Comorbidities, Mortality, and SUDEP

Lara Jehi, MD
Epilepsy Center
Cleveland Clinic

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• Guest editor for Neurotherapeutics

"Epilepsy is a chronic disorder characterized by recurrent seizures, which may vary from a brief lapse of attention or muscle jerks, to severe and prolonged convulsions."
Outline

- Psychiatric co-morbidities:
  - Epidemiology
  - Mechanisms and contributing factors
- Functional limitations
- Mortality
Outline

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  - Epidemiology
  - Mechanisms and contributing factors
- Functional limitations
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Psychiatric Comorbidities with Epilepsy

- Frequent finding: lifetime prevalence of depression and anxiety disorders 30%-35%
- Associated with worse response to AEDs and surgery and worse medication tolerance
- Affective disorders increase the completed suicide risk by 32-fold


Major correlation between depression and quality of life

Prevalence of Psychiatric Disorders in adult epilepsy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>In epilepsy (range)</th>
<th>In the general population (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>11-60%</td>
<td>2.0-4.0%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19-45%</td>
<td>2.5-6.3%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2-8%</td>
<td>0.5-0.7%</td>
</tr>
<tr>
<td>ADHD</td>
<td>25-30%</td>
<td>2.0-10.0%</td>
</tr>
</tbody>
</table>


Prevalence of Psychiatric and Behavioral Comorbidities

- Population-based, retrospective study
  - Incident cases of epilepsy (1980-1995)
  - Rochester, MN
- Prevalence
  - DSM-IV diagnosis: 51% (69/104)
  - Without mental retardation and/or pervasive developmental disorder: 40.4% (44/109)
- Children with newly diagnosed epilepsy frequently exhibit comorbid psychiatric or behavioral disorders


Prevalence of Psychiatric Disorders in pediatric epilepsy

2007 survey: 977 of 91,605 reported epilepsy/seizures

- Children with epilepsy/seizures
  - Depression (8 vs 2%)
  - Anxiety (17 vs 3%)
  - ADHD (23 vs 6%)
  - Conduct problems (16 vs 3%)
  - DD (51 vs 3%)
  - ASD (16 vs 1%)
  - Headache (14 vs 5%)

Epidemiology of psychiatric comorbidities

1- Higher prevalence in epilepsy

Epilepsy and Psychiatric Disorders: A Bidirectional Relation

• With epilepsy, significantly higher risk for developing:
  – Psychosis
  – Depression
  – Anxiety disorders
  – Suicidality

• With psychiatric disorders, significantly higher risk for developing epilepsy

• Psychiatric disorders not simply a reaction to psychosocial obstacles!

Hesdorffer, Ann Neurol, 2012

Epilepsy and Attention Deficit Hyperactivity Disorder (ADHD)

<table>
<thead>
<tr>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>ADHD                          5%</td>
</tr>
<tr>
<td>Epilepsy                      1%</td>
</tr>
<tr>
<td>ADHD in epilepsy              20%</td>
</tr>
<tr>
<td>ADHD in patients with epilepsy treated with AED 30%</td>
</tr>
</tbody>
</table>

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Psychiatric Disorders and Epilepsy
Bidirectional Relation: Neurobiological/Pathogenesis

- Neurotransmitters: serotonin, norepinephrine, dopamine, glutamate, GABA
- Endocrine: hyperactive hypothalamic-pituitary-adrenal axis producing high cortisol
- Inflammatory mechanisms

Kanner, Annals of Neurology, 2012

Epidemiology of psychiatric comorbidities
1. Higher prevalence in epilepsy
2. Bi-directional relationship with epilepsy

ADHD and Childhood Epilepsy
- ADHD in children
  - Up to 87% have ≥ 1 additional psychiatric disorder
- ADHD and epilepsy
  - Predominately inattention type
  - Differential diagnosis
    - Medical effect
    - Nocturnal seizures
    - Absence or complex partial seizures
  - Comparison with ADHD seen in psychiatric clinics
    - Children with epilepsy more inattentive
    - Equal male:female ratio

Epidemiology of psychiatric co-morbidities:
Main bullet points
1. Higher prevalence in epilepsy
2. Bi-directional relationship with epilepsy
3. Unique clinical features

Outline
• Psychiatric co-morbidities:
  – Epidemiology
  – Mechanisms and contributing factors
• Functional limitations
• Mortality

Mechanisms
• Common structural, biochemical abnormalities: bidirectional relationship
• Psychosocial limitations:
  – Fear of injury
  – Driving
  – Memory and cognitive challenges
• Medication effects
Unique treatment challenges...

1- medication choice

**Medication Effects on Seizures**

- Increase in seizures with antidepressants: amoxapine, maprotiline, clomipramine, bupropion
- Protective effect for unprovoked seizure: SSRIs (unless toxic)
  - Fluoxetine, citalopram: protective effect (animal models)
- High risk de novo seizures: 2nd generation antipsychotics: clozapine, olanzapine, quetiapine
- Stimulants: no seizure increase, unless toxic
Seizure Risks of Newer-Generation Antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Seizure Risk</th>
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</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>Sertraline, paroxetine, etc.</td>
<td>0.1% - 4.2%</td>
</tr>
<tr>
<td>SNRI</td>
<td>Duloxetine</td>
<td>0.3%</td>
</tr>
<tr>
<td>Third-rate antidepressant</td>
<td>Bupropion HCl (450 mg/day)</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>Bupropion HCl (400 mg/day)</td>
<td>0.4%</td>
</tr>
<tr>
<td></td>
<td>Bupropion HCl (300 mg/day)</td>
<td>0.4%</td>
</tr>
<tr>
<td>Third-rate antidepressant</td>
<td>Mirtazapine</td>
<td>0.1%</td>
</tr>
</tbody>
</table>


Unique treatment challenges..

1. medication choice
2. suicidality
Epilepsy, AEDs and Suicidality (FDA Alert; January 2008)

AEDs: Suicidal thoughts/behavior risk: 0.43 vs. 0.22 (pbo)
- Estimated 2/1000 more patients on AEDs vs. PBO
- Not specific to single drug or class

Recommendations: Class warning.
- Balance risk for suicidality with clinical need for AED
- Be aware of possibility of emergence or worsening of depression, suicidality, or unusual changes in behavior
- Inform patients, their families, and caregivers of the potential
- Symptoms such as anxiety, agitation, hostility, mania and hypomania may be precursors to emerging suicidality.

Twenty Leading Causes of Death Highlighting Suicide Among Persons Ages 10 Years and Older, United States, 2006

In 2006, suicide was ranked as the 11th leading cause of death among persons ages 10 years and older, accounting for 33,289 deaths.

Epilepsy and Suicidality: unique features to epilepsy

Encompasses
- Completed suicide
- Suicide attempt
- Suicidal ideation
- 3x suicide causing death
- Bidirectional relationship (suicidality 5x risk epilepsy)

Kanner, 2009
Suicidality with various AEDs


AEDs and Suicidality

FDA Alert

Questions Remain –
1) Assessment based on “spontaneous reports”
2) Risk associated with all AEDs, but significant with only TPM and LTG
   - Adding 3 additional LTG studies lost significance
   - VPA and CBZ demonstrated “small protective effect”
3) Most epilepsy trials adjunctive therapy
4) Geographic differences

Consider results with caution

Epilepsy and Suicidality

- History of attempt strongest predictor
  - 34.8% attempts, later successful
  - 46.2% successful with prior attempts

- Comorbid psychiatric disorders increased risk 14x
  - Mood – 32x
  - Anxiety – 12x

- Risk greatest 1st 6 months following diagnosis of epilepsy

Kanner, 2009
Epilepsy and Suicidality Recommendations

Identify psychiatric disorders
Neurologists not expected to manage

Most frequent associated risks:
Current or past history of mood/anxiety disorder
Family psychohistory of mood disorder; particularly suicidal behavior
Past suicide attempts

Document Assessment
Review
Referral

Psychiatric Comorbidities with Epilepsy

- Persons with epilepsy need screening throughout lifetime, particularly with
  - Medication changes
  - Life changes
  - Pregnancy/postpartum
- A barrier to successful epilepsy management
- A public health challenge

Cleveland Clinic
Kanner, 2009
Willmore, Pellock, 2009

Cleveland Clinic
Psychiatric Comorbidities with Epilepsy

- Persons with epilepsy need screening throughout lifetime, particularly with
  - Medication changes
  - Life changes
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Cleveland Clinic
Kanner, 2009
Willmore, Pellock, 2009

Epilepsy
FUNCTIONAL STATUS:
WORKING
DRIVING
COGNITIVE:
Memory
Language
Mood
EPILEPSY
SEIZURES
Outline

- Psychiatric co-morbidities:
  - Epidemiology
  - Mechanisms and contributing factors
- Functional limitations
- Mortality

Functional Limitations:

1. Driving

- Minimum required seizure-free period varies by state
- Responsibility for mandatory reporting varies by state

Know your state’s law

Commercial Driving License

- The U.S. Department of Transportation (DOT) regulations bar people with a diagnosis of epilepsy or medical history of seizures from driving trucks in interstate commerce (Title 49 of the Code of Federal Regulations Part 391 “Federal Carrier Safety Regulations”).
- The regulations only cover truckers who cross state lines as part of their job and those who transport products within a state that originated in another state.
Special circumstance that may allow safe and legal driving in PWE

1. Established pattern of exclusively nocturnal seizures
2. Reliable and sufficiently long aura that allows for PWE to safely stop driving should an aura occur while driving
3. Earlier return to driving if seizure occurs as a part of prescribed medication adjustment (not as a result of noncompliance)
4. Established seizure that does not impair the ability to drive (e.g., simple partial sensory seizure)

*Some states in the United States allow for these special circumstances, other do not. Check local laws and regulations. PWE—people with epilepsy.

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States requiring mandatory reporting to driving authorities for PWE and new-onset seizures

- Pennsylvania
- California
- Nevada
- Oregon
- New Jersey

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Mandatory reporting

- Major medical organizations that have publicly opposed mandatory reporting:
  - American Medical Association
  - Epilepsy Foundation of America
  - American Epilepsy Society.
**Functional Limitations:**

2- Flying

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Federal Aviation Administration neurologic standards for pilot certification

1. No established diagnosis of epilepsy
2. No disturbance of consciousness without satisfactory medical explanation of the cause
3. No transient loss of control of a nervous system function, without satisfactory medical explanation of the cause
4. No other seizure disorder or neurologic condition that the Federal Air Surgeon, based on the case history and appropriate qualified medical judgment, finds that disqualifies the person from being able to safely perform the duties of a class 1 pilot

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Counseling topics for PWE who are about to travel, especially by airplane

1. Remind about importance of medication compliance
2. Avoid travel plans that may promote sleep deprivation
3. Avoid alcohol
4. Consider prescribing “rescue” benzodiazepine
5. Consider preflight use of benzodiazepine, especially in a patient with frequent seizures and/or fear of flying (consider possible supervision with a travel companion)
6. Remind to take adequate medication to last the duration of the trip in their original package/bottle
7. Avoid medication changes just prior to travel
8. Remind that any new medications/over-the-counter treatments used on the trip potentially may exacerbate seizures or interact with their current therapy
9. If a vagal nerve stimulator is used, give a letter explaining the presence of the device and recommend patient avoid metal detectors when passing through security
10. Suggest the patient obtain a “medic alert” piece of jewelry or carry a brief synopsis of their diagnosis and condition along with emergency contacts
Functional Limitations:
3- Disability

Social Security’s five-step process to determine if an epilepsy patient qualifies for SSDI

- 1. Determine if an individual is “working (engaging in substantial gainful activity)” according to the SSA definition. (> $1,040/month)
- 2. Conclude the epilepsy disability must be severe enough to significantly limit one’s ability to perform basic work activities needed to do most jobs.
- 3. Epilepsy is evaluated under the neurological body system – medical listing 11.02 and 11.03.
- 4. Explore the ability of an individual to perform work they have done in the past despite their epilepsy.
- 5. Review age, education, work experience and physical/mental condition to determine what other work, if any, the person can perform.

Children

- Convulsive epilepsy: (definition)
- at least one detailed description of a typical seizure.
- Report of recent documentation should include a neurological examination with frequency of episodes and any associated phenomena substantiated.
- documentation of seizures during non-febrile periods is required.
- Convulsive episodes have persisted more than three months after prescribed therapy began.

http://www.ssa.gov/disability/professionals/bluebook/111.00-Neurological-Childhood.htm
Section 111.02
Major Motor Seizure Disorder

• A. Convulsive epilepsy.
  – In a child with an established diagnosis of epilepsy, the occurrence of more than one major motor seizure per month despite at least three months of prescribed treatment. With:
    • 1. Daytime episodes (loss of consciousness and convulsive seizures); or
    • 2. Nocturnal episodes manifesting residuals which interfere with activity during the day.

http://www.ssa.gov/disability/professionals/bluebook/111.00-Neurological-Childhood.htm

Section 111.02
Major Motor Seizure Disorder

• B. Convulsive epilepsy syndrome.
  In a child with an established diagnosis of epilepsy, the occurrence of at least one major motor seizure in the year prior to application despite at least three months of prescribed treatment. And one of the following:
  – 1. IQ of 70 or less; or
  – 2. Significant interference with communication due to speech, hearing, or visual defect; or
  – 3. Significant mental disorder; or
  – 4. Where significant adverse effects of medication interfere with major daily activities.

http://www.ssa.gov/disability/professionals/bluebook/111.00-Neurological-Childhood.htm

Children

• Nonconvulsive epilepsy. (definition)
  • Classical petit mal seizures must be documented by characteristic EEG pattern, plus information as to age at onset and frequency of clinical seizures.
  • Myoclonic seizures, whether of the typical infantile or Lennox-gastaut variety after infancy, must also be documented by the characteristic EEG pattern plus information as to age at onset and frequency of seizures.

http://www.ssa.gov/disability/professionals/bluebook/111.00-Neurological-Childhood.htm
Section 111.03
Non-convulsive Epilepsy

• In a child with an established seizure disorder, the occurrence of more than one minor motor seizure per week, with alteration of awareness or loss of consciousness, despite at least 3 months of prescribed treatment.

http://www.ssa.gov/disability/professionals/bluebook/111.00-Neurological-Childhood.htm

Adults

• Epilepsy (definitions):
• In epilepsy, regardless of etiology, degree of impairment will be determined according to type, frequency, duration, and sequelae of seizures.
• At least one detailed description of a typical seizure is required. Such description includes:
  – the presence or absence of aura,
  – tongue bites,
  – sphincter control,
  – injuries associated with the attack,
  – and postictal phenomena.

Adults

• Testimony of persons other than the claimant is essential for description of type and frequency of seizures if professional observation is not available.
• Impairment persists despite the fact that the individual is following prescribed antiepileptic treatment.
• Adherence (medication blood levels) need to be documented.
• If AED levels are low, adequate work-up needs to be documented.
Section 11.02
Convulsive Epilepsy

• *convulsive epilepsy, (grand mal or psychomotor), documented by detailed description of a typical seizure pattern, including all associated phenomena; occurring more frequently than once a month, in spite of at least 3 months of prescribed treatment.* With:
  • A. Daytime episodes (loss of consciousness and convulsive seizures) or
  • B. Nocturnal episodes manifesting residuals which interfere significantly with activity during the day.

Section 11.03
Non-convulsive Epilepsy

• *petit mal, psychomotor, or focal), documented by detailed description of a typical seizure pattern including all associated phenomena, occurring more frequently than once weekly in spite of at least 3 months of prescribed treatment.*
  • With alteration of awareness or loss of consciousness and transient postictal manifestations of unconventional behavior or significant interference with activity during the day.

Disability evaluations:
Main bullet points

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convulsive Epilepsy</td>
<td>≥ 1/month</td>
<td>≥ 1/month</td>
</tr>
<tr>
<td>Non-convulsive Epilepsy</td>
<td>≥ 1/week</td>
<td>≥ 1/week</td>
</tr>
</tbody>
</table>

Both require at least 3 months of AED treatment
Both require daytime dysfunction (either seizures or postictal manifestations)
Additional exceptions for convulsive epilepsy syndromes:
min 1/2/year
Outline

• Psychiatric co-morbidities:
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Long-Term Mortality in Childhood-Onset Epilepsy

Figure 1. Cumulative Risk of All Epilepsy-Related Deaths and Sudden, Unexplained Deaths in Children with Epilepsy. Data shown are for patients at risk (i.e., receiving medications, with or without 3-year seizure remission).

Figure 2. Cumulative Rates of Death According to Cause of Epilepsy. A febrile symptomatic cause indicates epilepsy that is associated with a major neurological abnormality or event.
Definition

- SUDEP has been defined as the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure, with exclusion of documented status epilepticus, and when post-mortem examination does not reveal a structural or toxicological cause for death.
Incidence rates of SUDEP in 26 studies in different epilepsy populations


Quotable risks of SUDEP

- **Overall rate of sudden unexpected death in people with epilepsy is more than 20 times higher than in the general population.**  
  
  - Incidence rates:
    - 0.09 to 0.35 per 1000 person-years: unselected cohorts of incident cases of epilepsy,  
    - 0.9 to 2.3 per 1000 person-years: general epilepsy populations  
    - 1.1 to 5.9 per 1000 person-years: chronic refractory epilepsy  
    - 15-24 and 6.3 to 9.3 per 1000 person-years in epilepsy surgery candidates or in patients who continue to have seizures after surgery  
  
  - In patients with **chronic refractory epilepsy** who attend epilepsy referral centres, SUDEP is the leading cause of premature death, accounting for 10–50% of all deaths.  

### SUDEP risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.42</td>
</tr>
<tr>
<td>Onset age &lt;16 years</td>
<td>1.72</td>
</tr>
<tr>
<td>Duration of epilepsy &gt;15 years</td>
<td>1.95</td>
</tr>
<tr>
<td>Polytherapy</td>
<td>1.95</td>
</tr>
<tr>
<td>GTCS frequency per year</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>5.07</td>
</tr>
<tr>
<td>at least 3</td>
<td>15.46</td>
</tr>
<tr>
<td>unknown</td>
<td>5.35</td>
</tr>
<tr>
<td>GTCS frequency/year and AED therapy</td>
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<tr>
<td>1-2 or unknown=0-1 AED</td>
<td>4.46</td>
</tr>
<tr>
<td>≥3 or unknown= polytherapy</td>
<td>9.18</td>
</tr>
<tr>
<td>≥3 GTCS ≥0-1 AED</td>
<td>13.49</td>
</tr>
<tr>
<td>≥3 GTCS ≥0-1 AED</td>
<td>22.64</td>
</tr>
</tbody>
</table>
THANK YOU!