OPENING

Behavioral Problems and Epilepsy

William E. Rosenfeld, M.D.
Director

The Comprehensive Epilepsy Care Center
For Children And Adults
St. Louis, Missouri

HISTORY

- Hippocrates is credited with demystifying epilepsy, the “sacred disease,” and proposing a direct relationship with “melancholia”.
- Reynolds (1861) noted the interactions between seizures and mood states, and observed depression before an epileptic event and as a frequent hallmark of interictal complaints.
- Gibbs (1948, 1952), reported an incidence of psychiatric symptoms in 40% of epileptics with psychomotor epilepsy

Incidence of Depression

- Incidence of depression in epilepsy higher than in a matched population of healthy controls (range 11% to around 62%)

- Rate of depression in the general population determined to be 4.9% for MDD, with a 3.3% incidence of dysthymia (lifetime prevalence)

Psychiatric or Behavioral Effects of Antiepileptic Drugs

- Behavior toxicity profile of most drugs is complex – drug may influence one aspect of behavior positively and another negatively

Behavioral Effects of AEDs

- May be dose related
- There may be subacute and chronic changes
- Duration of AED therapy
- Use of polytherapy
- Exposure of developing neuronal structures to maternal AEDs and CNS injury
- Intercurrent illness

Direct Effects

- Occur with prenatal exposure
- Mechanism not clear, although in vitro study findings include reduction in neuronal density, changes in neuronal morphology and changes affecting various neurotransmitters
- Chronic effects are typically unrelated to serum levels

Indirect Effects

- Include folate deficiency
- Hepatotoxicity
- Hyperammonemia
- Electrolyte imbalances
- Anemia
- Forced normalization
- Effects on monoamine, neuropeptides and endocrine function
- Related to polypharmacy, AEDs' withdrawal effects and drug interactions with psychotropics

- Need to be aware of behavior-related effects of AEDs

- Suppressing seizures at expense of deterioration in patient's behavior is not ideal

“The good physician is concerned not only with turbulent brainwaves but with disturbed emotions and with social justice, for the epileptic is not just a nerve-muscle preparation; he is a person, in health an integrated combination of the physical, the mental, the social, and the spiritual. Disruption of any part can cause or aggravate illness.”

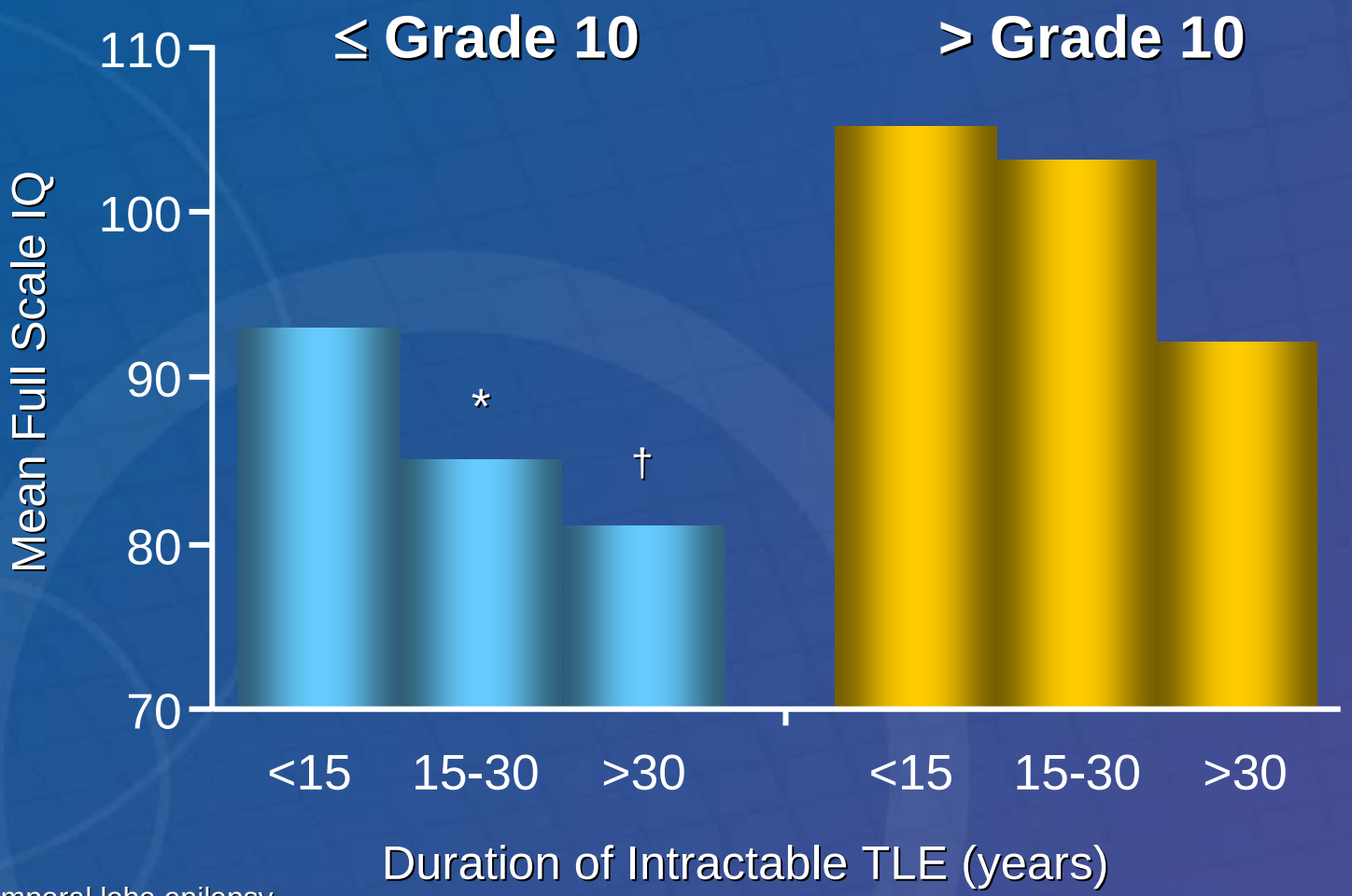
Lennox and Markham

Conditions Associated With Epilepsy

- Cognitive impairment
- Depression
- Anxiety
- Sleep disturbance
- Migraine

Kwan, Brodie. *Lancet*. 2001;357:216-222; Malow et al. *Neurology*. 2000;55:1002-1007; de Weerd et al. *Epilepsia.* 2004;45:1397-1404; Lipton et al. *Neurology*. 1994;44(suppl 7):S28-S32.

Effects of Duration of Epilepsy on Cognitive Impairment



TLE = temporal lobe epilepsy.
*P<.05; †P<.01

Jokeit, Ebner. In: *Progress in Brain Research*. 2002;135:455-463.

Epilepsy Patients Have a Higher Rate of Psychiatric Disorders

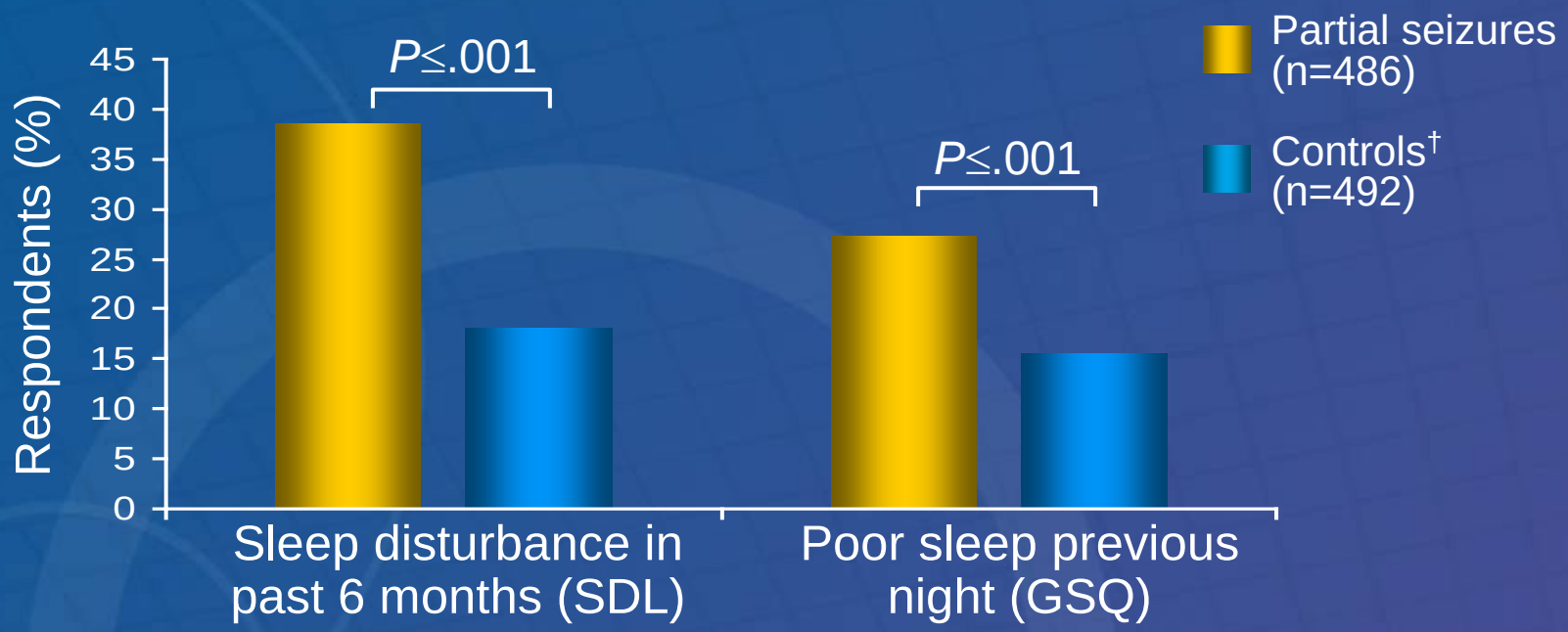
Prevalence Rates of Psychiatric Disorders

	Epilepsy Patients (Range)	General Population (Range)
Depression	11% - 80%	3.3% - 17%
Generalized anxiety disorders	15% - 25%	5.1% - 7.2%
Psychosis	2% - 9%	0.2% - 1.0%
Attention-deficit/hyperactivity disorder	12% - 37%	4% - 12%

Kanner, Palac. *Curr Neurol Neurosci Rep*. 2002;2:365-372.

Patients With Epilepsy Have a Higher Rate of Sleep Disturbance

Survey of Patients With Partial Seizures* vs Matched Controls



Some subscales/items were not completed by all respondents.
*Patients with partial seizures were receiving AED treatment.

SDL = Sleep Diagnosis List; GSQ = Groningen Sleep Questionnaire.

†Did not have epilepsy and weren't on any AEDs for any indication.

de Weerd et al. *Epilepsia.* 2004;45:1397-1404.

Epilepsy Patients Have Higher Rates of Headache/Migraine

- Headache is common in the general population
  - 15% lifetime prevalence of migraine
  - 66% lifetime prevalence of tension headache
- More common in epilepsy
  - Headaches and migraines may be induced by partial seizures
  - Seizures may be precipitated by migraine
- Some existing AEDs may treat some types of headaches (topiramate and valproate are approved for migraine prophylaxis)

Rasmussen, Olesen. *Neurology*. 1992;42:1225-1231; Mathew. *Headache*. 2001;41(suppl 1):S18-S24.

High Economic Burden of Epilepsy Societal Perspective

- Annual cost associated with treating epilepsy in the US is estimated at $12.5 billion in 1995 for 2.3 million existing cases
  - Direct costs: $1.7 billion (14%)
  - Indirect costs: $10.8 billion (86%)
- Epilepsy patients over 65 account for a disproportionate share of direct costs
- Lifetime costs for 181,000 incident cases are estimated at $11.1 billion

Begley et al. *Epilepsia*. 2000;41:342-351.

It Is Common for People With a Seizure Disorder to Experience Depression

Some symptoms of depression[1]:

- Feeling sad
- Loss of interest in enjoyable activities
- Changes in weight or appetite
- Loss of energy
- Difficulty concentrating
- Changes in sleep pattern
- Restlessness or being slowed down
- Feelings of worthlessness
- Thoughts of death or suicide

- About one third of people diagnosed with a seizure disorder may also be clinically depressed[2]
- Depression is 3 times more common among people with epilepsy[2]

[1]APA. DSM-IV-TR. 2000. [2]Ettinger A et al. *Neurology*. 2004;63:1008-1014.

If You Have Symptoms of Depression, Talk to Your Neurologist

In 6 out of 10 people with pharmacoresistant epilepsy who also have depression, the depression goes undiagnosed.[1]

Your depression may be more than just a reaction to seizures

- Clinical studies have shown that depression in people with epilepsy is not correlated with seizure frequency[1]

[1]Boylan LS et al. *Neurology*. 2004;62:258-261.

Depression Is Strongly Linked to Quality of Life

- Depression is a powerful predictor of quality of life in patients with epilepsy[1]
- Suicide risk in patients with epilepsy is up to 10 times greater than in the general population[2]

"The treatment of depression is of high importance for a patient with epilepsy, since it is strongly associated with the patient's quality of life."[3]

—Drs. Balabanov and Kanner, neurologists at Chicago's Rush University Medical Center

[1]Boylan LS et al. *Neurology*. 2004;62:258-261. [2]Robertson MM. In: *Epilepsy: A Comprehensive Textbook*. 1997:2141-2151.
[3]Balabanov A et al. *Psychiatric Times*. November 2004;13:23-26, 31-32.

Depression Can Be Treated, and Life Can Feel Better

Quality-of-life benefits from the treatment of depression may include[1]:

- Vitality—increased energy
- Social functioning—increased interaction with family and/or friends
- Emotional well-being—better function at work and in daily activities
- Mental health—more positive feelings

Kroenke K et al. JAMA. 2001; Vol 286, No. 23; 2947 – 2955

Comorbidity with Epilepsy

- Psychiatric disorders
- Migraine
- Reproductive dysfunction
- Accidents
- Osteoporosis
- Stroke, CVD, brain tumors
- Alzheimer's disease in people aged ≥65 y

Epilepsy Foundation of America, 2001. Wiegartz P, 1999. Bredkjaer SR, 1998. Breslau N, 2001. Hauser WA, et al, in Wyllie text, 2001: 139-145.

Anxiety Disorders

Anxiety disorders

- Large documented range
  - 0 – 60% prevalence
- Lower incidence reported in severe to profound MR patients
  - Higher prevalence of only behavioral symptoms
- Limited amount of specific disorder data
  - GAD rate in mild MR similar to non-MR pts
  - Social phobia may be much higher in some groups
    - Fragile X Syndrome

Bailey. *J Intellect Disabil Res* 2003; White P, Chant D, et al. Aust N Z *J Psychiatry* 2005; Masi G, Gavilla L, et al. *Psychiatry* 2000

Difficulties with Anxiety and MR

- Communication barrier
- Learned coping mechanisms
  - Dependence
  - Avoidance
- Over-shadowing diagnosis and symptoms
  - OCD vs. Autism

Non-Pharmacologic Treatments

- Desensitization
  - All degrees of cognitive impairment
  - For specific phobias
- Cognitive Behavioral Therapy
  - Efficacy in mild-moderate MR
- Counseling
  - Efficacy in mild-moderate MR

Convers C, Miltenberger RG, et al. *J Appl Behav Anal* 2004

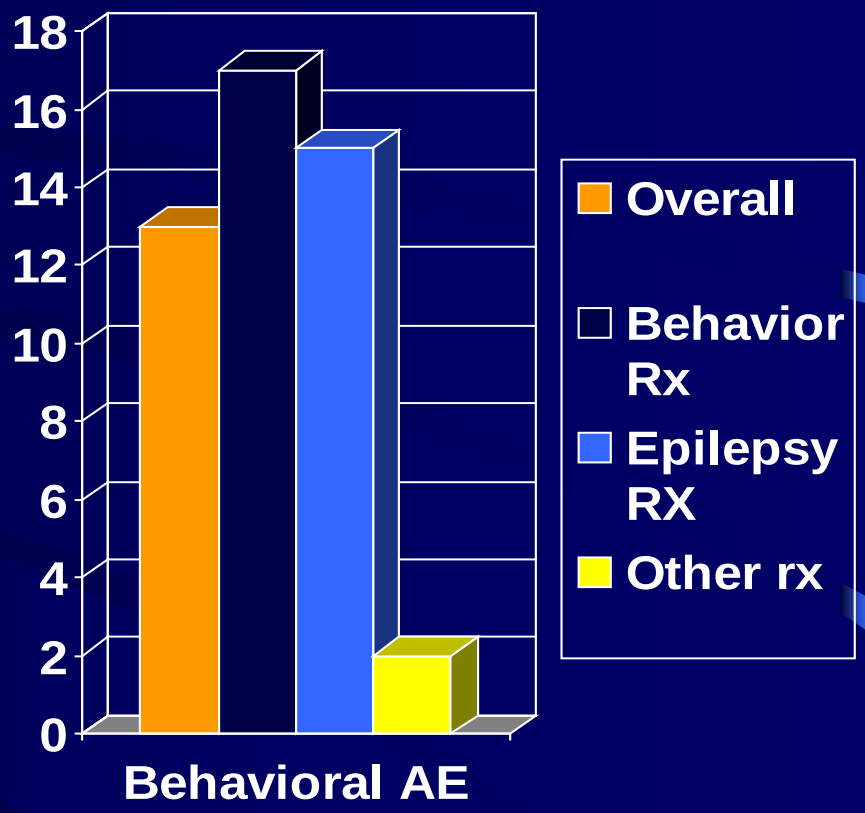
Pharmacologic Treatments

- Benzodiazepines
  - Helpful vs. Harmful
- Buspirone
- Antidepressant data
  - Not anxiety specific
  - Treating behavioral symptoms or depression

Aman MG, Collier-Crespin A, Lindsay RL. *Eur Child Adolesc Psychiatry* 2000

Benzodiazepines

- Behavioral Side Effects
  - Aggression
  - Agitation
  - Hyperactivity
  - Property Destruction
  - Irritability
  - Temper Tantrums



Kalachnik JE, Hanzel TE, et al. *Am J Ment Retard* 2002; Kalachnik JE, Hanzel TE, et al. *J Autism Dev Disord* 2003

Mood Disorders

Mood Disorders Statistics

- Bipolar Disorder
  - No ranges available
- Depression
  - Range 8-30 %
- Mood disorders more common in mild to moderate MR
- Suicidal Ideation
  - Present in 1 of 3
  - Previous Attempt
    - 11%
- About ¼ of the caretakers were unaware of ideation

White P, Chant D, et al. Aust N Z *J Psychiatry* 2005; Tsiouris JA, Mann R, et al. *J Intellect Disabil Res* 2003; Holden B, Gitlesen JP. *J Intellect Disabil Res* 2004; Janowsky DS, Davis JM. *Curr Psychiatry Rep* 2005

Symptom Disparity

- Traditional Depression symptoms
  - Seen in mild MR patients
  - ? Also severe to profound MR patients

- Behavioral symptoms as depression symptoms (?)
  - Apply more to severe to profound MR
  - Conflicting data

Tsiouris JA, Mann R, et al. *J Intellect Disabil Res* 2003; Marston GM, Perry DW, et al. *J Intellect Disabil Res* 1997; Janowsky DS, Davis JM. *Curr Psychiatry Rep* 2005

Treatment

- Lithium
  - Adverse effects ~60%
    - Similar to general mentally ill population
- Carbamazepine
- Valproic Acid
- Antipsychotic data not for affective disorders

Pary R. Am J Ment Retard 1991; Sovner R *J Clin Psychiatry* 1989; Vanstraelen M, Tyrer SP. *J Intellect Disabil Res* 1999

Antidepressants

- SSRI
  - Fluoxetine
    - Case series
  - Paroxetine
    - Open label adolescents
  - Citalopram
    - Open label
  - Wide dosage range
  - Limited adverse effects
- TCAs
  - Imipramine
    - Reports of behavior deterioration
    - Case report of efficacy
- No reports found on other antidepressants

Verhoeven WM, Veendrik-Meekes MJ, et al. *Eur Psychiatry* 2001; Howland RH *J Nerv Ment Dis* 1992; Masi G, Marcheschi M, Pfanner P *J Intellect Disabil Res* 1997; Aman MG, White AJ, et al. *J Autism Dev Disord* 1986; Field CJ, Aman MG, et al. *J Ment Defic Res* 1986

Psychosis

Psychosis in Adult MR

- Prevalence of psychosis ~1-4%
- Difficult to assess
  - Developmental level dependent
  - Communication barrier
  - More commonly seen in mild to moderate MR

Holden B, Gitlesen JP. *J Intellect Disabil Res* 2004; White P, Chant D, et al. Aust N Z *J Psychiatry* 2005; Deb S, Thomas M, et al. *J Intellect Disabil Res* 2001; Melville CA *J Intellect Disabil Res* 2003

Psychosis Treatment

- Non-pharmacologic
  - Environmental
  - Behavioral
- More effective in mild to moderate MR patients

- Antipsychotics
  - Typicals
  - Atypicals
- Doses lower than general population
- Long term treatment

Holden B, Gitlesen JP. *J Intellect Disabil Res* 2004; Janowsky DS, Barnhill LJ, et al. *J Clin Psychopharmacol* 2005

Dementia

Dementia Considerations

- Symptoms other than memory loss
  - Baseline functioning consideration
- Age of onset
  - Down's Syndrome at age 40 years
  - Earlier onset for MR patients (?)

Deb S, Braganza J. *J Intel Disabil Res* 1999

Use of ACHI

- Donepezil
  - Reports of efficacy up to 24 weeks
  - Mild to moderate disease
  - Down's syndrome patients
- Proposed roles for
  - Rivastigmine
  - Galantamine
  - Memantine

Heller JH, Spiridigliozzi GA, et al. *Am J Med Genet* A 2003; Prasher VP. *Int J Geriatr Psychiatry* 2004; Johnson N, Fahey C, et al. *Am J Ment Retard* 2003

Aggression and Agitation

Anticonvulsant Drugs Marketed in the U.S.

EPILEPSY CONCLAVE 2014

1912	Phenobarbital	Winthrop	No requirement for toxicity or efficacy until 1938 (toxicity) and 1962 (efficacy)
1935	Mephobarbital	Winthrop	
1938	Phenytoin	Parke-Davis	Toxicity but no requirement of efficacy data until 1962, without requirement for double-blind, randomized controlled trials
1947	Mephenytoin	Sandoz	
1954	Primidone	Ayerst	
1957	Methsuximide	Parke-Davis	
1957	Ethotoin	Abbott	
1960	Ethosuximide	Parke-Davis	
1968	Diazepam	Roche	Risk-benefit with toxicity and substantial evidence of efficacy (double-blind, randomized controlled trials)
1974	Carbamazepine	Ciba-Geigy	
1975	Clonazepam	Roche	
1978	Valproate	Abbott	
1981	Clorazepate	Abbott	
1992	Felbamate	Carter-Wallace	Era of double-blind, randomized controlled trials with superiority design to show significant treatment effect, ie, statistically significant difference between treatment arms
1993	Gabapentin	Parke-Davis	
1994	Lamotrigine	Glaxo-Wellcome	
1997	Topiramate	Ortho-McNeil	
1998	Tiagabine	Abbott	
2000	Zonisamide	Eisai	
2000	Levetiracetam	UCB Pharma	
2000	Oxcarbazepine	Novartis	
2004	Pregabalin	Pfizer	

Older Anti-Epileptic Drugs

- 1912 Phenobarbital
- 1938 Phenytoin (Dilantin)
- 1968 Carbamazepine (Tegretol)
- 1978 Valproic Acid (Depakene)/ Divalproex Sodium (Depakote)

Older Anti-Epileptic Drugs

- 1912 Phenobarbital
- 1938 Phenytoin (Dilantin)
- 1968 Carbamazepine (Tegretol)
- 1978 Valproic Acid (Depakene)/ Divalproex Sodium (Depakote)

Risk Factors and Co-Morbidities

- General Medical Diagnoses
  - Hypertension
  - Cardiovascular Disease
  - Diabetes Mellitus
  - Hyperlipidemia
  - Cerebrovascular Disease

- Neurologic Diagnoses/Disorders/Dysfunction
  - Epilepsy
  - Alzheimer-like diseases
  - Cerebrovascular Disease
  - Tumors
  - Cerebellar dysfunction
  - Gait abnormalities

Psychosocial Factors

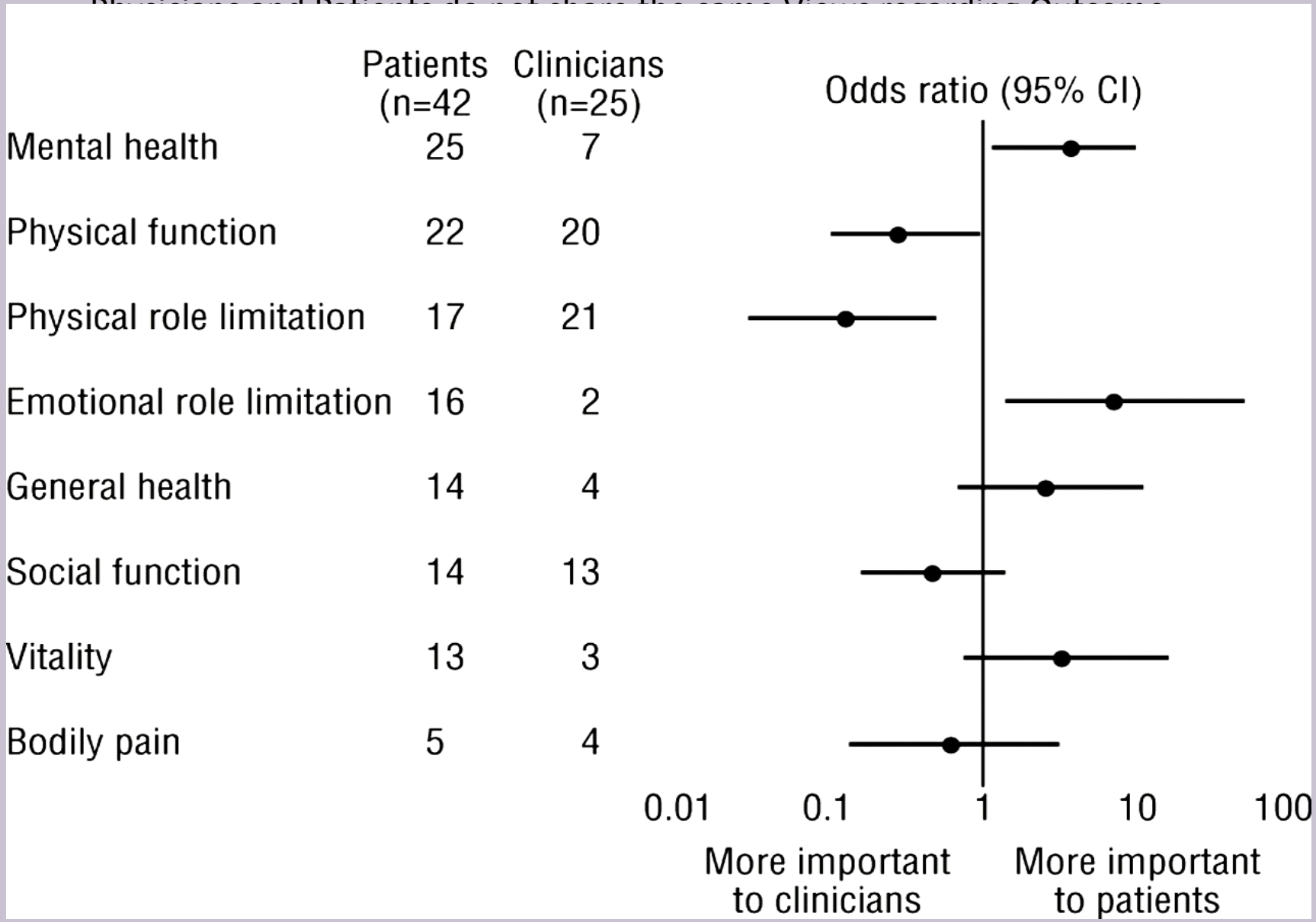
- 92 patients with poorly controlled epilepsy
  - 68% no personal friends
  - 57% never had steady relationship
  - 8% married

- Marriage rates
  - 61% females (83% of expected rate)
  - 38% males (59% of expected rate)

Thompson P, Oxley J. Epilepsia 1988; 29: 9-18
Dansky, et al. Epilepsia 1980: 21: 251-71

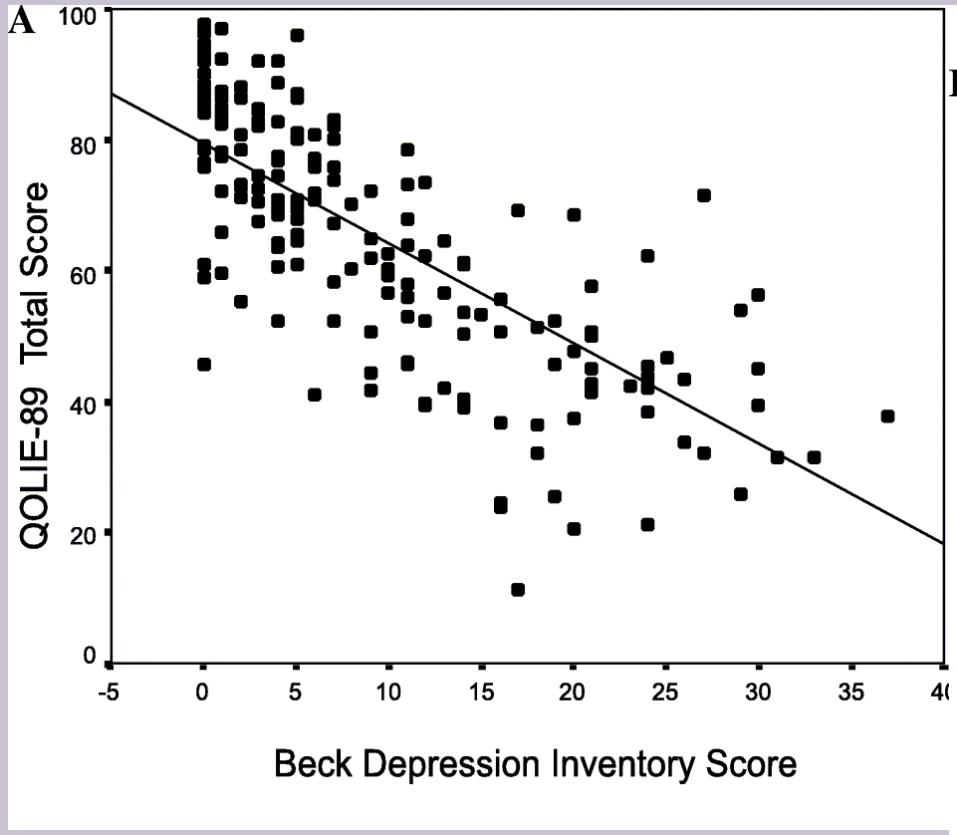
Psychiatric Co-Morbidities in Developmentally Disabled Patients

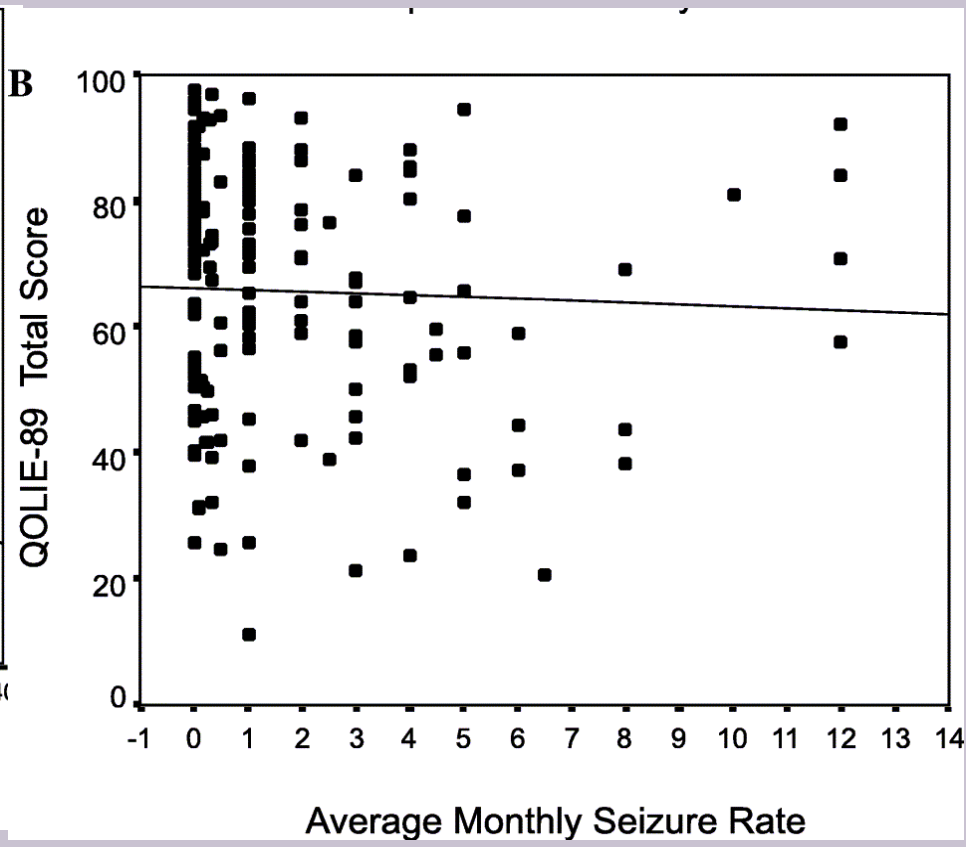
- Estimated to range from 10-60%
- Usual frequency approximately 25%
- Maladaptive behavior up to 55%
- Most common psychiatric disorders
  - aggressive (self and outward directed)
  - impulsive behaviors



Rothwell PM et al. BMJ 1997;314:1580-3

Depression but not Seizure Frequency determines Quality of Life in Treatment-Resistant Epilepsy*

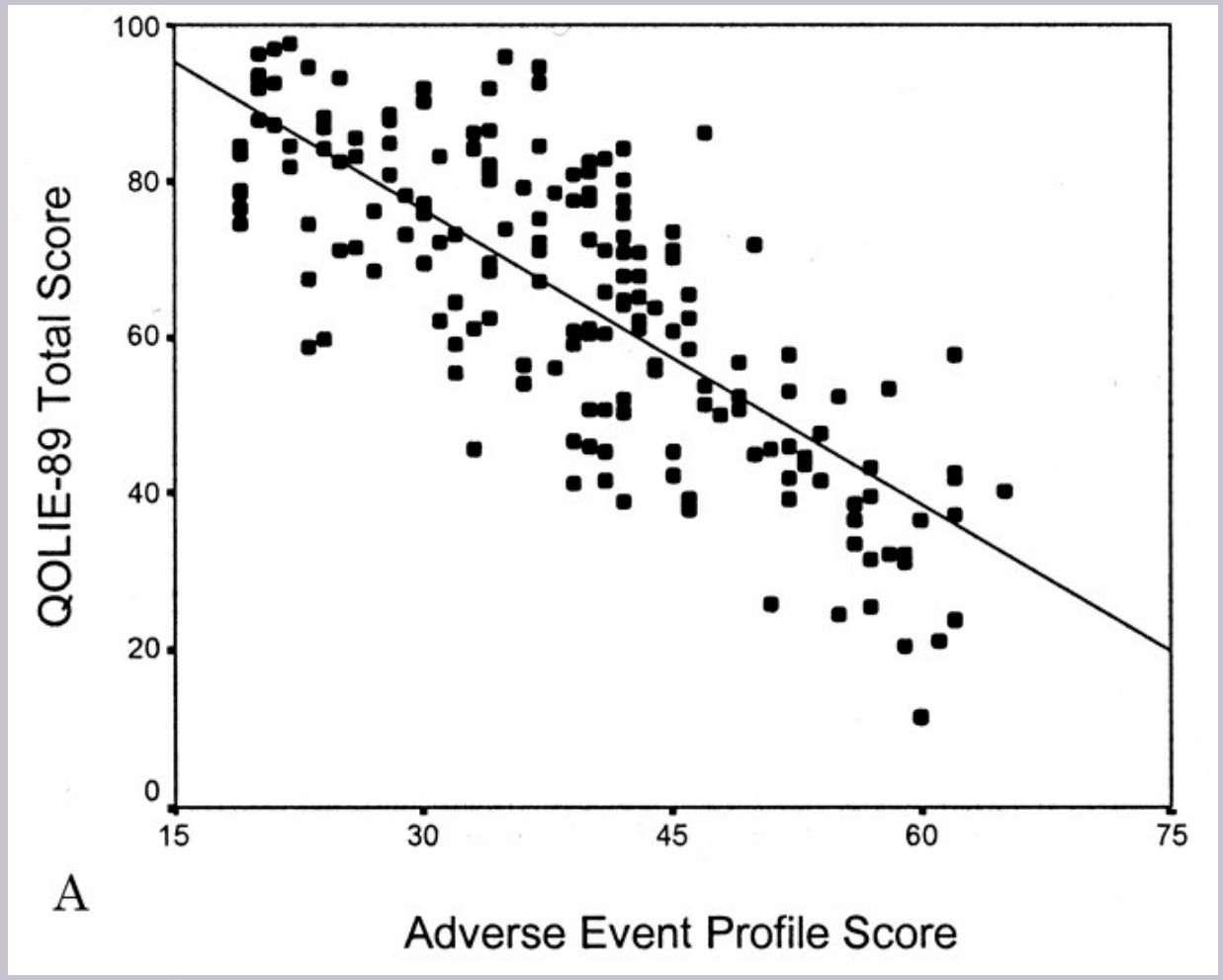




*** Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy Neurology. 2004;62:258-61**

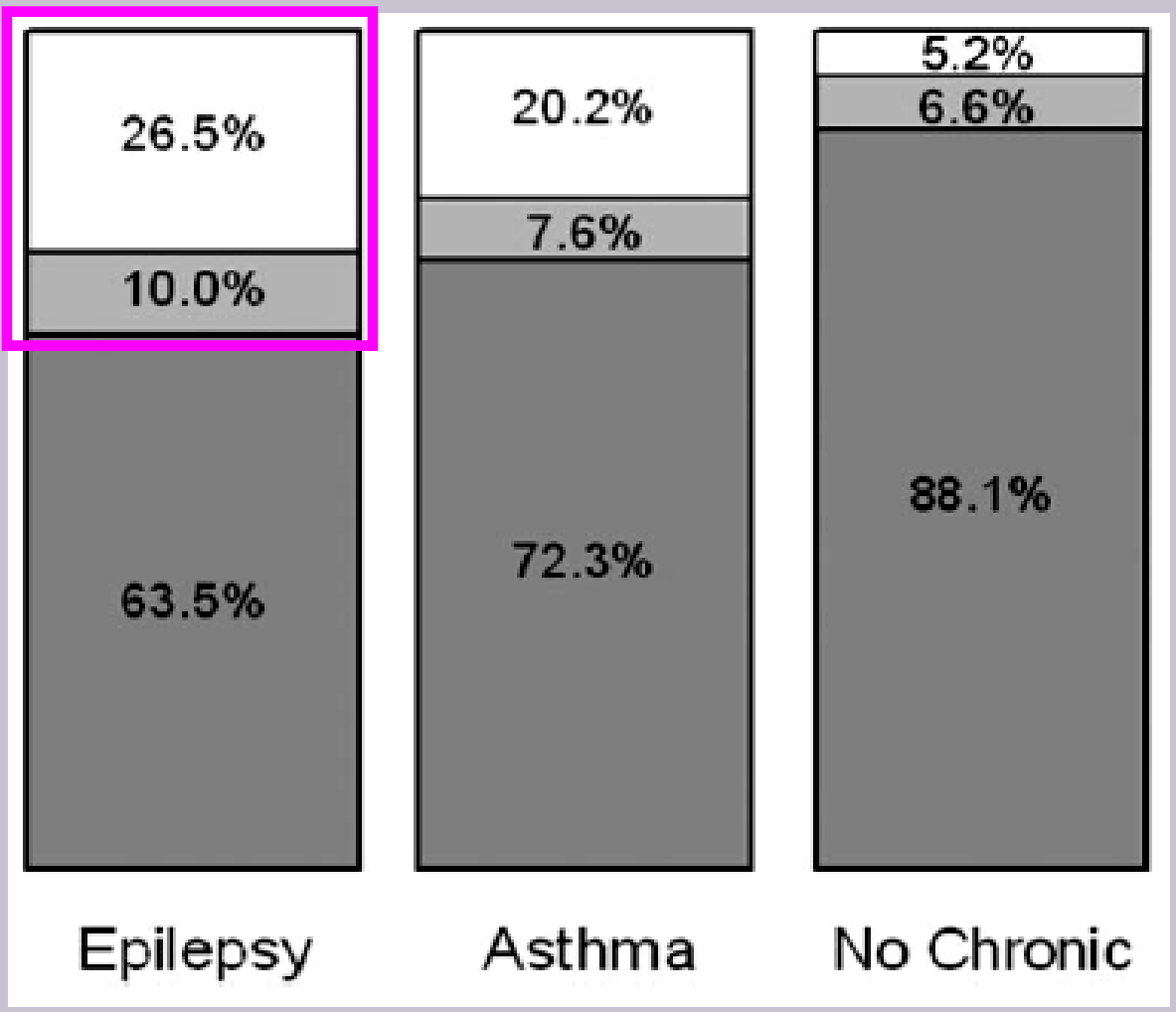
Gilliam F. Optimizing health outcomes in active epilepsy; Neurology 2002;58(S5):9-20.

Adverse Effect of AEDs: Impact on Quality of Life



Gilliam et al. Neurology 2004;62:23-27

Depression in Epilepsy: A Community-Based Study



$p < 0.001$

Ettinger et al. *Neurology* 63:1008-1014, 2004

Summary

- Adverse medication effects and comorbid psychiatric symptoms contribute substantially to poor health outcomes
- Newer AEDs vary in their positive and negative effects on neuropsychiatric symptoms
- New drug development has potential for further improved care in epilepsy

Medication-related Influences: Rules Of Thumb

- Most cognitive side effects follow a dose-response curve (e.g., higher doses -> increased likelihood of side effects)
- Side effects are more likely in polytherapy
- Side effects are more likely at faster titration schedules
- With some exceptions, the newer drugs (e.g., lamotrigine, levetiracetam) tend to be cognitively "cleaner" than the older drugs (e.g., phenytoin, valproic acid)

Drane DL & Meador KJ. *Epilepsy & Behavior*. 2002;3:S49-S53.

Summary of Literature

- Cognitive impairment can result from both the pathologies causing epilepsy as well as their treatments
- The AEDs least associated with cognitive decline are GBP, LEV, LTG, TGB and LCM.
- The AEDs most associated with at least some degree of cognitive decline are benzodiazepines, CBZ, OXC, PB, PHT, TPM and ZNS
- Measurement of cognition through an objective, computerized, validated battery in a naturalistic but blinded and randomized study should be the gold standard

Medication Interactions and Medical Disorders

- Metabolic dysfunctions
    - Hyponatremia
    - Hypocalcemia/Osteoporosis/Osteopenia
    - Hyperlipidemia
    - Hyperglycemia
    - Thyroid Abnormalities

- Hepatic dysfunction
- Decreased platelets and platelet aggregation

Comorbidity with Epilepsy

- Psychiatric disorders
- Migraine
- Reproductive dysfunction
- Accidents
- Osteoporosis
- Stroke, CVD, brain tumors
- Alzheimer's disease in people aged ≥65 y

Epilepsy Foundation of America, 2001. Bredkjaer SR, 1998. Breslau N, 2001. Hauser WA, et al in Wyllie text, 2001: 139-145.

Traditional AEDs as First-Line Therapy: Drawbacks

- Pharmacokinetics
- Drug interactions
- Acute idiosyncratic organ toxicity / hypersensitivity
- Chronic side effects

Traditional First-Line Therapy: A Sample of Clinically Significant Non-AED Interactions

EPILEPSY CONCLAVE 2014

PHT	CBZ	VPA
OCs	OCs	Aspirin
Analgesics/ antipyretics	Antibiotics	Warfarin
Antacids	Antidepressants	Haloperidol
Cimetidine	Neuroleptics	Fluoxetine
Antihistamines	Cimetidine	Chlorpromazine
Diltiazem	CCBs	AZT
Antineoplastics	Warfarin	

OCs, oral contraceptives; AZT, zidovudine

Unmet Medical Needs related to AEDs

- Third Generation AEDs
  - Anti-epileptogenesis / Disease Modification
  - Unsurpassed efficacy (seizure free rates) in therapy refractory patients
  - Targeted Drugs (Pharmacogenomics) for specific syndromes / channelopathies

➔ **Currently no compounds in development**

- **Second Generation AED Attributes**
  - Increased Safety
  - Broad spectrum activity
  - No Cognitive Side Effects
  - No Serious Psychiatric Side Effects
  - No Drug Interactions
  - High efficacy / seizure freedom
  - Convenient Dosing
  - Speed of Onset

➔ **Several compounds in development**

Epilepsy Unmet Medical Needs: Summary

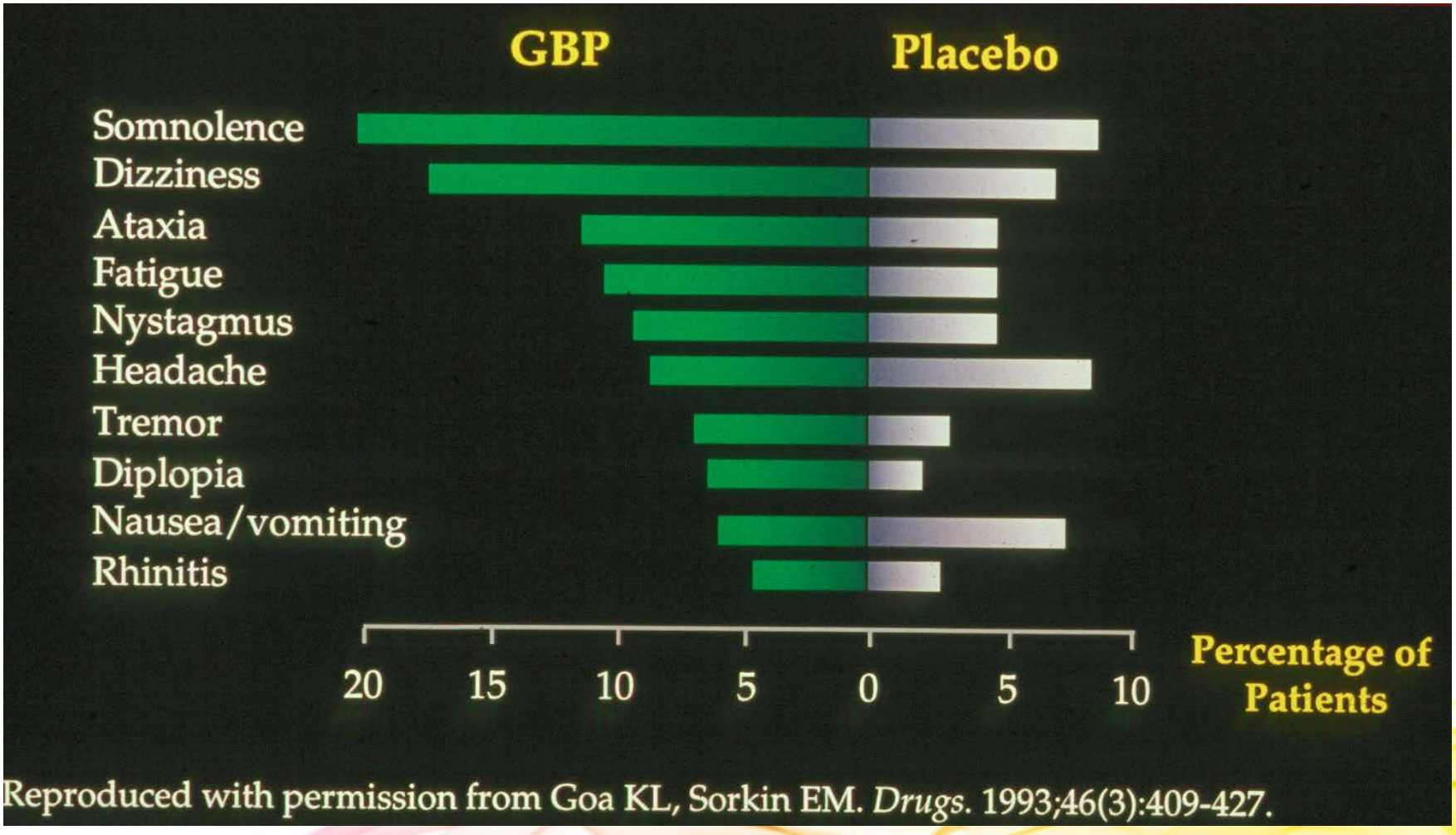
- Individualized treatment and trial and error is the rule
- There is no “silver bullet” on the horizon
- Second generation AEDs still leave room for further improvement
  - Novel MOAs
  - Increased (broad spectrum) efficacy
  - Enhanced safety
  - Improved tolerability
  - Positive psychotropic effects
  - Increased “ease of use” (dosing, titration)
- Development of novel AEDs leads to more and improved therapeutic options

Treatment Guidelines for Partial Onset Seizures of the International League Against Epilepsy (ILAE)

- Goals for treatment for adults and children with GTC seizures:
  - best quality of life with no seizures and the fewest adverse effects from treatment
- Treatment recommendation for individual patient based on systematic review of:
  - efficacy/effectiveness evidence
  - safety data
  - pharmacokinetic properties
  - formulations
  - expense

Glauser T, Ben-Menachem E et. al. ILAE treatment guidelines; Epilepsia. 2006;47:1094-120

Gabapentin:Adverse Effects



Reproduced with permission from Goa KL, Sorkin EM. *Drugs*. 1993;46(3):409-427.

Lamotrigine: Adverse Effects

Monotherapy	(%)	Adjunctive Therapy	(%)
Headache	20	Dizziness	38
Asthenia	16	Headache	29
Rash	12	Diplopia	28
Nausea	10	Ataxia	22
Dizziness	8	Nausea	19
Somnolence	8	Blurred vision	16
Insomnia	6	Somnolence	14
		Rhinitis	14
		Rash	10

itton A, Goa KL. *Drugs*. 1995; 50(4): 691-713.
amictal® prescribing information.

Effects of Lamotrigine on Cognition: Overview

- Clinical studies and retrospective data have described cognitive effects of lamotrigine (LTG)
  - Minimal effects in healthy volunteers vs other agents and placebo
  - Positive and negative outcomes on cognition, behavior, and mood in patients with epilepsy
  - Significant improvements from baseline in patients with bipolar I disorder
- Lack of consistency across neuropsychological tests

Cognitive Effects of Lamotrigine vs Topiramate in Healthy Volunteers

Neurobehavioral Evaluations

- Attention / Vigilance
  - Continuous Performance Task
  - Digit Cancellation
  - Visual Serial Addition Test
- Cognitive / Motor Speed
  - Choice Reaction Time
  - Grooved Pegboard
- Language
  - Boston Naming Test
  - Semantic Fluency Test
  - Controlled Oral Word Association (COWA) Test
- Memory
  - Medical College of Georgia (MCG) Paragraph
  - Selective Reminding Test (SRT)
- Other Cognitive
  - Symbol Digit Modalities Test
  - Stroop Test
- Subjective Behavioral Measures
  - AB Neurotoxicity
  - Profile of Mood States
  - Adverse Event Profile
  - QOLIE-89 (cognitive scales)
  - SEALS, SF-12

Total of 17 tests yielding 41 variables

Meador et al. Neurology 2005;64:2108-2114. (LAM40095)

Cognitive Effects of Lamotrigine vs Topiramate in Healthy Volunteers

Results on Variables Among Completers (n = 47)

- Lamotrigine > topiramate 80% (33 / 41)
- Topiramate > lamotrigine 0%

- Non-drug > topiramate 88% (36 / 41)
- Topiramate > non-drug 0%

- Non-drug > lamotrigine 17% (7 / 41)
- Lamotrigine > non-drug 10% (4 / 41)

Meador et al. Neurology 2005;64:2108-2114. (LAM40095)

Cognitive Effects of Lamotrigine vs Topiramate in Healthy Volunteers

Adverse Events in ≥10% of Subjects

	TPM (n = 66)	LTG (n = 67)
Appetite or Weight Change	11%	4%
Dizziness	14%	6%
Emotional changes	30%	9%
Fatigue	26%	11%
Digestive	38%	14%
Headache	11%	13%
Memory/Concentration	35%	10%
Respiratory	18%	11%
Skin problems	6%	10%
Sleep difficulties	12%	14%
Tingling	61%	7%

Meador et al. Neurology 2005;64:2108-2114. (LAM40095)

Cognitive Effects of Lamotrigine, Topiramate, and Gabapentin in Healthy Volunteers

Results

- **Acute dosing phase**
  - **Significant declines in measures of sustained attention/concentration and tests of verbal fluency with TPM vs baseline, LTG, and GBP**
- **Chronic dosing phase**
  - **TPM-treated subjects continued to have declines in measures of sustained attention/concentration, visuomotor processing speed/ability, and verbal learning/memory vs baseline and/or vs LTG or GBP**

Martin R et al. Neurology 1999;52:321-327.

Mood Effects of Lamotrigine, Topiramate, and Gabapentin in Healthy Volunteers

Results

- **Profile of Mood States (POMS)**
  - **TPM-treated subjects experienced more symptoms of depressed mood at week 4 vs baseline and vs LTG and GBP**
  - **TPM-treated subjects had more anger-hostility symptoms at week 4 vs baseline and vs LTG**
  - **TPM-treated subjects also scored higher on the confusion scale vs baseline at weeks 2 and 4**

Martin R et al. Neurology 1999;52:321-327.

Cognitive Effects of Lamotrigine vs Carbamazepine in Healthy Elderly Adults

- No significant differences on cognitive tests between LTG and CBZ
  - High dropout rate for CBZ may have confounded results
- LTG exerted a positive effect on mood
  - 5 of 6 scales for POMS favored LTG
  - Vigor scale ($P < 0.01$)
  - Sign test ($P < 0.05$)

Sinclair et al, Epilepsia 2000;41(suppl 7):255. (SCAA4007)

CNS Effects of Lamotrigine vs Phenytoin and Diazepam in Healthy Volunteers

- Assessment of CNS effects
  - Adaptive tracking, body sway, eye movements, and subjective adverse effects
- Lamotrigine did not have significant effects on any measures
- Phenytoin 1000 mg impaired tracking performance and increased sedation
- Diazepam impaired tracking performance, increased body sway, reduced peak saccadic velocity, impaired smooth pursuit eye movement, and increased subjective sedation

Cohen AF et al. Br J Clin Pharmac 1985;20:619-629.

Summary of Cognitive Effects of Lamotrigine

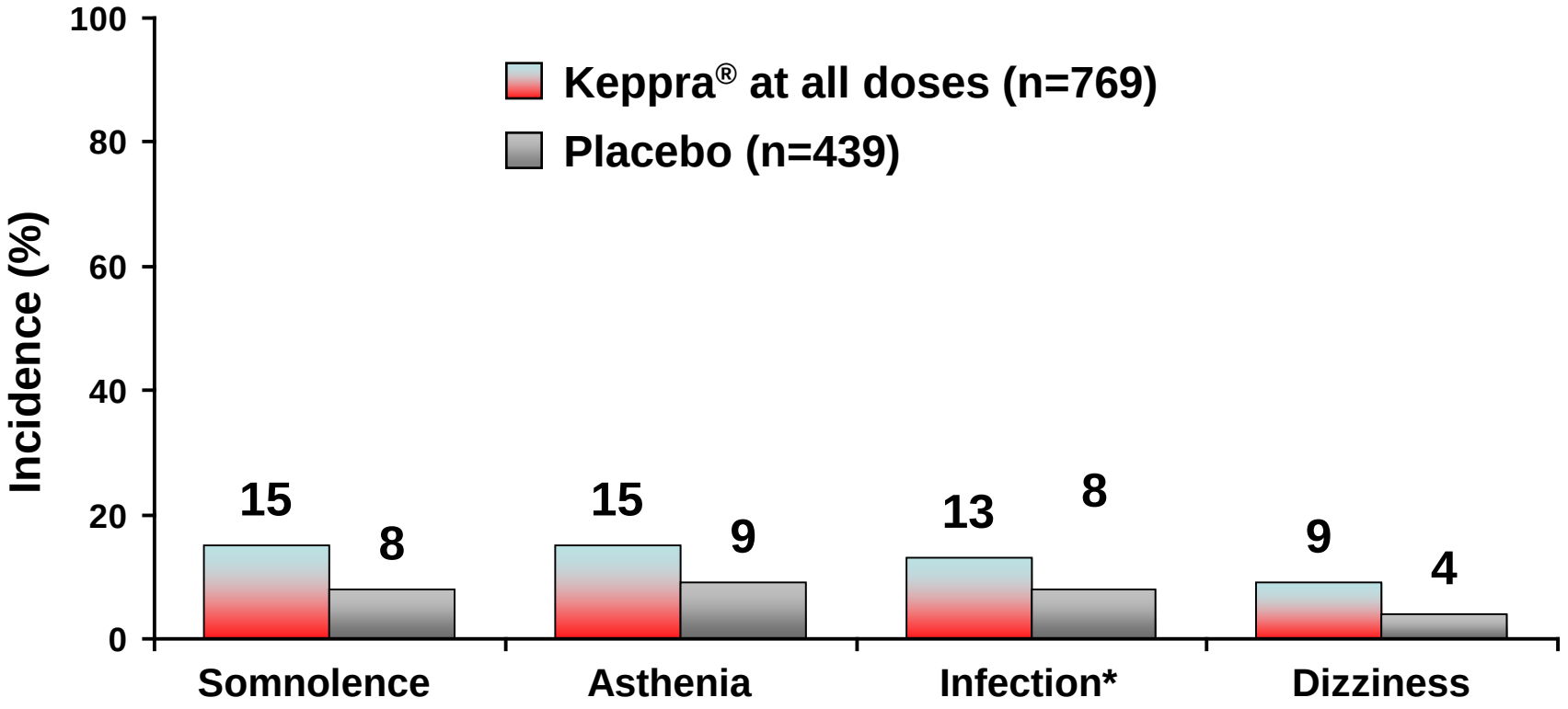
- Lamotrigine appears to have minimal cognitive effects in healthy adult volunteers
- Cognitive and behavioral effects of lamotrigine in patients with epilepsy have yielded both positive and negative outcomes
- Lamotrigine appears to have positive effects on cognition versus baseline in adults with bipolar I disorder

Warnings

- levetiracetam use is associated with the occurrence of CNS adverse events classified as somnolence and fatigue, behavioral abnormalities, and coordination difficulties, as well as hematological abnormalities

levetiracetam tablets/oral solution [prescribing information]. Smyrna, GA: UCB, Inc.; March 2007.

Adult Studies: Most Frequent Treatment-Emergent Adverse Events in Phase III Placebo-Controlled Trials



- **Somnolence, asthenia, and dizziness appeared to occur predominantly during the first 4 weeks of treatment with Keppra®**

All with concomitant AEDs.

*Most were common colds and upper respiratory tract infections.

Betts T, et al. *Seizure*. 2000;9:80-87.

Zonisamide

- Psychomotor slowing and difficulty with concentration occurred in first month of treatment and associated with 300mg/day
- Speech and language problems occurred after 6-10 weeks of treatment and at doses above 300 mg/day. Most cases events were of mild to moderate severity, at times led to withdrawal from treatment
- Somnolence and fatigue, mild to moderate severity, led to withdrawal from treatment in 0.2% patients enrolled in controlled trials. Somnolence and fatigue occurred within the first month of treatment and most frequently at doses of 300-500 mg/day.

eslicarbazepine

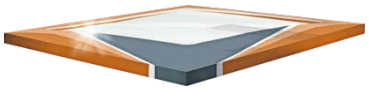
- Efficacious
- Approved for adjunctive therapy for partial onset seizures
- Low side effects -dizziness, hyponatremia
- Liver metabolism, some interactions
- Oral – tablets
- QD dosing

- The identification of subjects carrying the HLA-B*1502 allele and the avoidance of
- carbamazepine therapy in these subjects was strongly associated with a decrease in
- the incidence of carbamazepine-induced SJS–TEN.

lacosamide

- Efficacious
- Approved for adjunctive therapy, monotherapy, conversion to monotherapy for partial onset seizures age 17 and above
- Low side effects - dizziness
- Renal elimination – no significant interactions
- Oral - tablets, solution, IV
- BID dosing

VIMPAT® Adjunctive Therapy—
Most Common AEs in Placebo-Controlled Clinical Trials



POS Placebo-controlled Adjunctive Trials: Most common AEs (%) occurring in ≥10% of the total number of VIMPAT-treated patients and greater than placebo*

AE	Placebo (n=364)	VIMPAT 200 mg/day (n=270)	VIMPAT 400 mg/day (n=471)
Dizziness	8	16	30
Headache	9	11	14
Nausea	4	7	11
Diplopia	2	6	10

- The majority of AEs were generally mild to moderate and were generally dose related
- The onset of dizziness was most commonly observed during titration
- The discontinuation rates due to AEs were 8% and 17% in patients treated with VIMPAT at the recommended doses of 200 mg/day and 400 mg/day, respectively. The most common AEs leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and vision blurred

*Patients in these clinical trials were treated with 1 to 3 concomitant AEDs.

Reference: VIMPAT® (lacosamide): US prescribing information. Smyrna (GA): UCB, Inc., June 2015.

Please see additional Important Safety Information within this presentation. Please refer to full Prescribing Information provided by the UCB Representative, and visit www.VIMPAT.com/hcp.

VIMPAT® (lacosamide) C

VIMPAT® Monotherapy—
Most Common Adverse Events (AEs) in the Clinical Trial

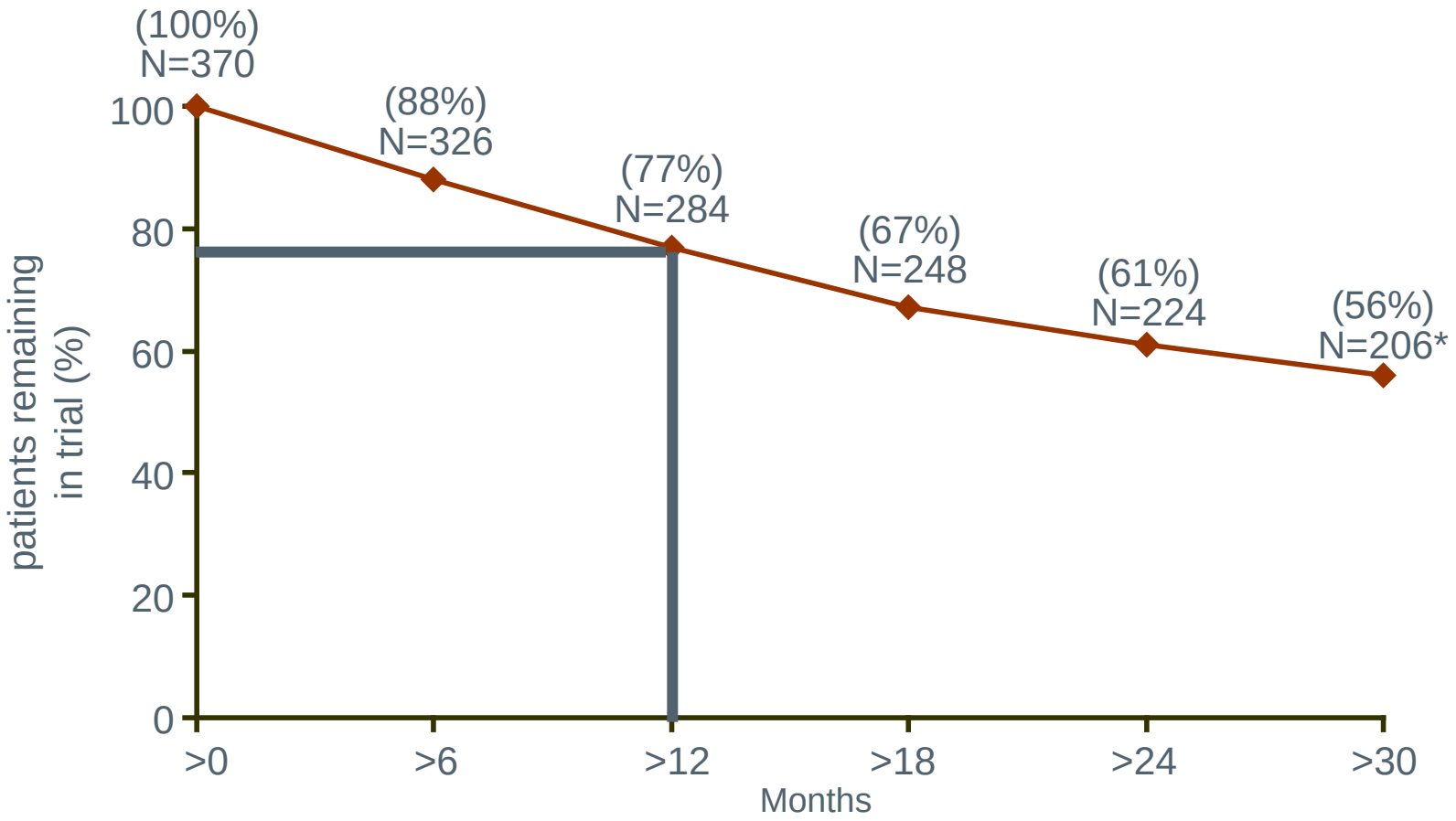
- In the clinical trial, adverse reactions were generally similar to those observed and attributed to drug in adjunctive placebo-controlled trials, with the exception of insomnia (observed at a higher rate of ≥2%)
- Dizziness, headache, nausea, somnolence, and fatigue were all reported at lower incidences during the AED withdrawal phase and monotherapy phase compared with the titration phase
- The discontinuation rate due to AEs was 16% in patients treated with VIMPAT. The most common AE leading to discontinuation was dizziness

Reference: VIMPAT® (lacosamide): US prescribing information. Smyrna (GA): UCB, Inc., June 2015.

Please see additional Important Safety Information within this presentation. Please refer to full Prescribing Information provided by the UCB Representative, and visit www.VIMPAT.com/hcp.

VIMPAT® (lacosamide) C V

Rosenfeld study: Long-term patient retention



*Last data cut-off where all patients had opportunity to complete trial (interim data cut: October 2006, up to 5.5 years of exposure)
LCM=lacosamide

Rosenfeld et al. Presented at AES, 2007.
Interim results

Rosenfeld study: Common adverse events

- Most frequently reported AEs included

Dizziness	37%
Headache	18%
Diplopia	14%
Fatigue	14%
Nasopharyngitis	14%
Confusion	13%
Coordination abnormal	13%
Nausea	13%
URTI	13%
Skin lacerations	12%
Vision blurred	12%
Vomiting	12%
Sinusitus	10%

- Adverse events were generally mild to moderate in severity

TEAE=treatment-emergent adverse event;
URTI=upper respiratory tract infection

Rosenfeld et al. Presented at AES, 2007.
Interim results

Rosenfeld study: Summary Long-term extension trial

- Long-term, open-label use of LCM (up to 5.5 years) was generally well tolerated, with no change in pattern of adverse events or safety measures
- Seizure reduction appeared to be maintained during this time period

LCM=lacosamide

Rosenfeld et al. Presented at AES, 2007.
Interim results

Summary of safety

- Low incidence of side effects that may be problematic with POS patients
  - Somnolence (7.2% vs placebo 4.7%)
  - Memory Impairment (2.3% vs placebo 1.6%)
  - Cognitive or behavioral side effects aggression (0.1% vs placebo 0.3%) anger (0.2% vs placebo 0%)
  - Weight gain and oedema (increase: 1.0% vs placebo 1.4%), (decrease: 1.6% vs placebo 1.4%)*
  - Rash (2.9% ve placebo 3.0%)

Tolerability includes adverse events reported up to a 600 mg daily dose. 600 mg/day is not recommended.
*Weight change defined as ≥ 10% gain or loss during the treatment phase versus baseline.

- LCM does not:
  - have clinically relevant interactions with AEDs
  - influence metabolic parameters

Ben-Menachem et al. Epilepsia 2007;48(7):1308–17
Chung et al. Presented at EFNS, 2007
Halasz et al. Published online, Epilepsia:1–11, 2009

Lacosamide Demonstrates Safety and Tolerability Benefits

- ✓ Low rate of somnolence comparable to placebo
- ✓ Low rate of cognitive impairment and behavioral abnormalities similar to placebo
- ✓ Low incidence of rash similar to placebo[1]
- ✓ Weight-neutral results[1]
- ✓ Can be given with or without food
- ✓ Pregnancy category C

- ✓ **NO** known clinically significant drug-drug interactions*, including 2nd- or 1st-generation AEDs, contraceptives†, digoxin, metformin, or omeprazole
- ✓ **NO** blood-level monitoring required
- ✓ **NO** lab monitoring required
- ✓ **NO** black-box warning

ude ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg.

1. Data on file; UCB, Inc. *Please see your UCB sales representative for full prescribing information.*

clobazam

- Fairly efficacious
- Approved for adjunctive treatment for seizures associated with Lennox-Gastaut Syndrome in adults and children 2 years of age and older
- Side effects – negative side effects - sedation, slight weight gain.
  Positive attribute- less development of tolerance
- Oral – tablets, oral suspension
- BID dosing

CONTAIN Trial: Safety Results

Onfi (clobazam) CV
10 mg, 20 mg Tablets
2.5 mg/mL Oral Suspension

Adverse Reactions Reported for ≥5% of ONFI (clobazam) Patients and More Frequently Than Placebo in Any Treatment Group[1]

		ONFI (clobazam) Dose Level			
	Placebo (n=59), %	Low[a] (n=58) %	Medium[b] (n=62) %	High[c] (n=59) %	All ONFI (n=179), %
Nervous System Disorders					
Somnolence or sedation	15	17	27	32	26
Somnolence	12	16	24	25	22
Sedation	3	2	3	9	5
Lethargy	5	10	5	15	10
Drooling	3	0	13	14	9
Ataxia	3	3	2	10	5
Psychomotor hyperactivity	3	3	3	5	4
Dysarthria	0	2	2	5	3
Psychiatric Disorders					
Aggression	5	3	8	14	8
Insomnia	2	2	5	7	5
Respiratory Disorders					
Cough	0	3	5	7	5

[a] Maximum daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight.
[b] Maximum daily dose of 10 mg for ≤30 kg body weight; 20 mg for >30 kg body weight.
[c] Maximum daily dose of 20 mg for ≤30 kg body weight; 40 mg for >30 kg body weight.

Reference: 1. ONFI [package insert]. Deerfield, IL: Lundbeck.

Please see Important Safety Information on slides 19-20.

perampanel

- Efficacious
- Approved for adjunctive therapy for partial onset seizures with or without secondarily generalized seizures ages 12 and older
- Side effects – moody, black box warning –homicidal ideations
- Interactions with enzyme inducers will lower perampanel levels and efficacy
- Oral – tablets
- QD dosing

Important Safety Information: Boxed WARNING

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA**
- **Closely monitor patients particularly during the titration period and at higher doses**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

FYCOMPA™ (perampanel) Prescribing Information. Woodcliff Lake, NJ: Eisai Inc.; October 2013.

Important Safety Information

Serious Psychiatric and Behavioral Reactions

Phase III Clinical Studies (pooled)	Placebo	FYCOMPA™	
		8 mg	12 mg
Hostility and aggression-related adverse reactions	6%	12%	20%

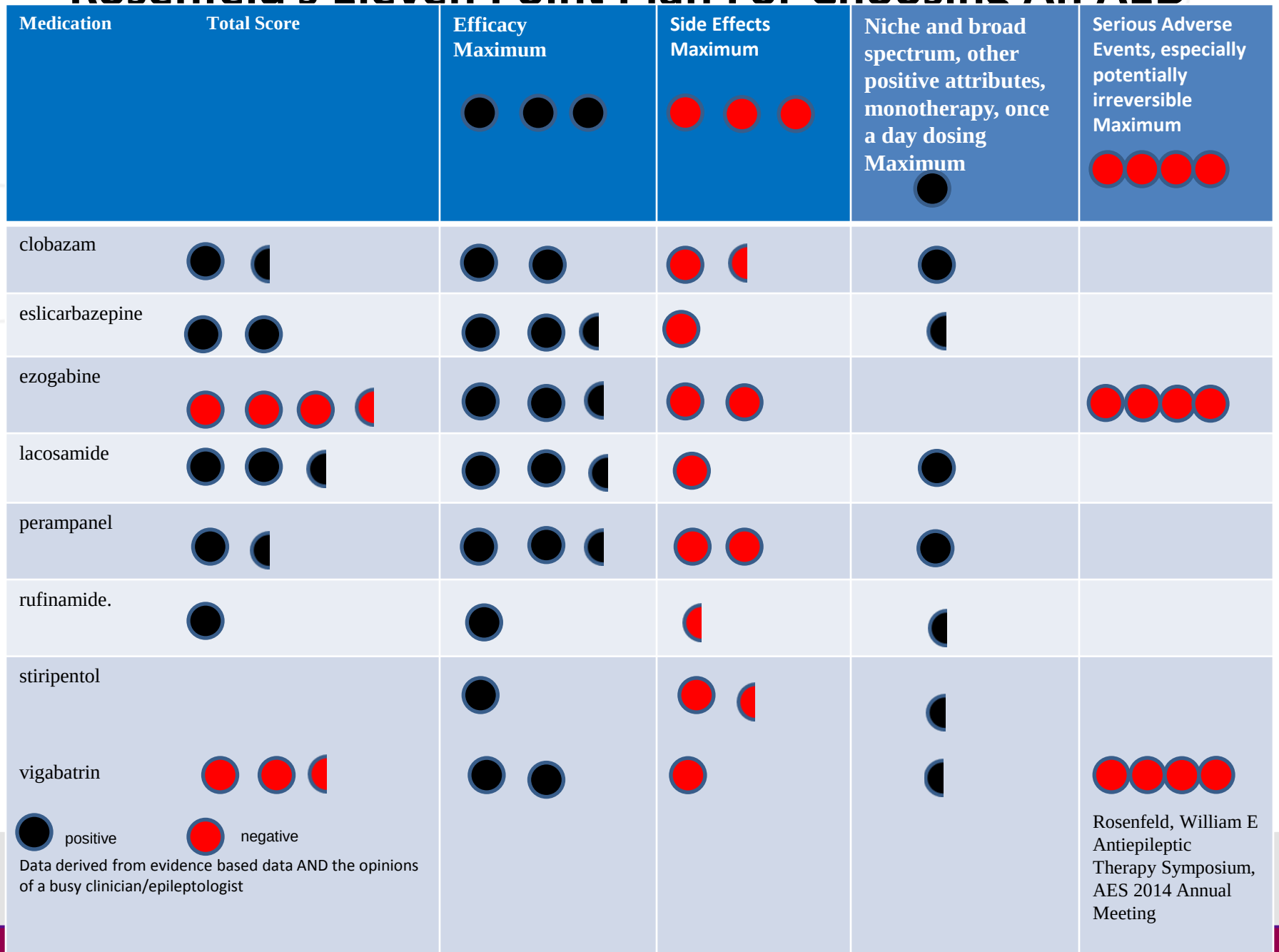
- Dose-related and generally appeared within the first 6 weeks of treatment, although new events were observed through more than 37 weeks
- Led to dose reduction, interruption, and discontinuation more frequently in FYCOMPA™ (perampanel)-treated patients

FYCOMPA™ (perampanel) Prescribing Information. Woodcliff Lake, NJ: Eisai Inc.; October 2013.

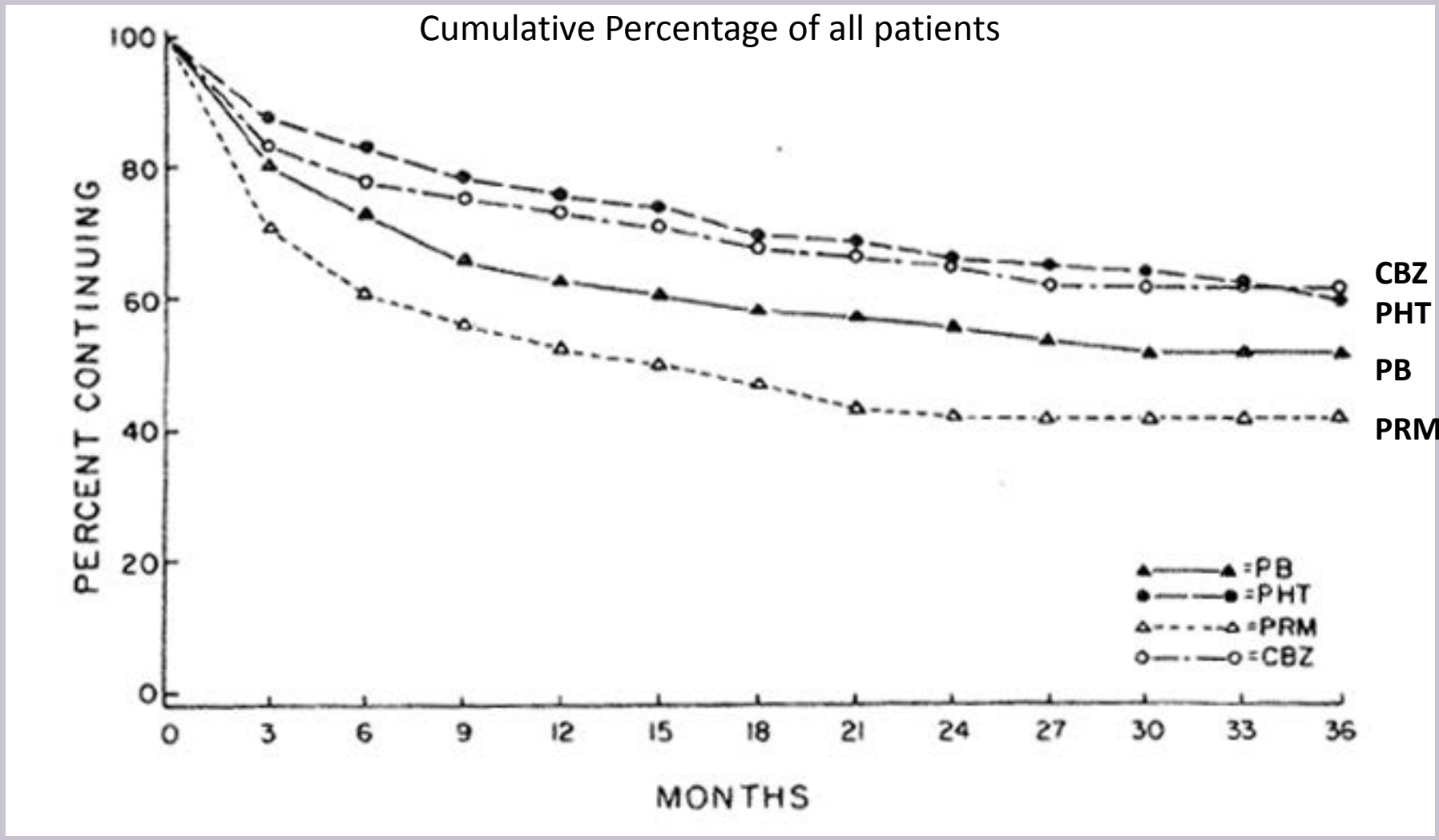
rufinamide

- Efficacy – low to medium
- Approved for seizures associated with Lennox-Gastaut Syndrome in children 4 years of age and older and adults
- Side effects - very little - mild dizziness
- Oral - tablets, suspension
- BID dosing

Rosenfeld's Eleven Point Plan For Choosing An AED



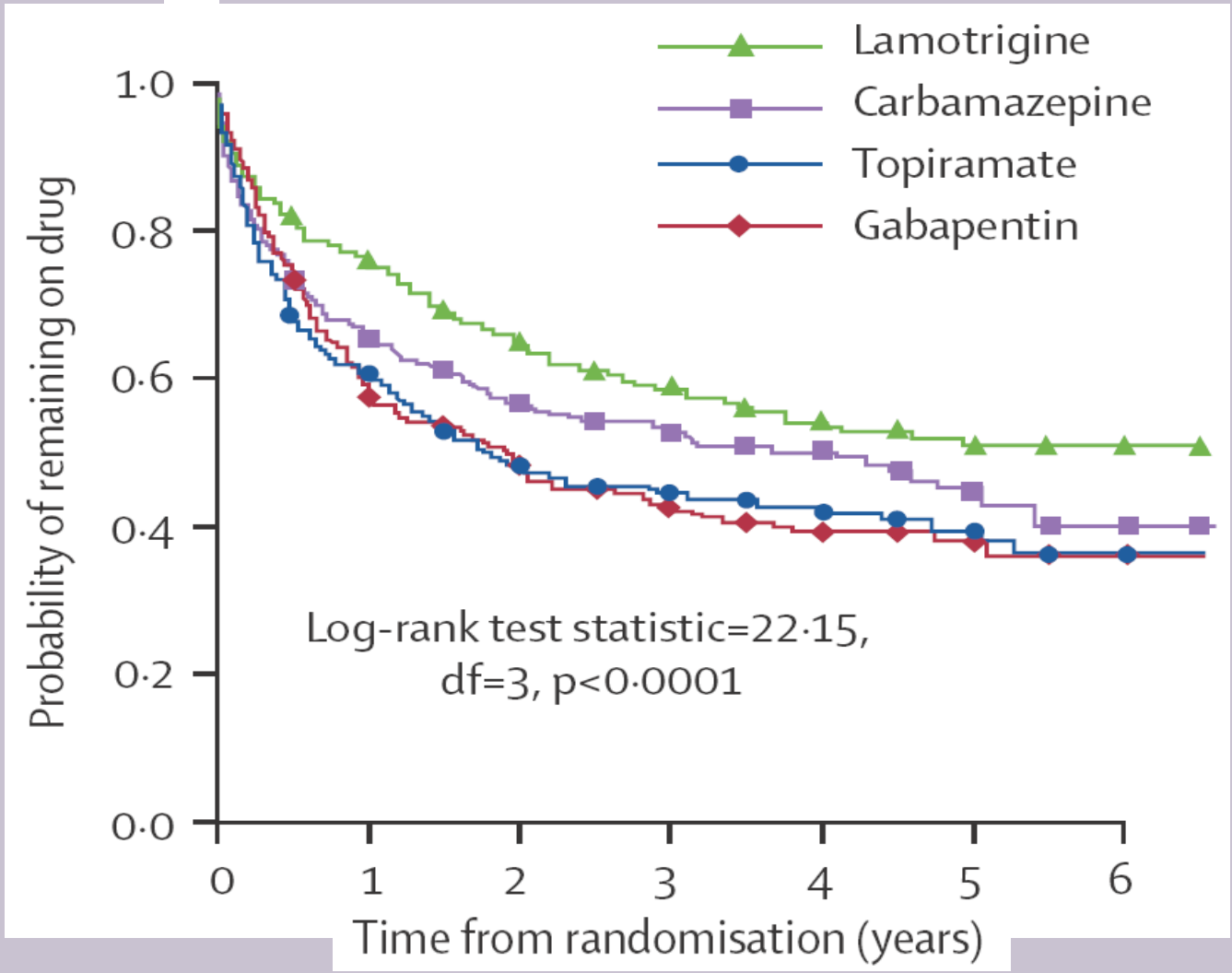
VA-Cooperative DB-Retention Study in POS



Mattson et. al.; NEJM 1985;313:145-151

SANAD Study in Monotherapy Patients with POS

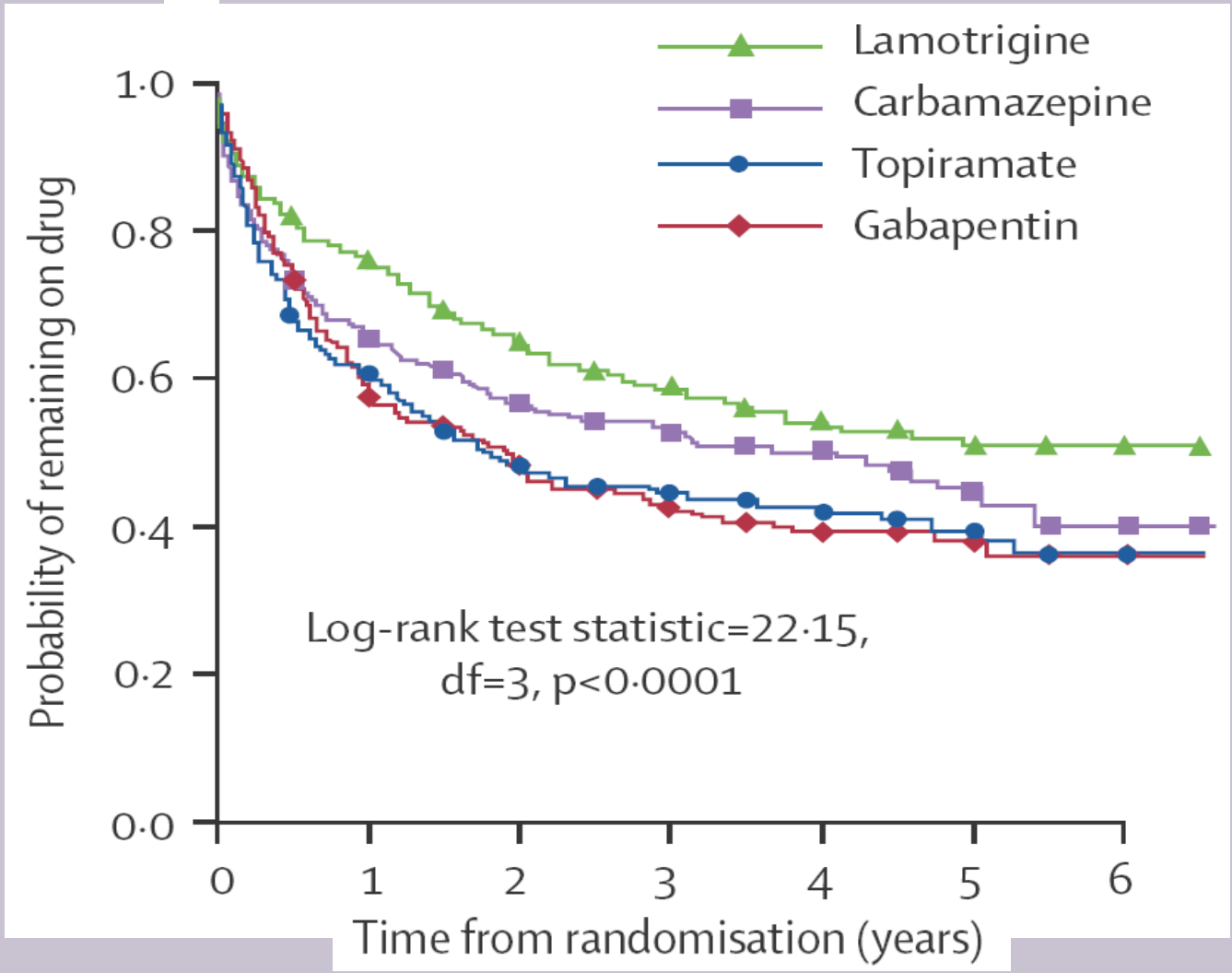
Randomized; Open-Label, Monotherapy Study in UK



Marson et. al.; SANAD Study; Lancet 2007;369:1000–15

SANAD Study in Monotherapy Patients with POS

Randomized; Open-Label, Monotherapy Study in UK



Marson et. al.; SANAD Study; Lancet 2007;369:1000–15

Retrospective Chart Analysis of Retention Rates for Pat. treated adjunctively with LTG, TPM, or GBP

Discontinuation Reason	Topiramate	Lamotrigine	Gabapentin
Adverse events	40% (n=157)	22% (n=93)	37% (n=58)
Lack of efficacy	19% (n=75)	34% (n=144)	39% (n=62)
Pregnancy	1% (n=3)	1% (n=3)	0
Deceased	1% (n=3)	1% (n=4)	0
Noncompliance	0	1% (n=4)	0
Total	61% (n=238)	58% (n=248)	76% (n=120)

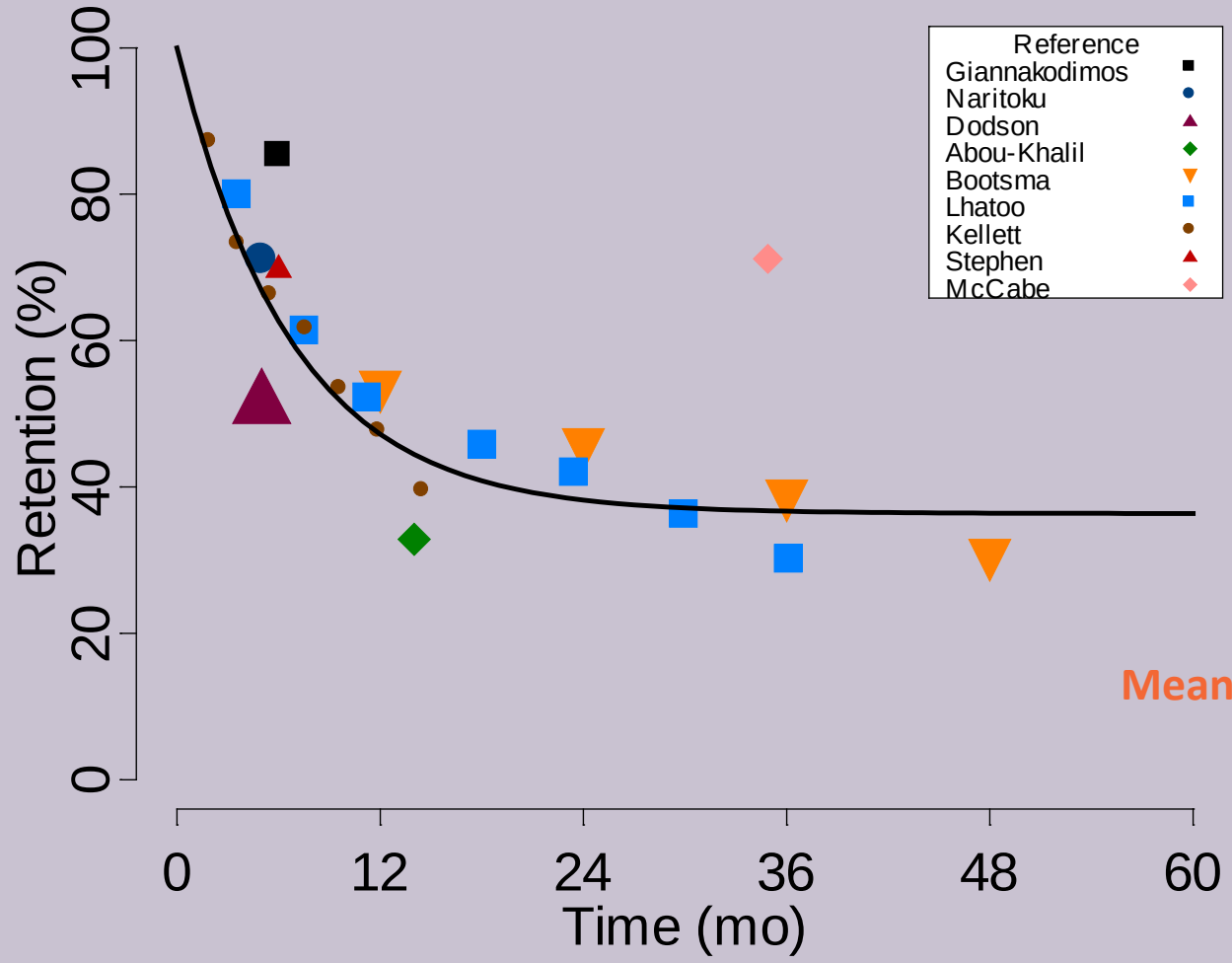
Lhatoo SD. et. al.; Epilepsia 2000;51:1592-6

Retrospective Chart Review of Retention Rates of Newer AEDs

	GPN	LEV	LTG	OXC	TPM	ZNS
N	94	299	498	146	222	180
Discontinuation Rate (%)	72.3	28.1	11.8	36.3	28.8	38.9
Lack of efficacy (%)	62.8	14.0	4.22	19.2	11.7	21.7
Adverse events (%)	6.38	13.4	6.43	13.7	14.0	15.6
Lethargy/sedation	2.13	1.34		0.68		1.11
Mood/behavior	2.13	7.69	0.60	2.05	2.70	6.11
Balance	2.13	0.67	0.40	5.48		
Headache		1.00	0.20	3.42		
Sleep difficulty		1.00	0.40			
Rash			3.41	0.68		0.56
Hyponatremia				1.36		
Visual symptoms				4.79		
Cognitive complaints					7.66	1.11
Kidney Stone					0.90	1.11
Appetite					0.45	0.56
Other (%)	3.19	0.67	1.00	3.42	2.25	1.67

McCabe; Second gen. AEDs: Clinical Use at Penn State University; Poster AES 2006

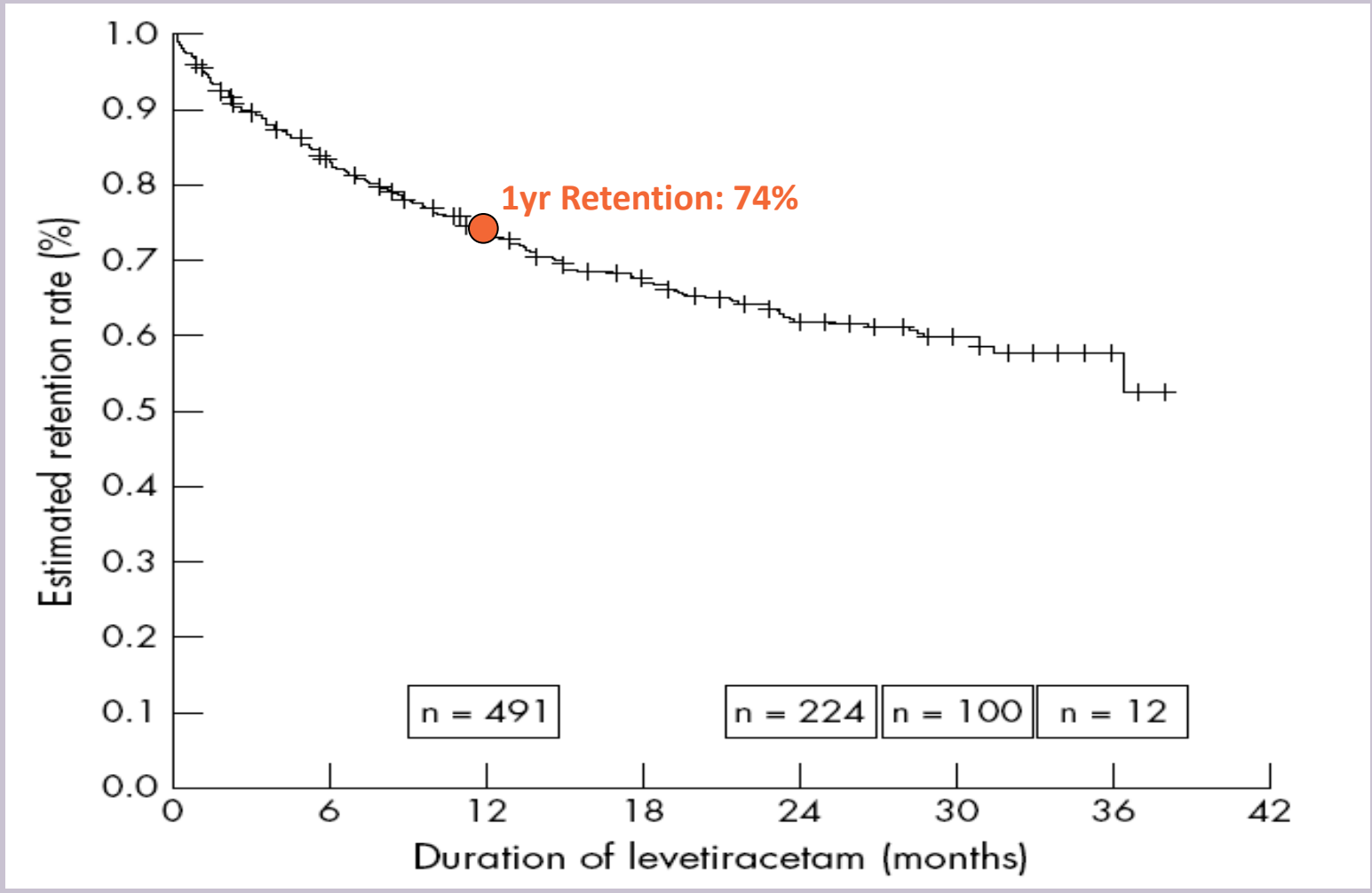
Topiramate retention profiles from OL studies



Mean dose = 338 mg

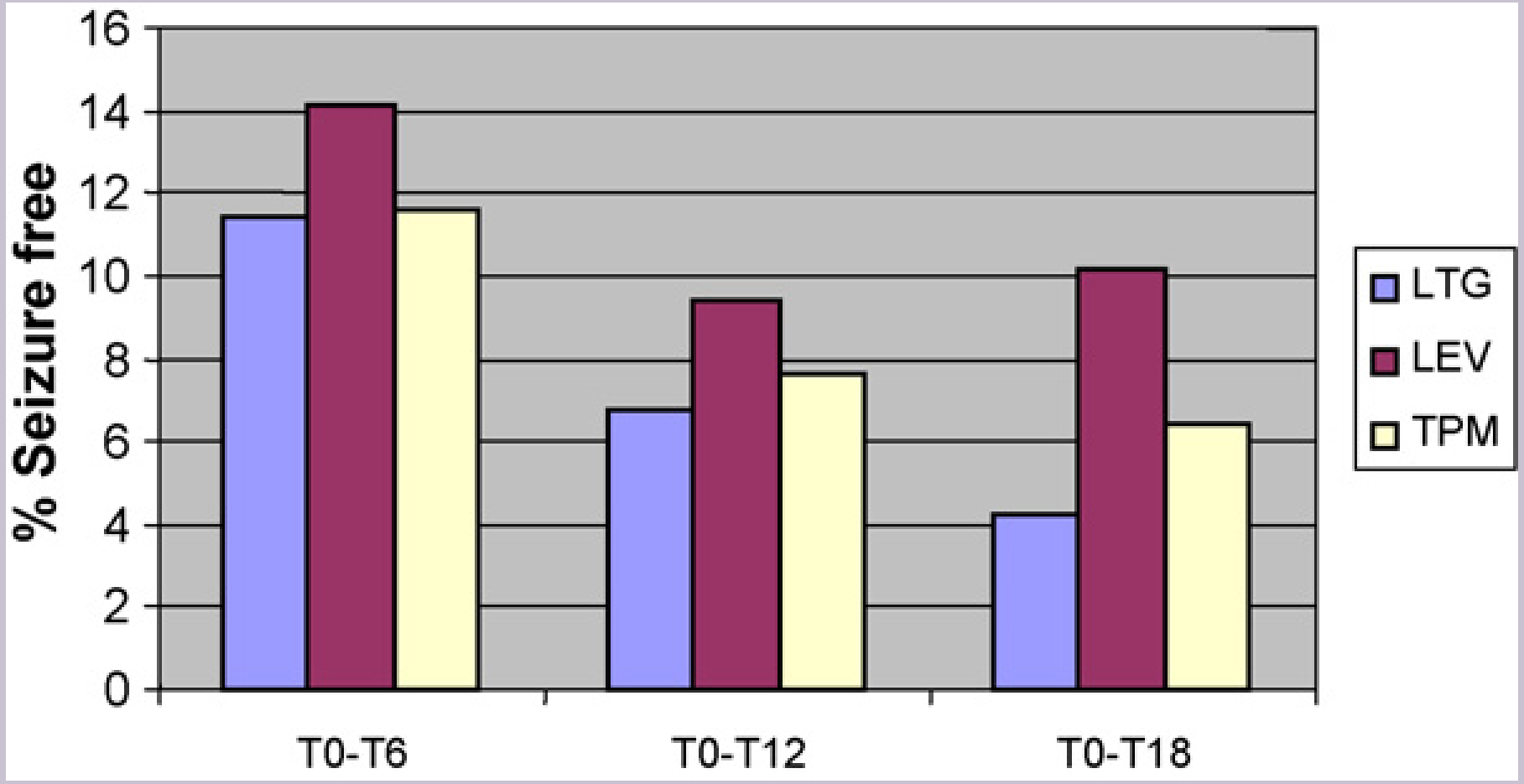
Curve is a weighted nonlinear least-squares regression fit to the points, excluding McCabe, accounting for sample size, but not for repeated measurements. Retention = (1-A*exp(-k1*Time)) * 100. A = 64%, k1=0.15 mo^{-1}. Point size is proportional to the square root of sample size. Repeated measures data are digitized from retention curves. Mean dose is the mean of the reported mean doses.

LEV Retention Rates in Adjunctive Therapy of Epilepsy Patients with POS



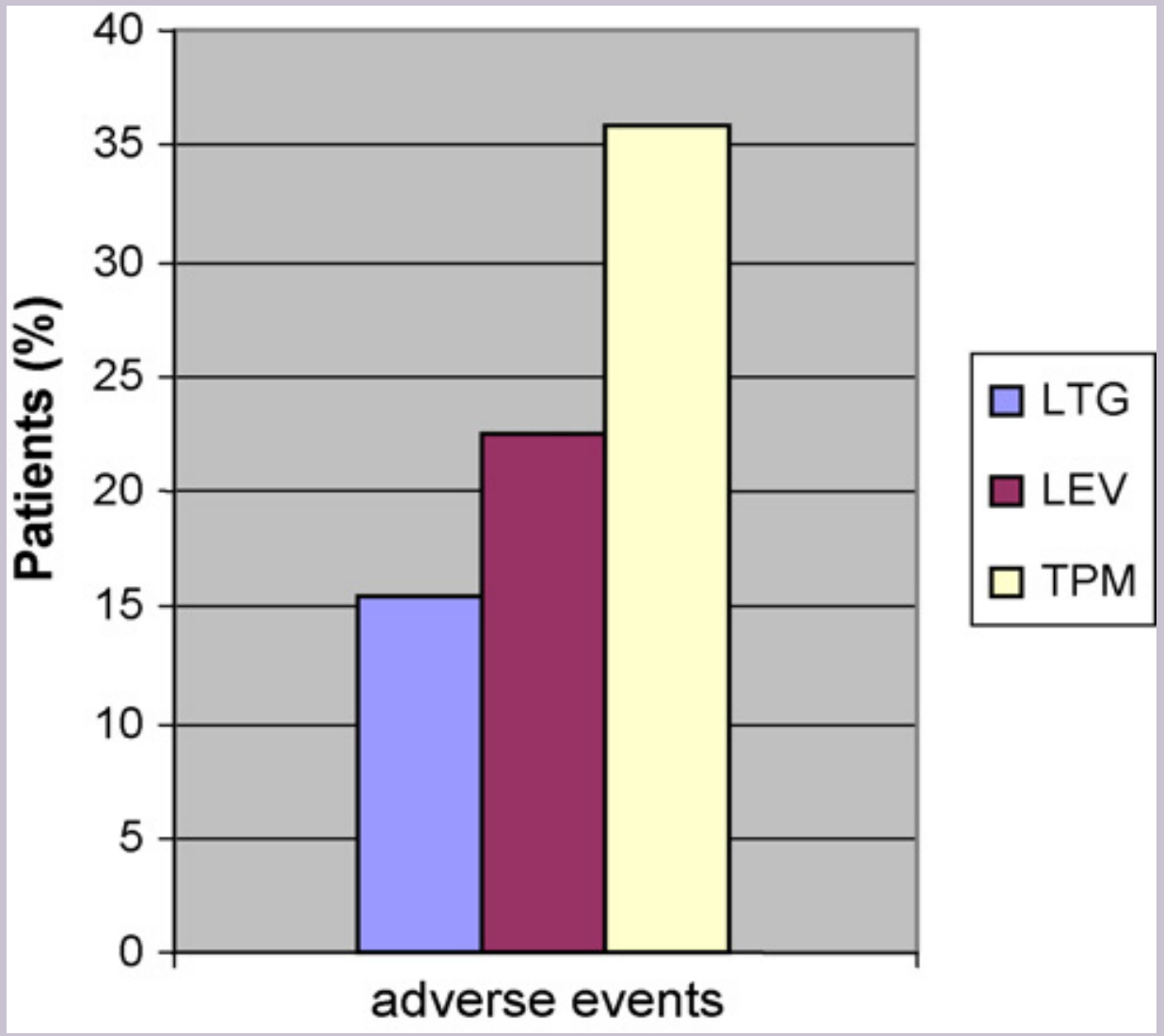
Despondt C et. al.; J Neurol. Neurosurg. Psychiatry 2006;77:101-103

Long-term seizure remission from baseline; comparison between LTG, LEV, and TPM



Bootsma HP et. al.; Seizure: Eur J Epilepsy (2008; doi: 10.1016/j.seizure.2008.11.006)

Percentage of study population discontinuing due to adverse events



Bootsma HP et. al.; Seizure: Eur J Epilepsy (2008; doi: 10.1016/j.seizure.2008.11.006)

Reported side effects in patients who discontinued drug treatment[a]

LTG	LEV	TPM
Dizziness (14.9%)	**Mood disorders ↑[b] (13.8%)**	**Mental slowing (27.8%)**
Mood disorders ↑(11.7%)	**Tiredness (13.8%)**	**Dysphasia[c] (15.0%)**
Rash (10.6%)	**Mood disorders ↓[d] (13.1%)**	**Mood disorders ↑(13.2%)**
Sleeplessness (7.4%)	**Sleepiness (8.5%)**	**Gastrointestinal (10.6%)**
Sleepiness (6.4%)		**Paresthesia (7.5%)**
		Appetite loss (7.0%)
		Skin (6.6%)
		Weight loss (6.2%)
		Mood disorders ↓(5.7%)
		Headache (5.7%)
		Dizziness (5.3%)

[a] Only side effects that occurred in >5% of patients are reported in the table

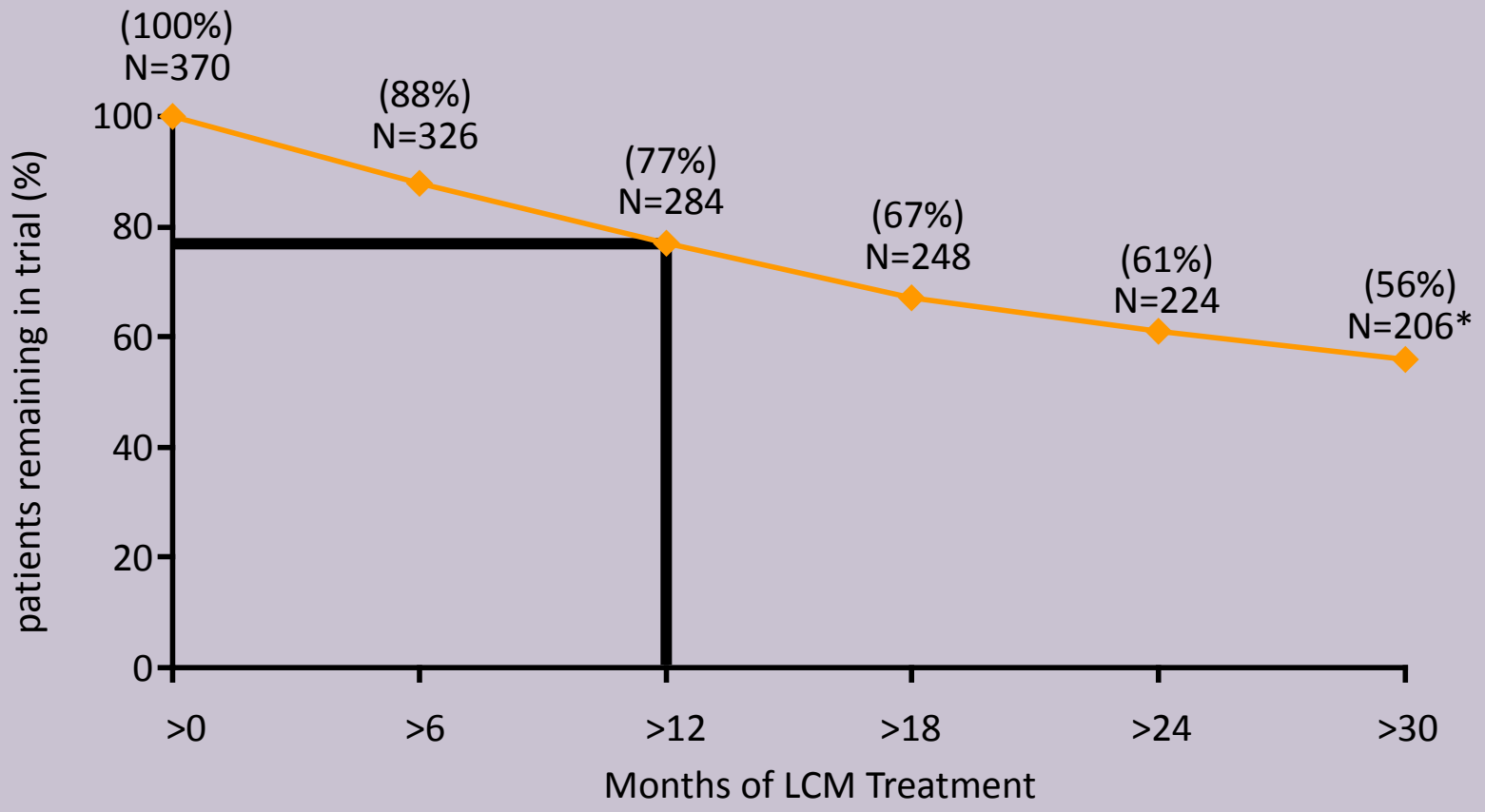
[b] Mood disorders ↑: agitation, aggression, hyperirritability

[c] Dysphasia: word-finding difficulties

[d] Mood disorders ↓: depression, apathy

Bootsma HP et. al.; Seizure: Eur J Epilepsy (2008; doi: 10.1016/j.seizure.2008.11.006)

Lacosamide
Long-term patient retention



*Last data cut-off where all patients had opportunity to complete trial (interim data cut: October 2006, up to 5.5 years of exposure)
LCM=lacosamide

Rosenfeld et al. Presented at AES, 2007

Conclusions

- Retention has been used as an outcome parameter in randomized trials up to 20 years ago
- Retention is a naturalistic, effectiveness outcome measure (utility parameter) that combines tolerability and efficacy and summarizes the degree of treatment satisfaction
- Pivotal trials too short to gain sufficient insight into the long term consequences of treatment of a life long condition such as epilepsy
- Long term head-to-head outcome studies, using retention as an endpoint, may generate meaningful (safety, tolerability, effectiveness) data for payers as well as physicians and patients


CLOSING