ANTI-SEIZURE MEDICATIONS
STRIVING FOR NO SEIZURES,
NO SIDE EFFECTS
PEDIATRIC PERSPECTIVES

Jules E.C. Constantinou, MD, FRACP
Director, Pediatric Neurology
Comprehensive Epilepsy Program
Henry Ford Health System
ANTI-SEIZURE MEDICATIONS: PEDIATRIC PERSPECTIVES

- smooth sailing epilepsy, the 60% rule
- rough riding epilepsy
- drug resistance, medical intractability
ANTI-SEIZURE MEDICATIONS: PEDIATRIC PERSPECTIVES

- the Brodie study; how do we predict intractability
- at least 14 new anti-epilepsy medications
- the age of choice: efficacy verses side-effects
- majority approved for partial seizures
- pediatric challenges
ANTI-SEIZURE MEDICATIONS

• monotherapy the mantra
• combining AED’s, rational or obligatory polytherapy

• can one and one make three

• “the combinations of bromides with other drugs are of much value in the treatment of epilepsy. In many cases a greater effect is produced by the combination than by other drugs given alone”

William Gowers, 1881
ANTI-SEIZURE MEDICATIONS
CHILDHOOD ABSENCE EPILEPSY

- age related epilepsy syndrome
- neurologically and developmentally normal children between 5 to 10 years of age
- absence seizures, pyknolepsy
- eeg: normal BG, hyperventilation activated $H_2$ spike and slow wave
- universal tendency to remission
- which medications
ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN CHILDHOOD ABSENCE EPILEPSY

- double blind, randomized, controlled trial in 453 children
- primary outcome: freedom from treatment failure
- secondary outcome: attentional dysfunction

NEJM 2010; 362: 790-9
ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN CHILDHOOD ABSENCE EPILESPY

- freedom from treatment failure – combination of efficacy and tolerability
- persistence of absence seizures week 16 or week 20
- generalized tonic clonic seizure at any time
- platelet count <50,000 per mm$^3$
- moderately severe rash
- Increase in BMI

NEJM 2010; 362: 790-9
ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN CHILDHOOD ABSENCE EPILEPSY

- free of treatment failure: 209/446 (47%)
- lack of seizure control: 109/446 (24%)
- intolerable side effects: 97/446 (22%)

- lack of seizure control
  - ethosuximide: 22/154 (14%)
  - lamotrigine: 69/146 (47%)
  - valproic acid: 18/146 (12%)

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ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN CHILDHOOD ABSENCE EPILEPSY

• secondary outcome: continuous performance testing (CPT)
• CPT confidence index ≥ 0.6
  – ethosuximide: 35/106 (33%)
  – lamotrigine: 25/104 (24%)
  – valproic acid: 52/106 (48%)
• no differences in the confidence index results between seizure free subjects and those who continued to have seizures
• attentional difficulties not simply a result of the seizures, but a core feature of the syndrome

NEJM; 2010: 362: 790-9
LENNOX GASTAUT SYNDROME

- childhood epileptic encephalopathy with slow spike waves
- 1 to 8 years; cryptogenic or symptomatic
- drops, nods, blinks, jerks
- slow BG; slow (1 ½ to 2 ½ Hz) spike and wave
- generalized paroxysmal fast activity
- typically medically intransigent
- at the onset of seizures, only 30% to 50% have intellectual delay, but after 4 years 78% to 96% will be affected
LENNOX GASTAUT SYNDROME

• no comparative drug studies
• six medications approved by the FDA
• lamotrigine, topiramate, felbamate, rufinamide, clobazam

• majority of practitioners still use valproate as initial treatment
• role of “partial” medications: dilantin, lacosamide, oxcarbazepine (multiple independent spike foci)
DOUBLE BLIND RANDOMIZED, CONTROLLED TRIALS IN LGS

- >50% median seizure reduction rates and side effects
- Lamotrigine: 33%: 9% rash (7% placebo)
- Topamax: 33%: somnolence, behavioral problems, weight loss, dizziness
- Felbamate: 50%: 6/73 seizure free
  - Aplastic anemia, liver toxicity
DOUBLE BLIND RANDOMIZED CONTROLLED TRIALS IN LGS

- Rufinamide: 31%, somnolence, vomiting
- Clobazam
  - high dose: 77%, somnolence, drooling
  - moderate dose: 58%
  - low dose: 43%
LGS: NON-PHARMACOLOGIC TREATMENT

• >50% median seizure reduction rates
• VNS: 21% - 83%
• corpus callosotomy: >80% reduction in drop attacks in 61% to 85%
• ketogenic diet: 51%
  – >23%, a 90% reduction in seizures
  – waning effectiveness after 12 months
DRAVETS SYNDROME

- severe myoclonic epilepsy of infancy
- 1 in 40,000; M:F = 2:1
- prolonged febrile seizures followed by Todd’s paresis in infancy
- myoclonic, atypical absence, and partial seizures over time
- cognitive impairment; visual attention, visual motor integration, visual perception and executive function
- SCN1a mutation; affects sodium currents in GABAergic (inhibitory) neurones
DRAVETS SYNDROME

• Topiramate: 3 of 5 had >50% reductions in seizure frequency
• Levetiracetam: 18/28 a positive response to one seizure type
  – 3/28 with tonic clonic seizures, 2/28 with myoclonic seizures, 3/28 with focal seizures and 1/28 with absence seizures became seizure free
DRAVETS SYNDROME

• Stiripentol: 8/37 in one study seizure free
  – 15/21 in another study had 50% drop in seizure frequency
• combination of valproic acid, clobazam and stiripentol especially effective
• levetiracetam also a good option
• topiramate, mixed results
MIXED SEIZURE SYNDROMES OF EARLY CHILDHOOD

- broad spectrum medications
- consider the seizure type
- absence, ethosuximide, lamictal, zonisamide, valproic acid
- myoclonic; levetiracetam, lamotrigine, topiramate, zonisamide, valproic acid
- tonic; lamictal, zonisamide, rufinamide, clobazam, valproic acid
- avoid sodium channel blockers
THE HOLY GRAIL

• the balance between seizure control and side effects
• what is optimal seizure control
• what are acceptable side effects
• rational, methodical trials of effective anti-seizure medications
THE HOLY GRAIL

• obligatory polytherapy
• the cross-over trap
• early consideration of non-pharmacologic options
• the care team, communication and dialogue
• maximise neurodevelopmental outcomes and quality of life