A Refresher of the Treatment of Dementia (as we forgot the evidence)

G. Michael Allan
Evidence & CPD Program, Alberta College of Family Physicians
Professor, Dept Family Med, U of A.

Dementia

1) Understanding dementia treatment trials
2) Options for Treatment
   - Cholinesterase Inhibitors Benefit
   - Cholinesterase Inhibitors Harms
3) Dose, Severity, withdrawing, prevention.
4) Other options
   1) Memantine
   2) Cognitive Enhancement.

Understanding Dementia Research

- Dementia category by MSE
  - Mild 21-26; Moderate 10-20; Severe <10
- Scales! Need to know
  - Mini-mental Status Exam (MSE), 0-30, higher better
  - Alzheimer's Disease Assessment Scale (ADAS-Cog), 0-70, lower better
  - Global Impression of Change (physician rated), (out of 7)
- Minimal Important Clinical Difference
  - MSE = 1.4 and in ADAS Cog = 4
- To evaluate: What is the mean change & how many got MCID

	Placebo	Rivastigimine	Difference	Attain 1.4 change
MSE At 6 months	-0.6	+0.2	0.74	?

What's NEW ?

Rivastigmine Cochrane reviews 2009 and 2015

	MSE change (out of 30)	ADAS-Cog change (out of 70)	Global Impression of Change
2009 (9 RCTs)	0.82	1.99	0.66 (0.55-0.79)
2015 (13 RCTs)	0.74	1.79	0.68 (0.58-0.80)

Meta-analysis of Dementia RCTs

- What is the scientific evidence for Cholinesterase Inhibitors in the treatment of Alzheimer's disease.
- 22 Trials: 12 Donepezil, 5 Rivastigmine, 5 Galantamine: 27 to 978 pt/trial, 6 wks-3yrs long
- **Findings:** 1.5-3.9 (ADAS-cog & Min clinical sign ≥ 4)
- **Limitations:** Numerous
  - ITT flaws (pt exclusion after randomization)= 15/22 (68%),
  - Last Observation Carried Forward (declining illness)
  - Use of Means (in scales),
  - No correction for multiple comparison
  - Funding (often authored by employees)

BMJ 2005; 331: 321-27

Cholinesterase Inhibitors: Summary

- Cholinesterase trials vs Placebo: MSE 10-26*
  - Poor reporting (e.g. 12% of Donepezil report mortality)
  - Alzheimer's Disease Assessment Scale (ADAS-cog)=4 is clinical significant,
  - Quality of Life scores unchanged

	Donepezil[1]	Galantamine[2]	Rivastigmine[3]	All[4]
MMSE	1.44	?	0.74	1.37
ADAS - Cog	2.81	3.38	1.79	2.73
ADAS – Cog of 4	?	NNT 6	NNT 18*	?
Glob Clin State	NNT 10	NNT 7	NNT 13	NNT 14
Adverse Events	NNH 18	?	NNH 8	NNH 8

? Not given

* Health Technol Assess 2012;16(21). 1) Cochrane. 2006;(1):CD001190 (10mg x 6 months). 2) Cochrane 2006; 1: CD001747. 3) Cochrane 2015; 9: CD001191. (*2009) 4) Cochrane 2006; Issue 1: CD005593.

Other Outcomes: Example Donepezil

- ADL & IADL: Most statistically significant
  - Lots of different ones used, so summing up hard
  - Basically, move about <4% on different scales.
    - E.g. updated rivastigmine: change = 2.15 out of 100.

- Quality of Life: Patient rated.
  - No difference.

- Behavior: Primarily NPI used
  - No difference 12 wks, 10mg
  - Difference (24 wks, 10 mg): 2.94 (out of 144)

Cochrane 2006;1:CD001190. Ann Intern Med. 2008;148:379-97. *Cochrane 2015,(9): CD001191.*

Adverse Events: Example Donepezil

- Statistically significant
  - Anorexia: 7.3% vs 2.1%, NNH 20
  - Diarrhea: 14.5% vs 5.3%, NNH 11
  - Nausea: 14.5% vs 5.4%, NNH 11
  - Vomiting: 11.3% vs 4.7%, NNH 16
  - Weight Loss: 8.2% vs 4.5%, NNH 28
  - Fatigue: 9.4% vs 4%, NNH 19
  - Asthenia (weakness): 7.9% vs 4.7%, NNH 32
  - Dizziness: 8.1% vs 5.4%, NNH 38
  - Insomnia: 9.9% vs 4.4%, NNH 19
- Others Borderline (accidental injury, rhinitis)

Ann Intern Med. 2008;148:379-397. Adverse Event Appendix Table 4

Is one better than another?

- 3 Trials compare Head to Head[1]
  - Multiple Flaws & potentially biased
    - Industry funded, Employee written, results favoring sponsor.
  - In Meta-analysis : "There is no evidence of any difference between them"[2]
- Four new RCTs: 3 weak and no reliable difference.[3]
  - Fourth: Rivastigmine vs donepezil,
    - No difference in cognition/behavior
    - Marginal (very) differences in function and global effect.

- **Bottom-Line: No reliable difference**.

1) Lancet Neurol 2004; 3: 622:26. Therapeutics Letter 2005; 56:1-4. 2) Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593. 3) Health Technol Assess 2012;16(21).

Prevention of Dementia:

- Vitamin E : No help
- Exercise: No help.
- Meta-analysis Donepezil:
  - In 1 of 2 trials, 1 of 5 scores had a 3% less decline
  - Stopping due to adverse events: NNH 7.
- Meta-analysis Galantamine:
  - Marginal to no clinical Benefit
  - ++ Harms: NNH (for death) = 94.
- **Bottom-Line: None.**

1) NEJM 2005; 352:2379-88. 2) Cochrane 2015;(4):CD005381 3) Cochrane Database Syst Rev. 2006;3:CD006104. 4) Cochrane 2006;(1):CD001747. Therapeutics Letter 2005; 56:1-4.

What about withdrawing?

- 295 Community dwelling Patients on Donepezil (most >2 yrs)
  - mean age 77, mean MSE 9, followed 1 yr.
  - Stopping of med worsened MSE by 1.9 pts
    - Less effect if severe dementia (<9 MSE)
    - Don't give number attaining MCID (1.4)
  - Withdrawal from study more if stopped!
  - Death: no difference

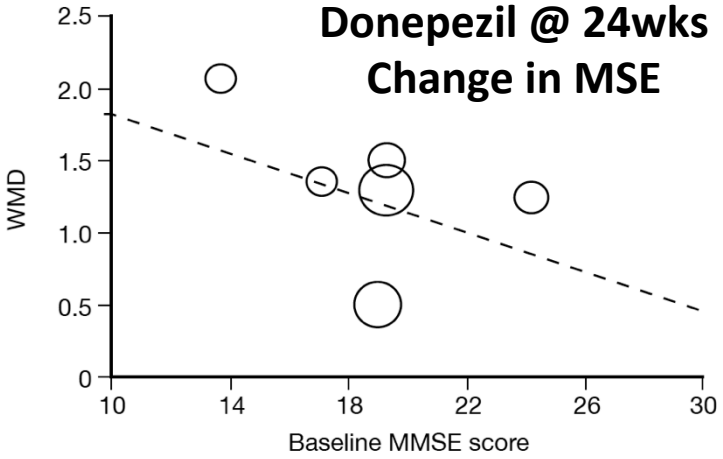
N Engl J Med 2012;366:893-903.

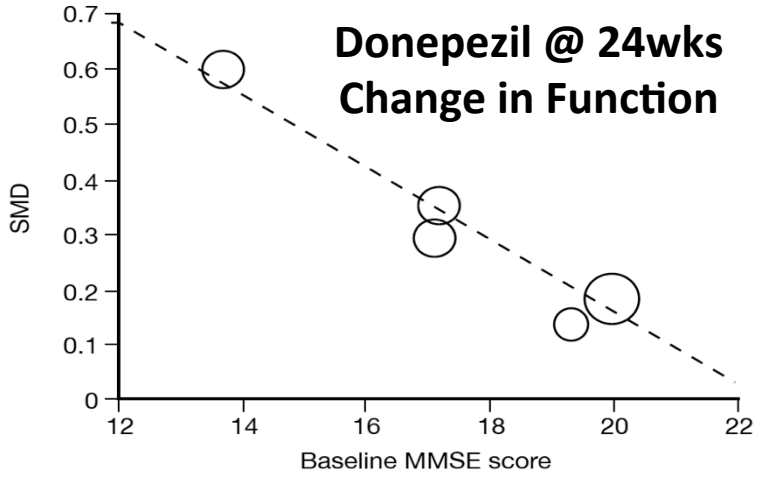
Does Dose Matter?

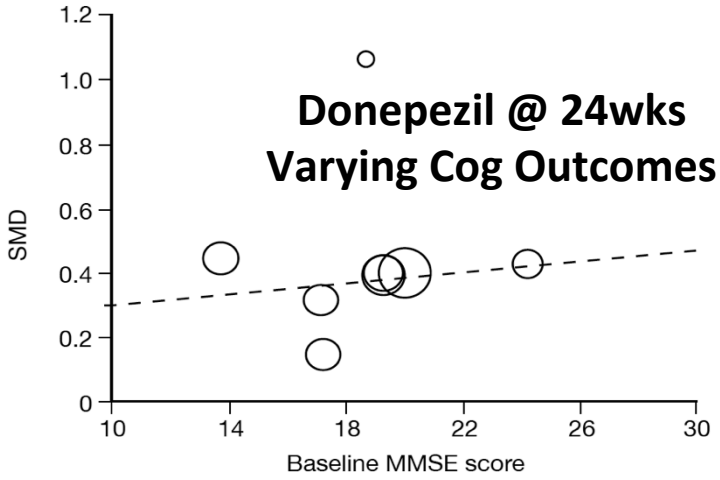
- Moderate dose may matter
  - Donepezil: ADAS-Cog 2.15 (5mg) vs 2.45 (10mg)
    - MSE results equal at 5 or 10mg.
  - Rivastigmine: ADAS-Cog 0.84 (1-4 mg) vs 1.99 (6-12mg)
  - Galantamine: Global rating OR 1.17 (8mg) vs 1.63-1.84 (16-32mg)
- **Bottom-Line: Use mostly indirect comparison. May be that some low doses have a somewhat weaker effect. Probably avoid Galantamine 8mg and rivastigmine 1-4 mg.**

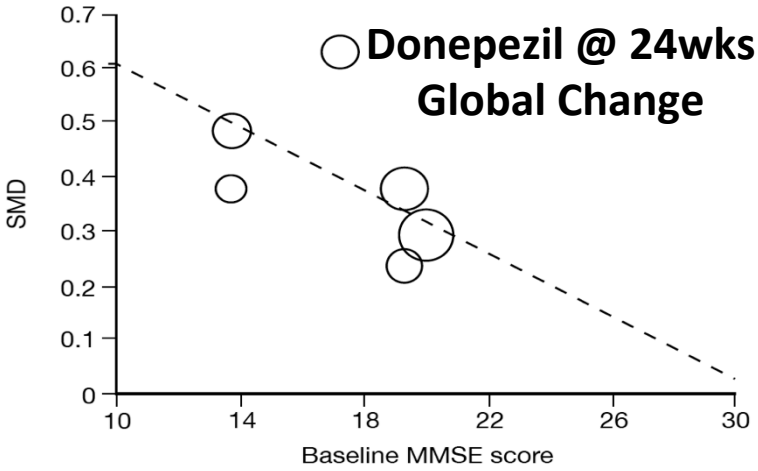
1) Cochrane. 2006;(1):CD001190 (10mg x 6 months). 2) Cochrane 2006; 1: CD001747. 3) Cochrane 2015; 9: CD001191. (*2009)

Does Severity Matter









- Bottom-Line: Maybe more effective in moderate severity, but no formal patient level analysis, data sparse and somewhat inconsistent?

Health Technol Assess 2012;16(21).

Cognitive Enhancement

- 15 RCTs with 718 participants
  - Example: naming objects & people, word association, remembering the past, discussion of hobbies, activities & current affairs, using money, knowing the way around and orientation topics
- Outcomes: change in scale
  - ADAS-Cog at 1-12 months: 2.27 (0.99, 3.55)
  - MSE at 1-12 months: 1.74 (1.13, 2.36) better
    - Longer seems better but based on only one study.
- **Bottom-Line: Seems to have some positive effects (similar to drugs).**

Cochrane 2012; 2: CD005562.

Drugs with Potential: Memantine

- Mostly Moderate - Severe Dementia
  - ADCS -ADL score, Severe impairment battery, Functional assessment Staging, Clinician Impression of Change (CIBIC): All 0-4% change
  - Possibly <agitation (NNT= 63) - if already on
  - Well Tolerated (no diff in drop-out due to AE)
  - Other studies use SMD statistic & can't interpret.[3]

- **Bottom-Line: Effects are small & inconsistent.**

Cochrane 2006;(2):CD003154. Health Technol Assess 2012;16(21). 3) PLoS ONE 10(4): e0123289.

Combining Medicines

- Adding Memantine to Cholinesterase inhibitors
  - 4 RCTs with 1439 pts, ~10 (mean range 7-16)
- 6 months
  - ADAS cog: 1.6 better
  - MSE: 0.5 better
  - Neuro-Psychiatric inventory: 1.6 better (out of 144)
- **Bottom-Line: The best this combination can offer is 1-2% change.**

Health Technol Assess 2012;16(21).

A New Hope: Aducanumab

- RCT 165 pts, age 73, 50% female, dose q-month IV 1,3,6,10 mg/kg or placebo
- Outcome: at one year

Measure	Scale	Worse	Baseline	Placebo vs 10	Main Types of AE
MSE	0-30	low	24	2.7 vs 0.5 worse	Edema (NNH 3), Headache (NNH 5), superficial iron deposition in CNS (8)
CDR-SoB	0-18	high	3.2	1.8 vs 0.7 worse	
FCSRT	0-48	lower	14	No diff	
Discontinue due to AE				10% vs 31% (ss)	

Clinical Dementia Rating—Sum of Boxes. Free and Cued Selective Reminding Test;

- **Bottom-Line: Preliminary evidence suggests potential benefit but very early and will need evidence in moderate to severe dementia.**

Nature. 2016 Aug 31;537(7618):50-6.

Summing-Up

- Cholinesterase inhibitors basically
  - Improve dementia for 1 in 10 (over placebo)
  - Cause Adverse events severe enough to stop taking for 1 in 10 (over placebo)
  - If really working (or was working), stay on.
- All meds the same, Don't give for prevention, don't combine meds
- Cognitive enhancement measures wherever possible
- Hope for Aducanumab (but still just hope)