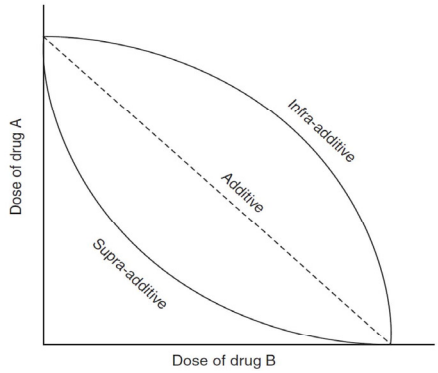


**Fig. 1.** Hypothetical isobologram showing the doses of two drugs required to produce a specified effect (either efficacy or toxicity) where the drugs have additive, supra-additive (synergistic), or infra-additive (antagonistic) effects.

**Table I.** Theoretical interactions between two drugs[a,b]

| Efficacy | Toxicity |
|---|---|
| Infra-additive | Infra-additive |
| Infra-additive | Additive |
| Infra-additive | Supra-additive |
| Additive | Infra-additive |
| Additive | Additive |
| Additive | Supra-additive |
| Supra-additive | Infra-additive |
| Supra-additive | Additive |
| Supra-additive | Supra-additive |

a Pure 'additive' implies absence of a positive interaction.

b The ideal interaction would be supra-additive for efficacy but infra-additive for toxicity.

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*Kaminski et al., Epilepsia 2009;50:387*

# Effects of combinations of some antiepileptics (AEDs) evaluated experimentally with isobolography in mice

| Drug A | Drug B | | | | | |
|---|---|---|---|---|---|---|
| | LTG | OXC | TGB | TPM | VGB | VPA |
| CBZ | $Ant^{Add}$ | $Add^{Add}$ | $Add^{Ne}$ | $S^{Ne}$ | NE | NE |
| GBP | S* | $S^{0}$ | $S^{Add}$ | $S^{Add}$ | $S^{0}$ | $S^{Add}$ |
| LEV | $Add^{0}$ | $S^{0}$ | NE | $S^{0}$ | NE | $Add^{0}$ |
| OXC | $Ant^{Syn}$ | - | $Add^{\Lambda}$ | $S^{add}$ | NE | $Add^{Add}$ |
| TGB | $Add^{Ne}$ | $Add^{An}$ | - | $Add^{Ne}$ | $S^{Add}$ | $Add^{Ne}$ |
| TPM | $S^{An}$ | $S^{Add}$ | $Add^{Ne}$ | - | NE | NE |
| VPA | $S^{An}$ | $Add^{Add}$ | $S^{Ne}$ | NE | $Add^{0}$ | - |

Ant – Antagonism; S – synergy; Add – additivity; * – the increased level of GBP in brain has been observed; – no neurotoxicity observed for antiepileptics at the fixed dose ratio of 1:1, recorded in the chimney test or passive avoidance task; – additive neurotoxicity in the chimney test calculated by isobolography; – antagonistic neurotoxicity; – synergistic neurotoxicity; CBZ – carbamazepine; GBP – gabapentin; LEV – levetiracetam; LTG – lamotrigine; – – no possibility of combination; – neurotoxicity not evaluated; NE – not evaluated by isobolography; OXC – oxcarbazepine; – synergistic neurotoxic effects; TGB – tiagabine; TPM – topiramate; VGB – vigabatrin; VPA – valproate

*Lason et al. – Phamacological Reports, 2011;63:2742*

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## A Mechanistic Assessment of Pharmacodynamic AED Interactions in Animal Models

| AEDs Combined | | | | Outcome |
|---|---|---|---|---|
| $Na^+$ blocker | + | $Na^+$ blocker | → | Additive efficacy or antagonism |
| $Na^+$ blocker | + | AED with multiple actions | → | Variable and unpredictable |
| AED with multiple actions | + | AED with multiple actions | → | Synergistic efficacy |
| Gabapentin | + | Any other AED | → | Synergistic efficacy |
| Levetiracetam | + | Other AEDs | → | Additive or synergistic efficacy |

*Deckers, Epilepsia 2000;41:1364-74; Czuczwar, Epilepsy Res 2002;52:15-23, Luzsczki , Epilepsia 47:10-20, 2006; Jonker, Epilepsia 2007;48:412-434; Kaminski, Epilepsia 200*

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## Pharmacodynamic Interaction

### Clinical studies

(a) Adverse Interactions in combinations of Na-channel blockers

| Drug combination | Level of evidence* |
|---|---|
| Oxcarbazepine + Carbamazepine | +++ |
| Lamotrigine + Carbamazepine | +++ |
| Lamotrigine + Oxcarbazepine | ++ |
| Lamotrigine + Phenytoin (?) | ++ |
| Lacosamide + Na-Channel blockers | +++ |
| * +++ Controlled trials ++ Case series studies | |

*Sake et al., CNS Drugs 2010;24:1055-1068*
*Brodie, Epilepsy Res 1997;26:423-32; Besag, Epilepsia 1998;39:183-7; Barcs, Eilepsia 2000;41:1597-*

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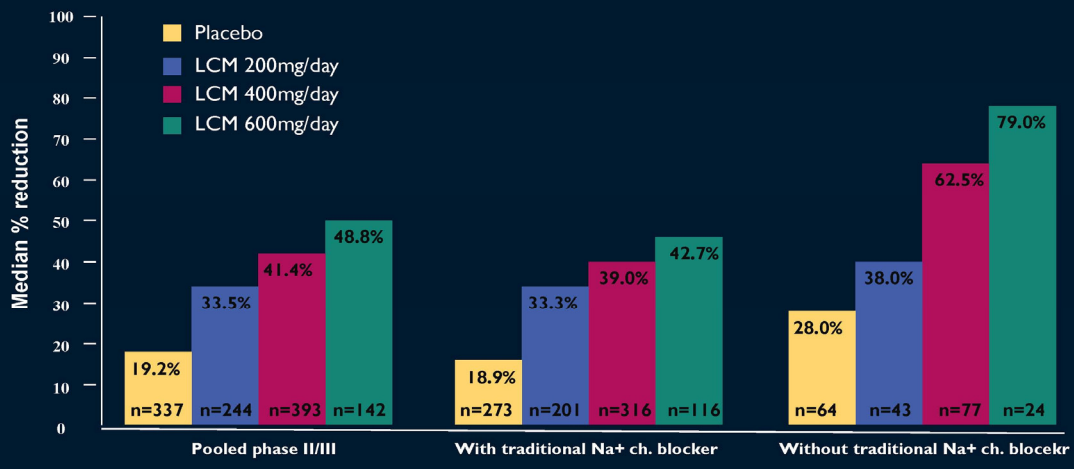
# Effect of Na-Channel Blocker

Clinical studies

(b) Poorer efficacy in combinations of Na-channel Blockers

- Pooled analysis of phase II/III trials of LCM add-on therapy




*Sake et al., CNS Drugs 2010:24:1055-1068*

# Pharmacodynamic Interactions

Positive interactions in combinations of different mechanisms

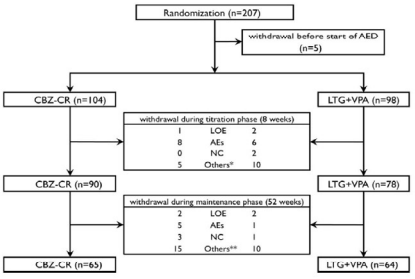
| Drug combination | Level of evidence* |
|---|---|
| Valproate + Lamotrigine | +++ |
| Valproate + Ethosuximide | ++ |
| Phenobarbital + Phenytoin | + |
| Valproate + Carbamazepine | + |
| Carbamazepine + Vigabatrin | + |
| Tiagabine + Vigabatrin | + |
| Topiramate + Lamotrigine | + |

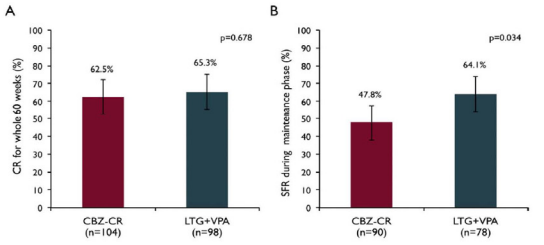
* +++ Controlled trials ++ Case series studies + Anedoctical

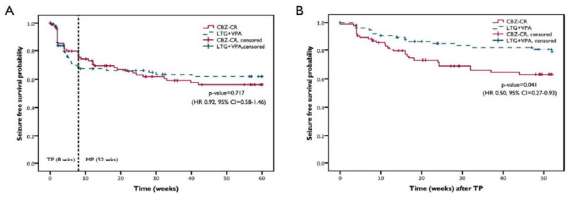
*Kwan and Brodie, Drugs 2006:66:1817-29*

## LTG with VPA vs CBM CR in Initial Treatment

LTG 75mg VPA 500mg/day vs CBM CR 600mg/day

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*Lee BI et al., Seizure 2018*

## IASP Guideline for Neuropathic Pain

**First line medication**

- TCAs
- Pregabalin / Gabapentin
- SNRIs
- Lidocaine patch**

** in PHN

**Second line medication**

- Tramadol
- Opioids

**Third line medication**

- Other AEDs
- SSRIs
- Capsaicin cream**

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## EFNS Guideline for Neuropathic Pain

| Etiology | Level A rating | Level C rating | Recommendation for first line |
|---|---|---|---|
| Diabetic NP | Duloxetine<br>Gabapentin/Pregabalin<br>TCA<br>Oxycodone/Tramadol | Carbamazepine<br>Phenytoin | Duloxetine<br>**Pregabalin / Gabapentin**<br>TCA<br>Venlafaxine ER |
| PHN | Capsaicin 8% patch<br>Gabapentin/Pregabalin<br>Lidocain plaster<br>TCA | | **Pregabalin / Gabapentin**<br>TCA<br>Lidocaine plaster |
| TG | Carbamazepine | Baclofen<br>Lamotrigine | **Carbamazepine**<br>**Oxcarbazepine** |
| Central pain | Cannabinnoid (MS)<br>Pregabalin (SCI) | | **Pregabalin / Gabapentin**<br>TCA |

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## 편두통의 예방약물

| Substances | Daily dose | Level |
|---|---|---|
| Propranolol | 40-240 mg | A |
| Flunarizine | 5-10 mg | A |
| Topiramate | 25-100 mg | A |
| Valproic acid | 500-1,800 mg | A |
| Amitriptyline | 50-150 mg | B |
| Naproxen | 2 x 250-500 mg | B |
| Gabapentine | 1,200-1,600 mg | C |
| Candesartan | 16 mg | C |
| Lisinopril | 20 mg | C |

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## Summary

- Initiation of AED: definition of epilepsy
  - Two unprovoked seizure
  - One seizure with 10 yr recurrence risk > 60%
- Choice of appropriate AED
  - Similar efficacy between the AEDs
  - Characteristics and adverse effect of individual AED
- Ideal combination of AEDs
  - Combination of different mechanisms of action
- AED in pain control
  - CBM, PGB/GBP in neuropathic pain
  - TPM, VPA in migraine prophylaxis

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