New(ish) developments in dementia treatments
CONFLICT OF INTEREST DECLARATION

Research support, conference attendance assistance, and/or honoraria for consultancies and/or lecturing from AstraZeneca, Bristol Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Organon, Parke Davis, Pfizer, Prana, Protodigm, Roche, Sandoz

• Advisory boards for Pfizer, Janssen, Novartis
• Editor *International Psychogeriatrics*
• Member 3 Wagner societies and GFC
Dementias where there is some evidence for efficacy of drug treatment of cognitive impairment

- Alzheimer’s disease
- Vascular dementia
- Dementia with Lewy bodies
- Dementia due to alcohol
- Dementia due to B12 deficiency
Dementias where there is as yet no evidence for the efficacy of pharmacological treatment of cognitive impairment

- Frontal dementias
- Huntington’s Disease
The present: MARKETED APPROVED TREATMENTS

Cholinesterase inhibitors: Donepezil (Aricept), Galantamine (Reminyl), Rivastigmine (Exelon)

Memantine (Ebixa)

Gingko biloba?

Brahmi??

Vitamin E?

Risperidone
THE FUTURE - TREATMENTS IN CURRENT OR ARRESTED DEVELOPMENT

Amyloid de-aggregating agents
  Secretase inhibitors
  Vaccines
  Anti-inflammatory agents
  MAO B inhibitors
Homocysteine lowering strategies
Antihypertensives
  Statins
  Oestrogens
Cholinergic treatments

Based on autopsy findings from mid 1970s of correlation between reduced choline acetyl transferase levels and impairment of cognitive function in patients with Alzheimer’s disease.

Anticholinergic drugs (e.g. scopolamine) produce cognitive impairment with some similarities to that seen in Alzheimer’s disease.
Historical development

Initial reports of tacrine being helpful in treating the cognitive deficits of Alzheimer’s disease published in 1980s, particularly NEJM November 1986 (Summers et al., 1986).

Later drugs developed after initial enthusiasm for tacrine waned because of high rates of adverse events.
TACRINE

• Of historical interest only now

• Shown to be more effective than placebo in double blind placebo controlled trials in treatment of cognitive deficit in Alzheimer’s Disease over 6 months (ADAS-Cog, global)

• 25% developed raised AST

• Extremely high incidence of nausea and diarrhoea

• QID dosing and complex dose titration
CHOLINESTERASE INHIBITORS FOR THE TREATMENT OF ALZHEIMER’S DISEASE

• Do they work?
• What do we mean by “work”?
• If they do “work”, do some work better than others?
• Are the side effects worth the result?
• Do some drugs have more or less side effects than others?
• Are they ‘cost effective’ (whatever that means)?
DO THEY WORK?

• 3 Cochrane reviews and 2 meta-analyses (Whitehead et al. and Ritchie et al.) conclude that the drugs have detectable but modest benefits on ADAS-Cog and CGI.

• AD 2000 failed to find any effect on institutionalisation or deterioration on an ADL scale, but despite recruitment failure and high drop out rates did find consistent modest benefits on cognitive function sustained throughout the study period which were c/w those found in industry sponsored trials, as well as a diminution in caregiver assistance and supervision time of 30 minutes per day.

• Kaduszkiewicz BMJ meta-analysis claimed the drugs don’t have any evidence of benefit at all, but this has been strongly disputed – see 2008 debate in *Int Psychogeriatrics* between H.K. and Jacqui Birks (Cochrane collaboration statistician) in relation to these methodological controversies.
GAL-USA-9: Change From Baseline in ADAS-cog/11 Scores

Mean change from baseline (± SE) in ADAS-cog/11

Month

Howard et al., 2011 NEJM

- Only decent discontinuation study
- 298 participants – 4 groups
- Continue donepezil, add memantine, substitute memantine, stop donepezil
- Only placebo group was differentiated in terms of outcome
- Worse behaviour, function, cognition
COST EFFECTIVENESS

- AD 2000 wide CIs but no evidence of cost saving to NHS
- Caregiver time little considered
- NICE agreed drugs worked but said not cost effective until moderate dementia
- Depends on how much you value effects
- Methodology for cost-effectiveness studies far from perfect
CHOLINESTERASE INHIBITORS

- Have modest but clearly demonstrable effects on cognition and global rating and may save caregiver time. Seem to be equivalent in efficacy if dosed appropriately.
- Have side effects which are most notable at high doses of galantamine and rivastigmine.
- Are costly but are highly valued by caregivers and society must choose how it spends its money – are old people with dementia of less intrinsic worth than some people with other illnesses?
- In Australia it is likely that the improvement criterion in qualifying for long term treatment acts to increase cost effectiveness.
- Not all patients will benefit or tolerate the drugs. Some will and a small number will show marked benefit.
Other uses for cholinesterase inhibitors

• DLB – one study (McKeith et al., 2000) indicates some usefulness for rivastigmine in treating neuropsychiatric symptoms but not cognition

• PDD – some evidence for rivastigmine being useful

• MCI – no evidence from 2 large trials of donepezil and galantamine

• Delirium – theoretical only
MEMANTINE

- NMDA receptor antagonist
- May protect neurones from toxicity due to pathologically elevated glutamate levels
- Actual mechanism of action complex and not utterly clear but related to effects on Calcium flux across membranes
- 2 AD trials of 12 and 24 weeks with 167 and 252 mod-sev subjects showed global and/or cognition benefit
- Trials in VaD showed significant effects on cognition but not global outcome
- 10 mg tablets
- 5 mg daily for 1 week increasing by 5 mg per day every week until dose of 10 mg bd is reached
- Has been shown to be effective in combination with donepezil
- Generally well tolerated with few side effects
- Agitation and restlessness may worsen in some cases
- May increase bioavailability of L-dopa containing medications
- Subsidised at present in Australia only for sole use MMSE 10-14, Vet Affairs more generous
- No data on use without donepezil in mild AD
- May help with agitation in advanced AD
GINGKO BILOBA

• Derived from leaves of Chinese tree
• May have anti-inflammatory, anti-oxidant and anti-platelet-aggregation properties
• Meta-analysis of 4 trials reported tiny cognitive benefit (3% difference in ADAS-Cog at 3 and 6 months).
• Recent well conducted 6.1 year study in 3069 subjects was utterly negative – incident dementia 3.3 per 100 person years in treated group, 2.9 in placebo group (Dekosky et al. (2009) JAMA 300, 2253-63).
• May cause bleeding – should not be used!
BRAHMI (Bacopa Monniera)

- Marketed as herbal memory booster
- No clinical data support any benefit
Vitamin E

- Sano study (2000 IU/day) deeply flawed but Vitamin E often recommended in USA on basis of this study

- Recent meta-analysis of use in double blind RCTs suggests modestly raised death rate among subjects taking vitamin E in doses above 400 IU/day

- No evidence of benefit in MCI (like AchEIs)

Risperidone

- Approved for PBS reimbursement in the treatment of behavioural disturbances in dementia characterised by aggression and/or psychosis (dosage up to 2 mg/day)

- At least 3 large RCTs (n = 1150) support modest efficacy in this regard

- Raised rates of CVAEs (significant), stroke (NS) but not overall increased death rates in risperidone RCTs. This signal also seen with olanzapine. No meaningful RCT data on haloperidol. Most strokes in trials occurred in people with a hatful of poorly controlled risk factors

- No raised rate of stroke or death in large US and Canadian real-life data bases (Finkel, Herrmann) nor in large open trials by Wancata, Durán or Kurz for risperidone or olanzapine - rates lower than or comparable to haloperidol and benzodiazepines.

- These drugs are not smarties – use cautiously when no other alternatives and review regularly.
The amyloidocentric theory of Alzheimer's disease
Amyloidogenesis

APP secretase

APP

IN

OUT

Cell membrane

Amyloid Aβ_{40/42}

Plasma/Extracellular matrix

APP
Clioquinol prevents Cu(II) interaction with Aβ

Cherny et al., 2001
CQex ADAS-cog Change from Baseline

ADAS-Cog. \\

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![Graph showing ADAS-cog change from baseline with Clioquinol and Placebo groups over 20 months.](image)
PBT2 Improves the performance of APP/PS1 mice in the Morris water maze

Adlard et al, Neuron (2008)
Effect of PBT2 and placebo on the change from pretreatment at 12 weeks in NTB

(A) Category fluency test, (B) trail making test part B, (C) composite factor Z-score, (D) memory factor Z-score and (E) executive factor Z-score.

(B) Executive function is not as impaired as memory, which is at floor levels, in this group of AD subjects. ADAS-cog has no tests of executive function.

Lannfelt et al., Lancet Neurology (2008)
SECRETASE--
MODIFYING APPROACHES

- Inhibit gamma secretase – unacceptable side effects, ineffective in trials

- Inhibit $\beta$ secretase
  - but a large molecule

- Upregulate $\alpha$ secretase
VACCINES

• Aβ cleared from plaques in genetically engineered mice exposed to immunisation against Aβ

• Human trials of active immunisation abandoned after 5% developed meningoencephalitis – equivocal signals of possible benefit in some patients

• Attempts to initiate immune response without T cell activation underway – fragments of Aβ may cause less problems than immunising against whole molecule?

• Monoclonal antibodies appear promising and apparently safe, especially non-glycosylated variants

• Treatment would have to be initiated early – prior to the emergence of cognitive impairment? Demonstrating cost effectiveness will be a challenge even if the treatment “works” and is safe
REMOVAL OF AMYLOID PLAQUES

- Aβ Vaccination
  - Works!
    - First autopsy reported in Nature Medicine, 2003

  - almost no amyloid
  - abundant tangles
  - some “ghost” plaques with amyloid in microglial cells

- BUT: inflammatory meningoencephalitis
  review of 17 cases in Neurology (2003, Jean Marc Orgogozo)
VACCINATION

- MRI was the other primary endpoint for trial
- GREATER rate of loss of total brain volume (p=.007), greater ventricular enlargement (p<.0001) and non-significantly greater hippocampal volume loss in active vs placebo treated patients¹
  - unexpected
  - possibly explained by volume loss associated with loss of amyloid
    - brain areas affected are chock-full of amyloid in AD
- Hippocampal volume did increase in those with good antibody response
- New studies of solenuzemab and aducanumab show promise

¹ Fox et al. Neurology 2005; 64:1863-72
ANTI-INFLAMMATORIES

- Epidemiological evidence encouraging
- Clinical trial evidence from prednisolone, diclofenac, indomethacin, disappointing
- Propentofyline had some evidence of benefit but this was insufficient for marketing
- Anti-inflammatories have nasty side-effects
- If they are to be of benefit this will likely be in prevention rather than treatment
- Flurizan underwent phase 3 testing – inhibits amyloid aggregates and reduces amyloid levels. Although technically an anti-inflammatory it has little if any anti-inflammatory effect and it had a negative trial outcome
ASPIRIN

• Widely used in VaD

• Limited evidence of efficacy
MONOAMINE OXIDASE B INHIBITORS

SELEGILINE
- 15 RCTs
- Insufficient evidence for beneficial effects
- Only available to treat Parkinson’s disease

LAZABEMIDE
- Some promising results in at least 4 studies
- Development ceased

RASAGALINE
- Study underway
FOLATE / HOMOCYSTEINE

• Ingestion of folic acid reduces serum homocysteine levels
• Maybe protective against AD
• No prospective RCT evidence yet
ANTI HYPERTENSIVE DRUGS

• Possible association between atherosclerosis and development of AD

• Individuals taking potassium sparing diuretics in Cache county study had 0.64 (0.41-0.98) incidence of AD of those who were not (Khachaturian et al. *Arch Neurol* 2006, 63, DOI 10.1001/archneur.63.5.noc60013).

• No specific role in the treatment of AD

• May be helpful in patients with vascular dementia or in prevention of same.
STATINS

• Observational studies suggest possible decrease in AD incidence

• Under ongoing prospective evaluation

• Very recent very large Cochrane meta-analysis concludes they show no evidence of prevention for AD or dementia (McGuiness et al. 26,340 participants)
OESTROGENS

- Oestrogens protect hippocampal dendrites and augment AchE transferase

- Initial epidemiological studies suggested benefit, but women who get HRT are less likely to have HT, diabetes and stroke history and tend to be better educated and of higher social class than non-users

- Trials in people with AD most disappointing

- WHIMS study found HRT increased dementia risk (HR 1.8, 95% CI 1.2-2.6)!

- Prevention trials largely halted because of adverse cardiovascular outcome data

- For review see Almeida & Flicker *Int Psychogeriatrics* 17: 155-64 (2005)
Pharmacological Management of Dementia

Cholinesterase inhibitors are the mainstay of drug management for most individuals with Alzheimer’s disease.

Memantine may be appropriate for trial in those who cannot tolerate AChEIs or who are deteriorating on an AChEIS.

Other psychotropic medications may be used on a symptomatic basis.
Referral of patients

- Patients with prodromal AD or mild early dementia due to AD sought for drug trial participation
- dames@unimelb.edu.au
- Also asymptomatic 65-85 year olds in possible preclinical phase sought for A4 study
- maree.mastwyk@florey.edu.au