Research and Advances in Epilepsy

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Epilepsy History

- Greek physician Hippocrates wrote the first book on epilepsy in 400 BC and disputed the idea that epilepsy was a curse or a sign from the gods.

Images – German Epilepsy Museum
History of Epilepsy medical treatment

- Bromides as treatment for hysterical/catamenial seizures -1857 (Charles Locock & Samuel Wilks)
- Phenobarbital -1912 (Hauptmann)
- Phenytoin -1937 (Merritt & Putnam)
- Ethosuximide -1950
- Carbamazepine -1968
- Valproate -1974
First generation anti-epileptic medications

- Phenobarbital (Luminal)
- Phenytoin (Dilantin)
- Primidone (Mysoline)
- Ethosuximide (Zarontin)
- Carbamazepine (Tegretol)

- Valproate (Depakote)
- Benzodiazepines – Diazepam (Valium, Diastat), Midazolam (Versed)
Second generation anti-epileptic medications

- Felbamate (Felbatol)
- Gabapentin (Neurontin)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Tiagabine (Gabitril)

- Levetiracetam (Keppra)
- Oxcarbazepine (Trileptal)
- Zonisamide (Zonegran)
- Pregabalin (Lyrica)
Newer anti-epileptic medications

- Brivaracetam - 2016
- Topiramate extended release (Quedexy XR) - 2014
- Eslicarbazepine (Aptiom) - 2013
- Topiramate extended release (Trokendi XR) - 2013
- Oxcarbazepine extended release (Oxtellar XR) - 2012
- Perampanel (Fycompa) - 2012
- Clobazam (Onfi) - 2011
- Ezogabine (Potiga) - 2011
- Vigabatrin (Sabril) - 2009
- Rufinamide (Banzel) - 2008
- Lacosamide (Vimpat) - 2008
What do we expect from newer anti-epileptic medications?

- More effective for seizure control
- Less side effects
- Less interactions with other medications
- Easy dosing and monitoring
- Cost effective

- Newer anti-epileptic medications offer novel pharmacokinetics with easy dosing and monitoring and improved tolerability with less adverse effects
- Newer anti-epileptic medications offer novel mechanism of action, improved efficacy and fewer drug interactions
Indication – adjunctive treatment of partial onset seizures

Mechanism of action - novel high affinity synaptic vesicle protein 2A (SV2A) ligand, multiple other mechanisms involving sodium channels

Analog of Levetiracetam (Keppra) with more than 30 fold affinity for SV2A

It is available as oral or intravenous formulation

Efficacy based on 3 clinical trials. Median % reduction in seizure frequency was 10-26% for doses ranging from 50 to 200mg/day

SE – somnolence and sedation (16%), dizziness (12%), fatigue (9%), nausea and vomiting (5%), irritability (3%)
Eslicarbazepine (Aptiom)

- **Indication** – adjunctive treatment of partial onset seizures
- **Mechanism of action** - inhibition of voltage gated sodium channels
- **3rd generation carbamazepine.** It is a prodrug which is converted to S-Licarbazepine - active metabolite responsible for therapeutic effect (without R- Licarbazepine)
- **Efficacy** based on 3 clinical trials. Median % reduction in seizure frequency 30-40% at doses 800mg and 1200mg
- **SE** – dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, tremor.
Perampanel (Fycompa)

- **Indication** – adjunctive treatment for partial onset seizures with or without secondary generalized seizures in age group 12 years and older
- **Mechanism of action** – highly selective non competitive AMPA type glutamate receptor antagonist
- **Efficacy** – based on 3 studies the median % reduction in seizure frequency from placebo was **19-33%** for 2-12mg day
- **Side Effects** - dizziness, somnolence, fatigue, irritability, headache, weight gain, falls, ataxia, vertigo, rare aggression/homicidal ideation (black box warning)
Future advances in medical treatment of epilepsy - Cannabidiol

• Cannabidiol (CBD) the primary nonpsychoactive constituent

• Mechanism of action

• THC - cannabinoid receptor 1 (CB1)– G protein coupled receptor – inhibition of synaptic transmission through voltage gated channels

• CBD - multiple actions - serotonergic 5HT1alpha receptors, NMDA receptors, regulation of Ca++ flow, enhancement of adenosine signaling or increased inhibition through GABA-A receptors

Acute Seizures or Status Epilepticus - Treatment Overview

- Prehospital Treatment
- Emergent Initial Therapy
- Urgent Control Therapy
  - Treatment of Refractory Status Epilepticus
  - Seizures Stop
Status Epilepticus - Prehospital Studies

- Double blind Study – Diazepam 10mg vs Lorazepam 4mg had equal efficacy in seizure termination. Seizure control with no recurrence 76% vs 89%
  Leppick et al., JAMA 1983

- VA cooperative study – Lorazepam as Emergent therapy
  Control of Status within 20 minutes
  - Lorazepam 0.1mg/kg  65%
  - Phenobarbital 15mg/kg  58%
  - Diazepam 0.15mg/kg +Phenytoin 18mg/kg  56%
  - Phenytoin 18mg/kg  44%
  Treiman et al., NEJM 1998

- RAMPART Study – 10mg IM Midazolam was found to be non inferior to 4mg IV Lorazepam
  Silbergleit et al., NEJM 2012
Future advances in medical treatment of epilepsy – Intranasal Midazolam

• Intranasal midazolam as alternative rescue medication
• Rapid onset of action, high effectiveness
• Easily crosses nasal mucosa and blood-brain barrier with rapid rise in plasma and the cerebrospinal fluid concentrations
• Mechanism of action – benzodiazepine acts on GABA
• Ideal for at home termination of seizure clusters

Advances in medical treatment of Epilepsy

Anti–epileptic medication choice and rational polytherapy should be based on

• Epilepsy type (partial/generalized)
• Patient profile (age, gender, medical history)
• Pharmacology of anti-epileptic medication
• Side effect profile
• Cost of medication

• The proportion of patients with pharmaconesistant epilepsy has remained constant at about 20-30%.
Resources

- New therapies Pipeline – Epilepsy foundation
- Finding a clinical trial – Epilepsy foundation
  - http://www.epilepsy.com/clinical_trials
- Epilepsy clinical research trials – Centerwatch
Alternatives to medical treatment

Devices
- Vagal Nerve Stimulator
- Responsive Neurostimulator (Neuropace)

Surgery
- Temporal lobectomy
- Lesion resection
- Nonlesional resection

History of Epilepsy surgical treatment
RNS (Neuropace)

• First of a kind device to provide targeted responsive stimulation for epilepsy
• Acute and sustained efficacy in adults with partial onset seizures
• Provides another treatment option for adults with medically intractable partial onset seizures
In clinical trials, adults treated with the RNS® System experienced significant, long-term seizure reduction and compelling quality of life improvements. Some individuals also showed benefit in memory and language. The chart shows seizure reduction over time for patients treated with the RNS System. By year three, patients reported 60% seizure reduction. This continued to improve, with 72% median seizure reduction by year seven.

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4 Morrell et. al American Epilepsy Society 2016

Data at 7 years were presented at the 2016 American Epilepsy Society meeting and are from a more recent data cut-off than those published by Bergey et al. As a result, more patients had completed 7 years of post-implant follow-up. Data are from open label study.
RNS (Neuropace)

- Detection
- ECoG storage
- Responsive stimulation

Physician sets up detection
RNS (Neuropace)

- Neurostimulator stores ~6 minutes of ECoG
- The number of ECoGs stored is determined by
  - The number of ECoG channels
  - The duration of each ECoG segment
- Once memory is full, oldest stored ECoGs replaced by newly stored ECoGs
- Patients asked to upload neurostimulator data to PDMS daily and after seizures
  - The clinician programs the neurostimulator to store specific types of ECoGs
  - Most common triggers for ECoG storage are
    - Magnet swipe by the patient
    - Changes in the ECoG suggestive of electrographic seizures
RNS (Neuropace)

- Physician identifies electrocorticographic activity to be detected
- Detection settings specific to that activity are programmed
- Stimulation is enabled using standard settings
- Detection and stimulation is adjusted as needed
Video EEG
Intracranial monitoring
Intracranial monitoring
Surgical treatment of Epilepsy

When do we consider epilepsy surgery?
• focal seizures resistant to medical treatment
• adverse side effects to medications
Surgical treatment of Epilepsy

Why should we consider surgery?

• Rate of seizure freedom with continued trials of seizure medications is low
• Potential for injury with uncontrolled epilepsy is high
• Rate of seizure control with respective surgery is high
• Reduction or elimination of seizure medication may be possible
Minimally invasive form of epilepsy surgery using laser treatment

Research and Advances in Epilepsy

Why is research important?

• New treatment can decrease seizures
• Better treatment modalities
• Better understanding of causes of epilepsy
Conclusion

• Most epilepsy cases well controlled with minimal side effects
• Correct diagnosis essential to guide treatment
• For difficult to treat cases – surgery, neuromodulation (Neuropace) and clinical trials

• Comprehensive care – Level 4 epilepsy center