Epilepsy and the New Antiseizure Drugs

November 10-12, 2016
Hard Rock Hotel® at Universal Orlando
Orlando, FL

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Disclosures

Relevant financial relationship(s) with industry
- Royalties: Demos Publishers Inc., Springer Publishers
- Stipend: Epilepsy & Behavior Case Report journal: Editor-in-Chief
- Grant support:
  - Mayo Clinic
  - Brain Sentinel®
- Consultant: SK Life Science (Safety Board)
- References to off-label usage(s) of pharmaceuticals or instruments
  - None
More than 30 ASDs Exist Globally

- First generation: Bromide, Borax, Phenobarbital, Mephenytoin, Mephobarbital
- Second generation: Valproate, Carbamazepine, Diazepam, Sulthiame, Chlordiazepoxide

Year of introduction:
- 1850: Bromide
- 1870: Borax
- 1890: Phenobarbital
- 1910: Mephenytoin, Mephobarbital
- 1930: Valproate, Carbamazepine, Diazepam, Sulthiame, Chlordiazepoxide
- 1950: Eslicarbazepine acetate, Lacosamide, Stiripentol, Pregabalin, Levetiracetam, Topiramate
- 2010: Progabide

Number of AEDs:
- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35
- 40

AES 2013 Page B. Pennell
The First Seizure as Epilepsy

• High Risk for Seizure Recurrence-Treatment
  • Abnormal neurological examination
    • Focal features
    • Intellectual disability
  • Symptomatic Etiology
    • Clinical history
    • Neuroimaging (brain lesion)
  • Epileptiform EEG

Anti-seizure Drugs

- Prospective longitudinal outcome study\textsuperscript{1,2}.
- 31.4\% never had another Sz after an ASD\textsuperscript{2}.
  - 504/780 (64.6\%) were SF for at least 1 year (59.2\% still SF by 8 years).
  - 92\% became SF did so by the 3\textsuperscript{rd} yr.
- 35\% never got Sz control\textsuperscript{2}
  - Drug resistance is considered after 2 AED failures.\textsuperscript{3}
  - The 1st ASD is the best predictor.

### AED-Naïve Patients

- Seizure-free with 1st drug: 35.4\%
- Seizure-free with 2nd drug: 50.4\%
- Seizure-free with 3rd or multiple drugs: 13\%
- Refractory: 1\% (2\%)

### Monotherapy Trial: 5 year follow-up

ASDs and Response to Treatment

• All current ASDs provide symptomatic treatment.
  • Effective in focal seizures 2/3rds of the time
  • Effective in generalized seizures 80-85% of the time
• None alter the course of the disease process.
  • No treatments are truly “prophylactic” for prevention of epilepsy.
• Response to treatment remains stable over time
• All ASDs have side-effects; none treat non-seizure symptoms.
Response to ASDs Over Time in Newly Diagnosed

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>Analysis</th>
<th>N</th>
<th>One ASD</th>
<th>Multiple ASDs</th>
<th>Total Sz Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982-1997</td>
<td>1999</td>
<td>470</td>
<td>61</td>
<td>3.0</td>
<td>64%</td>
</tr>
<tr>
<td>1982-2001</td>
<td>2003</td>
<td>780</td>
<td>59</td>
<td>5.4</td>
<td>64.4%</td>
</tr>
<tr>
<td>1982-2006</td>
<td>2008</td>
<td>1098</td>
<td>62</td>
<td>6.4%</td>
<td>68.4%</td>
</tr>
</tbody>
</table>

- About 15 new ASDs approved in the last 20 years.
- Response in Focal Epilepsy: 50.4% (1st); 10.7% (2nd); 2.7% (3rd); 0.8% (>3rd).\(^1\)
- 2nd drug worked in 11% (failed treatment); 41% (SE); 55% (idiosyncratic rxn.).\(^1\)

10 years later...

- The SF rate improved from 64.0% to 68.4%.\(^2\)
  - ? modest + influence from the new ASDs); more did well on 1 ASD.
  - Elderly found to have a better response.

\(^2\) Brodie MJ. Epilepsia 2013;54(Suppl S2):5-8.
Choosing an ASD

- Confirm the diagnosis of epilepsy
- Determine the seizure type
- Consider comorbidity
- Choose the most effective medication
- Consider safety and tolerability
- Determine initiation and dosing strategy
- Mechanism of Action
- Assess cost and availability
Step 1: Confirm the Diagnosis

A 17 y/o boy grew up in a dysfunctional home environment. He had a right craniotomy at 12 years for a parietal lesion (DNET) with subsequent CDH.

Grand mal seizures started at age 13 years and continued despite 5 ASDs.

He was on PHT 500 mg po qD (17 ug/dl) and GBP 800 mg po TID.

CBZ 800 mg po qD added but levels were low (PHT= 7 ug/dl and CBZ 3.6 ug/dl); seizures increased.
EIASD Interactions

• Reasons
  • Non-compliance was suspected but excluded.
  • “Fast metabolizer” (20% of AA for 2C9 drugs).
  • Reciprocal induction: both ASDs together lead to combined reduction in serum concentrations.

• Solution
  • Transition to CBZ monotherapy (3A4, 2C9)
  • Substitute a different ASD to PHT (2C9)
Step 2: Classify Epilepsy for ASD Choice

<table>
<thead>
<tr>
<th>Narrow Spectrum Focal seizures</th>
<th>Narrow Spectrum Generalized Seizures</th>
<th>Broad Spectrum Focal and Generalized</th>
<th>Spectrum Unestablished</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Ethosuximide</td>
<td>Levetiracetam</td>
<td>Lacosamide</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Rufinamide</td>
<td>Lamotrigine</td>
<td>Ezogabine</td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td>Zonisamide</td>
<td>Perampanel</td>
</tr>
<tr>
<td>Pregabalin</td>
<td></td>
<td>Valproic acid</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td></td>
<td>Topiramate</td>
<td></td>
</tr>
<tr>
<td>Vigabatrin (+Spasms)</td>
<td></td>
<td>Felbamate</td>
<td></td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td></td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clobazam</td>
<td></td>
</tr>
</tbody>
</table>

*New AEDs used as adjunctive therapy in patients refractory to standard AEDs in RCTs.

Additional references:

Slide courtesy of Jacqueline French, MD
An 19 y/o male with migraine experienced his first “grand mal” seizure. In the ED he was given IV PHT and maintained on PHT 200 mg po BID (15 ug/dl). He experience an increase in “dropsies”.

MRI was normal, EEG showed GSW and GPSW. In follow-up VPA 250 mg po bid was added and increased to VPA ER 1000 mg po q hs. He complained of dizziness, blurry vision and difficulty walking.
Inhibitor + Inducer

• Reason
  • VPA and PHT are both highly protein bound ASDs and compete for the carrier protein albumin.
  • The ASD with the higher concentration usually predominates (VPA > PHT).
  • PHT free fractions rise (bioactive) with toxicity!

• Solution
  • Taper PHT
  • Substitute an alternative ASD (i.e. LEV)
Step 3: Consider the Individual

- Seizure type and epilepsy syndrome
- Age
- Gender
- Pregnancy potential
- Comorbidities
  - Depression, weight
  - Systemic compromise
- Co-medications
- Lifestyle

1. [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm3708a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm3708a1.htm)
Consider Comorbidities

• Mental Health issues
  • Select: LTG, VPA, OXC, PGB
  • Avoid: PB, TPM, LEV, ZNS, PER

• Pain
  • Select: GBP, PGB, TPM, CBZ

• Eating disorder: avoid drugs that impact weight
  • Weight gain: VPA, GBP, PGB, CBZ, OXC, EZO
  • Weight loss: TPM, ZNS, FBM

• Hyponatremia (elderly, on diuretics)
  • Avoid: CBZ, OXC, ESLI (CBZ derivatives)

• Cardiovascular risks (e.g. high cholesterol)
  • Avoid: CBZ, PHT ("inducers")
ASDs

• The mainstay of treatment in >90% of patients.

• Choices;
  • **Conventional**: PB, PHT, CBZ, VPA
  • **Newer**: LTG, TPM, GBP/PGB, OXC, LEV, ZNS, LCS, RUF, CLB, GVG, EZO, PER, ESLI [FBM, TGB]
  • Based upon seizure type and epilepsy syndrome
    • Focal: Essentially all ASDs
    • Generalized: VPA, LTG, TPM, ETH (absence only)

• Advantages of the newer ASDs include tolerability; the advantages of conventional ASDs is cost.

Seizure Reduction In CCT*

50% seizure reduction (minus placebo)

*New AEDs used as adjunctive therapy in patients refractory to standard AEDs.


Slide courtesy of Jacqueline French, MD
Consider Safety

- Steven-Johnson Syndrome
  - Most ASDs
- Aplastic Anemia
  - CBZ/OXC, FBM
- Organ Failure
  - VPA, FBM
- Nephrolithiasis
  - TPM, ZNS
- Visual loss
  - GVG, EZO
- Weight Loss
  - FBM, TPM, ZNS
- Weight Gain
  - CBZ/OXC, GBP/PGB, PER, GVG, VPA

General Population: 1.1%

North American Pregnancy Registry Fall 2014

Teratogenesis
All ASDs

Baker GA et al. IQ after in utero exposure to AEDs: a controlled cohort study. Neurology 2015;84:382-390
Mood and ASDs

Valproate
Lamotrigine
Carbamazepine
Oxcarbazepine
Phenytoin
Clobazam

Zonisamide
Lacosamide
Levetiracetam

Topiramate
Perampanel
ASD Interactions

- Some ASDs (PHT, PB, CBZ and OXC) *induce the* hepatic P450 enzyme system.

- Induction increases metabolism of lipid soluble drugs, clearance and reduces efficacy of ASDs. Dose increases of other drugs may be required.
  - e.g. contraception and anticoagulation compromise.

- Some ASDs (VPA, FBM, RUF) *inhibit* hepatic enzyme, reduce metabolism of other ASDs/drugs and cause toxicity requiring dose reductions.

- Some ASDs do both (TPM, ZNS)-variable effects.
ASDs-Hormonal Contraception

**Pregnancy Potential**
- Carbamazepine, OXC, Eslicarbazepine
- Phenobarbital
- Phenytoin
- Primidone
- Topiramate*
- Rufinamide
- Clobazam
- Perampanel

*Potential inactivation at 200 mg/day

**Safe**
- Divalproex
- Ethosuximide
- Gabapentin/pregabalin
- Lamotrigine^*
- Levetiracetam
- Zonisamide
- Lacosamide
- Vigabatrin
- Ezogabine

^HC interaction with LTG reduction

The New ASDs

• 7 new ASDs available in the last 4 years.
  – Vigabatrin: Spasms & add-on focal epilepsy
  – Rufinamide: atonic seizures in LGS
  – Lacosamide: add-on focal epilepsy (monotherapy and adjunctive)
  – Clobazam: add-on LGS 2 years old
  – Ezogabine: add-on focal epilepsy
  – Perampanel” add-on focal epilepsy
  – Eslicarbazepine: add-on focal epilepsy
Old v New AED as the DOC
The SANAD (Standard and New AEDs) trials

SANAD A (Focal)
- CBZ v GBP v LTG v OXC v TPM (N=1721)
- LTG was superior to CBZ, GBP, TPM in time to treatment failure but not to 1 year remission
- CBZ > GBP in time to 1st seizure.

Conclusion
- LTG is the DOC for focal epilepsy

SANAD B (Generalized)
- VPA v LTG v TPM (N=716)

Outcome (efficacy)
- VPA was superior to TPM & LTG in time to treatment failure
- VPA was equal to TPM in time to 1 year remission.

Conclusion
- VPA is the DOC for generalized or unclassified epilepsy

New Extended Release

- Lamotrigine
  - Lamictal XR®
- Levetiracetam
  - Keppra XR® (available in generic)
- Oxcarbazepine
  - Oxtellar XR®
- Topiramate
  - Qudexy XR®, Trokendi XR®
- Gabapentin
  - Gralize® (not directly interchangeable)

- All available as a single daily dose.
- Theoretically less impact on AEs with better efficacy
Lacosamide (Vimpat®)

• Acts on long acting Sodium Channels
• Indicated for focal epilepsy in monotherapy
  • Some data for GGE and Status epilepticus
• BID dosing
• IV formulation
• Renal excretion
• Side Effects
  • Dizziness, nausea, diplopia, vertigo, mood
  • PR prolongation of the EKG

IV ASDs
Phenytoin
Fosphenytoin
Phenobarbital
Valproic acid
Levetiracetam
Lacosamide
Clobazam
Frisium®; Onfi®

• Long acting benzodiazepine, BID dosing
• Side Effects
  • Drowsiness
  • Dizziness
  • Poor Coordination
  • Drooling
  • Restlessness or aggressiveness
• ? Low dependance/addiction potential
Eslicarbazepine Aptiom®

- ESLI = S-enantiomer of OXC (carbamazepine family)
- <5% active metabolite is OXC; may increase PHT; affect OCPs
- Indicated for focal seizures in 3 pivotal CCTs.
  - 41% RR v 21% placebo in 12 wk maintenance phase
- Same side effects as CBZ and OXC
  - Reportedly better tolerated
  - Less hyponatremia, hepatic induction and rash
  - Dizziness, nausea and vomiting, somnolence, and diplopia

Ezogabine; Retigabine (Potiga®)

- Novel ASD with unique MOA (potentially useful as polytherapy).
  - Selectively activates the KCNQ channel
  - Hyperpolarization stabilizes hyperexcitable neurons.

- Three Phase III trials (35% median % reduction at 1200 mg/d)
  - Initially approved in US in 2010 with concerns about bladder abnormalities including urinary retention (about 2% in CCT) and rare flaccid bladder.
  - QT prolongation (single study) 7.7 msec in healthy volunteers
  - Spring 2013: Reports of risks to retinal function with potential vision loss, blue skin discoloration that may be permanent

- Black Box warning placed because of retinal abnormalities similar to retinal pigment dystrophies.

Brodie M et al. Neurology 2010;75:1817-1824;
Ezogabine
Potiga®

• TID administration
• Common SE: sleepiness, dizziness and confusion
• Others include;
  • Urinary retention or inability to empty the bladder (2%)
  • Neuropsychiatric symptoms (hallucinations, irritability, anxiety, depression)
  • Changes in heart rhythm
  • Suicide thoughts
  • Blue skin discoloration
  • Visual loss

courtesy of FDA.gov

Perampanel (Fycompa®)

- Indicated for localization-related epilepsy
  - GGE results preliminarily appear favorable
- Unique highly selective, noncompetitive AMPA-type glutamate receptor antagonist
- Extensively metabolized via hepatic P450 isoenzyme CYP3A4 and clearance is increased 2-3 fold with EIASDs
- T1/2 about 75-100 hours w/o EIASDs
- Side Effects
  - Anxiety, irritability, homicidal ideation (black box warning)
  - CNS AEs include somnolence, fatigue, dizziness, irritable-euphoric mood, nausea, imbalance, vertigo, weight gain
- Go slow at 2 mg/day week with target of 4-8 mg/day

Perampanel

BLACK BOX WARNING: Severe Psychiatric and Behavioral reactions may occur.

- Includes aggression, hostility, irritability, anger, and homicidal ideation and threats.
- Occurred with and without prior psychiatric history, aggressive behavior, or with other meds associated with hostility and aggression.
- Closely monitor patients especially during titration and if higher doses are used.
- Reduce PER if symptoms occur (may be able to re-increase).
- D/C PER if the side-effects are severe or getting worse.
What about other New ASDs?

- Animals induce a variety of inflammatory signaling.
  - IL-1b, Cox2, TNF-a, IL6 etc.
- Anti-inflammatory Rx are anticonvulsant and neuroprotective.
  - VTX 765, TG6 10-1
- Losartan may be disease modifying.
  - Situation specific (e.g. BBB disruption in stroke/TBI)
- Epilepsy associated inflammation suggests novel ASD targets and may help some with PTE & DRE.

Diamond ML et al. IL-1β associations with PTE development. Epilepsia 2014;55:1109–1119