Update in Clinical Guidelines in Epilepsy
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Why We Need Clinical Guidelines?
Clinician needs advice!

Table 1: Percentage of types of physicians responsible for epilepsy patients per hospital category

<table>
<thead>
<tr>
<th>Department of Medical service</th>
<th>Hospitals under Mental Health</th>
<th>Hospitals under Others</th>
<th>General hospitals</th>
<th>Community hospitals</th>
<th>Private hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department of Mental Health</td>
<td>Hospitals under Mental Health</td>
<td>Hospitals under Others</td>
<td>General hospitals</td>
<td>Community hospitals</td>
<td>Private hospitals</td>
</tr>
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<td>General hospitals</td>
<td>Community hospitals</td>
<td>Private hospitals</td>
</tr>
</tbody>
</table>

Why We Need Clinical Guidelines?
Clinician needs advice!

Table 2: Number and types of physicians that providing care for persons with epilepsy in Thailand and other countries

<table>
<thead>
<tr>
<th>Number (persons)</th>
<th>Thailand</th>
<th>Laos*</th>
<th>Mongolia*</th>
<th>Angola*</th>
<th>Zambia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population, million</td>
<td>69.5</td>
<td>6.3</td>
<td>2.8</td>
<td>19.6</td>
<td>15.3</td>
</tr>
<tr>
<td>Neurologists</td>
<td>387</td>
<td>1</td>
<td>280</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Neurosurgeons</td>
<td>235</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatrists</td>
<td>540</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
</tr>
</tbody>
</table>

Guideline Development

- Pick topic
- Build a team
- Form a clinical question
- Disseminate
- Develop Recommendations and Algorithm
- Validate
- Evidence a. Find b. Abstract c. Analyze d. Grade/Rate

Ben-Menachem, 2013

What are the major Treatment Guidelines for Epilepsy?

- ILAE = International League Against Epilepsy (www.ilae.org)
- NICE = www.nice.org.uk- National Institute for Clinical Excellence (England and Wales)
- SIGN = www.sign.ac.uk- Scottish Intercollegiate Guidelines Network (Scotland). (Revision 2014)
- AAN = www.aan.com-American Academy of Neurology (USA) 2004
Based on the best evidence available, which AEDs have the best documentation for use as initial monotherapy for patients with newly diagnosed or untreated epilepsy (2006)?

- Since July 2005, 3 class I and 2 class II RCT have been published
- Total 64 RCT (> class I, > class II, > meta-analyses)

ILAE Evidence Review

- For patients with newly diagnosed or untreated epilepsy, which AEDs have the best evidence for long term efficacy or effectiveness as initial monotherapy?
- Situations:
  1. Partial onset seizure - Adults
  2. Partial onset seizure - Children
  3. Partial onset seizure - Elderly
  4. GTC seizure - Adults
  5. GTC seizure - Children
  6. Absence seizure - Children
  7. BECTS
  8. JME

Searching the Evidences for the ILAE Review 2013

- The authors evaluated available evidence found through a structured literature review including Medline, Current Contents and The Cochrane Library for all applicable articles from 1940 until July 2005 – 31 March 2012
- Question: best evidence to evaluate efficacy and effectiveness of AEDs in recently diagnosed patients.
Epilepsy Guidelines:

- **Classes Rating 4**
  - **Class I**: A masked RCT, meeting all key variable criteria
  - **Class II**: A masked prospective matched group cohort study in a representative population that meets all key variable criteria OR an RCT in a representative population that lacks one of the key variable criteria
  - **Class III**: All other controlled trials in a representative population, where outcome assessment is independent of patient treatment
  - **Class IV**: Evidence from uncontrolled studies, case series, case reports or expert opinion

Guideline Methodology:

Grading the evidence for each AED

- **Recommendations – 6 Levels**
  - **Level A**: ≥ 1 Class I RCTs OR ≥ 2 Class II RCTs
  - **Level B**: 1 Class II RCTs OR ≥ 3 Class III RCTs
  - **Level C**: 2 Class III RCTs
  - **Level D**: Class III, or IV RCTs OR expert opinions
  - **Level E**: Absence of clinical evidence
  - **Level F**: Positive evidence of lack of efficacy OR Significant risk of seizure aggravation

Partial Seizures: Adults

Available Evidence

- A total of 33 (+6) randomized clinical trials (RCTs) and 5 (+4) meta-analyses examined initial monotherapy of adults with partial-onset seizures

  Division of trials
  - Class I (n=2+2=4)
  - Class II (n=1)
  - Class III (n=30+4=34)

Partial Seizures in Adults

Listing of Class I-III Double-Blind RCTs

**Class I**
- Mattson (1985) CBZ, PB, PHT, PRM
- Chadwick (99) CBZ, VGB

**Class II**
- Mattson (92) CBZ, VPA

**Class III**
- Because of low power (DNIB) or forced exit
  - Brodie (95) CBZ, LTG
  - Chadwick (98) GBP
  - Brodie (92) GBP, LTG
  - Sachdeo (00) TPM
  - Christe (97) OXC, VPA
  - Gilliam (03) TPM
  - Bill (97) OXC, PHT
  - Prud’homme (03) CBZ, TPM, VPA
  - Dam (89) CBZ, OXC
  - Arroyo (86) TPM
  - Brodie (02) CBZ, REM
  - Steinert (99) PHT, LTG
  - Ramsay (83) CBZ, PHT
  - Gibberd (82) PHT, PNT
  - Mikkelsen (81) CBZ, CLP

French JA, Epilepsia 2004, 45(5):401-409 and 410-423
Partial Seizures: Adults
Recommendations

Level A: CBZ (n=23), PHT (n=12), LEV (n=1), ZNS (n=1)
Level B: VPA (n=11)
Level C: GBP, LTG, OXC, PB, TPM, VGB
Level D: CZP, PRM
Level E: Others
Level F: None

Partial Seizures: Children
Available Evidence

- A total of 25 (+2) RCTs and 1 (+4) meta-analysis examined initial monotherapy of children with partial-onset seizures
- Division of trials
  - Class I (n=1)
  - Class II (n=0)
  - Class III (n=17 + 2)

Partial Seizures: Children
Recommendations

Level A: OXC (no new AEDs)
Level B: None
Level C: CBZ, PB, PHT, TPM, VPA, VGB
Level D: LTG, CLB, CLZ, ZNS
Level E: Others
Level F: None

Partial Seizures: Elderly
Available Evidence

- A total of 30 (+1) RCTs with elderly participants included which examined initial monotherapy for partial-onset seizures
- Division of trials
  - Class I (n=1)
  - Class II (n=0)
  - Class III (n=2 + 1)

Partial Seizures: Elderly
Recommendations

Level A: GBP, LTG (no new AED)
Level B: None
Level C: CBZ
Level D: TPM, VPA
Level E: Others
Level F: None

Generalized Tonic Clonic Seizures: Adults
Available Evidence

- A total of 23 (+4) RCTs and 5 (+4) meta-analyses examined initial monotherapy of adults with generalized-onset tonic clonic seizures
- Division of trials
  - Class I (n=0)
  - Class II (n=0)
  - Class III (n=10 + 4): CBZ, GBP, LTG, OXC, PB, PHT, TPM, VPA
**Generalized Tonic Clonic Seizures: Adults**

*Recommendations*

- **Level A:** None
- **Level B:** None
- **Level C:** CBZ*, LTG, OXC*, PB, PHT*, TPM, VPA
- **Level D:** GBP, VGB
- **Level E:** Others
- **Level F:** None

*may aggravate tonic clonic seizures and more commonly other generalized seizure types, should be used with caution*

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**Generalized Tonic Clonic Seizures: Children**

*Available Evidence*

- **Available Evidence:**
  - A total of 20 (+0) RCTs examined initial monotherapy of children with generalized onset tonic clonic seizures
  - Division of trials
    - Class I (n=0)
    - Class II (n=0)
    - Class III (n=14): CBZ, CLB, OXC, PB, PHT, TPM, VPA

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**Generalized Tonic Clonic Seizures: Children**

*Recommendations*

- **Level A:** None
- **Level B:** None
- **Level C:** CBZ*, PB, PHT*
- **Level D:** OXC
- **Level E:** Others
- **Level F:** None

*may aggravate tonic clonic seizures and more commonly other generalized seizure types, should be used with caution*

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**Childhood Absence Epilepsy:**

*Available Evidence*

- **Available Evidence:**
  - A total of 6 (+2) RCTs examined initial monotherapy of children with Childhood Absence Epilepsy
  - Division of trials
    - Class I (n=0+1)
    - Class II (n=0)
    - Class III (n=6+1) - 3 Double Blinded ETX, LTG, VPA

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**Childhood Absence Epilepsy:**

*Recommendations*

- **Level A:** None
- **Level B:** None
- **Level C:** LTG
- **Level D:** None
- **Level E:** Others
- **Level F:** CBZ, GBP, OXC, PB, PHT, TGB, VGB

---

**BECTS:**

*Available Evidence*

- **Available Evidence:**
  - A total of 3 (+1) RCTs examined initial monotherapy of children with BECTS, 2 were DB
  - Division of trials
    - Class I (n=0)
    - Class II (n=0)
    - Class III (n=2+1)
**BECTS:**

**Recommendations**

- **Level A:** None
- **Level B:** None
- **Level C:** CBZ, VPA
- **Level D:** GBP, STM, LEV, OXC
- **Level E:** Others
- **Level F:** None

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**Juvenile Myoclonic Epilepsy:**

**Available Evidence**

- A total of 0 (+1) RCTs examined initial monotherapy of children with Juvenile Myoclonic Epilepsy
- Division of trials
  - Class I (n=0)
  - Class II (n=0)
  - Class III (n=0+1)

---

**Juvenile Myoclonic Epilepsy:**

**Recommendations**

- **Level A:** None
- **Level B:** None
- **Level C:** None
- **Level D:** TPM, VPA
- **Level E:** Others
- **Level F:** CBZ*, GBP, OXC*, PHT*, TGB, VGB

*May aggravate myoclonic seizure types, should be used with caution

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**Summary of Evidence for Focal Onset Seizures**

Update 2013
### Summary of Evidence for Generalized Onset Seizures

<table>
<thead>
<tr>
<th>Seizure type or epilepsy syndrome</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Level of efficacy and effectiveness evidence (alphabetic order)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCIGS: Adults</td>
<td>0</td>
<td>0</td>
<td>23+6</td>
<td>Level A: None, Level B: None, Level C: CDZ, LTG, OXC, PB, PHT, TPM, VPA, Level D: None</td>
</tr>
<tr>
<td>TCIGS: Children</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>Level A: None, Level B: None, Level C: CDZ, PB, PHT, TPM, VPA, Level D: None</td>
</tr>
<tr>
<td>Absence seizure</td>
<td>0</td>
<td>6+4</td>
<td></td>
<td>Level A: None, Level B: None, Level C: None, Level D: None</td>
</tr>
</tbody>
</table>

### Variables that affect initial AED selection

<table>
<thead>
<tr>
<th>AED-specific variables</th>
<th>Patient-specific variables</th>
<th>Nation-specific variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure type or epilepsy syndrome</td>
<td>Specific efficacy or effectiveness</td>
<td>Genetic background</td>
</tr>
<tr>
<td>Drug-dependent adverse effects</td>
<td>Disorder-specific reactions</td>
<td>Age</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Seizure frequency</td>
<td>Gender</td>
</tr>
<tr>
<td>Tolerance</td>
<td>Carcinogenicity</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>Teratogenicity</td>
<td>Insurance coverage</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Idiosyncratic reactions</td>
<td>AED availability</td>
</tr>
<tr>
<td>Interaction potential</td>
<td>Chronic toxicities</td>
<td>AED cost</td>
</tr>
<tr>
<td>Formulations</td>
<td>Dose-dependent adverse effects</td>
<td>Insurance coverage</td>
</tr>
<tr>
<td>• Dose-dependent adverse effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Idiosyncratic reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chronic toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Teratogenicity</td>
<td></td>
<td></td>
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<tr>
<td>• Carcinogenicity</td>
<td></td>
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</tr>
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<td>• Pharmacodynamics</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Formulations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### AEDs in use/ Available in Thailand

- **Older Drugs**
  - Phenobarbital
  - Phenytoin
  - Valproate
  - Carbamazepine
  - Benzodiazepine

- **Newer Drugs**
  - Vigabatrin
  - Lamotrigine
  - Oxcarbazepine
  - Zonisamide
  - Levetiracetam
  - Topiramate
  - Gabapentin
  - Pregabalin

- **Newest Drugs**
  - Lacosamide
  - Perampanel

### AEDs in use/ Available in Thailand

#### Table 5: Percentage of hospitals having standard antiepileptic drugs available classified by hospital types

<table>
<thead>
<tr>
<th>Center hospitals</th>
<th>General hospitals</th>
<th>Community hospitals</th>
<th>University hospitals</th>
<th>Hospitals under Department of Medical Service</th>
<th>Hospitals under Department of Health</th>
<th>Others*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=12)</td>
<td>(n=57)</td>
<td>(n=87)</td>
<td>(n=35)</td>
<td>(n=37)</td>
<td>(n=36)</td>
<td>(n=7)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>100.0</td>
<td>99.1</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>100.0</td>
<td>94.5</td>
<td>88.5</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100.0</td>
<td>98.2</td>
<td>99.2</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>100.0</td>
<td>98.9</td>
<td>89.9</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Topiramate</td>
<td>100.0</td>
<td>89.1</td>
<td>81.9</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100.0</td>
<td>78.3</td>
<td>78.3</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>100.0</td>
<td>89.1</td>
<td>89.1</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100.0</td>
<td>78.3</td>
<td>78.3</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>100.0</td>
<td>89.1</td>
<td>89.1</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Hospitals affiliated with Bangkok Metropolitan, the Military, the Police, and State Enterprises.

#### Table 6: Percentage of hospitals having new antiepileptic drugs available classified by hospital types

<table>
<thead>
<tr>
<th>Center hospitals</th>
<th>General hospitals</th>
<th>Community hospitals</th>
<th>University hospitals</th>
<th>Hospitals under Department of Medical Service</th>
<th>Hospitals under Department of Health</th>
<th>Others*</th>
</tr>
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<tbody>
<tr>
<td>(n=12)</td>
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<td>(n=35)</td>
<td>(n=37)</td>
<td>(n=36)</td>
<td>(n=7)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>100.0</td>
<td>98.9</td>
<td>89.9</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Topiramate</td>
<td>100.0</td>
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<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100.0</td>
<td>89.1</td>
<td>89.1</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>100.0</td>
<td>89.1</td>
<td>89.1</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100.0</td>
<td>89.1</td>
<td>89.1</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>100.0</td>
<td>89.1</td>
<td>89.1</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Hospitals affiliated with Bangkok Metropolitan, the Military, the Police, and State Enterprises.

#### Table 7: Percentages of hospitals with equipment for diagnosing epilepsy available in different hospital categories

<table>
<thead>
<tr>
<th>Center hospitals</th>
<th>General hospitals</th>
<th>Community hospitals</th>
<th>University hospitals</th>
<th>Hospitals under Department of Medical Service</th>
<th>Hospitals under Department of Health</th>
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<tbody>
<tr>
<td>(n=12)</td>
<td>(n=57)</td>
<td>(n=87)</td>
<td>(n=35)</td>
<td>(n=37)</td>
<td>(n=36)</td>
<td>(n=7)</td>
</tr>
<tr>
<td>EEG</td>
<td>63.6</td>
<td>54.4</td>
<td>57.9</td>
<td>57.9</td>
<td>57.9</td>
<td>57.9</td>
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<tr>
<td>CT Scan</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>MRI</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Others*</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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ILAE Reports & Guidelines

• **Antiepileptic Drugs**
  • Antiepileptic drugs and suicidality: an expert consensus statement (2013)
  • Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (2013)
  • Antiepileptic drug selection for people with HIV/AIDS: Evidence-based guidelines from the ILAE and AAN (2012)
  • Antiepileptic drugs – Best practice guidelines for therapeutic drug monitoring (2008)
  • ILAE Treatment Guidelines (2006)
    • Treatment Guidelines Excel spreadsheet
    • Guidelines PPT Presentation

• **ILAE Reports & Guidelines**
  • Antiepileptic Drugs (Pediatric)
    • Guidelines for imaging infants and children with recent-onset epilepsy (2009)
    • Guidelines on Neonatal Seizures (WHO, ILAE) (2011)

• **Other ILAE Guidelines**
  • cavernoma-related epilepsy: Review and recommendations for management (2013)
  • Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: A staged approach (2013)
  • Identification of new epilepsy treatments: issues in preclinical methodology (2012)
  • Epilepsy imaging study guideline criteria: Commentary on diagnostic testing study guidelines and practice parameters (2011)
ILAE Reports & Guidelines

- Other ILAE Guidelines
  - Standards for epidemiologic studies and surveillance of epilepsy (2011)
  - Recommendation for a definition of acute symptomatic seizure: Report from the ILAE Commission on Epidemiology (2009)
  - Definition of drug resistant epilepsy: Consensus proposal by the ad hoc task force of the ILAE Commission on Therapeutic Strategies (2009)

Conclusion about Guidelines

- When selecting a patient’s AED, all relevant variables and not just efficacy and effectiveness should be considered.
- Guidelines or evidence reviews can be seen as additional tool, not the only tool in the clinical decision.
- Most guidelines actually not guidelines but more recommendations based largely by “expert opinion” and common practice
  — Totally pointless if not circulated, read, and widely available

Thank You Very Much