

Classification of seizure_2010

- Seizures are categorized into 3 main types
 - Generalized seizures
 - Focal seizures
 - Unknown seizure type

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GENERALIZED SEIZURE

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Generalized seizures

- Originate at some point within, and rapidly engage, **bilaterally** distributed networks
- Individual seizure onsets can appear localized.
- The location and lateralization are not consistent from one seizure to another.
- Bilateral networks
 - Include cortical and subcortical structures
 - Not necessarily include the entire cortex
- Generalized seizures can be asymmetric.

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Generalized seizures

- Tonic-clonic seizure (in any combination)
 - Absence
 - Myoclonic seizure
 - Clonic seizure
 - Tonic seizure
 - Atonic seizure

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Absence

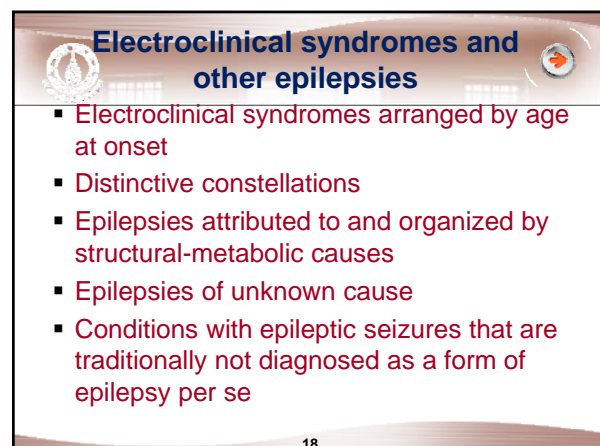
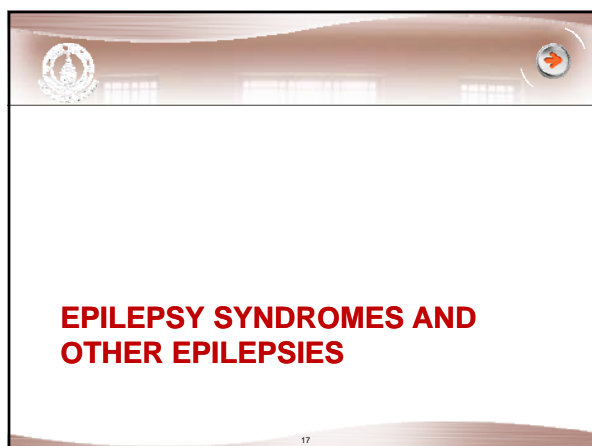
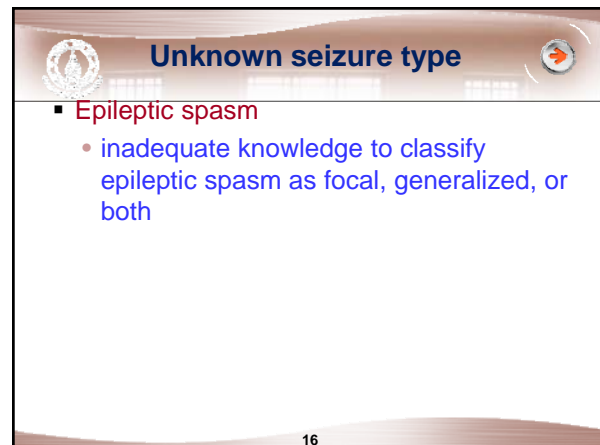
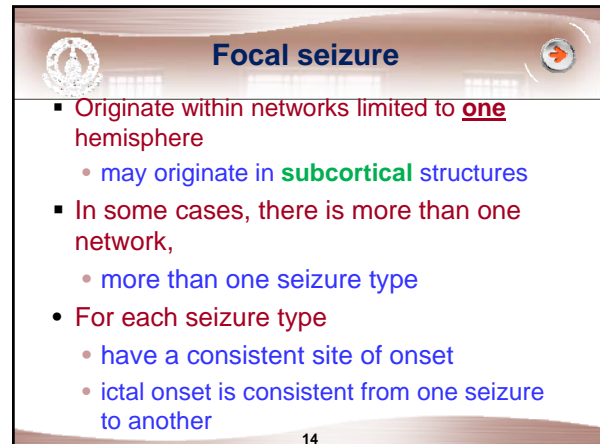
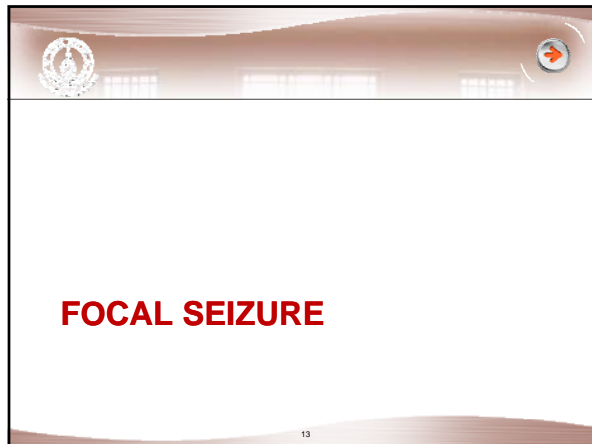
- Subtype
 - Typical absence
 - Atypical absence
 - Absence with special features
 - Myoclonic absence
 - Eyelid myoclonia

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Myoclonic seizure

- Subtype
 - Myoclonic seizure
 - Myoclonic atonic seizure
 - Myoclonic tonic seizure

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Electroclinical syndromes arranged by age at onset

- Neonatal period
- Infancy
- Childhood
- **Adolescence – Adult**
- Less specific age relationship

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Electroclinical syndromes Onset at adolescence – adult

- Juvenile absence epilepsy (JAE)
- **Juvenile myoclonic epilepsy (JME)**
- Epilepsy with generalized tonic-clonic seizures alone
- Progressive myoclonus epilepsies (PME)
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

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Distinctive constellations

- **Mesial temporal lobe epilepsy with hippocampal sclerosis**
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion–hemiplegia–epilepsy

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Seizures not diagnosed as epilepsy

- Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
 - Febrile seizure
 - Benign neonatal seizures (BNS)

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EXAMPLE

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Example

- ชาย อายุ 52 ปี มีอาการกระตุกที่แก้มข้างขวา ก่อนแล้วจึงกระตุกทั้งตัว หมดสติขณะที่กระตุกทั้งตัว CT scan of brain พบ right frontal lobe tumor
- Seizure type
 - Focal motor seizure at right face evolving to a bilateral, convulsive seizure
- Epilepsy type
 - Epilepsy attributed to right frontal lobe tumor

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Clinical use of AEDs

- How correct diagnosis is important!
- Indication for starting antiepileptic drug
- AED selection
- Maintenance therapy
- Strategies when treatment fails



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HOW CORRECT DIAGNOSIS IS IMPORTANT !!!

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Why correct diagnosis is important?

- Etiology management
- Prognosis
- AED selection
- AED-induced seizure
- Non-epileptic attack disorders

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AED choice according to epilepsy syndrome

- Infantile spasm
 - Vigabatrin, nitrazepam, valproate, B₆, adrenocorticotrophic hormone, surgery
- Juvenile myoclonic epilepsy
 - Valproate, lamotrigine, topiramate, levetiracetam

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AED choice according to epilepsy type

- Epilepsy with focal seizure
 - Many AEDs
- Epilepsy with generalized seizure
 - Many AEDs
 - Epilepsy syndrome with generalized seizure prefer valproate, phenobarbital, lamotrigine, topiramate, levetiracetam, zonisamide
 - Some AEDs may induce seizure !!

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AED choice according to seizure type

- Generalized tonic-clonic seizure
 - Any AED
- Focal seizure
 - Any AED
- Absence
 - Valproate, lamotrigine, topiramate, levetiracetam
- Myoclonic seizure
 - Phenobarbital, valproate, lamotrigine, topiramate, levetiracetam

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AEDs induce seizure

- AEDs induce absence
 - phenytoin, carbamazepine, phenobarbital
- AEDs induce myoclonic seizure
 - phenytoin, carbamazepine

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INDICATION FOR STARTING ANTI-EPILEPTIC DRUG

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Indication for starting AED

- Based on assessing consequence of epilepsy versus consequence of AED
- Consider
 - How seizures interfere with
 - ability to function
 - quality of life
 - Perspective view of patient, family, society

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Consequence of epilepsy depend on

- Seizure type
- Timing and frequency of attack
- Age and condition of patients
- Type of employment
- Response of patient, family and society
- Driving license

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All patients with epilepsy need Rx?

- Average risk of having further seizure after a first unprovoked seizure = 46%
(Berg and Shinnar, Neurology 1991)
- Risk of subsequent seizures after a second seizure = more than 70%
(Hauser et al, N Engl J Med 1998)

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Recurrence risk factors after first seizure

(++ strong, + weak)

- With recurrence risk factor, risk of recurrence after a first seizure might be similar to the average risk after two unprovoked seizure (Berg and Shinnar, Neurology 1991)
 - Known etiology ++
 - Epileptiform EEG ++
 - Family history: first degree relatives +
 - Time elapsed from seizure +
 - Todd's paresis +

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Indication for starting AED

- In conclusion
 - No single guideline applicable to all !!
 - Individually interactive decision-making among patient, family and doctor

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AED SELECTION

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Why AED selection important

- Goal of epilepsy treatment :
 - Achieve seizure freedom
 - No or tolerated side effects
 - Affordable cost
 - Comply to local guideline
- Different AED choices must be informed!!

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Beneficial characteristics for AED selection

- Epilepsy syndrome / epilepsy type
 - Age
 - Gender
 - Co-morbidities
 - Co-medication

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Key factors to maximized AEDs' benefit

- Initial therapy
- Efficacy
- Safety and tolerability
- Initiation/dose
- Hepatic enzyme induction
- Drug-drug interaction
- Evidence for Rx of newly diagnosed epilepsy
- Co-morbidities
- Special groups

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Initial therapy


- 40% of newly diagnosed epilepsy will be seizure free on first AED
- However, some patients suffer from AED side effects
- Some patients remain on troublesome AED with a fear of seizure attack.
- These patients may have better life with other AED.

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Sample case


Unwanted adverse effect



ผู้ป่วยหญิง

- ผู้หญิง เริ่มมีอาการชักชนิด **generalized myoclonic seizure** เมื่ออายุ 15 ปี
- ไม่เคยมีอาการชักชนิดอื่น
- ไม่มี neurological deficit
- ไม่มี learning disability
- ไม่มี family Hx of epilepsy


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ผู้ป่วยหญิง

- **EEG:** generalized multiple spikes and slow wave complex on a normal background activity
- **Diagnosis:**
Juvenile myoclonic epilepsy (Generalized epilepsy)
- **Antiepileptic drug:**
First gen AED: sodium valproate


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ผู้ป่วยหญิง

- 6 เดือนต่อมา มีปัญหา รอบเดือนมาไม่สม่ำเสมอ และออกกะปริดกะปรอย
- Irregular menstruation and spotting อาจจะ
เป็นผลข้างเคียงของ valproate ได้
- **Alternative AED:**
 - Lamotrigine
 - Topiramate
 - Levetiracetam


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AED Efficacy

- Despite great hopes, no new AED proven to be more efficacious than standard AED in newly-diagnosed epilepsy

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AEDs recommendation as first-line therapy for adults with focal seizures


	AAN	NICE	SIGN	ILAE
PHT	Y		Y	Y (level A)
CBZ	Y	Y	Y	Y (level A)
VPA	Y	Y	Y	Y (level B)
PHB	Y			Y (level C)
GBP	Y			Y (level C)
LTG	Y	Y	Y	Y (level C)
TPX	Y	Y		Y (level C)
OXC	Y	Y	Y	Y (level C)
LEV				Y (class I)

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Sample case


Efficacy



ครูหญิง อายุ 56 ปี

- 1 ปีก่อน มีอาการหมดสติไม่ทราบสาเหตุ และไม่มีอาการเตือน มา 3 ครั้ง
- ตรวจร่างกายปกติ
- EEG :
 - Normal background activity
 - Localized sharp wave at left temporal lobe
- Normal CT scan of brain


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ผู้ป่วยรายที่ 2 ครูหญิง อายุ 56 ปี

- Dx : Focal epilepsy of unknown cause
- Rx:
 - Start with phenytoin 300 mg/d
 - Another seizure attack
 - Titrate up to 350 mg/d
 - Another seizure attack and dizziness


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ผู้ป่วยรายที่ 2 ครูหญิง อายุ 56 ปี


- Do not want to take risk of
 - drug rash
 - over weight
 - drowsiness
 - cognitive impairment

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Adverse effect	Antiepileptic drug
▪ Drug rash	❖ Carbamazepine, oxcarbazepine, lamotrigine
▪ Over weight	❖ Valproate, gabapentin, pregabalin
▪ Drowsiness	❖ Phenobarbital, gabapentin, pregabalin
▪ Cognitive impairment	❖ Phenobarbital, topiramate

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ผู้ป่วยรายที่ 2 ครูหญิง อายุ 56 ปี

- She is well at 1,000 mg bid of levetiracetam.

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Safety and tolerability

- New generation AED proved to have better side effect profile
- However, new generation AED still carry some significant side effect, for example
 - Topiramate:
 - glaucoma, renal calculi, cognitive impairment

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Initiation/dose

- Patients remain at risk for another seizures until reaching therapeutic level
- Favorable AED :
 - Initiation at therapeutic dose
 - Rapid titration
 - Linear relationships pharmacokinetics

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AEDs initiated at therapeutic dose (minimum effective dose)

- **1st generation AEDs**
 - Sodium valproate 500-750 mg/d
- **2nd generation AEDs**
 - Levetiracetam 250 mg, bid
 - If necessary, 500 mg, bid

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AEDs initiated at therapeutic dose (minimum effective dose)

- **Phenytoin & Phenobarbital**
 - Despite of starting with therapeutic dose, steady state of serum drug level need a week (5-half life period)
 - Phenytoin : 3-5 mg/kg/d (300 mg/d)
 - Phenobarbital : grain 1 /d

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Rapid titration

1 st gen AEDs	2 nd gen AEDs
❖ Sodium valproate	❖ Levetiracetam
▪ If necessary,	▪ If necessary,
▪ 250-500 mg/d	▪ 500 mg/d
▪ every few days	▪ every day

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Hepatic enzyme induction

- Most 1st gen AEDs except valproate strongly induce cytochrome P450 system
- Most new generation AED have no or minimal enzyme inducing effect
- Many intrinsic substances such as vitamins and hormones are subjected to induced metabolism
- Several drugs are metabolized via cytochrome P450 system

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Drug-drug interaction

- Better knowledge on pharmacokinetics and pharmacodynamics help to select proper AED particular in patients who need polytherapy AED and polypharmacy
- New generation AEDs have better pharmacokinetics such as lower or non protein binding property, no liver metabolism etc.

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Sample case

Drug interaction

ผู้ป่วยหญิง อายุ 63 ปี

- เกิด focal epilepsy attributed to stroke ซึ่งควบคุมได้ด้วย carbamazepine มาตลอด
- ต่อมาเกิด deep vein thrombosis
- ไม่สามารถปรับระดับยา warfarin

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ผู้ป่วยหญิง อายุ 63 ปี

- มีประวัติ valproate-induced thrombocytopenia
- ควรเปลี่ยนยากันชักเป็นชนิดใด ?
- อาจจะเลือกให้ AED อื่นๆ ที่ไม่มี liver enzyme inducing effect ได้แก่
 - Topiramate (ถ้าขนาดไม่เกิน 200 mg/d ไม่มี liver enzyme inducing effect)
 - Levetiracetam

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Co-morbidities

- New generation AEDs have better pharmacokinetics such as non liver metabolism
- The more suitable drug profile may be needed in epileptic patient with other co-morbidity such as liver cirrhosis

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Sample case

Co-morbidities

ผู้ป่วยชาย อายุ 64 ปี

- Dilated cardiomyopathy
- Chronic atrial fibrillation
- Cardiac liver cirrhosis
- Epilepsy attributed to old cerebral embolism

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ผู้ป่วยชาย อายุ 64 ปี

- He needs AED with better pharmacokinetic profile
 - No liver toxicity
 - Not induce hepatic coma
 - Not metabolized by liver
 - Not induce cyp 450 enzyme that metabolize warfarin
- Therefore, all 1st gen AEDs not suitable

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ผู้ป่วยชาย อายุ 64 ปี

- 2nd gen AED that has suitable profile are
 - Levetiracetam
 - Pregabalin
 - Gabapentin
- Topiramate > 200 mg/d may have liver toxicity.
- Lamotrigine is glucuronidated by liver.

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Special groups

- Children
- Women
- The elderly

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AED in women

- Women with childbearing potential
 - Hormonal contraception
 - Pregnancy
 - Breast feeding
- Bone health particularly in post menopausal period

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Valproate in pregnancy

- Several observational studies reported
 - higher rates of major congenital malformations with use of valproate Vs other AEDs such as carbamazepine or lamotrigine

(Harden et al, Epilepsia 2009; Artama et al, Neurology 2005; Vajda et al, Obstet Gynecol 2007; Wide et al, Acta Paediatr 2004; Wyszynski et al, Neurology 2005; Morrow et al, J Neurol Neurosurg Psychiatry 2006; Veiby et al, Epilepsia 2009)

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Valproate in pregnancy

- Compared with other AEDs, valproate carries an increased risk of teratogenicity
 - spina bifida, atrial septal defects, cleft palate, and craniosynostosis (Jentink et al, N Engl J Med 2010)
 - significantly lower IQ (although within the normal range) (Meador et al, N Engl J Med 2009)

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Valproate in pregnancy

- The teratogenic effects of valproate seem to be
 - dose-dependent
 - more prominent at doses of 800 mg per day or more (Perucca and Tomson, Lancet Neurol 2011)

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AED in the elderly

- Physiologic changes of aging needed to be more concern
- The elderly tend to have lower threshold of side effects such as sedation, cognitive dysfunction, unsteady gait
- New generation AEDs with superior pharmacokinetics may be necessary in some older patients

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Other key factors on appropriate use of new generation AEDs

- Current health economic status in Thailand, other two factors are vital :
 - Cost
 - Drug availability

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MAINTENANCE THERAPY

Maintenance AED therapy

- Start with small dose
 - to minimize risk of initial side effects and allergic reaction
- Gradually increase to minimum effective dose
- Allow sufficient time between dose or drug changes for efficacy evaluation

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	Titration rate	Minimum dose (mg/d)	Maintenance (mg/d)	Frequency
CBZ	Start with 200 mg/d, increase 200 mg/d/wk	400-600	400-1600	CR form = bid, tid
VPA	Start with 500 mg/d, increase 500 mg/d/wk	500-1000*	500-2500	Bid, OD if chrono 500 mg/d
TPM	Start with 25 mg/d, increase 25-50mg every 2 weeks	100	100-400	bid
LTG	Start with 25 -50 mg/d for 2 weeks, increase by 50-100 mg/d every 1-2 wks	200	200-500	Bid
LTG & VPA	Start with 25 mg on alternate days 2 wks, then 25 mg/d 2 wks; further increases by 25-50 mg/d every 1-2 wks	100	100-200	Bid

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	Titration rate	Minimum dose (mg/d)	Maintenance (mg/d)	Frequency
OXC	Start with 300 mg/d, Increase 300 mg/d/wk	600-900	600-2400	bid, tid
LEV	Start with 500 mg/d (or 1000 mg/d), Increase 500 mg/d/wk	1000	1000-3000	bid
GBP	Start with 300-900 mg/d increase to target dose over 5-10 days	900	900-3600	bid, tid
Pregabalin	Start with 50-75 mg/d, increase to 150 mg over 2-4 weeks; further increases by 75-150 mg every 2 wks	150-300	150-600	bid, tid
ZNS	Start with 50 mg/d, increases by 50 mg/d every 1-2 weeks	200	200-600	bid

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Maintenance AED therapy

Principles of adding a second drug

- After reaching un-tolerable level of first AED
- Adjust un-tolerable level of 1st AED
- Sufficient drug titration time
- If seizures not under control, switch to another combination

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Maintenance AED therapy

Principles of adding a second drug

- If becoming seizure-free, stay on poly-therapy or only add-on AED
- If seizures return during or after first AED withdrawal, back to previous effective dose of poly-therapy

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Rational poly-therapy AEDs

- Polytherapy
 - Efficacy: less than additive
 - Side effects: supra-additive
- Two or not more than three AEDs!
- Consider
 - Modes of action
 - Drug to drug interaction (metabolism induction, protein binding, etc.)
 - Adverse effect profiles

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Strategies when treatment fails

- About 50% will achieve seizure freedom without intolerable side effects on the initially prescribed AED.
- If idiosyncratic reaction, avoid, if possible, AED that are likely to show cross reactivity.
- Carbamazepine has cross reaction of rash with
 - Phenytoin for 58%,
 - Phenobarbital for 27%
 - Oxcarbazepine for 33%
 - Lamotrigine for 20%.

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 **Strategies when treatment fails** 

- If lack of efficacy with highest tolerated dose,
 - Check drug compliance
 - Re-evaluate diagnosis
 - Re-evaluate AED (choice and dosage)
 - Switch to other monotherapy
 - Consider rational polytherapy

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