Advances in Diagnosis, Neurobiology, and Treatment of Neurological Disorders

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Common Psychiatric Comorbidities in Epilepsy: What Every Neurologist Must Know and Do to Properly Treat Patients with Epilepsy

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Learning Objective

Recognize the impact of psychiatric comorbidities on the management of the disorder in patients with epilepsy.
Dr. Kanner has no disclosures to report.
How big of a problem is it?
# Lifetime Prevalence

<table>
<thead>
<tr>
<th>Psychiatric Disorder</th>
<th>Controls (%)</th>
<th>Epilepsy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depressive Disorder</td>
<td>10.7 (10.2–11.2)</td>
<td>17.4 (10.0–24.9)</td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>11.2 (10.8–11.7)</td>
<td>22.8 (14.8–30.9)</td>
</tr>
<tr>
<td>Mood/Anxiety Disorders</td>
<td>19.6 (19.0–20.2)</td>
<td>34.2 (25.0–43.3)</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>13.3 (12.8–13.8)</td>
<td>25.0 (17.4–32.5)</td>
</tr>
<tr>
<td>Any Psychiatric Disorder</td>
<td>20.7 (19.5–20.7)</td>
<td>35.5 (25.9–44.0)</td>
</tr>
</tbody>
</table>

What Type of Psychiatric Symptom Is It?

- **Perictal**
  - Preictal
  - Ictal
  - Postictal

- Interictal

- Depressive and / or Anxiety Episode

- **Iatrogenic**
  - Pharmacologic
  - Surgical
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

Family History
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

Family History
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

Family History
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

Family History

- Mood Disorders
- Anxiety Disorders
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
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- Mood Disorders
- Anxiety Disorders
Psychiatric Comorbidities Over Time

- Mood Disorders
- Anxiety Disorders

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

Family History
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

Family History

- Mood Disorders
- Anxiety Disorders
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

Family History

- Mood Disorders
- Anxiety Disorders

Epilepsy
- Severity
- Type

Time
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

Family History

Epilepsy
- Severity
- Type

Iatrogenic Symptoms
- Pharmacologic
- Surgical

- Mood Disorders
- Anxiety Disorders

Time
Psychiatric Comorbidities Over Time

Family History

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

Epilepsy
- Severity
- Type

Iatrogenic Symptoms
- Pharmacologic
- Surgical

Time
Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy
- Mood Disorders
- Anxiety Disorders

Family History

Epilepsy
- Severity
- Type

Iatrogenic Symptoms
- Pharmacologic
- Surgical

Time
Peri-ictal Episodes...
Ictal Psychiatric Symptoms

- n = 100 pts. with “psychologic auras"
  - n = 21 with depression
  - n = 61 with fear
  - n = 18 with pleasurable or displeasurable emotions

Panic disorder…
or is it ictal panic?
Case Study

- 34 year-old left handed man admitted following a first secondarily GTC
- Evaluated in ER; discharged on no meds. CT scan: read as unremarkable
- For the previous 7 years, the patient had complained of recurrent episodes of a “panic feeling” often associated with nausea lasting up to 1 minute
- After panic episodes, patient usually feels “emotionally exhausted” and had to take a nap

GTC = Generalized tonic seizure
ER = Emergency room
Case Study

- On days when he had a panic episode, concentration was poor.
- Panic episodes occurred in awake (75%) and sleep (25%) states.
- Patient’s primary care physician interpreted the panic symptoms as anxiety disorder and placed him on alprazolam without relief of symptoms.
- Also treated with SSRIs.
Clinical Differentiation Between Panic Disorder and Complex Partial Seizures

<table>
<thead>
<tr>
<th></th>
<th>Panic Disorder</th>
<th>Partial Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness</td>
<td>Usually preserved</td>
<td>Impaired</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Duration of attack</td>
<td>&gt;5 min</td>
<td>&lt;120 seconds</td>
</tr>
<tr>
<td>AEDs</td>
<td>Occasional helpful</td>
<td>Very often helpful</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Helpful</td>
<td>Rarely worsen seizures</td>
</tr>
<tr>
<td>Abnormal sleep-deprived interictal EEG</td>
<td>Usually absent</td>
<td>Often present</td>
</tr>
<tr>
<td>Anticipatory anxiety</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Automatisms</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
</tbody>
</table>

### Number of Patients with Postictal Symptoms by Category

- **N = 100**
- **Depression, n = 43**
  - Postictal suicidal ideation, n = 13
- **Anxiety, n = 45**
- **Psychosis, n = 7**
- **Neurovegetative, n = 62**
- **Cognitive, n = 82**
- **Cognitive without psychiatric, n = 14**
- **No Symptoms, n = 12**
### Postictal Symptoms of Depression

<table>
<thead>
<tr>
<th>Postictal symptom</th>
<th>Frequency (N = 100)</th>
<th>Duration (range, hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Frustration</td>
<td>36</td>
<td>24 (0.5-108)</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>33</td>
<td>24 (0.1-148)</td>
</tr>
<tr>
<td>Hopelessness</td>
<td>25</td>
<td>24 (1.0-108)</td>
</tr>
<tr>
<td>Helplessness</td>
<td>31</td>
<td>24 (1.0-108)</td>
</tr>
<tr>
<td>Crying Bouts</td>
<td>26</td>
<td>6 (0.1-108)</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>13</td>
<td>24 (1.0-240)</td>
</tr>
<tr>
<td>Irritability</td>
<td>30</td>
<td>24 (0.5-108)</td>
</tr>
<tr>
<td>Guilt</td>
<td>23</td>
<td>24 (0.1-240)</td>
</tr>
<tr>
<td>Self depreciation</td>
<td>27</td>
<td>24 (1.0-120)</td>
</tr>
</tbody>
</table>

Any postictal symptom of depression, n = 43 patients
Median number of symptoms: 5 (range: 2-9)

# Postictal Symptoms of Anxiety

<table>
<thead>
<tr>
<th>Symptoms of Anxiety</th>
<th>N = 45</th>
<th>Median Duration (Range in Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant worrying</td>
<td>33</td>
<td>24 (0.5 – 108)</td>
</tr>
<tr>
<td>Panicky feelings</td>
<td>10</td>
<td>6 (0.1 – 148)</td>
</tr>
<tr>
<td>Agoraphobic symptoms</td>
<td>29</td>
<td>24 (0.5 – 296)</td>
</tr>
<tr>
<td><em>Due to fear of seizure recurrence</em></td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Compulsions</td>
<td>10</td>
<td>15 (0.1 – 72)</td>
</tr>
<tr>
<td>Self consciousness</td>
<td>26</td>
<td>6 (0.05 – 108)</td>
</tr>
</tbody>
</table>

Why should neurologists care?
Impact of Depression and Anxiety Episodes

- Increased mortality risk
- Worse tolerance of antiepileptic drugs
- Worse quality of life
- Increased risk of psychiatric iatrogenic adverse events
Impact of Depression and Anxiety Episodes

- Worse seizure control with pharmacotherapy
  - Petrovsky, et al. *Neurology* 2010

- Higher likelihood of persistent seizures after epilepsy surgery with antero-temporal lobectomies
Old Assumption...

- In patients with epilepsy, depressive and anxiety disorders,
  - Are a complication of the seizure disorder
Bidirectional Relation Between Epilepsy and Psychiatric Disorders

- Patients with epilepsy have a 5- to 20-fold higher risk of developing depression

- Patients with depression have a 2- to 5-fold higher risk of developing epilepsy

Are antidepressant drugs safe in patients with epilepsy?
Impact of Mood Disorders and Antidepressant Drugs on the Occurrence of Spontaneous Seizures

- Assessment of seizure incidence between patients randomized to SSRIs, SNRIs, and placebo in regulatory studies
- Antidepressant treatments associated with lower seizure incidence relative to placebo for all SSRIs and SNRIs
- Standardized seizure ratio: 0.48, 95% CI 0.36-0.61
- The incidence of seizures among patients randomized to placebo was 19-fold higher than that of the general population.

Higher Incidence of Seizures in Patients Exposed to Antidepressants than Placebo

- Clomipramine
- Bupropion immediate release (IR)

Glutamate
## Glutamate in Depressive Disorders

- **High** glutamate plasma and CSF concentrations
- Dysfunction of glutamate transporter proteins (identified in animal models of depression)
- **Increased** Cortical Glutamate identified in brain MRS
- Antidepressant effects of NMDA antagonists
GABA Disturbances

- **Decreased** CSF concentrations
- **Decreased** cortical concentrations in:
  - Post-mortem studies of patients with mood disorders
  - Brain MRS studies
    - Normalization of GABA concentrations has been demonstrated with antidepressant therapy and electroshock therapy
- **Decreased** GABA-A activity identified in studies with TMS:
  - Reduced silent period
  - Reduced intra-cortical inhibition
Impact of ↑HPA
HPA in Patients with Epilepsy

- 16 patients with Temporal Lobe Epilepsy
- 16 patients with Major Depressive Disorder
- 16 healthy controls
- Lack of inhibitory control of the HPA system in patients with epilepsy and major depression.

Relation Between Duration of Depression and Hippocampal Volume Loss in Recurrent Depression

Abnormalities of Frontal Lobe Structures
Structural and Functional Abnormalities in the Frontal Lobe of Patients With Primary Depression

- Structural changes in
  - Orbito-frontal and prefrontal cortex
  - Cingulate gyrus
  - White matter
- Smaller volume of orbito-frontal cortex in young adults and geriatric patients with Major Depressive Disorders
- The magnitude of prefrontal volume changes related to severity of the depression
Neuropathologic Findings in Frontal Lobe Structures in Primary Depression

- Decrease in
  - Cortical thickness
  - Neuronal sizes
  - Neuronal densities in layers II, III, and IV of the rostral orbito-frontal region in the brains of depressed patients

- In the caudal orbito-frontal cortex
  - Significant reductions in glial densities in cortical layers V and VI
  - Associated with decreases in neuronal sizes

- In the dorsolateral prefrontal cortex
  - A decrease in neuronal and glial density and size in all cortical layers
Neuroimaging Changes in Mesial Temporal Lobe Epilepsy are Magnified in the Presence of Depression

- To investigate differences in gray matter volume between patients with mesial temporal lobe epilepsy (MTLE) with and without depression using voxel-based morphometry.
- 96 neurologically healthy adult subjects and 48 people with MTLE participated in this study.
- 24 patients had MTLE with and 24 without major depression.
- The number of areas of gray matter volume loss was higher in patients with MTLE with depression than in those with MTLE without depression.

## Areas with Significantly Greater Cortical Thinning in Depressed Patients with TLE

<table>
<thead>
<tr>
<th>Anatomical Structure</th>
<th>Laterality</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesial structures</td>
<td>Bilateral</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Left</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inferior &amp; superior temp gyrus</td>
<td>Bilateral</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inferior &amp; middle frontal gyrus</td>
<td>Bilateral</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Middle occipital gyrus, cuneus, fusiform gyrus</td>
<td>Left</td>
<td>.016</td>
</tr>
<tr>
<td>Caudate body</td>
<td>Right</td>
<td>.023</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>Left</td>
<td>.03</td>
</tr>
</tbody>
</table>

Identifying patients with epilepsy with depressive and/or anxiety disorders in the outpatient neurology clinic...
# Neurological Disorders Depression Inventory in Epilepsy (NDDI-E)

For the statements below, please circle the number that best describes you over the last two weeks including today.

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>Always or Often</th>
<th>Sometimes</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everything is a struggle</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Frustrated</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nothing I do is right</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Feel guilty</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Difficulty finding pleasure</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>I’d be better off dead</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

A score of > 15 is suggestive of major depressive episode


Generalized Anxiety Disorder-7 (GAD-7)

Please circle the number that best describes you over the last 2 weeks, including today

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>Nearly every day</th>
<th>More than half the days</th>
<th>Several days</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling nervous, anxious or on edge</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Not being able to stop or control worrying</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Worrying too much about different things</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Trouble relaxing</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Being so restless that it is hard to sit still</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Being easily annoyed or irritable</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Feeling afraid as if something awful might happen</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

A score of > 10 is suggestive of generalized anxiety disorder

Treatment...

- Pharmacotherapy
  - Cognitive behavior therapy
  - Both
Principle #1: Make Sure that the Depressive and Anxiety Episodes are Not the Expression of an Iatrogenic Effect…

- Introduction of AED with negative psychotropic properties in vulnerable patients.
- Increase dose of AED with negative psychotropic properties.
- Withdrawal of AED with positive psychotropic properties in vulnerable patients.
- Pharmacokinetic interaction between enzyme-inducing AED and concomitant psychotropic drug.
## AEDs with Psychotropic Properties

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Barbiturates</td>
<td>● Carbamazepine</td>
</tr>
<tr>
<td>● Benzodiazepines</td>
<td>● Valproic acid</td>
</tr>
<tr>
<td>● Levetiracetam</td>
<td>● Oxcarbazepine</td>
</tr>
<tr>
<td>● Topiramate</td>
<td>● Lamotrigine</td>
</tr>
<tr>
<td>● Zonisamide</td>
<td>● Gabapentin</td>
</tr>
<tr>
<td>● Vigabatrine</td>
<td>● Pregabalin</td>
</tr>
<tr>
<td>● Tiagabine</td>
<td>● Benzodiazepines</td>
</tr>
<tr>
<td>● Perampanel</td>
<td></td>
</tr>
</tbody>
</table>
Principle #2: Aims of Pharmacotherapy...

1. Remission of all symptoms of depression and anxiety.
   - Can use screening instrument of symptoms of depression and anxiety

2. Adjust dose of antidepressant drug in the presence of enzyme-inducing antiepileptic drugs
### Pharmacotherapy of Depression and Anxiety Disorders in Epilepsy

<table>
<thead>
<tr>
<th>CLASSICAL</th>
<th>SSRI</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>1st choice Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Paroxetine CR, Sertraline</td>
<td>Bupropion XL</td>
</tr>
<tr>
<td>MAOI</td>
<td>SNRI</td>
<td>NDM</td>
</tr>
<tr>
<td>Phenelzine, Tranylcypromine</td>
<td>Venlafaxine-XR, Duloxetine</td>
<td>Mirtazapine</td>
</tr>
</tbody>
</table>

*In patients with bipolar disorder antidepressant medication should be used with great caution!!!*
## SSRIs and SNRIs with Antidepressant and Anxiolytic Properties

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Depression</th>
<th>Panic disorder</th>
<th>Generalised anxiety</th>
<th>Starting dose</th>
<th>Maximal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>25</td>
<td>200</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Citalopram</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>37.5</td>
<td>300</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>40</td>
<td>120</td>
</tr>
</tbody>
</table>
Psychiatric Comorbidities that Neurologists Should be Able to Provide Pharmacologic Treatment

- Major depressive episode
  - That is not part of a bipolar disorder
- Dysthymic disorder
- Generalized anxiety disorder
- Panic disorder
Psychiatric Comorbidities that Neurologists Should *Not* Provide Pharmacologic Treatment

- Patients with epilepsy with:
  - Bipolar disorder
  - Suicidal risk
  - Major depressive episodes that have failed to remit after two effective trials
  - Psychotic episodes
Can screening for depression and anxiety disorder facilitate their remission?
# Screening for Depression and Anxiety in the Outpatient Epilepsy Clinic

- N = 636 consecutive adults (age >18 old) with epilepsy.
- Normal intelligence.
- All patients completed at each visit:
  - NDDI-E (to identify major depressive episodes)
  - GAD-7 (to identify generalized anxiety disorder)
  - Suicidality of the module of the MINI

Screening for Depression and Anxiety in the Outpatient Epilepsy Clinic

- Six epileptologists reviewed the scores of these screening instruments
- Intervention included:
  - Referral to mental health professional
  - Start or adjust psychotropic drug
  - No change in treatment

Screening for Depression and Anxiety in the Outpatient Epilepsy Clinic

- Changes in NDDI-E, GAD-7 and suicidality module of 115 patients between 2 consecutive visits investigated
- Percentage of patients whose scores of the NDDI-E, GAD and /or suicidality normalized between visits 1 and 2
- Number of patients with de-novo psychopathology at visit 2

### Screening for Depression and Generalized Anxiety Disorder at the Rush Epilepsy Center

- **N = 636 consecutive English-speaking adults**
  - Age: ≥ 18 year-old
  - Gender: 54.5% women

- **NDDI-E >15: 17.1%**
- **GAD-7 >10: 20.8%**
- **Only NDDI-E >15: 5.9%**
- **Only GAD-7>10: 9.6%**
- **Both: 11.2%**

Changes in Psychiatric Comorbidities Between 2 Consecutive Visits

- N = 115
- Duration between the 2 visits: 123 ± 77 days
- Symptomatic on visit 1 with NDDI-E and /or GAD-7: n = 40 (34.7%)
- Symptomatic on visit 2: n = 15 (13%)
- Previous history of depression, n = 25
- Previous treatment for depression, n = 21
- Previous history of anxiety, n = 24
- Previous treatment for anxiety, n = 20

### Changes in NDDI-E, GAD-7 and NDDI-E + GAD-7 Scores Between 2 Visits: N = 115

<table>
<thead>
<tr>
<th>Condition</th>
<th>Remission at Visit 2</th>
<th>No Remission at Visit 2</th>
<th>New Onset at Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission of MDE</td>
<td>6/10 (60%)</td>
<td>4 (40%)</td>
<td>3</td>
</tr>
<tr>
<td>Remission of GAD</td>
<td>7/13 (47%)</td>
<td>6 (53%)</td>
<td>5</td>
</tr>
<tr>
<td>Remission of MDE+GAD</td>
<td>12/17 (66%)</td>
<td>5/18 (33%)</td>
<td>4</td>
</tr>
<tr>
<td>Total Remission</td>
<td>25/40 (63%)</td>
<td>15/40 (37%)</td>
<td>12/115 (10.5%)</td>
</tr>
<tr>
<td>Total De-Novo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Points to Take Home…

In patients with epilepsy…
● Mood and anxiety disorders are relatively frequent psychiatric comorbidities.
● They yield serious and negative impacts on the management of the seizure disorder and life of these patients at several levels.
   ● Worse seizure control
   ● Worse tolerance of AEDs
   ● Increased suicidal risk
   ● Worse quality of life
● Depression and anxiety can be safely treated with SSRIs and /or SNRIs.
Questions & Answers
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