New Onset of Epilepsy in the Elderly
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Disclosure
During my almost 40 years in this field, I have received honoraria, consulting fees and or research grants from almost all companies developing or manufacturing drugs and devices related to epilepsy. The majority of my research funding has come from the NIH or other federal sources.

My current commitments are: chairing the data and safety committee for the Medtronic deep brain stimulator and consulting with Eisai. Upsher Smith, UCB and Lundbeck.
Learning Objectives

• Appreciate complexities of choosing the optimal AED
• Learn about proper use of therapeutic drug monitoring in the elderly
• Understand the importance of life situations on the quality of life
Impact on Clinical Care and Practice

• Deciding if to treat after a single seizure
• Choosing the best AED for elderly
• Best use of AED monitoring
The Elderly with Epilepsy

- Community dwelling
- Nursing home
- Hospital intensive care unit
• I’m supposed to respect my elders

• But it’s getting harder and harder for me to find one now
Health status is more important than age
Defining Epilepsy

• Classical = Two or more unprovoked seizures
Could a single seizure in the context of a CNS disorder be diagnosed as epilepsy?
  – Debate at AES 2007*

• A diagnostic must be assigned to prescriptions
  – 345.xx (epilepsy) or 780.39 (convulsion)

• Who makes the diagnosis in elderly?
  – Very few neurologists involved

• A seizure may not be epilepsy
  – Cardiac, Metabolic, Respiratory, Drugs/ alcohol, Infections
Etiology of Epilepsy, Age 65+

- Cryptogenic: 51%
- Stroke: 38%
- Degenerative: 12%
- Tumor: 5%
- Trauma: 2%
- Infection: 2%

Seizures in Alzheimer’s

• Clinically apparent (mostly convulsive) seizures in Alzheimer’s
  – 7% to 21% of persons with sporadic AD have at least one unprovoked seizure.
  – Seizure incidence increases in earlier onset AD*
    • Risk ratio = 87 if onset 50-59
    • Risk ratio = 3 if onset 70-79 years of age

*Amatniek et al. Epilepsia 2006; 47:867-872.
Age-Specific Incidence of Epilepsy
By gender, in Rochester, MN
Up-slope starts at age 50 (1935-1984)
(overall ~ 169/100 K PY)

Incidence of Epilepsy in US Nursing Homes*

- US Medicare data base of 8 million plus subjects.
- Entry = No epilepsy on admission; 1-3 year of follow-up.
- 3,613,926 NH residents followed forward
- Overall = 1,642 / 100KPY (10 fold higher than outpatients)
- stroke = 2,762/ 100K PY.
- head injury= 4,566 /100K PY.
- Parkinson's Disease = 1,766/100K PY.
- dementia (any type) =1,644/100K PY.
- No predisposing diagnoses, 1,245/100K PY.

Prevalence (cases at a point in time)

• In Community higher as older *
  – 1.8% identified as having epilepsy by having an ICD-9-CM code representative of this condition.*

• In nursing homes, lower as older**
  – Overall 6% to 10% by ICD-9 codes 345.xx or 780.3
  – 16.4% in 65-74; 8.3% in 75-84; 3.7% in 85+

• In intensive care units***
  – 30% of patients following cardiorespiratory arrest.
  – 1% to 21% with intracerebral hemorrhage,

Seizure Types

- CPS: 38.3%
- GTC: 27.1%
- SPS: 14.3%
- GTC & Partial: 12.8%
- Mixed Partial: 7.5%


VA Coop Study #428*
Geriatric Epilepsy Management

Management

- Aging Process
- Seizure Frequency
- Pharmaco-kinetics
- Medication Side Effects
- Comorbidities
- Underlying Pathology
Co-morbidities-medical

• Incidence and severity of these are unknown
  – Depression
  – Anxiety
  – Visual impairment
  – Osteoporosis
  – Memory loss
  – Other medical disorders
Social Issues

• Loss of driving privileges
• Lack of spousal support
• Emotional shock of developing epilepsy
• Cost of medication
• Fear of seizures, falling, embarrassment
• Adult children of parents (role reversal from pediatric practice)
First Seizure in Elderly: To treat or not to treat, that is the question

• Reasons to treat
  – Prevent another seizure

• What is the risk of 2\textsuperscript{nd} seizure
  – After a stroke, in Alzheimer’s, etc?
  – Unknown etiology?

• Reason not to treat
  – Cognitive side-effects
  – Increasing falls and fractures
“First” seizure in Elderly

• Prospective observational study of adults seen by a hospital-based first seizure service between 2000 and 2011#.
• The likelihood of a second seizure at one year was 53% (95% CI 45-62) in older patients and 48% (95% CI 44-51) in younger patients.
• Independent predictors of seizure recurrence were:
  – remote symptomatic etiology.
  – first seizure arising from sleep.
  – epileptiform abnormality on EEG.
  – partial seizures.
  – not age.

2\textsuperscript{nd} seizure after “1\textsuperscript{st}” seizure: stroke

• 159 patients
  – Early-onset seizures occurred in 57 patients
  – late-onset (>14 days post-stroke) in 102 patients
• 68 (43%) with “1\textsuperscript{st}” seizure had recurrence
• Risk factors for more seizures
  – Late onset “1\textsuperscript{st}” seizure (p>0.01)
  – Hemorrhagic component
  – Occipital involvement
  – Low Rankin score after “1\textsuperscript{st}” seizure
WHICH AED?
Ideal Properties of an AED for Elderly

- Efficacy
- Safety
- No drug interactions
- Good bioavailability
- Linear elimination kinetics
- Wide therapeutic index
- Weight neutral
- Renal elimination
- Broad spectrum
- No protein binding
- Parenteral formulations
- Lack of idiosyncratic effects

Ideal AED for patient: The one that works
## Summary of Properties

<table>
<thead>
<tr>
<th>AED</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Broad Spectrum</th>
<th>No relevant interactions</th>
<th>Renal Excretion</th>
<th>IV</th>
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GBP, LTG, CBZ in Elderly*

• 18-center, randomized, double-blind, double dummy, parallel study of 593 elderly subjects with newly diagnosed seizures.
• Patients were randomly assigned to one of three treatment groups:
  – GBP 1,500 mg/day
  – LTG 150 mg/day
  – CBZ 600 mg/day
• Early terminations:
  – LTG 44.2%, GBP 51%
  – CBZ 64.5% (p = 0.0002)
• Seizure control was similar among groups.
• LTG and GBP should be considered as initial therapy for older patients with newly diagnosed seizures.


Studies of Other AEDs in Elderly

• LEV vs CBZ, 128 patients, prospective, 1 year*
  – no significant difference in number of seizure-free patients between LEV and CBZ (p = 0.08);
  – LEV caused significantly fewer (p = 0.02) side effects than CBZ;
  – attention deficit, frontal executive functions and functional scales) were significantly worse in the CBZ group.

• Lamotrigine vs CBZ, double-blind, newly diagnosed 125 eligible subjects**
  – A borderline difference in the SEALS Dysphoria subscores favored lamotrigine.
  – “Neither LTG nor CBZ seems likely to cause significant changes in health-related quality of life measure at therapeutic doses.”

• Zonisamide pooled analysis of data from clinicall studies (N=95)***
  – Incidence was lower in elderly versus adult patients for treatment-related TEAEs (55.8% vs. 72.7%), severe TEAEs (11.6% vs. 20.4%), serious TEAEs (12.6% vs. 16.6%), and TEAEs leading to withdrawal (17.9% vs. 22.1%)


Evidence for choosing among AEDs in elderly

- There is some evidence for superiority of newer AEDs over CBZ
- No comparisons for phenytoin vs newer AEDs
- My opinion:
  - Avoid AEDs with significant drug interactions
    - Elderly healthy are like women of childbearing potential—may have new medical conditions next visit.
  - Avoid AEDs that are highly protein bound
  - Favor AEDs with long half-lives
  - Favor AEDs with suspension, sprinkle or IV formulations
Polypharmacy in the Elderly

- All elderly are treated with polypharmacy, but only one of them is an AED.
- Many studies have been done about AED-AED interactions,
  But very few about AED- other drugs
# Effect of Enzyme-Inducing AEDs

<table>
<thead>
<tr>
<th>Non-AEDs</th>
<th>Plasma Level Reduction</th>
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<tbody>
<tr>
<td>Anticoagulants</td>
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<tr>
<td>Warfarin</td>
<td>50%</td>
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<tr>
<td>Clopidogrel</td>
<td>??? – 3A4/5 metabolism</td>
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<tr>
<td>Ca-channel blockers</td>
<td>30%–93%</td>
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<tr>
<td>Statins</td>
<td>50%–80%</td>
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<tr>
<td>Antidepressants</td>
<td>27%–31%</td>
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Effect of CBZ on Serum Simvastatin – 2 subjects

Age-related changes affecting PK and TDM

• Pharmacokinetics (PK)
  – Absorption
    • Gastric Ph
    • GI transit time
  – Elimination
    • Hepatic
    • Renal

• Therapeutic Drug Monitoring (TDM)
  – Protein binding
    • Of AED
    • Of other drugs
Indications for Therapeutic Drug Monitoring*

• When therapeutic goal has been reached
  – At least 4 half-lives beyond dose change
• Side-effects
• Breakthrough seizure
• Co-medications added or removed
• Change in health status
• Monitor compliance

Case report: The woman who inspired me

- 76 year old woman from northern Minnesota
- Developed complex partial seizures, poorly controlled
- Local MD prescribed phenytoin and valproate
- Developed “Alzheimer's and Parkinson’s”
- Total AED levels “normal range”
- Sent to MINCEP last stop before NH.
- Unbound levels high
- Lived for 18 more years after adjustment of AEDs enjoying independent life,
- Into NH because of lack of care givers and arthritis
- We traded copies of our books; she wrote it in NH because she did not want to partake in activities with the old people!
- Lived to 94 years of age
• The woman who inspired me 2 decades ago
Effect of Age on AED “Dosing Ranges”

adapted from:
TDM Caveats

• Usual laboratory values are inappropriate
  • Abnormal protein binding
  • Elderly may need lower concentrations for efficacy
  • May have side-effects more readily
• Unbound (free) levels needed for AEDs that have binding greater than 70%
• Monitoring of drugs other than AEDs should be done (but is rarely performed)
• Usual fluctuations in compliant outpatients is less than 20%, but levels in some NH patients “bounce” more than 200%.
Individual Total Phenytoin Serum Concentrations in Elderly Nursing Home Residents

Conclusions

• Epilepsy is common in elderly
• Elderly have many co-morbidities
• Although there is little evidence for it, the first seizure in elderly often leads to treatment
• Because of drug interactions of AEDs with other drugs, those AEDs with few interactions are preferred
• TDM is important but “laboratory ranges” may not be appropriate.
• Much more research needs to be done in elderly.
Choosing the right dose is important.

Use TDM to guide.