

VA
HEALTH
CARE

Defining
EXCELLENCE
in the 21st Century

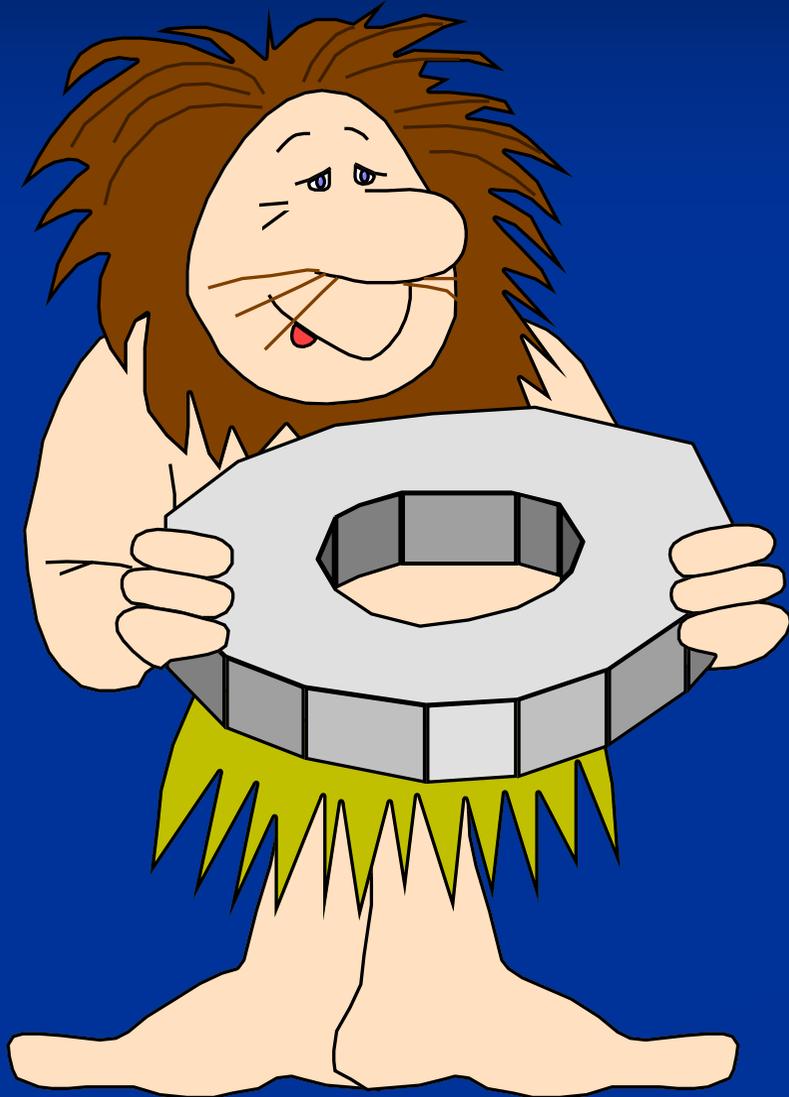
INTRACTABLE EPILEPSY: NEW OPTIONS IN 2012

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EPILEPSY



- MOST COMMON SERIOUS DISEASE CARED FOR BY NEUROLOGISTS
- 3% OF THE US POPULATION IS AFFECTED BY EPILEPSY
- IT HAS LONG BEEN A **TREATABLE** DISORDER
- BUT IT IS ALSO A **CHRONIC** DISORDER AND NOT EVERYONE WITH EPILEPSY RESPONDS TO TREATMENT

NATURAL HISTORY OF EPILEPSY

- ~70% of patients will have seizures completely controlled at some point
- ~20% will continue to have some seizures but be functional
- ~10% will be severely disabled by their epilepsy



INTRACTABLE EPILEPSY: NEW OPTIONS IN 2012

- Characterize **INTRACTABLE** or **REFRACTORY**
EPILEPSY
- Consequences and significance
- Treatment options today
- Treatment options on the horizon

Refractory/Intractable Epilepsy Def.

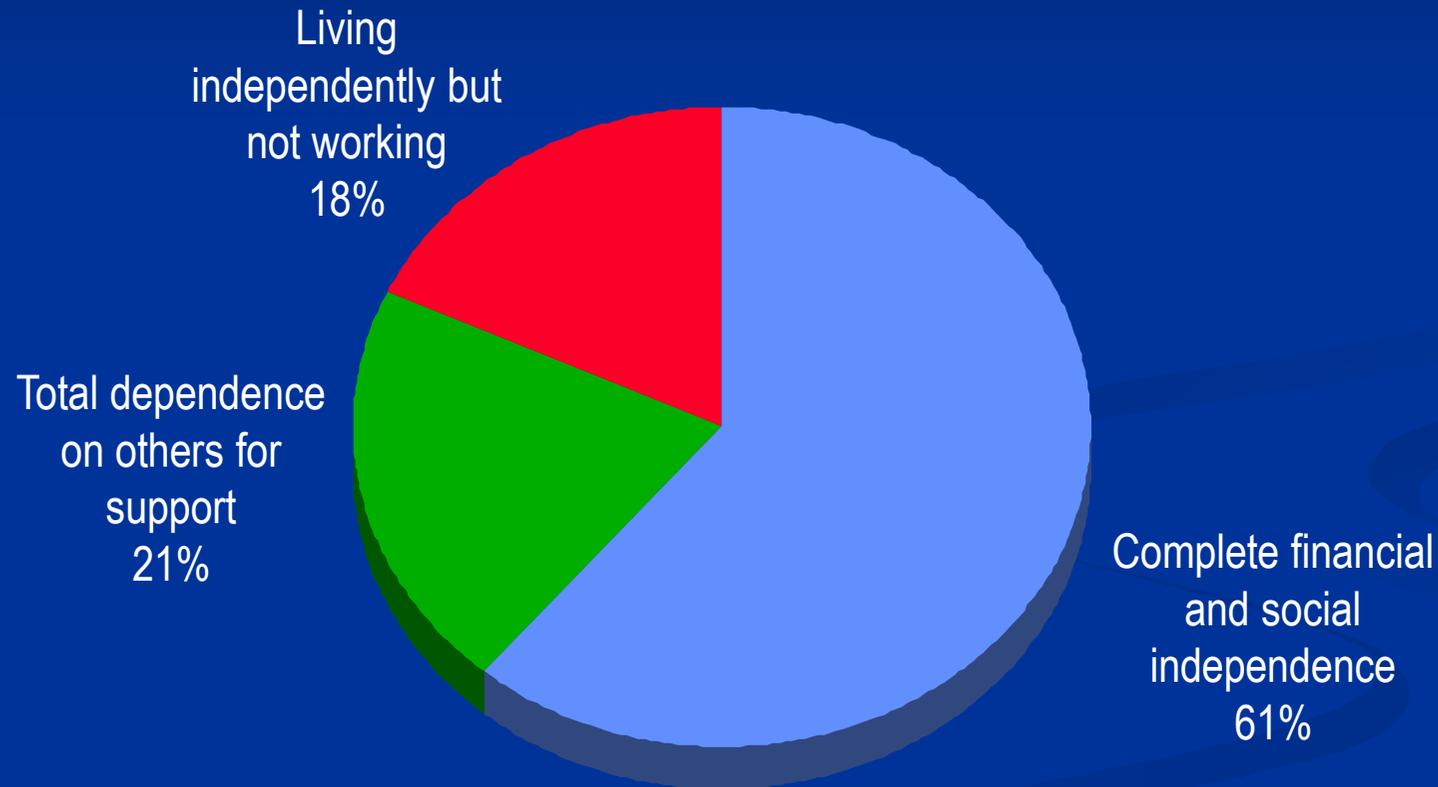
- Seizures persist despite treatment with at least 2 or 3 antiepileptic drugs tolerated at reasonable dosage
- Minimum frequency of seizures, such as e.g. 1 per month or every few months, without remissions for 6-12 months - or longer
- Durations of 1-10 years or more of such uncontrolled seizures
- Substantially disabling the individual

PREDICTORS OF EPILEPSY INTRACTABILITY

- Greater **number** of seizures prior to initiation of antiepileptic drug therapy (e.g. 3 versus 100)
- Higher seizure **frequency** (e.g. weekly versus yearly)
- Longer **duration** of epilepsy
- **Focal** versus Generalized Epilepsy
- **Structural**/Metabolic or Unknown versus Genetic etiology

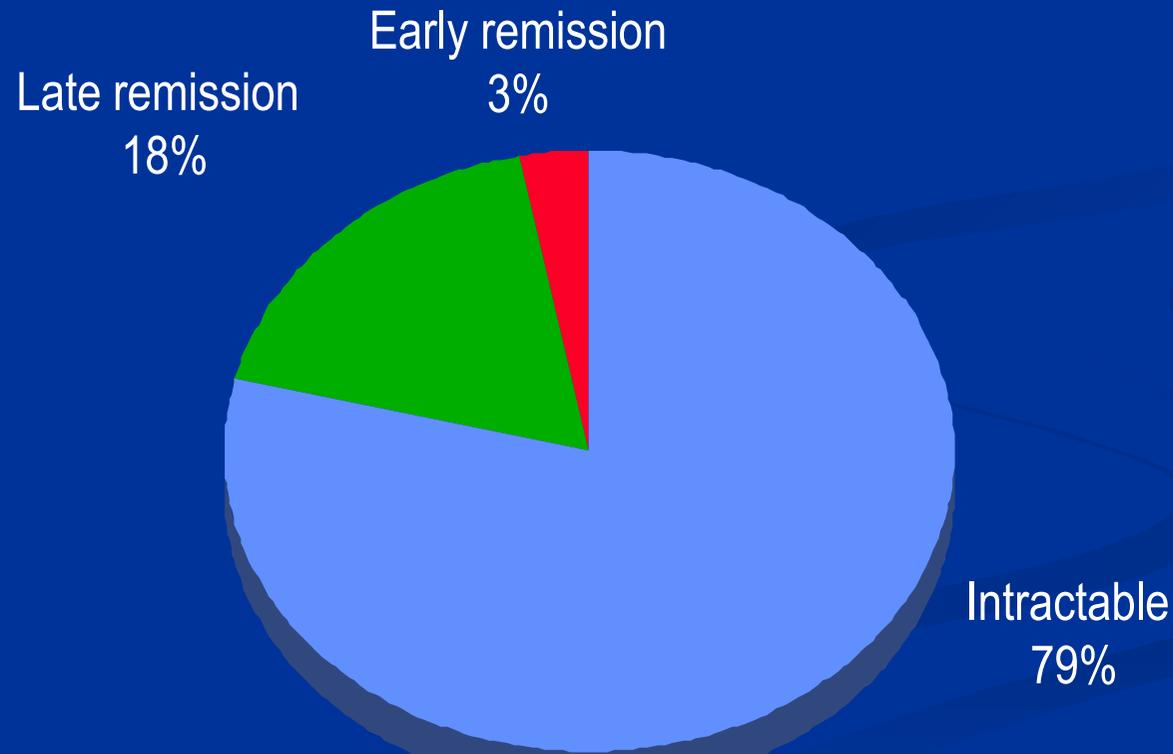


Epilepsy-Related: Quality of Life



Consequences to Society: **Costs**

- High proportion of costs attributed to patients with intractable epilepsy - due mainly to lost productivity



Begley, 2000.

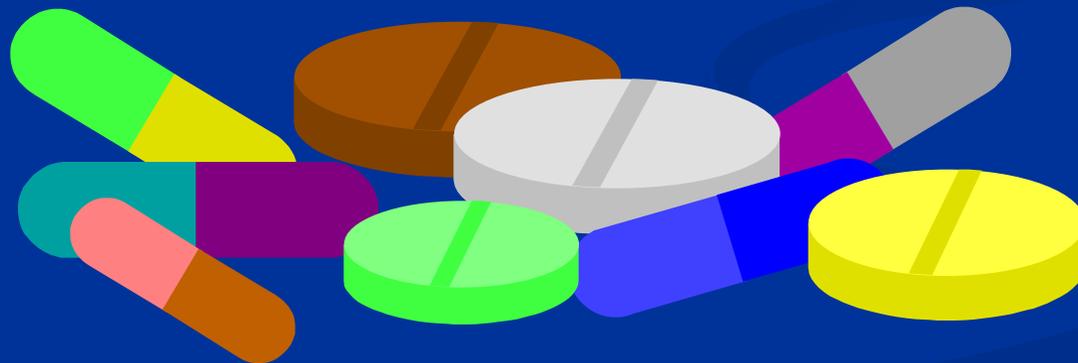
In 1995 \$12.5 billion in US

2010 - EPILEPSY TREATMENT OPTIONS

- ANTIEPILEPTIC MEDICATIONS
- EPILEPSY SURGERY
- NEURO-STIMULATION
- RADIATION THERAPY
- IMMUNOTHERAPY
- GENETIC THERAPIES
- PSYCHOLOGICAL/
SOCIAL
INTERVENTIONS



ANTIEPILEPTIC MEDICATIONS



Goal: No Seizures And No Side Effects

- 1. Determine the seizure or epilepsy type
- 2. Select the optimal class of drugs for that seizure type (efficacy is similar)
- 3. Choose medication with best side effect profile for that individual
- 4. Increase drug slowly to reasonable or maximal dosage
- 5. If unsuccessful change agents (once, twice or more)
- 6. If seizures persist, combine drugs (2 or 3 at most)



Response to Antiepileptics in Newly Diagnosed Epilepsy

- **First** antiepileptic: ~ 47% seizure-free
- **Second** antiepileptic ~ 13% seizure-free
- **Third or more** drugs or multiple drugs ~ 4% eventually become seizure-free

Therefore, if a patient fails to respond to **2** or **3** standard antiepileptic drugs, there is a very **low** probability of medication completely controlling the seizures. (Kwan, Brodie NEJM 2000;342:314)

Classification of Seizures (ILAE 2010)

A. Generalized Seizures

- Absence
- Myoclonic
- Clonic
- Tonic
- Tonic-clonic
- Atonic

B. Focal Seizures

- Without impairment of consciousness (motor, sensory, autonomic)
- With impairment of consciousness (evolving to bilateral convulsive)

C. Epileptic Spasms

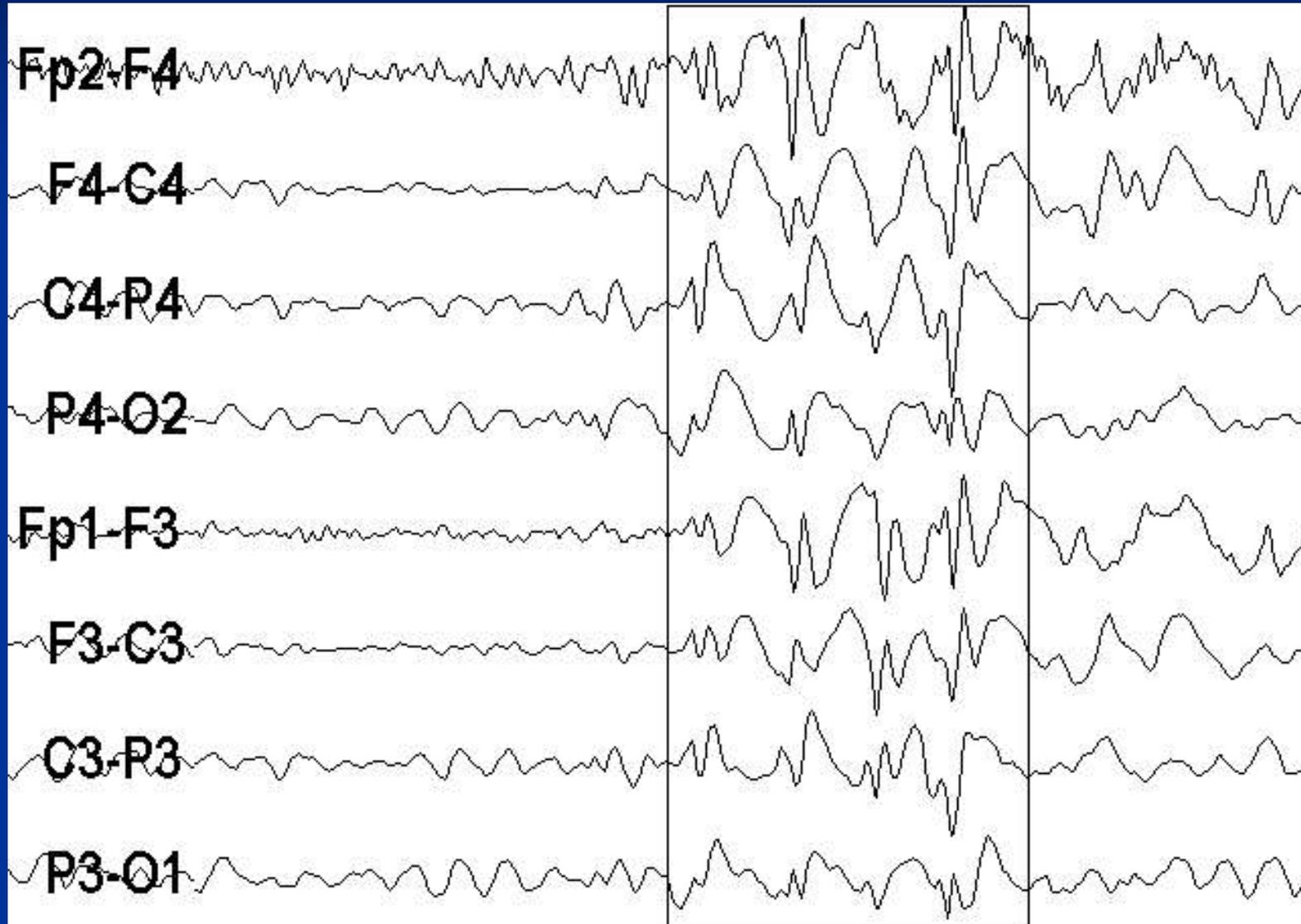
D. Unknown

E. Unclassified

Primary Generalized Epilepsy



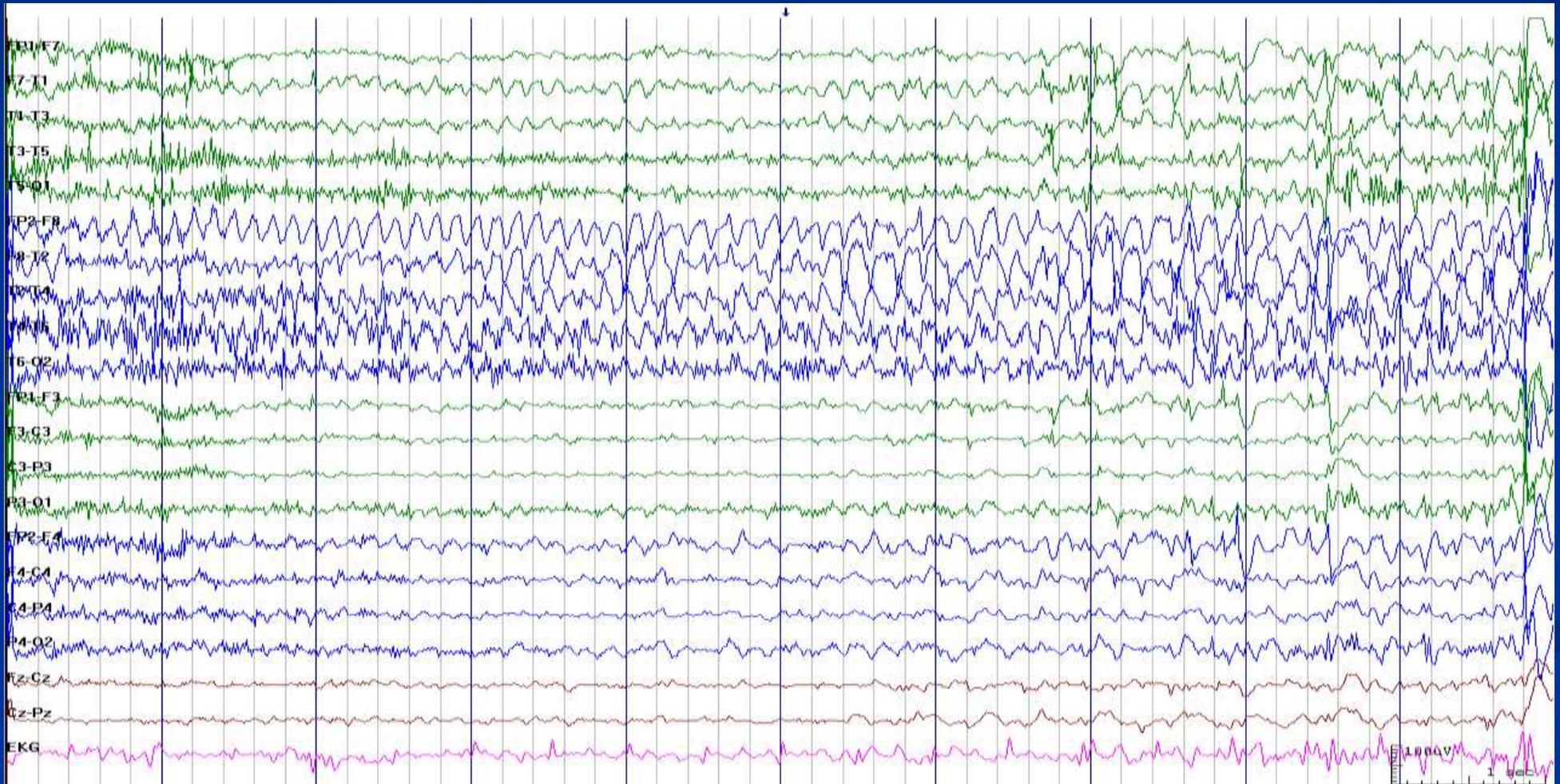
Primary Generalized Epilepsy EEG



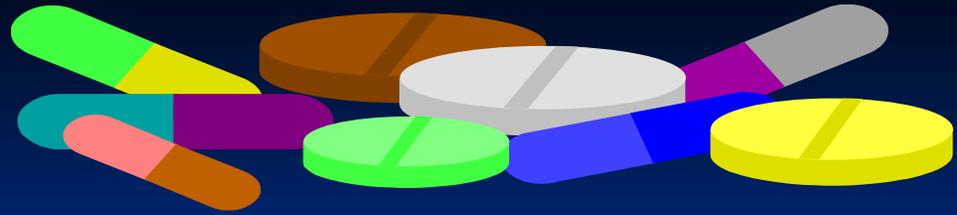
Focal Epilepsy



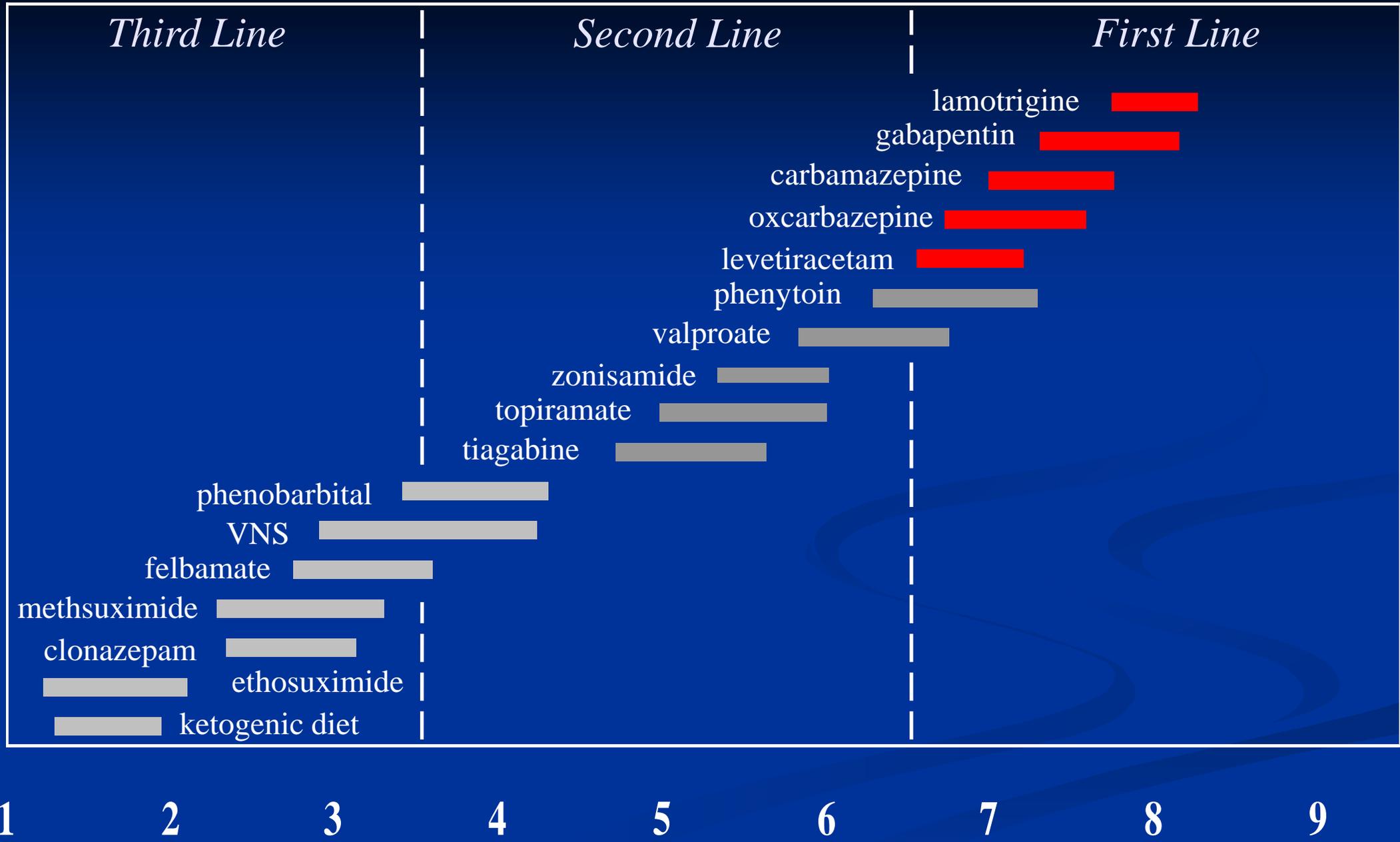
Seizure onset - phase reversal theta at T2 (anterior temporal)



Antiepileptic Medications



- Phenytoin-*Dilantin*.
- Phenobarbital.
- Carbamazepine-*Tegretol*.
- Valproate- *Depakote*.
- Ethosuximide- *Zarontin*
- Primidone - *Mysoline*.
- Benzodiazepines- *Klonopin*
- Acetazolamide-*Diamox*
- Lacosamide – *Vimpat**
- Clobazam – *Frisium***
- Felbamate - *Felbatol*.
- Gabapentin - *Neurontin*.
- Lamotrigine -*Lamictal*.
Topiramate-*Topamax*
- Tiagabine - *Gabatril*.
- Levetiracetam.- *Keppra*
- Zonisamide-*Zonegran*
- Oxcarbazepine- *Trileptal*.
- Pregabalin - *Lyrica*
- Rufinamide – *Banzel**
- Vigabatrin – *Sabril**
- Ezogabine – *Potiga***



16b. Symptomatic Localization-related, Medically Stable Elderly Man or Woman



TAILOR THE DRUG TO BEST FIT THE INDIVIDUAL

- i.e. - MOST DRESSES OR SUITS WILL DO THE JOB, SO AN INDIVIDUAL'S PERSONAL PROFILE GUIDES THE CHOICE
- MOST AEDs HAVE SIMILAR EFFICACY FOR SEIZURE CONTROL, SO SIDE EFFECT PROFILES FOR THAT INDIVIDUAL LARGELY GUIDE THE CHOICE





AEDs – Cognitive Profiles

■ Best

- Lamotrigine
- Levetiracetam
- Valproate
- Felbamate
- Gabapentin
- Lacosamide

■ Relatively Good

- Carbamazepine
- Phenytoin
- Oxcarbazepine

• Intermediate

- Tiagabine
- Zonisamide

• Least Favorable

- Phenobarbital
- Primidone
- Topiramate

Special Considerations in Treating Women With Antiepileptic Drugs

- Fertility and ovulatory function, menstrual cycle regularity
- Hormonal contraception
- Pregnancy
- Teratogenic effects
- Breastfeeding
- Bone health

Morrell MJ. *Epilepsia*. 1996;37(suppl 6):S34-S44.

Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 1998;51:944-948.

EPILEPSY SURGERY



Candidates for Epilepsy Surgery

- Intractable epilepsy
- Present for a substantial duration (usually years)
- Refractory to medical therapy
- Substantially impairing quality of life
- Benefit of surgery should outweigh the risks



Evaluation of Candidates for Epilepsy Surgery

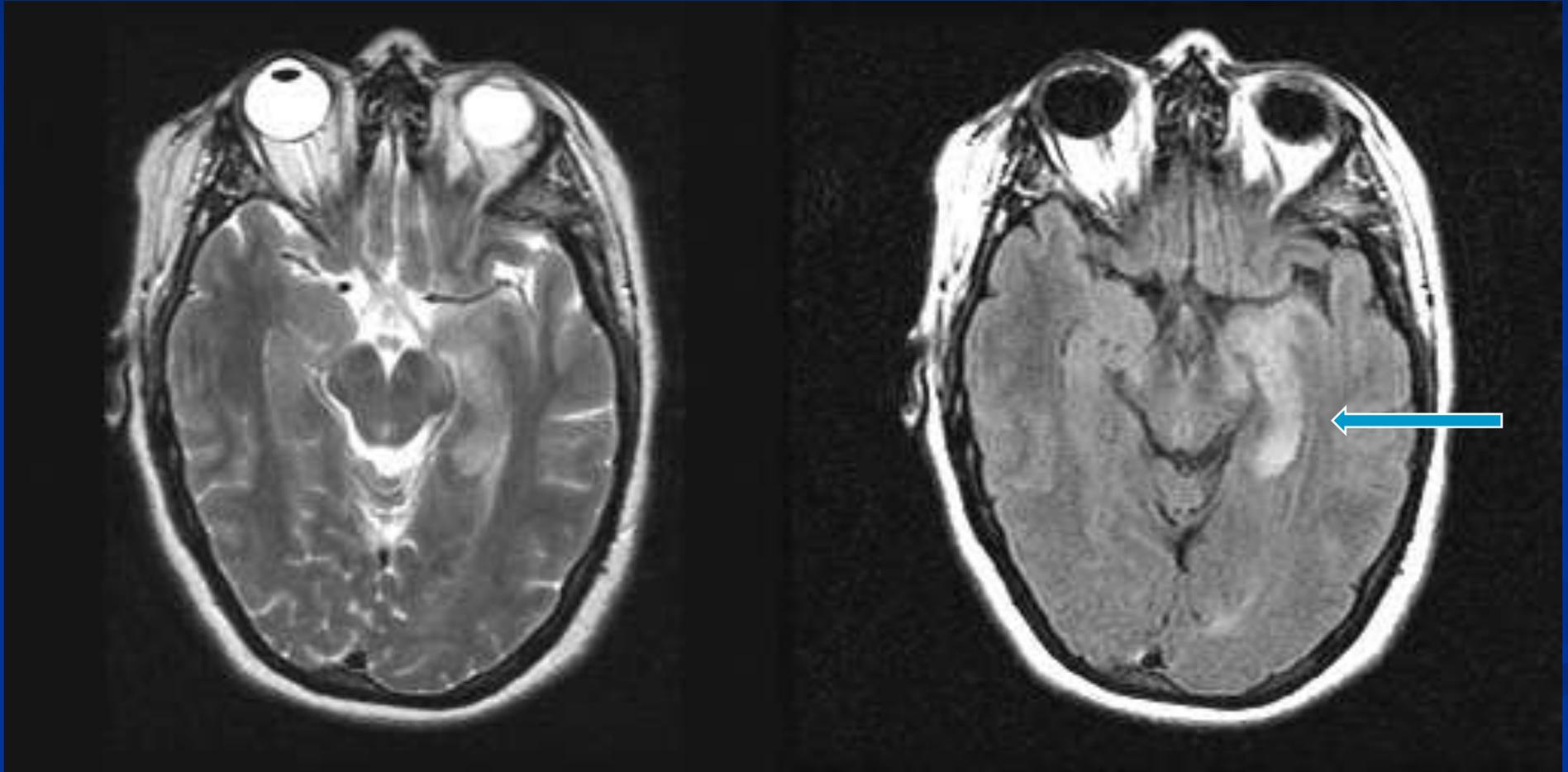
- Localization of seizures by interictal EEG
- Localization by brain imaging-MRI; PET scanning
- Localization by video-EEG monitoring of seizures (may combine with ictal SPECT)
- Localization by neuropsychological testing
- Convergence of localization data



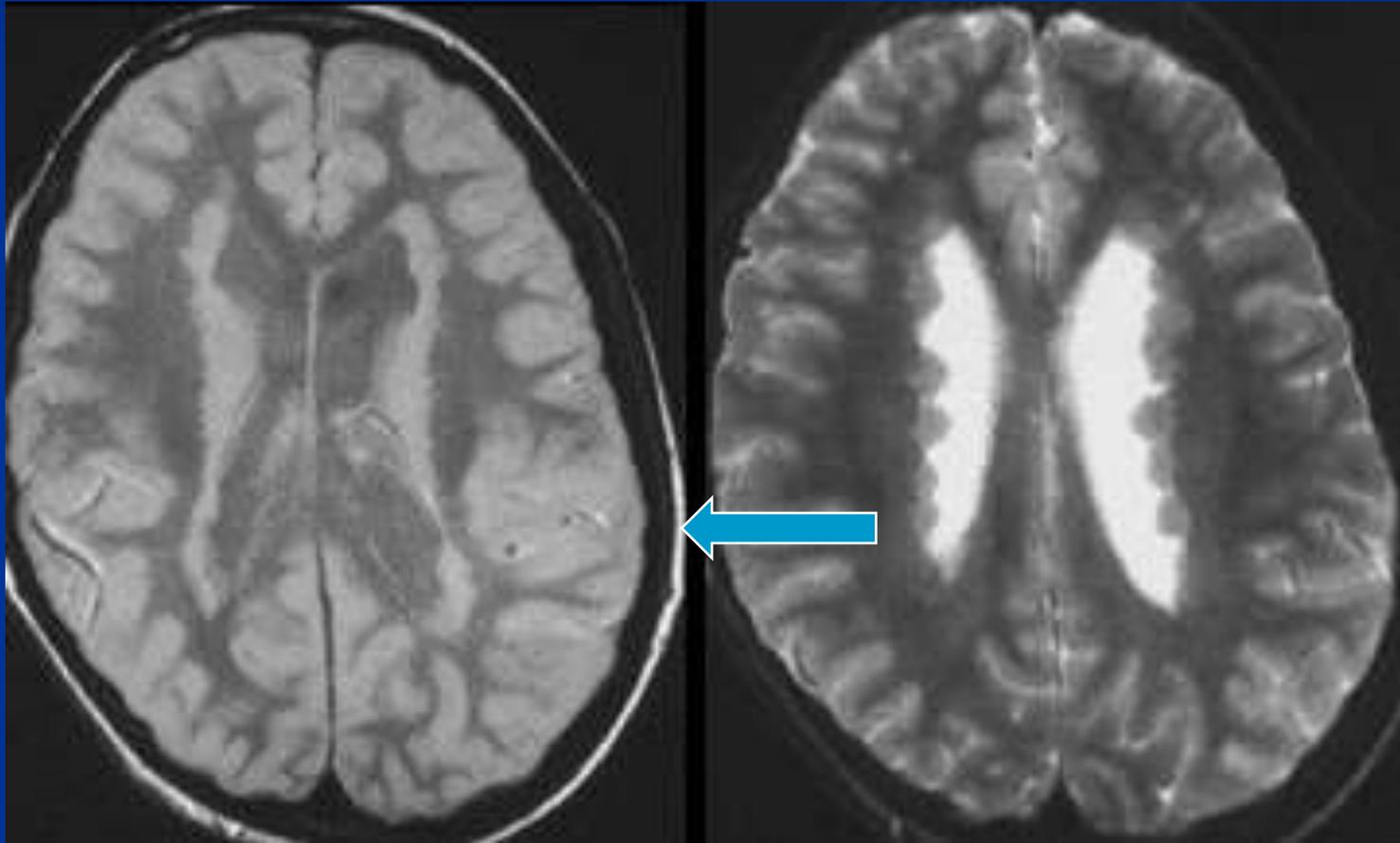
MRI – Subtle Temporal Atrophy



Mesial Temporal Sclerosis



HETEROTOPIAS



Further Methods of Determining a Potentially Seizure Focus

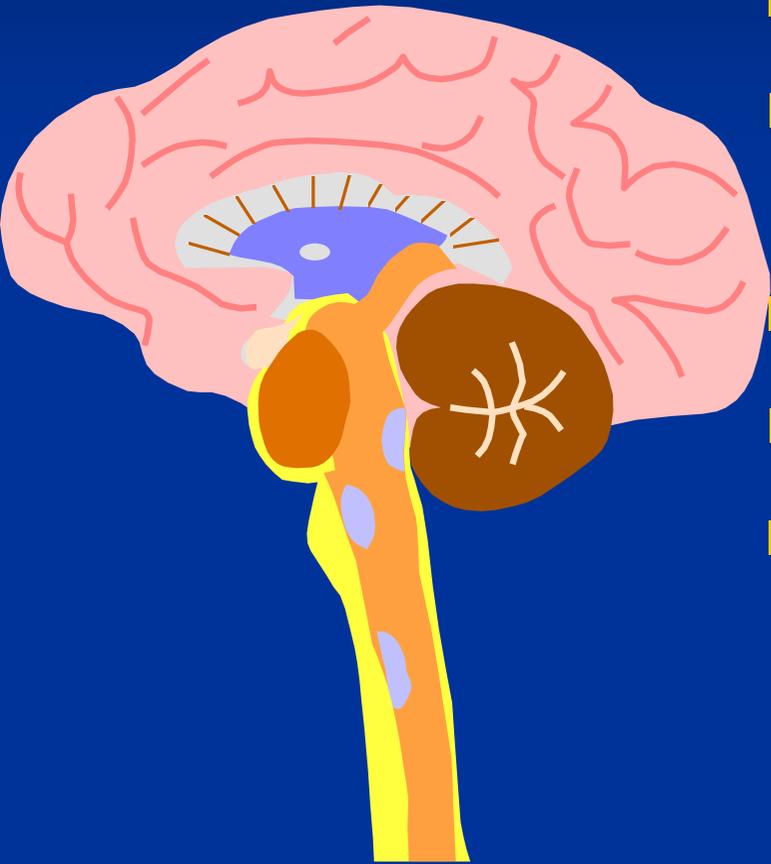
- PET
- Depth electrodes
- Cortical grids or strips
- Ictal SPECT scans
- Nuclear magnetic resonance scans
- Magnetoencephalography



Extratemporal Subdural Grid

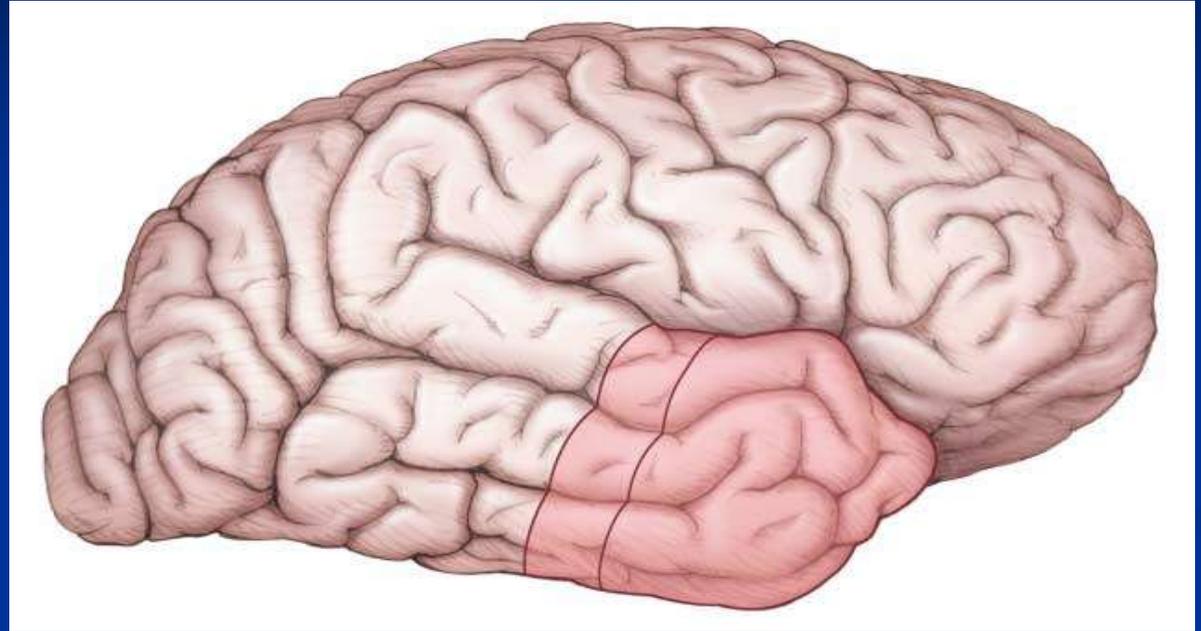
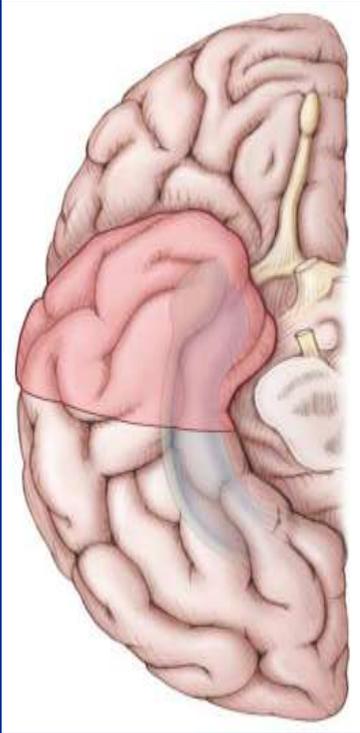


Types of Resective Epilepsy Surgery



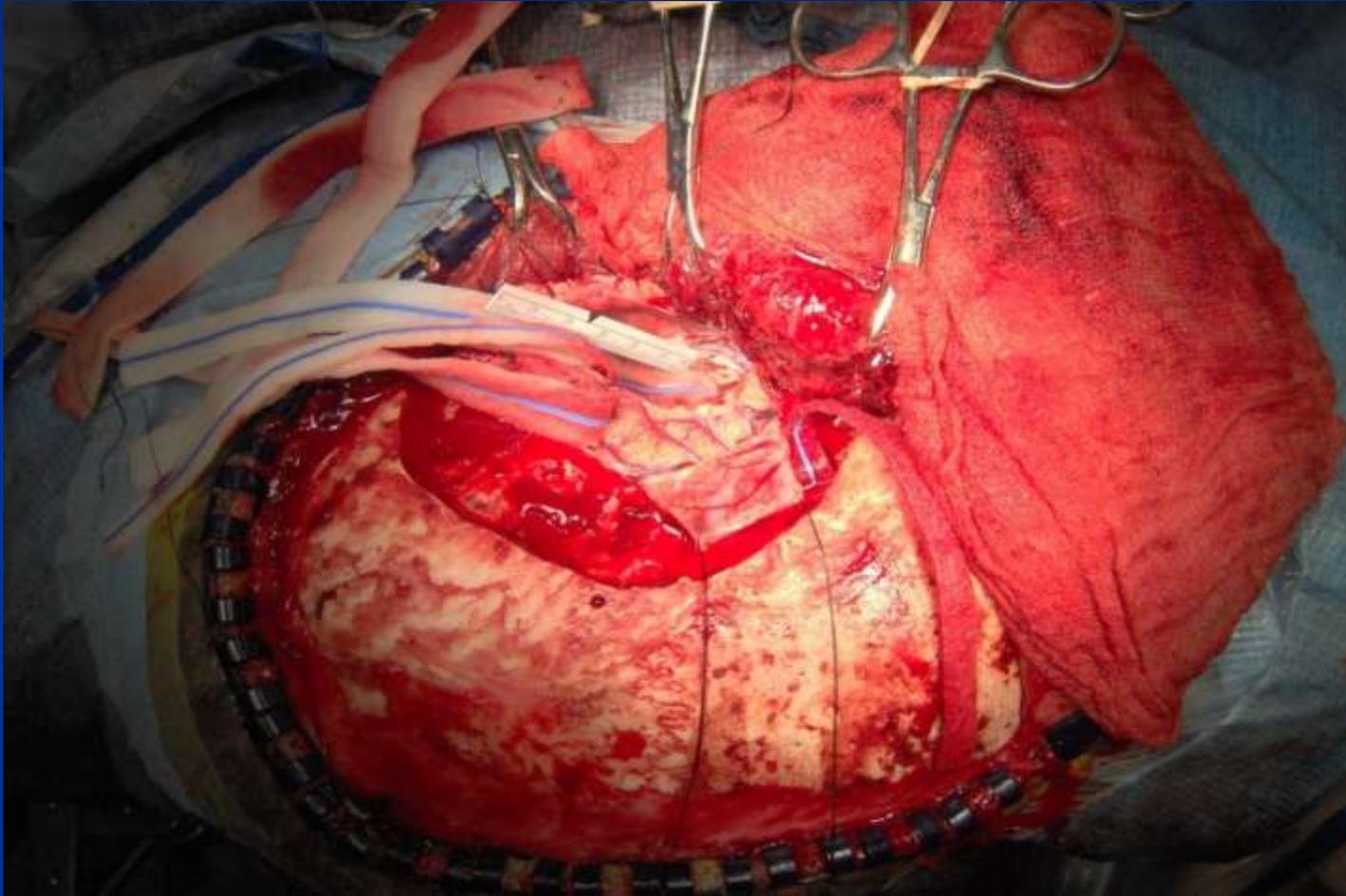
- Temporal lobectomy
- Extratemporal resections (lobar: frontal, occipital)
- Corpus Callosotomy
- Hemispherectomy
- Multiple subpial transections

Temporal Lobectomy (AMTL)



Adapted from Wiebe S et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001 Aug 2;345(5):311-8.

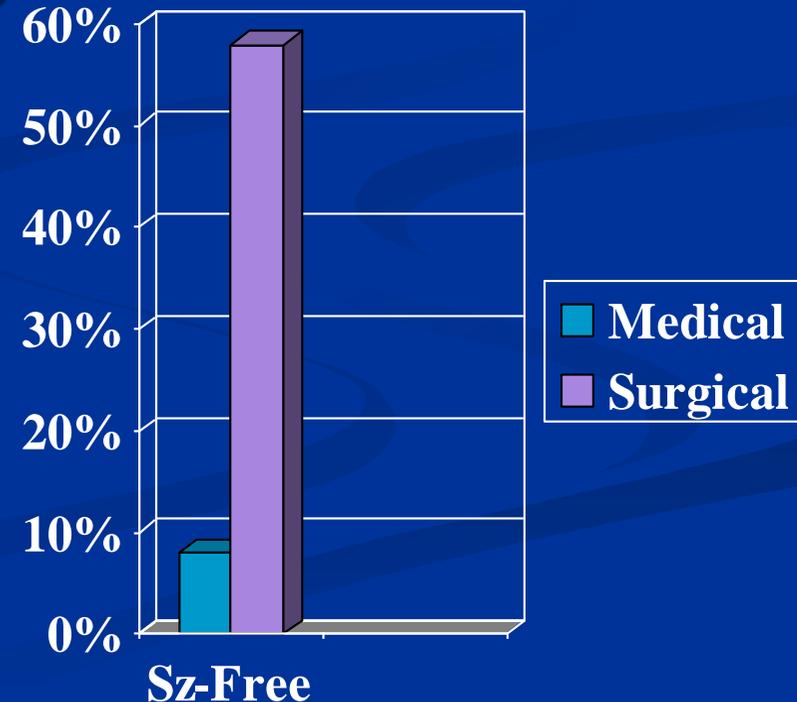
Right anterior temporal resection



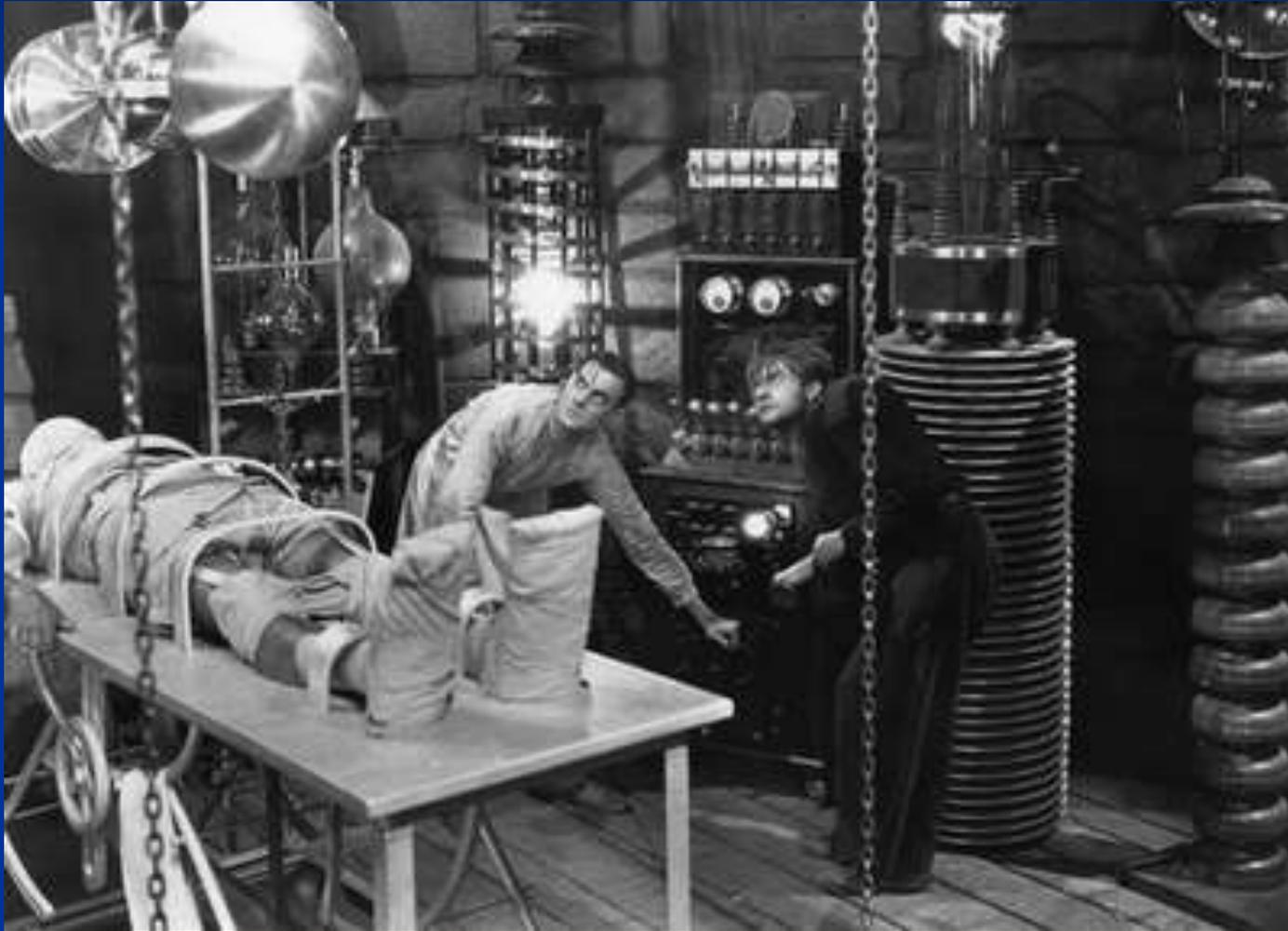
Controlled Trial of Surgery for Temporal Lobe Epilepsy

- Randomized 80 patients (40 medically and 40 surgically treated) with F/U at 12 mos.
- Significantly better outcomes for surgical group: 1) seizure-free, 2) decreased seizures, 3) improved quality of life ($P < 0.001$)

NEJM 2001;345:311-8

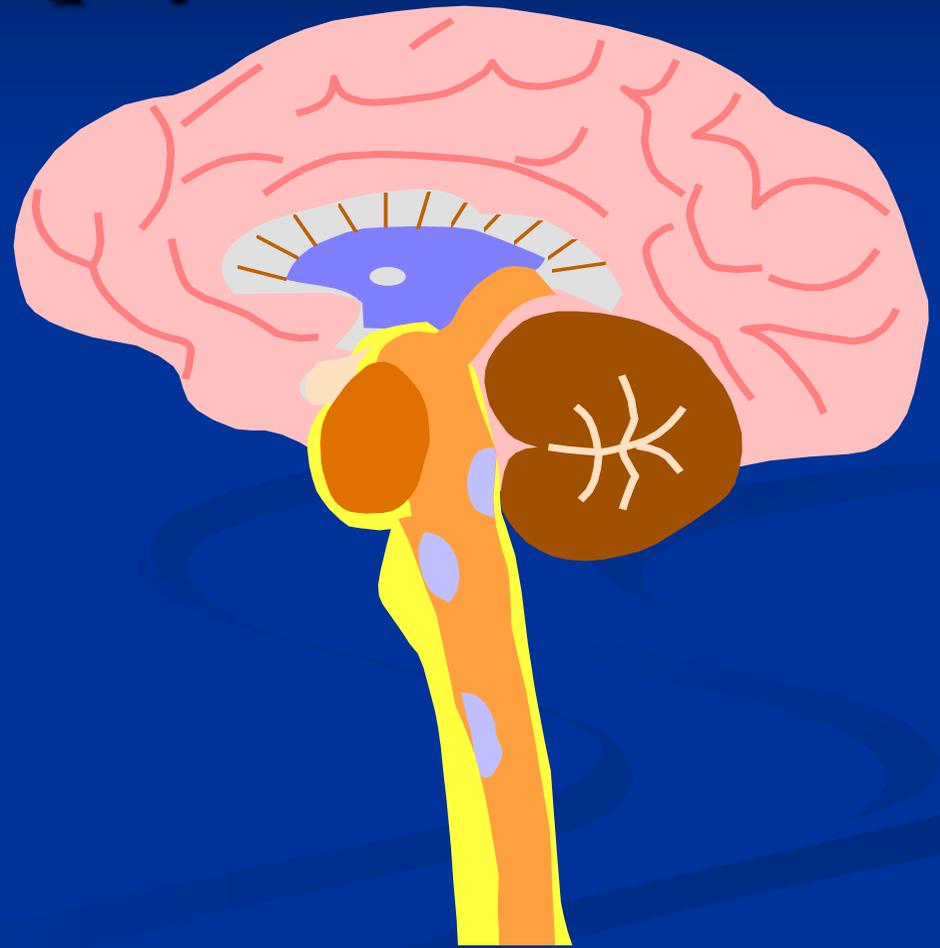


NEUROSTIMUATION



History of Brain Stimulation for Epilepsy

- 1970's - Cerebellar stimulation
- 1990's to today - Vagus Nerve Stimulation (VNS)
- 1980's and perhaps (?) again – Deep Brain (Thalamic) Stimulation (DBS)
- Reactive Neural Stimulation (RNS)



Vagus Nerve Stimulation (VNS)



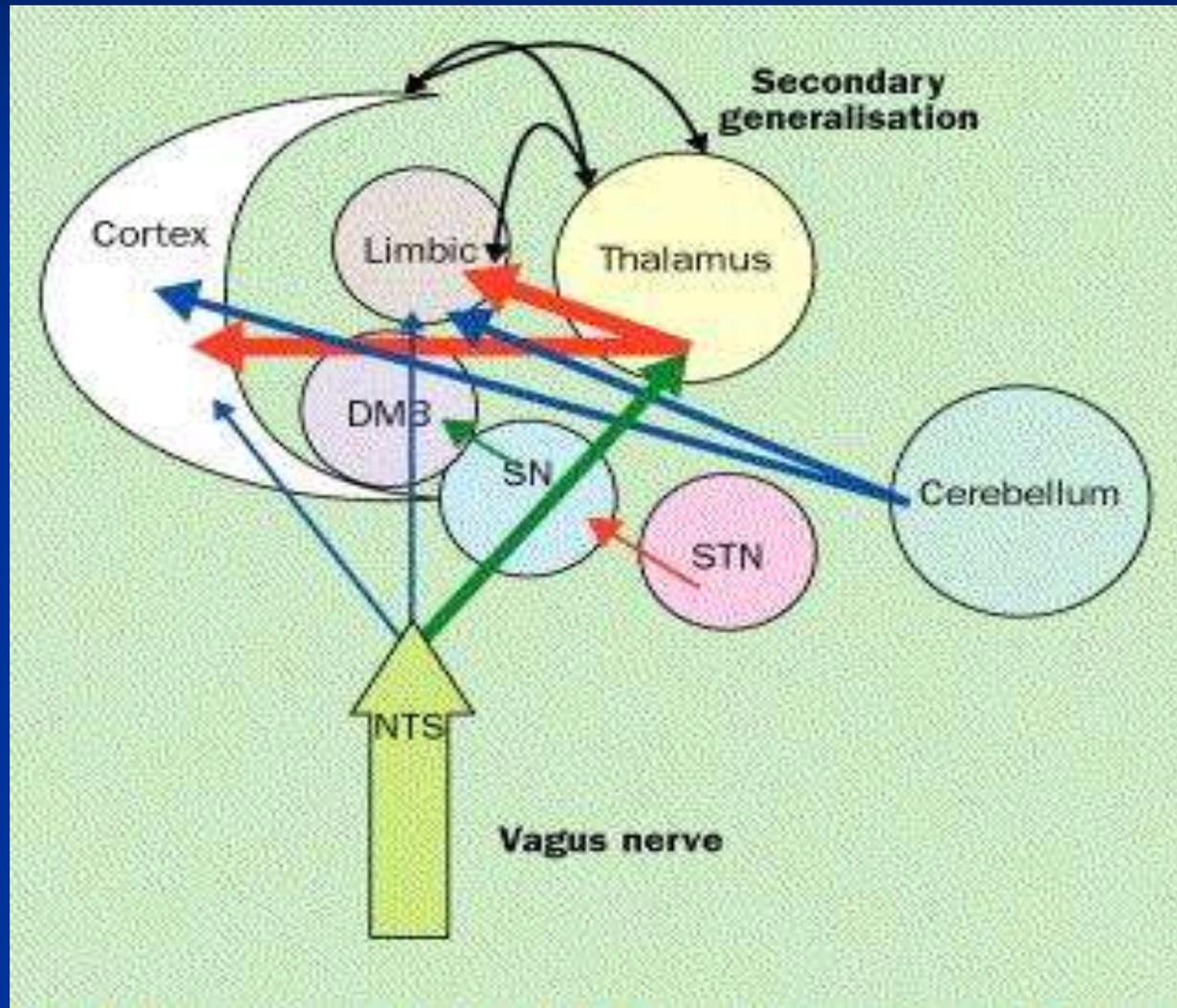
- Approved by FDA in July 1997
- Patients with intractable epilepsy ≥ 12 yo
- First device approved to treat epilepsy

Courtesy of Cyberonics, Inc.

Benefits of Vagus Nerve Stimulation

- Seizures decrease 50% or more in 50% of patients
- Effect increases over time
- Seizure severity decreased
- Improved level of alertness (medication may be decreased)
- Few adverse effects-Hoarseness, infection (rare)
- Batteries require replacement every ~ 10 yrs

Neurostimulation



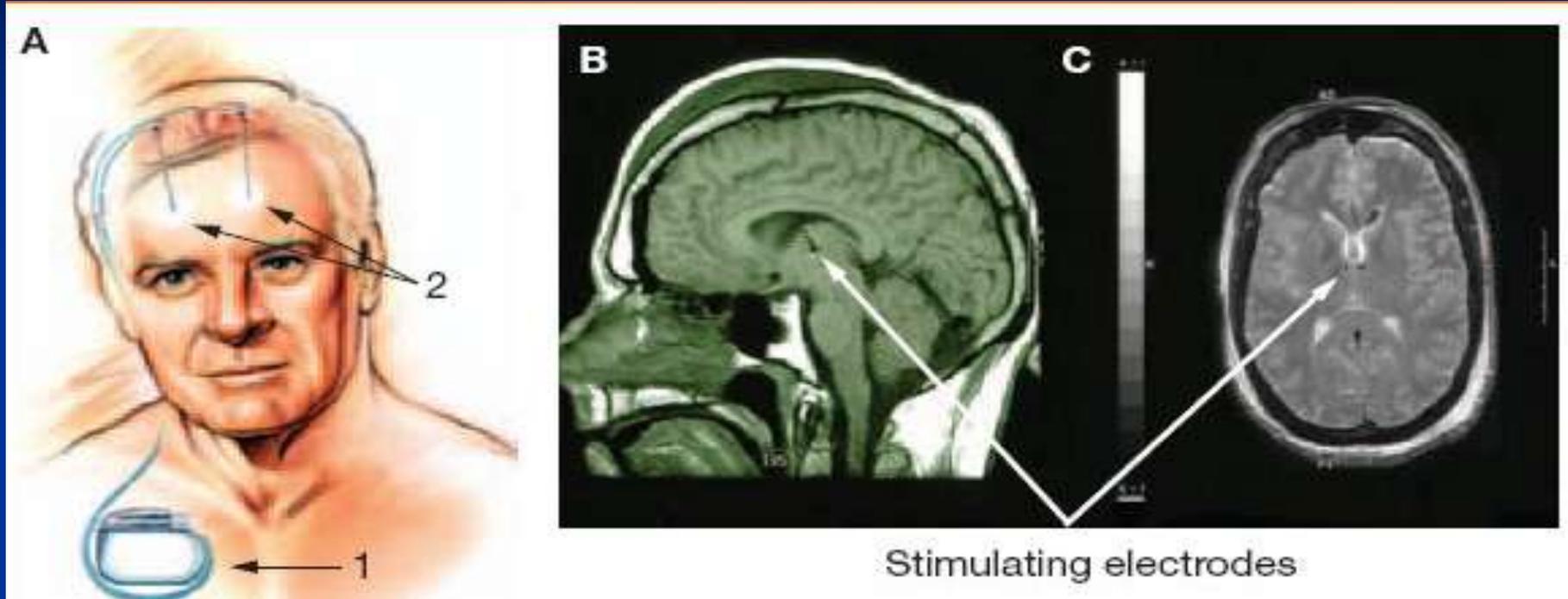
Proposed Mechanisms of Action for Vagus Nerve Stimulation

- Desynchronization of EEG
- Suppression of spikes
- Block ictal rhythmic build-up in a seizure
- Release of GABA and Glycine
- Effects on limbic and brainstem systems

Investigational Neurostimulation

- Deep Brain Stimulation (DBS)
- Responsive Neurostimulation (RNS) (Neuropace)

Deep Brain Stimulation



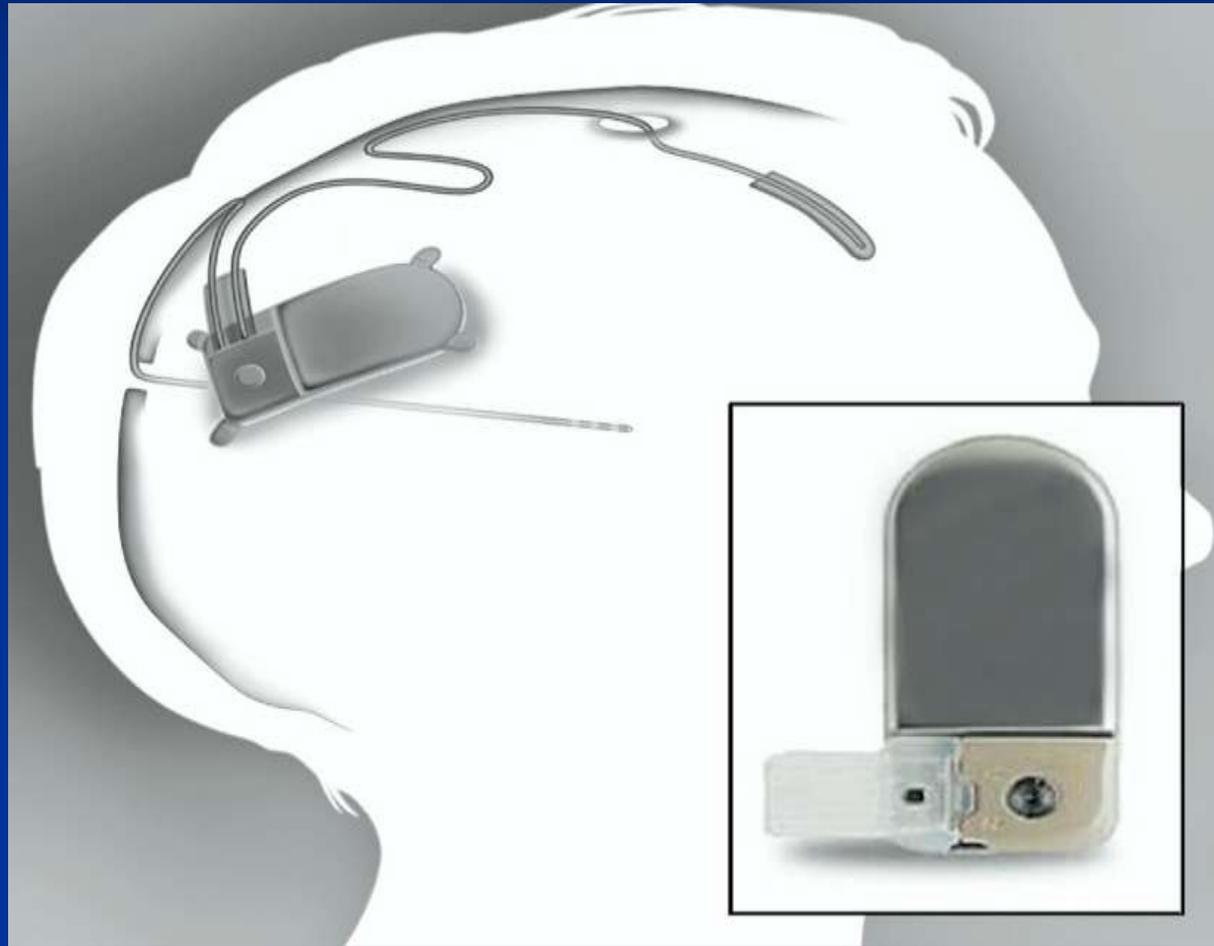
- Implanted with leads in the left and right anterior nucleus of the thalamus
- Wires leading to a dual-channel stimulator

Deep Brain Stimulation*

- More than 6 partial or secondarily generalized seizures per month
- Seizures refractory to more than 3 AEDs
- 4 phases: 3 month baseline, 3 mo double-blind phase, 9 mos open-label phase, long term follow up
- Responder rate significantly higher than controls and increases past 3 month trial (*seizure reduction 29% greater in subjects versus controls*)
- FDA considering approval

* Protocol

Responsive Neurostimulation

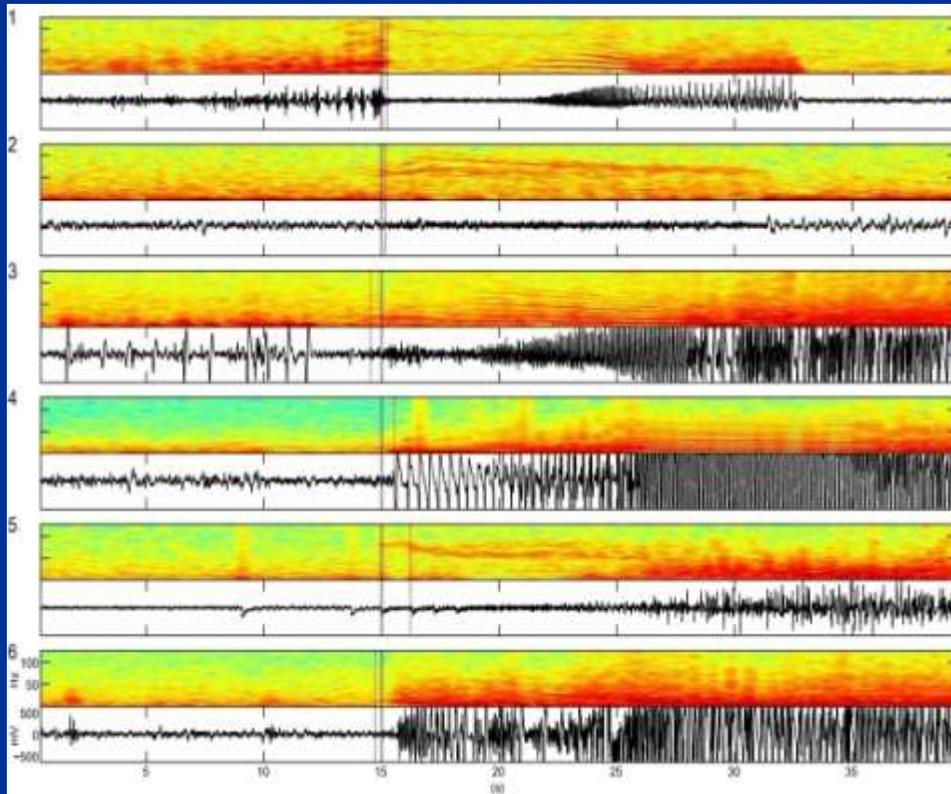


Responsive Neurostimulation

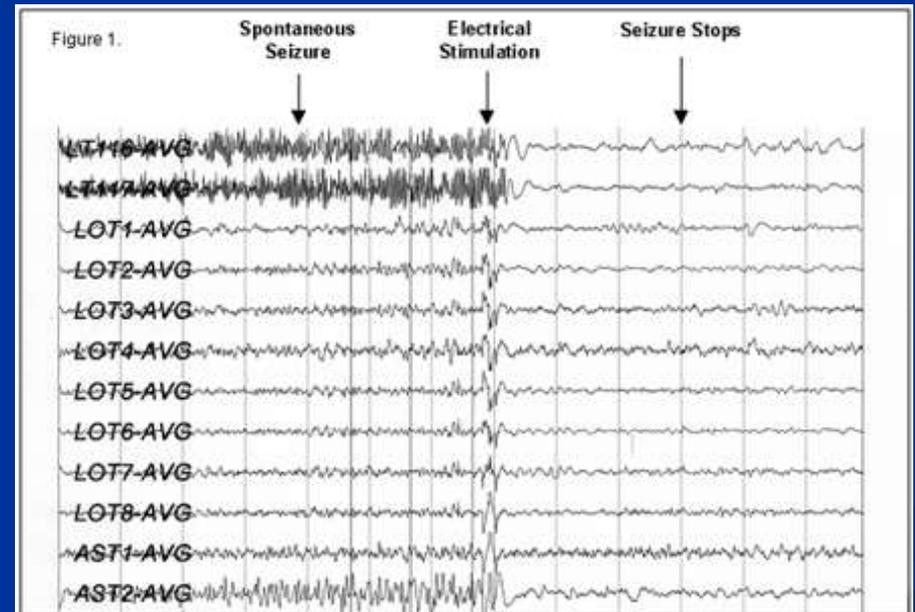
- Electrodes record intracranial EEG and input to algorithm that determines if seizure has started or may begin
- Triggers focal electrical stimulation to prevent or stop seizures

Responsive Neurostimulation

Seizure Detection - Examples



Stimulation Effect

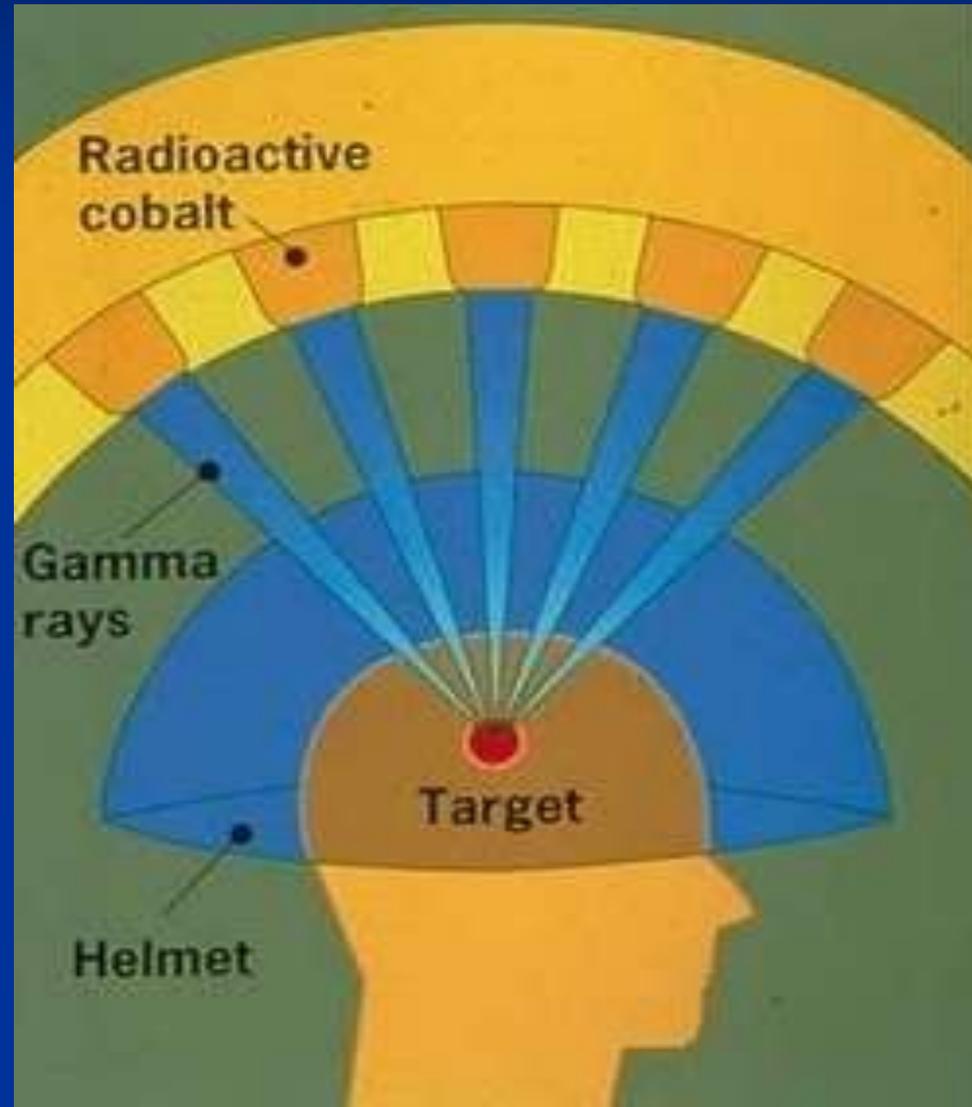


Responsive Neurostimulation

- Randomized, double-blinded multicenter trial
- Enrollment of ~240 adult subjects
- Medically refractory partial epilepsy
- Average of 3 or more disabling seizures every 28 days
- Data showed some benefit but FDA is still considering approval

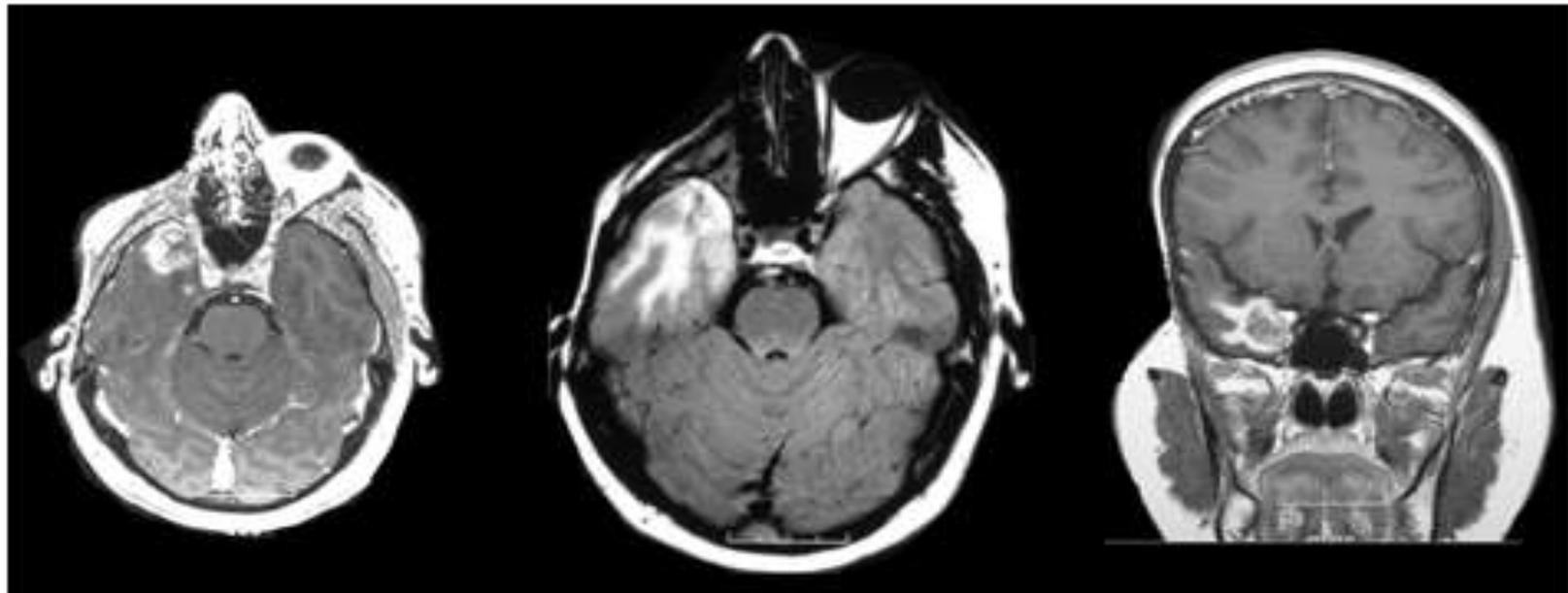
RADIOTHERAPY FOR EPILEPSY

Gamma
Knife



Target is the
Temporal
Lobe

POST RADIATION CHANGES



INFLAMMATORY & IMMUNE MECHANISMS IN EPILEPSY

Infectious

- Neurocysticercosis
- Viral encephalitis (herpes, EB, rotovirus, etc.)
- Mycoplasma pneumoniae
- Syphilis
- Chronic meningitis

Autoimmune

- Systemic lupus erythematosus
- Neurosarcoidosis
- Multiple sclerosis
- Rasmussen's encephalitis
- Limbic encephalitis –
paraneoplastic (*with or without antineuronal antibodies*)
post-viral
post vaccination
drug hypersensitivity

LIMBIC ENCEPHALITIS

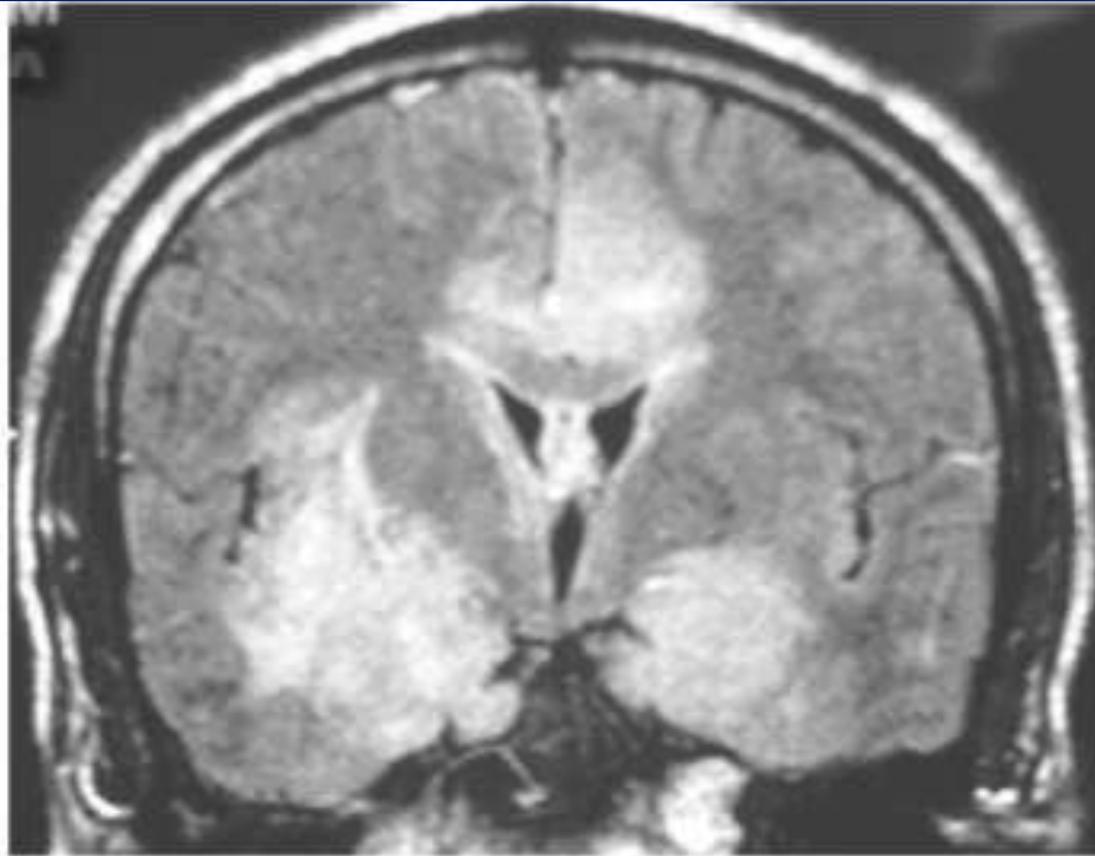


Figure 1 - Flair MR imaging showing hyperintense lesions in both medial temporal lobes and cingulate gyrus compatible with limbic encephalitis.

AUTOIMMUNE REFRACTORY EPILEPSIES

- Limbic encephalitis
- Anti-NMDA receptor encephalitis
- Antiglutamate receptor encephalitis
- Voltage Gated Potassium Channel (VGPK) Antibodies
- Anti-glycolipid antibody syndrome
- Hashimoto's encephalopathy (autoimmune thyroid encephalopathy)

IMMUNOSUPPRESSIVE THERAPIES FOR REFRACTORY EPILEPSIES

- Corticosteroids
- Intravenous immunoglobulin
- Plasma exchange
- Cyclophosphamide
- Calcineurin antagonists

INTRACTABLE EPILEPSY: GENETIC IMPLICATIONS

- RISK FOR ADVERSE DRUG REACTION
- POTENTIAL FOR RESISTANCE TO DRUG THERAPY
- ANTIPILEPTIC DRUG TARGETS
- SPECIFIC GENE THERAPY

GENETIC IMPLICATIONS & THERAPIES

Drug effects

- Carbamazepine serious adverse reactions associated with HLA-B* 1502 allele in Asians
- Multiple drug resistance gene (MDR-1) MDR-1 has been demonstrated to be over-expressed in seizure foci of some drug-resistant patients.

Epilepsy control

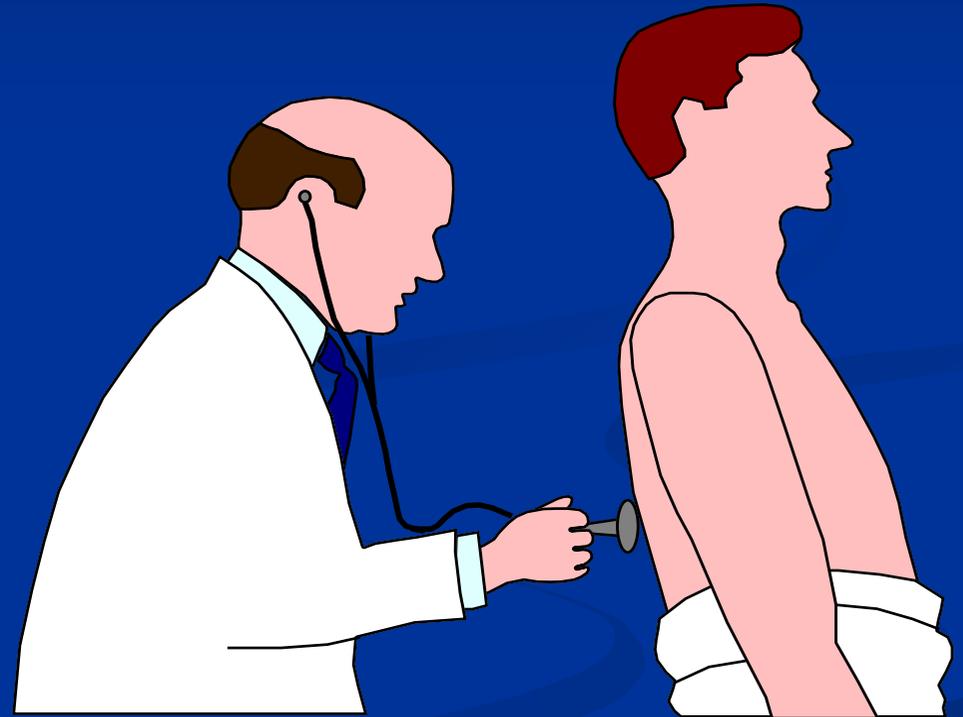
- Some genetic epilepsies respond best to specific AEDs (e.g. ADNLE to CBZ ; JME to VPA)
- 21 genes associated with idiopathic generalized epilepsy – channelopathies- Na , Ca, K, Cl channels; GABA and Ach receptors
- Neuronal migration disorders – (e.g. Lissencephaly (LIS1, DCX))

POTENTIAL GENETIC THERAPIES

- GENE TRANSFER THROUGH VIRAL VECTORS
- GENE TRANSFER WITH BRAIN GRAFTS OF CELLS (e.g. – with specific inhibitory or excitatory transmitter effects)

Care for Epilepsy

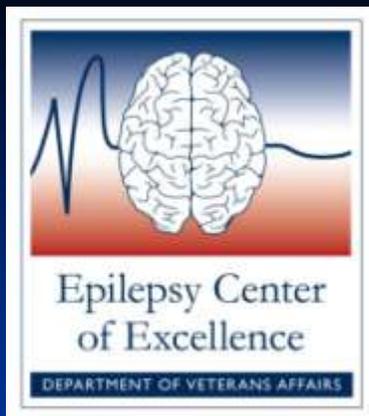
- Diagnose properly
- Medical therapy
- Education and support
- Psychosocial RX
- Epilepsy surgery, etc...
- Maximize patient's adjustment and coping strategies



CONCLUSIONS

- EPILEPSY IS A **TREATABLE** DISORDER
- THE GOAL OF TREATMENT SHOULD BE “**NO SEIZURES AND NO SIDE-EFFECTS**”.
- OLDER TREATMENTS WORK WELL FOR MOST PATIENTS (~70%)
- BUT WHEN SEIZURES PERSIST AND ARE **INTRACTABLE** ...
- THERE ARE STILL MANY **RX OPTIONS**





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