Experience with medications: Community-Based Epilepsy Survey

- 50% of respondents were unsatisfied with their current AED therapy
- 50% reported "complete control"
  
  Yet a substantial number had breakthrough seizures in past year
- Fear of seizures is the most difficult aspect of living with epilepsy (47%)
Considerations with Drug Interactions

- Drug interactions are a concern when initiating a new medication
  - Induction of drug metabolizing enzymes
  - Inhibition
- And when removing an existing medication
  - De-induction
  - Reversal of inhibition

Oldies but Goodies

- 1912 Phenobarbital
- 1938 Phenytoin (Dilantin® and Phenytek®)
- 1960 Ethosuximide (Zarontin®)
- 1974 Carbamazepine (Tegretal® and Carbatrol®)
- 1978 Divalproex Sodium (Depakote and ER®)

“Newer” Medications

- 1992 Felbamate (Felbatol®)
- 1994 Gabapentin (Neurontin®)
- 1995 Lamotrigine (Lamictal®)
- 1997 Topiramate (Topamax®)
- 1997 Tiagabine (Gabitril®)
- 1999 Levetiracetam (Keppra®)
- 2000 Zonisamide (Sonoran®)
- 2001 Oxfendate (Oxcarbazepine)
- 2005 Pregabalin (Lyrica®)
- 2008 Rufinamide (Banzel®)
- 2008 Lacosamide (Vimpat®)
- 2009 Vigabatrin (Sabril®)
- 2011 Clobazam (Onfi, Frisium®)
- 2012 Ezogabine (Potiga®)

Potential AED Adverse Effects

- Liver failure
- Aplastic anemia, agranulocytosis, thrombocytopenia
- Rash, Stevens-Johnson
- Teratogenicity
- Pancreatitis
- Suicide
- Long-term: Bone health?

Effects of Dose on AED Pharmacokinetics

Nonlinear Pharmacokinetics: Clearance decreases as dose increases
- PHT

Linear Pharmacokinetics: Clearance remains constant as dose increases
- PB

Nonlinear pharmacokinetics: Clearance increases with dose
- CBZ, VPA

Adapted from Cloyd, JC and Remmnel, RP. Pharmacotherapy, 2000

Effects of Dose on AED Pharmacokinetics

Nonlinear Pharmacokinetics
- Linear Pharmacokinetics: Clearance remains constant as dose increases
- FBM, TGB, TPM, VGB, PGB, ZNS?, OXC, LEV

Nonlinear pharmacokinetics: Absorption decreases with dose
- GBP

Adapted from Cloyd, JC and Remmnel, RP. Pharmacotherapy, 2000
The Tour

- **Felbamate (Felbatol®):** Lennox Gastaut (concern is 1/5000 chance of aplastic anemia or liver failure other S.E. are anorexia, Headaches) Can increase level of PHT, VPA, PB an CBZ epoxide. Level of Felbatol can be decreased by PHT, CBZ and PB.

- **Gabapentin (Neurontin®):** Partial onset seizures (Drowsiness, weight gain, may need renal adjustment, may require high doses for efficacy, occasional irritability in children) May be useful for neuropathic pain and mood stability.

- **Lamotrigine (Lamictal and XR®):** 2yrs and older with Partial onset seizures, primary generalized seizures, Lennox Gastaut. Monotherapy conversion in 16yrs and older. Bipolar indication (Rash possibility. Need to start low and go slow, VPA doubles T1/2 while enzyme inducers cuts it in half EIAED decreases LTG level and LTG can reduce level of BCP.

- **Topiramate (Topamax®):** Partial onset seizures, 2 y/o and above, primary generalized sx., Lennox Gastaut, JME, now approved for migraine prophylaxis (cognitive S.E., Possible ophthalmodis, angle closure glaucoma and psychosis 1% paresthesias, kidney stones 1.5% Need higher doses in presence of enzyme inducer) Possible decreased BCP effect.

- **Tiagabine (Gabatril®):** Partial onset seizures ages 12 and older, may exacerbate absence or JME, provoke stupor or spike wave stupor. (Start low and go slow, typical possible AED SE, no known idiosyncratic rxns). May improve anxiety symptoms and SWS in insomnia.

- **Oxcarbazepine (Trileptal®):** Partial onset and secondarily generalized sz and monotherapy in 4 years and older (works similar to CBZ but perhaps better tolerated, conversion is 1.5:1.0 of OXC to CBZ, 20-30% cross allergy, hyponatremia. BID dosing. Possible decreased BCP efficacy or decrease clearance of dilantin.

- **Pregabalin (Lyrica®)** Add on x for adults with partial onset seizures; post herpetic neuralgia, neuropathic pain and fibromyalgia. More potent than Gabapentin. Reduced dosing in renal patients. Wgt gain more pronounced than with Gabapentin.

- **Rufinamide (Banzel®):** Add on tx for ages 4 and older with Dx of Lennox Gastaut. Typical possible S.E. People with “short QT syndrome” should not take Banzel. VPA can increase level of Banzel and Banzel can reduce effect of BCP.

- **Zonisamide (Zonegran®):** Add on tx in Partial onset sz. Ages 16 and older. (Idiosyncratic rash 6%, kidney stones 1-2%, somnolence, oligohidrosis). Half life 60hrs: QD dosing. EIAED’s can reduce level of ZNS.

- **Levetiracetam (Keppra and XR®):** Partial onset seizures may be promising for generalized sz. (can produce behavioral changes and adjust for renal disease). QD dosing with XR

- **Lacosamide (Vimpat®)** Add on tx for partial onset seizures in adults. SE include dizziness, nausea / vomiting

- **Vigabatrin (Sabril®)** Add on tx for partial onset seizures in adults and infantile spasms. Main concern is risk of concentric vision loss (not central). Dosage adjustment in Renal impairment
**Ezogabine (Potiga®)** Tx of adults with partial onset seizures. Typical S.E. Urinary retention.

**Clobazam (Onfi, Frisium®)** Tx of Lennox-Gastaut and classified as a benzodiazepine (like Valium and Klonopin). Typical S.E.

**Clinical Trial Drugs:** Brevetiracetam

**Eslicarbazepine**

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**Four Commandments of Pharmacological Treatment**

- Strive for monotherapy at an optimal dose
- If adding a 2nd drug pick one that is complementary (i.e. one with a different MOA)
- After lack of adequate response to 3 different AED’s alone or in combination then consider comprehensive evaluation for clarification of the seizure type and location.
- Appreciate the impact of side-effects on quality of life

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**Questions?**