IMSANZ Annual Scientific Meeting, Alice Springs, September 2005

Acetylcholinesterase inhibitors on trial

Ian Scott
Director of Internal Medicine
Princess Alexandra Hospital
Brisbane

With acknowledgement to
Annette Broome

Growing Health Problem of Dementia

- Predictions for Australia:
  174,300-194,000 people living with Alzheimer's by 2006

- USA estimate 14 million patients by 2050
  Current treatment and lost productivity:
  $61 billion/year

?A New Therapeutic Advance

- Acetylcholinesterase inhibitors developed as reduced acetylcholine postulated as a principal neurotransmitter deficit in Alzheimer's disease
  - **Donepezil (Aricept)**
  - **Galantamine (Reminyl)**
  - **Rivastigmine (Exelon)**

- Launch in 1996
  - **"marks a sea change in dementia care"**
  - **"alleviate the burden of a terrible disease"**
  - **"give hope to many people and their carers"**
  - **"would reduce care costs"**
  - **"halve the incidence of Alzheimer's disease"**

- Drug use in Australia: 584,000 PBS scripts to Dec 2003 = $92.6 million

Case Study

Ms LV 68 yr old lady Living at home with husband

Presented 9/2/05 with chest pain, nausea, 1000ml haematemesis

Background history

- Presumed Alzheimer's disease with superimposed multi-infarct syndrome
- Ischaemic heart disease
- Type II diabetes mellitus
- Hypertension
- Past CVA
- Gastro-oesophageal reflux disease
- Vitamin B_{12} deficiency
- Elevated homocysteine level

Case Study

Medications

- Metformin 1gm bd
- Simvistatin 20mg nocte
- Glibenclamide 2.5mg mane
- Amlodipine 10mg mane
- Isoptin SR 60mg bd
- Irbesartan 300mg mane
- Asasantin SR 1 cap bd
- Folic acid 5mg mane
- Pyridoxine 25mg bd
- Vit B_{12} 1mg 3-monthly
- Galantamine 12 mg bd
- Meloxicam 7.5mg mane
- Serepax, Temazepam, GTN spray prn

Case Study

- Upper GI endoscopy: acute gastric ulcer with large visible vessel and adherent clot
  - transfused
  - adrenalin injected, coagulated, haemostatic clip applied
  - omeprazole infusion
  - H. pylori serology neg
- No further bleeding or chest pain
- No evidence of myocardial infarction
- Meloxicam, Galantamine, Asasantin, Serepax ceased
- Discharged day 5

Case Study

- Prescribed donepezil 10mg/dy November 2002 for impaired cognitive function MMSE 23/30
- Geriatrician review July 2004
  - **Cognitive status continuing to worsen MMSE 21/30**
  - **Worse short-term memory; constructional problems**
  - **Remains independent in ADLs; does some housework; good personal hygiene**

  Assess: "Natural progression of Alzheimer's disease despite cholinesterase inhibitor. Worthwhile changing to a different agent"

  Donepezil ceased; Galantamine 8mg bd commenced

  Dose increased to 12mg bd four months later
- MMSE this admission 21/30

Question

- ***Population***
  - In patients with Alzheimer's disease and moderate cognitive impairment but without behavioural or neuropsychiatric symptoms

are

- ***Intervention/comparator***
  - Acetylcholinesterase inhibitors (AChEIs) compared to placebo
- ***Outcome***
  - effective and safe in bringing about clinically meaningful improvement or stabilisation in cognitive function and reducing the risk of death, institutionalisation, overt disability or carer stress?

Literature Search

- 137 systematic reviews (actually 73)
- Cochrane reviews
  - Donepezil 16 trials: 4365 pts (May 2003)
  - Rivastigmine 8 trials: 3450 pts (Aug 2000)
  - Galantamine 7 trials: 3777 pts (Aug 2004)
- Non-Cochrane reviews
  - Use of AChEIs for neuropsychiatric symptoms
    - » JAMA February 2005
  - Efficacy and safety
    - » Am J Geriatr Psychiatry Jul-Aug 2004
    - » CMAJ Sept 2003
    - » JAMA 2003

General Comments

- Mild to moderate dementia
- Small sample sizes in each trial (<500)
- Duration limited to 12 mo. - usually 6 mo.
- Use of multiple drug doses
- Primary outcome: differences between groups in scores on scales of cognitive function, ADL, behavioural symptoms, and global functioning
  - No measures on rates of death, hospitalisation, residential care placement
  - Very few trials measured carer burden/stress, costs
- Limited data on adverse effects

Scales

- Tests of cognitive function
  - ADAS-Cog 10 domains; 0 (best) -70 (worst)
    - **Spoken language comprehension (0-5)**
    - **Recall of test instructions (0-5)**
    - **Word finding difficulty (0-5)**
    - **Following commnads (0-5)**
    - **Object naming (0-5)**
    - **Construction drawing (0-5)**
    - **Ideational praxis (0-5)**
    - **Orientation (0-8)**
    - **Word recall (0-10)**
    - **Word recognition (0-12)**
  - MMSE 9 items; 0-30

Scales

- Tests of ADL
  - Bristol ADL — 20 items
  - Progressive Deterioration Scale (PDS) — 27 items
  - Disability Assessment for Dementia (DAD) — 40 items; 0-100
  - Instrumental Activities of Daily Living (IADL) adapted for dementia patients — 8 domains
  - PSMS modified for dementia — 9 items
- Tests of behavioural/neuropsychiatric symptoms
  - Neuropsychiatry Inventory (NPI) — 10 items; 0-120

Scales

- Overall global assessment
  - Global Rating/Clinician's Interview -Based Impression of Change plus Caregiver Input (CIBIC-plus) (ADCS-CGIC) — 1-7; 4=no change; <4=improve; >4=worse
  - Gottfries, Brane and Steen (GBS) — 27 items; each 0-6
  - Clinical Dementia Rating Scale (CDR-SB) — 0-18
  - Global Deterioration Scale (GDS) — 1-7
- Carer stress
  - Abridged Relative Stress Scale (aRSS) — 10 items; each 0-4
  - Caregiver Activity Survey (CAS) — Carer time for 6 items/24 hr

Psychometric Issues

Property	*Measure*	*Rating of commonly used scales*
Validity • Content: all relevant aspects • Construct: expected relations seen • Convergent: internally consistent	**Factor analysis** **Correlation coefficient** **Cronbach-α**	Fair to very good Small sample sizes Inappropriate measures of correlation
Reliability • Inter-rater • Test-retest	**Kappa scores** **Correlation coefficient**	
Sensitivity to change **(Responsiveness)**	**$\Delta/\sqrt{2}$ x MSE** **Δ=mean diff** **MSE=mean square error**	Very little information
Minimal clinically important difference (MCID)	**Δ**	Clinical consensus ?validation

Donepezil

Scale	Diff	95%CI	MCID	NNT
MMSE at 1 year **10mg/day**	**1.84**	**0.53-3.15**	**2**	**109**
ADAS-Cog at 24 weeks **5mg/day** **10mg/day**	 **-2.02** **-2.92**	 **-2.77 to -1.26** **-3.74 to -2.10**	**4**	 **200** **138**
PDS at 52 weeks **10mg/day**	**3.80**	**1.70-5.90**	**2**	**53**
DAD at 24 weeks **10/mg/day**	**8.00**	**3.61-12.39**	**7**	**114**
NPI at 24 weeks **10mg/day**	**-4.42**	**-7.91 to -0.91**	**6**	**137**
CIBIC-plus at 24 weeks **10mg/day**	**12.0%** **(improved)**	**Not stated**	**NA**	**8**
CDR-SB	**-0.53**	**-0.73 to -0.33**	**1**	**189**

Galantamine

Scale	Diff	95%CI	MCID	NNT
MMSE	Not reported			
ADAS-Cog at 24 weeks 32 mg/day	-3.3	-4.1 to -2.4	4	121
ADCS-ADL at 24 weeks 24 mg/day (OC)	-2.3	-4.0 to -0.6	2	87
DAD at 24 weeks 24/mg/day	3.7	1.4 – 6.9	7	189
NPI at 24 weeks 16 mg/day	-2.1	-4.0 to -0.2	6	286
Global rating scales (CIBIC or ADCS-CIBIC) at 24 weeks 24 mg/day	OR 1.9 (improved)	1.6 – 2.3	NA	NA

Rivastigmine

Scale	Diff	95%CI	MCID	NNT
MMSE at 26 weeks 6-12 mg/day	0.83	0.53-1.12	2	241
ADAS-Cog at 26 weeks 6-12 mg/day	-2.1	-2.6 to -1.5	4	190
PDS at 26 weeks 6-12 mg/day	2.2	1.1 – 3.2	2	91
CIBIC-plus at 26 weeks 6-12 mg/day	-7.0% (no improv[t])	Not stated	NA	14
GDS at 26 weeks 6-12 mg/day	-4.0% (score >4)	Not stated	NA	25

Interpretation

- Reporting of mean differences may obscure substantial changes in selected individuals in some domains
- Subjective global scales (such as CIBIC) report greater clinically important levels of improvement than domain-specific scales
  - Better content validity
  - Over-estimates (non-linear ordinal scale)
- Little use of standardised measures of treatment effect (effect size – Cohen's *d*) - prevents comparison across scales and trials of clinically important effects
  - Most trials: Cohen's *d* = 0.2-0.4 (small but clinically detectable)
    - Rockwood and MacKnight 2001
- Apart from CIBIC, little use of NNT in relation to MCID
  - Eg NNT to achieve a 4-point change on ADAS-cog

Safety

Excess drop-out at 24 weeks

- **Donepezil**
  - **5 mg/dy** — **no difference**
  - **10 mg/dy** — **4.6%**
- **Galantamine**
  - **24 mg/dy** — **OR 1.7**
  - **32 mg/dy** — **OR 2.6**
    14%
- **Rivastigmine**
  - **1-4 mg/dy** — **no difference**
  - **6-12 mg/dy** — **18.2%**

Excess adverse events at 24 weeks

- **Donepezil**
  - **5mg/dy** — **6.3%**
  - **10mg/dy** — **4.8%**
- **Galantamine**
  - **24 mg/dy** — **OR 2.1**
  - **32 mg/dy** — **OR 3.6**
    12%
- **Rivastigmine**
  - **1-4 mg/dy** — **no difference**
  - **6-12 mg/dy** — **12.1%**

Most common: nausea, vomiting, diarrhoea, insomnia, peripheral oedema

Safety

- Increased cholinergic drive
  - Cardiac arrhythmias: 6/10,000 (ADRAC Oct 2004)
    - Bradycardia, BBB, AV block, syncope
    - ?Under-reported
  - Gastric acid hypersecretion
    - GI intolerance most common side-effect
    - ?Increased risk of peptic ulcers
  - Interactions with other cholinomimetics, anticholinergics, NSAIDs, digoxin, beta-blockers, fluoxetine, erythromycin, ketaconazole

Long-term patient-centred outcomes

AD2000: Multisite RCT of effects of donepezil (5-10mg/dy) in 565 patients referred from memory clinics with DSM-IV diagnosis of mild-mod Alzheimer's disease

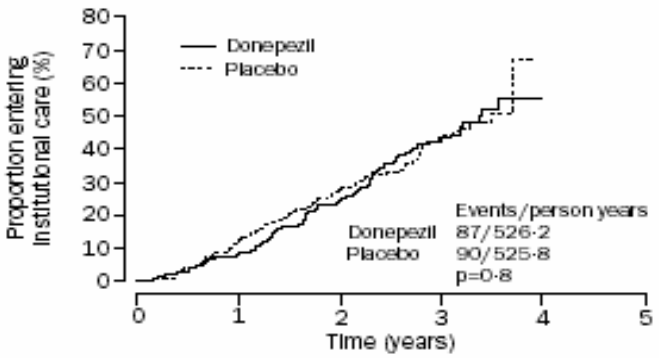
Lancet 2004; 363: 2105-2115

- **Exclusions: patients without regular carer; already taking a cholinesterase inhibitor; already in residential care; contraindications to donepezil; clinical impression that patient unlikely to obtain a worthwhile clinical benefit from donepezil.**
- **First randomisation to donepezil (5mg/day) or placebo for an initial run-in period of 12 weeks**
- **Second randomisation of all patients (after withdrawals) to long-term donepezil (subrandomised between 5 and 10mg/day) or placebo.**
- **Allocations minimised by age, severity of dementia (mild or moderate), and presence or absence of vascular dementia, parkinsonism, and psychotic symptoms.**
- **Patients continued to receive allocated treatment for consecutive phases of 48 weeks each followed by washout periods (6 weeks after phase 1; 4 weeks thereafter) for as long as possible but aiming for at least 3 phases totalling 3 years.**
- **At each washout period, patients, their carers and their doctors were allowed to decide whether they wished to continue.**

Long-term patient-centred outcomes

- **Primary end-points, analysed by intention to treat:**
  - **Entry to institutional care**
  - **Progression of disability, defined as loss of either 2 of four basic, or 6 of 11 instrumental, activities on the Bristol ADLS**
- **Secondary end-points**
  - **Functional ability (BADLS)**
  - **Behavioural and psychological symptoms (NPI)**
  - **Cognition function (MMSE)**
  - **Progress to severe cognitive disability (MMSE<10)**
  - **Psychological wellbeing of the principal caregiver (GHQ, range 0-30)**
  - **Death from Alzheimer's disease (ignoring deaths from other causes)**
  - **Safety (serious adverse events)**
  - **Compliance (numbers stopping treatment)**
  - **Economic evaluations: carer questionnaires; use of formal care services (domiciliary services, doctor and hospital services) using national average unit costs; active and passive unpaid care.**
- **Cognitive and behavioural measures taken at the end of each treatment phase 1-2 weeks prior to washout period**

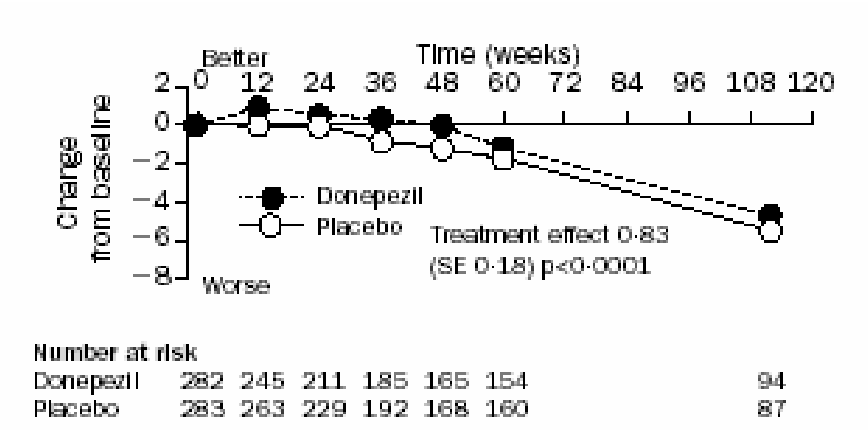
Results



Number at risk					
Donepezil	282	212	134	57	1
Placebo	283	209	135	60	0

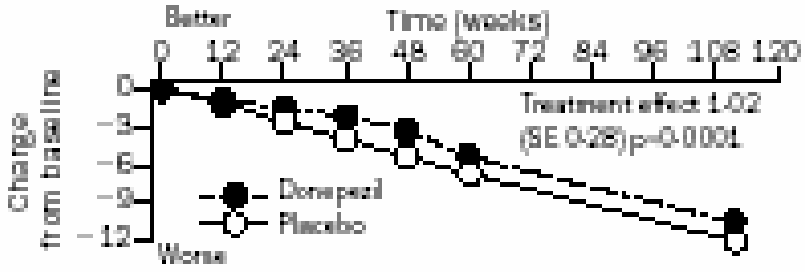
Entry to institutional care

Results



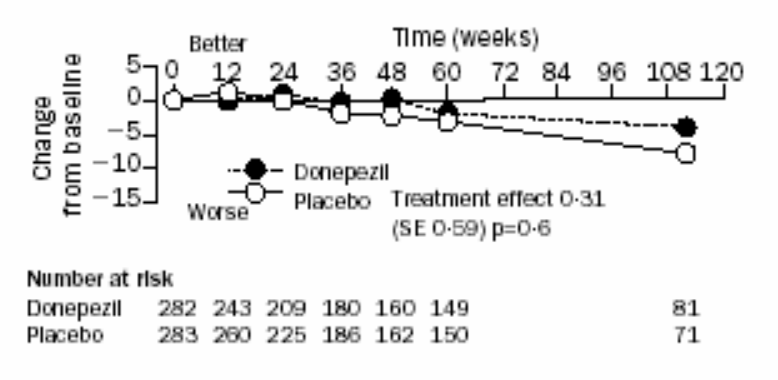
Change in MMSE

Results



Change in BADS

Results



Change in NPI

Clinical Implications

- AChEIs provide at best very modest benefits in improving functional scales and control of neuropsychiatric symptoms, and do not appear to impact on hard clinical end-points, including carer burden and use of health services
- AChEIs have frequent side-effects and multiple drug interactions; incidence of serious adverse events may be under-reported
- Considerable resources spent on AChEIs may be better spent on non-pharmacological management options, respite and nursing care, carer education and support

Other management options

- Decrease use of drugs with anticholinergic actions
  - PAQUID study: 1780 pts ≥70 years living at home: 13.7% using at least 1 drug with anticholinergic effects Br J Clin Pharmacol 2004: 59: 143-151
  - multivariate analysis: low performance on visual memory (OR=1.6), verbal fluency (OR=1.9), MMSE (OR=1.4)
- Identify and manage medical and environmental factors that may worsen cognitive and physical performance
- Treat co-existent delirium, depression, anxiety
- Target atypical antipsychotics to problematic neuropsychiatric symptoms JAMA 2005; 293: 596-608
- AChEIs should be withdrawn if no stabilisation or improvement after 6 months