Dementia

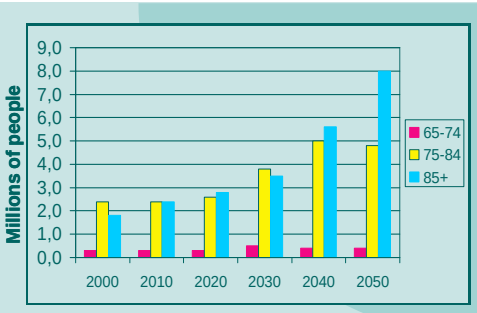
What do we know about dementia??

Deterioration of intellectual faculties – such as memory, concentration, and judgment – resulting from an **organic disease** or a disorder of the brain, sometimes accompanied by personality changes.

Introduction and epidemiology

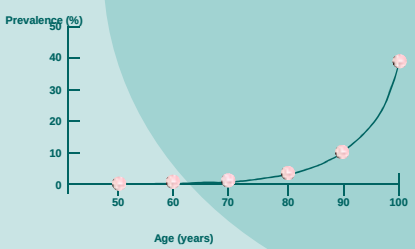
Dementia is a loss of mental ability severe enough to interfere with normal activities of daily living, lasting more than six months, **not present since birth**, and not associated with a loss or alteration of **consciousness**.

Prevalence of AD in the EU



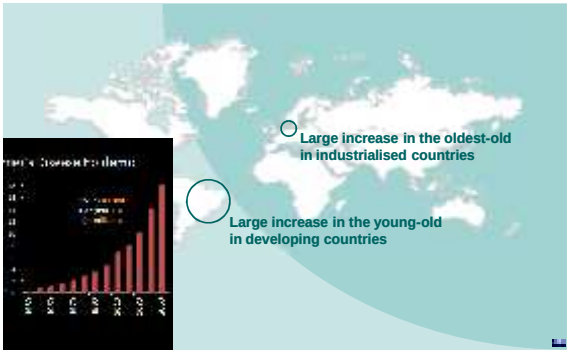
Hebert, et al, 2003, Archives of Neurology

Dementia: a prevalent disorder of late life

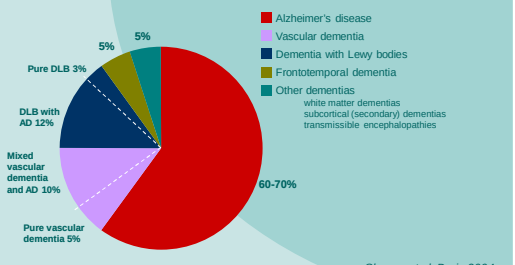


Hofman *et al* (2010)

Dementia is becoming even more common



Relative frequencies of the main dementias



Sleeger et al, Brain 2004.

What is "impaired"?

"Gold" standard:
Premorbid baseline data

Standard benchmark:
Compare to the average performance within an age group

Mild cognitive impairment (MCI)

- MCI: Relatively recent term, used to describe people who have some problems with their memory but do not actually have dementia.
- Some people (80%?) will be in the early stages of Alzheimer's disease or another dementia.
- Others, however, will have MCI as a result of stress, anxiety, depression, physical illness or just an 'off day'.
- 5% of the population (estimated) may be experiencing MCI.
- Currently extensive research on MCI is ongoing.
- At the moment there is not enough evidence to recommend any specific treatments.

MCI: Mild Cognitive Impairment

- **Objectively measured deficits in memory**
- **Subjective memory complaint**
- **Normal ADLs**

Conversion to dementia is significantly higher in people with MCI:

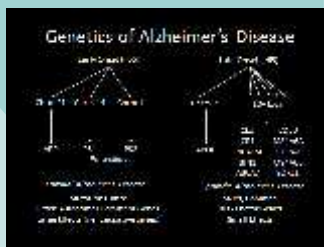
MCI	**12-15% per year**
Normal controls	**1-2% per year**

(Petersen et al., 1999, 2011)

Alzheimer Disease:
Risk and protective factors

AD: Using epidemiology to understand etiology

- Risk-modifying factors for AD:
  - **age**
  - **family history** (chromosome 1,14, 21 - PS1, PS2, APP genes)
  - head injury
  - vascular factors
  - diabetes
  - education
  - depression
  - dietary factors
  - heavy metals
  - maternal age
  - smoking?
  - etc...



APOE gene is associated with AD

APOE ε4 increases risk
APOE ε2 decreases risk

- ε2/ε4 OR = 2.6
- ε3/ε4 OR = 3.2
- ε4/ε4 OR = 14.9
- ε2/ε2 OR = 0.6
- ε2/ε3 OR = 0.6

Vascular risk factors

- Hypertension
- Evidence of cardiac disease
- Peripheral atherosclerosis

. . . increase risk of AD

- But: What does this mean for vascular dementia?

Breteler *et al* (1994); Tariska *et al* (2007)

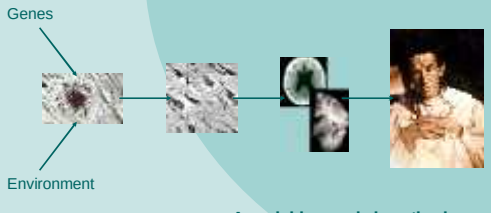
Education

- Low educational level increases risk of dementia
- Demonstrated by prospective studies and the "Nun Study"

Launer at al. (1999); Snowdon *et al* (1996)

The etiology and pathogenesis of the dementias

The process of Alzheimer's disease is nearly understood



Amyoloid cascade hypothesis

Plaques

- Central amyloid core
- Degenerating peripheral neurites

Distribution of plaques

- Wide distribution throughout cortex, but with relative sparing of **primary motor and sensory cortex**
- Cerebellar plaques consist of amyloid only – no abnormal neurites or highly phosphorylated tau accumulations

Tangles

- Intraneuronal accumulations of paired helical filaments
- Paired helical filaments formed from highly phosphorylated tau

Regional distribution of pathology

- Distribution of pathology in AD is not random, but starts in transentorhinal cortex and ends in neocortex

Braak *et al* (1994); Delacourte *et al* (1999); Duyckaerts *et al* (2008)

Diagnosis and assessment

Clinical symptoms of cognitive decline

- **Memory loss is often the most commonly reported symptom:**
  - **Forgetfulness**
  - **Repeats self in conversation**
  - **Asks the same questions over and over**
  - **Gets lost in familiar areas**
  - **Can't learn new information**

Clinical symptoms cont . . .

- **Presenting symptoms can also consist of changes in one or more of these areas:**
  - **Attention**
  - **Language**
  - **Visuospatial abilities**
  - **Executive function**
  - **Personality / Judgment / Behavior**

Impairments in attention

- Starting jobs but not finishing them
- Difficulty following a conversation
- Distractibility
- Losing train of thought

Impairments in language

- Problems expressing one's thoughts in conversation (can't find the right words)
- Consistently misusing words
- Trouble spelling and/or writing
- Difficulty understanding conversation

Impairments in visuospatial function

- Getting turned around (even in one's own home)
- Trouble completing household chores (using knobs or dials)
- Difficulty getting dressed
- Trouble finding items in full view

Impairments in executive functions

- Disorganization
- Poor planning
- Decreased multi-tasking
- Perseveration
- Decreased ability to think abstractly

Clinical symptoms of AD

- Amnesia
  - memory loss is early and invariable
  - recent memory loss before remote memory
- Aphasia
  - nominal dysphasia early
  - both expressive and receptive dysphasia in moderate stages
  - severely disrupted speech in late phases
- Apraxia
  - functional difficulties, subsequently basic activities of daily living
- Agnosia
  - difficult to assess, but probably more prevalent than often realised
- Behavioural and psychiatric symptoms (BPSD)
  - depression
  - psychotic features
  - personality change
  - activity disturbance

Diagnosis: NINCDS–ADRDA criteria for probable AD

- Criteria for **clinical** diagnosis of AD include
  - dementia
  - deficits in two (or more) areas of cognition
  - progressive
  - no disturbance of consciousness
  - onset ages 40–90 years
  - absence of other systemic or brain disease that could account for the condition

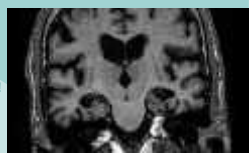
Dubois et al (2007)

Features making the diagnosis of "Probable AD" unlikely

- Sudden, apoplectic onset
- Focal neurological deficit(s)
- Seizures or gait disturbance early in the disease

AD: Structural imaging

- **Background**
  - pathological process results in atrophy are also expressed elsewhere
  - hippocampus is affected first by neuropathology
- **Hypothesis**
  - could regional atrophy visible on structural imaging be used as a biomarker of AD?
- **Findings**
  - medial temporal lobe atrophy can be detected by MRI
    - an early change in AD
    - might distinguish AD from VaD
    - correlates with disease
- **But:**
  - **questionable specificity and sensitivity!**



Tau in CSF as a biomarker

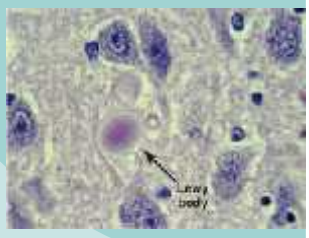
- **Background:**
  Highly phosphorylated tau accumulates in tangles is one of the earliest neuropathological changes in AD
- **Hypothesis**
  Could tau be a biomarker of AD?
- **Finding**
  Tau protein is elevated in CSF in AD
- **Reservations**
  - no clear correlation with disease progression
  - questionable specificity
  - requires LP
  - expensive

Diagnosis of "Definite AD"

May only be made in the presence of a clinical diagnosis of probable AD together with neuropathological evidence of AD

Lewy-body dementia: Criteria

- Progressive cognitive decline and **two of three** core features:
  - fluctuation
  - visual hallucinations
  - parkinsonism



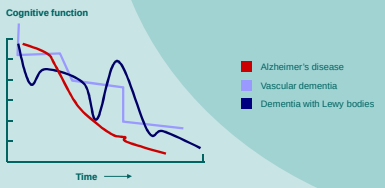
Galvin *et al* (2008)

Features supportive of the diagnosis of DLB

- Repeated falls
- Syncope
- Delusions
- Hallucinations
- **Neuroleptic sensitivity**

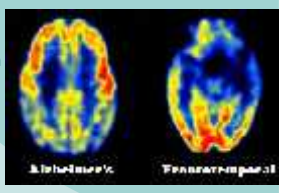
Natural history of dementia with Lewy bodies (DLB)

- **Onset** May be gradual, but may also be sudden; in retrospect, onset may have been first diagnosed as delirium
- **Progression** Fluctuating
- **Duration** Total duration of illness shorter than for AD



Frontotemporal dementia: Clinical symptoms

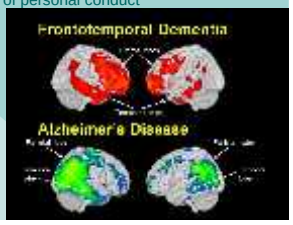
- **Neuropsychiatric symptoms**
  - inertia and loss of motivation
  - loss of organisational abilities
  - lack of insight
- **Speech problems**
  - early loss of expressive speech
  - stereotyped phrases
  - late mutism



Cherrier *et al* (1997); Duara *et al* (1999); Neary *et al* (2008)

Frontotemporal dementia: Criteria

- Core diagnostic features:
  - insidious onset and gradual progression
  - early decline in social conduct
  - early impairment in regulation of personal conduct
  - early emotional blunting
  - early loss of insight



Neary *et al* (2008)

FTD: Supportive diagnostic features – speech and language

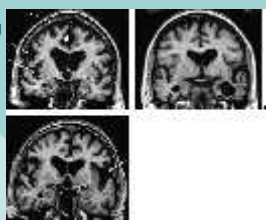
- Altered speech output
- Stereotypy
- Echolalia
- Perseveration
- Mutism

FTD - Supportive diagnostic features: physical signs

- Primitive reflexes
- Incontinence
- Akinesia
- Low and labile blood pressure

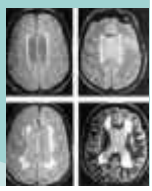
FTD: Investigations

- Neuropsychology: Significant impairment on frontal lobe tests in absence of severe amnesia or visuospatial deficits
- Normal EEG despite clinically evident dementia
- Prominent frontal and/or anterior temporal atrophy on neuroimaging



Vascular dementia (VaD)

- Overdiagnosed condition which accounts for less than 10% of cases of dementia.
- VaD is caused by multiple strokes („Silent strokes")
- Dementia occurs „stroke by stroke", with progressive focal loss of function.
- Clinical features of stroke profile – hypertension, diabetes, etc. – are present. More often in males.
- Diagnosis is obtained from the history and confirmed by CT or MRI scan (the presence of multiple areas of infarction).
- Treatment: Maintain adequate blood pressure control, anti-platelet aggregants (ASA).



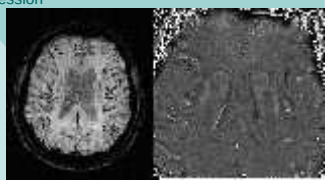
Vascular Dementia (VAD): Natural history

- Vascular dementia is classically described as a disorder of:
  - sudden onset
  - "stepwise" deterioration
- However, there are problems with the notion as:
  - vascular factors are risk factors for AD
  - mixed disease is common
  - relationship between degree of vascular damage and dementia is not direct
  - vascular dementia is found in many forms

Criteria for probable vascular dementia (NINCDS)

- Dementia
- Cerebrovascular disease evident on history, examination or imaging
- Two disorders must be related by:
  - onset of dementia within 3 months
  - abrupt or stepwise progression

Roman *et al* (2003)

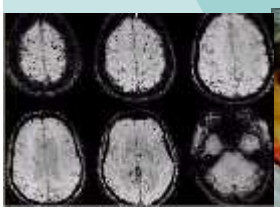


Clinical features supportive of vascular dementia

- Early gait disorder *(marche à petit pas)*
- Frequent falls
- Urinary incontinence early in disorder
- Pseudobulbar palsy
- Personality and mood changes

Features that make VAD diagnosis uncertain or unlikely

- Early memory loss and progressive deterioration in the absence of corresponding focal lesions on imaging
- Absence of focal neurological signs
- Absence of cerebrovascular lesions on CT or MRI



Clinical symptoms of subcortical dementias

- Bradyphrenia
- Perseveration
- Executive function deficits
- Language and visuospatial preservation
- Mild amnesia
- **Social functioning often preserved**
- **Neurological symptoms of the primary disorder**

Cummings (1994); Cummings and Benson (1984); Savage (2007)

Parkinson's disease and dementia

- Occurs in 20–40% patients
- Occurs after motor disorder
- Mild amnesia
- Severe slowing of thought
- Depression common

Elwan *et al* (1996); Hughes *et al* (2003)

Normal pressure hydrocephalus (NPH)

= term applied to the triad of:

1. Dementia
2. Gait disturbance
3. Urinary incontinence....

occuring in conjunction with hydrocephalus and normal CSF pressure.

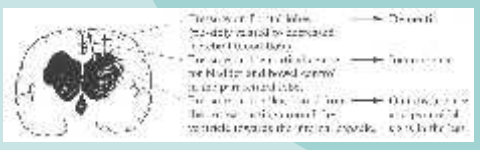
Two types:

- NPH with a preceding cause (SAH, meningitis, trauma, radiation-induced).
- NPH with no known preceding cause – idiopathic (50%).

Normal pressure hydrocephalus

Aetiology is unclear.

It is presumed that at some preceding period, impedence to normal SCF flow causes raised intraventricular pressure and ventricular dilatation. Compensatory mechanisms permit a reduction in CSF pressure yet the ventricular dilatation persists and causes symptoms.



Normal pressure hydrocephalus (NPH)

Diagnosis is based on clinical picture plus CT scan/MRI evidence of ventricular enlargement.

NPH must be differentiated from pts whose ventricular enlargement is merely the result of shrinkage of the surrounding brain, e.g. AD. These pts do not respond to CSF shunting, whereas a proportion of NPH pts (but not all) show a definitive improvement with ventriculo-peritoneal shunting.

AIDS-dementia complex

- Approximately two-thirds of persons with AIDS develop dementia, mostly due to AIDS-dementia complex.
- In some patients HIV is found in the CNS at postmortem.
- Dementia is initially of a "subcortical" type.
- CT: atrophy; MRI: increased T2 signal from white matter.
- Treatment with Zidovudine (AZT) halts and partially revers neuropsychological deficit.

Investigations in dementia

- **Routine investigations**
  - full blood count
  - serum electrolytes
  - glucose
  - renal function
  - liver function
  - thyroid function tests
  - vitamin B_{12}/folate
  - Lues/HIV serology
- **Neuroimaging**
  - CT
  - MRI
  - SPECT
- **Special investigations**
  - EEG
  - LP

Causes that mimic dementia
(but are treatable)

Toxic/metabolic	Medications, B_{12} deficiency, hypothyroidism
Systemic illnesses	Infections, cardiovascular disease, pulmonary
Other	Depression, sleep apnea, psychosocial stressors, drugs

Treatment may improve, but not fully reverse, symptoms

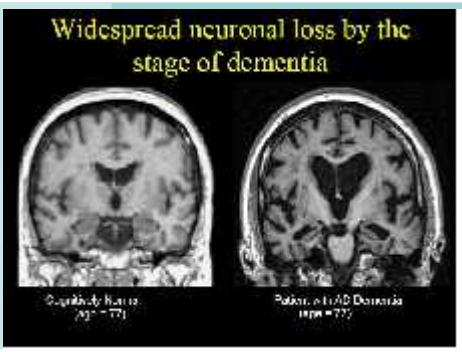
Pseudodementia

- Differentiate the following conditions
  - depression
  - dementia
  - pseudodementia
  - concurrent depression and dementia
- Identify and treat physical disease / contributory factors
- Specialist investigations — CT, MRI, EEG
- **Psychological tests**

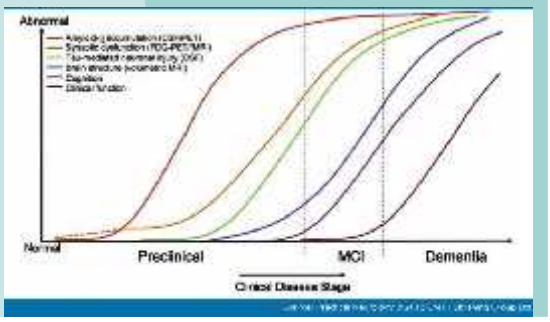
The confused patient

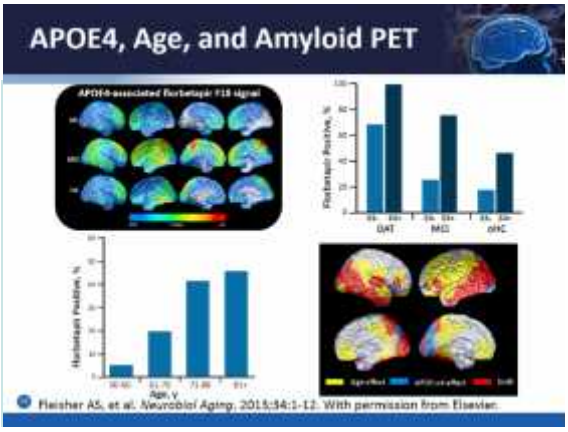
- Confusion: “The inability to think with one’s customary clarity and coherence” (*Lishman*)
- Primary causes of confusion include dementia and delirium
- Confusion also arises as a consequence of other events and pathologies
- It may be the doctor and not the patient who is confused!

Hyppocampal atrophy in AD

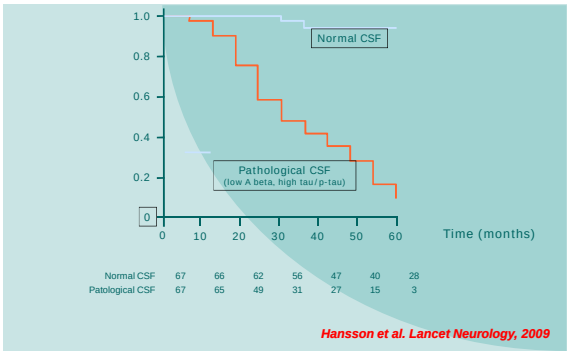


Different phases of AD and possible markers – biological, cognitive and clinical

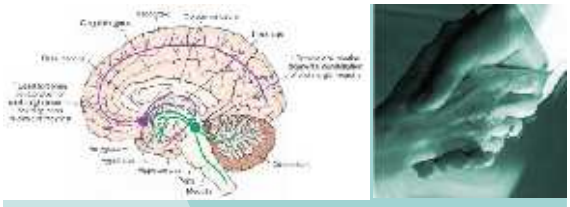




Pattern of CS fluid changes in AD: lower a-beta; elevated tau and P-tau



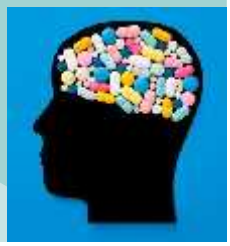
Hansson et al. Lancet Neurology, 2009



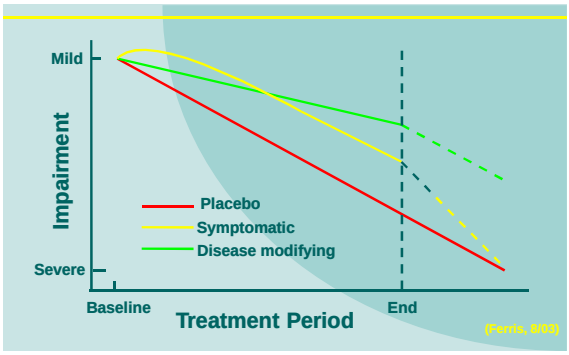
Clinical management of dementia

Alzheimer's disease is a treatable disorder

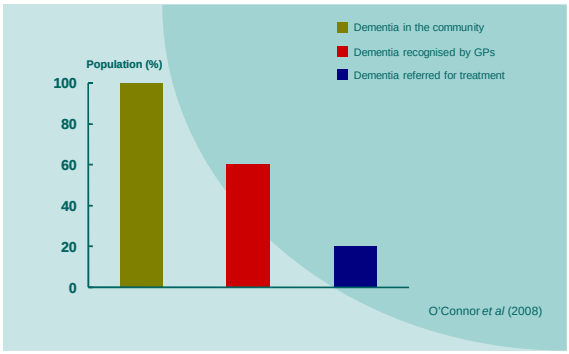
- Treating the symptoms
- Treating the carers



Symptomatic effects versus slowing disease progression



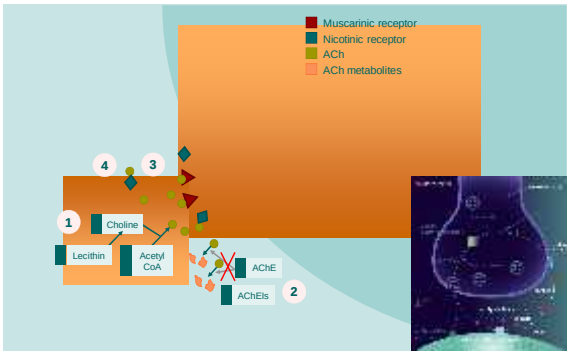
Alzheimer's disease goes unrecognised and untreated



O'Connor *et al* (2008)

Acetylcholinesterase inhibitors

Correcting cholinergic loss in AD



Donepezil

- Reversible acetylcholinesterase (AChE) inhibitor
- Half life < 70 hours
- Once-daily dosing
- Doses: 10 mg/day (21mg?)
- Subjected to Cochrane review
- Evidence for improvement in cognition, global state and possibly function
- Side-effects similar to other AChEIs — nausea and vomiting
- Side-effects often mild and attenuate with time

Rivastigmine

- Pseudo-irreversible acetylcholinesterase (AChE) inhibitor
- Half life ~2 hours / effects on AChE ~10 hours
- Twice-daily dosing
- Greater efficacy (and more side-effects) at higher doses
- Evidence for improvements in cognition, global state and possibly function
- Side-effects similar to other AChEIs — nausea and vomiting
- Few interactions with other drugs

Galantamine

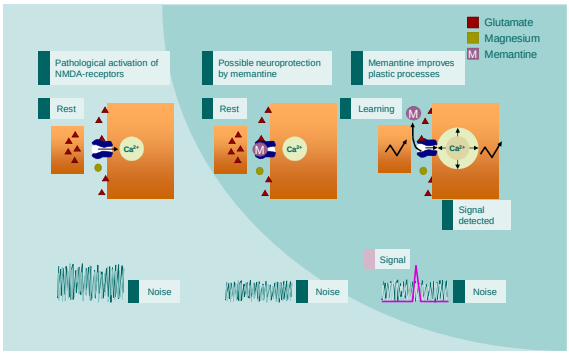
- Competitive reversible acetylcholinesterase (AChE) inhibitor
- Half life ~2 hours / effects on AChE ~10 hours
- Slow dose-titration reduces side-effects
- Evidence for improvement in cognition, global state and possibly function
- Benefit maintained to 12 months
- Side-effects similar to other AchEIs — nausea and vomiting


NMDA-receptor antagonism

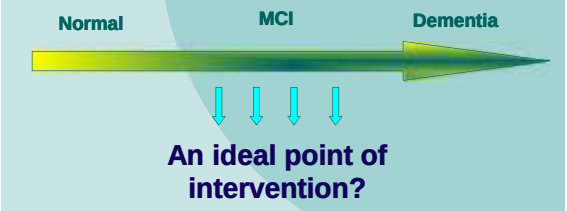

Glutamatergic hypothesis of dementia

- Glutamate is the main fast excitatory transmitter in regions associated with cognition and memory
- Cortical and subcortical structures that contain glutamatergic receptors are structurally damaged in AD
- Glutamate acts as an excitotoxin, causing neuronal death when chronically released
- Animal data suggest that NMDA-receptor antagonists provide neuroprotection

Mechanism of action of memantine



Mild Cognitive Impairment



An ideal point of intervention?

Treating behavioural disturbance

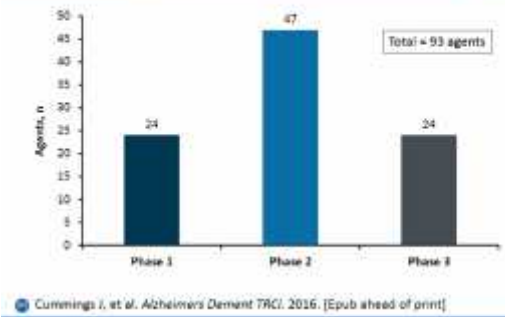
Importance of treating BPSD

- Reduction in carer stress
- Improvement in ability of carers to care
- Reduction in service costs
- Improvement in quality of life

Improvement in quality of life

- Quality of life is difficult to measure, especially in dementia
- Depression, agitation and anxiety appear to be prima facie causes of reduced quality of life
- Treating BPSD is likely to improve quality of life in dementia as much as in other conditions

Number of Agents in the AD Pipeline



Cummings J, et al. *Alzheimers Dement TRCI*. 2016. [Epub ahead of print]