Medical Decision Making in Dementia Pharmacotherapy

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Case

- 74 y/o female
- Visit to clinic prompted by family concerns regarding memory
  - Worse in the past couple years
  - Not much change in last 6 months
- Testing today
  - MoCA: 23/30
  - GDS: 7/15
  - Clock Drawing: normal
Case (con't)

- ADL’s: 5/5
  - Needs some assistance with IADL’s
- Lives with daughter and her husband
- Local day care 3d/week
  - Staff reports participation in activities but “slow”
- Patient appears uninterested in today’s visit
- Little facial expression
- Lab work-up and head CT normal
Case (con't)

- Medications
  - Atenolol 25 mg once daily (HTN)
  - Donepezil (Aricept©) 10 mg daily (Alzheimer's type Dementia)
  - Multivitamin one daily
  - Ranitidine 150 mg once daily prn dyspepsia
Considerations

- Should the donepezil be continued?
- Should the donepezil have been started in the first place?
- Is an anti-depressant indicated?
Pharmacotherapy For Dementia

- Cholinesterase Inhibitors
  - Donepezil (Aricept®)
  - Galantamine (Razadyne®)
  - Rivastigmine (Exelon®)

- NMDA Receptor antagonist
  - Memantine (Namenda®)
Clinical Trials: RCTs

- Short term (6 month)
  - Long-term condition
  - Vs. placebo some compare among agents
- Often selective of patients
- “Ideal” conditions
- Primary and Secondary efficacy measures
  - ADAS-cog
  - SIB
  - MMSE
Clinical Trials: Follow-up

● Open label follow-up studies (observational)
  – At conclusion of RCT
  – Up to 5 years
  – Not highest level of evidence!
    • Confounding
    • Un-blinded
    • No control group
ADAS-cog

- Alzheimer's Disease Assessment Scale-Cognitive subscale
- Score is 0 to 70 (0 is normal)
- Measures memory, language and praxis
- Many regulatory authorities recognize a four-point change on the ADAS-Cog at 6 months as indicating a clinically important difference, a proposal that has impacted how clinical trials are interpreted
Randomized Clinical Trial (RCT) of CEI’s – mediocre outcome measures

Fig. 2. Mean (SE) change from baseline in score on 11 item cognitive subscale of Alzheimer's disease assessment scale over time, observed case analysis

Progression of Alzheimer's disease

Early diagnosis
- Cognitive symptoms

Mild-moderate stage
- Loss of functional independence
- Behavioral problems
- Nursing home placements

Severe stage
- Death

MNSE Score
- 30
- 25
- 20
- 15
- 10
- 5
- 0

Years
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9

Adapted from Feldman and Gracon.

Natural progression of AD

Range

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Results

• All agents have been shown to be efficacious
  – Statistically better than placebo
• Does this result in clinically important benefits??

That is the question
Two Systematic Reviews


● **Background:** The effectiveness of approved pharmacologic therapies for dementias in achieving *clinically relevant* improvements is unclear.

● **Purpose:** To review the evidence for the effectiveness of cholinesterase inhibitors and memantine in achieving clinically relevant improvements, primarily in cognition, global function, behavior, and quality of life, for patients with dementia.

● **Data Sources:** Cochrane Central Register of Controlled Trials, MEDLINE, PREMEDLINE, EMBASE, Allied and Complementary Medicine Database, CINAHL, AgeLine, and PsycINFO from January 1986 through November 2006.

● **Study Selection:** English-language RCTs

- **Data Extraction:**
  - Data extracted on study characteristics and outcomes, including ADRs
  - Effect sizes calculated and data e combined when appropriate

- **Data Synthesis:**
  - 96 publications representing 59 unique studies
  - Both cholinesterase inhibitors and memantine had consistent effects in the domains of cognition and global assessment, but summary estimates showed small effect sizes
  - Outcomes in the domains of behavior and quality of life were evaluated less frequently and showed less consistent effects
  - Most studies were of short duration (6 months)
  - Three studies directly compared different cholinesterase inhibitors and found no differences in cognition and behavior

- Limitations of studies:
  - Short duration
  - Inclusion of only patients with mild to moderate Alzheimer disease
  - Poor reporting of adverse events
  - Lack of clear definitions for clinical significance
  - Limited evaluation of behavior and quality-of-life outcomes
  - Limited direct comparison of different treatments

- Conclusion:
  - Treatment of dementia with cholinesterase inhibitors and memantine can result in statistically significant but clinically marginal improvement

- **Introduction:**
  - National Institute of Health and Clinical Excellence (NICE) restricted the use of acetylcholinesterase inhibitors and memantine in 2007

- **Methods:**
  - A health technology assessment (HTA) of the effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of AD to re-consider and up-date the evidence base used to inform the 2007 NICE decision.
  - Targeted RCTs
  - Searched MEDLINE, EMBASE and the Cochrane Library from January 2004 to March 2010.
  - Cost-effectiveness assessed using a cohort-based model with three health states: pre-institutionalized, institutionalized and dead

- **Results:**
  - Confidence about size and statistical significance of estimates of effect of galantamine, rivastigmine and memantine improved on function and global impact in particular
  - Cost-effectiveness also changed
  - For donepezil, galantamine and rivastigmine, in 2010 the same drugs ‘dominated’ best supportive care (improved clinical outcome at reduced cost). Primarily because of changes in modeled costs of introducing drugs
  - For memantine, the cost-effectiveness improved

- **Conclusion:**
  - There has been a change in the evidence base between 2004 and 2010 consistent with the change in NICE guidance. Further evolution in cost-effectiveness estimates is possible particularly if there are changes in drug prices
Back to Our Questions……

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Discussion and Questions