EPILEPSY UPDATE

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Disclosures

• Speaker bureau LivaNova
Outline

• New onset Seizure
• Investigations in patients with epilepsy
• Medical management of epilepsy
• Non Pharmacological options in treatment of epilepsy
• Women and epilepsy
• Status epilepticus
• Future trends

Epidemiology of Seizures and Epilepsy

• Seizures
  – Incidence: 80/100,000 per year
  – Lifetime incidence: 9%

• Epilepsy
  – Incidence: 45/100,000 per year
  – Point prevalence: 1 %

American Epilepsy Society 2015
EVALUATING A FIRST SEIZURE

Questions raised by a First Seizure

♦ Seizure or not?
♦ Provoked? (i.e metabolic precipitant?)
♦ Which studies should be obtained?
♦ Should treatment be started?
♦ Which drug should be used?
• Seizure recurrence risk is greatest early within the first 2 years (21%–45%) (level A)
• Immediate AED might reduce recurrence risk for 2 yrs but over longer term unlikely to improve prognosis. (level B)
• Risk of AED adverse events (AEs) may range from 7% to 31% (Level B)
• MRI with epilepsy protocol

• EEG to establish type of seizure
**To treat or not**

- Risk of seizure recurrence in patients with normal EEG, normal MRI & exam – 24%

- Risk of seizure recurrence in patients with either an abnormal EEG or MRI/Exam – 48%

- Risk of seizure recurrence in patients with an abnormal MRI/exam and an abnormal EEG – 65%

Hauser et al – NEJM, 1998

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**Revised definition of Epilepsy**

- At least 2 unprovoked seizures occurring >24 hrs apart

- One unprovoked seizure and a probability of further seizures estimated to be at least 60% over the next 10 yrs

ILAE 2015
Main Treatment Modalities

- Medications
- Epilepsy Surgery
- Neurostimulation Devices
- Diet

Available AEDs

<table>
<thead>
<tr>
<th>1st Generation</th>
<th>2nd Generation</th>
<th>3rd Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Felbamate (93)</td>
<td>Vigabatrin (09)</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Gabapentin (93)</td>
<td>Lacosamide (09)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Lamotrigine (94)</td>
<td>Rufinamide (09)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Levetiracetam (99)</td>
<td>Clobazam (11)</td>
</tr>
<tr>
<td>Primidone</td>
<td>Oxcarbazepine(00)</td>
<td>Ezogabine (11)</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Pregabalin (05)</td>
<td>Perampenel (12)</td>
</tr>
<tr>
<td></td>
<td>Tiagabine (98)</td>
<td>Eslicarbazepine (13)</td>
</tr>
<tr>
<td></td>
<td>Topiramate (97)</td>
<td>Brivaracetam (16)</td>
</tr>
<tr>
<td></td>
<td>Zonisamide (00)</td>
<td>Everolimus (18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cannabidiol (18)</td>
</tr>
</tbody>
</table>
Cannabidiol (CBD) (Epidiolex)

- Approved by FDA June 2018 for two rare and severe forms of epilepsy
- Lannox-Gastaut Syndrome and Dravet Syndrome.
- Chemical component of the Cannabis Sativa plant
- (does not cause the high or intoxication)

Response to AED’s in Newly Diagnosed Epilepsy

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to first drug</td>
<td>222 (67)</td>
</tr>
<tr>
<td>Seizure-free during therapy with first drug</td>
<td>207 (64)</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 (18)</td>
</tr>
<tr>
<td>Seizure-free during therapy with second drug</td>
<td>41 (13)</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 (6)</td>
</tr>
<tr>
<td>Seizure-free during therapy with third drug</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Seizure-free during therapy with two drugs</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>201 (64)</td>
</tr>
</tbody>
</table>
### AEDs Preferences

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Antiepileptic drug preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>Topiramate, Valproate</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>Pregabalin, Gabapentin, Oxcarbazepine, Carbamazepine, lacosamide</td>
</tr>
<tr>
<td>Obesity</td>
<td>Topiramate, zonisamide</td>
</tr>
<tr>
<td>Depression/mood issues</td>
<td>Lamotrigine, Valproate</td>
</tr>
<tr>
<td>Kidney Stones</td>
<td>Avoid Topiramate, Zonisamide</td>
</tr>
<tr>
<td>Asians</td>
<td>Avoid Carbamazepine</td>
</tr>
</tbody>
</table>

### Women and Epilepsy

- Catamenial Epilepsy
- Seizures during pregnancy
- Contraception
- Bone Health
Pregnancy and Epilepsy

- 50% of pregnancies in women with epilepsy are unplanned

- All women with epilepsy of reproductive age should be counseled about the effects of epilepsy and AEDs on a future pregnancy

- Pregnancy planning starts with the first AED prescription for a woman of childbearing age and drug changes should be made a year before conception when possible
Before Pregnancy

– Confirm epilepsy diagnosis (exclude non-epileptic seizures)
– Attempt AED monotherapy with lowest effective dose
– Consider switching AEDs prior to pregnancy, particularly if on valproate
– Establish baseline therapeutic levels
– Folate supplementation

During Pregnancy

• Continue folate supplementation
• Ante natal care with ultrasound
• Monitor AED levels at least monthly and adjust dose accordingly
• Lamotrigine clearance increases dramatically over the course of pregnancy
• Patients need a post-partum dosing plan to avoid toxicity post-partum
Breast Feeding and Epilepsy

- Breastfeeding should be encouraged for most women with epilepsy
- Known benefits of breastfeeding likely outweigh theoretical risks of medication exposure for most drugs
- Six-year old breastfed children of mothers taking carbamazepine, lamotrigine, phenytoin or valproic acid monotherapy had higher IQs and verbal abilities than children who were not breastfed. No adverse effects were noted
- Some recommendations advise caution with drugs with longer half-lives including ethosuxamide, phenobarbital and zonisamide but concerns are mostly theoretical. More data is needed on these drugs

[PubMed]

Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate

- Prenatal exposure to levetiracetam and topiramate were not found to be associated with reductions in child cognitive abilities.
- Exposure to valproate was associated with poorer IQ (-10.6 to -16.3) non verbal and language ability
**AED’s and Hormonal Contraception**

AEDs that may decrease the efficacy of hormonal contraception:

- Carbamazepine (Tegretol, Carbatrol)
- Clobazam (Onfi)
- Eslicarbazepine (Aptiom)
- Felbamate (Felbatol)
- Oxcarbazepine (Trileptal)
- Perampanel (Fycompa)
- Phenobarbital (Phenobarbital, Primidone)
- Phenytoin (Dilantin)
- Rufinamide (Banzel)

AED – Anti epileptic drug


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**Pharmacoresistance / Intractable Epilepsy**

Failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.
Non pharmacologic approaches

• Epilepsy Surgery

• Neurostimulation Devices

• Diet

Neurology’ s Silent Killer: Drug-Resistant Epilepsy

• As a community, we by far favor the nonsurgical treatment options

• Only 124 patients of 10,661 (1.2%) with DRE underwent epilepsy surgery within 2 years of being defined as medically intractable.

• Only about 2% had received a video-EEG evaluation within the same time frame
Mayo Epilepsy Surgery Outcomes

Treatment Gap

325 million people live in the U.S.

3.4 million people in the US have Epilepsy

~1.2 million people (35%) are drug resistant

~360,000 people (30%) are surgical candidates

~7000 Epilepsy Surgeries Performed Annually

Neuromodulation is a palliative treatment option but not a curative one.

**Vagal Nerve Stimulator (VNS)**
Responsive Neuro Stimulation (RNS) (Neuropace)

Devices for direct Brain Stimulation

Medtronic Intercept
• Anterior Nucleus Thalamus
Why Anterior Nucleus

• Stimulation of the AN, which projects both to superior frontal and temporal lobe structures commonly involved in seizures, produces electroencephalography inhibits chemically induced models
Neuromodulation

- **VNS**
  - 40-45% chance of at least 50% improvement in seizure frequency

- **Responsive Neurostimulation (RNS – Neuropace)**
  - 47% of pts with at least 50% reduction in seizure frequency

- **Thalamic Stimulation** *(FDA approved May 2018)*
  - 54% of pts with at least 50% reduction in seizure frequency

*Epilepsia, Fisher et al. 51(5):899–908, 2010*
Experimental

- Transcranial Magnetic stimulation
- Laser ablation
- Stereotactic radiosurgery
- Focused ultrasound

Status Epilepticus - pre hospital Rx

- IM Midazolam
- Intranasal midazolam
- Rectal diazepam
Probability of seizure stopping with time

Chart 1: Revised Status epilepticus protocol

Stage I
0-5 Min
Stabilize Patient (maintain ABC - Airway, breathing & circulation)
Assess Blood Glucose (GLU)
Rapid IV 100mg of thiamine and 50ml D5W
Attempt 2 large bore IV and obtain blood for LUMBAR

Stage II
5-20 min
Benzodiazepines
- If no IV - IM Midazolam (10mg for <40kg or 1.5mg for 13-40kg) OR
- IV Lorazepam (0.1mg/kg/dose max 4mg/dose) OR
- IV Diazepam (0.15-0.2mg/kg/dose, max 10mg/dose)
alternatives: Rectal diazepam (0.2-0.5mg/kg, max 20mg OR
Intranasal midazolam spray

Stage III
20-40 min
IV fosphenytoin 20mg PE/kg Max 1500mg PE/dose at 150mg/min OR
IV Valproate 40mg/kg max 3600mg/dose OR
IV Levetiracetam 50mg/kg, max 5000mg/dose

Stage IV
40-60 min
Move to ICU
Repeat IV fosphenytoin 5mg/PE/kg or Phenobarbital 15mg/kg OR
Propofol 1.2mg/kg load and 2-10mg/hr maintenance vs.
Midazolam 0.2mg/kg/10min and 0.1-0.4mg/kg/hr maintenance vs.
Pento-barbital limited to burst suppression
Monitor with EEG
Are they still Seizing

- Always ask this question after a prolonged seizure

When to Suspect Non convulsive seizures

- Fluctuating mental status changes
- Unexplained alteration of mental status
- Acute supratentorial brain injury with altered mental status
- After convulsive status epilepticus
Weaning of AED’s

• Seizure freedom for ≥ 2 years implies overall >60% chance of successful withdrawal in some epilepsy syndromes

✧ Consider relative risks/benefits (e.g., driving, pregnancy)

Factors to consider before discontinuation

**Favorable**
- Idiopathic etiology
- Normal mentation and exam
- Prompt initial AED response
- Infrequent seizures
- Low drug levels
- Seizure free > 2 years

**Unfavorable**
- Age on onset >10-12 yrs
- Symptomatic etiology
- Mental retardation
- Abnormal exam
- Poor initial AED response
- More than one AED
- EEG abnormalities
- Family history
EpiWatch

Share data with epilepsy researchers

Compare results with other patients

Document your quality of life

Track your seizures

Track your daily medications

Track possible drug side effects

3D Printing

ZipDose® Technology Using 3D Printing: How It’s Made

1. A powder is added to a tray to form a layer.
2. A drug is added to the powder.
3. The powder is compacted into a pill.

The result is a dissolvable, solid dosage form that disintegrates in the stomach and can be taken with water.