How to choose/use anti-epileptic drugs wisely?

Dr. Chusak Limotai, MD., M.Sc., CSCN(C)
Talk overview

• When to start treatment?
• Which drug?
• Monotherapy
• Combining AEDs (Rational polytherapy)
• Old AEDs versus new AEDs
• Drug level monitoring
• When to discontinue AEDs?
When to start treatment?

• Correct diagnosis

• Generally start after the second unprovoked seizure
  – **First unprovoked seizure**: A seizure or flurry of seizures or occurring within 24 hrs in the person > 1 month old of age with prior history of unprovoked seizure
  – **Epilepsy**: 2 or more epileptic seizures occur unprovoked by any immediately identifiable cause
Cumulative risk of recurrence after a first unprovoked seizure

- 67% at 1 yr
- 60% at 6 mo
- 78% at 3 yrs
- 44% at 3 yrs
- 32% at 3 yrs
- 17% at 3 yrs

Hart YM et.al; The Lancet 1990
• Treatment after the **first unprovoked seizure**
  1. EEG shows IEDs and/or
  2. lesion on MRI or
  3. physical or psychosocial consequences of a seizure recurrence outweigh the risks associated with drug treatment
Factors associated with increased/lower risk

• Increased risk:
  – Adolescence onset
  – associated neurological deficits
  – occurrence while asleep or awakening
  – simple partial seizure/CPS (> GTC)

• Lower risk:
  – seizure occurred within 3 mo after acute insult e.g. head injury, stroke
  – alcohol withdrawal
IEDs and risk of recurrence (idiopathic epilepsy in adults)

Van Donselaar CA et.al; BMJ 1991
Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy

Massimo Musicco, MD; Ettore Beghi, MD; Alessandra Solari, MD; and Francesco Viani, MD; for the First Seizure Trial Group (FIRST Group)*

Patients immediately treated
- 87% had no seizures for 1 year
- 68% had no seizures for 2 years

Patients treated after seizure recurrence
- 83% had no seizures for 1 year
- 60% had no seizures for 2 years

“Same time-dependent probability of achieving 1 and 2 seizure-free years”

Neurology 1997
Which drug?

- Seizure type and epileptic syndrome
- Age and sex
- Associated medical conditions
- Potential side effect on QOL
- Medical expertise
- Regulatory aspects and cost

“Case-by-case basis”
At first visit prior to starting AEDs

• Nature of disease, its prognostic implications
• Objectives of therapy
• Risks and benefits of treatment
• Alternative therapeutic strategies
• Counseling about marriage, reproduction, driving regulations
• Psychological and social support
Goals of treatment with AEDs

• Complete seizure free without side effects
Polytherapy in 19\textsuperscript{th} and early 20\textsuperscript{th} century

William Gowers (1881):
“The combinations of bromide with other drugs are of much value in the treatment of epilepsy”
- Other drugs included digitalis, belladonna, cannabis, opium, borax

• Pervasive belief that polytherapy was more efficacious than monotherapy
• Most of the treatments offered at the time were of doubtful antiepileptic efficacy
Polytherapy
Bromide + Digitalis
Henri Gastaut (1956);

Identified van Gogh's major illness during the last 2 years of his life as **temporal lobe epilepsy** precipitated by the use of **absinthe** in the presence of an early limbic lesion.
Since 1980 “Monotherapy era”

✓ equally or higher efficacious than polytherapy
✓ better tolerated
✓ no drug interaction
✓ possibly better compliance
✓ better cost effective
✓ Particularly desirable in
  - women
  - elderly
  - patients with co-morbid conditions
# Seizure types

<table>
<thead>
<tr>
<th>Effective or possibly effective against all seizure types</th>
<th>Effective against all seizure types except absence</th>
<th>Effective against partial and GTCs</th>
<th>Effective against absence seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>Phenobarbital</td>
<td>Carbamazepine</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Primidone</td>
<td>Phenytoin</td>
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<tr>
<td>Benzodiazepines</td>
<td></td>
<td>Oxcarbazepine</td>
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<tr>
<td>Topiramates</td>
<td></td>
<td>Gabapentin</td>
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<tr>
<td>Zonisamide</td>
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<td>Pregabalin</td>
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<tr>
<td>Levetiracetam</td>
<td></td>
<td>Tiagabine</td>
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<tr>
<td>Felbamate</td>
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<td>Vigabatrin</td>
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</table>

**Broad spectrum**

**Narrow spectrum**
Epileptic syndromes

• **JME**: initially presented with absence seizure later developed GTCs and myoclonus may initially consider starting **VPA** or **LTG** instead of **ETX**

• If a clear diagnosis cannot be made e.g. only GTCs wise to choose a broad-spectrum AED
Seizure aggravation by AEDs

- Increase in seizure frequency or the appearance of a new seizure type

<table>
<thead>
<tr>
<th>AEDs</th>
<th>Aggravated seizure types/epileptic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ, OXC, PHT, TGB, VGB (drugs for focal epilepsy)</td>
<td>Myoclonus, absence seizure in IGE/SGE</td>
</tr>
<tr>
<td>CBZ</td>
<td>Epileptic negative myoclonus, atonic seizure in BCERS</td>
</tr>
<tr>
<td>GBP</td>
<td>Myoclonus</td>
</tr>
<tr>
<td>PB</td>
<td>Absence seizure</td>
</tr>
<tr>
<td>LTG</td>
<td>Myoclonus in Dravet’s syndrome</td>
</tr>
<tr>
<td>BZD</td>
<td>Tonic seizure/tonic status epilepticus in LGS</td>
</tr>
</tbody>
</table>
Seizure aggravation by AEDs

• Alternative explanations
  - spontaneous fluctuation (need adequate baseline frequency)
  - known seizure aggravators (e.g. sleep deprivation, alcohol)
  - drug interactions (lowering the level of the baseline effective AEDs)
  - noncompliance
  - development of drug resistance

• Mechanisms (speculative and unproven)
  - overdosage (CBZ)
  - metabolic derangement (hyponatremia in CBZ/OXC)
  - varying effects of NT facilitation in different epileptic syndromes
  - drug interactions
  - sedation (tonic seizure in LGS)

“If possible, continue AED until it is clear that the seizure increase is not transient”
Age and sex

**Age**

- VPA-induced liver toxicity in children < 2 yrs
- PHT-induced acne, hirsutism, gum hypertrophy and coarsening of facial features when taking during childhood: **consideration against the first-line use of PHT in children and young females**
- LTG/GBP comparably effective as CBZ, but better tolerable in elderly

**Sex**

- VPA-induced teratogenicity in childbearing-age women
- CBZ, PHT, PB, Primidone, OXC, TPM ≥ 200 mg/d (enzyme-inducing AEDs): increase metabolism of OCP (decrease efficacy)
**Associated medical conditions**

- **AEDs benefit other conditions**
  - VPA, TPM, GBP
  - ✔ migraine
  - GBP, PGB, CBZ, OXC, LTG
  - ✔ neuropathic pain/post-stroke pain
  - CBZ, OXC, VPA, LTG
  - ✔ mood stabilizer

- **AEDs used in specific conditions**
  - LVT, GBP, PGB
  - ✔ hepatic impairment
  - ✔ adjusted dose in renal insufficiency/supplement if dialysis
  - LVT, GBP, PGB, LCM
  - ✔ HIV taking ARV (may consider VPA, LTG, but may need to increase LTG dose; may need to reduce ARV dose if taking VPA)
  - VPA, LVT, GBP, PGN
  - ✔ low risk of hypersensitivity
  - LTG, GBP
  - ✔ elderly
Associated medical conditions

• Avoidance
  ▪ VPA, CBZ, GBP, PGB, RTG (wt gain)
    ✓ avoid in obese pts
  ▪ TPM, ZNM
    ✓ not be 1st line in pts with renal calculi
  ▪ Enzyme-inducing AEDs
    ✓ avoid in pts with chronic medical conditions

• Potential side effects
  ▪ LVT (PB in children)
    ✓ produce irritability
  ▪ TPM, PB, Primidone, VGB
    ✓ cause depression
  ▪ LTG, FBM (stimulant):
    ✓ cause anxiety and insomnia
CASE 1

- 18 yo gentleman, university student, BW 86 kg
- Seizure started at age 17 yrs
- Seizure types:
  - Vocalization with GT/GTC, duration 5 min, 7 episodes in life since onset (Dec 2012), Last episode 2 wks ago
- Medicine: TPM 50 mg BID from another hospital
- EEG, MRI: normal
- Co-morbidity
  - Difficulties with word finding and memory since taking TPM
- Allergic to sulfa drug (face swelling)
Considerations

• Seizure type and epileptic syndrome
• Age and sex
• Associated medical conditions
• Potential side effect on QOL
• Medical expertise
• Regulatory aspects and cost
Which drug?

• **Broad spectrum**
  - Valproic acid
  - Lamotrigine
  - Benzodiazepines
  - Phenobarbital
  - Topiramates
  - Levetiracetam

• **Narrow spectrum** (focal epilepsy is still possible)
  - Carbamazepine
  - Phenytoin
  - Oxcarbazepine
  - Gabapentin
  - Pregabalin

VPA, LVT → LVT

HLA-B*1502 requested and revealed positive result

OXC, GBP, PGN
Effectiveness of first AED

- Seizure-free for at least 1 yr
  - 1\textsuperscript{st} drug: 47%
  - 2\textsuperscript{nd} drug mono: 13%
  - 3\textsuperscript{rd} drug mono: 1%
  - two drugs: 3%

Medically controlled: 64%
Medically refractory: 36%

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**Table 2. Success of Antiepileptic-Drug Regimens in 470 Patients with Previously Untreated Epilepsy.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to first drug</td>
<td>222 (47)</td>
</tr>
<tr>
<td>Seizure-free during continued therapy with first drug</td>
<td>207 (44)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of first drug</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Response to second drug</td>
<td>61 (13)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with second drug</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of second drug</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Response to third drug or multiple drugs</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with third drug</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Seizure-free during therapy with two drugs</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>301 (64)</td>
</tr>
</tbody>
</table>

Kwan P and Brodie M; Epilepsia 2001
Substitution Vs add-on after the first drug fails

No significant difference in efficacy and intolerable side effects observed between alternative monotherapy and add-on therapy

More pts become seizure-free in combination between sodium channel blockers and a drug with multiple mechanisms as opposed to other combinations

*Kwan P and Brodie M; Seizure 2000*
Early rational combinations is possible

- Explosion of new AEDs with better tolerability
- Less drug interactions
- Mechanistic diversity of new AEDs

ILAE definition (2009) Drug-resistant (refractory) epilepsy as “a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”

Refractory epilepsy

Non-pharmacologic treatments (e.g. resective surgery or VNS or KD)
AED mechanism of action

Different mechanistic groups suitable for combination therapy.

1. Sodium channel blockers
   (a) Fast-inactivated state—phenytoin, carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine
   (b) Slow-inactivated state—lacosamide

2. Calcium channel blockers
   (a) Low voltage activated channel—ethosuximide
   (b) High voltage activated channel—gabapentin, pregabalin

3. GABA-ergic drugs
   (a) Prolongs chloride channel opening—barbiturates
   (b) Increased frequency of chloride channel opening—benzodiazepines
   (c) Inhibits GABA-transaminase—vigabatrin
   (d) Blocks synaptic GABA reuptake—tiagabine

4. Synaptic vesicle protein 2A modulation—levetiracetam

5. Carbonic anhydrase inhibition—acetazolamide

6. Multiple pharmacological targets—sodium valproate, felbamate, topiramate, zonisamide, rufinamide
Sodium channel
- Activation gate
- Inactivation gate

Sodium channel
- Fast inactivation
- Slow inactivation
Rational polytherapy

- Rational combinations
  - evidence is still lacking
  - common sense: combine with different, perhaps multiple mechanisms of action
  - “LTG + VPA”: synergism

- Avoidance
  - similar mechanisms with similar side effects profiles
    - CBZ + LTG
    - CBZ + LCM
    - OXC + LCM
    - LTG + LCM
  - certain combinations produce more side effects
    - PB + VPA: sedation, weight gain
    - PHT + CBZ: dizziness, diplopia
    - VPA + LTG: dizziness, increased risk of SJS (but very efficacious in some patients)

Pisani F et.al; Epilepsia 1999
Brodie MJ and Yuen AWC; Epilepsy Res 1997
LTG dosing

- **LTG added to enzyme-inducing AEDs**
  - Week 1 and 2: 50 mg/day
  - Week 3 and 4: 100 mg/day
  - Increase by 100 mg/day every 1-2 weeks
  - Usual targeted dose: 300-500 mg/D

- **LTG added to a regimen containing VPA**
  - Week 1 and 2: 25 mg AD
  - Week 3 and 4: 50 mg/day
  - Increase by 25-50 mg/day every 1-2 weeks
  - Usual targeted dose: 100-400 mg/D
  (if adding to VPA alone: usual targeted dose at 100-200 mg/day)
Old versus New AEDs

- New AEDs which shown similar efficacy and equal or better tolerability than old AEDs in focal epilepsy
  - LTG
  - OXC
  - ZNM
  - LVT

- New AEDs which shown inferior efficacy to CBZ in focal epilepsy
  - VBG
  - TGB
  - GBP

- LTG, TPM are inferior to VPA in treating generalized epilepsy

**Advantages of new AEDs**
- Comparable efficacy with old AEDs (inconclusive one AED is more or less effective)
- Mostly better tolerability
- Less drug interactions (much less or no protein binding / most drugs are not hepatic metabolism)

*References*

Brodie MJ et al; Neurology 2012
Marson AG et al; Lancet 2007
Kalviainen R et al; Arch Neurol 1995
Mattson RH et al; NJEM 1992
Drug level monitoring

- **“Therapeutic range”**: The plasma concentration at which most patients respond

- Therapeutic decisions must be based primarily on direct evaluation of clinical response rather than drug measurement alone

- AED therapy can often be optimized on purely clinical grounds
Drug level monitoring

- Indications
  1) To minimize the difficulties in dosage adjustment, particularly in pts with polytherapy
  2) The presence of physiological or pathological conditions
  3) Establish a DDx of drug toxicity
  4) When poor compliance is suspected
  5) Critically-ill pts for whom clinical toxicity cannot be evaluated
  6) Individualized therapeutic drug concentration
When to discontinue AEDs?

- After a seizure, risk of a seizure in the next year – 50%
  - After 1-year seizure free – 20%
  - After 4-5 years seizure free – 10%

- Considering AED discontinuation
  - Adults: 2-5 yrs after seizure remission

MRC AED withdrawal study group; Lancet 1991
Some factors adversely affect the risk of seizure relapse after AED discontinuation

- Short duration of seizure freedom prior to drug withdrawal
- Epilepsy with onset in adolescence or adulthood
- JME
- Remote symptomatic epilepsy
- Hx of myoclonic seizures
- Hx of multiple seizure types
- Hx of primary or secondarily GTC
- Prolonged period before achieving seizure control

- Seizure while on treatment
- Seizure control requiring multiple drug therapy
- Abnormal EEG (?)
- Learning disability
- Associated neurological handicaps
- Previous failed attempts to stop medication
How do we practice?

- Increased risk for relapse
  - JME
  - Adolescent or adult onset
  - Focal epilepsy (semiology, EEG, imaging)
  - Associated neurological deficit/mental retardation
  - Previous failed attempts to stop medication
  - Previous multiple seizure types/multiple AEDs

If seizure relapse, greater psychosocial impact in adults than children

Most of self-remission epileptic syndromes are in childhood (CAE, BCERS)
How do we practice?

Discussion with the patient is the key!!!

- Provide statistic evidence to the patient
- Longer seizure remission is better (2-5 yrs)
- Balance risk of adverse effect associated with relapse of seizure and AED side effects
- Mild, brief, focal seizure, nocturnal occurrence is preferable to consider discontinuing the AEDs
- Clinical decision depends upon the patient
- If seizures recur after AED discontinuation, reinstition of treatment leads to a good outcome, with ~90% of patients again attaining another 2-year remission.

Adverse effects related to seizure relapse (e.g. injury, psychosocial impact)

Tolerability and AED side effects (esp. during planned pregnancy)
CASE 2

• 82 yo gentleman
• Presented with altered LOC which has occurred since 30 min prior to arriving the ER
• At ER: stuporous, equally spontaneous movements of all limbs, intubated
  – BP 200/120 mmHg
    Positive Doll’s eye in both directions,
    Asymmetric pupils size: 4 mm at Rt, 3 mm at Lt, both RTL
    No long tract signs
    Blood glucose 187 mg/dl
    EEG: normal sinus rhythm

• Underlying:
  – DM, HTN
  – 10 yrs ago: SDH at Rt frontal with right-sided limb clonic seizures requiring AED (details unknown) with subsequent discontinuation
  – NPH requiring shunt insertion
Hospital courses

- **At ward:** intubated and still obtunded with occasionally intermittent spontaneous limbs movements
- Gradually regained consciousness after 12 hours after the episode onset
- Spontaneous eye opening and followed simple commands at 24 hrs after the onset
- **Labs:** unremarkable, except for low Mg++ level
CT brain at ER (4 Aug 2013)
MRI brain at ward (still obtunded)
What’s the DDx?

(A) TIA
(B) Epileptic seizure
(C) Transient increased ICP
(D) Intoxication
(E) Metabolic derangement
5 Aug 2013
(30 hrs after the onset, alert)

8 Aug 2013
5 uV/mm
CASE 3

- 29 yo lady, LHD, housewife
- Seizure started at age 15 yrs
- Only seizure type
  - Generalized tonic seizure
  - Frequency: 0-1/3 months
- MRI: left F-T-P encephalomalacia with porencephaly
- Medication:
  - VPA 400 mg BID (800 mg/day)
  - Folic acid 5 mg/d
  - previous allergy to PHT (rash)
- At clinic, informed us that she has got pregnant with GA at 10 weeks, G1P0A0

- What should the treating physician do with her AED?
(A) Reducing the VPA dosage to < 500 mg/d
(B) Switching the VPA to another AED e.g. LTG
(C) Keeping VPA at the same total dose per day, but splitting to 4 times a day
Relative Timing and Developmental Pathology of Certain Malformations

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Malformations</th>
<th>Postconceptional Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Neural tube defect</td>
<td>28 d</td>
</tr>
<tr>
<td>Heart</td>
<td>Ventricular septal defect</td>
<td>42 d</td>
</tr>
<tr>
<td>Face</td>
<td>Cleft lip</td>
<td>36 d</td>
</tr>
<tr>
<td></td>
<td>Cleft maxillary palate</td>
<td>47–70 d</td>
</tr>
</tbody>
</table>
Rates of major congenital malformations at 1 year after birth in relation to exposure to AED monotherapy according to data from the International Registry of Antiepileptic Drugs and Pregnancy

Tomson T et al, Lancet Neurol 2011
Risk of major malformations by average valproate dose (mg) during the first trimester

Child IQ at 6 years of age, by exposure to maternal antiepileptic drug use and periconceptional folate

What should we do next?

• Maternal serum AFP
  ✓ examined at 14 wks GA = 38.77 ng/ml (0-10)

• VPA level while taking VPA 800 mg/d
  ✓ 34 µg/ml (50-100)

• High-resolution USG at 14 wks GA
  ✓ no fetal anomaly
  ✓ will repeat at 18-20 wks GA
Nomogram constructed to identify 95th percentile serum AFP at each week of gestation for maternal weights between 36.4 kg (80 lbs.) 127 kg (280 lbs.)