Psychiatric comorbidities and long-term outcomes of epilepsy treatment

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Outline

• Psychiatric Co-morbidities:
  • Epidemiology
  • Mechanisms
  • Treatment

• Long-term outcomes of epilepsy treatment
Outline

• Psychiatric Co-morbidities
• Mortality
Psychiatric Comorbidities with Epilepsy

• Frequent finding: lifetime prevalence of depression and anxiety disorders 30%-35%
• Associated with worse response to ASMs 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>2.5-6.5%</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>2.0-10.0%</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 co-morbidities

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)

Prevalence

- ADHD 5%
- Epilepsy 1%
- ADHD in epilepsy 20%
- ADHD in patients with epilepsy 30%

treated with ASM
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 co-morbidities

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
Mechanisms

• Common structural, biochemical abnormalities: bidirectional relationship
• Psychosocial limitations:
  • Fear of injury
  • Driving
  • Memory and cognitive challenges
• Medication effects
<table>
<thead>
<tr>
<th></th>
<th>Motor and cognitive speed</th>
<th>Memory</th>
<th>Mood</th>
<th>Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>↔</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>–</td>
<td>–</td>
<td>+*/↔</td>
<td>↔</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>–</td>
<td>–</td>
<td>–/↔</td>
<td>– (related to toxicity)</td>
</tr>
<tr>
<td>Valproate</td>
<td>–</td>
<td>–</td>
<td>+*/↔</td>
<td>↔</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>↔</td>
<td>↔</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>↔</td>
<td>↔</td>
<td>+*/↔</td>
<td>↔</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>↔</td>
<td>↔</td>
<td>+*/↔</td>
<td>↔</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>↔</td>
<td>↔</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>–/↔</td>
<td>↔</td>
<td>+*/↔</td>
<td>↔</td>
</tr>
<tr>
<td>Topiramate</td>
<td>–/↔</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>–/↔</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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

Kanner, Annals of Neurology, 2012

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### Seizure Risks of Newer-Generation Antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Seizure Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>Sertraline, paroxetine, etc.</td>
<td>0.1%-0.2%</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Duloxetine</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine (&gt;150 mg/day)</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>Desvenlafaxine</td>
<td>Reported in premarketing clinical trials^a^</td>
</tr>
<tr>
<td>Atypical antidepressant</td>
<td>Bupropion IR (≤450 mg/day)</td>
<td>0.4%</td>
</tr>
<tr>
<td></td>
<td>Bupropion ER (≤400 mg/day)</td>
<td>0.4%</td>
</tr>
<tr>
<td></td>
<td>Bupropion SR (≤300 mg/day)</td>
<td>0.1%</td>
</tr>
<tr>
<td>Tetracyclic antidepressant</td>
<td>Mirtazapine</td>
<td>Premarking clinical trials: 0.04%; postmarketing reports: low risk suggested</td>
</tr>
</tbody>
</table>

^a Patients with seizures were excluded from premarketing clinical trials.

**Dosing of Antidepressants**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Range (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>Citalopram</td>
<td>20-40</td>
</tr>
<tr>
<td></td>
<td>Escitalopram</td>
<td>10-20</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>20-60</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>20-60</td>
</tr>
<tr>
<td></td>
<td>Sertraline (R)</td>
<td>50-200</td>
</tr>
<tr>
<td>TCAs</td>
<td>Amitriptyline</td>
<td>100-300</td>
</tr>
<tr>
<td></td>
<td>Clomipramine</td>
<td>100-250</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>100-300</td>
</tr>
<tr>
<td></td>
<td>Doxepin (S)</td>
<td>100-300</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>100-300</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>50-150</td>
</tr>
</tbody>
</table>

*SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.*

Unique treatment challenges..

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

AEDS: Suicidal thoughts/behavior risk: 0.43 vs. 0.22 (pbo)
- Estimated 2.1/1000 more patients on ASMs vs. PBO
- Not specific to single drug or class

Recommendations: Class warning.
- Balance risk for suicidality with clinical need for ASM
- 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.
Suicidality with various ASMs

ASMs and Suicidality: FDA Alert

Questions Remain –
1) Assessment based on “spontaneous reports”
2) Risk associated with all ASMs, 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 psyche history of mood disorder; particularly suicidal behavior
   Past suicide attempts

Document Assessment
   ?Format
   Referral

Kanner, 2009
Willmore, Pellock, 2009
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

Outline

• Psychiatric Co-morbidities:
  • Epidemiology
  • Mechanisms
  • Treatment

• Long-term outcomes of epilepsy treatment
Long-term, epilepsy surgery is superior to medical therapy in both effectiveness and cost.

Epilepsy surgery is effective: (Wiebe, NEJM, 2001)

Epilepsy surgery is cost-effective: (Sheikh, Neurology, 2020)
On average:

For a 35 yo undergoing temporal lobectomy:

- average life expectancy increases by 5 years
- **adjusted quality of life years** increase by 7.5 years
Longitudinal trajectory of quality of life and psychological outcomes following epilepsy surgery

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c Psychiatry and Psychology, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Quality of life continues to improve years after epilepsy surgery...
...but mood and anxiety symptoms reach their maximal improvement by 1 year postoperatively.

Follow-up of psychiatric comorbidities needs to continue after successful epilepsy treatment.
Main take aways

• Psychiatric comorbidities are very common in epilepsy and have unique clinical features
• One cannot assume that treating seizures will take care of psychiatric pathology
• Managing psychiatric problems in patients with epilepsy is a lifetime commitment
THANK YOU