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

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

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


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

- **Data Synthesis:**
  - 86 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