Clinical Challenges in Epilepsy
The Role of Comorbidities in Diagnosing and Treating People with Epilepsy and Seizures

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DISCLOSURES

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DISCLOSURES

Kathalene Cassels, PA-C is a consultant for SK Pharmaceuticals and a speaker for Livanova/VNS.

OBJECTIVES

- Identify 3 types of comorbidities that may affect diagnosis and treatment of epilepsy.
- Identify 2 ways that misdiagnosis of emotional health conditions may impact treatment of seizures in a person with suspected epilepsy.
- Implement referrals to community agencies and epilepsy professionals for programs to manage or support emotional health comorbidities in people with epilepsy.

OUTLINE

- Pre-tests
- Basics of epilepsy and treatment
- Types of comorbidities in epilepsy
- Diagnosing epilepsy
- Treating seizures and depression
- Integration/coordination of care
- Post-tests
Question 1:
What is the most frequent psychiatric comorbidity of epilepsy?

a) ADHD  
b) Anxiety  
c) Depression  
d) Psychosis

Question 2:
What should be done when a person with poorly controlled epilepsy has a worsening of mood?

a) Start an antidepressant first  
b) Refer to an epilepsy specialist or epilepsy center to evaluate seizures, mood and treatment options for both  
c) No changes but follow up more closely  
d) Change the anti-seizure medication

Question 3:
How likely would you be to refer a person with epilepsy to community agencies or professionals to manage or support emotional health comorbidities?

a) Unlikely  
b) Neutral  
c) Likely  
d) I don’t currently treat people with epilepsy
IMPORTANCE OF RECOGNIZING AND TREATING COMORBIDITIES IN EPILEPSY CARE

WHY ARE COMORBIDITIES IMPORTANT?

- Epilepsy is the 4th most common neurological disorder in the U.S., but is vastly misdiagnosed or undertreated in many communities.

- Other medical conditions/comorbidities
  - Lead to misdiagnosis or delayed access to appropriate care
  - Affect care of persons with epilepsy
  - Are often the reason a person presents to health care provider
  - May affect quality of life for persons with epilepsy

EPILEPSY – WHAT IS IT?

- Not a single entity or disease but a family of syndromes

- Defined as:
  - 2 or more unprovoked seizures > 24 hours OR
  - 1 seizure with risk of recurrent seizures OR
  - Diagnosis of an epilepsy syndrome OR
  - Tendency to have unprovoked recurring seizures, not caused by any known medical condition

- The term “epilepsy” = “seizure disorder”, but seizures are not always due to epilepsy

HOW COMMON IS EPILEPSY?

- Prevalence of active epilepsy
  - ~3.4 million in U.S with epilepsy (self report)\(^1\)\(^-\)\(^3\)
  - 50 million worldwide
- Cumulative incidence of epilepsy increases with age
  - Risk of developing epilepsy increases from 1% by age 20 to 3% by age 75-80\(^4\)
  - Risk of having a seizure is 10% by age 75 to 80
- Each year
  - 300,000 have a first convulsion
  - 150,000 – 200,000 new cases of epilepsy diagnosed
- **1 in 26 people will develop epilepsy during their lifetime**\(^4\)

CAUSES OF EPILEPSY

Symptomatic 30%

- Brain injury at birth
- Brain lesions (tubers, tumors)
- Congenital malformations
- Past head injury, trauma, stroke
- Infections of the brain
- Metabolic problems
- Other neurological conditions

TYPES OF COMORBIDITIES IN EPILEPSY

- Cognitive (Thinking, Memory, Learning)
- Attention deficit disorder, Autism, Dementia
- Developmental delay, Intellectual disabilities
- Sleep Disorders
- Physical disabilities (weakness, difficulty walking, poor balance or coordination)
- Sleep Disorders
- Injuries
- Traumatic Brain Injury (TBI)
- Migraines, MS
- Depression, Anxiety, Other Mental Disorder
- Physical disabilities (weakness, difficulty walking, poor balance or coordination)
PREVALENCE OF COMORBIDITIES IN ADULTS WITH EPILEPSY

Mental health comorbidities

- Prevalence of any mental health disorder in past 12 months
  - 23.5% - with epilepsy
  - 10.9% - without epilepsy
- Lifetime prevalence suicidal ideation
  - 25% - with epilepsy
  - 13.3% - without epilepsy

Physical comorbidities

- Greater in people with epilepsy
  - Any heart disease, HTN
  - Stroke
  - Overweight/obesity
  - Respiratory problems
  - Arthritis
  - Pain, headache, migraine
  - Ulcer
- People with epilepsy more likely to have 4 or > medical comorbidities

SEIZURE THRESHOLDS AND TRIGGERS

Seizure Threshold

Seizure Tendency

Time

Alcohol

Menses

Stress

Illness

Missed Medication

Illness

Adapted with permission: Susannah Cornes MD, UCSF
Michael Privitera MD, U. Cincinnatti

WHAT ARE THE GOALS OF EPILEPSY CARE?

- “No seizures, no side effects”
- Prevention and treatment of comorbidities
- Prevention of mortality
- Cure versus resolved epilepsy
CAN EPILEPSY BE CONTROLLED?

- ~60% of people with new onset epilepsy respond to the first few AEDs.
- People with symptomatic causes of epilepsy more likely to have persistent seizures:
  - Traumatic brain injury
  - Stroke
  - Tumor
- Comorbidities may delay diagnosis

<table>
<thead>
<tr>
<th>% Seizure Free</th>
<th>Responded to 1st AED</th>
<th>Responded to 2nd AED</th>
<th>Responded to 2 or more AEDs</th>
<th>Seizures Not Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>47%</td>
<td>36%</td>
<td>14%</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>


WHAT IS DRUG RESISTANCE?

- Drug resistant epilepsy occurs when seizures continue despite at least 2 medication trials with appropriate drugs tried for appropriate length of time.
- Can not be determined until diagnosis of epilepsy and type is confirmed, other factors that may affect seizure control assessed, and appropriate medication trials assessed.


EARLY DEATH IN EPILEPSY

- Causes of early death:
  - Status epilepticus
  - Complications of seizures
  - Accidents and drowning
  - Drug reactions
  - Suicide
  - SUDEP
- SUDEP - Sudden Unexpected Death in Epilepsy
  - No obvious cause for death
  - Affects 1 of 1,000 adults & 1 of 4,500 children each year
  - Highest risk in people with uncontrolled seizures; > 3 tonic clonic seizures a year, seizures at night

SUDEP guidelines, AES/AAN, 2017 (http://www.neurology.org/content/88/17/1674.full)
CLINICAL CHALLENGE: IS IT EPILEPSY?

CASE SCENARIO

- A 36 year old male, moderately overweight
- Episodes of ‘passing out’, behavioral outbursts and sleep problems
- Onset 2 years ago, thought to be seizures
  - Routine EEG and CT scan normal
  - Treated initially with levetiracetam – episodes loss of consciousness persist, behavioral problems worse
- Presents to clinic for routine checkup

What is the next step in his care?

- Obtain detailed description of events
- View any home video obtained of events
- Screen for other health problems
- Obtain blood level of levetiracetam
- Order brain MRI
- Refer to comprehensive epilepsy center
WHAT ARE THE QUESTIONS?

- Are any of the symptoms a seizure?
- Is this epilepsy, and what is the cause?
- Is more than one problem present?
- Are there triggers to the events?
- What needs to be addressed first?

**The Role of Comorbidities in Diagnosing and Treating Epilepsy**

- Occasional seizures
- Mild co-morbidities
- Persistent seizures
- Moderate to severe co-morbidities

**Referral to Epileptologist/Epilepsy Center**

- Health care specialists for co-morbidities

**Suspected Seizure**

- Evaluation in emergency room, by primary care provider, or by neurologist
- Seizure not confirmed
- No second seizure

- Seizure confirmed
- Second seizure
- Referral to neurologist
- Seizures controlled
- No co-morbidities
- Follow-up neurology and primary care

**Seizure not confirmed**

- Persistent seizures
- Moderate to severe co-morbidities

- Occasional seizures
- Mild co-morbidities

- Referral to Epileptologist/Epilepsy Center

**IS IT A SEIZURE?**

- A seizure is...
  - Symptom of a disturbance in the brain
  - Sudden surge of abnormal electrical discharges from complex chemical changes in brain cells
  - Can be manifestation or symptom of many medical problems
  - Provoked seizures
  - Unprovoked seizures
ARE THE SEIZURES UNPROVOKED?

- Provoked
  - Seizure provoked by an acute insult or injury to the brain or another medical condition
  - Seizures do not recur after the acute illness or has resolved
- Do we have enough information to rule out provoked seizures? (Initial work-up already ruled out infectious/metabolic causes.)
  - Yes
  - No

WHEN IS IT NOT EPILEPSY?
NONEPILEPTIC EVENTS OR SEIZURES

Physiologic
- Syncope
- Migraine
- Cardiac rhythm disorders
- Sleep disorders
- Movement disorders
  - Responds to treatment of physiological condition

Psychogenic
- Events often atypical
- Not associated with epileptiform brain activity
- Often not at conscious level
- Often associated with history of trauma or abuse
  - Treatment options: cognitive behavioral therapy, treatment of psychological/behavioral problems

NEXT STEPS IN DIFFERENTIAL DIAGNOSIS

- History and observation of events
- MRI for any adult with new-onset seizures or difficult to diagnose*
- Physical/Neurological exam – look for focal deficits
- Assess for cardiac disorders
  - EKG, Holter monitor
- Assess for sleep disorder
  - Sleep history
  - Sleep tests – when should this be done?

*Fountain NB. Neurology. 2015;84:1483-87*
The Role of Comorbidities in Diagnosing and Treating Epilepsy

**HOW USEFUL ARE EEGS?**

- **Routine** – normal EEG does not rule out epilepsy
- **Sleep deprived** – increases likelihood of interictal activity and precipitating events in people with poorly controlled seizures
- **Ambulatory EEG monitoring** – records spontaneous events, typically not used with medication withdrawal; may record up to 3 days or longer; higher yield of interictal abnormalities
- **Video-EEG long term monitoring** – best to record episodic events; correlates video, audio and EEG of recorded events; able to compare to reports of typical events; gold standard for establishing diagnosis of nonepileptic seizures

**REFERRING PATIENTS TO AN EPILEPSY MONITORING UNIT**

- **When to Refer**
  - Diagnosis is unclear or treating nonepileptic seizures
  - Seizures persist after one year from diagnosis
  - Seizures are not controlled after 2 or more trials with appropriate AEDs
  - Surgery or other therapies are being considered
- **Other Consultations**
  - AED withdrawal in person who is seizure free
  - Change from old to new generation AEDs
  - Pregnancy counseling/management
FINDINGS: Results of EMU Testing

- Episodes loss of consciousness:
  - Cardiac arrhythmia noted prior to onset, corrected with pacemaker
- Behavioral changes: improved with tapering off levetiracetam
- Sleep problems: O2 desaturations on pulse oximetry, suggestive of sleep disordered breathing
- Diagnoses: seizure provoked by cardiac arrhythmia, possible sleep disorder

CASE SCENARIO: Treating Epilepsy and Emotional Health

- 18 year old female, involved in MVA, first seizure on scene
- Initially placed on valproate sodium/valproic acid, seizure free for 6 months, taken off medicine
- Seizures recurred, seen in ER, valproate sodium restarted
- Parents concerned about depressed mood, socially withdrawn, declining grades
CASE SCENARIO: Treating Epilepsy and Emotional Health

- What would you do?
  - Work up as new patient
  - Continue current treatment
  - Consider change in treatment
  - Refer directly to an epilepsy center

IS SHE ON THE RIGHT ANTI-SEIZURE DRUG (ASD)?

- Seizure type/syndrome
- Age and gender
- Side effect profile
- Safety in different ages
- Easy to use
- Impact on reproduction
- Impact on cognition, mood, behavior, weight, bone health

Commonly used ASDs in epilepsy for young adults
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Topiramate

INITIAL DRUGS FOR EPILEPSY - USA

- 1857 bromides
- 1912 phenobarbital
- 1937 phenytoin
- 1954 trimethadione
- 1964 primidone
- 1960 ethosuximide
- 1974 carbamazepine
- 1975 clonazepam
- 1975 valproate

- 1975 carbamazepine
- 1975 clonazepam
- 1975 valproate
NEWER DRUGS FOR EPILEPSY - USA

- 1993: felbamate, gabapentin
- 1994: lamotrigine, topiramate
- 1995: levetiracetam
- 1996: oxcarbazepine, tiagabine
- 1997: gabapentin, zonisamide
- 1999: levetiracetam
- 2000: oxcarbazepine, zonisamide
- 2005: pregabalin
- 2006: gabapentin, zonisamide
- 2007: lacosamide
- 2008: gabapentin, zonisamide
- 2009: rufinamide, vigabatrin, lacosamide
- 2011: clobazam
- 2012: perampanel
- 2013: eslicarbazepine
- 2014: brivaracetam
- 2015: perampanel
- 2016: brivaracetam

ASSESSING MOOD AND BEHAVIOR

- Interview and exam
- Screening tools
  - Relevance for epilepsy
  - Sensitivity to ASD
  - Neurological Disorders Depression Inventory in Epilepsy (NDDI-E)
  - Patient Health Questionnaire-2 (PHQ-2)
- Differentiating seizure behaviors from traumatic brain injury (TBI) symptoms
- Are mood symptoms due to:
  - TBI symptoms
  - Side effects of ASD
  - Adjustment disorder
  - Co-existing depression
- Which came first?
- Should patient be referred to psychiatry?

PREVALENCE OF PSYCHIATRIC DISORDERS IN PEOPLE WITH EPILEPSY

<table>
<thead>
<tr>
<th>Disorder</th>
<th>In Epilepsy (Range)</th>
<th>In the General Population (Range)</th>
</tr>
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<tbody>
<tr>
<td>Depression</td>
<td>11-60%</td>
<td>12-15%*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19-45%</td>
<td>2.5-6.5%*</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>2-10%*</td>
</tr>
</tbody>
</table>

*Kessler RC, et al. Arch Gen Psychiatry. 1994;51(1);8-19.

(From LaFrance & Kanner. 2006. Epilepsy. In The Asp. Of Epilepsy.)
DEPRESSION IN EPILEPSY

- Most frequent psychiatric comorbidity
  - 10-20% of people with controlled epilepsy
  - 20-60% in people with refractory epilepsy
- Bidirectional relationship
  - Depression may increase risks of epilepsy
  - Epilepsy may increase risk of depression
  - Should depression be treated?
    - YES
  - Avoid misconception that all antidepressants increase risk of seizures.

MOST ANTIDEPRESSANTS ARE SAFE TO USE IN PEOPLE WITH EPILEPSY

- SSRIs and SNRIs - safe in people with epilepsy when used at therapeutic doses.
- 4 antidepressants can facilitate seizures at therapeutic doses: clomipramine, bupropion, amoxapine and maprotiline.
- Choice of SSRI or SNRI - base on adverse effect profile and whether depression and anxiety co-exist
- Failure to reach remission of symptoms after trial with an SSRI at optimal doses - switch to an SNRI and vice versa.

Proposed Algorithm for Depression in Epilepsy:
Stages of Medical Therapy

Stage 1: Monotherapy – SSRI (eg. Citalopram, escitalopram), venlafaxine, or mirtazapine and/ or CBT

Partial response or nonresponse → possible augmentation agents

Stage 2: Monotherapy – switch to another agent

Send to psychiatry for additional trials and options

*From Kanner AM. A Epilepsy Behav 2016;61:182-86
DRUG INTERACTIONS: Antidepressants and AntiSeizure Drugs

- Start low doses and go slow
- Watch for side effects
- Increase seizure activity
- Increased depression

Fluoxetine and Sertraline can increase levels of some ASDs
ASDs can interact with some antidepressants
- Carbamazepine
- Oxcarbazepine
- Phenobarbital, primidone
- Phenytoin
- Lacosamide
- Lamotrigine
- Clobazam

Kanner AM. A Epilepsy Behav 2016;61:182-86

USING SEIZURE MEDICATIONS IN WOMEN WITH EPILEPSY

- Contraception
  - Enzyme inducers and risk for birth control failure
- Use in Pregnancy
  - VPA - Greatest risk of major birth defects and impact on child development
- North American AED Pregnancy Registry
  - 1.888.233.2334
  - www.aedpregnancyregistry.org

1 http://www.epilepsy.com/information/women/all-women/contraception
2 Harden CL et al. Neurology July 14, 2009 vol. 73 no. 2 133-141

COUNSELING AND EDUCATION

- Manage symptoms and impact of depression and epilepsy
- Promote positive coping strategies
- Promote healthy living
- Behavior changes for triggers of seizures and depression
- Individual and family psychotherapy as indicated
MULTICENTER PILOT TREATMENT FOR PSYCHOGENIC NONEPILEPTIC SEIZURES

Key findings from randomized control trial

- **SMC**: No significant seizure reduction or secondary outcome measures
- **Med**: seizure reduction (trend) and depression

N=35 participants

- **CBT-ip**: seizure and symptom reduction, improved function & QOL
- **CBT-ip+med**: seizure reduction, function, QOL, improvement depression

(LaFrance, et al. JAMA Psychiatry 2014;71(9):997-1005.)

WHAT’S NEXT FOR THIS PATIENT

- Epilepsy center referral
- Outpatient evaluation - cognitive and mood testing
- Admission to epilepsy monitoring unit - unwitnessed seizures and focal interictal activity
- Medication changes - begin taper off valproate and start a newer ASD appropriate for age, gender, mood and cognition
- Referred for mental health - follow-up and self-management program for epilepsy and depression
INTEGRATION AND ORGANIZATION OF EPILEPSY CARE

- Patient-centered approaches
- Coordinate and integrate care across settings
- Epilepsy center collaboration with primary care, neurology, community is critical
- Enhance self-management education and support in all settings


HOW TO FIND NEXT LEVELS OF CARE?

- Find an Epilepsy Center
- National Association of Epilepsy Centers
  - http://www.naec-epilepsy.org
- VA Epilepsy Centers of Excellence
  - http://www.epilepsy.va.gov
- American Epilepsy Society
  - http://www.aesnet.org

EPILEPSY SELF-MANAGEMENT EDUCATION

Epilepsy-Specific Management
- Seizures - types, syndromes, triggers
- Diagnosis
- Medications
- Other treatments
- Safety
- Comorbid conditions

Chronic Care Management
- Access to quality care
- Active partnership with health care team
- Maintaining healthy lifestyle
- Independent living

SELF-MANAGEMENT PROGRAMS FOR DEPRESSION AND EPILEPSY

Managing Epilepsy Well Network

PROJECT UPLIFT
Using Practice and Learning to Increase Favorable Thoughts
- Phone and web-based program (10 sessions) for adults with epilepsy
- Uses cognitive behavioral therapy and mindfulness techniques
- Aim: Prevent or reduce depression in people with epilepsy
- Findings:
  - Significantly decreased episodes of major depressive disorder; improved knowledge, skills and life satisfaction

PACES IN EPILEPSY
Program for Active Consumer Engagement in Self-Management
- An in-person and phone/online-based program for adults with epilepsy
- Aim: To improve
  - Comorbid conditions, cognition, stress, depression
  - Community participation
  - Assertive communication
  - Managing care to improve overall well-being
- Findings:
  - Improved self-management skills for managing lifestyle, energy/fatigue, and medication effects
  - Improved self-efficacy and quality of life
PEARLS
Program to Encourage Active, Rewarding Lives for Epilepsy
- An in-home, in-person program
  - For adults with epilepsy who are isolated or with multiple chronic health problems
  - Uses problem-solving treatment, behavioral activation and psychiatric consultation
- Aim: To improve depression and comorbidities
- Results:
  - Significant improvement in depressive symptoms, lower hospitalization rates, health-related QOL
  - In some cases, complete remission of depression

HOBSCOTCH
Home Based Self-management and Cognitive Training Changes Lives
- In-person program for adults with epilepsy
  - Uses problem-solving therapy, memory strategies and self-awareness training
  - Being tested in an online format
- Aim: Improve memory performance and quality of life
- Findings:
  - Improved quality of life and objective memory

TEXTING 4 CONTROL
- A text messaging and online program
  - For people with epilepsy 13 years and older
  - Sends text messages with medication reminders and motivational messages
  - Low cost option to support provider follow-up, especially in rural or lower income areas
- Aim: Medication adherence, self-efficacy, stigma
- Findings: Improved self-efficacy and adherence
MY SEIZURE DIARY

- Track seizures
- Monitor response to treatment
- Identify clusters, use of rescue therapies
- Reminders to improve adherence
- Track medicine usage and side effects
- Keep seizure response plans current
- Share with family and clinicians

MY SEIZURE DIARY

Diary.epilepsy.com

THE ROLE OF COMORBIDITIES IN DIAGNOSING AND TREATING EPILEPSY

EPILEPSY.COM

- Leading website for epilepsy world-wide
- Over 800,000 to 1 million visits monthly
- Content covers spectrum of epilepsy and management needs
- Connect, chats and online forums

EPILEPSY.COM

THE ROLE OF COMORBIDITIES IN DIAGNOSING AND TREATING EPILEPSY

Question 1:
What is the most frequent psychiatric comorbidity of epilepsy?

a) ADHD
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d) Psychosis
EPILEPSY CCCS POST-TEST

Question 2:
What should be done when a person with poorly controlled epilepsy has a worsening of mood?

a) Start an antidepressant first
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EPILEPSY CCCS POST-TEST

Question 3:
How likely would you be to refer a person with epilepsy to community agencies or professionals to manage or support emotional health comorbidities?

a) Unlikely
b) Neutral
c) Likely
d) I don’t currently treat people with epilepsy

CLOSING THOUGHTS

• Early diagnosis and treatment of comorbid conditions may affect the diagnosis and management of seizures/epilepsy

• Physician assistants critical in early recognition and treatment

• Referral to multidisciplinary epilepsy centers have unique capabilities for care of people with epilepsy

• Integration and coordination of care can enhance self-management care and improve quality of life for families living with epilepsy