Cognitive and Behavioral Effects of AEDs Old and New

Carl B. Dodrill, Ph.D.

Regional Epilepsy Center
Harborview Medical Center

Department of Neurology
University of Washington School of Medicine
Seattle, Washington USA

cdodrill@u.washington.edu

Older AEDs

Generic name	Trade name
Phenobarbital	Luminol
Phenytoin	Dilantin
Carbamazepine	Tegretol
Valproic acid	Depakote

Phenobarbital in Young Children

- *Patients:* 217 children 8-36 months of age with febrile seizure(s) and risk of further seizures
- *Study design*: Randomly/blindly assigned to phenobarbital (4-5 mg/kg/d) or placebo 2 years
- *Results:*
  --At 2 years, mean Stanford-Binet IQ score was 7.03 points lower for pb than placebo ($p < .01$)
  --Off medications for 6 months IQ was 4.3 points lower for pb (n.s.)

Farwell et al. *New Eng J Med* 1990;322:364-369

Follow-up of Farwell (1990) Study

- *Follow-up:* 55% of pb children and 72% of placebo children retest after Grade 1 and usually 3+ years after all medication; mean age 7.7 yrs.
- *Tests:* Stanford-Binet Intelligence Scale, Wide Range Achievement Test-Revised
- *Results:* IQ: Pb vs placebo, -3.7 (n.s.); WRAT-R: Reading -7.5 (*p*=.007), Spelling -4.2 (n.s.), Arithmetic -0.7 (n.s.)

Sulzbacher et al. *Clinical Pediatrics* 1999;38:387-394

Healthy Adults: Pb, PHT, and VPA

- Subjects: 59 healthy adults (48 men, 11 women)
- Study Design: Double-blind, randomized, cross-over, counterbalanced, incomplete block design (1m on each of 2 drugs). Washout periods. Testing at end of every study phase
- Drugs: Titrated to required blood level over 7d:

Drug	Dose	Required SL	Average SL
Pb	170 mg	15-40 µg/ml	20.6 µg/ml
PHT	404 mg	10-20 µg/ml	14.3 µg/ml
VPA	951 mg	50-100 µg/ml	71.7 µg/ml

Meador et al. *Neurology* 1995;45:1494-1499

Healthy Adults: Pb, PHT, and VPA

- Tests: 9 cognitive measures plus P3 plus Hopkins Symptom Checklist, Profile of Mood States (POMS)--22 variables total

- Results: Number of test variables worse than

Drug	Baseline	Pb	PHT	VPA
Pb	12	--	6	7
PHT	9	0	--	1
VPA	7	0	0	--

- Conclusions: Effects small, but Pb worse than either PHT or VPA; PHT and VPA, no difference

Meador et al. *Neurology* 1995;45:1494-1499

Elderly: Cognitive Effects of AEDs

- *Patients*: 23 patients 60-88 yrs (m=70) on monotherapy CBZ (10), VPA (8), or PHT (5)
- *Study design:* Patients took extra medication (200 mg CBZ, 500 mg VPA, 100 mg PHT) for one month or matched placebo in random order
- *Tests:* (baseline, end of treatment periods)
  --Cognitive: intelligence, reaction time, motor, attention, memory
  --Subjective: Visual analogue: mood, memory, concentration, sedation

Read et al. *Seizure* 1998;7:159-162

Elderly: Cognitive Effects of AEDs

- *Results:* Serum levels
  --CBZ: increased from 7.7 to 9.4 *u*g/ml
  --VPA: increased from 60 to 85 *u*g/ml
  --PHT: increased from 13 to 16 *u*g/ml
- *Results:* Cognitive tests showed no changes
- *Results:* Subjective measures showed no changes in any area of mental abilities, mood, or sedation

Read, Brodie, et al. *Seizure* 1998;7:159-162

Established AEDs: Summary of Cognitive Effects

All of the AEDs produce some cognitive side effects. However, when used in monotherapy with anticonvulsant blood levels within the standard therapeutic ranges, these effects are modest. There is no convincing evidence at this time of clinically significant differential cognitive effects except for phenobarbital and by inference bromides and benzodiazepines.

Kim Meador, M.D.
AES News, Fall,1995, p. 9

Newer AEDs

Generic name	Trade name
Gabapentin	Neurontin
Tiagabine	Gabitril
Lamotrigine	Lamictal
Topiramate	Topamax
Zonisamide	Zonegran
Levetiracetam	Keppra
Oxcarbazine	Trileptal

Gabapentin: USA Multisite Conversion to Monotherapy Study

- *Patients*: 201 patients with refractory partial seizures on stable doses of 1 or 2 drugs
- *Study design:* Patients randomized to mono-therapy 600, 1200, or 2400; + placebo group
- *Tests:* Baseline and double-blind testing
  --Cognitive: 8 tests of abilities (19 variables)
  --Mood/adjustment: 3 tests (18 variables)
- *Analyses*: Placebo vs. all GBP; placebo vs. dose groups; analysis by relief from seizures

Dodrill et al. *Epilepsy Research* 1999;35:109-121

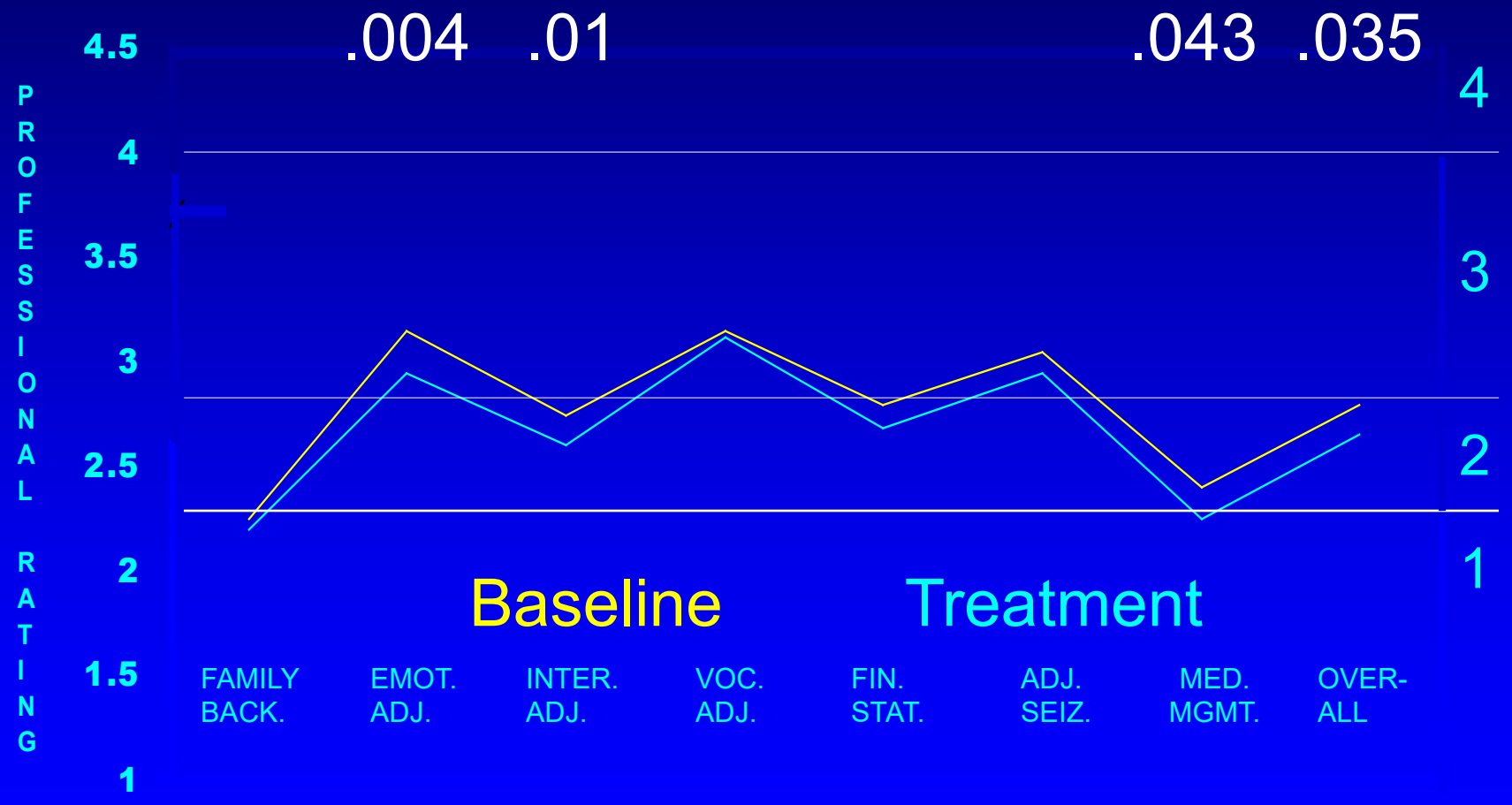
Results: All Analyses

Area	Number of statistically signif. findings	Number of statistical tests run
Mental abilities	3	57
Mood/adjustment	11*	54

* GBP always improved, placebo always unchanged; all from the Washington Psychosocial Seizure Inventory

Washington Psychosocial Seizure Inventory

Patients on gabapentin (n = 201)



Reports of Favorable Psychiatric Effects of Gabapentin

- Social phobia
- Panic disorder
- Obsessive-compulsive disorder
- Anxiety disorders

Gabapentin: Summary

- Add-on gabapentin--no cognitive change but improved sense of well-being
- Gabapentin vs. other AEDs--fewer cognitive effects, greater sense of well-being, but poorer seizure control
- Psychiatric effects--generally favorable, especially in social phobia

Tiagabine: Summary

- Add-on tiagabine--no cognitive/well-being changes if titrated slowly
- Tiagabine vs. other AEDs--no changes if monotherapy achieved; worse if mono-therapy not achieved or if titrated quickly
- Psychiatric effects--favorable at low doses only; otherwise same or worse

Lamotrigine vs. Carbamazepine: Cognitive Effects

- *Patients:* 168 newly diagnosed epilepsy cases
- *Experimental design:*
  --Randomized and blinded assignment to LTG (n=86) or CBZ (n=82) monotherapy
  --Memory, problem solving, and attention were tested 5x during 48 weeks of treatment
- *Results:* Of 9 compound test measures, 0 favored CBZ, 6 favored LTG (faster and more accurate on tests of reading and comprehension)

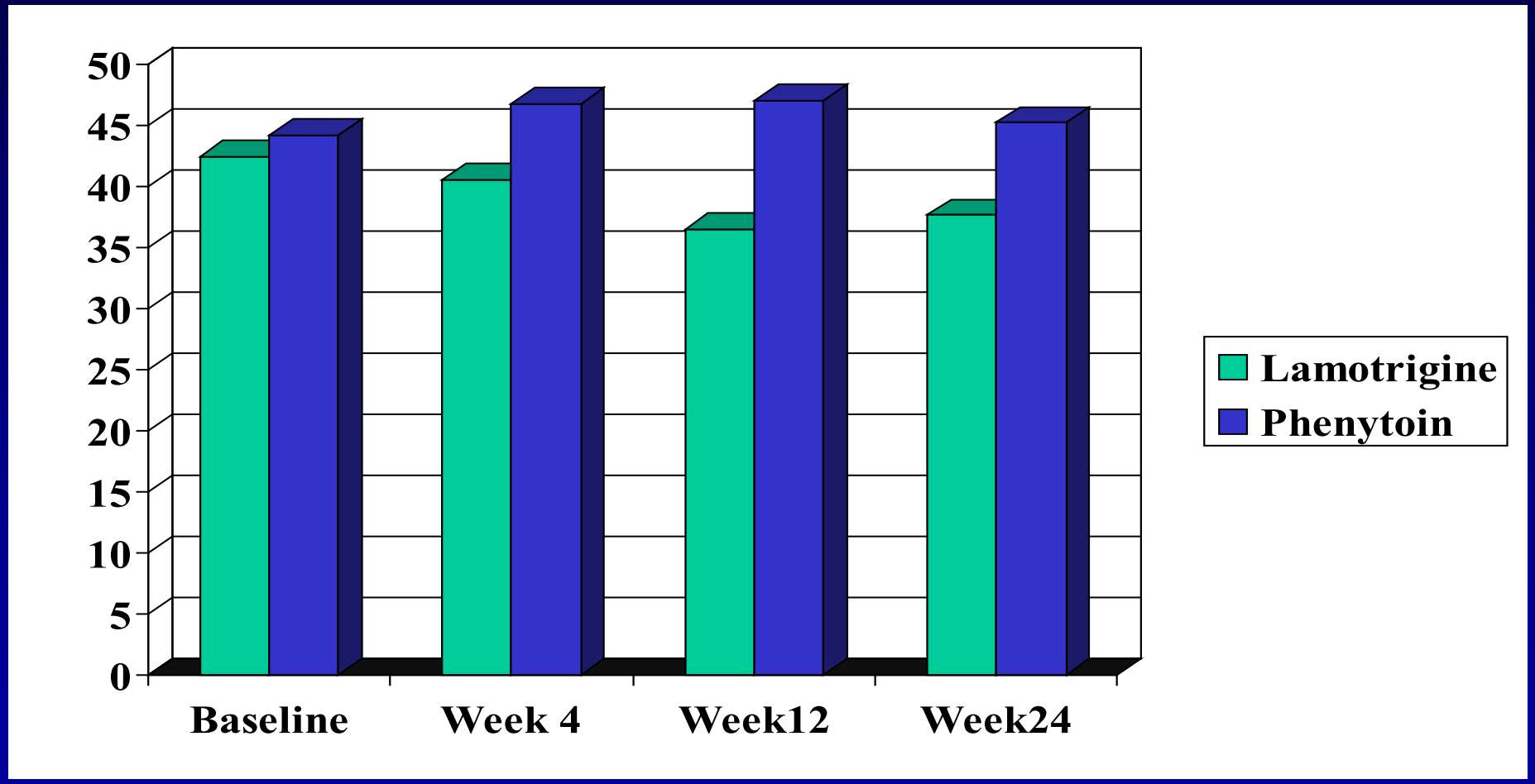
Brodie et al. *Epilepsia* 1999;40(Suppl 2);94

Lamotrigine vs. Phenytoin: QOL

- *Patients:* 181 newly diagnosed epilepsy cases
- *Experimental design:*
  --Random and blind assignment to monotherapy LTG (n=86; SL=3.4) or PHT (n=95; SL=13.4)
  --Side Effects and Life Satisfaction inventory given at baseline and at 4, 12, and 24 weeks
- *Results:*
  --Seizure control similar
  --Adverse events: LTG--rash mostly; PHT--CNS effects (asthenia, somnolence, ataxia)

Steiner et al. *Epilepsia* 1999;40;601-607

Mean Scores on the Side Effects and Life Satisfaction Inventory



Favorable Psychiatric Effects of Lamotrigine

- Bipolar disorder
  --Bipolar depression
  --Rapid cyclers
  --Refractory patients
- Improved sense of well-being generally

Lamotrigine: Summary

- Add-on lamotrigine--no changes in cognition, some ? changes in behavior
- Lamotrigine vs. other AEDs--better, both cognitively and behaviorally; seizure control maintained/improved
- Psychiatric effects--favorable, especially in mood disorders, behavioral problems

Language-Related Effects of Topiramate

- *Patients:*
  --42 adults given TPM in clinical practice--open study
- *Language:*
  --12 (29%) complained of language problems (anomia, impairment of verbal expression)
  --Neuropsychological testing (4 toxic cases): verbal fluency: -47%; problem solving time: -55%; reading speed: -11%; attention: -26%.

Ojemann et al. Epilepsy & Behavior 2001;2;579-584

Cognition: Effects of TPM

- *Subjects (retrospective study):*
  --18 adults placed on TPM (300 mg median dose)
  --18 adults with no changes in drug regimens
- *Cognitive tests*: Given 2x, 36 months apart
- *Results:*
  --11 of 21 test measures showed significant losses with TPM vs. comparison group --
  Verbal abilities had greatest change (VIQ down 12 points; verbal memory: -25%; verbal fluency: -39%). Also: PIQ down 12 points; vis-spatial same

Thompson et al. *J Neurol Neurosurg Psych* 2000;69:636-641

Effects of Topiramate:
Clinical Observations (Seattle)

- *Patients:*
  --Difficult to manage seizure patients (adults and older children)
- *Observations:*
  --Diminished speed of response generally
  --Slowing of speech; diminished verbal fluency
  --Seen occasionally as soon as 200 mg/d with adults, and fairly often by 400 mg

Adjunctive Topiramate & Cognition

- *Study #1*
  --22 patients on TPM and other AEDs were given various cognitive test and TPM was withdrawn
  --Cognitive testing after withdrawal showed significant improvements on 13/41 test variables including language, attention, speed of response
- *Study #2*
  --16 patients tested off then on TPM
  --3/8 variables (verbal fluency, speed, language) significantly declined on TPM

Lee et al. *Epilepsia* 2003;44;339-347

Topiramate & Psychiatric Effects

- *Psychiatric disorders developed on TPM (n=103)*
  --46 affective disorder -
  -22 aggressive behavior -
  -16 psychosis -
  -11 anxiety
  --8 personality disorder (anger, agitation, hostility
- *Emotional/behavioral problems less likely if*
  --Lower dose, start more slowly
  --Patients with psychosis were more likely to be seizure free

Mula & Trimble *Epilepsy & Behavior* 2003;4;430-434

Topiramate: Summary

- Add-on topiramate--dosage-related adverse changes in speed of response, rate of speech; good seizure control
- Topiramate vs. other AEDs--adverse cognitive changes; seizure control maintained/improved
- Psychiatric effects--under investigation

Zonisamide: Summary

- Cognitive studies--dosage-related adverse changes in cognitive functioning, verbal fluency, speed of response
- QOL--largely unstudied
- Future cognitive/QOL studies--few in progress

Levetiracetam: Summary

- Cognitive studies--some small studies done in drug development were suggestive of few adverse effects
- Psychiatric/QOL studies--no change in anxiety; QOL improved; MR and behavior problem cases may show increased irritability; psychosis
- Future cognitive/QOL studies--few in progress

Oxcarbazine

- Cognitive studies--two studies published with basically favorable outcomes
- QOL studies--none done
- Future cognitive/QOL studies--in progress:
  --Mood: 20 center child study--USA
  --Cognition: Child study in Europe

Oxcarbazine: Summary

- Cognitive studies--some preliminary work; likely to be fewer adverse effects than with carbamazepine due to absence of epoxides
- QOL studies--none done
- Future cognitive/QOL studies--few or none in progress

Summary: AED Effects

- *Older AEDs:*
  --Most have mild adverse cognitive effect
  --Barbiturates worse, including behavior
- *Newer AEDs:*
  --All have been incompletely evaluated
  --Gabapentin and lamotrigine--most favorable cognitively and behaviorally
  --Side effects of topiramate and zonisimide should be watched closely