Seizures and Epilepsy Diagnosis and Treatment

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National Director
VA Epilepsy Centers of Excellence
San Francisco VA Medical Center
Objectives

- Define seizures and epilepsy
- Classification of seizures and epilepsy
- Evaluation/diagnosis of seizures
- Treatment of epilepsy
  - Anticonvulsant medication
  - Medical Devices and surgery
- Referral to epilepsy center
- Organization of VA Epilepsy Centers of Excellence
SEIZURE

- result of sudden, usually brief, excessive electrical discharges in a group of brain cells (neurons)
- can occur in different parts of the brain
- depending on where in the brain this occurs, the person will experience different symptoms
EPILEPSY

A tendency to have recurrent seizures
1% by age 20
3% by age 75
Epilepsy
Disorder characterized by recurrent, unprovoked seizures
Incidence of Epilepsy
per 100,000

Age (Years)

Hauser et al., 1993
International League Against Epilepsy (ILAE)

- The ILAE Classifications of Seizures and the Epilepsies have been used since 1981
- Although imperfect, they have provided invaluable means of communication
- Efforts continue to refine and upgrade the current classifications
- Based on review of video recorded seizures of clinical and electroencephalographic events provided from epilepsy centers worldwide.

*Epilepsia, 51(4):676–685, 2010*
## Terminology

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<tr>
<th>Old</th>
<th>Recent Past</th>
<th>Current (April 2010)</th>
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<tbody>
<tr>
<td>Focal Motor</td>
<td>Simple Partial</td>
<td>Focal</td>
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<tr>
<td>Psychomotor Temporal Lobe</td>
<td>Complex Partial</td>
<td>Focal with impaired consciousness</td>
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<tr>
<td>Grand Mal</td>
<td>Tonic Clonic</td>
<td>Generalized</td>
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<td>Petit Mal</td>
<td>Absence</td>
<td>Generalized</td>
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Classification of Seizures

Focal seizures
- **Without** impaired consciousness or responsiveness
  - With motor or autonomic components
  - Involving subjective sensory or psychic phenomena (aura)
- **With** impaired consciousness or responsiveness
- Evolving to a bilateral convulsive seizure

Generalized seizures
- Absence seizures
  - Typical vs Atypical
- Tonic-clonic seizures
- Myoclonic seizures
- Tonic seizures
- Clonic seizures
- Atonic seizures
Epilepsy Types
(past classification)

**Idiopathic**
(Primary)

- Onset in childhood or young adult
- Probably genetic
- Good AED response
- Favorable prognosis
- “Normal” brain

**Symptomatic**
(Secondary)

- Onset any age
- Multiple etiologies
- Variable response
- Variable prognosis
- Brain pathology
Classification of Epilepsy by Etiology

- Electroclinical syndromes (idiopathic)
  - i.e. Childhood absence, West syndrome, Familial temporal lobe epilepsy, Juvenile Myoclonic Epilepsy

- Distinctive Constellations
  - i.e. Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE with HS)

- Secondary to specific metabolic or structural lesions or conditions (symptomatic)
  - i.e. Tumor, Infection, Trauma, Stroke, Cortical Malformations

- Unknown cause (cryptogenic)

Epilepsia 2010; 51: 676-685.
Post-Traumatic Epilepsy

- Epilepsy is a sequela of head trauma
- Seizures may begin hours to years after injury
- Report of the Vietnam Head Injury Study: 15 years after penetrating brain injury, 53% had epilepsy
- Animal data suggest blast injury may be more injurious to neurons than blunt trauma
- Despite reduced penetrating brain injury, epilepsy incidence in OEF/OIF Veterans may be higher than expected

Salazar, et al., 1985
Garga & Lowenstein, 2006
Epilepsy in the elderly

- Under diagnosed and misdiagnosed
- Clinical Manifestations in Elderly may be different
  - Aura-less frequent or is non-specific (Dizziness)
  - Automatisms-less frequent
  - Post-ictal confusion may be prolonged
  - May present with altered mental status, confusion, or memory disturbance

Ramsey, Rowen & Pryor, 2004
Diagnostic Work-Up for Seizure

- History & Physical
  - Was it seizure or other LOC?
  - Identify risk factors: Brain Infection or lesion, metabolic disturbance, drug or alcohol related, FHx, trauma

- Labs
  - Chemistry Panel, Consider Lumbar Puncture

- Electroencephalography
  - Stat if patient not returning to baseline

- Imaging
  - MRI with gad (usually not urgent)
Routine EEG Findings in Childhood Absence Epilepsy: Generalized 3Hz Spike and Wave Discharges

Comment

CLINICAL SZ
EVENT
Photic Start (20 Hz)
Photic End (20 Hz)
MRI in Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
Epilepsy Treatment in 2011

- FDA-Licensed Antiepileptic Drugs
- Epilepsy Surgery
- Vagus Nerve Stimulation
- Ketogenic Diet
- Investigational Therapies
  - Deep brain stimulation
  - Responsive neurostimulation
Goals of Therapy

Seizures

Side Effects
Pharmacotherapy

- Up to 70% of newly diagnosed children and adults can be successfully treated
- Ascend monotherapy to maximum tolerated dose (regardless of serum levels!)
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<th>3-letter abbreviation</th>
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Antiepileptic Drug (AED) Therapy

“2nd Generation”
1\textsuperscript{st} Generation AEDs

- Vast Clinical Experience
- Use in Both Partial and Primary Generalized Epilepsies
  - exception: CBZ-Absence
  - Incomplete Efficacy
  - Unfavorable Kinetics
  - Narrow Therapeutic Range
  - Adverse CNS Effects
  - Drug Interactions
Hepatic Metabolism-1st Generation AEDs

- Inducers
  - Phenobarbital
  - Phenytoin
  - Carbamazepine

- Inhibitor
  - Valproate

- Clinical Significance (statins, OCPs, ABX, coumadin)
2nd Generation AEDs

- Safer
- More expensive (not as expensive as admission)
- Specific MOA
- Simple Pharmacokinetics
- Better Tolerability
- No therapeutic monitoring
- Lower Drug Interactions
- NO generics (bioavailability issues)
- Not profoundly more potent
How to Choose the Right AED

- **Spectrum**: Broad or Narrow
- **Adverse and Side Effect Profiles**
  - Long term and Short term
- **Interactions with Other Medications**
- **Dosing Frequency and Compliance**
- **Comorbid Indications**
  - TPX for weight loss or headache
  - VPA for migraine
  - LTG for mood disorders

- Refer to Neurology or Epilepsy Center for Expertise
AED Treatment Options by Seizure Type

Focal
• Without Impaired Responsiveness
• With Impaired Responsiveness
• Evolving to convulsion

Generalized
- Tonic-clonic
- Tonic
- Myoclonic
- Atonic
- Absence

CBZ, OXC, PHT
GBP, TGB, LCM, VGB, PGB

VPA, LTG*, TPM**, LEV*, (FBM) (?ZNS)
(broad-spectrum agents)

*?Myoclonic  **?Absence
CNS Adverse Effects of Antiepileptic Drugs

- Most frequent side effects of AEDs are similar
  - Drowsiness
  - Incoordination
  - Dizziness
  - Cognitive impairment
- Toxicities are additive
Drug Specific AEs

- Pedal Edema – GPN & VPA
- Weight Gain – CBZ, GPN & VPA
- Weight Loss – FBM, TPM & ZNA
- Word Finding Difficulty – TPM
- Peripheral Paresthesia – TPM and ZON
- Renal calculi – TPM, ZNG
- Concentric visual field restriction – VGB
- Osteoporosis – CYP450 Inducers + VPA
- Hyponatremia – CBZ and OXC
- Rash – LTG, CBZ, PHB, DPH
- Hyperammonemia – VPA
- Encephalopathy – TGB and VPA
- Peripheral Neuropathy – PB, PHT and CBZ
- Closed angle glaucoma – TPM, ZNG
Serum AED Levels are...

- Only a rough guide to efficacy & toxicity
- Of little value when performed on a “routine” basis
- Not predictors of serious adverse reactions (unlike levels for other drugs, e.g., digoxin, lithium, theophylline)
- Of little help if not trough
- Potentially dangerous to patients!!!
- Over-used!!!
Response to AED Treatment: Complete Seizure Control

- *First Drug*: ~40%
- *Second Drug*: ~20%
- *Third Drug*: <10%
- *Add’l Drugs*: <5%

>20% Refractory!
Medically Refractory Epilepsy

- Definition: Persistent disabling seizures despite adequate trials of 2 AEDs that are appropriate for seizure type
- 30-40% of patients with partial seizures
- Increased overall mortality rate
- Increased cognitive morbidities
- 200,000 patients in US with MR epilepsy are candidates for surgical treatment but only 2-3,000 epilepsy surgeries are performed annually
Uncontrolled seizures need evaluation in an Epilepsy Center

- Video EEG Telemetry
  - Are the events seizures?
  - What type of seizures? Are AEDs appropriate?
  - Does the seizure onset allow for surgical options?
Epilepsy Monitoring Unit
Video/EEG telemetry
Presurgical Evaluation done at Epilepsy Centers

- MRI Seizure protocol
  - Sensitive for specific lesions of interest
- Magnetoencephalography (MEG)
- PET
- Wada
- Neuropsychological testing
Multi-Modality Evaluation
Epilepsy Surgery
Vagus Nerve Stimulation

- FDA approved to treat epilepsy not controlled by medication
- Often reduces, but usually does not completely control seizures
- Offered at SFVA since 1998
Emerging Treatments

- **Deep Brain Stimulation: SANTE**
  - Bilateral stimulation of the anterior nuclei of the thalamus (ANT)
  - Continuous cyclic stimulation similar to VNS
  - Did not receive FDA approval in US

- **Responsive Neurostimulation**
  - Implanted device detects electrical seizure activity in the brain
  - Delivers electrical stimulation to suppress the propagation
When to Refer a Patient

- Newly diagnosed epilepsy or 1st unprovoked seizure:
  - AEDs: start? which one(s)?
  - Counseling: driving, psychosocial issues

- Patients with established epilepsy
  - AEDs: continue? change? tailor…
  - Special populations: women, elderly, medically refractory
  - New concerns: drug interactions, side effects

- Patients with indeterminate spells
If seizure control is not promptly achieved...

Refer the patient to an epilepsy specialist
Establishment of VA Epilepsy Centers of Excellence

Response in 2008 to Section 404 (Epilepsy Centers) of Veterans Mental Health and Other Care Improvements Act of 2008 (PL110-387)
Requirements of PL110-387

- VHA is to establish 4-6 epilepsy centers and appoint an overall director
- Centers must:
  - link to existing polytrauma centers
  - link to academic centers and conduct research
  - be established by a Peer Review Panel
  - be geographically dispersed
  - be involved with education and fellowship training
- Funding level of $6 million per year 2009-14
## Facilities Specific Strengths

<table>
<thead>
<tr>
<th>ECOE</th>
<th>Linked Polytrauma Site</th>
<th>Sites of Epilepsy Strength</th>
<th>States Covered (note that these may need to change for balance)</th>
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<tr>
<td>Northwest</td>
<td>Minneapolis</td>
<td>Madison, Portland, Seattle</td>
<td>AK, WA, OR, ID, MT, WY, ND, SD, MN, IA, IL, IN, MI, WI</td>
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<td>Southwest</td>
<td>Palo Alto (San Antonio in future)</td>
<td>San Francisco, West Los Angeles, Albuquerque, Houston</td>
<td>CA, UT, CO, KS, NE, NV, HI, AZ, NM, TX, OK</td>
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<td>Tampa</td>
<td>Miami, Gainesville, Durham</td>
<td>FL, AL, GA, MS, TN, KY, SC, PR, AR, LA, NC, MO</td>
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<td>Northeast (Atlantic)</td>
<td>Richmond</td>
<td>Baltimore, New Haven</td>
<td>VA, WV, OH, IN, PA, DE, NJ, NY, VT, MA, CT, RI, NH, ME, DC</td>
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NORTHEAST REGIONAL CENTERS

Maryland Health Care System
Regional and Site Director: Alan Krumholz
10 North Greene Street Baltimore, MD 21201

West Haven VA CT Healthcare System
Site Director: Huned Patwa
950 Campbell Avenue, West Haven, CT 06516

Richmond VAMC
Site Director: Alan Towne
1201 Broad Rock Boulevard Richmond, VA 23249
NORTHWEST REGIONAL CENTERS

William S. Middleton Memorial VA Hospital
Regional and Site Director: Paul Rutecki
   2500 Overlook Tr. Madison, WI, 53705

Minneapolis VA Healthcare System
Site Director: Stephen Holloway
   One Veterans Dr Minneapolis, MN 55416

Portland Oregon VA
Site Director: Martin Salinsky
   3710 SW U.S. Veterans Hospital Road Portland, OR 97239

Puget Sound Health Care System
Site Director: William Spain
   1660 S. Columbian Way Seattle, WA 98108-1597
SOUTHEAST REGIONAL CENTERS

Durham VA Healthcare System
Regional and Site Director:  Aatif Husain
508 Fulton Street Durham, NC 27705

Miami VAMC
Site Director:  Enrique Carazanas
1201 N.W. 16th Street, Miami, FL 33125

Malcolm Randall VAMC
Site Director:  J. Chris Sackellares
1601 S.W. Archer Road Gainesville, FL 32608

James A Haley Tampa
Site Director:  Alfred Frontera
13000 Bruce B. Downs Blvd. Tampa, FL 33612
SOUTHWEST REGIONAL CENTERS

VA Greater Los Angeles Health Care System
Regional and Site Director: Claude Wasterlain
11301 Wilshire Boulevard Los Angeles, CA 90073

San Francisco VA Medical Center
Site Director: Karen Parko
4150 Clement Street San Francisco, CA 94121

Michael E. DeBakey VA Medical Center
Site Director: Richard A. Hrachovy
2002 Holcombe Blvd. Houston TX, 77030

New Mexico VA Health Care System
Site Director: Larry E. Davis
1501 San Pedro Dr. SE Albuquerque, NM 87108

Audie L. Murphy VA Hospital
Site Director: Jose Cavazos
7400 Merton Minter
San Antonio, TX 78229
## VA Epilepsy Centers Established under PL-110 in 2009

<table>
<thead>
<tr>
<th>Directors</th>
<th>Regions</th>
<th>Facilities</th>
<th>Station</th>
<th>Contact Information</th>
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<tr>
<td><em>Claude Wasterlain</em></td>
<td>West LA VA</td>
<td>Greater Los Angeles HCS</td>
<td>691</td>
<td>(310) 268-3595</td>
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<tr>
<td>Richard A Hrachovy</td>
<td>Houston</td>
<td>Michael E. DeBakey VAMC</td>
<td>580</td>
<td>(713) 791-1414 x 4007</td>
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<tr>
<td>Karen Parko</td>
<td>San Francisco</td>
<td>San Francisco VAMC</td>
<td>662</td>
<td>(415) 221-4810 x 4702</td>
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<tr>
<td>Larry E. Davis</td>
<td>Albuquerque</td>
<td>New Mexico VAHCS</td>
<td>501</td>
<td>(505) 265-1711 x 2752</td>
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<td><em>Aatif Husain</em></td>
<td>Durham</td>
<td>Durham VAMC</td>
<td>558</td>
<td>(919) 286-0411 x2230</td>
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<tr>
<td>Enrique Carazanas</td>
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<td>J. Chris Sackellaes</td>
<td>Gainesville</td>
<td>Malcolm R</td>
<td>150</td>
<td>(352) 376-1611</td>
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<td>Alfred Frontera</td>
<td>Tampa</td>
<td>J. A. Haley</td>
<td>673</td>
<td>(813) 972-2000 x7633</td>
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<td>Baltimore</td>
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<td>Huned Patwa</td>
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ECOE Goals

- Delivery the highest quality care to veterans with epilepsy
- Establish network for regional epilepsy care
- Promote outreach and educational efforts
- Provide an efficient and cost-effective mechanism of care delivery
Resources

- [www.epilepsy.va.gov](http://www.epilepsy.va.gov)
- [www.epilepsyfoundation.org](http://www.epilepsyfoundation.org)
- [www.epilepsy.com](http://www.epilepsy.com)
- [www.cureepilepsy.org](http://www.cureepilepsy.org)
- [www.ninds.nih.gov/disorders/epilepsy](http://www.ninds.nih.gov/disorders/epilepsy)