Definition

- A seizure is a clinical event associated with an abnormal, excessive and hypersynchronous electrical discharge in a group of cortical neurons.
- Epilepsy refers to recurrent and unprovoked seizures.
Epidemiologic Highlights (US)

- 2.5 million cases
- 150,000 to 200,000 new cases/year
- Age-specific incidence has changed over the last 3 decades
  - Decreased in younger age groups, increased in patients over age 60
- Comparable prevalence in men vs women (as of 1995)

*MMWR Weekly*. November 11, 1994/43(44);810-811, 817-818.
ILAE Classification

**Partial seizures**
- Simple partial seizures
- Complex partial seizures

**Generalized seizures**
- Primary generalized
  - Absence
  - JME
- Secondary generalized
  - Lennox-Gastaut Syndrome
Epilepsy Incidence Rates by Age*

*Data from Rochester, MN (1975-84)
Epilepsy in Children: Seizure Type and Etiology

Seizure Type (children <15 years)
- Generalized tonic-clonic 19%
- Myoclonic 7%
- Simple partial 11%
- Complex partial 23%
- Other generalized 11%
- Absence 13%
- Unknown/multiple 9%
- Other focal 7%

Etiology (children <15 years)
- Idiopathic 68%
- Congenital 20%
- Trauma 5%
- Degenerative 1%
- Infection 4%
- Vascular 2%
- Neoplastic 2%

Adapted from Hauser WA. Epilepsia. 1992;33(suppl 4):S6-S14. Used with permission.
Etiology in Adult Epilepsy

Proportion of Incidence of Cases with Known Etiology Within Age Groups

**Adults Age 15-34**
- Tumor 22%
- Congenital 22%
- CVA 8%
- Degenerative 5%
- Infection 16%
- Trauma 29%

**Adults Age 35-64**
- Tumor 23%
- CVA 33%
- Degenerative
- Infection 4%
- Trauma 22%
- Congenital 7%

Epilepsy in the Elderly: Seizure Type and Etiology (≥60 Years)

Seizure Type (elderly ≥60 years)
- Complex Partial: 51.7%
- Generalized Tonic-Clonic: 21.3%
- Simple Partial: 19.1%
- Myoclonic: 4.5%
- Partial Unclassified: 3.4%

Etiology (elderly ≥60 years)
- Stroke: 40.7%
- Degenerative: 16.5%
- Trauma: 2.2%
- Other: 2.2%
- Tumor: 5.5%
- Unknown: 33%

Brain injury

Epileptogenic lesion
- Head trauma
- Stroke
- Infection
- Status epilepticus

Reorganisation during epileptogenesis
- Neuronal loss (acute, delayed)
- Neurogenesis
- Gliosis
- Plasticity (axonal, dendritic)
- Inflammation
- Molecular reorganisation

Latency period (epileptogenesis)

Cognitive decline

Epilepsy (spontaneous seizures)

Reorganisation continues owing to recurrent seizures
- Neuronal loss (acute, delayed)
- Neurogenesis
- Gliosis
- Plasticity (axonal, dendritic)
- Molecular reorganisation

Recurrent seizures

Good seizure control

Worsening of cognitive decline

Drug refractory temporal-lobe epilepsy

No progression

Sutula 2002
Magnitude of the Problem

• Epilepsy affects 1-2% of the population
• Seizures occur in a larger number
• Chronic disease
• Economics
• Social stigma
• Outcome dependant on type and timing of intervention
Advances in Antiepileptic Drug Therapy

• **Decade of the Brain 1990-2000**
  - Felbamate
  - Gabapentin
  - Lamotrigine
  - Topiramate
  - Tiagabine

• **The New Millennium**
  - Levetiracetam
  - Zonisamide
  - Oxcarbazepine
  - Pregabalin
  - Lacosamide
  - Rufinamide
  - Retigabine
  - Vigabatrin
Antiepileptic Therapy

- Fundamental principles
  - Patient advocacy
  - Establish the diagnosis conclusively
  - Appropriate first line agent will control seizures in 70% of patients
  - In patients who fail initial therapy half will remain intractable even with other agents as well as rational polytherapy
Antiepileptic Therapy

• Fundamental principles
  - Use a single agent at maximally tolerated doses before introducing second agent which initially should also be used as monotherapy
  - Avoid sudden discontinuation of drugs as it may lead to withdrawal seizures
  - Combine agents with different mechanisms of agents for synergy
Antiepileptic Therapy

• Fundamental principles
  - Side effects are common and should be prevented
  - Avoid side effects by slow titration especially with valproate, lamotrigine, carbamazepine, tiagabine and topiramate
  - Serum levels may vary considerably in individuals and may not correlate with adverse effects or efficacy
Initiating Therapy

- First seizure 30 %
  - Risk increased by
    - Abnormal examination
    - Abnormal EEG
    - Abnormal imaging

- Second seizure 70 %
Common Adverse Effects of AEDs

- **Phenytoin**
  - Rash, gingival hyperplasia, ataxia

- **Carbamazepine**
  - Ataxia, rash, neutropenia

- **Valproate**
  - Weight gain, teratogenic, hepatopathy, pancreatitis

- **Lamotrigine**
  - Rash

- **Levetiracetam**
  - Behavioral abnormalities, sedation

- **Topiramate**
  - Weight loss, renal stones

- **Lacosamide**
  - Dizziness
Success With Antiepileptic Drug (AED) Regimens

Previously Untreated Epilepsy Patients (N=470)

- Seizure free with 1st drug: 47%
- Seizure free with 2nd drug: 13%
- Seizure free with 3rd or multiple drugs: 4%
- Not seizure free: 36%

Therapy For Primary Generalized Epilepsy

- Conventional agents
  - Valproate
  - Ethosuximide

- New agents
  - Lamotrigine
  - Topiramate
  - Levetiracetam
  - Zonisamide
Therapy For Partial Epilepsy

- Conventional agents
  - Carbamazepine
  - Phenytoin
  - Valproate
- Newer agents
  - Oxcarbazepine
  - Lamotrigine
  - Topiramate
  - Levetiracetam
  - Zonisamide
  - Gabapentin
  - Pregabalin
  - Lacosamide
Syndrome of TLE

• Temporal lobe seizures
  - Most common form of partial seizures
  - Commonly a rising epigastric sensation
  - Motionless stare, orofacial or limb automatisms with prominent post-ictal confusion
  - Characteristic EEG, MRI, PET
  - Under diagnosed
  - Response to surgery is excellent
Mesial Temporal Lobe Epilepsy

History

- Increased incidence of febrile convulsions
- Increased incidence of family history
- Onset in the latter half of the first decade
- Auras common
- Secondary generalization infrequent
- Remission and subsequent intractability
- Interictal behavioral disturbances
MTLE

Neurological evaluation

Memory deficits

Anterior temporal epileptiform abnormalities

Ictal EEG- 5-7 Hz rhythmic activity in basal temporal leads

MRI - Hippocampal atrophy or mesial temporal sclerosis
MRI IN TLE

• Comparison of “standard” MRI vs special protocol
  - 84 patients, 51 with standard MRI- 34 normal
  - 32 of the 34 were abnormal on special protocol
  - 27 with hippocampal atrophy, 2 with tumors and 1 with dysplasia

MTLE - MRI
AWeibe S, Blume W. NEJM 2001;345:211-8

B

Surgical group (n=40) 58%
Medical group (n=40) 8%

Surgical group (n=40) 38%
Medical group (n=40) 3%
Role Of EEG In Epilepsy

- Confirm diagnosis
- Classify seizure type and epilepsy syndrome
- Guide therapy
  - Prognosis
  - Initiation of AED
  - Discontinuing AEDs
- Non-convulsive status epilepticus
EEG And Epilepsy

• Yield of first EEG for interictal abnormalities is 50-60%
• Serial EEG increases the yield to 92%
• Normal EEG in about 8% after serial EEGs
• EEG abnormal in 0.5-3.5% without history of epilepsy
  • Cavazzuti GBC, Capella L, Nalin A. Epilepsia 1980;21:43-55
70 μV I __1 sec __
Monitoring Strategies

• Synchronized video-EEG monitoring (surface electrodes)
  - To differentiate non-epileptic events from seizures
  - Localize seizure focus for surgical intervention

• Intracranial recording
  - Depth electrodes
  - Subdural electrodes
Section IV: Semiology of Epileptic Seizures
Chapter 33
Myoclonic Seizures
N. So
Video by H.O. Lüders & S. Noachtar 1995
Case 1
Generalized myoclonic seizure ->
generalized tonic-clonic seizure
(Juvenile myoclonic epilepsy)
Video from H.O. Lüders & S. Noachtar 1995
Section VI: Factors That Precipitate Seizures
Chapter 51
Activation of Seizures by Hyperventilation
I. Drury
Section IV: Semiology of Epileptic Seizures
Chapter 38
Hypermotor Seizures
H. Holthausen, M. Hoppe
Case 1
Hypermotor Seizure
(Left Frontal Epilepsy)
Video from H.O. Lüders & S. Noachtar 1995
Non-Epileptic Seizures

- Epileptic
- Non-epileptic
  - Physiologic
    - Syncope, behavioral events, parasomnias
  - Psychogenic
NES

- Prevalence of 1.4/100,000
- 12-30% of LTME
- Risk factors
  - Trauma
  - Family dysfunction
  - Borderline PD
  - Psychopathology
  - Cognitive impairment

*M. Reuber / Epilepsy & Behavior 12 (2008) 622-635*
NES

- **Clinical Features**
  - Prolonged duration
  - Gradual onset
  - Tremulousness
  - Asymmetric shaking
  - Pelvic thrusting
  - Side to side head movements
  - Eyes closed
  - Waxing and waning pattern
  - Crying

*From Richer P. *Etudes Cliniques sur la Grande Hysterie ou l’Hysteroepilepsie.* London: New Syndenham; 1885*
NES

• Prognosis
  - 34 % seizure free @ 1 year
  - Poor outcome
    • Long duration
    • Recurrent major depression
    • Personality disorder
    • Dissociative disorders
    • Refusal of treatment
Nes

- Treatment
  - Presentation of diagnosis
  - Communicate effectively
  - Discontinue AEDs gradually
  - Tailor therapy to the underlying etiology
  - Cognitive Behavioral Therapy
    - Goldstein et al Cogn Behav Neur 2004
Drug Therapy

Which drug and why
Seizure type and syndrome
Etiology and EEG
Patient characteristics
Conventional versus new agents
Expertise and drug monitoring
Cost
New Onset Seizures

Trial of Drug A
50-60% seizure free

Trial of Drug B
10-15% seizure free

Trial of Drugs B+C
5-10% seizure free

Consider Surgery
10-70% seizure free

Investigational Trials
## Drug Resistance

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Probability of seizure freedom %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Failure with first drug</td>
<td>&lt; 30-35</td>
</tr>
<tr>
<td>2</td>
<td>Failure with two drugs alone or in combination</td>
<td>&lt; 10-15</td>
</tr>
<tr>
<td>3</td>
<td>Failure with three or more drugs alone or in combination</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

*Perucca 1996*
Definition

Inability to achieve acceptable seizure control despite adequate trials with a sufficient number of drugs (three ?) at doses that are associated with no side effects or with acceptable side effects only

Bourgeois 1999
VNS Implant Procedure

- 1 to 2 hour procedure
- General or regional/local anesthesia
- Chest/axillary border incision for pulse generator
- Neck incision for lead
- Outpatient or inpatient
VNS Long-Term Responder Rates (E01-E05)

% of patients with >50% seizure reduction vs. baseline

Last Visit Carried Forward (N=440)

- 3 Months: 23%
- 1 Year: 37%
- 2 Years: 43%
- 3 Years: 43%

Morris GI, Mueller WM. Neurology. 1999;53(7):1731-1735
General Health Concerns In Women

**Weight gain**
- Valproate
- Gabapentin
- Pregabalin
- Oxcarbazepine

**Weight loss**
- Topiramate
- Felbamate
- Zonisamide

**Weight neutral**
- Lamotrigine
- Levetiracetam

**Bone health**
- Phenytoin, Phenobarbital
- Carbamazepine
- Valproate
- Primidone
Specific Health Concerns for WWE

- Hormonal influences
- Contraception
- Polycystic Ovarian Syndrome
- Pregnancy
- Teratogenecity of AEDs
- Post-partum issues
- Growth and development of off-springs
Congenital Malformations

Malformations with specific drugs

**Fetal AED Syndrome**

- Epileptic mothers without AED: 3.1%
- Primidone: 14.1%
- Valproate: 11.1%
- Phenytoin: 9.1%
- Phenobarbital: 7.1%
- Carbamazepine: 5.7%
Teratogenicity

Major malformations (4-11%)

Associated with clinical, functional or genetic significance

Orofacial clefts
- Cleft lip - Day 35
- Cleft palate - Day 70

Neural tube defects - Day 21-28
Cardiac defects - Day 42
Urogenital defects - Day 40
Lamotrigine Registry

12/414 first trimester monotherapy exposure - 2.9 %
11/88 first trimester exposure to VPA & LTG - 12.5 %
4/182 with other drugs - 2.7 %

*Neurology 2005; Messenheimer et al*

North American Registry (2006)

Cluster of cleft lip and palate 1%
Effects of AEDs on Cognition

- 249 children born to WWE
- Neuropsychological Evaluation ages 6-16
- Exposure to VPA in utero - significant drop in verbal IQ
- Also affected by mother’s VIQ and number of GTC during pregnancy
  - Neurology 2005; 64: 949-54
Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

Table 2. IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Carbamazepine (N = 73)</th>
<th>Lamotrigine (N = 84)</th>
<th>Phenytoin (N = 48)</th>
<th>Valproate (N = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ (95% CI) †</td>
<td>98 (95–102)</td>
<td>101 (98–104)</td>
<td>99 (94–104)</td>
<td>92 (88–97)</td>
</tr>
<tr>
<td>Mean difference in IQ from valproate group (95% CI) ‡</td>
<td>6 (0.6–12.0)</td>
<td>9 (3.1–14.6)</td>
<td>7 (0.2–14.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>P value †</td>
<td>0.04</td>
<td>0.009</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

Antiepileptic Drug  | No. of Children | Mean IQ |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>47</td>
<td>97</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>52</td>
<td>100</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>28</td>
<td>98</td>
</tr>
<tr>
<td>Valproate</td>
<td>22</td>
<td>87</td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>46</td>
<td>100</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>48</td>
<td>102</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>27</td>
<td>98</td>
</tr>
<tr>
<td>Valproate</td>
<td>39</td>
<td>97</td>
</tr>
</tbody>
</table>

Mean IQ at Age 3 Yr (95% CI)
# Newer-Generation Antiepileptic Drugs and the Risk of Major Birth Defects

**Table 2.** Associations Between Newer-Generation Antiepileptic Drug Use During Pregnancy and Major Birth Defects in a Cohort of 837,795 Live Births in Denmark

<table>
<thead>
<tr>
<th>Exposure During First Trimester</th>
<th>No. of Women(^a)</th>
<th>Birth Defects, No. (%)</th>
<th>POR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Crude</td>
</tr>
<tr>
<td>Newer-generation antiepileptic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>1532</td>
<td>49 (3.2)</td>
<td>1.35 (1.02-1.80)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>836,263</td>
<td>19,911 (2.4)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Lamotrigine, mg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 250)</td>
<td>1019</td>
<td>38 (3.7)</td>
<td>1.59 (1.15-2.2)</td>
</tr>
<tr>
<td>(&gt;250)</td>
<td>766</td>
<td>31 (4.0)</td>
<td>1.73 (1.21-2.48)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>253</td>
<td>7 (2.8)</td>
<td>1.17 (0.55-2.47)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>393</td>
<td>11 (2.8)</td>
<td>1.18 (0.65-2.15)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>108</td>
<td>5 (4.6)</td>
<td>1.99 (0.81-4.88)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>59</td>
<td>1 (1.7)</td>
<td>0.71 (0.10-5.10)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; POR, prevalence odds ratio.
\(^a\)The numbers of women exposed to each individual antiepileptic drug sums to more than 1,532 because some of them took more than 1 drug.
\(^b\)Adjusted for use of older-generation antiepileptic drugs during the first trimester and diagnosis of epilepsy before the second trimester.

Ditte Mølgaard-Nielsen, MSc
Anders Hviid, MSc, DrMedSci

JAMA, May 18, 2011—Vol 305, No. 19 1999
Use Of AEDs In Women

Drugs for partial epilepsy
- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Levetiracetam
- Topiramate
- Lacosamide

Drugs for generalized epilepsy
- Lamotrigine
- Topiramate
- Valproate
- Levetiracetam
- Zonisamide
VA Cooperative Study

New onset geriatric epilepsy
A randomized study of gabapentin, lamotrigine, and carbamazepine

A.J. Rowan, MD; R.E. Ramsay, MD; J.F. Collins, ScD; F. Pryor, MPH; K.D. Boardman, RPh;
B.M. Uthman, MD; M. Spitz, MD; T. Frederick, MD; A. Towne, MD; G.S. Carter, MD, PhD; W. Marks, MD;
J. Felicetta, MD; M.L. Tomyanovich, MD; and the VA Cooperative Study 428 Group

NEUROLOGY 2005;64:1868–1873
VA Cooperative Study

- Multicenter, randomized, double blind study of 593 elderly patients with new onset seizures
- Patients 60 or older were randomized to GBP, LTG, or CBZ
- Primary outcome: retention in the study for 12 months (as a measure of efficacy and tolerability)
- Secondary outcome: seizure freedom
VA Cooperative Study

- Retention better for LTG > GBP > CBZ
- No difference in rates of seizure freedom between groups
- Excluding dose titration phase, seizure freedom rate 63% at one year
Management of Bone Health

- Guidelines AES 2002
  - General measures for those on AEDs > 6 months and no evidence of osteoporosis
    - Optimize physical activity
    - Maintain balanced nutrition
    - Cessation of smoking
    - Moderation in alcohol and caffeine consumption
    - Take 1200-1500 mg of calcium and 400 IU of Vitamin D daily

Management


• **Specific Measures**
  - Identify those at risk
  - Monitor serum Ca, AP, Vitamin D levels yearly
  - If levels abnormal or a history of fractures, obtain DEXA scan
  - If BMD reduced > 2.5 SD below mean consider bisphosphonates or high dose Vitamin D and obtain endocrinology consult
  - If BMD b/w 1-2.5 SD below mean consider higher dose Vitamin D or bisphosphonates after consultation with endocrinologists
  - Consider AED change
Final Comments

- Epilepsy is a chronic neurological disorder affecting 1-2% of the population.
- Epilepsy is a disorder associated with significant social and economic costs.
- Better diagnostic modalities and management strategies are having a very positive effect on improving the quality of life in patients with epilepsy.