Outline

- Impact of Mood in Epilepsy
- The Brain, Mood & Epilepsy
- Medicine, Mood & Epilepsy
- The Mind, Mood & Epilepsy
“So What?”

- Why should you care about the relationship between depression and seizures?
  - Depression impacts QOL
  - Depression associated with worse seizure control
  - People with epilepsy DIE from suicide
Clinical Relevance

- 35 year old woman carries a 15 year h/o epilepsy
  - Recent attempted suicide (O.D.) after breaking up with boyfriend
  - In psychiatry ward had multiple tonic clonic seizures, requiring multiple stat Ativan
  - Rx: Keppra 1500mg, Dilantin 300mg, Lexapro 20mg
  - PE: neurologically normal, dysphoric, No SI/HI
Clinical Relevance

- Does Lexapro (anti-depressants) worsen seizures?
- Does Keppra (anti-convulsants) worsen depression?
- Is uncontrollable seizures a significant risk for suicide?
Three reasons you should care

1. Suicide!
2. Quality of Life
3. Seizure Control?
Quality of life vs seizure frequency or depression

QOL Associated W/ Depression

- Depression impacts QOL
  - Not seizure frequency
  - Not anxiety/anticipation
  - Not social functioning
  - Not seizure stigma

Tracy 2007, Boylan 2004, Gilliam 2002
Bidirectional Relationship

- Depression 3x more likely → Epilepsy
- Suicide 5x more likely → Epilepsy
- People enrolled in anti-depressant clinical trials who were taking placebo were 17X more likely to experience a seizure than general population
Impact of mood disorders on seizure control

Predictors of Rx resistant epilepsy:
- Traumatic Brain Injury OR: 3.26 (1.97 – 5.40)
- Psychiatric co-morbidity OR: 2.35 (1.48 - 3.73)
- Family History of Epilepsy OR: 2.02 (1.30 - 3.13)
- Substance abuse OR: 4.76 (2.37 - 9.58)
- > 10 Seizures before Rx OR: 2.71 (1.99 – 3.69)

Predictors of Excellent Epilepsy Surgery Outcome
- Large surgical resection OR: 4.6 (1.6 – 15.3)
- No psychiatric history OR: 13.1 (4.4 – 45.3)

(Hitris et al 2007, Kanner et al 2009)
Risk of Suicide in People with Epilepsy

- 6-25x greater risk of suicide in people with epilepsy
- 5.3 x greater risk within 6 months of initial diagnosis
- >20x greater risk with co-morbid psychiatric disease
- 7-13x greater risk after epilepsy surgery
Depression in Epilepsy Co-morbidity

- Standard DSM Definition of Depression:
  - 24% (Jones 2005)

- National Community Based Survey
  - 3x more than non-epilepsy controls (Kobau 2006)

- 37% of Epilepsy > 28% of Asthma > 12% Healthy Controls (Ettinger 2004)
Depression as Co-Morbidity

Ettinger A et al. Neurology 2004;63:1008-1014
Anything Special About Epilepsy: Temporal Relation to Seizure?

- Interictal Dysphoric Disorder
  - Labile depression: depressed, anergia, pain, insomnia
  - Labile affective symptoms: fear, anxiety
  - Paroxysmal irritability and euphoric moods

- Due to periodicity, may be misdiagnosed as bipolar d/o
- Case reports describe good response to SSRI, TCAs

(Mula 2008, Blumer 2004, Mula 2010)
Outline

+ Impact of Mood in Epilepsy
+ The Brain, Mood & Epilepsy
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Deconstructing the Anatomy of Depression

1. Depressed mood often
2. Anhedonia
3. Change in weight
4. Change in sleep
5. Psychomotor agitation
6. Fatigue/loss of energy
7. Worthlessness/Guilt
8. Concentration problems
9. Suicidal ideation

Vegetative-Somatic

Attention-Cognition
Primary Depression Anatomy

- Hippocampal Atrophy most common finding
- Decrease by 8% on Left and 10% on Right

(Videbech & Ravnkilde 2004)
Primary Depression Anatomy

+ Connections: Decreased Frontal and Temporal White Matter

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Method</th>
<th>Anisotropy</th>
<th>Diffusivity</th>
<th>ROI/Tract</th>
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Primary Depression Networks

- Mayberg 1997
Primary Depression Networks

- Amygdala Centric “Lesion Model”
Primary Depression Networks

- Circuit Model - Clusters of cognitive/emotional function
Temporal Lobe Epilepsy and Mood

Temporal Lobe Epilepsy and Mood

- somatic symptoms $\rightarrow$ epileptogenic hippocampus/parahippocampal regions
- anhedonia $\rightarrow$ cingulate gyrus
- negative cognitions $\rightarrow$ insula

(Lothe et al 2004)
Anatomy of Depression in Epilepsy

What happens to mood when a large piece of brain (which is involved in the depression network) is removed?
Depression 5 years after surgery

Figure 1. Percentage of patients scoring in the not depressed, mildly depressed, and moderate to severe depression range pre-surgically versus five years post-surgically. Number of respective patients in each category labeled within the columns.

Note: Out of the 379 adult subjects in the study, 256 subjects had both baseline and five year follow up depression score summarized above. A total 123 subjects were excluded: 101 with baseline depression score only; n=7 with five year depression score only and 15 missing both baseline and five year depression scores.
Depression 5 years after surgery

- Long term depression outcomes after epilepsy surgery
Epilepsy - Deep Brain Stimulation
Figure 3.
Histogram of seizure frequency changes from baseline to 25 months of stimulation (2 years after randomization, n = 81) for participants with at least 70 days of diary. Negative values indicate a seizure frequency reduction compared with baseline.

Epilepsia © ILAE
### Table 3. Adverse events occurring in >5% of subjects in either the active or control group during the Blinded Phase, ordered by difference between groups

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Active</th>
<th>%</th>
<th>(n = 54)</th>
<th>Control</th>
<th>%</th>
<th>(n = 55)</th>
<th>Differencea</th>
<th>p-valueb</th>
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<td>Depression</td>
<td>8</td>
<td>14.8%</td>
<td></td>
<td>1</td>
<td>1.8%</td>
<td></td>
<td>13.0%</td>
<td>0.0162</td>
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<td>Memory impairment</td>
<td>7</td>
<td>13.0%</td>
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<td>1</td>
<td>1.8%</td>
<td></td>
<td>11.1%</td>
<td>0.0316</td>
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<td>Confusional state</td>
<td>4</td>
<td>7.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.4%</td>
<td>0.0568</td>
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<td>Anxiety</td>
<td>5</td>
<td>9.3%</td>
<td></td>
<td>1</td>
<td>1.8%</td>
<td></td>
<td>7.4%</td>
<td>0.1130</td>
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<tr>
<td>Paraesthesia</td>
<td>5</td>
<td>9.3%</td>
<td></td>
<td>2</td>
<td>3.6%</td>
<td></td>
<td>5.6%</td>
<td>0.2706</td>
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<tr>
<td>Influenza</td>
<td>3</td>
<td>5.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.6%</td>
<td>0.1182</td>
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<tr>
<td>Partial seizures with secondary generalization</td>
<td>5</td>
<td>9.3%</td>
<td></td>
<td>3</td>
<td>5.5%</td>
<td></td>
<td>3.8%</td>
<td>0.4890</td>
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<tr>
<td>Simple partial seizures</td>
<td>3</td>
<td>5.6%</td>
<td></td>
<td>1</td>
<td>1.8%</td>
<td></td>
<td>3.7%</td>
<td>0.3634</td>
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<tr>
<td>Complex partial seizures</td>
<td>5</td>
<td>9.3%</td>
<td></td>
<td>4</td>
<td>7.3%</td>
<td></td>
<td>2.0%</td>
<td>0.7420</td>
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<tr>
<td>Anticonvulsant toxicity</td>
<td>3</td>
<td>5.6%</td>
<td></td>
<td>4</td>
<td>7.3%</td>
<td></td>
<td>−1.7%</td>
<td>1.0000</td>
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<tr>
<td>Dizziness</td>
<td>3</td>
<td>5.6%</td>
<td></td>
<td>4</td>
<td>7.3%</td>
<td></td>
<td>−1.7%</td>
<td>1.0000</td>
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<tr>
<td>Headache</td>
<td>2</td>
<td>3.7%</td>
<td></td>
<td>3</td>
<td>5.5%</td>
<td></td>
<td>−1.8%</td>
<td>1.0000</td>
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<tr>
<td>Excoriation</td>
<td>1</td>
<td>1.9%</td>
<td></td>
<td>3</td>
<td>5.5%</td>
<td></td>
<td>−3.6%</td>
<td>0.6180</td>
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<tr>
<td>Contusion</td>
<td>1</td>
<td>1.9%</td>
<td></td>
<td>4</td>
<td>7.3%</td>
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<td>−5.4%</td>
<td>0.3634</td>
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<td>Nasopharyngitis</td>
<td>1</td>
<td>1.9%</td>
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<td>5</td>
<td>9.1%</td>
<td></td>
<td>−7.2%</td>
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<td>Upper respiratory tract infection</td>
<td>1</td>
<td>1.9%</td>
<td></td>
<td>4</td>
<td>7.3%</td>
<td></td>
<td>−7.3%</td>
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<td>Injury</td>
<td>1</td>
<td>1.9%</td>
<td></td>
<td>6</td>
<td>10.9%</td>
<td></td>
<td>−9.1%</td>
<td>0.1130</td>
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</table>

*a* Positive, more frequent in the active group; negative, more frequent in the control group.

*b* Fisher’s exact test.

*c* Statistically significant.

*d* New or worse seizures, or seizures meeting serious adverse event criteria.
Outline

+ Impact of Mood in Epilepsy
+ The Brain, Mood & Epilepsy
+ Medicine, Mood & Epilepsy
+ The Mind, Mood & Epilepsy
Anti-convulsants implicated as depressive

- Potentially Depressogenic:
  - Phenobarbital
  - Primidone,
  - Tiagabine,
  - Vigabatrin,
  - Felbamate,
  - Topiramate,
  - Levetiracetam,
  - Zonisamide
Anti-Epileptic Drugs & Suicide

- FDA Meta-analysis:
  - 199 studies
  - >27,000 subjects
  - 11 AEDs used for seizure control, psychiatric or 'other' indications.
  - TPM and LEV only significant increase risk SI.
  - 4 completed suicides + AEDs
  - 0 suicides placebo.

- Odds ratio for suicidal behavior or ideation was 1.8 (95% CI 1.24, 2.66),

- FDA Black Box warning: "Patients being treated with antiepileptic drugs for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior"
Suicide and Seizures

Figure 1. Standardized mortality ratios (SMRs) (with 95% confidence intervals) for death by suicide in studies of people with epilepsy. The figure includes only those cohorts with any deaths due to suicide. inc, incidence; prev, prevalence; i&p, incidence and prevalence. Epilepsia © ILAE

Bell 2009
What medications anti-depressants are most appropriate?

Incidence rate of seizures controlling for years on Rx:

- SSRI = 0.48
- Bupropion IR only = 1.58
- Antipsychotics = 2.05
- Antipsychotics (excluding clozapine) = 1.35
- Clozapine only = 9.50
My Recommendations

+ MUST ask about Anxiety & Mania

+ Pick Two SSRI (one generic)
  + Celexa/Lexapro (QT syndrome)
  + Zoloft
  + Effexor (more activating, HTN)
  + Welbutrin SR (more activating, no sexual dysfunction)
Outline

- Anatomy of Mood & Epilepsy
- Pharmacology of Mood & Epilepsy
- Psychology of Mood & Epilepsy
Outline

- Impact of Mood in Epilepsy
- The Brain, Mood & Epilepsy
- Medicine, Mood & Epilepsy
- The Mind, Mood & Epilepsy
Psychological State

Coping Styles
- Negative
  - Escape Avoidance
  - Distancing
  - Self-controlling
  - Confrontational
- Positive
  - Seeking support
  - Accepting responsibility
  - Planful problem solving
  - Positive appraisal
Even if Epilepsy if Epilepsy is Cured: Burden of Normality

After living with chronic disease, feeling disabled, building a network around your epilepsy…. now you are cured!

Psychological
- Sense of loss
- Grieving for epilepsy
- Proof of Normality
- Increased Expectations
- The Lost Years - To make up for

Affective
- Mood Elevation
- Anxiety
- Depression

Behavioral
- Excessive Activity
- Increased Sex drive
- Shirking behavior-
- Other somatization

Sociological
- New family dynamics
- New vocational expectations
- New social skills
What can a person do?
Case study

35 year old woman carries a 15 year h/o epilepsy

- Recent attempted suicide (O.D.) after breaking up with boyfriend
- In psychiatry ward had multiple tonic clonic seizures, requiring multiple stat Ativan
- Rx: Keppra 1500mg, Dilantin 300mg, Lexapro 20mg
- PE: neurologically normal, dysphoric, No SI/HI