Epilepsy: An Update on Pediatric Treatments

Ismail S Mohamed, MD, FRCPC
Pediatric Epileptologist, IWK Health Center
Objectives:

• Provide an overview of Epilepsy and its associated comorbidities.
• Discuss the factors affecting the choice of antiepileptic drugs in children and adolescents.
• Discuss the role of new antiepileptic drugs in the treatment of Epilepsy.
No Disclosure
‘Sacred illness’

• **Hippocrates** 400 BC: It is thus with regard to the disease called sacred: it appears to me to be in no way more divine nor more sacred than other diseases [...]. The brain is the cause of this affliction [...].

• “When the [surplus] phlegm [from the brain] runs down through the veins, the patient loses his speech and foams at the mouth, his hands are contracted, the eyes contorted, he becomes insensible, and in some cases the bowels are emptied [...]. The patient kicks with his feet [...]. The patient must endure all these symptoms when the cold phlegm flows into the warm blood."
Questions

What is Epilepsy?
What are the epilepsy “Comorbidities”?
How do seizures develop?
What does AEDs do?
How do we choose AEDS
Generic substitution of AEDS
New antiepileptic drugs
Definitions

- **Seizure**: the clinical representation of an abnormal and excessive synchronization of a population of cortical neurons.

- **Epilepsy**: a tendency toward recurrent seizures unprovoked by any systemic or acute neurologic insults.

- **Epileptogenesis**: sequence of events that converts a normal neuronal network into a hyperexcitable epileptic network.
Epidemiology

- **Seizures**
  - Incidence of new onset seizures: 80/100,000 per year
  - 60% of new onset seizures will go on to develop epilepsy

- **Epilepsy**
  - Point prevalence: 0.5-2%
Epilepsy: Incidence/100,000

Epidemiology

Hauser, Epilepsia 33:1992
Epilepsy: Etiology vs. Age of Onset

- Perinatal injury
- Metabolic defect
- Congenital malformation
- Infection
- Genetic epilepsy
- Postnatal trauma
- Brain tumor
- Vascular disease

Age (yr)
National and Regional Prevalence of Self-reported Epilepsy in Canada per 1000 individuals

Tellez-Zentino et al, Epilepsia 33:2004
Economic Burden

The PHAC estimates that total costs associated with epilepsy in 2000–2001 were $797.7 million.

- Direct costs were $99.6 million: $44.8 million (45%) for hospital care, $25.6 million (25.7%) for physician care and $29.1 million (29.2%) for drugs.
- Indirect costs associated with epilepsy were $698.1 million: $162.5 million (23.3%) in mortality cost and $535.6 million (76.7%) in morbidity cost.

Disability-Adjusted Life Years (DALYs)
In 2000–2001, PHAC estimates that epilepsy was associated with more than 15,000 DALYs, accounting for 0.3% of the DALYs for all illnesses in Canada. The years of healthy life lost due to disability represented a larger part (62.3%) of the DALYs for epilepsy than the years of life lost due to premature mortality (37.7%).
Comorbidities

- Seizures are not the only problem in epilepsy
- Other co-morbidities exist:
  - Language Problems
  - Cognitive dysfunction
  - Sleep disturbances
  - Psychiatric problems
Comorbidities

Hermann et al., The Lancet Neurology, 2008
Comorbidities

Hermann et al., The Lancet Neurology, 2008
Epilepsy: Natural History

Evidence-based review on the natural history of the epilepsies.
Schmidt, Dieter; Sillanpaa, Matti
Current Opinion in Neurology. 25(2):159-163, April 2012.
Epilepsy: Response to Treatment

Patterns of treatment response in newly diagnosed epilepsy.
Brodie, MJ; Barry, SJE; Bamagous, GA; Norrie, JD; Kwan, P; MD, PhD
Epilepsy: Natural History
Patterns of treatment response in newly diagnosed epilepsy.
Brodie, MJ; Barry, SJE; Bamagous, GA; Norrie, JD; Kwan, P; MD, PhD
Seizures: Cellular Mechanisms

**Excitation (too much)**
Ionic-inward Na\(^+\), Ca\(^{++}\) currents
Neurotransmitter: glutamate, aspartate

**Inhibition (too little)**
Ionic-inward Cl\(^-\), outward K\(^+\) currents
Neurotransmitter: GABA
Seizures

Partial
- Simple Partial
- Complex Partial
- Secondarily Generalized

Generalized
- Absence
- Myoclonic
- Atonic
- Tonic
- Tonic-Clonic
Seizures: Neurophysiology
Seizures: Neurophysiology
<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Gene symbol</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ion channel genes in idiopathic epilepsy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinic acetylcholine receptors</td>
<td>CHRNA4/CHRNB2</td>
<td>ADNFLE</td>
</tr>
<tr>
<td>Potassium channels</td>
<td>KCNQ2/KCNQ3</td>
<td>BFNC</td>
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<tr>
<td>Sodium channels</td>
<td>SCN1A/SCN2A/SCN1B</td>
<td>GEFS⁺</td>
</tr>
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<td>Chloride channels</td>
<td>CLCN2</td>
<td>IGE</td>
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<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
<td>GABRG2/GABRA1</td>
<td>GEFS⁺/IGE</td>
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<td><strong>Non-ion channel genes in idiopathic epilepsy</strong></td>
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<tr>
<td>Function unknown</td>
<td>LGI1</td>
<td>ADLTE</td>
</tr>
<tr>
<td>G-protein coupled receptors</td>
<td>MASS1/VLGR1</td>
<td>FS</td>
</tr>
</tbody>
</table>

Steinlein, Nature Reviews Neuroscience, 2004
Epileptogenesis

Initiating event
- e.g., genetic malformations, head trauma, febrile seizures, infections, stroke, status epilepticus

Repair (or control)

Failure to repair

No consequence

Onset of epileptogenesis
- e.g., by "second hit", polymorphisms, susceptibility genes, critical modulators, comorbidities

Functional and structural alterations during epileptogenesis
- e.g., hyperexcitability of neurons and/or neuronal circuits, alterations in expression and function of receptors and ion channels (in part recapitulating ontogenesis), neuronal loss, neurogenesis, axonal and dendritic sprouting, gliosis, inflammation

Spontaneous seizures
(Clinical onset of epilepsy)

Cognitive and behavioral alterations

No progression

Progression of epilepsy

Chronic epilepsy
often pharmacoresistant

Initial insult modification

Anti-epileptogenic/disease-modifying

Anticonvulsant ("antiepileptic")

Disease-modifying

Therapeutic intervention

Wolfgang Loßcher and Claudia Brandt
Epilepsy: Diagnosis

- Clinical History & Examination
- Routine EEG
- Video EEG monitoring
- Imaging
- Other tests: Genetic and metabolic testing, PET, SPECT, MEG
Patient Perspectives: What is Important

![Graph showing seizure frequency and QOLIE-10 scores](image)

- Mean QOLIE-10 Scores
  - Daily: 32.3
  - Weekly: 29.4
  - Monthly: 27.7
  - Yearly: 24.2
  - Less than Yearly: 20.2

1. Quality of Life in Epilepsy-10 inventory
2. \( p < 0.001 \) Spearman Rho
3. Error bars show 95% confidence intervals

Ramon Edmundo D. Bautista, E. Tannahill Glen, Peter S. Wludyka, Namrata K. Shetty

Epilepsy Research Volume 79, Issues 2-3 2008 120 - 129
Patient Perspectives: What is Important

Piero Perucca, Frank G. Gilliam, Bettina Schmitz

Epilepsy & Behavior Volume 15, Issue 2, Supplement 1 2009 S46 - S50
Antiepileptic drugs

- A drug which decreases the frequency and/or the severity of seizures.
- Treat the symptoms of seizures, **NOT** the underlying condition.

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**Characteristics of the ideal AED**

- Broad spectrum
- Safe
- No drug–drug interaction
- Long half-life
- No cognitive side effects
- Use-dependent mechanism
- Alters natural history of epilepsy

Donner & Snead, 2007
Antiepileptic drugs

Bialer and White, Nature Reviews 2012
Antiepileptic drugs

Bialer and White, Nature Reviews 2012
Antiepileptic drugs: Multiple mechanisms of action

Table 1 | Antiepileptic drugs and their molecular targets

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sodium channels*</th>
<th>Calcium channels*</th>
<th>GABA system*</th>
<th>Glutamate receptors*</th>
<th>Partial seizure†</th>
<th>GTC seizure‡</th>
<th>Absence seizure§</th>
<th>Myoclonic seizure∥</th>
<th>Infantile spasms‡‡</th>
<th>Lennox-Gastaut‡‡‡</th>
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</thead>
<tbody>
<tr>
<td>Phenytin</td>
<td>$\text{Na}^+$, $\text{Na}^+$</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Carbamazepine</td>
<td>$\text{Na}^+$</td>
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<tr>
<td>Oxcarbazepine</td>
<td>$\text{Na}^+$</td>
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<tr>
<td>Lamotrigine</td>
<td>$\text{Na}^+$</td>
<td>$\text{HVA}$</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>(+/-)</td>
<td>+</td>
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<tr>
<td>Zonisamide</td>
<td>$\text{Na}^+$</td>
<td>T-type</td>
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<td>(+)</td>
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<td>(+)</td>
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</table>

**Mixed, complex or poorly understood actions**

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>$\text{Na}^+$? $\text{Na}^+$?</td>
<td>T-type?</td>
<td>$\uparrow$ GABA turnover</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>$\text{Na}^+$</td>
<td>$\text{HVA}$</td>
<td></td>
<td>GABA$_A$, NMDA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
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<tr>
<td>Topiramate</td>
<td>$\text{Na}^+$? $\text{Na}^+$?</td>
<td>$\text{HVA}$</td>
<td></td>
<td>GABA$_A$, KA/AMPA</td>
<td></td>
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<td>(+)</td>
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<td>(+)</td>
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<td>Ethosuximide</td>
<td>$\text{Na}^+$?</td>
<td>T-type</td>
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<td>+</td>
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<tr>
<td>Gabapentin</td>
<td>$\text{HVA (α28)}$</td>
<td>$\uparrow$ GABA turnover</td>
<td></td>
<td></td>
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<tr>
<td>Levetiracetam</td>
<td>$\text{HVA}$</td>
<td>Reverses DMCM</td>
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<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<tr>
<td>Phenobarbital</td>
<td>$\text{HVA}$</td>
<td>GABA$_A$, AMPA</td>
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**GABA-mediated mechanisms**

<table>
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<tr>
<th>Drug</th>
<th>Sodium channels*</th>
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<th>GABA system*</th>
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<th>Infantile spasms‡‡</th>
<th>Lennox-Gastaut‡‡‡</th>
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<tbody>
<tr>
<td>Benzodiazepines</td>
<td>GABA$_A$</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>(+)</td>
<td></td>
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<tr>
<td>Vigabatrin</td>
<td></td>
<td>GABAT</td>
<td></td>
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<td></td>
<td></td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Tiagabine</td>
<td></td>
<td>GABA-transporter</td>
<td></td>
<td></td>
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<td></td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Goals of Epilepsy Treatment

- Control of seizures
- Minimal adverse events
- Treat associated co-morbidities
- Good patient compliance
Therapeutic principles

• Aim: maximal seizure control, minimal side effects
• Monotherapy preferred to polytherapy
• Usually gradual titration of AED
• Assessment of AED effect (reduction in seizure frequency)
  • After AED has reached steady state
  • Depends on the average time interval of seizures before treatment
Selection of AEDs

- Selection of AED is based on:
  - Seizure type / epilepsy syndrome,
  - Side effects profile
  - Pharmacology, drug interactions,
  - Comorbidities
  - Safety and tolerability,
  - Ease and speed of initiation of the drug,
  - Need for laboratory monitoring
  - Cost
Matching drugs to patients:
- Epilepsy Syndrome
- Side effects
- Work
- Sleep
- Mood/School
Selection of AEDs

Partial Seizures
- Simple
- Complex
- Secondary Generalized

Generalized Seizures
- GTC
- Tonic
- Atonic
- Myoclonic
- Absence
- Infantile Spasms

- PHT, PB
- CBZ, OXC
- GBP, LEV, PGB

- ESM
- VGB
- ACTH

- VPA, LTG, TPM, ZNS, (FBM)

Elizabeth J. Donner, O. Carter Snead III

New Generation Anticonvulsants for the Treatment of Epilepsy in Children
NeuroRX Volume 3, Issue 2 2006 170 - 180
Possible causes of AED Failure

- Inadequate dose → dose escalation
- Lack of compliance → measure blood AED levels
- Inaccurate diagnosis: the patient doesn’t have epilepsy
- Inappropriate selection of AED
- True inefficacy of AED
  - Other AED on monotherapy
  - AED combination
AED combinations

• Rules of AED combination:
  • Try to avoid combining similar modes of action
  • Add drug with multiple mechanisms of actions
  • Titrate new drug slowly
  • Be aware of drug interactions
  • Replace either drug if response is poor

• Some effective combinations:
  • valproate-lamotrigine
  • Steripentol-Clobazam
Titration of AEDs

**Pharmacogenomics** (2011) 12(10), 1429–1447
Drug Interactions

**Pharmacokinetics**
- Dose
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
- Total Serum Concentration
- Bound Concentration
- Unbound Concentration

**Pharmacodynamics**
- Receptor Site - Brain
- Pharmacological Response
- Therapeutic Outcome
  - Side Effects
  - Seizure Freedom

BBB
The Cytochrome P-450 Enzyme System

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
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<tbody>
<tr>
<td>Phenobarbital</td>
<td>Erythromycin</td>
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<tr>
<td>Primidone</td>
<td>Valproate</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
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<tr>
<td>tobacco/cigarettes</td>
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## AED combinations

<table>
<thead>
<tr>
<th>Enzyme inducers</th>
<th>Increase of metabolism / decrease of efficacy</th>
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<tbody>
<tr>
<td>carbamazepine, phenytoin</td>
<td>valproate, lamotrigine, carbamazepine</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>oral contraception</td>
</tr>
<tr>
<td></td>
<td>oral anticoagulation</td>
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</table>

<table>
<thead>
<tr>
<th>Enzyme inhibitors</th>
<th>Decrease of metabolism / increase in efficacy - toxicity</th>
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</thead>
<tbody>
<tr>
<td>valproate</td>
<td>lamotrigine, carbamazepine</td>
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<table>
<thead>
<tr>
<th>Pharmacodynamics</th>
<th>Increased risk of Toxicity</th>
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<tr>
<td>similar mechanism of action</td>
<td>Carbamazepine- Oxcarbazepine</td>
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<table>
<thead>
<tr>
<th>Does not cause interaction</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Gabapentin, Topiramate, levetiracetam</td>
<td></td>
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</table>
Not only drugs

Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy

Objectives: To examine the effect of grapefruit juice on the bioavailability of carbamazepine in patients with epilepsy.

Methods: This was a randomized crossover study consisting of 2 phases. Ten patients with epilepsy who had received therapy with 200 mg carbamazepine 3 times a day for the previous 3 to 4 weeks participated. They were given either grapefruit juice or 300 mL water at 8 AM along with 200 mg carbamazepine. Each treatment was separated by 2 days; subjects continued to receive carbamazepine therapy during the 2-day period. On both occasions, blood samples were collected at different time intervals between 0 to 8 hours. Carbamazepine levels were estimated by reversed-phase HPLC technique.

Results: Compared with water, grapefruit juice significantly increased the steady-state peak concentration (6.55 versus 9.20 μg/mL), trough concentration (4.51 versus 6.28 μg/mL), and area under the plasma concentration–time curve (43.99 versus 61.95 μg · h/mL) of carbamazepine. No significant effect was found in the time to reach peak plasma concentration.

Conclusion: Grapefruit juice increases the bioavailability of carbamazepine by inhibiting CYP3A4 enzymes in gut wall and in the liver. (Clin Pharmacol Ther 1998;64:286-8.)

Santosh K. Garg, PhD, Naresh Kumar, MSc, Vinod K. Bhargava, PhD, and Sudesh K. Prabhakar, DM Chandigarh, India
Figure 1. Steady-state carbamazepine concentrations (in micrograms per milliliter; mean ± SEM,
Pharmacogenomics: CYP gene family
Some AEDs can aggravate some seizure types:

- Carbamazepine, Oxcarbazepine, Phenytoin can aggravate absence and myoclonic seizures.
- Lamotrigine can worsen patients with severe myoclonic epilepsy of infancy.
- Tiagabine can induce tonic status epilepticus in patients with Lennox-Gastaut syndrome.
RUFINAMIDE (Banzel)

- Mechanism of action: limiting of excessive firing of sodium-dependent action potentials. i.e works on sodium channels with “new mechanism”.
- Approved in Europe and USA for treatment of Lennox-Gastaut syndrome.
- Orphan drug status
Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome.
Glauser, T; Kluger, G; Sachdeo, R; Krauss, G; Perdomo, C; Arroyo, S; MD, PhD
DOI: 10.1212/01.wnl.0000303813.95800.0d

RUFINAMIDE (Banzel)
## RUFINAMIDE (Banzel)

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Number of patients with the most common adverse events (in ≥10% of patients in either treatment group)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Rufinamide, n (%)</td>
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<tr>
<td>Total patients studied</td>
<td>74</td>
</tr>
<tr>
<td>Total patients with an adverse event</td>
<td>60 (81.1)</td>
</tr>
<tr>
<td>Most common adverse events</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>18 (24.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (21.6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (13.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (5.4)</td>
</tr>
</tbody>
</table>

Patients with a history of Familial Short QT syndrome should not be treated with BANZEL.
New antiepileptic drugs

Lacosamide (Vimpat)

- Acts on sodium channels, like Carbamazepine and Phenytoin
- It selectively enhances slow inactivation of sodium channels, whereas the older drugs work on fast inactivation resulting in a shift towards hyperpolarization and a reduction in the availability of voltage-gated sodium channels.
Lacosamide

[Graph showing the comparison of different dosage levels of Lacosamide across different studies.]

*Placebo*  |  200 mg/day  |  400 mg/day  |  600 mg/day
---|---|---|---
Ben-Menachem (phase II) | 10 | 26 | 39 \( \dagger \) 40 \( \dagger \)
Halász (phase III) | | | 20.8
Chung (phase III) | | | 37.3 \( \dagger \) 37.8 \( \dagger \)

*Expert Opin. Pharmacother.* (2010) 11(9)
## Lacosamide

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n = 364(%)</th>
<th>Lacosamide</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>200 mg/day, n = 270 (%)</td>
<td>400 mg/day, n = 471 (%)</td>
</tr>
<tr>
<td>Any Event</td>
<td>4.9</td>
<td>8.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Coordination abnormal</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Diplopia</td>
<td>0.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Convulsion</td>
<td>1.1</td>
<td>0.7</td>
</tr>
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</table>
New antiepileptic drugs

Perampanel (Fycompa)

- A selective, noncompetitive antagonist of AMPA-type glutamate receptors
- Adjunctive therapy for the treatment of refractory partial-onset seizures.
- Seizure reduction seem to be sustained in patients who continued >1 year.
- Approved (Just last week) in USA for treatment of partial seizures in patients with epilepsy who are at least 12 years of age.
Perampanel (Fycompa)

G. L. Krauss et al.

Figure 1.
(A) Median percent change in seizure frequency per 28 days (relative to pre-perampanel baseline) and (B) responder rate, by 13-week interval during open-label perampanel treatment (intent-to-treat analysis set).
Epilepsia © ILAE
Retigabine (potiga)

- Works on low-threshold voltage-gated potassium channels leading to hyperpolarization of the membrane potential thereby suppressing repetitive firing
- Defect in potassium channel linked to benign neonatal seizures.
- Retigabine is an option for the adjunctive (add-on) treatment of partial onset seizures with or without secondary generalization in adults
AEDs: Adverse Effects

♦ Acute dose-related—reversible

♦ Idiosyncratic
  ♦ rare
    • potentially serious or life threatening

♦ Chronic—reversibility and seriousness vary: Purkinje cell degeneration with chronic phenytoin toxicity.
A marker for Stevens–Johnson syndrome

Stevens–Johnson syndrome and the related disease toxic epidermal necrolysis are life-threatening reactions of the skin to particular types of medication\textsuperscript{1-3}. Here we show that there is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen $HLA-B^*1502$, and Stevens–Johnson syndrome induced by carbamazepine, a drug commonly prescribed for the treatment of seizures. It should be possible to exploit this association in a highly reliable test to predict severe adverse reaction, as well as for investigation of the pathogenesis of Stevens–Johnson syndrome.

Chung WH, Hung SI, Hong HS \textit{et al.}
Medical genetics. a marker for Stevens–Johnson syndrome.
Pharmacogenomics

The overall average frequency is 1.39%, but frequency is substantially lower among European Caucasians (about 0.001%) and higher in Asian populations originating from the regions highlighted in grey. Because considerable migration has occurred over the centuries, the frequency distribution shown in this illustration does not necessarily reflect the frequency of the allele in populations currently living in the highlighted areas. In particular, high-frequency pockets exist within communities of Asian ancestry living outside Asia. White areas (n.a., no data available) may include regions where only populations that migrated in the past 1000 years were studied. Based on a meta-analysis of 171 native population samples [20].

Genetic basis for idiosyncratic reactions to antiepileptic drugs.
Franciotta, Diego; Kwan, Patrick; Perucca, Emilio

DOI: 10.1097/WCO.0b013e328328f276
### AEDs: Idiosyncratic reactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effect</th>
<th>Estimated incidence</th>
<th>Year of drug introduction</th>
<th>First report of adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Shoulder-hand syndrome</td>
<td>Up to about 30%</td>
<td>1912</td>
<td>1934</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Pseudolymphoma</td>
<td>82 cases reported in the first 20 years of use</td>
<td>1938</td>
<td>1940</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Agranulocytosis</td>
<td>1:200,000</td>
<td>1963</td>
<td>1964</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Hepatotoxicity</td>
<td>1:35,000</td>
<td>1967</td>
<td>1977</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Hepatotoxicity, often as part of DRESS syndrome</td>
<td>About 20 cases published to date</td>
<td>1991</td>
<td>1992</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Aplastic anemia</td>
<td>1:7500</td>
<td>1993</td>
<td>1994</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Acute closed-angle glaucoma</td>
<td>86 cases reported up to 2006</td>
<td>1996</td>
<td>2001</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Oligohidrosis</td>
<td>1:5000 patient years</td>
<td>1989</td>
<td>1988</td>
</tr>
</tbody>
</table>

*Epilepsia, 48(7):1223–1244, 2007*
## Generic AEDs

### Table 3. Generic and Brand-Name Antiepileptic Drug Formulations: Price of One Tablet

<table>
<thead>
<tr>
<th>Antiepileptic Drug, Dose (Brand Name, Manufacturer)</th>
<th>Generic</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine 200 mg (Tegretol, Novartis Pharmaceuticals Corporation)</td>
<td>$0.16</td>
<td>$1.10</td>
</tr>
<tr>
<td>Ethosuximide 250 mg (Zarontin, Pfizer Inc.)</td>
<td>$1.18</td>
<td>$1.49</td>
</tr>
<tr>
<td>Gabapentin 600 mg (Neurontin, Pfizer Inc.)</td>
<td>$1.03</td>
<td>$3.48</td>
</tr>
<tr>
<td>Lamotrigine 100 mg (Lamictal, GlaxoSmithKline)</td>
<td>$4.00</td>
<td>$5.33</td>
</tr>
<tr>
<td>Levetiracetam 500 mg (Keppra, UCB)</td>
<td>$2.67</td>
<td>$3.67</td>
</tr>
<tr>
<td>Oxcarbazepine 600 mg (Trileptal, Novartis Pharmaceuticals Corporation)</td>
<td>$4.33</td>
<td>$6.04</td>
</tr>
<tr>
<td>Phenytoin Sodium Extended 100 mg (Dilantin, Pfizer)</td>
<td>$0.36</td>
<td>$0.52</td>
</tr>
<tr>
<td>Topiramate 100 mg (Topamax, Ortho-McNeil Neurologics)</td>
<td>$0.83</td>
<td>$7.24</td>
</tr>
<tr>
<td>Valproic Acid 250 mg (Depakene, Abbott Laboratories)</td>
<td>$0.30</td>
<td>$2.53</td>
</tr>
<tr>
<td>Zonisamide 100 mg (Zonegran, Eisai Inc.)</td>
<td>$1.89</td>
<td>$2.85</td>
</tr>
</tbody>
</table>

*Prices from druastore.com, based on a prescription of 100 tablets, as of September 20, 2009*
Generic AEDs

- Generics can have 10% difference in bioavailability compared to the original drug.
- No well performed blinded studies to assess risk from switching between generics.
- Additives may be different, leading to allergic reactions.
- Dissolution properties may vary.
- It is recommended not to change manufacturer’s version of anti seizure medication when the patient is well controlled especially in difficult to control patients.
Switching from one generic to another

- Further variability in drug concentrations is allowed by the bioequivalence standards because generic drugs are tested against the brand name drug but not against each other.
- Current standards permit a difference in bioavailability between generic formulations that is greater than the difference between the generic and brand name drugs.
Changing to Generic: what to do

- Watch closely for breakthrough seizures or toxicity.
- Obtain baseline blood levels if possible.
- Check blood level again when stable on new preparation.
- Ideally limit changes between different generic manufacturers.
Other Treatment Options

• Ketogenic Diet

Dispense **NO** absorbable carbohydrates (capable of altering ketosis) from medications—therefore generally no syrups, elixirs, suspensions, chew tablets.

• Epilepsy Surgery

Certain antiepileptic drugs might need to be discontinued prior to surgery such as valproic acid.
Status Epilepticus

First AED: Lorazepam 0.05–0.1 mg/kg IV (max 5 mg over 1–4 min)
If no IV: Diazepam 0.2–0.5 mg/kg/dose PR (max 20 mg/dose)

Second AED: Fosphenytoin 20 mg PE/kg IV
(If no Fosphenytoin: Phenytoin 20 mg/kg IV)

Third AED: Phenobarbital 20 mg/kg IV
or Levetiracetam, Valproic acid, others

Midazolam 0.1–0.3 mg/kg or Pentobarbital 3–15 mg/kg bolus
followed by continuous infusion to maintain burst suppression
*If < 2 years, consider Pyridoxine 100 mg IV

ABCs

Labs
EKG
Imaging

Hypoxia
Hemodynamics
Hyperthermia
Hypoglycemia
Hyponatremia

EEG
monitoring

Status Epilepticus

- Intravenous Leveticetam, Lacosamide are not available in Canada.
Conclusions

• Development of antiepileptic drugs resulted in new AEs with less side effects but did not affect epilepsy outcome

• Promising new antiepileptic drugs with novel mechanisms of actions are being developed

• New genetic tools hold promise for individualized therapy