

# CIAN

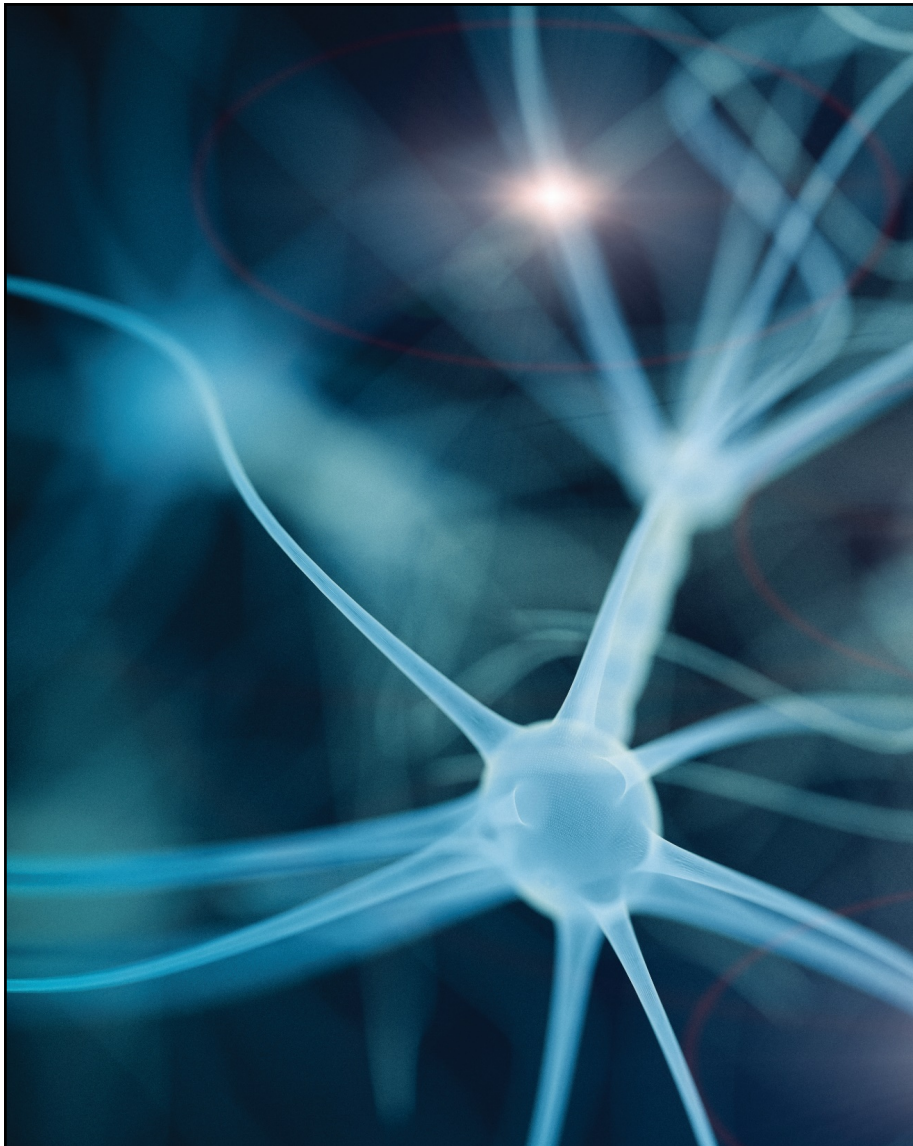
PRIMER CURSO INTERAMERICANO DE  
ACTUALIZACIÓN EN NEUROLOGÍA



## Advances in Diagnosis, Neurobiology, and Treatment of Neurological Disorders

University of Miami, March 20 and 21, 2017

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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

# 1

Recognize the impact of psychiatric comorbidities on the management of the disorder in patients with epilepsy.

# Andres M. Kanner, MD, FANA, FAES

## Disclosures

- Dr. Kanner has no disclosures to report.



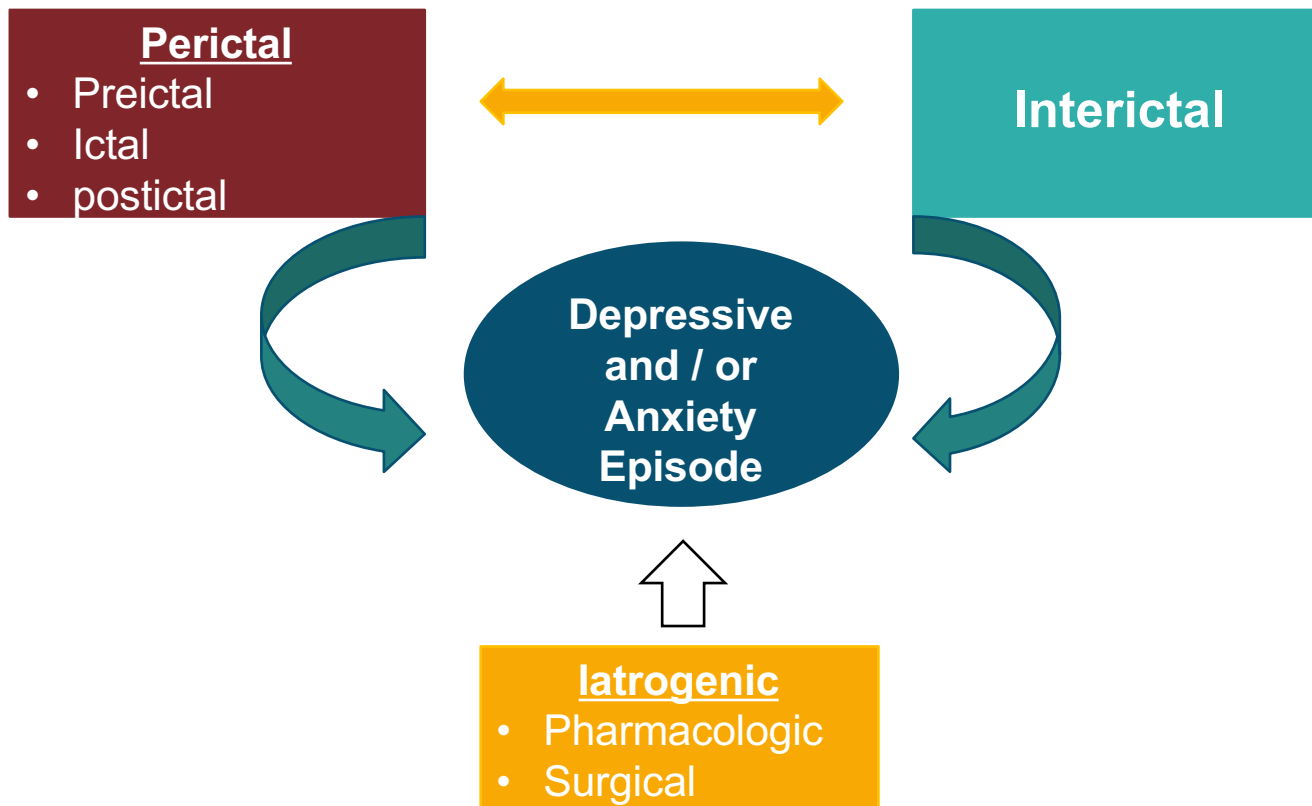
**How big of a problem is it?**

# Lifetime Prevalence

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

Tellez-Zenteno JF, et al. *Epilepsia*, 2007;48:2336-2344.

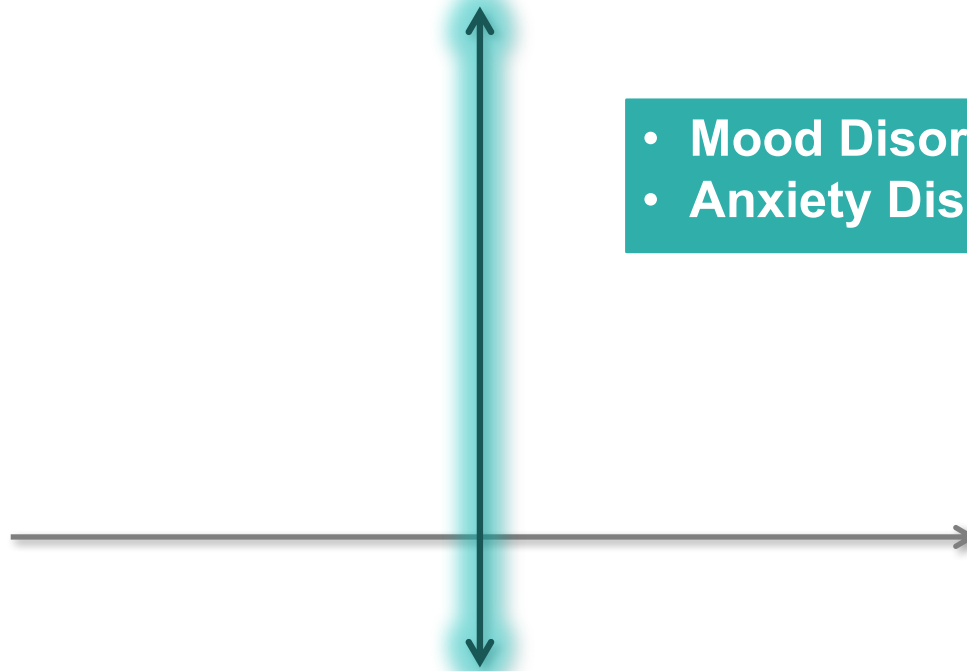
# What Type of Psychiatric Symptom Is It?



# Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

- Mood Disorders
- Anxiety Disorders

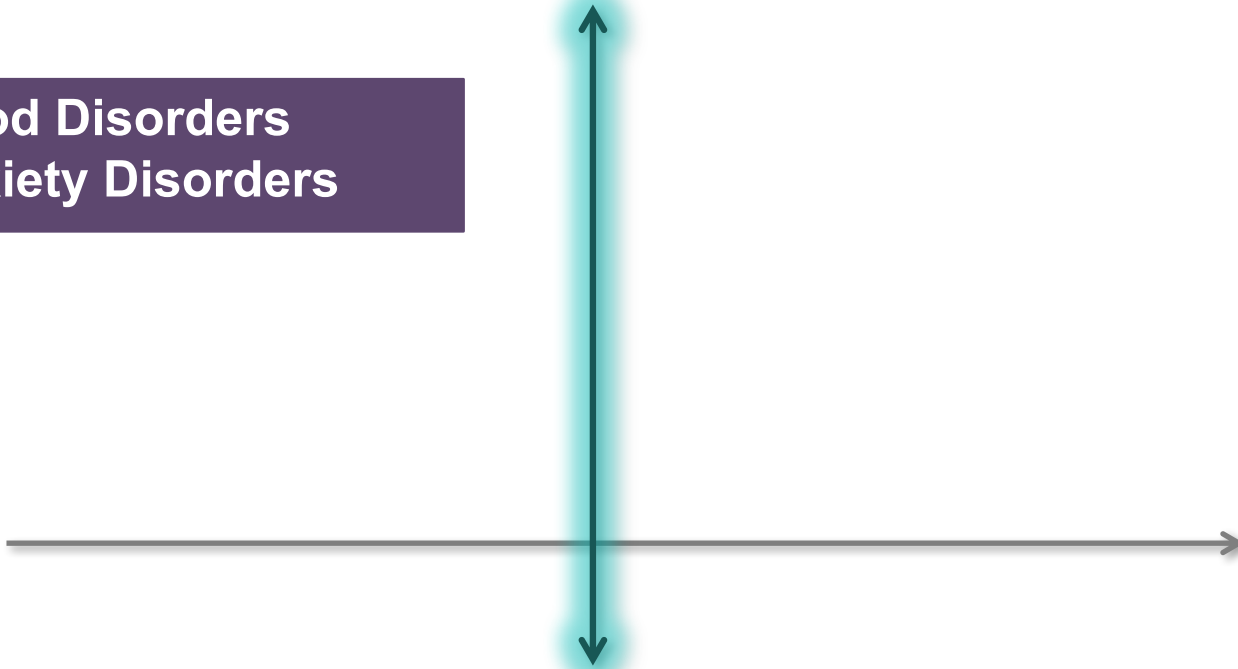




# Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

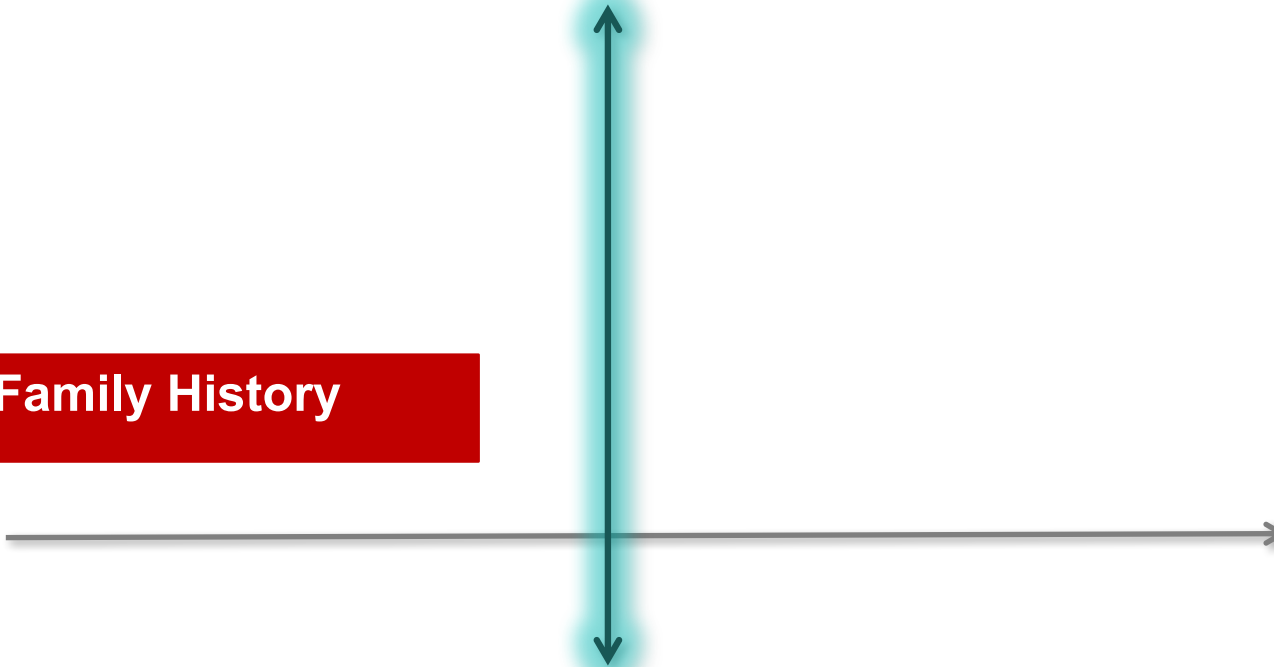
- Mood Disorders
- Anxiety Disorders



# Psychiatric Comorbidities Over Time

Diagnosis of Epilepsy

Family History



# Psychiatric Comorbidities Over Time

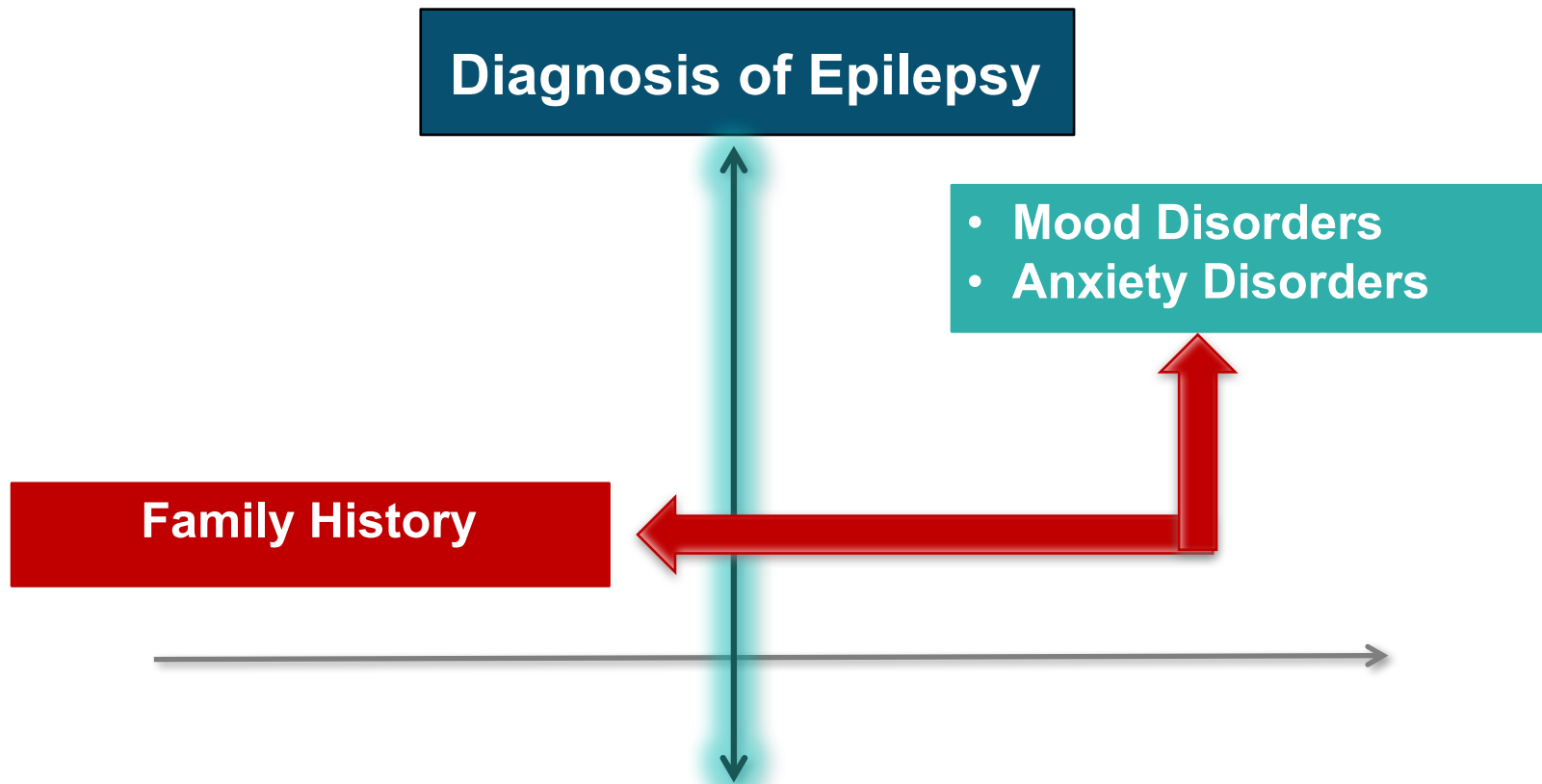
**Diagnosis of Epilepsy**

- Mood Disorders
- Anxiety Disorders

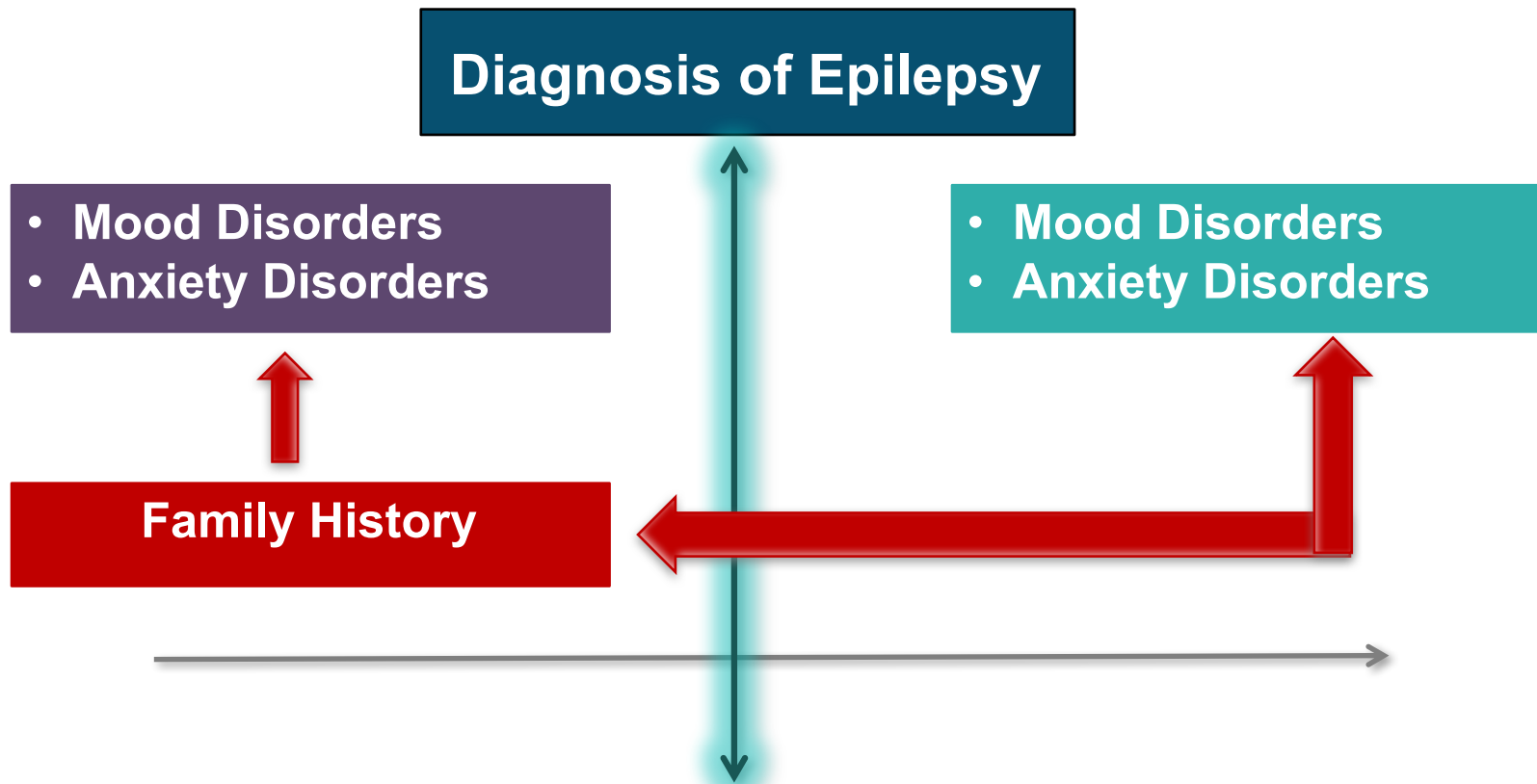
**Family History**



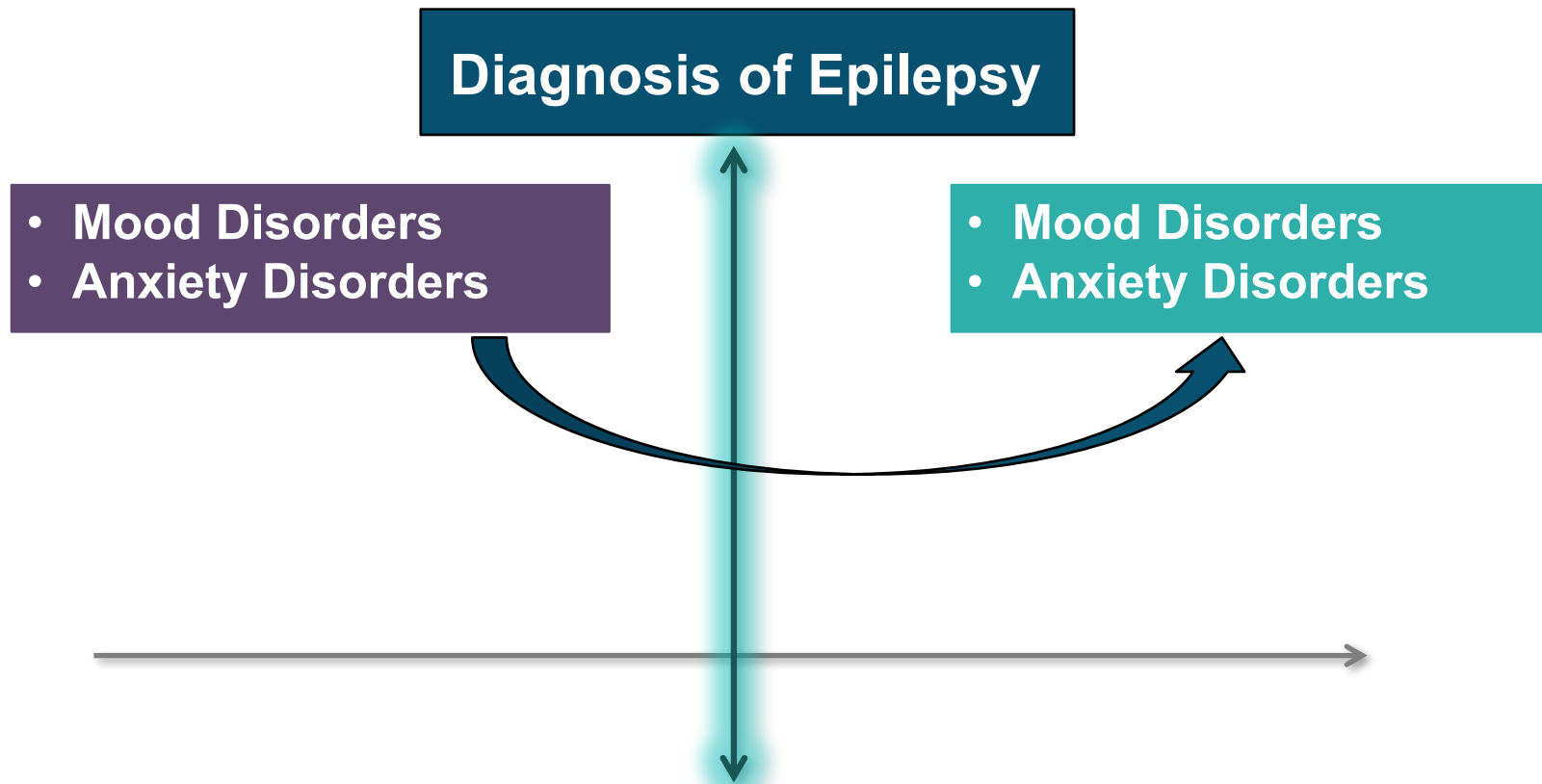
# Psychiatric Comorbidities Over Time



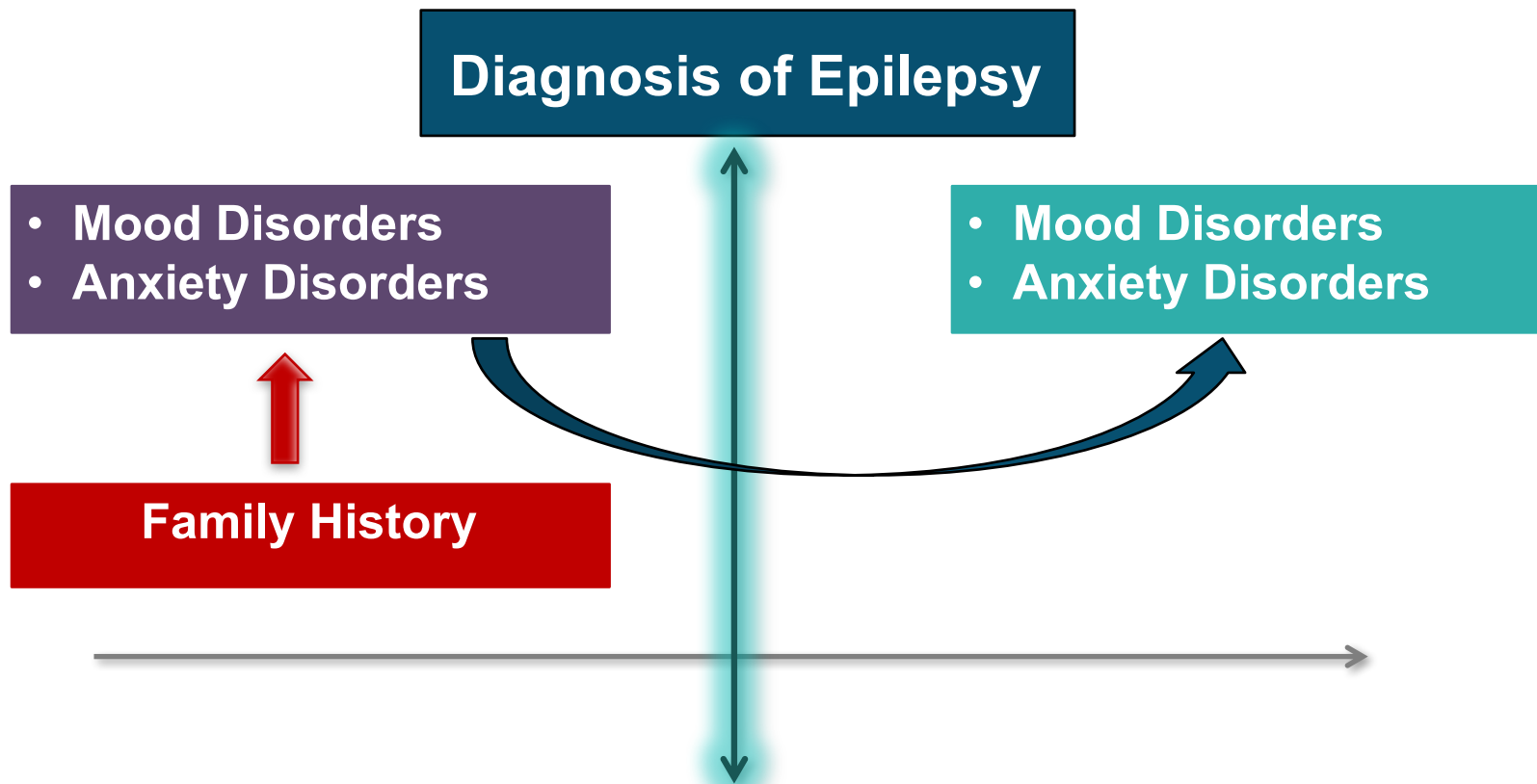
# Psychiatric Comorbidities Over Time



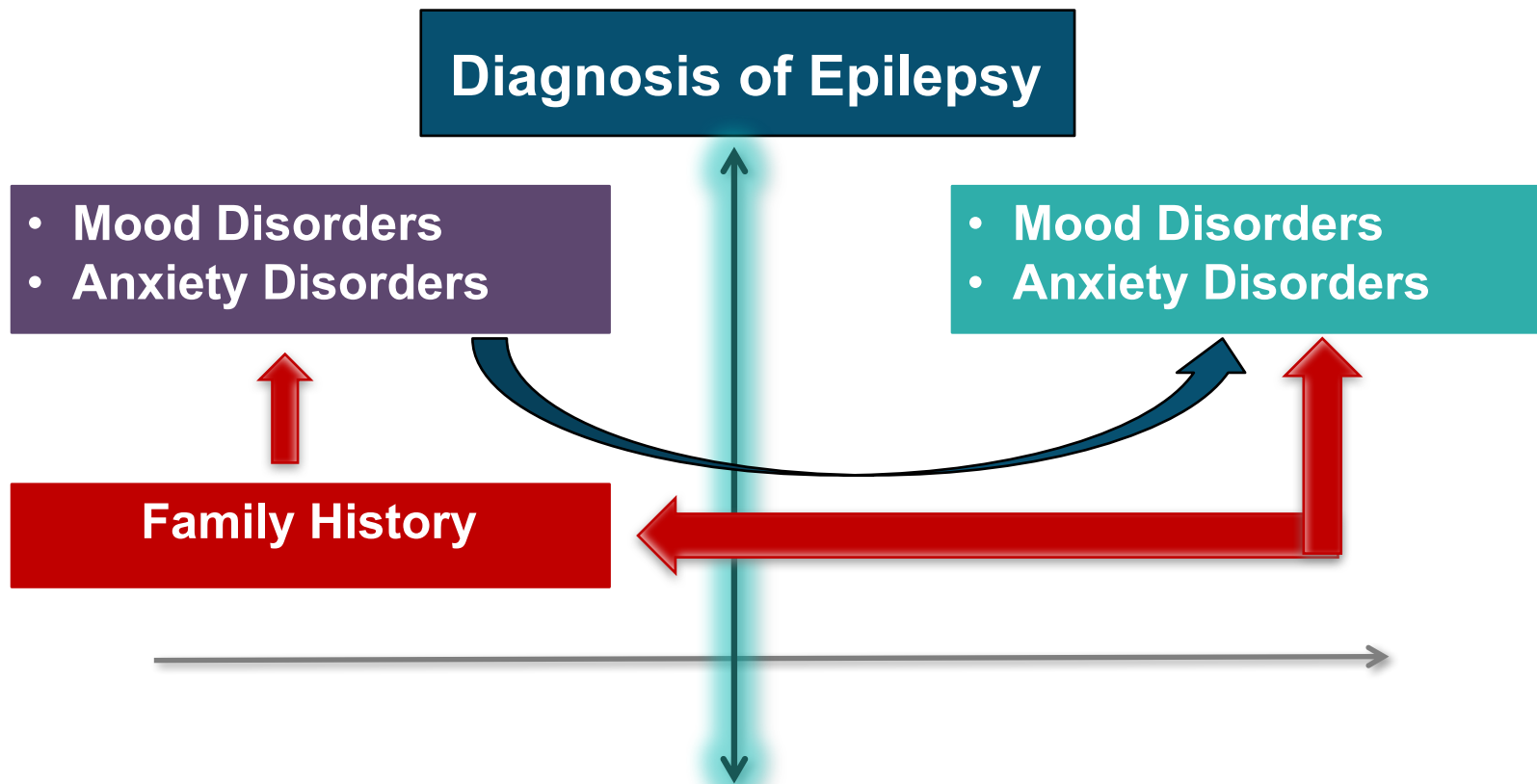
# Psychiatric Comorbidities Over Time



# Psychiatric Comorbidities Over Time

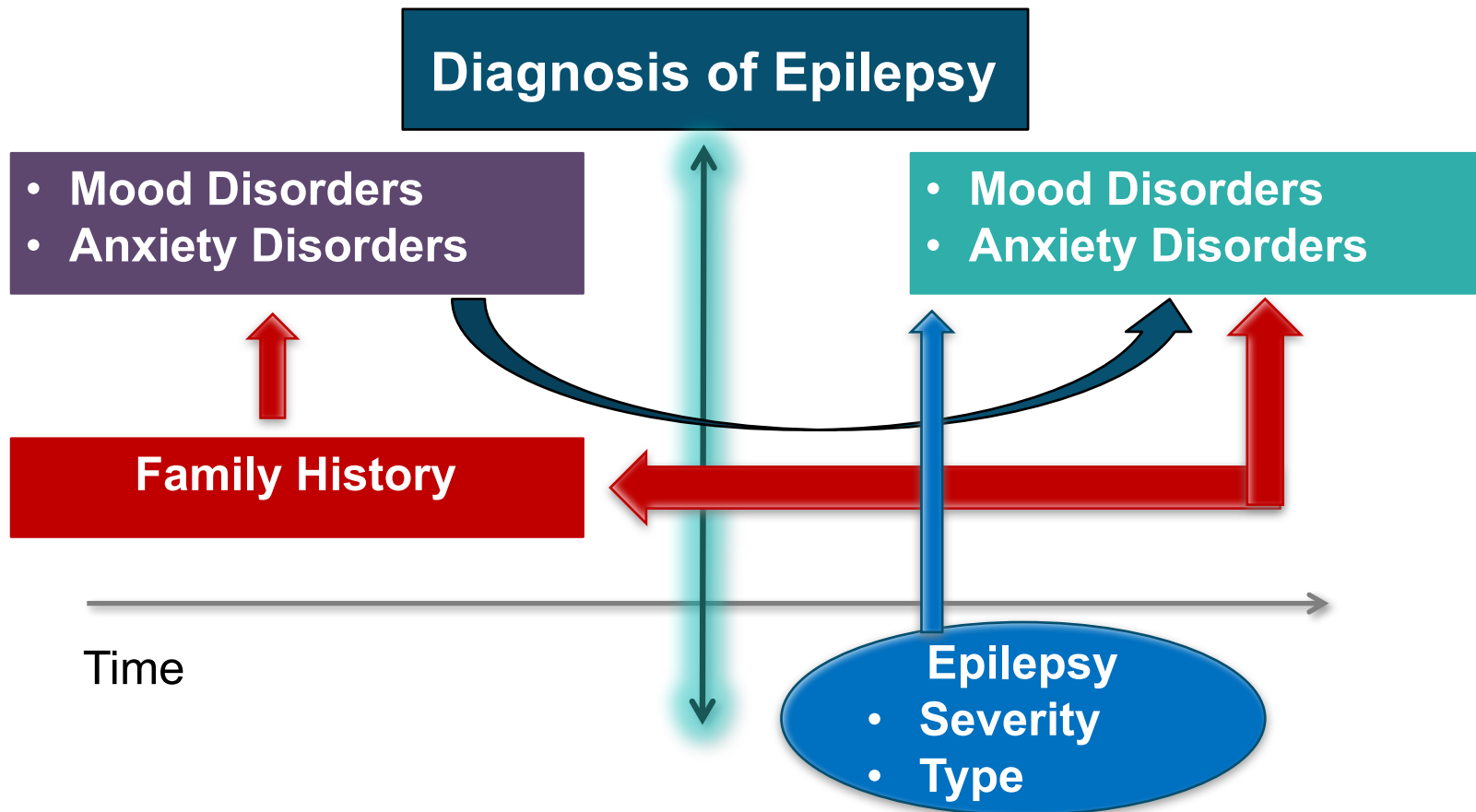


# Psychiatric Comorbidities Over Time

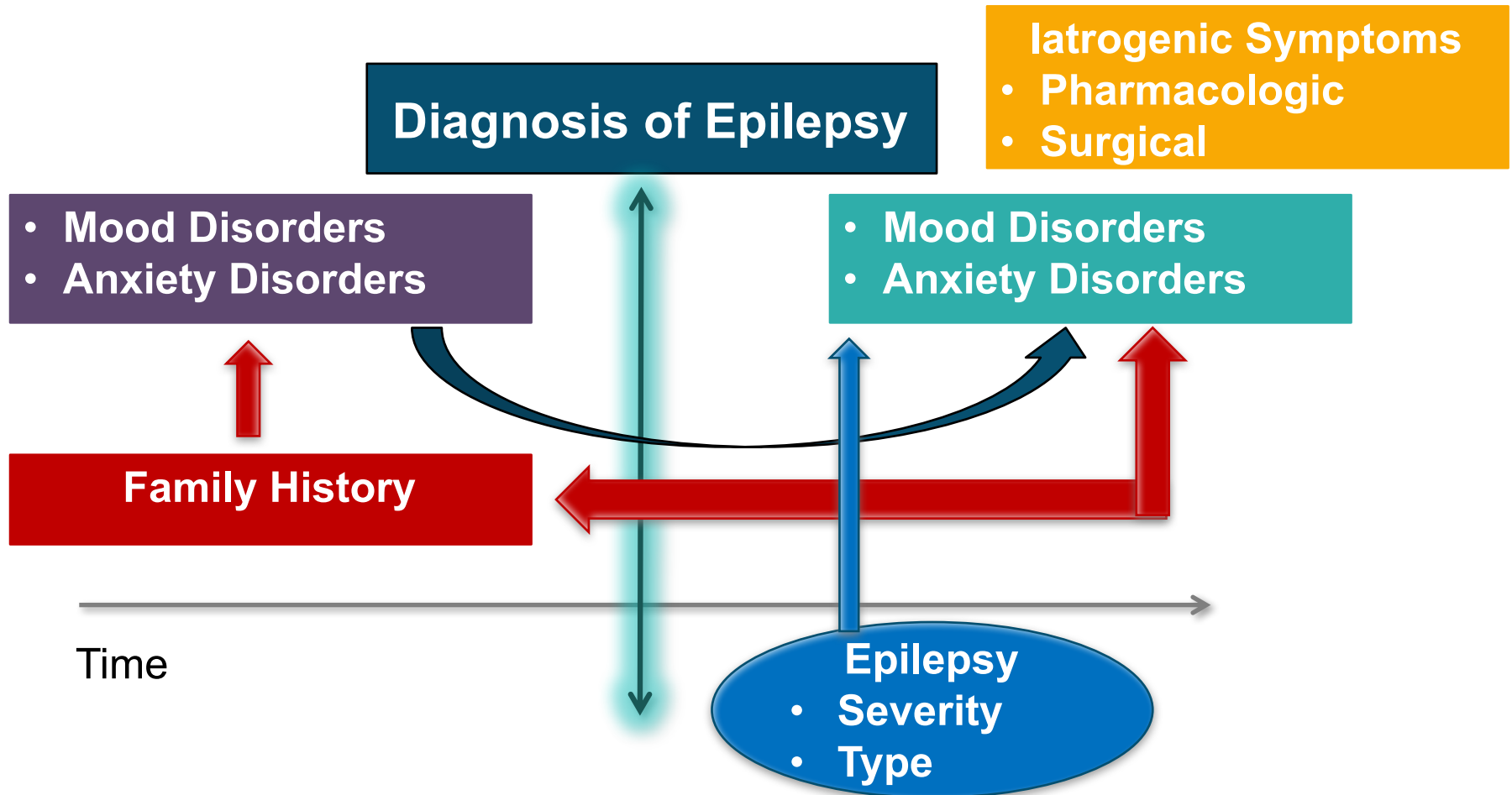




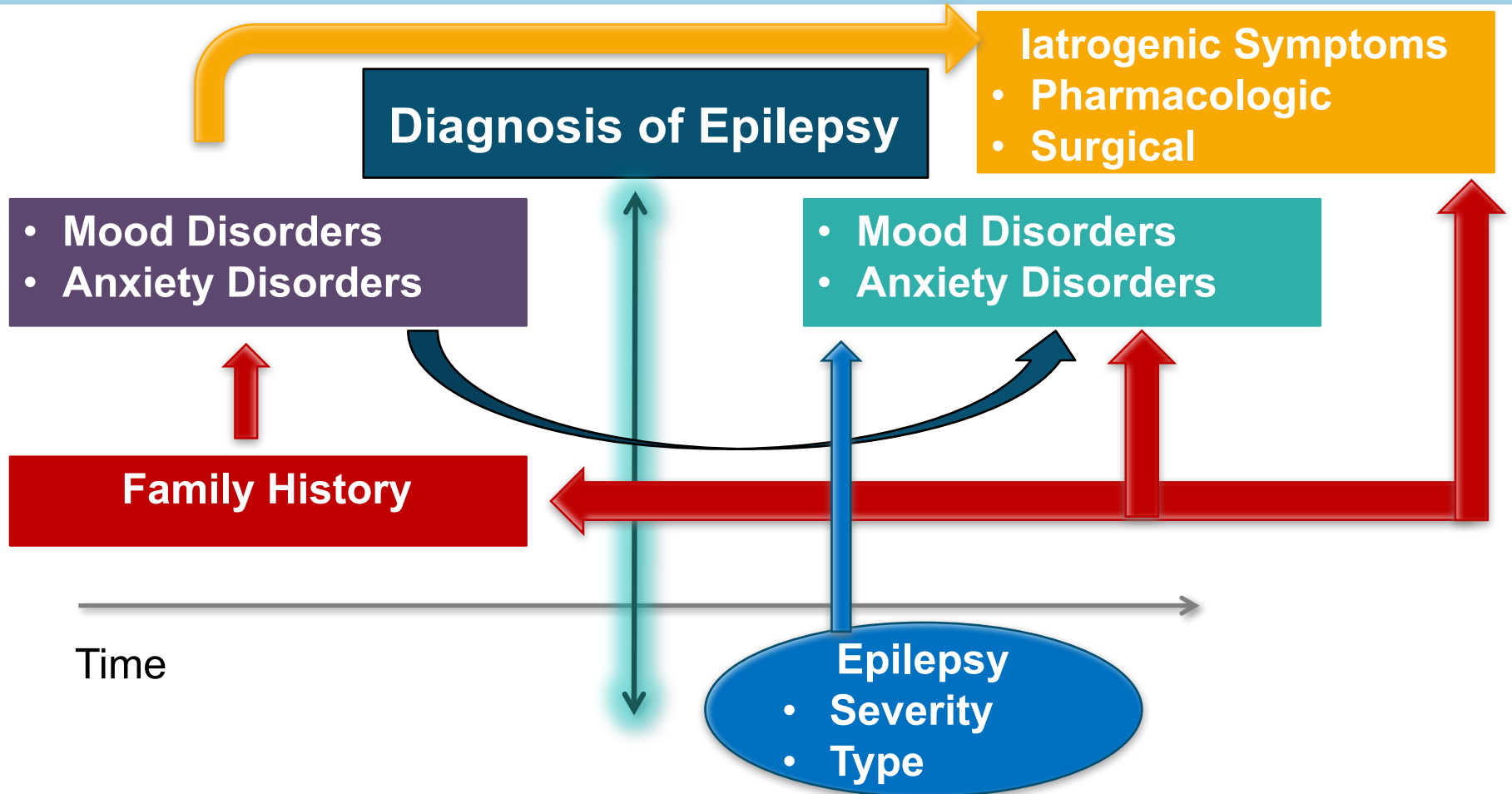
# Psychiatric Comorbidities Over Time



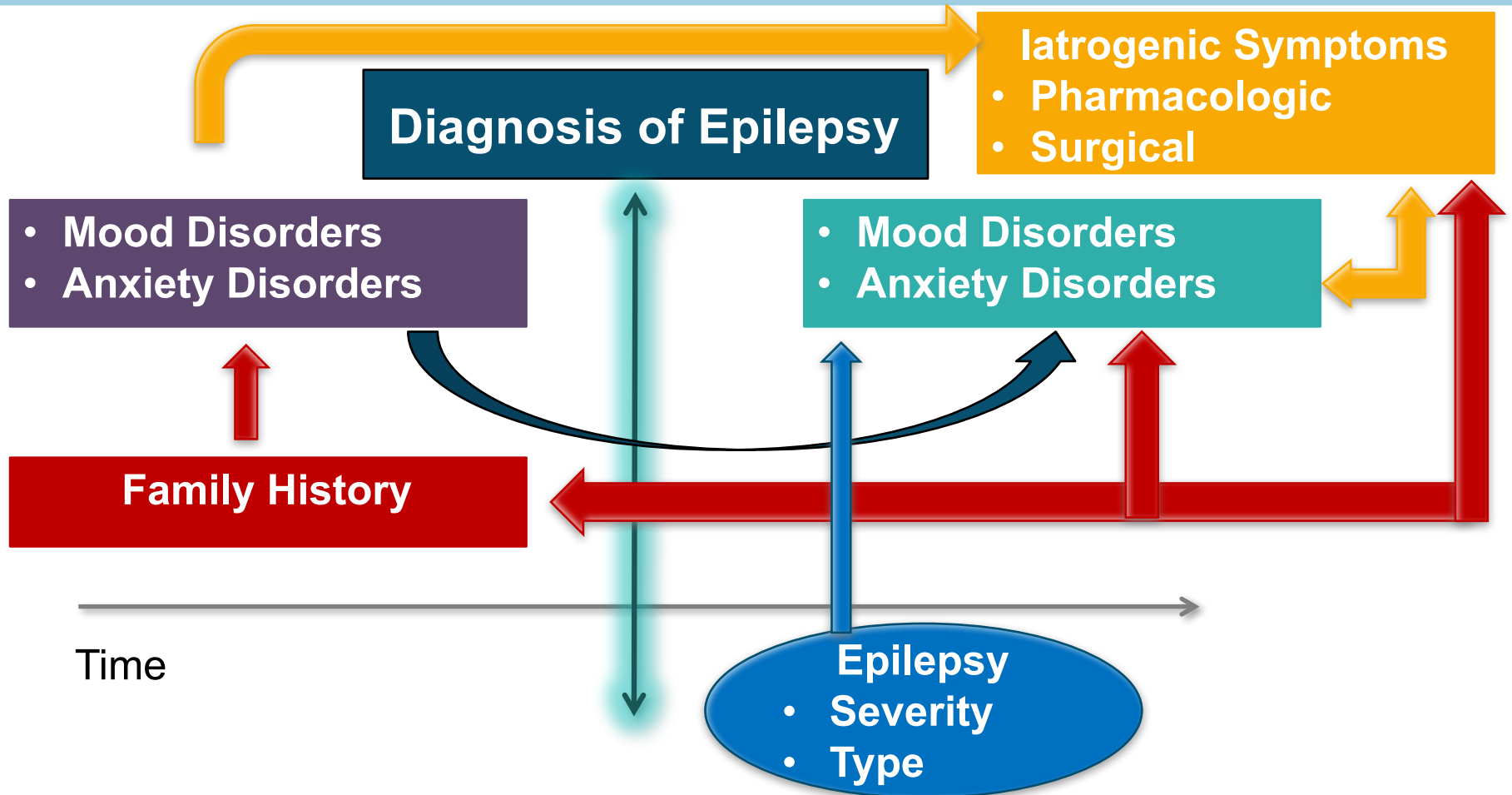
# Psychiatric Comorbidities Over Time



# Psychiatric Comorbidities Over Time



# Psychiatric Comorbidities Over 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

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

Handal NM, et al. *Psychosomatics*. 1995;36:498-501.

## 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

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

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

# Postictal Symptoms of Anxiety

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

Kanner AM, et al. *Neurology*. 2004;62(5):708-713.



**Why should neurologists  
care?**

# Impact of Depression and Anxiety Episodes

- Increased mortality risk
  - Christiansen, et al. *Lancet Neurol*, 2007
  - Fazel, et al. *Lancet* 2013
- Worse tolerance of antiepileptic drugs
  - Perucca, et al. *Neurology* 2011
  - Kanner, et al. *Epilepsia* 2012
- Worse quality of life
  - Guillian, et al. *Neurology* 2002
  - Kanner, et al. *Epilepsia* 2011
- Increased risk of psychiatric iatrogenic adverse events
  - Mula, et al. *Epilepsia* 2003, 2007

# Impact of Depression and Anxiety Episodes

- Worse seizure control with pharmacotherapy
  - Hitiris, et al. *Epilepsy Res*, 2007
  - Petrovsky, et al. *Neurology* 2010
  - Josephson, et al. *JAMA Neurol*, 2017
- Higher likelihood of persistent seizures after epilepsy surgery with antero-temporal lobectomies
  - Kanner, et al. *Neurology* 2009
  - Cleary, et al. *Epilepsia* 2012
  - De Araujo, et al. *Epilepsia* 2012



## 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

Hesdorffer DC, et al. *Ann Neurol.* 2006;59(1):35-41.

Hesdorffer DC, et al. *Ann Neurol.* 2012;72(2):184-191.



**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

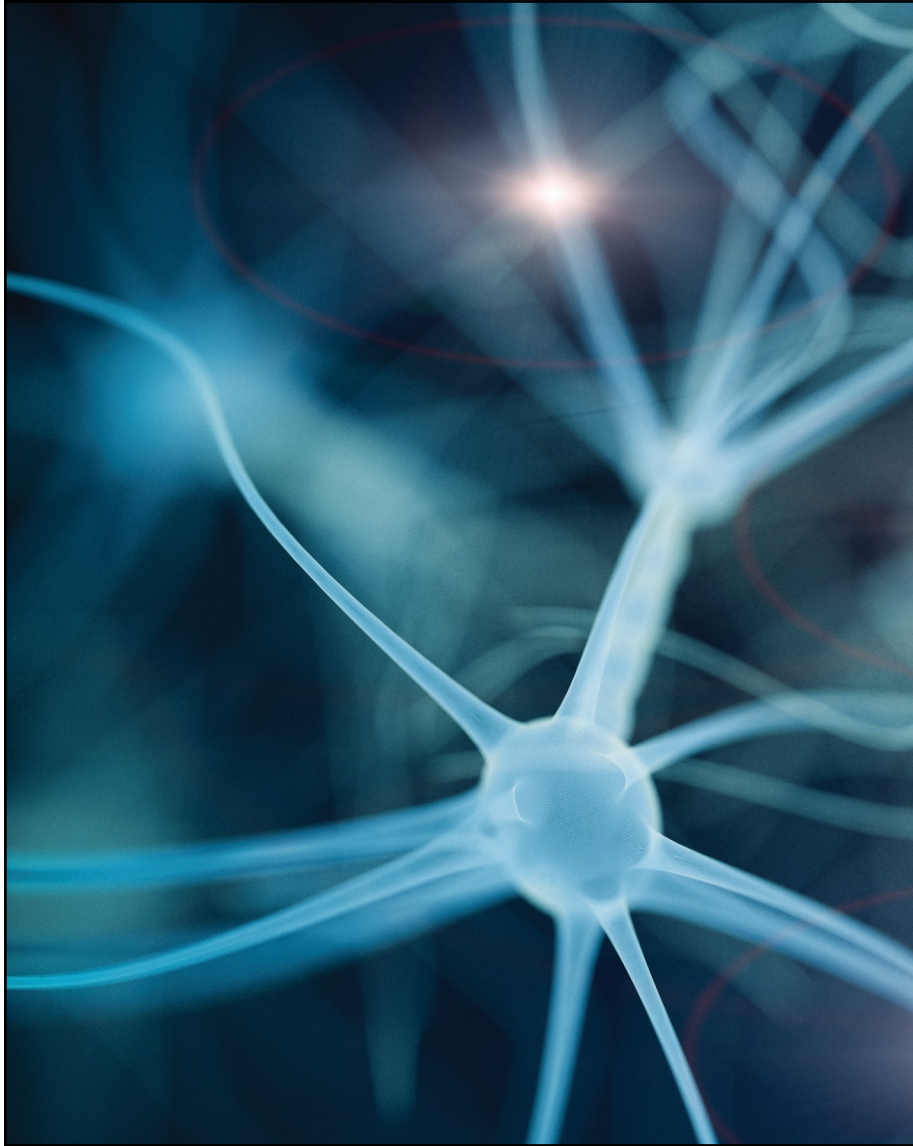
- Clomipramine
- Bupropion immediate release (IR)



# 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**



# 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

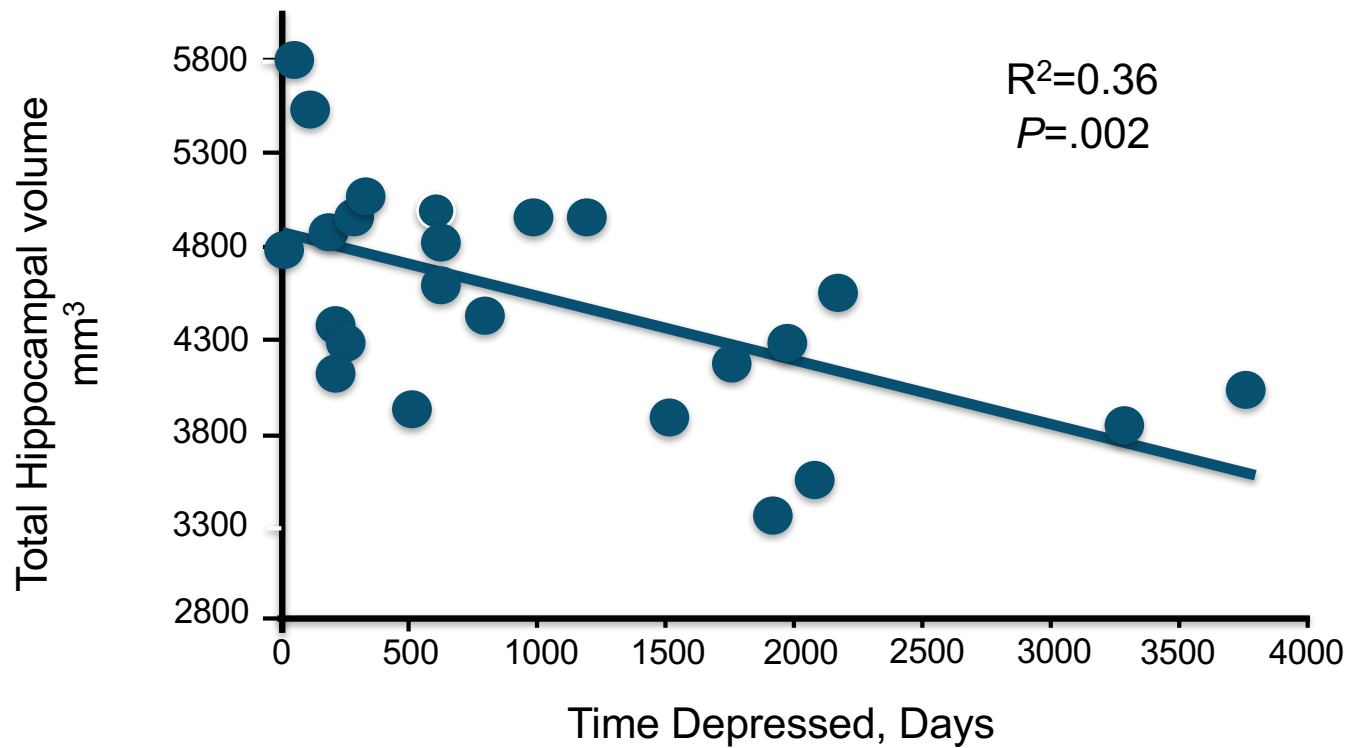


## Impact of ↑HPA

## ↑ 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



Sheline YI, et al. *J Neurosci.* 1999;19(12):5034-5043.



# **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<sup>1</sup>
- 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

Anatomical Structure	Laterality	<i>P</i>
Mesial structures	Bilateral	<.001
Thalamus	Left	<.001
Inferior & superior temp gyrus	Bilateral	<.001
Inferior & middle frontal gyrus	Bilateral	<.001
Middle occipital gyrus, cuneus, fusiform gyrus	Left	.016
Caudate body	Right	.023
Postcentral gyrus	Left	.03



**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*

SYMPTOMS	Always or Often	Sometimes	Rarely	Never
Everything is a struggle	4	3	2	1
Frustrated	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
Difficulty finding pleasure	4	3	2	1
I'd be better off dead	4	3	2	1

**A score of > 15 is suggestive of major depressive episode**

Gilliam FG, et al. *Lancet Neurol.* 2006;5(5):399-405.

NDDI-E available at [https://www.commondataelements.ninds.nih.gov/Doc/NOC/Neurological\\_Disorders\\_Depression\\_Inventory\\_in\\_Epilepsy\\_Link.pdf](https://www.commondataelements.ninds.nih.gov/Doc/NOC/Neurological_Disorders_Depression_Inventory_in_Epilepsy_Link.pdf)

# Generalized Anxiety Disorder-7 (GAD-7)

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

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

**A score of > 10 is suggestive of generalized anxiety disorder**

Spitzer RL, et al. *Arch Int Med.* 2006;166:1092-1097.  
GAD-7 available at <http://www.integration.samhsa.gov/clinical-practice/GAD708.19.08Cartwright.pdf>.

# 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

## Positive

- Barbiturates
- Benzodiazepines
- Levetiracetam
- Topiramate
- Zonisamide
- Vigabatrine
- Tiagabine
- Perampanel

## Negative

- Carbamazepine
- Valproic acid
- Oxcarbazepine
- Lamotrigine
- Gabapentin
- Pregabalin
- Benzodiazepines

## 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

## CLASSICAL

TCA

MAOI

Phenelzine  
Tranylcypromine

In patients with bipolar disorder antidepressant medication should be used with great caution!!!!

## SSRI

Citalopram

Escitalopram

Fluoxetine

Fluvoxamine

Paroxetine

Paroxetine CR

Sertraline

1<sup>st</sup>  
choice

## OTHER

~~NM~~

Bupropion XL

SNRI

Venlafaxine-XR

Duloxetine

NaSSA

Mirtazapine

2<sup>nd</sup>  
choice

3<sup>rd</sup>  
choice

# SSRIs and SNRIs with Antidepressant and Anxiolytic Properties

Antidepressant	Depression	Panic disorder	Generalised anxiety	Starting dose	Maximal dose
Paroxetine	+	+	+	10	60
<b>Sertraline</b>	<b>+</b>	<b>+</b>	<b>+</b>	<b>25</b>	<b>200</b>
Fluoxetine	+	+	+	10	80
<b>Citalopram</b>	<b>+</b>	<b>+</b>	<b>+</b>	<b>10</b>	<b>60</b>
<b>Escitalopram</b>	<b>+</b>	<b>+</b>	<b>+</b>	<b>5</b>	<b>30</b>
Venlafaxine	+	+	+	37.5	300
<b>Duloxetine</b>	<b>+</b>		<b>+</b>	<b>40</b>	<b>120</b>

## 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



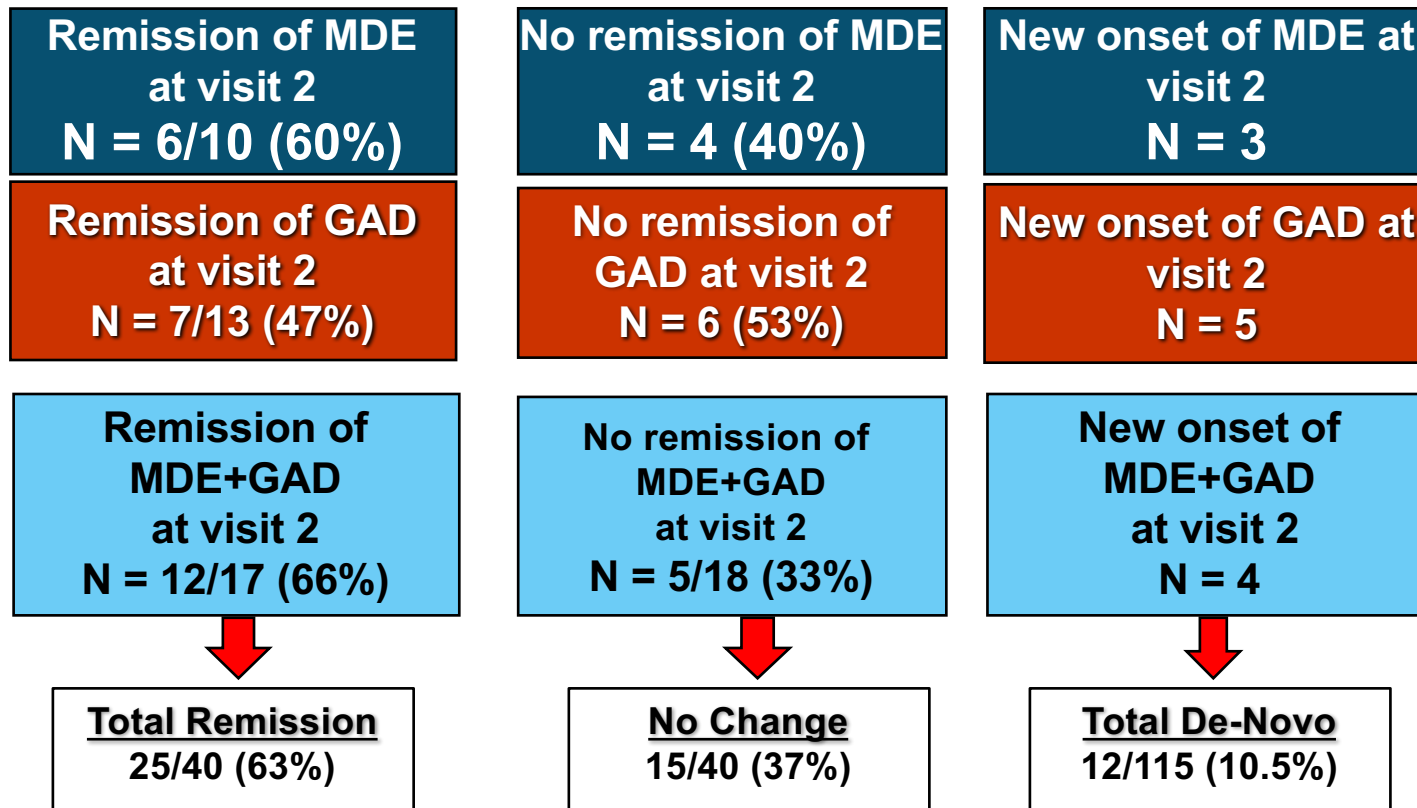
## Screening for Depression and Generalized Anxiety Disorder at the Rush Epilepsy Center

- N = 636 consecutive English-speaking adults
  - Age:  $\geq 18$  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:  $123 \pm 77$  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



## 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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