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Cognitive and behavioral endpoints as primary outcome variables in epilepsy clinical trials

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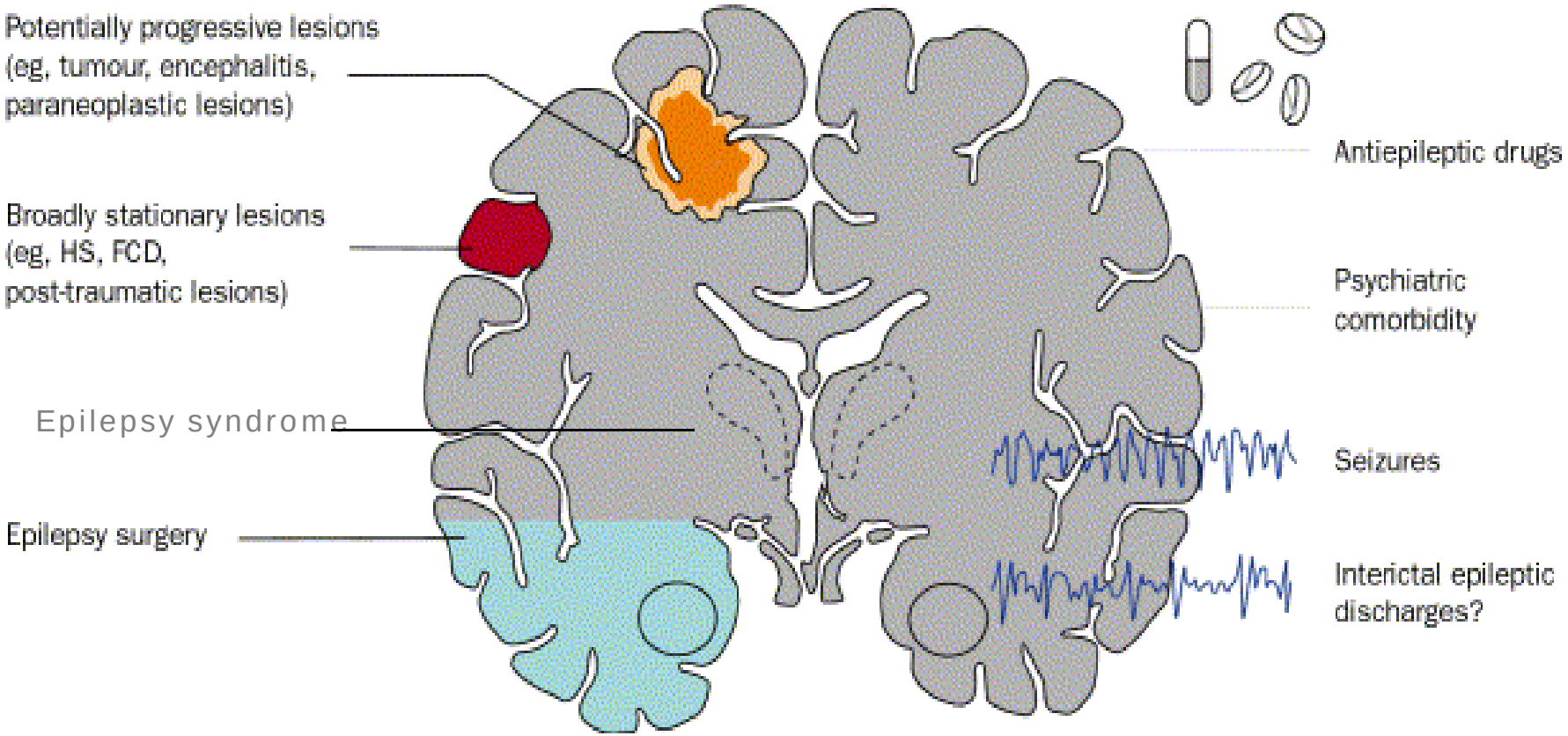
Epilepsy

- Unique disease
  - High incidence of neuropsychological deficits
  - High incidence of psychiatric comorbidities
- Antiepilepsy Drugs (AEDs) have risk of neuropsychological and behavioral side effects / adverse events (AEs)
  - psychotropic benefit

Morphological factors
(non-modifiable)

Clinical and demographic features
Age at onset
Lateralisation or topography of epileptogenic area
Duration of epilepsy

Functional factors
(modifiable)



Elger et al. *Lancet Neurology* 2004;3:663-672.

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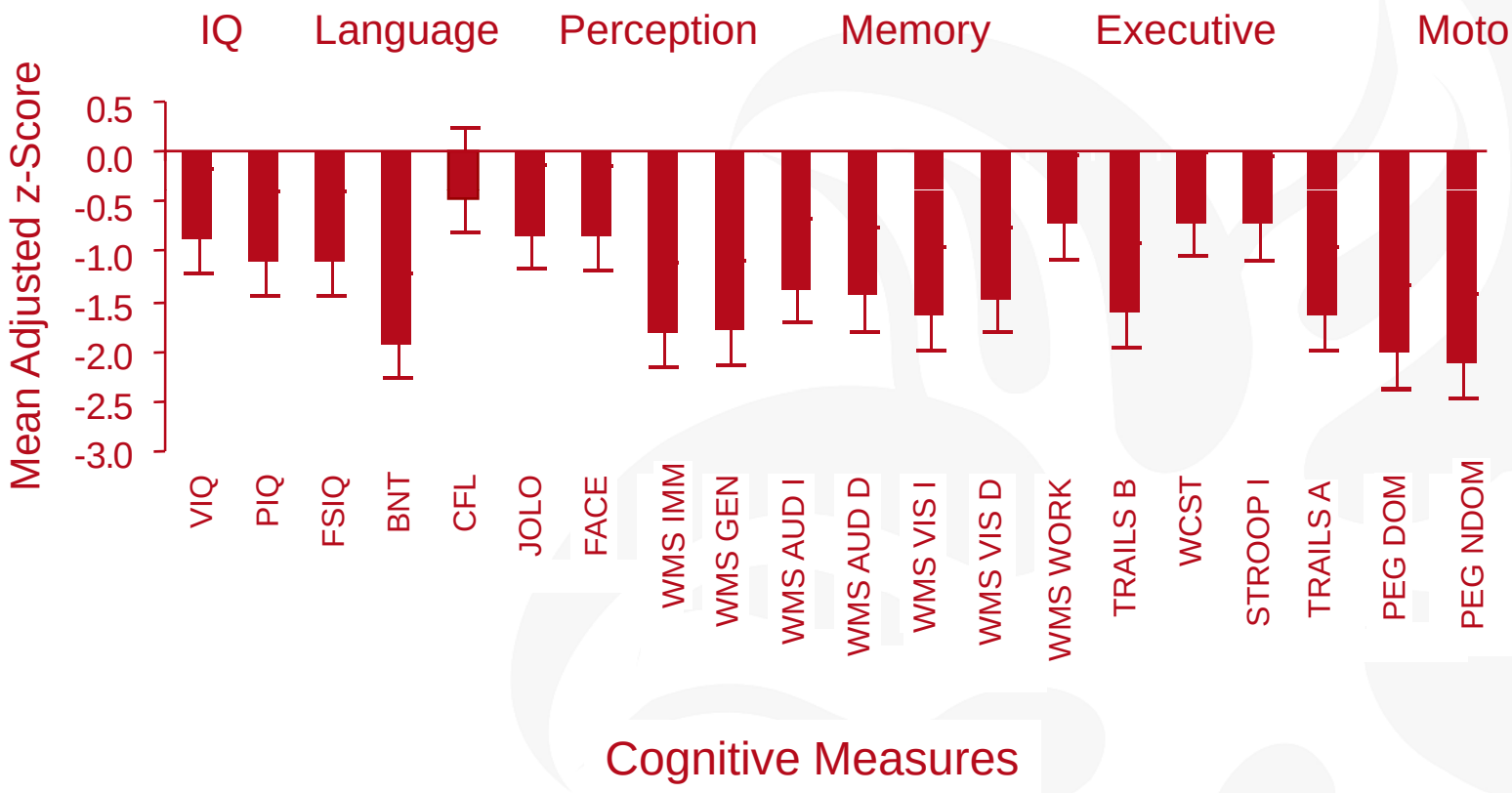
Cognition in Chronic TLE



Oyegbile et al. *Neurology* 2004;62:1736-1742.

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Neuropsych & Epilepsy

- Clinical trials concerned with cognitive or behavioral AEs rather than beneficial treatment effect
- AEDs do not differ in efficacy for appropriate indications/epilepsy syndrome
- AEDs are not anitepileptogenic/ neuroprotective

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Common Efficacy Criteria

- Adjunctive Therapy
  - Median percent reduction vs. placebo
  - 50% reduction in seizure frequency

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Adjunctive Therapy

- Add-on design in refractory patients
  - Sufficient seizure count to demonstrate reduction
  - Non-representative patient sample
    - Cognitive AED effects are smaller against backdrop of greater generalized cognitive impairment
    - Frequent seizures may affect cognitive endpoint
  - Doses chosen for efficacy, not designed for smallest effective dose (minimize behavioral AEs)

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Blinded Designs

- Intention to treat – avoids bias with differential survival within study
- Appropriate for dichotomous outcome (e.g., success/failure, survival)
- Inappropriate to characterize magnitude of cognitive effect

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Intention To Treat (ITT)

- Farwell et al. (1990) - modified ITT
- PB exposure associated 8.4 IQ decline
  - 94 placebo: 65 no meds, 24 phenobarbital
  - 83 PB: 27 no meds, 53 phenobarbital
- Assuming no drug equivalent to placebo
  - Magnitude of “real” difference 21 IQ points

Farwell et al., *NEJM* 1990;322:364-369.

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No Blinding – SANAD

- Standard And New Antiepileptic Drugs
  - Unblinded randomised controlled trial in hospital-based outpatient clinics in the UK
- Time to treatment failure
  - Lamotrigine > Carbamazepine
    - HR= 0.78 (95% CI 0·63–0·97)
  - Lamotrigine > Gabapentin
    - HR =0.65 (0.52–0.80)
  - Lamotrigine > Topiramate
    - HR=0.64 (0.52–0.79)

Brodie et al. *Neurology* 2007;68:402-408.

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SANAD

- Rash associated with LTG and CBZ
  - 21% CBZ treatment failures due to rash
  - 14% LTG treatment failures due to rash
- Overall CBZ rate of 32% rash compared to 5.5% with slower titration
- Rash related to titration
  - LTG being newer, titrated more slowly
  - CBZ being older, titrated more quickly

Brodie et al. *Neurology* 2007;68:402-408.

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RCI Cognitive AEs

- Primary Goal: Weight loss associated with topiramate/Topamax
- Secondary Goal: Cognitive effects
- Clinical trial of weight effects has dependent measure that does not interact with cognition
- Randomized trial contains placebo condition for comparison group permitting RCI calculation
- Design permits analysis of dose-dependent effects

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RCI Analysis (90% RCI)

Cognitive Outcomes

	Placebo N=38	TPM 64 N=42	TPM 96 N=36	TPM 192 N=41	TPM 384 N=31
Better/ No Change	38 100%	39 93%	34 94%	37 90%	23 74%
Worse	0 0%	3 7%	2 6%	4 10%	8 26%

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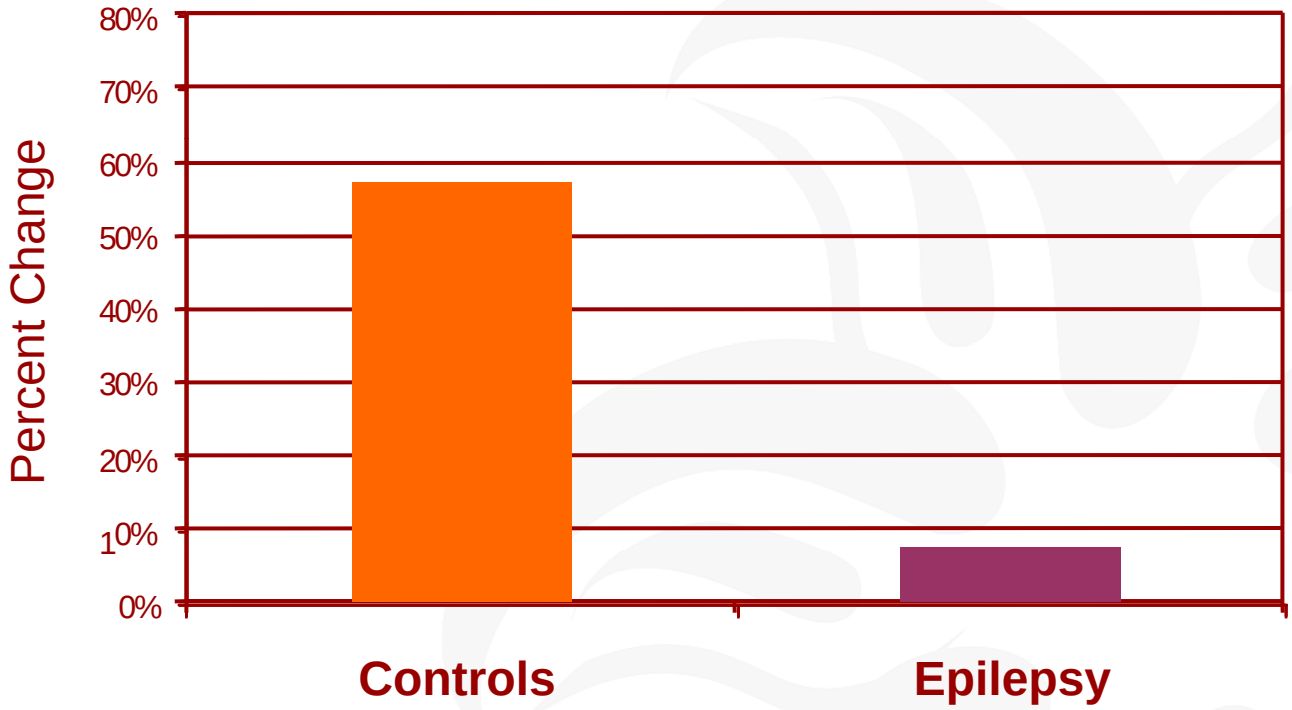
Significant Test-Retest Improvements



Hermann et al (2006). *Ann Neurol, 60*, 80-87.

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Psychiatric Disorders

Prevalence	Epilepsy	General Population
Depression	11%–60%	2%–4%
Anxiety	19%–45%	2.5%–6.5%
Psychosis	2%–8%	0.5%–0.7%
ADHD	?	2%–10%

[1]Anthony, et al. *Epidemiol Rev.* 1995;17:240-242. [2]Weissman, et al. *J Clin Psychopharmacol. 1*986;Suppl 6:11-17. [3]Kessler, et al. *Arch Gen Psych.* 1994;51:8-19. [4]Costello EJ. *J Am Acad Child Adolesc Psychiatry.* 1989;28:836-841.

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Coding Psychiatric AEs

- Behavioral and psychiatric side-effects not formally assessed in most clinical trials
- Reported by combining events into a single overall psychiatric variable
- Psychiatric AEs poorly defined in common reporting systems (e.g., WHO, COSTART, MedRDA)
- Absence of standardized or structured approaches to characterize behavioral AED-induced changes makes replication by independent investigators difficult

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Suicide Risk and AEDs

- In December 2008, FDA announced warning of increased risk of suicidal ideation or behaviors to prescribing information for AEDs
  - 0.43% AEDs vs. 0.22% placebo
  - Completed suicides: AED=4 vs. placebo=0
  - Patients: AED=27,863 vs. placebo= 16,029

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FDA Analysis

- Based on spontaneous reports, not systematically collected data
  - Suicidal Behavior (OR=2.92) > Ideation (OR=1.45)
  - North America (OR=1.38) < Elsewhere (OR=4.53)
  - Epilepsy (OR=3.53) > Psychiatric (OR=1.51) and Other Indication (OR=1.87)

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FDA Warning Effects

- Risk from SSRIs increased 1.95 fold based on spontaneous reports[1]
- No increased risk (RR=0.92; CIs= 0.76-1.11) when data collected systematically from rating scales[2]
- Prescription rates fell for youths after FDA warning[3,4]
- Incidence of completed suicides for youths increased after warning[3]

[1]Hammad et al. *Arch Gen Psychiatry* 2006;63:332-9.

[2]Mann et al. *Neuropsychopharmacology* 2006;31:473-92.

[3]Gibbons et al. *Am J Psychiatry* 2007;164:1356-63.

[4]Nemeroff et al. *Arch Gen Psychiatry* 2007;64:466-72.

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What is IQ?

- Wechsler Adult Intelligence Scale (WAIS)
- Wechsler Abbreviated Scale of Intelligence (WASI)
- High correlations, but in healthy samples
- Processing speed and attention more sensitive to neuropsychological impairment
- WASI IQ will be overestimated given absence of working memory and processing speed
- Not equivalent for characterization of sample

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Patients vs. Controls

172 pairs

WISC/WAIS	Patient	Control	P-value
FSIQ	99 (18)	105 (14)	.0001
Verbal Comprehension	104 (18)	108 (17)	.001
Perceptual Organization	102 (18)	104 (15)	.09
Working Memory	98 (98)	102 (14)	.004
Processing Speed	96 (16)	103 (14)	.0001

WASI equivalent			
FSIQ	103	106	

Berg et al. *Epilepsy Behav* 2008;13:614-619.

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Recommendations

- Trials independent of efficacy designs for FDA approval
- New onset patients
- Control group of monotherapy patients
- Cognitive endpoints; Reliable Change Indices
- Questionnaires - beneficial mood effects
- Psychiatric Interviews (SCID)