

Dementia

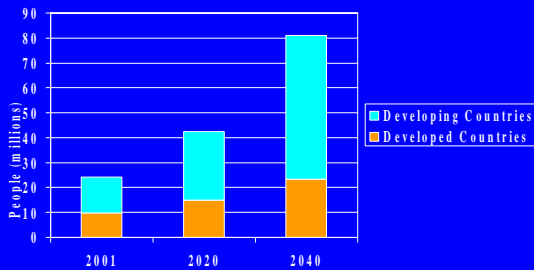
Associate Professor Brian Draper

Dementia in the World (Ferri et al, 2005)

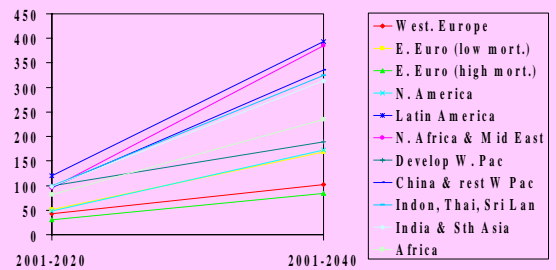
- In 2005, 24.3 million have dementia
- 4.6 million new cases every year
- The number of people affected will double every 20 years to 80.1 million by 2040
- Rates of increase in dementia cases will be much greater in developing countries



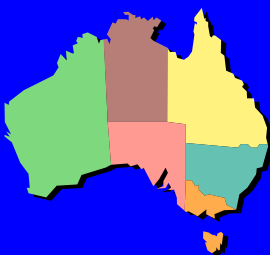
People aged 60+ with Dementia in the World 2001-2040 Ferri et al, 2005



Proportional increase in the number of people with dementia in the world (Ferri et al, 2005)

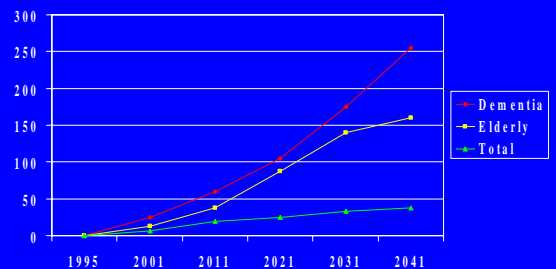


Prevalence in Australia

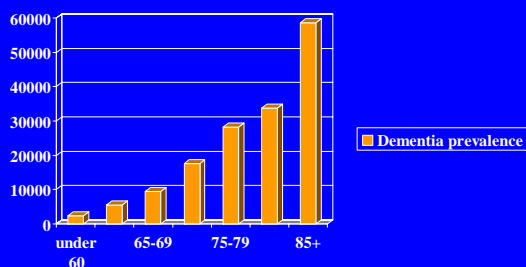


- 200,000 with dementia in 2005
 → 0.5 million by 2040 (2.3%)
- more common than skin cancer
 - AD most common (50-70%)
 - Vascular dementia (VaD, 20-30%)
 - Lewy body dementia (10%-15%)
 - 1000 new cases per week

Projected increase in dementia cases, elderly population and total Australian population, 1995-2041 Henderson & Jorm, 1998



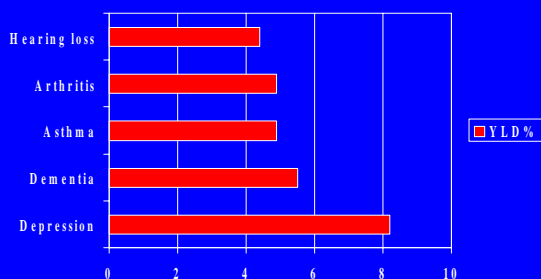
Estimated Prevalence of Dementia in Australia in 2000



The health system annual costs of dementia in Australia (Access Economics, 2003)

Source of cost	\$ billion
Direct Costs (includes residential care at \$2.9 billion)	3.2
Indirect costs (includes \$1.7 billion costs to carers)	2.4
Transfer costs (taxes, welfare payments)	1.0
Total	6.6

Leading causes of years of life lost due to disability (YLD), Australia 1996 Mathers & Vos, 1999



Leading Causes of Disease Burden in Older Australians, 1996 Mathers & Vos, 2000

Women		Men	
1. Ischaemic heart disease	20%	1. Ischaemic heart disease	22%
2. Stroke	11%	2. Stroke	9%
3. Dementia	9%	3. Lung Cancer	7%
4. COPD	4%	4. COPD	6%
5. Breast Cancer	4%	5. Dementia	5%

An Australian Government Initiative

Dementia – a National Health Priority



DEMENTIA

prevention and early intervention
care and support
information, awareness and education
research

Helping Australians with dementia and their carers

An Australian Government Initiative

Dementia
a National Health Priority



The Dementia Initiative - \$320.6 million

Three key program areas:

- \$70.5 million for research and innovation, improved care initiatives and early intervention programs
- \$225.1 million for Extended Aged Care at Home Dementia packages
- \$25 million for additional dementia specific training for aged care and community workers



An Australian Government Initiative

Dementia
a National
Health Priority

Three Collaborative Research Centres

- \$7m over 3 years
- 1. Assessment and better care outcomes (UNSW – Primary Centre)
- 2. Early Intervention, Prevention and Risk Reduction (ANU)
- 3. Consumers, Carers and Social Research (QUT)



What Is Dementia

DSM IV definition

- A. The development of multiple cognitive deficits manifested by both:
 1. Memory impairment.
 2. At least one of: aphasia, apraxia, agnosia, disturbance in cognitive functioning.
- B. Significant decline in social or occupational functioning
- C. There is evidence of organic etiology
- D. Does not occur exclusively during the course of a delirium.

Epidemiology

- 50 –87% of cases of dementia missed
- Prevalence of moderate to severe dementia 5% of population ≥ 65
- Incidence 0.5% of population > 65 years of age

Diagnosing dementia in primary care (Boustani et al, 2005)

- 6% of older primary care patients found to have dementia
- Only 19% of these were identified as having dementia by the GP

Clinical Presentations

- Gradually progressive STM impairment
- Personality change
- Word finding difficulties
- Depression
- Confusional episodes
- Behavioral disturbances

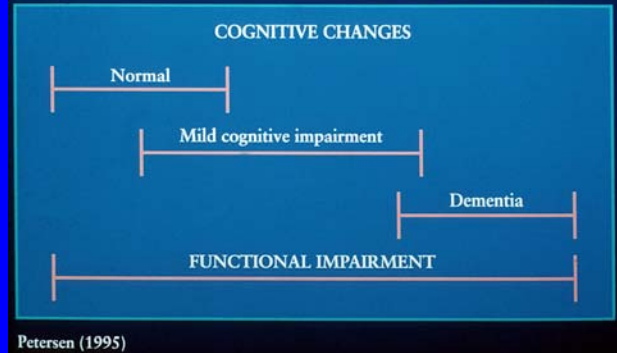
Differential diagnosis of dementia

- Normal ageing
- Mild cognitive impairment (MCI)
- Depression
- Reversible medical illness – hypothyroidism, syphilis,
- Drugs

Assessment of the cognitively impaired patient

- History
 - Duration of perceived impairment (preferably at least 6 months)
 - Specific difficulties – STM, spatial, lists, topographical
 - Impact on the patient's life and functioning (eg stopped driving, retired)

Continuum from normal aging to AD



Normal Forgetfulness vs Early Dementia

Brodaty 1998

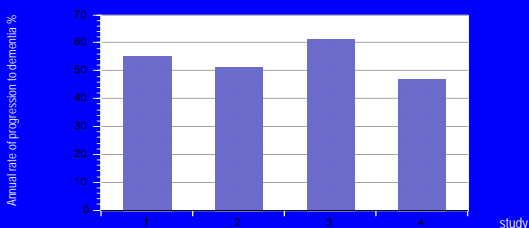
Description	Dementia	Normal Elderly
Forgets	Whole experience	Part experience
Forgets words/names	Progressive	Occasional
Delayed recall	Often	Rarely
Follows commands	Gradually unable	Usually able
Ability to use notes, reminders	Gradually unable	Usually able
Follow a story on TV, book	Gradually unable	Retains usual ability
Calculations	Gradually unable	May be slower
Self care	Gradually unable	Usually able

Mild cognitive impairment

- Not an absolute difference between MCI and AD
- Memory below one standard deviation for age
- 10 –15% will develop AD per year

Progression to dementia: Long-term data

Half of patients with MCI **do not** develop dementia after 5 years

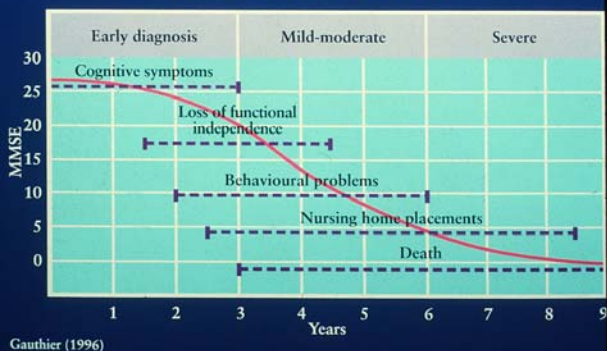


1 Petersen et al., JAMA 273: 1274-1279, 1995
 2 Hogan & Eddy, Can J Neurol Sci 27: 18-24, 2000
 3 Morris et al., Arch Neurol 58: 379-405, 2001
 4 Tuokko et al., Arch Neurol 60: 577-582, 2003

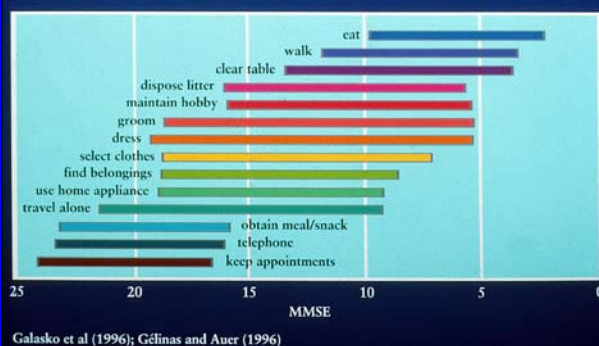
Course of Dementia

- Early or Mild – MMSE > 20
- Middle or Moderate - MMSE 11- 20
- Late or Severe – MMSE < 11

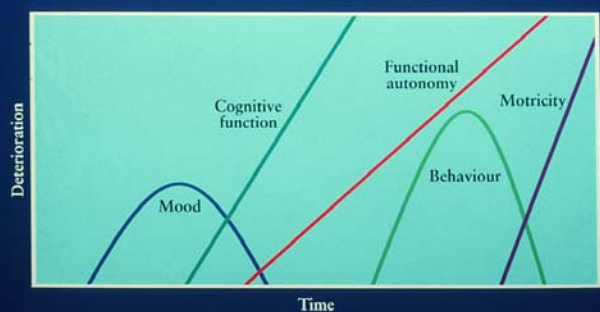
Natural history of AD



Progression of ADL impairment over time



Symptomatic domains of typical AD over time



Assessment

1. Dementia vs pseudodementia
2. Acute vs Chronic
3. Global vs Focal
4. Irreversible vs Reversible dementia
5. Deficits
6. Comorbid problems
7. Strengths
8. Effect on family/ carer

Examination

Physical examination

- Examine for reversible risk factors for vascular dementia.
- Examine for Parkinsonian features

Cognitive examination

- MMSE (Folstein et al)
- Clock drawing test

Investigations for the Causes of Depression and Cognitive Impairment

Investigation	Conditions
Full blood count / ESR	Anaemia, infections, e.g. subacute bacterial endocarditis, vasculitis
Urea and electrolytes	Hypokalaemia, hyponatraemia, uraemia
Blood sugar level	Diabetes
B12, folate levels, homocysteine	Pernicious anaemia, malnutrition
Thyroid function tests	Hyper/hypothyroidism
Calcium/phosphate	Hyper/hypocalcaemia
Urinalysis	Urinary tract infection, renal disease
Liver function tests	Hepatitis, liver cancer
Chest X-ray	Lung cancer, pneumonia
Brain CT Scan (no contrast)	Exclude CVA, neoplasia, subdural
Syphilis serology	Neurosyphilis

Investigations for the Causes of Depression and Cognitive Impairment

These Additional Tests Should be Considered in the Following Circumstances:

Investigation	Conditions
EEG	When prolonged delirium or encephalopathy is a concern
ECG	In patients with prominent complaints of fatigue and breathlessness
Brain MRI	To exclude cerebral vasculitis, posterior brainstem lesions
HIV	Exposure to potentially contaminated blood products, high-risk sexual practices, intravenous drug abuse
SPECT / PET	May assist in early onset AD and DD with VaD
Drug levels	Digoxin, phenytoin, carbamazepine, theophylline
Carotid Doppler	To exclude carotid vessel disease in VaD
Lumbar puncture	If chronic meningitis or encephalitis suspected

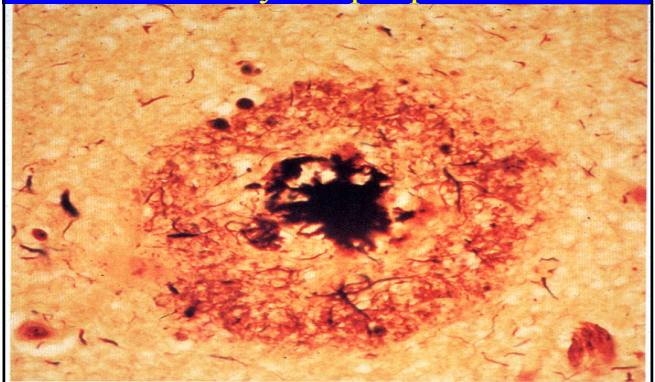
What type of dementia is it?

- Alzheimer's Dementia
- Vascular Dementia
 - Apathy or depression, psychomotor slowing, naming difficulties,
- Dementia with Lewy Bodies
 - Rapid dementia, mild parkinsonian symptoms especially with antipsychotic medication, fluctuating cognition, visual hallucinations
- Fronto-temporal Dementia

Alois Alzheimer

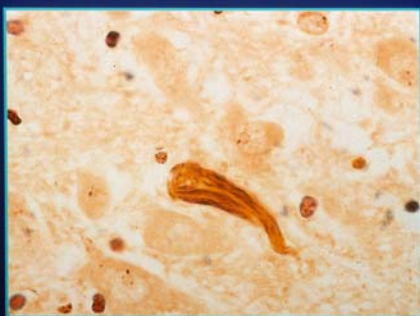


Amyloid plaque



PLAQUE OF AMYLOID BETA-PROTEIN in the brain of an Alzheimer patient is visible as a black globular mass in this stained image. The plaque is surrounded by a halo of abnormal neurites (axons and dendrites) and degenerating neural cell bodies that appear darker than the normal neurons.

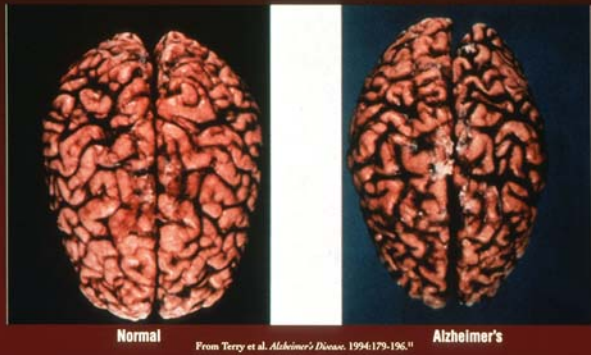
Neuropathology of AD – neurofibrillary tangles



Courtesy of Dr J Richardson, Montreal, Canada



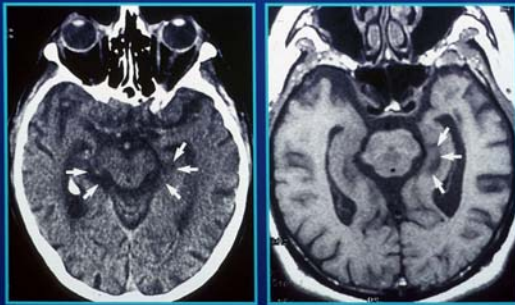
CEREBRAL ATROPHY



Neuroimaging

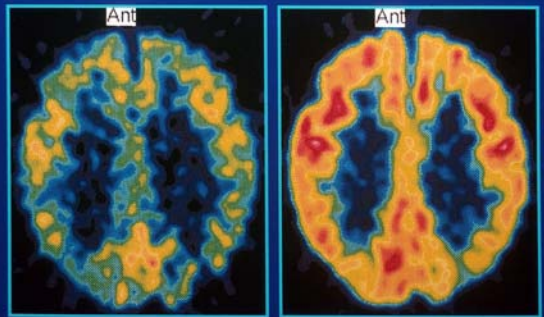
- Atrophy of the temporal lobe occurs early in AD.
- MRI more sensitive than CT
- Serial examination helpful

Structural imaging in AD



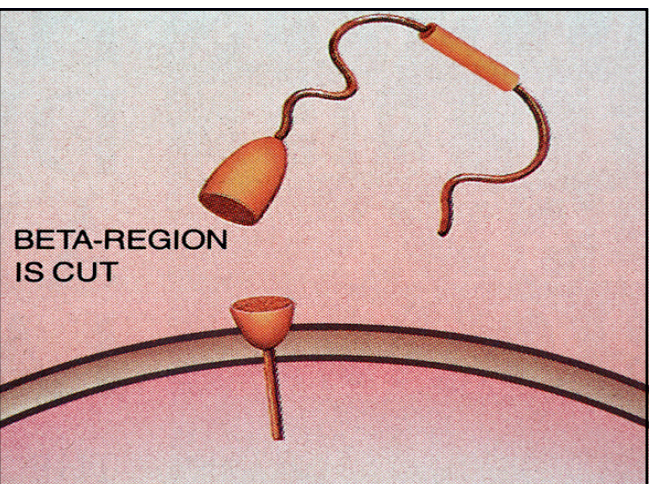
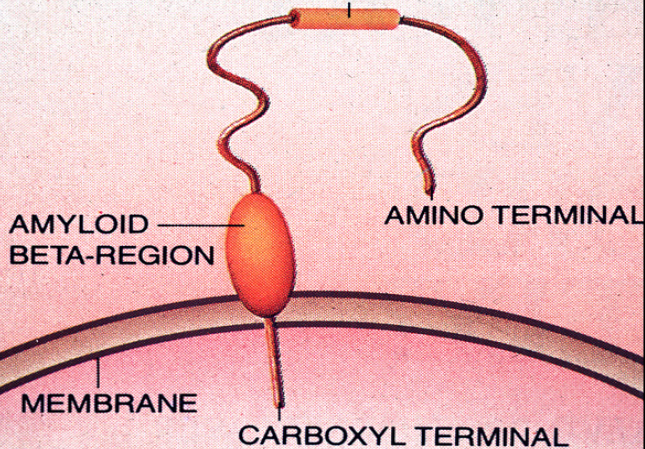
Gauthier (1996); Smith and Jobst (1996). Images courtesy of Dr S Fontaine, Montreal, Canada

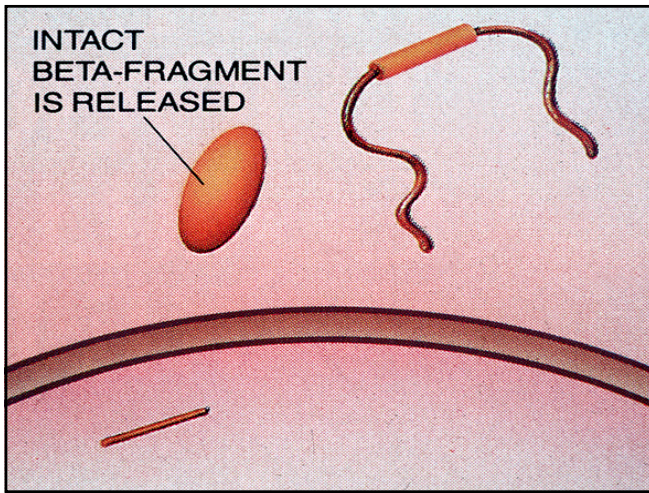
Functional imaging in AD



Gauthier (1996). Images courtesy of Dr A Nordberg, Uppsala, Sweden

PROTEASE-REGULATING REGION





Risk Factors for Dementia

- Age
- Sex
- Genetic Factors
- Education
- Vascular factors – cholesterol, homocysteine, hypertension
- Smoking
- Head injury
- Alcohol
- Thyroid disease
- Exposure to electromagnetic fields

Risk Factors for Dementia - Sex

- Women – slightly higher rate of Alzheimer's disease
- Men – slightly higher rate of vascular dementia

Risk Factors for Dementia - Genetic

- Family Hx of Dementia RR 3.5 (2.6-4.6)
- Family Hx of Parkinson's RR 2.4 (1.0-5.8)
- Family Hx of Downs Synd RR 2.7 (1.2-5.7)

Risk Factors for Dementia - Genetic

Early Onset Alzheimer's Disease

- Chromosome 21 – Amyloid Precursor protein (APP) – at least 3 mutations known
- Chromosome 14 – Familial AD, not a single gene

Risk Factors for Dementia - Genetic

Late – onset Alzheimer's disease

- Chromosome 19 – Apo Lipoprotein E, 25% have ApoE4 allele, associated with around 60% AD cases
- Chromosome 10
- Sorl 1 gene – faulty versions contribute to development of amyloid plaque

Risk Factors for Dementia - Genetic

- Fronto-temporal dementia – tau gene
- Huntingtons disease – chromosome 4

Risk Factors for Dementia - Education

- Many studies show that more highly educated people less likely to develop dementia, especially AD
- ?? Effects of education delaying AD
- ?? ↑ brain reserve with education
- ?? Intelligence masks AD

Risk Factors for Dementia – Vascular Factors (1)

- Increasing evidence that these factors increase risk of both VaD and AD
- Hypertension – control of systolic BP reduced strokes and AD by 50% over 2 years (Forette et al, 1998)
- Cholesterol – Statins may reduce risk of dementia (Ad & VaD) by 70-80% over 6 years

Risk Factors for Dementia – Vascular Factors (2)

- Homocysteine – metabolic by-product that may increase risk of stroke, associated with VaD and AD, reduced by folic acid in diet
- Anti-platelet therapy e.g. aspirin MAY reduce VaD

Risk Factors for Dementia – Smoking

- Early studies suggested protection from AD
- BUT
- More recent larger studies show increased risk of dementia (Vad & AD) by approx. twofold

Risk Factors for Dementia – Head Trauma

- When defined as loss of consciousness, some studies suggest increase risk of AD by 1.8 times , but others do not

Risk Factors for Dementia – Electromagnetic Fields

- Occupations involving use of electronic motors close to the body have around 3 times the risk of developing AD in some, but not all, studies

Risk Factors for Dementia – Hypothyroidism

- Used to be regarded as a 'reversible' cause of dementia, but most cases have AD
- Increased risk of Alzheimer's disease by approximately 2.3 times

Risk Factors for Dementia - Depression

- Depression may increase risk of dementia by 2-3 times
- Early onset depression - ?? Increased risk of VaD
- Late onset depression – more likely that if dementia develops the depression was part of the dementing process

Other Factors that may prevent Dementia

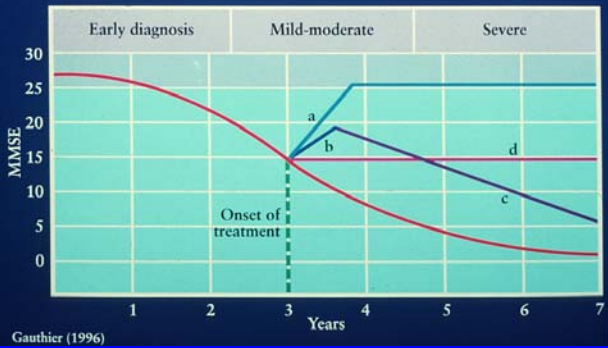
- Anti-inflammatory drugs – approx 50% risk of developing AD
- Oestrogen replacement in post menopausal women - unlikely
- Antioxidants – Vitamins E & C
- Gingko Biloba

Antioxidants – Polyphenols

- Polyphenols – most abundant dietary antioxidants - possess stronger neuroprotection than antioxidant vitamins
- Found in fruit and vegetable juices
- Prospective study of Japanese Americans in Washington found a significant reduction of AD in those that drank 3 or more fruit or vegetable juices/week (Hazard Ratio 0.24) compared with those that drank less than once per week (HR 0.84) (Dai et al 2006)

Management of Dementia

Hypothetical treatment responses in AD



Current treatments for AD are symptomatic

1. Acetylcholinesterase inhibitors (ChIs)
 - Cognitive effects of acetylcholine are mediated via muscarinic M1 receptor
 - 4 ChIs approved, 3 currently used
 - Donepezil (Aricept)
 - Galantamine (Reminyl)
 - Rivastigmine (Exelon)
 - Tetrahydroaminoacridine (Tacrine)

Who Should Receive Acetylcholinesterase Inhibitors

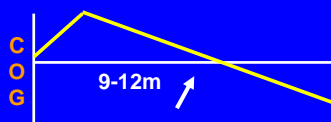
- Mild to moderate Alzheimers disease (MMSE > 10) until of no further benefit
- Modest slowing down of cognitive decline in up to 60-70% patients for 12-18 months
- May improve behaviour, reduce carer stress and benefit function

UK National Institute for Clinical Excellence - NICE review of ChIs

- NICE review (2005) ... not cost effective
 - No subsidised ChIs
 - Political storm (UK election May)
- NICE *draft* review January 2006
 - Modest efficacy, some cost-benefit
 - Only approve subsidy if MMSE 10-20

Benefits of ChIs

- Period of modest cognitive enhancement
- Symptomatic treatments not cures
- i.e., not shown to modify disease progression
- 2 in 3 respond: maintain baseline or improve
- Functional and behavioural benefits
- Mean 9-12 months before patients cross baseline of cognitive decline



Memantine (Ebixa)

- Memantine is a Glutamate NMDA receptor antagonist
- The only drug of this class with FFA and TGA approval for Moderate-Severe AD
- Not reimbursed by PBS
- Some cognitive benefits may be apparent for the first few months of treatment
- Subsequent rate of decline is similar to that of untreated patients ie symptomatic Rx

Chl + memantine?

(Tariot et al, 2004)

- In patients w. moderate to severe AD, a 2 year trial showed combination Rx of donepezil + memantine was > effective than donepezil alone:
 - Cognition
 - Global outcome
 - ADLs and behaviour
- The combination was well tolerated

Other Treatments - Antioxidants



- Gingko Biloba
 - Weak positive evidence but high dropout rates
 - Can increase risk of bleeding if used with anticoagulants
 - Await large US trial
- Vitamin E
 - Inconclusive evidence,
 - increased mortality when high dose supplementation used
 - Nuts, seeds, wheat germ, vegetable oils

Other therapies

- Folic acid – Low folate linked to AD in observational studies but not in clinical trials
 - Good clinical practice: check folate and Homocysteine levels in AD pts; Rx if necessary
 - No evidence that makes difference to cognition
- HRT - Robust epidemiological evidence that HRT lowered risk of AD in post-menopausal women
 - No evidence that HRT makes any difference to cognition in dementia
 - **Increases** risk of dementia in post menopausal women

Psychosocial Management

- Interview with patient and carer to discuss financial and legal matters
- Alzheimer's Association – carer support
- Community support – Aged Care Assessment Team

Psychosocial Interventions

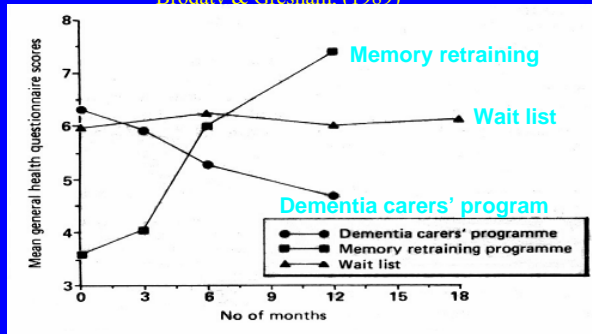
- Counselling,
- Skills training
- CBT
- Behavioural management
- Information provision
- Education Support groups alone
- Stress Management

Overview Carer Intervention Effects

- Interventions have modest efficacy
 - Reducing carer stress
 - Improving knowledge
 - Delaying NH admission
- Combinations of pharmacotherapy + carer intervention may be more effective
- Interventions need to be tailored to the individual

Dementia Carers Program – Effects on Carer Stress

Brodaty & Gresham (1989)



Dementia Carers Program – Survival at Home

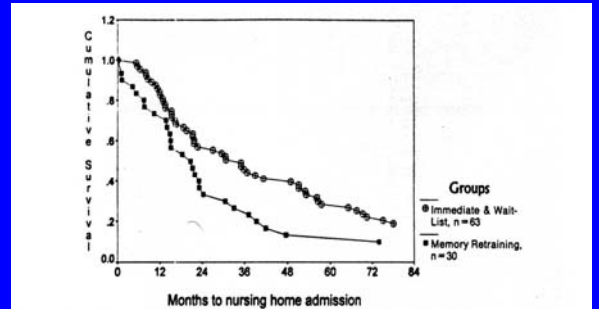


Figure 2. Kaplan-Meier survival functions for nursing home admission comparing the combined training groups with the memory retraining group

(Odds ratio 5.03, 1.73- 14.7)

Living With Memory Loss Program

- 7 week program for carer and person with early dementia
- Based on models of published carer interventions
- Funded by Federal government, administered by Alzheimer's Association in partnership with Aged Care Services and NGOs

Challenging Behaviour and Caregivers

- Challenging behaviour accounts for about 25% variance in carer psychological morbidity



Dementia in residential care

In Australia (1999 estimates)

- 60,000 hostel residents (25% dementia)
- 75,000 nursing home residents (60-70%)
- 13,750 community care packages

Dementia in residential care, 2001

- Deliberate policy over last decade of capping NH beds and expanding lower level care and community care
- Result is that admissions are :
 - more severely impaired
 - more frail
 - more behaviourally disturbed

Behavioural Disturbances In Eastern Sydney Nursing Home Residents

Brody, Draper et al, 2001

- 80% nursing home residents were rated as having a behavioural disturbance on BEHAVE-AD
- Associated with Psychosis and affective disturbances, severity of dementia, age and gender (females > males)

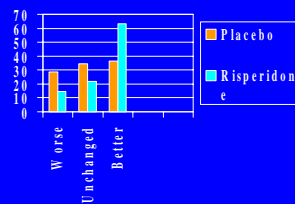
PREVALENCE OF PSYCHOTROPIC PRESCRIPTION IN EASTERN SYDNEY NURSING HOMES Draper et al, 2001

Psychotropics	Regular	As required in	Total
	n(%) N=647	past month n(%) N=647	n(%) N=647
Sedative / Hypnotics	149 (23.1%)	50 (7.7%)	197 (30.5%)
Antipsychotics	138 (21.4%)	26 (4.0%)	158 (24.5%)
Antidepressants	128 (19.8%)	2 (0.3%)	130 (20.1%)
Anxiolytics	55 (8.5%)	12 (1.9%)	66 (10.2%)
Lithium	4 (0.6%)	0	4 (0.6%)
Any Psychotropic	333 (51.5%)	85 (13.2%)	381 (58.9%)
Anticonvulsants	63 (9.7%)	0	63 (9.7%)

Controversy – Use of Atypical Antipsychotics in Dementia

- RCTs showed that Risperidone (and to lesser extent Olanzapine) to be effective in treating Aggression, Agitation & Psychosis in Dementia
- Similar efficacy to Haloperidol but more tolerable

RCT Risperidone (Brody et al 2003)



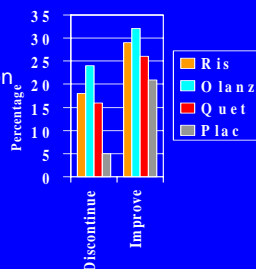
FDA Safety Committee Reports Dementia Rx with atypicals

- 2003 - increased risk of CVAEs w. RISP
- 2005 - increased mortality rate
- Relative risks: Atypicals 1.47; Typicals 1.68
- Deaths mostly from CVS causes & infections
- Recent Australian study (Hollis et al 2006) of DVA data found ↑ mortality haloperidol

CATIE-AD study

Schneider et al 2006

- Multicentre DB placebo controlled RCT of olanzapine, risperidone and quetiapine in psychosis, aggression, agitation in 421 outpatients with AD
- No significant difference in efficacy, placebo significantly better tolerated
- 'Adverse effects offset advantages in efficacy of atypicals'



Recommended Pharmacotherapy for Challenging Behaviour in Dementia

- Only after a reasonable trial without medication
- Risperdal is the only oral AP approved for use in BPSD – aggression and psychotic symptoms 0.5-1.5 mg/day
- Olanzapine is the only antipsychotic approved for parenteral use in BPSD in Australia

Future Times – Rejoice?



Dementia in the Future

- Detection of pre-symptomatic Alzheimer's disease
 - Diagnostic blood tests – tau protein, APP and A beta protein
 - Scans – fMRI, PET
 - Brain function – computerised tests

Blood/CSF Biomarkers for AD

- Currently no reliable biomarkers for clinical use
- CSF concentration of phosphorylated tau protein increases in AD and other neurodegenerative disorders
- Blood levels of β amyloid not reliable, though ratio of β 40 to β 42 better

CSF/Blood Biomarkers and Progression of Mild Cognitive Impairment to Dementia

- The combination of beta amyloid and tau generated sensitivity and specificity values of > 85 % for progression to dementia within 4-6 years in one study (Hansson et al, 2006)
- However, relatively low positive predictive values (30-70 %) have also been reported (Hampel et al, 2004; Parnetti et al, 2006)

Possible New Treatments - Amyloid Production

Treatment	Mechanism	Potential. effect	When
Metal Chelators e.g. Clioquinol	↓ accumulation & promotes β Amyloid clearance	Moderate – toxicity issues	5 years
glycosaminoglycan (GAG) mimetic (Tramiprosate)	Reduces fibrillisation of β amyloid <i>in vitro</i>	Moderate	5 years
β Amyloid Vaccine	Increase breakdown β Amyloid	Very – toxicity issues	5- 10 years
Secretase Inhibitors	Reduce Production β Amyloid	Very – toxicity issues	10-15 years
GSK Inhibitors	Reduce production β Amyloid & tau	Very – toxicity issues	10-20 years

Other New Treatments

Treatment	Mechanism	Potential. effect	When
Gene Therapy	Neurotrophic	Very – combined with drugs	> 20 years
Fetal Stem cell grafts	Neurotrophic	Very – combined with drugs	> 20 years
Hormonal - leuprolide, RU468, antiandrogens	↓ production β Amyloid	Low	5 years
Paclitaxel	Stabilise tau	Very – toxicity	5 –10 years
Antioxidants e.g. colostrinin,	↓ production β Amyloid	Low-moderate	Now
Anti-inflammatory agents	↓ production β Amyloid	Low	Now

Other New Treatments - 2

Treatment	Mechanism	Potential. effect	When
Statins	May ↓ β Amyloid	Low - unproven	Now
Muscarinic receptor activity	Enhance muscarinic receptors	Symptomatic	5 years
Huperzine C (from China)	CHI and Antioxidant	Symptomatic - toxicity	Now
5-HT _{1A} receptor antagonists	promotes release of glutamate & ACh, inhibits 5HT	Low - unproven	< 5 years
TAK 147 Zanapezil	CHI & neurotrophin	Low	< 5 years
Curry spice curcumin	Antioxidant, metal chelator	Low	< 5 years

