

# Epilepsy and cognition

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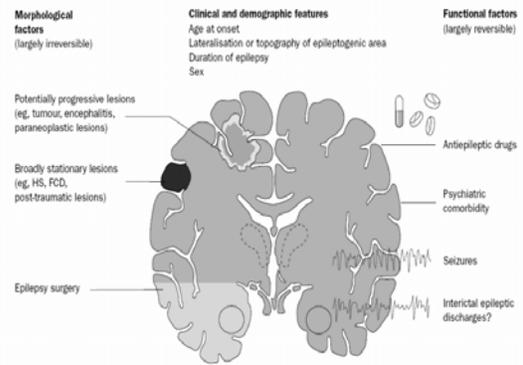
## Cognitive dysfunction

- Auditory/ verbal/ visual memory deficits
- Language deficits
- Executive dysfunction (e.g., deficit involving problem solving, response inhibition, complex attention, or organization)
- Impaired psychomotor speed
- Global cognitive dysfunction

## Behavioral and emotional syndromes

- Depression
- Anxiety
- Psychosis
- Impaired attention, vigilance
- Fear/aggression (asso. with ictal discharges)

Elger CE, et al. *Lancet Neurology*, 2004;3:663-72.



## Antiepileptic drugs and cognition

Adverse cognitive effects (similar to alcohol) depend on

- Higher doses, higher blood level
- Rapid upward titration
- Polypharmacy
- Long-term use



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### Epilepsy and antiepileptic drug use in elderly people as risk factors for dementia

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#### Abstract

**Objective:** To assess the role of epilepsy and antiepileptic drugs (AEDs) as risk factors for probable Alzheimer's disease (AD) and for all dementia in the Canadian Study of Health and Aging (CSHA). A secondary objective was to isolate the effect of the AED phenytoin on the development of dementia and AD.

**Methods:** The cohort consists of 3376 participants aged 65 years or older with no evidence of dementia, defined as Modified Mini-Mental State (3MS) score  $\geq 78$ . Primary exposure was self-report or clinical diagnosis of epilepsy at baseline ( $n=393$ ), or self-report of AED therapy ( $n=67$ ). Primary outcomes were development of dementia, defined as 3MS  $< 78$ , or AD, determined by clinical examination using standard criteria, during a 3-year follow-up period. People whose 3MS score remained  $\geq 78$  served as the comparison group.

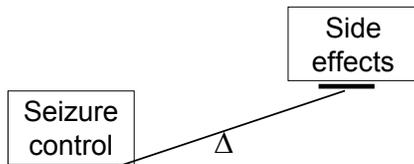
**Results:** People reporting AED use at baseline had an age, sex and baseline 3MS adjusted odds ratio (OR) of 2.11 (95% CI 1.11 to 4.01) for developing dementia compared to those not taking AEDs at baseline. The association remained significant using only phenytoin as the exposure. No significant association was found between AED use and development of AD, nor between epilepsy and development of either AD or dementia.

**Conclusions:** Older adults taking AEDs are at a significantly higher relative risk of developing dementia than those not taking AEDs. Further investigation is warranted.

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**Keywords:** Epilepsy; Antiepileptic drugs; Phenytoin; Dementia; Alzheimer's disease; Canadian Study of Health and Aging (CSHA)

## Treatment with AEDs



## Antiepileptic drugs and cognition

- When treated with AEDs >>> seizures reduced >>> improved cognitive function
- Series of studies in healthy adults compared the cognitive and behavior effects of AEDs by Meador and colleagues

## Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults

K.J. Meador, MD; D.W. Loring, PhD; E.E. Moore, BA; W.O. Thompson, PhD; M.E. Nichols, MD; R.E. Oberzan, BA; M.W. Durkin, MD; B.B. Gallagher, MD, PhD; and D.W. King, MD

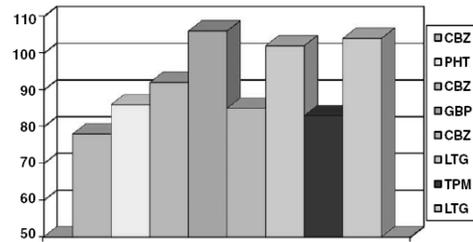
**Article abstract**—The relative effects of antiepileptic drugs (AEDs) on cognition are controversial. We compared the cognitive effects of phenobarbital, phenytoin, and valproate in 59 healthy adults using a randomized, double-blind, incomplete-block, crossover design. Cognitive assessments were conducted at baseline, after 1 month on each drug (two AEDs per subject), and at two repeat baselines 11 weeks after each AED treatment. The neuropsychological battery included 12 tests, yielding 22 variables: Choice Reaction Time, P3 Event-Related Potential, Finger Tapping, Lafayette Grooved Pegboard, Selective Reminding Test, Paragraph Memory, Complex Figures, Symbol Digit Modalities Test, Stroop Test, Visual Serial Addition Test, Hopkins Symptom Checklist, and Profile of Mood States. More than one-half of the variables exhibited AED effects when compared with nondrug baselines, and all three AEDs produced some untoward effects. Differential AED effects on cognition were present for approximately one-third of the variables. Phenobarbital produced the worst performance; there was no clinically significant difference between phenytoin and valproate.

NEUROLOGY 1995;45:1494-1499

B. Hermamm et al. *Epilepsy & Behavior* 2010; 17 : 1-5.

## MCG Stories: Delayed Recall

% Compared to Non-Drug Average  
Healthy Volunteer Studies



Meador et al, 1991, 1993, 2000, 2001, 2005

## Summary of effects of AEDs on cognition

- Effects of most AEDs are relatively modest
- Polypharmacy and high AED doses/blood levels increase risk for cognitive impairment
- AED-associated cognitive impairment is clinically significant in some patients, may be offset by reduced seizures
- Impaired attention, vigilance, psychomotor speed

Motamedi G, Meador K. *Epilepsy & Behavior* 4 (2003) s25-s38.

## Summary of relative effects of AEDs

- PB has worse S/E profile than CBZ, PHT and VPA
- In general the "new" AEDs (OXC, VGB, GBP, LTG, ZNS, TGB and LEV) seem to display minor or no cognitive side effects
- TPM commonly reported of impaired concentration and memory, slow thinking and word-finding difficulties
- LTG as an add-on Rx may improve cognitive problems, and health-related QoL

Shulman MB and Barr W, *Epilepsy Behav* 2002;3 : S30-S34.

## Treatment

- Choosing AEDs that best control seizures with minimal cognitive side effects
- Slow titration, keep therapeutic levels
- Avoiding polypharmacy
- Treating associated depression or other mood disorders

**Reassess the severity of seizures and efficacy of AEDs in use**

## Treatment

### Medications

- **Donepezil**, 5-10 mg improved memory but not attention, visual sequencing, mental flexibility, psychomotor speed or QoL in patients with epilepsy <sup>1</sup>
- **Methylphenidate (MPH)** used in epileptic patients with multi- AEDs improved cognition and QoL and relief from sedation w/o increase seizure frequency<sup>2</sup>

1. Fisher RS, et al., *Epilepsy Behav* 2001;2 : 330-4.
2. Moore JL, et al., *Epilepsy Behav* 2002;3 : 92-5.

## Treatment

### Medications

- **Ginkgo biloba** No controlled trials investigating memory complaints in epilepsy patients, several isolated reports note ginkgo-induced seizures \*
- **Haloperidol** has little effect on seizure threshold, but chlorpromazine and clozapine possibly increased risks of seizure

\* Shulman MB and Barr W, *Epilepsy Behav* 2002;3 : S30-S34.

## Treatment

### Medications

- TCAs and SSRIs are used successfully to treat depression and anxiety in patients with epilepsy
- Some SSRIs, (fluoxetine, paroxetine, fluvoxamine, and ,lesser degree, sertraline) inhibit CYP 450 >>> may increase PHT, CBZ and VPA levels
- Citalopram and sertraline are asso. with enhanced psychomotor responses, sustained attention and verbal fluency

## Treatment

### Vagal nerve stimulation

- Several studies have shown no or mild cognitive and behavioral improvement following VNS
- Chronic VNS application did not show any negative effects on mood, behavior, cognition or QoL\*

\* Aldenkamp AP,et al. *Epilepsy Behav* 2002; 3 : 475-9.

## Treatment

### Epilepsy surgery

- Most common is temporal lobectomy
- Typically, **left temporal lobectomy** induces verbal memory and learning deficits \*\*\*
- Right temporal lobectomy is asso. with visual-spatial memory and cognitive declines

## Treatment

### Epilepsy surgery

- The case of H.M., who underwent bilateral temporal lobe resection for a relief of intractable epilepsy in