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Psychiatric comorbidities and long-term outcomes of epilepsy treatment

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2020

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Outline

- Psychiatric Co-morbidities:
  - Epidemiology
  - Mechanisms
  - Treatment
- Long-term outcomes of epilepsy treatment

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Outline

- Psychiatric Co-morbidities
- Mortality

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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

Bateman, et al, Ep Currents, 2012

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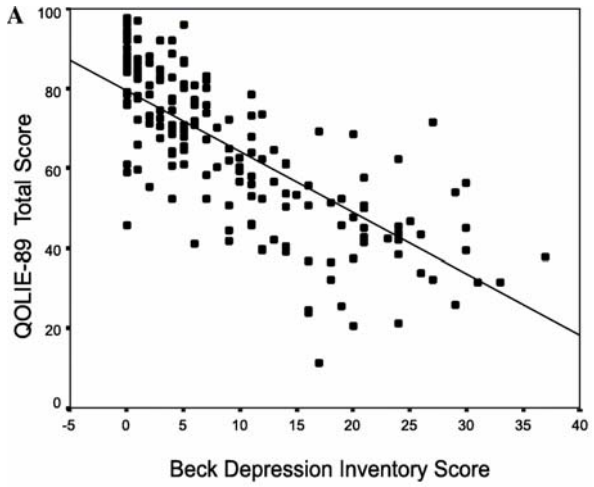

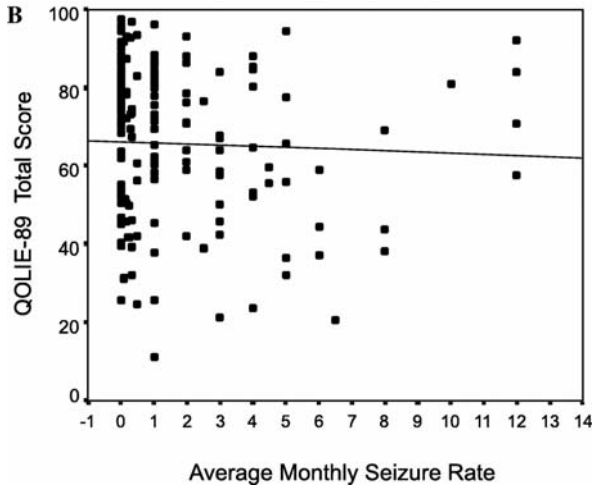

Major correlation between depression and quality of life

F. Gilliam A. Kanner. Treatment of depressive disorders in epilepsy patients. Epilepsy and BehaviorVolume 3, Issue 5, Supplement, October 2002, Pages 2–9

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Prevalence of Psychiatric Disorders in adult epilepsy

	In epilepsy (range)	In the general population (range)
Depression	11-60%	2.0-4.0%
Anxiety	19-45%	2.5-6.5%
Psychosis	2-8%	0.5-0.7%
ADHD	25-30%	2.0-10.0%

Kanner, *Epilepsia* 2003;44(5):3-8.

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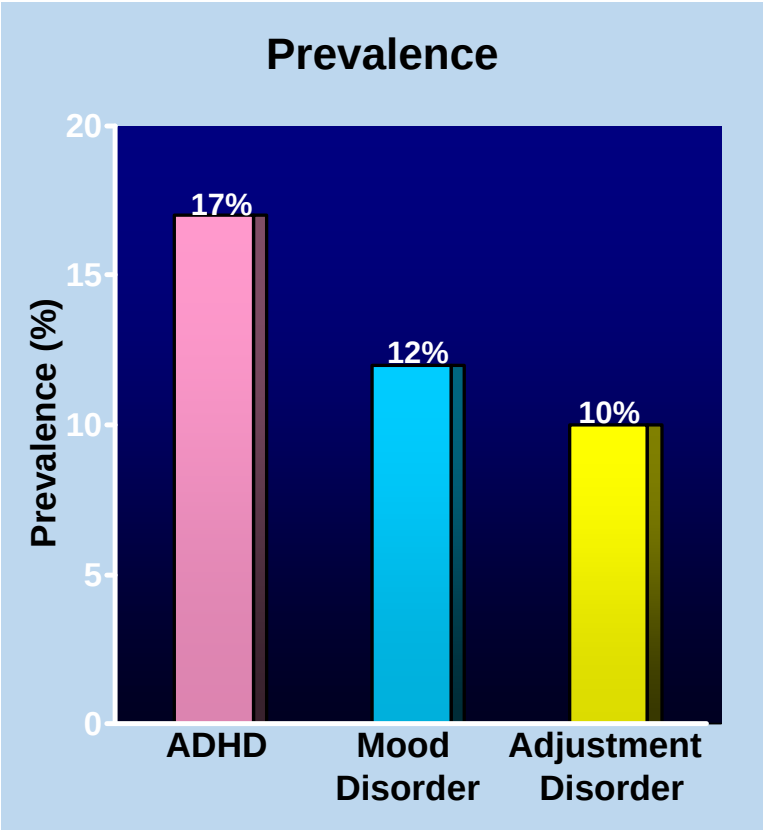
Prevalence of Psychiatric and Behavioral Comorbidities

- 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



Hedderick E, et al. *Ann Neurol*. 2003;54(suppl 7):S115. Abstract E12.

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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%)

Russ, Larson, Halfon: Pediatrics, 2012

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Epidemiology of psychiatric co-morbidities

1- Higher prevalence in epilepsy

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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

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Epilepsy and Attention Deficit Hyperactivity Disorder (ADHD)

	Prevalence
• ADHD	5%
• Epilepsy	1%
• ADHD in epilepsy	20%
• ADHD in patients with epilepsy treated with ASM	30%

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Psychiatric Disorders and Epilepsy Bidirectional Relation: Neurobiological/Pathogenesis

- Neurotransmitters: serotonin, norephinephrine, dopamine, glutamate, GABA
- Endocrine: hyperactive hypothalamic-pituitary-adrenal axis producing high cortisol
- Inflammatory mechanisms

Kanner, Annals of Neurology, 2012

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Epidemiology of psychiatric co-morbidities

1- Higher prevalence in epilepsy

2- Bi-directional relationship with epilepsy

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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

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Epidemiology of psychiatric co-morbidities: Main bullet points

1- Higher prevalence in epilepsy

2- Bi-directional relationship with epilepsy

3- Unique clinical features

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Mechanisms

- Common structural, biochemical abnormalities: bidirectional relationship
- Psychosocial limitations:
  - Fear of injury
  - Driving
  - Memory and cognitive challenges
- Medication effects

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	Motor and cognitive speed	Memory	Mood	Psychosis
Phenobarbital	–	–	–	↔
Carbamazepine	–	–	+*/↔	↔
Phenytoin	–	–	–/↔	– (related to toxicity)
Valproate	–	–	+*/↔	↔
Vigabatrin	↔	↔	–	–
Oxcarbazepine	↔	↔	+*/↔	↔
Gabapentin	↔	↔	↔	↔
Lamotrigine	↔	↔	+*/↔	↔
Levetiracetam	↔	↔	–	–
Pregabalin	–/↔	↔	+*/↔	↔
Topiramate	–/↔	–	–	–
Tiagabine	–	–	–	–
Zonisamide	–/↔	–	–	–

Mula M, Monaco F. Antiepileptic drugs and psychopathology of epilepsy: an update. Epileptic Disord 2009; 11: 1–9.

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Unique treatment challenges..

1- medication choice

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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 anti-psychotics: clozapine, olanzapine, quetiapine
- Stimulants: no seizure increase, unless toxic

Kanner, Annals of Neurology, 2012

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Seizure Risks of Newer-Generation Antidepressants

Class	Drug	Seizure Risk
SSRIs	Sertraline, paroxetine, etc.	0.1%-0.2%
SNRIs	Duloxetine	0.2%
	Venlafaxine (>150 mg/day)	0.3%
	Desvenlafaxine	Reported in premarketing clinical trials[a]
Atypical antidepressant	Bupropion IR (≤450 mg/day)	0.4%
	Bupropion ER (≤400 mg/day)	0.4%
	Bupropion SR (≤300 mg/day)	0.1%
Tetracyclic antidepressant	Mirtazapine	Premarketing clinical trials: 0.04%; postmarketing reports: low risk suggested

[a] Patients with seizures were excluded from premarketing clinical trials.
ER: extended-release; IR: immediate-release; SR: sustained-release; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

1. Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. *Int J Clin Pract*. 2005;59:1435-1440.
2. Pristiq (desvenlafaxine) product information. Philadelphia, PA: Wyeth Pharmaceuticals Inc; October 2011.
3. Khawam EA, Laurencic G, Malone DA Jr. Side effects of antidepressants: an overview. *Cleve Clin J Med*. 2006;73:351-353,356-361.

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Dosing of Antidepressants

Class	Drug	Range (mg/day)
SSRIs	Citalopram	20-40
	Escitalopram	10-20
	Fluoxetine	20-60
	Paroxetine	20-60
	Sertraline	50-200
TCAs	Amitriptyline	100-300
	Clomipramine	100-250
	Desipramine	100-300
	Doxepin	100-300
	Imipramine	100-300
	Nortriptyline	50-150

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

Rogers SJ, Cavazos JE. Epilepsy. In: Talbert RL, DiPiro JT, Matzke GR, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York, NY: McGraw-Hill Medical; 2011

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Unique treatment challenges..

1- medication choice

2- suicidality

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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.

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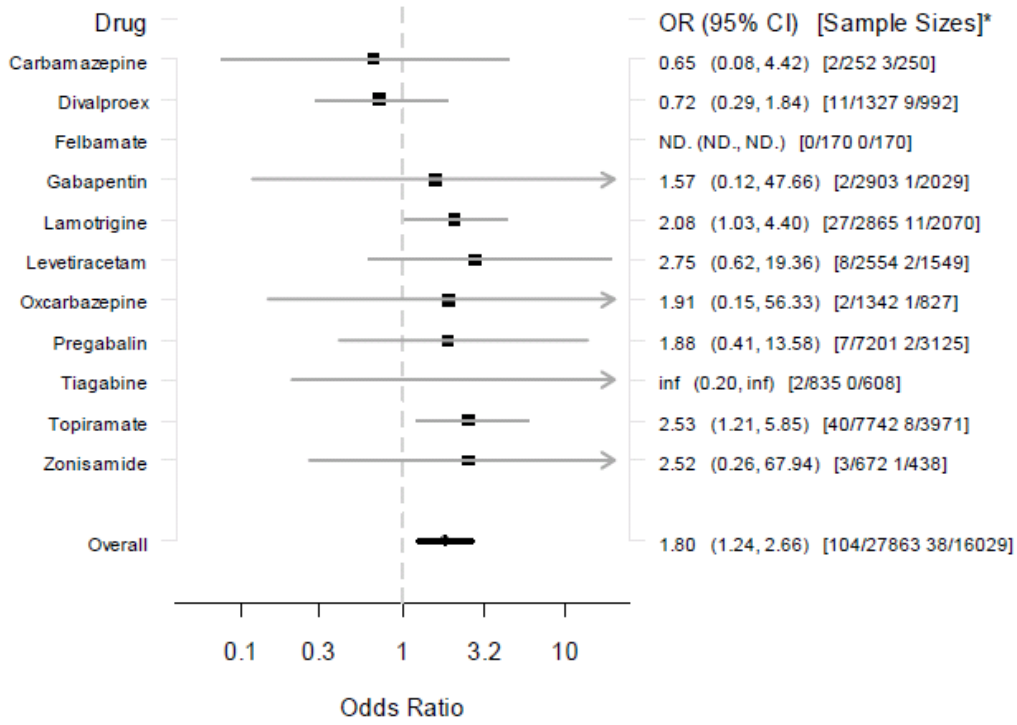
Suicidality with various ASMs



Katz R. Briefing document for the July 10, 2008 advisory committee meeting to discuss antiepileptic drugs (AEDs) and suicidality. Memorandum. (Accessed July 9,2010, at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA-Katz.pdf

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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

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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

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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

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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

Bateman, et al, Ep Currents, 2012

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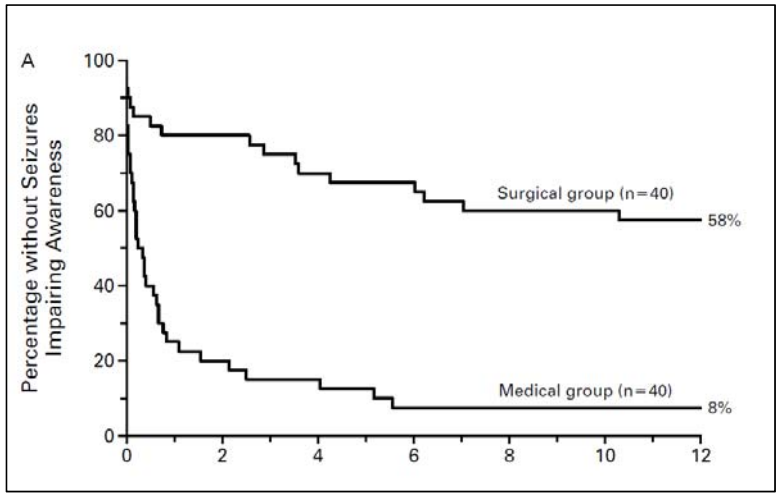
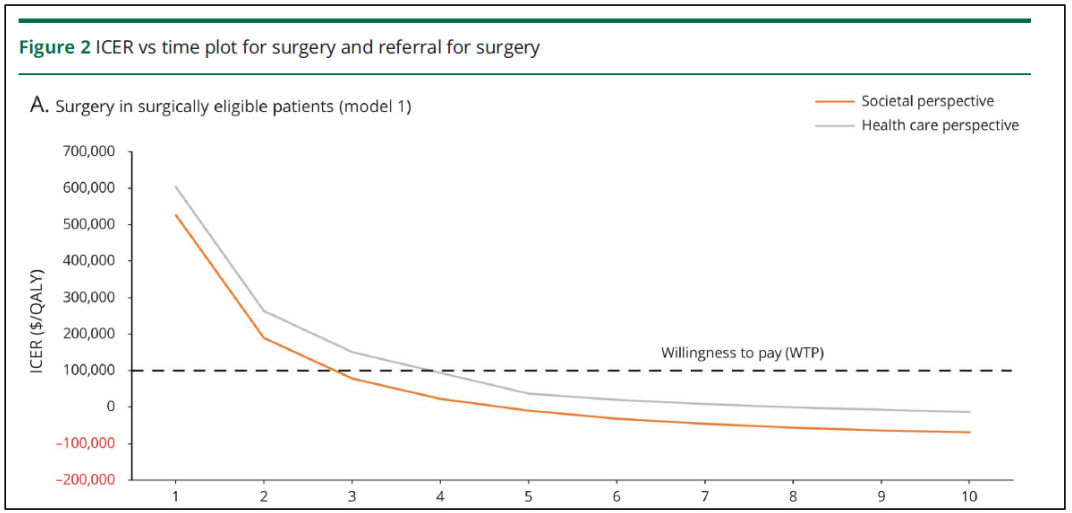
Outline

- 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)

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Epilepsy Surgery for Pharmacoresistant Temporal Lobe Epilepsy

A Decision Analysis

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Randall L. Sell, ScD
Leslie Lenert, MD, MS
Peter Muennig, MD, MPH
Robert R. Goodman, MD, PhD
Frank G. Gilliam, MD, MPH
John B. Wong, MD

Context Patients with pharmacoresistant epilepsy have increased mortality compared with the general population, but patients with pharmacoresistant temporal lobe epilepsy who meet criteria for surgery and who become seizure-free after anterior temporal lobe resection have reduced excess mortality vs those with persistent seizures.

Objective To quantify the potential survival benefit of anterior temporal lobe resection for patients with pharmacoresistant temporal lobe epilepsy vs continued medical management.

Conclusion The decision analysis model suggests that on average anterior temporal lobe resection should provide substantial gains in life expectancy and quality-adjusted life expectancy for surgically eligible patients with pharmacoresistant temporal lobe epilepsy compared with medical management.

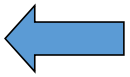
JAMA. 2008;300(21):2497-2505 www.jama.com

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



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Longitudinal trajectory of quality of life and psychological outcomes following epilepsy surgery

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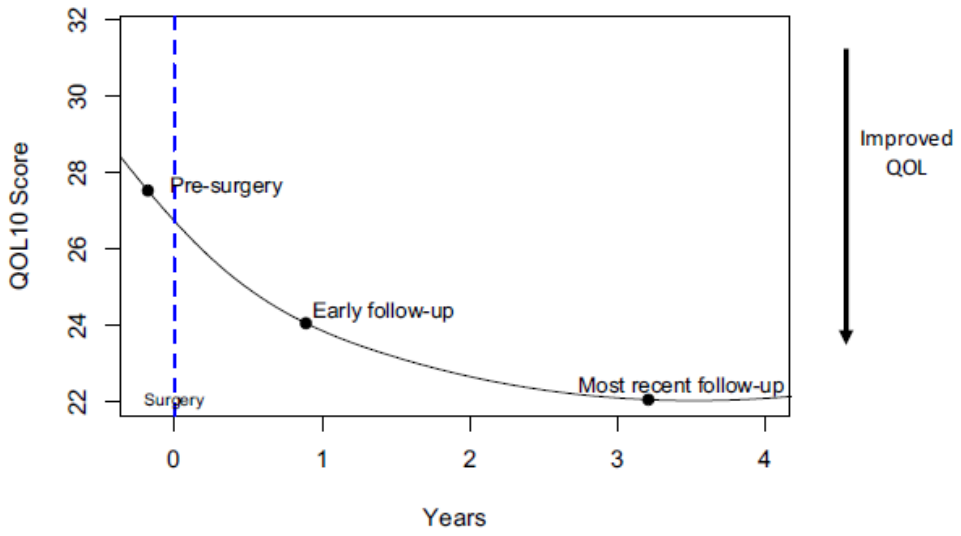
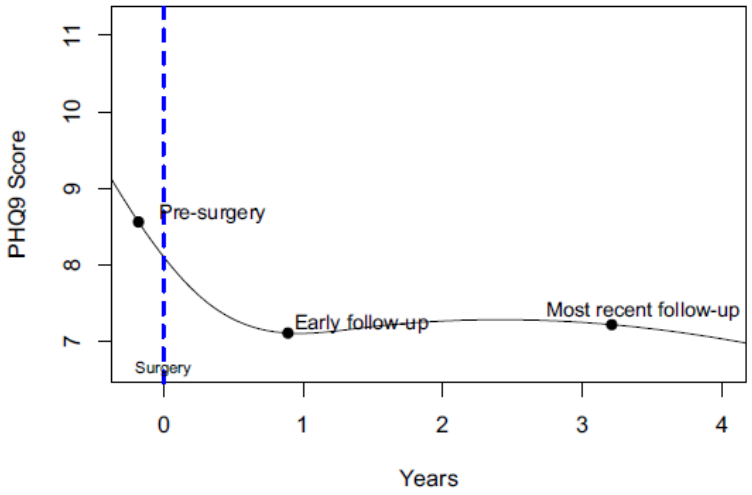
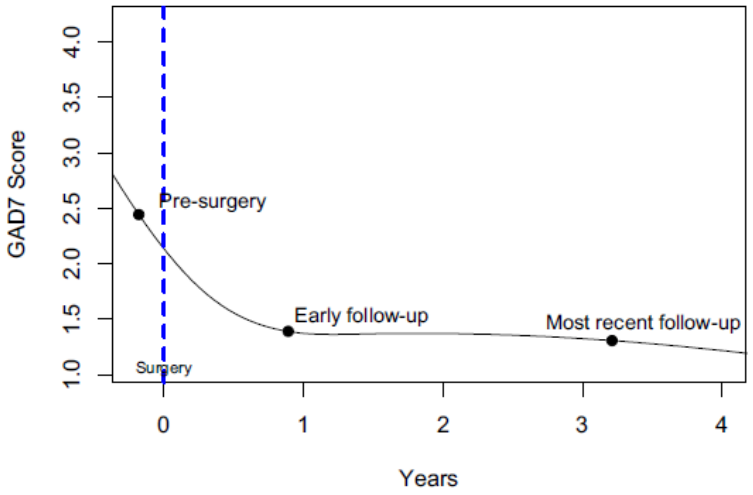


Quality of life continues to improve years after epilepsy surgery…

…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