Carers (experts by experience) - preventing crisis in dementia care

Dr Penny Hibberd

Consultant Admiral Nurse

The Good Care Group

- Working with family carers to maintain a healthy lifestyle for the person with dementia and themselves
- Avoiding hospital admission and carer crisis
- Understanding the perspective of care as a family carer

Case study

Gentleman diagnosed 8 years ago with Lewy body disease:

- Hallucinations
- Aggression
- Distress
- Inguinal hernia
- Scrotal abscess
- Progressive aphasia

Cared for by his wife of 30 years:

- Works part time
- Managed to care alone for 8 years
- Injured shoulder waiting for surgery
- Exhausted and distressed
- Restraining her husband during personal care

A healthy lifestyle

- Sleep deprivation
- Eating and drinking
- Work/caring role balance
- Connecting to the local community
- Carer support
- Maintaining activities and feelings of well-being

Avoiding Admission

- Life history
- Pain
- Medication
- Medical interventions
- End of life planning
- Working collaboratively

A carer perspective

- The need to carry on
- The ‘right time’ to access help and care
- Planning ahead – the right thing to do?
- Juggling your own well-being with caring role
- Differences of care delivery by family members and professionals – the processes

Questions

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Thank you

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Patient and Carer participation in clinical trials and research

IMPERIAL MEMORY UNIT
Charing Cross Hospital

Ginnette Kitchen RMN.RGN.MSc

Clinical trial phases

- Phase I trials check that treatments are ‘safe’. Treatments are tested in small doses and on a limited number of people without disease

- Phase II tests both safety and efficacy the treatment on a larger number of people (usually a few hundred) who have disease.

- Phase III trials proceed when phase II trials have shown some efficacy and are relatively safe. Trials examine both safety and efficacy in large populations of thousands with disease and are conducted globally.

Ethical dilemma in dementia

- **GCP**

  Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected.

- **Informed consent**

  Patient and Carer are given approved information to make an informed decision. They are encouraged to ask any questions that may be important in helping to reach a decision. Withdrawal of consent at any point and without reason does not affect ongoing clinical care

The Team

- Dedicated trials unit with onsite facilities

- Neurologists PI and SI
- Research nurses/Trial Coordinators
- Psychologists
- Admin support
- Pharmacist
- Imaging staff
- Hospital departmental staff (PIU, EEG, Cardiology, Dermatology, Ophthalmology)

The matching process

- **The trial has to be right for the patient**
- Managing expectations
- Understanding the commitment needed
- Understanding all the procedures required
- Type of study…observational/IMP
- **The patient has to be right for the study**
- Meeting inclusion/exclusion criteria
- Being otherwise healthy
- Disease diagnosis and staging
- Can manage all the tests

What is involved

Study dependant

- Consenting
- Medical history
- Cognitive tests
- Functional scales
- ECG
- EEG
- Imaging
- LP
- Vitals
- Bloods

Pros and cons

- **Pros**
- Access to newest treatments
- Support of clinical trials staff for patient and carer
- Feel good factor of being pro-active
- Constant health screening
- Transport/subsistence
- **Cons**
- Potential side effects
- No guarantee of success
- Could be on placebo
- Time and effort to attend

Recruitment

- Neurology clinics
- Psychiatry clinics
- Website **www.imperial.nhs.uk/services/neurology/memory/index.htm**
- Advertising/posters/information leaflets/media
- General Practitioners

Mild Cognitive Impairment

Thursday 26th November 2015

Dr Ruth Mikhail
Clinical Research Doctor, Imperial Memory Unit, Charing Cross Hospital

- Definitions of MCI vs Dementia
- Causes
- MCI due to AD
- Benefits to diagnosis
- Treatment

Mild Cognitive Impairment: definition

"Mild cognitive impairment (MCI) is a condition in which someone has minor problems with cognition – their mental abilities such as memory or thinking. In MCI these difficulties are worse than would normally be expected for a healthy person of their age. However, the symptoms are not severe enough to interfere significantly with daily life, and so are not defined as dementia."

Alzheimer's Society factsheet MCI
https://www.alzheimers.org.uk/site/scripts/download_info.php?fileID=1773

Diagnosing Mild Cognitive Impairment

progressive cognitive (often memory) impairment for at least 6 months

witnessed by others and measurable on testing, showing mild impairment for age

no metabolic cause found (eg thyroid disease, Vitamin B12 deficiency)

symptoms not severe enough to impact on activities of daily living, although the symptoms may well be annoying or frustrating

Prevalence of MCI

The Alzheimer's Society estimate that between

5 and 20 % of people

aged over 65 have MCI

Vs. Definition of Dementia

At least 6/12 cognitive decline

Severe enough to result in a handicap to independent living – unable to function without assistance of another in daily living

New information retained only occasionally and very briefly

Causes of MCI

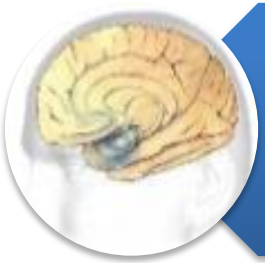
Alzheimer's Disease – most common

- Also known as amnestic MCI, or prodromal Alzheimer's Disease.

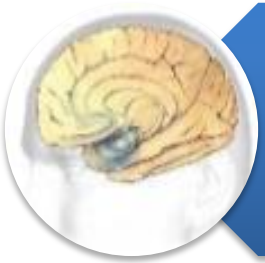
Others include:

- Depression and anxiety
- Vascular dementia
- Endocrine disorders e.g. hypothyroidism, low B12 / folate
- Rare forms of dementia e.g. frontotemporal dementia, dementia with Lewy bodies, posterior cortical atrophy

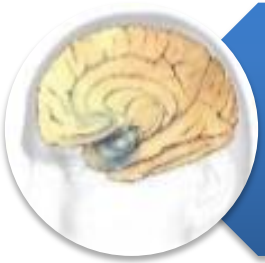
Why is MCI important?



Syndrome that represents the earliest clinical features of cognitive disorders such as Alzheimer's Disease and other dementias

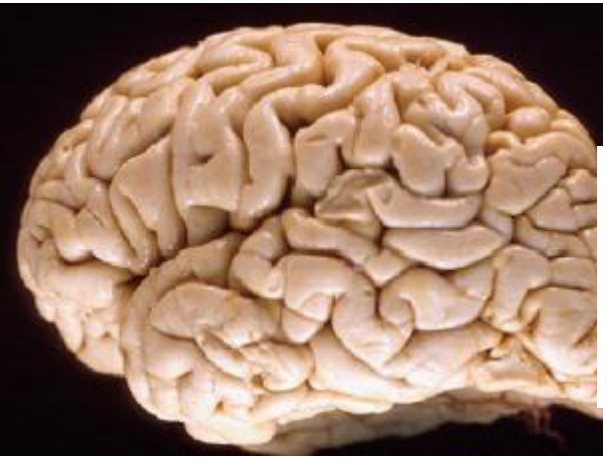


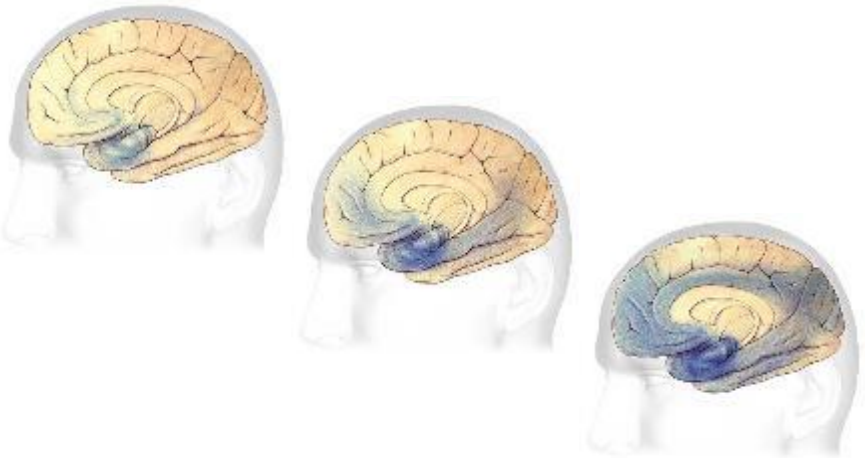
"A diagnosis that has evolved to capture the pre-dementia phase of cognitive dysfunction" *Petersen et al, 2009*

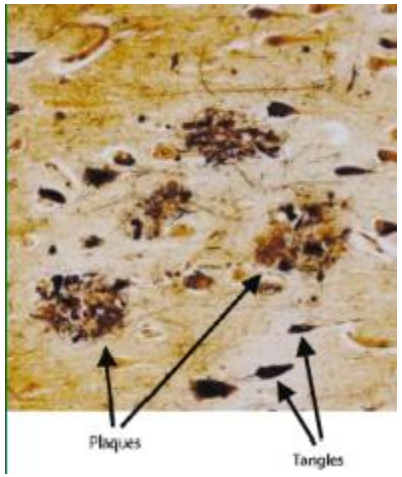


Mild cognitive impairment is 'the symptomatic pre-dementia stage on the continuum of dementia'. *Dr Jill Rassmussen, RCGP*

Pathology of Alzheimer's Disease

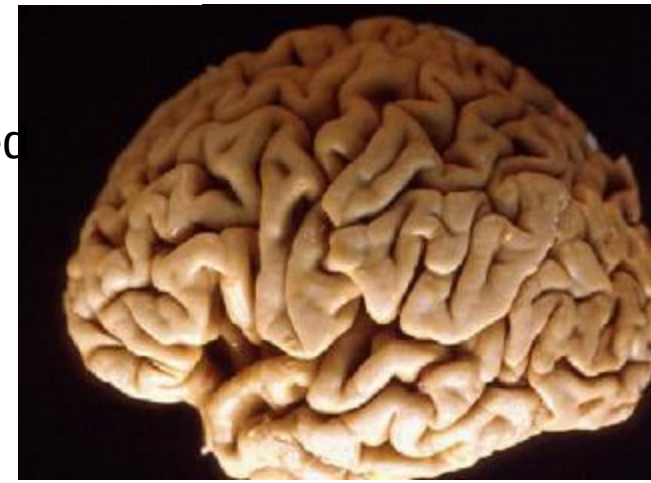






β Amyloid – plaques, extracellular
Tau – abnormally hyperphosphorylated tau → neurofibrillary tangles

Plus neuronal and synaptic loss



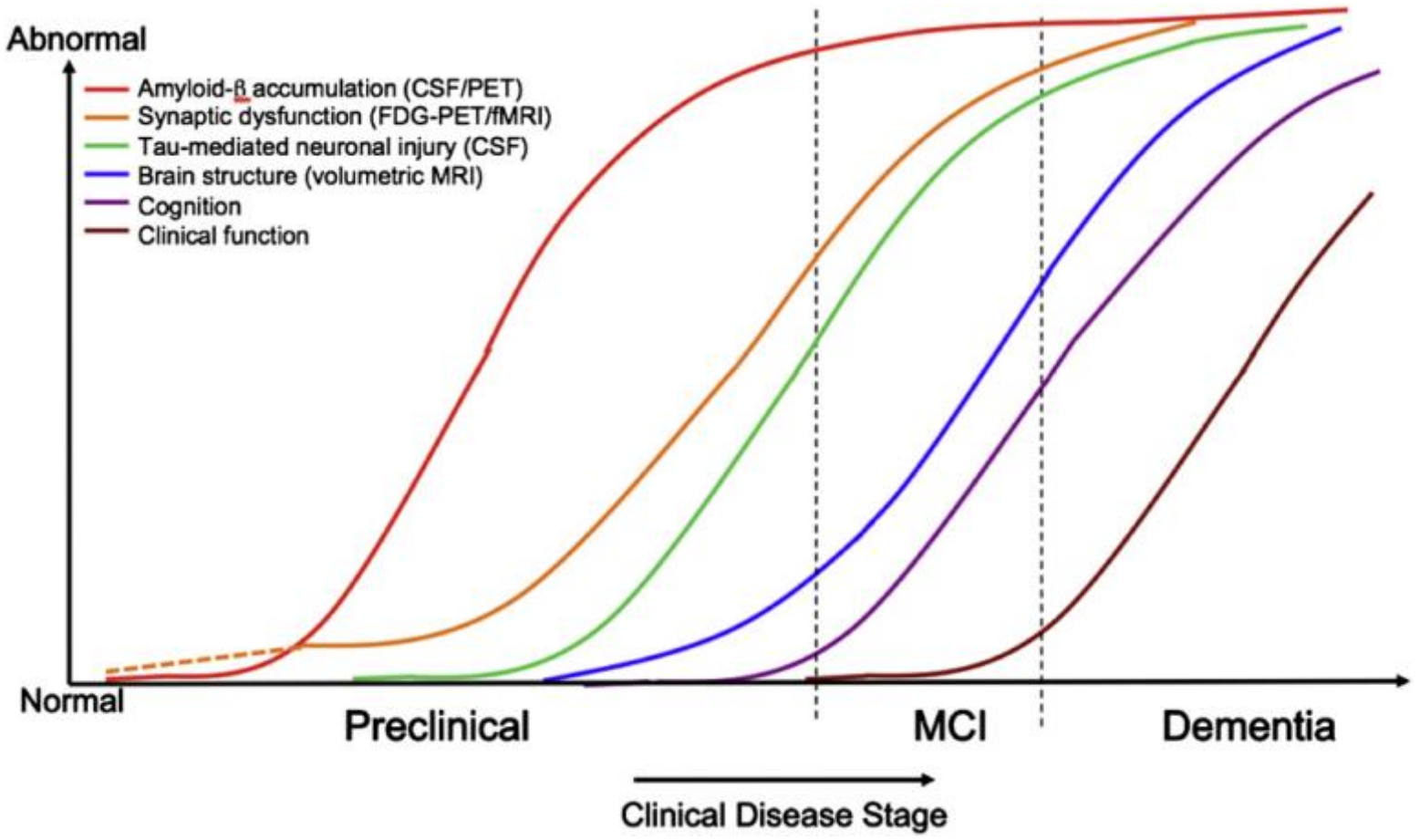
(With thanks to Dr Perry for his slide)

MCI due to AD

- It is possible to have MCI which is shown to be most likely due to Alzheimer's Disease pathology **without** having Alzheimer's dementia

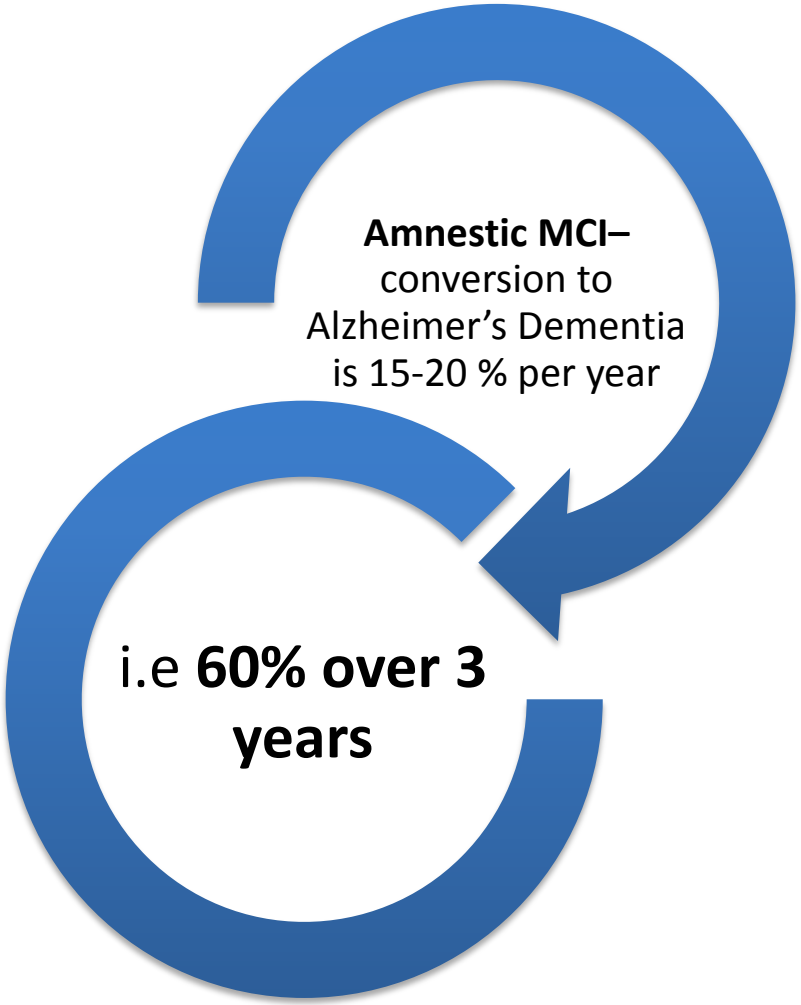
  - Biomarkers available to support a diagnosis of MCI due to AD include MRI, CSF analysis, PET imaging.

Phases of cognitive impairment



R.A. Sperling et al. / Alzheimer's & Dementia 7 (2011) 280–292

Progression to Alzheimer's Dementia



Making a **timely** diagnosis

When a patient presents with memory symptoms they should be investigated – if they come they are ready for answers

Consider how long a patient has lived with symptoms before presenting to you

NICE guidance – refer people with signs of MCI to memory clinic, where they can then be followed up if MCI is diagnosed

Benefits to diagnosing MCI

For patients:

- Make sense of symptoms
- Plan for future – LPA, wills, get affairs in order, place of living
- Memory aids
- Managing at work – strategy development

For medical professionals:

- Improved patient access to services (NICE guidance – MCI patients should not be denied access to support services)
- Knowledge of patients - chance of conversion to AD
- Managing secondary prevention (diet, exercise, BP, medications, etc)
- Identify potential patients for involvement in research

For caregivers:

- Information and support
- Become understanding of symptoms
- Practical arrangements for future


Lifestyle advice
If MCI due to AD we might use donepezil
Opportunity for DM treatments via clinical trials
Treat reversible metabolic causes
Management of other medical conditions
Address mood / anxiety
Treatment of MCI

Summary: MCI

Cognitive decline but essentially normal functional activities, not demented

Patients with signs of MCI should be referred to memory assessment services (NICE guidance 2012)

Often is pre-dementia phase in Alzheimer's disease dementia

Important to diagnose when patients are concerned so they can be supported

Thank you for listening – enjoy the afternoon

Useful resources:
Alzheimer's Society factsheet – ‘What is mild cognitive impairment (MCI)?’
NICE guidance on dementia

Young Onset Dementia

Helen Rice & Heidi Crook

Memory Nurses, Imperial Memory Unit,
Charing Cross Hospital

What is Young Onset Dementia?

Sometimes referred to as early onset dementia or working age dementia

Umbrella term: Any Dementia diagnosed in persons aged under 65

Over 40,000 younger people with a diagnosis of Dementia in the UK

(Alzheimer's Society, 2014)

Aetiology

(Alzheimer's Society, 2014)

Type of Dementia	Overall Dementia Population	Young Onset
Alzheimer's Disease	62%	33%
Vascular Dementia	17%	20%
Frontotemporal Dementia	2%	12%
Korsakoff's Syndrome	-	10%
Dementia with Lewy Bodies	4%	10%
Other	15%	15 %

Mrs A

54 Year Old Woman

Persistent language Difficulties ?Cause

Wife & Mother to two teenagers

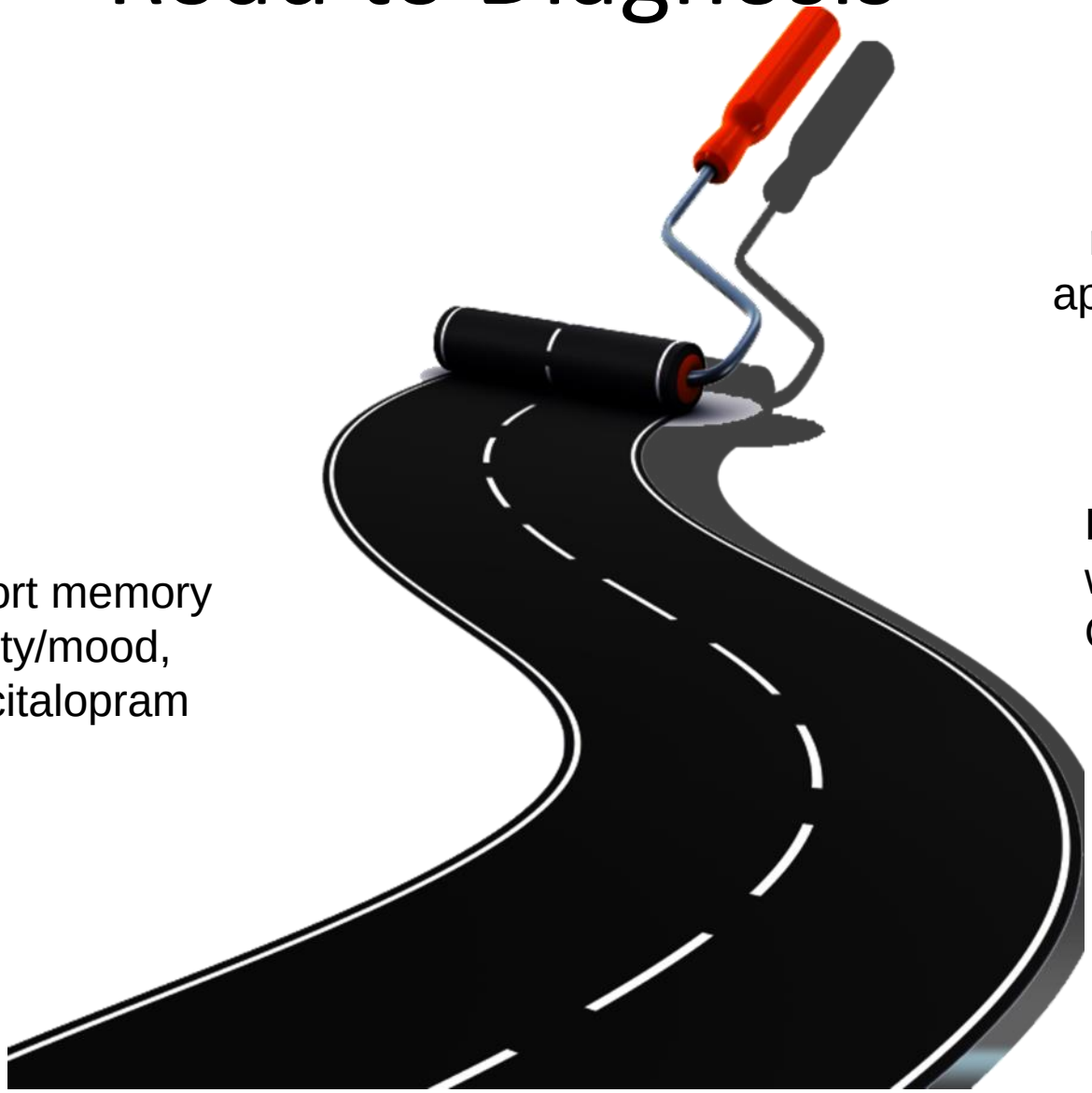
Daughter to elderly parents

Travel agent for 20 years: took early retirement due to ‘stress at work’

Road to Diagnosis

Delay in presenting to GP

GP visits
Testing: short memory test, ?anxiety/mood, started on citalopram



Private neurology appointments

Diagnosed with Young Onset AD

Key Themes:

Diagnosis

- The challenge of differential diagnosis

'I knew it wasn't normal to keep forgetting things…I knew in the back of my mind it was there, but he* (the doctor) *assured us that the way he was presenting…that he didn't really think he had an issue…'

(wife of person with young onset dementia)

The challenge of differential diagnosis

- Primary neurodegenerations
    - *e.g. Alzheimer's disease, frontotemporal dementia*
-Vascular
    - *e.g. multiple cortical infarcts, small vessel disease*
- Prion
    - *e.g. CJD*
- Inflammatory
    - *e.g. Multiple Sclerosis*
- Neoplastic/paraneoplastic
    - *e.g. Tumours*
- Infections
    - *e.g. HIV*

From Sampson, Warren and Rossor (2004)

Key Themes:

Diagnosis

- Time to diagnosis

It often takes much longer to receive a diagnosis of early onset dementia compared to late onset dementia

- Barriers to diagnosis:

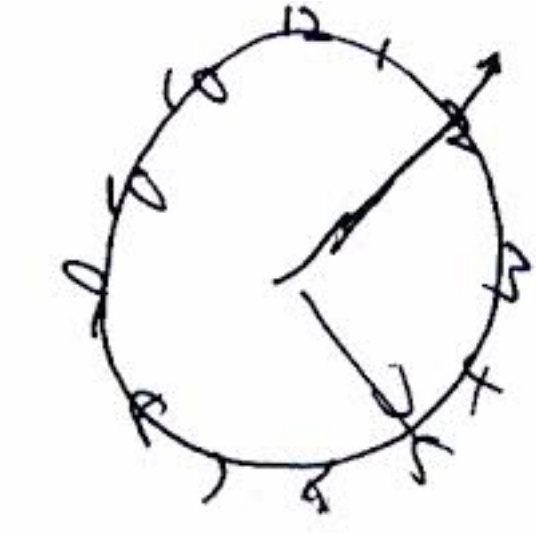
Dementia as a slow progressing condition

People with a young onset dementia may recognise symptoms earlier in the disease process

Physician difficulty in recognising the diagnosis and risk of misdiagnosis

Caregiver understanding and attribution of symptoms – psychosocial cause

The challenge of adequate service provision – neurology and psychiatry



Key Themes:

Diagnosis

- The value of a timely diagnosis

Excluding reversible causes

Explaining symptoms

Accessing symptomatic therapies

Planning for the future

Research participation

Impact of diagnosis: stigma

Dislike of word ‘Dementia’

Tearfulness

Need to find people in similar situation

Internet: Information Overload

Felt existing services not suited to age

Young Onset DSW service

Fear: breaking the news

Key Themes:

- Dementia as an older person's illness

Key Themes:

Stigma

- Issues around terminology

  e.g. Young onset dementia versus *early* onset dementia

'If this department had dementia in its name, I never would have come along…'

(person with young onset dementia)

Accepting the change: Home Life

- Impact on social life: loss of friendships

- Change in family dynamics

- Husband now planning early retirement

- Concern about caring for elderly parents as well

Key Themes:

Home Life

- Strain on relationships

- May be children still at home to consider – impact on them

'That feels like I'm, a grown up and [Dad]'s my kid but, he's not'

(young carer of a person with young onset dementia; Svanberg et al., 2010)

- Loss of role

- Adjustment of life plans

'…it was like having your future taken off you'

(wife of person with young onset dementia)

Key Themes:

Working Life

- Early retirement
- Loss of role
  - ***'I lost everything that defined me as a productive and meaningful man when I had to stop working because of my symptoms…The whole role in life shifted from being the main breadwinner to now being Mr. Mom.'***
- Loss of income

Other themes

- Developing and accessing appropriate health, social care and third sector services

- Variability in the course or progression of the condition

- People with young onset dementia are likely physically very fit and well

Young Onset Dementia

Jeremy and Josephine's story

Video courtesy of BBC South Today 2015

Available from: www.youtube.com/watch?v=-w8sqS-y2FU

Useful Resources

Young Dementia UK
Informing Influencing Inspiring

Web: www.youngdementiauk.org

Alzheimer's Society
Leading the fight against dementia

Web: www.alzheimers.org.uk

Dementia UK
Helping families face dementia

Web: www.dementiauk.org
Dementia Helpline: 0800 888 6688

Thank you for listening

Any questions?

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Dementia: Diagnostics and Treatment

GP Study Afternoon

Paresh Malhotra
Imperial College London
Imperial College Healthcare NHS Trust

Overview

- Diagnosing Dementia
- Excluding Non-Neurodegenerative Causes
- Confirmatory Tests and Differentiating between different causes of dementia

- Investigating Young-onset/Atypical Dementia

Diagnosing dementia

It is relatively straightforward to diagnose dementia in an elderly patients with typical symptoms and a moderate stage of dementia

DSM-IV and DSM-5 criteria for dementia

DSM-IV criteria for dementia	DSM-5 criteria for major neurocognitive disorder (previously dementia)
A1. Memory impairment	**A.** Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*: - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
A2. At least one of the following: - Aphasia - Apraxia - Agnosia - Disturbance in executive functioning	
B. The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning	**B.** The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively during the course of delirium	**C.** The cognitive deficits do not occur exclusively in the context of a delirium
	D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)

For diagnostic criteria of dementia subtypes such as Alzheimer disease or frontotemporal dementia, please refer to UpToDate topics on the clinical manifestations and diagnosis of individual dementia subtypes.

DSM: diagnostic and statistical manual.
* Evidence of decline is based on: Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

References:

1. *American Psychiatric Association Diagnostic and Statistical Manual, 4th ed, APA Press, Washington, DC 1994.*
2. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.*

Excluding Non-Neurodegenerative Causes

- Thyroid Function
- B12

- Syphilis
- HIV

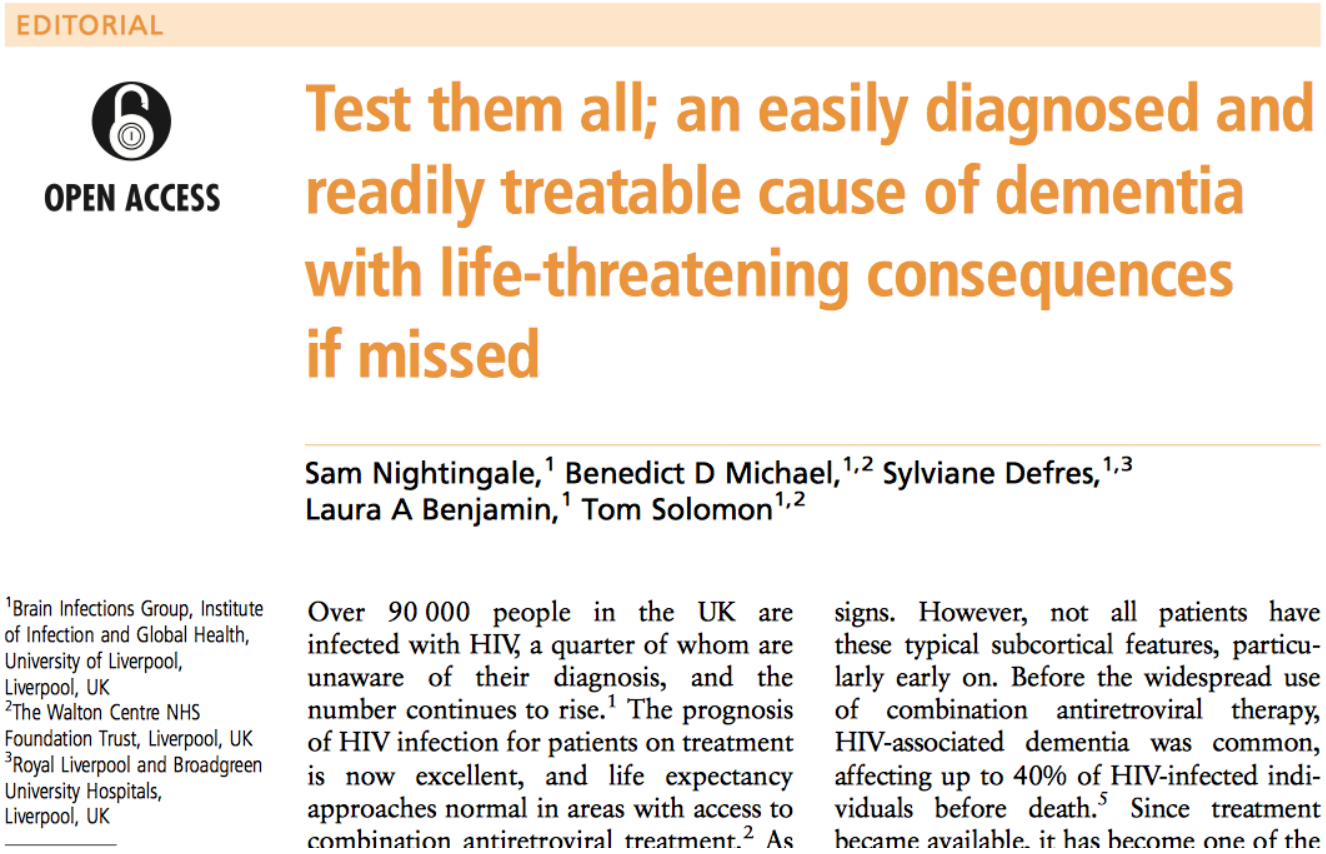
Excluding Non-Neurodegenerative Causes

- Thyroid Function
- B12

- Syphilis
- HIV

Excluding Non-Neurodegenerative Causes

- HIV



EDITORIAL

OPEN ACCESS

Test them all; an easily diagnosed and readily treatable cause of dementia with life-threatening consequences if missed

Sam Nightingale,[1] Benedict D Michael,[1,2] Sylviane Defres,[1,3] Laura A Benjamin,[1] Tom Solomon[1,2]

[1]Brain Infections Group, Institute of Infection and Global Health, University of Liverpool, Liverpool, UK
[2]The Walton Centre NHS Foundation Trust, Liverpool, UK
[3]Royal Liverpool and Broadgreen University Hospitals, Liverpool, UK

Over 90 000 people in the UK are infected with HIV, a quarter of whom are unaware of their diagnosis, and the number continues to rise.[1] The prognosis of HIV infection for patients on treatment is now excellent, and life expectancy approaches normal in areas with access to combination antiretroviral treatment.[2] As

signs. However, not all patients have these typical subcortical features, particularly early on. Before the widespread use of combination antiretroviral therapy, HIV-associated dementia was common, affecting up to 40% of HIV-infected individuals before death.[5] Since treatment became available, it has become one of the

Nightingale et al, Practical Neurology

Excluding Non-Neurodegenerative Causes

- HIV

HIV testing in dementia: test some, perhaps more, but not all

Jonathan M Schott

Correspondence to
Dr Jonathan M Schott, Dementia Research Centre, Department of Neurodegenerative Disease, Institute of Neurology, UCL, Queen Square, London WC1N 3BG, UK;j.schott@ucl.ac.uk

Nightingale *et al* argue that all patients presenting to neurologists with cognitive impairment should undergo HIV testing.[1] This view, prompted by a highly unusual case of a patient with HIV-related cognitive impairment, is based on the following reasoning: HIV is potentially treatable and testing is quick and relatively inexpensive; dementia is listed as an indication for testing by the British HIV Association, and suspected encephalitis is an indication for HIV testing in the Association of British Neurologists and British Infectious Association National Encephalitis guide-

HIV infection, in the absence of evidence to the contrary the numbers are likely to be vanishingly small, at least in a typical Western clinic population. Presuming such cases do exist, such is the prevalence of Alzheimer's in the elderly that it may well be that any cognitive impairment is due to amyloid plaques and neurofibrillary tangles rather than primary HIV infection, albeit with the possibility that the two might be mechanistically linked. I suspect that members of the British HIV Association are unlikely to see many 80-year-olds presenting with amnestic syndromes developing over several years,

Excluding Non-Neurodegenerative Causes

- Syphilis
- American Academy of Neurology Guidelines state that syphilis serology should not be tested unless the patient has a specific risk factor
- BUT it is a treatable cause of dementia

Excluding Non-Neurodegenerative Causes

- Syphilis
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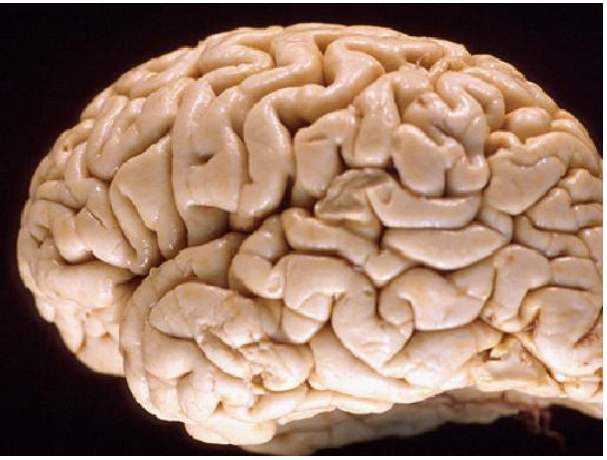
- BUT it is a treatable cause of dementia

Confirming the Diagnosis

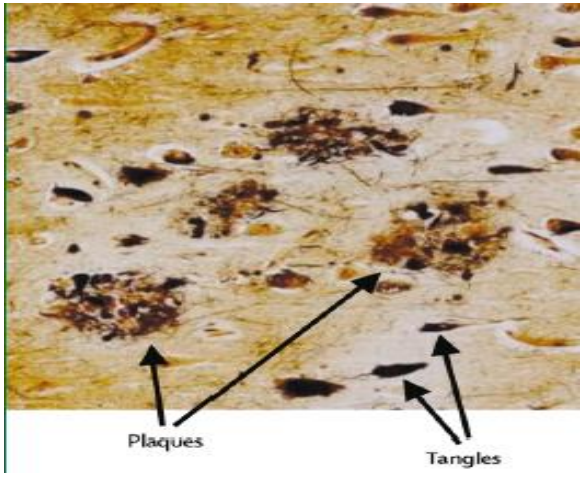
Diagnosing Alzheimer's Disease



•Definite AD
clinical diagnosis with histopathological confirmation

β Amyloid – plaques, extracellular
Tau – abnormally hyperphosphorylated tau
→ neurofibrillary tangles

Plus neuronal and synaptic loss



Diagnostics: Neuropsychology

Advantages

Low cost of technology

Portable

Disadvantages

Time Intensive

Variance in population

Affected by culture and education

Lacks specificity and sensitivity e.g. depression or prodromal AD

Single snapshot of longitudinal process

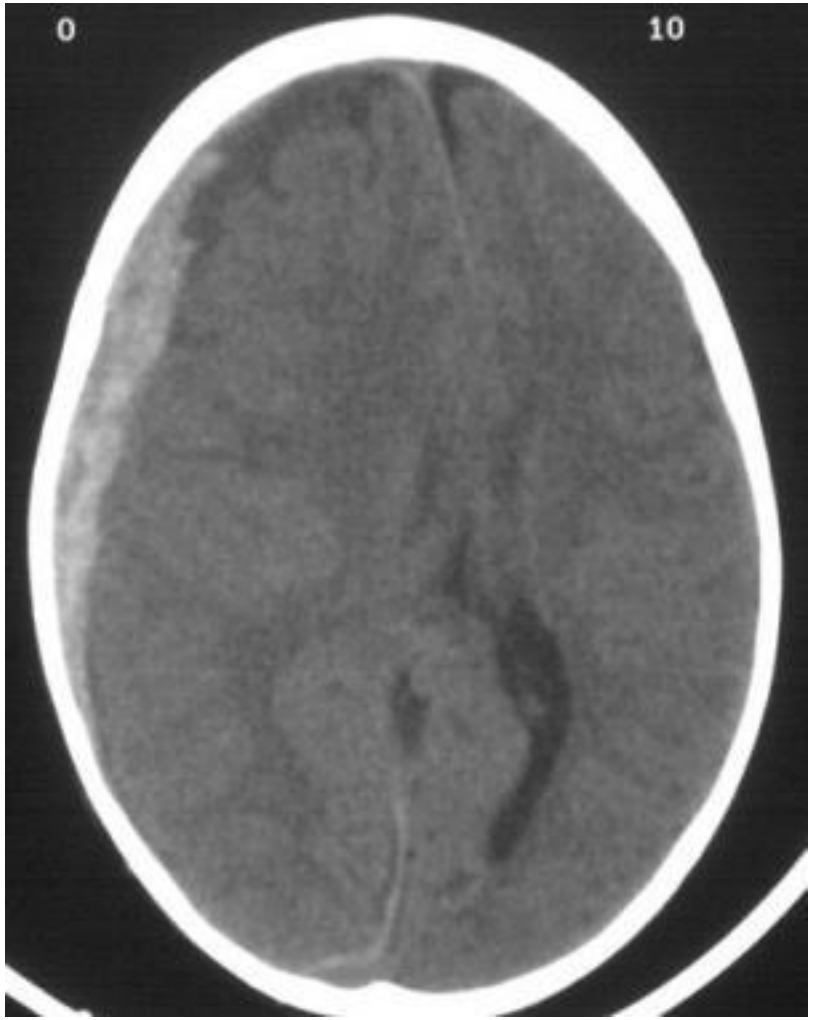
BUT

Establishes a baseline

Helps differentiate between different aetiologies

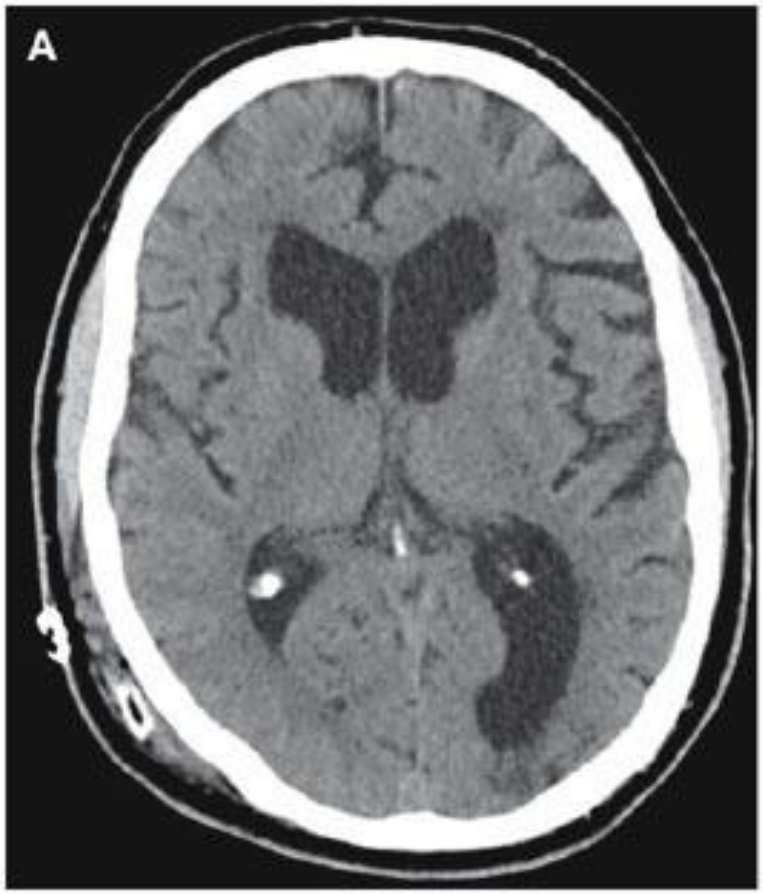
Useful for assessing competencies and guiding recommendations e.g. driving

Diagnostics: Imaging (CT)



Subdural Haematoma

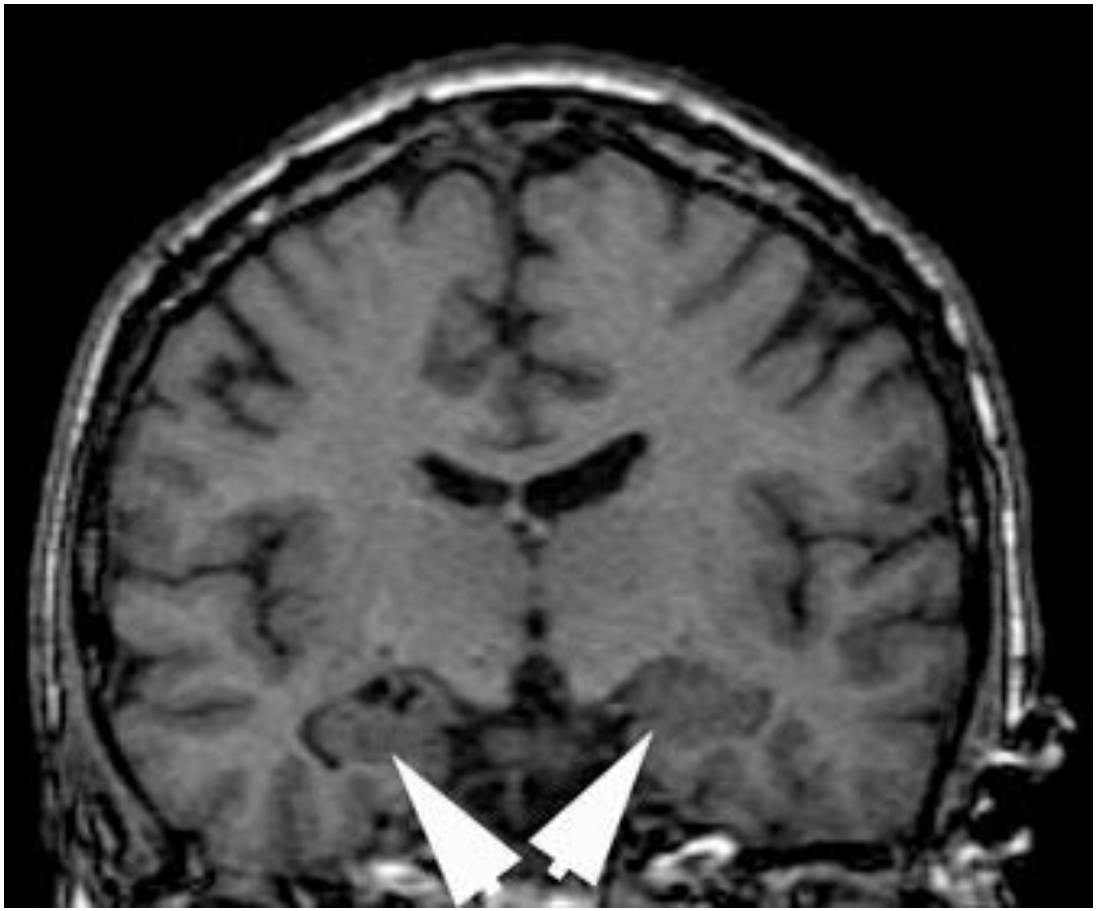
Diagnostics: Imaging (CT)



Normal Pressure Hydrocephalus

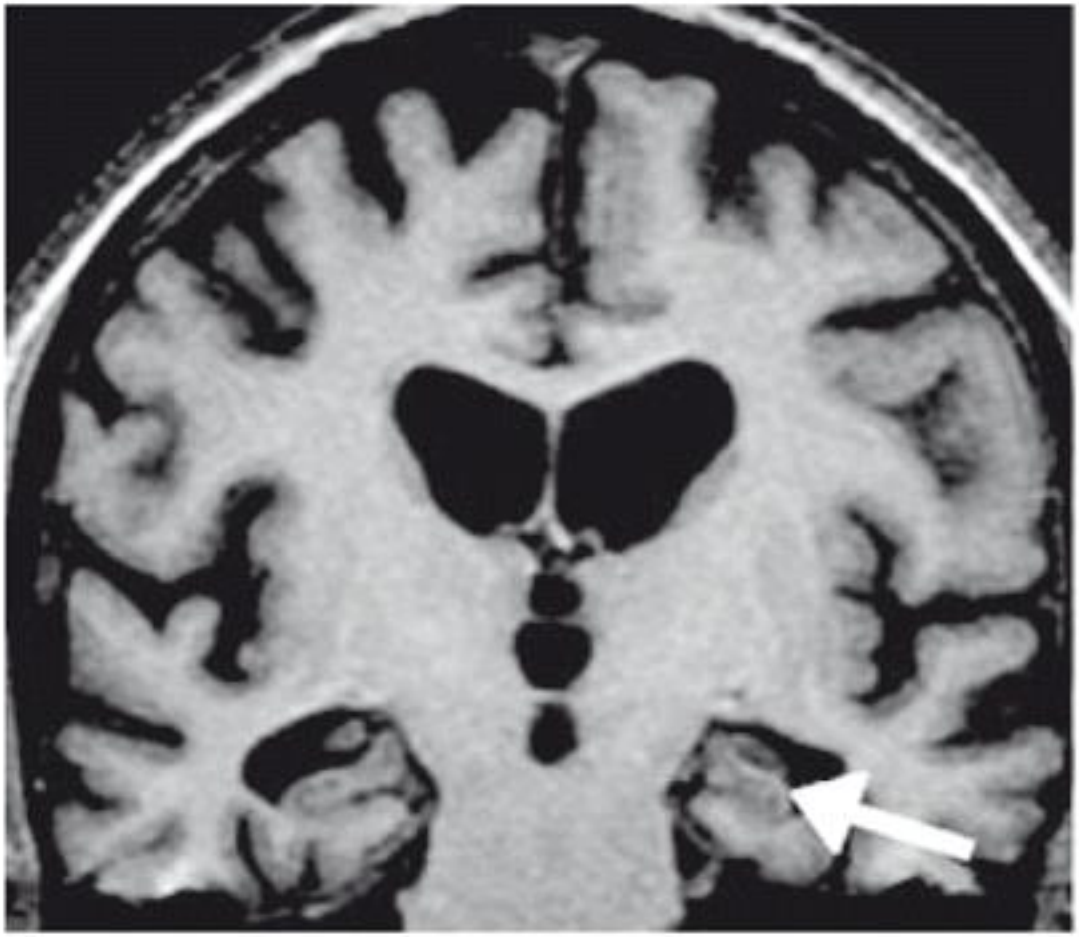
nature CLINICAL PRACTICE NEUROLOGY

Diagnostics: Imaging (MRI)



Normal Hippocampi

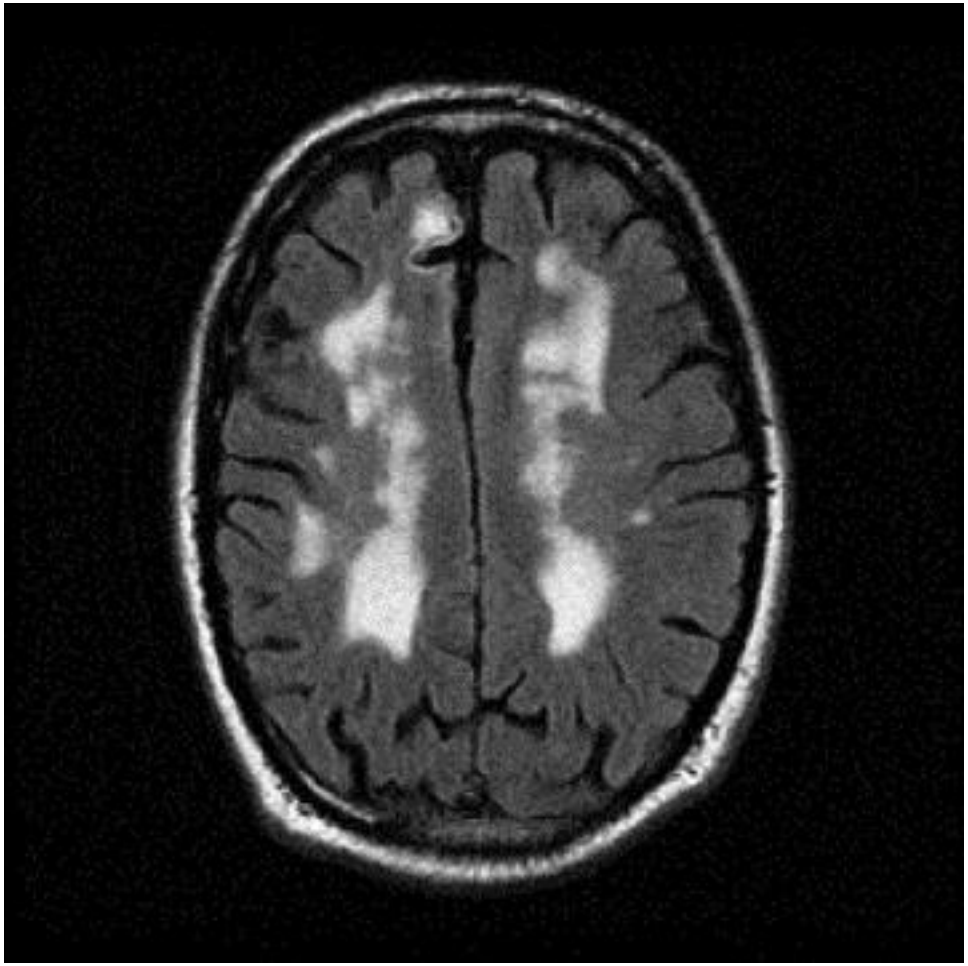
Diagnostics: Imaging (MRI)



Alzheimer’s Disease

Jefferies and Agrawal, Advances in Psychiatric Treatment

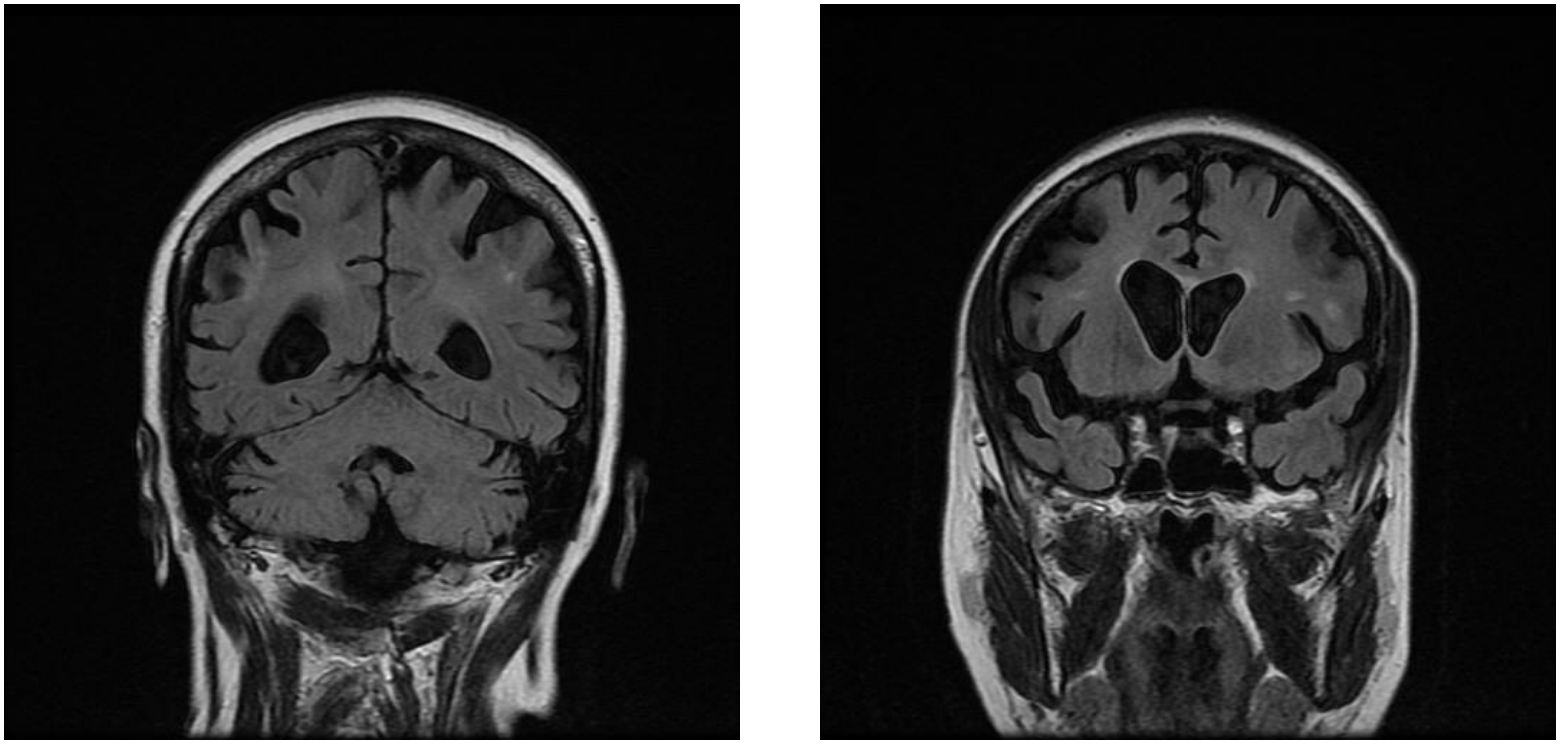
Diagnostics: Imaging (MRI)



Subcortical Vascular Disease

O'Brien et al, Lancet Neurology

Diagnostics: Imaging (MRI)



Frontotemporal Lobar Degeneration

Diagnostics: Imaging (MRI)

Pitfalls

The Normally reported scan

Is reported atrophy out-of-keeping with age?

Atypical pattern of AD?

Is the small vessel disease significant?

Single snapshot in time

Diagnostics: Imaging (MRI)

Pitfalls

The Normally reported scan

Is reported atrophy out-of-keeping with age?

Atypical pattern of AD?

Is the small vessel disease significant?

Single snapshot in time

All of the above are best addressed by reviewing the clinical presentation which may involve repeat assessments and involving a Neuroradiologist with an interest/experience in Dementia

Atypical/ Young-onset Dementia

- Different Differential Diagnosis
  - AD, but more likely to be 'atypical'
  - FTLD
  - Vascular Disease
  - Lewy-Body Dementia

  - Autoimmune Disease-systemic (eg. SLE), CNS (eg. Voltage-gated K channel Abs)
  - Infective- eg HIV, Syphilis, Lyme
  - Metabolic-eg Coeliac
  - Prion Disease
  - Other Genetic-e.g Gaucher's, Mitochondrial Disease

Atypical/ Young-onset Dementia

- Investigations for More Common Causes

  -MRI, Neuropsychology, ‘Standard’ Blood Tests

  Additional Investigations

  CSF

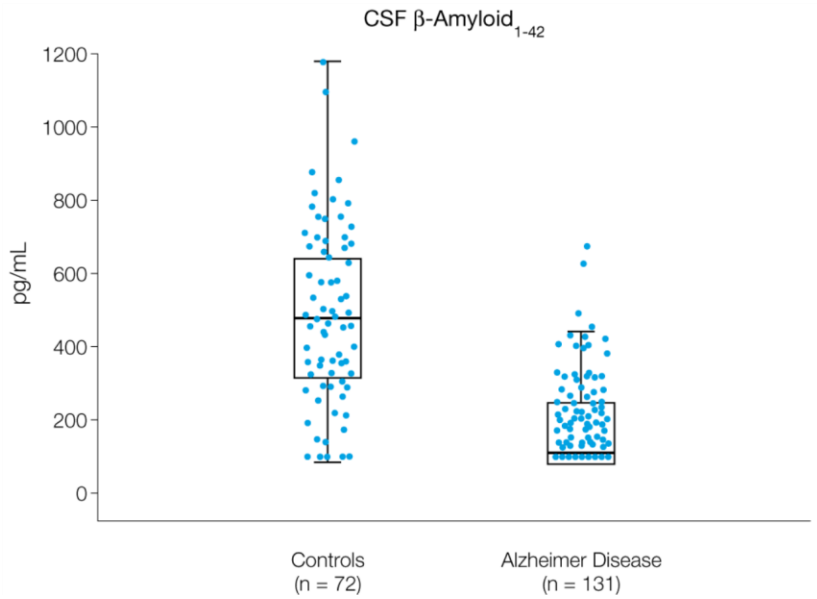
  PET Imaging-Amyloid PET (Amyvid), FDG-PET/SPECT/DaT

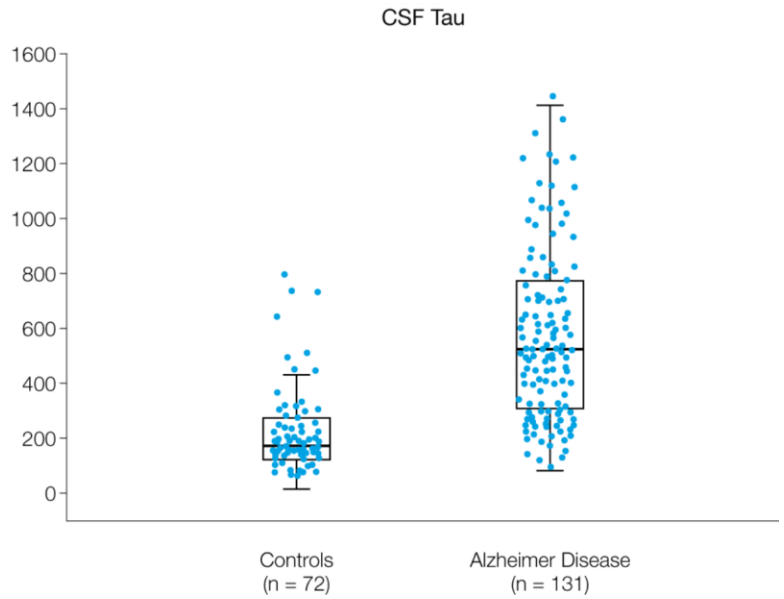
  EEG

  Specific Blood Tests-VGKCA, Autoimmune Screen

  Genetics-for Early onset AD, FTLD, rarer inherited causes

Atypical/ Young-onset Dementia- CSF



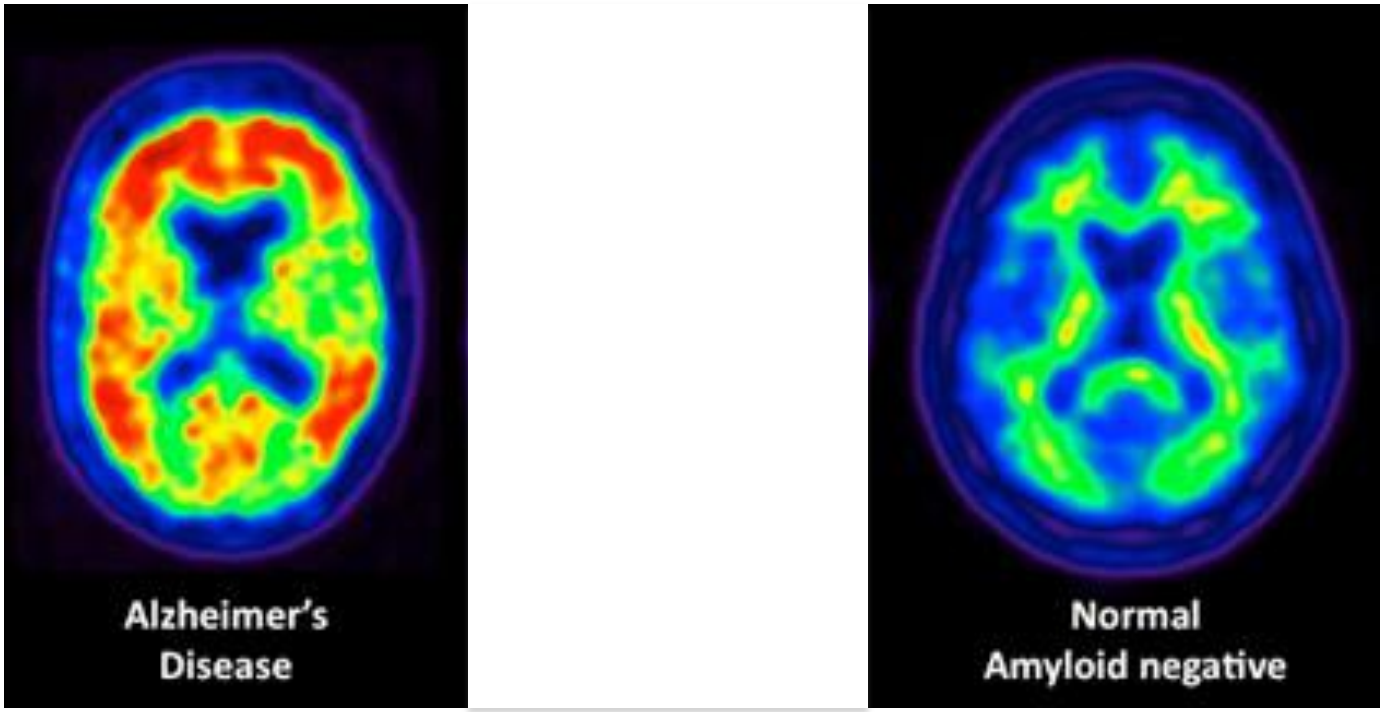


- Advantages
  - –Pathology specific for tau and abeta
  - –Sensitive

- Disadvantages
  - –Invasive
  - –Dependent on processing and assay stability

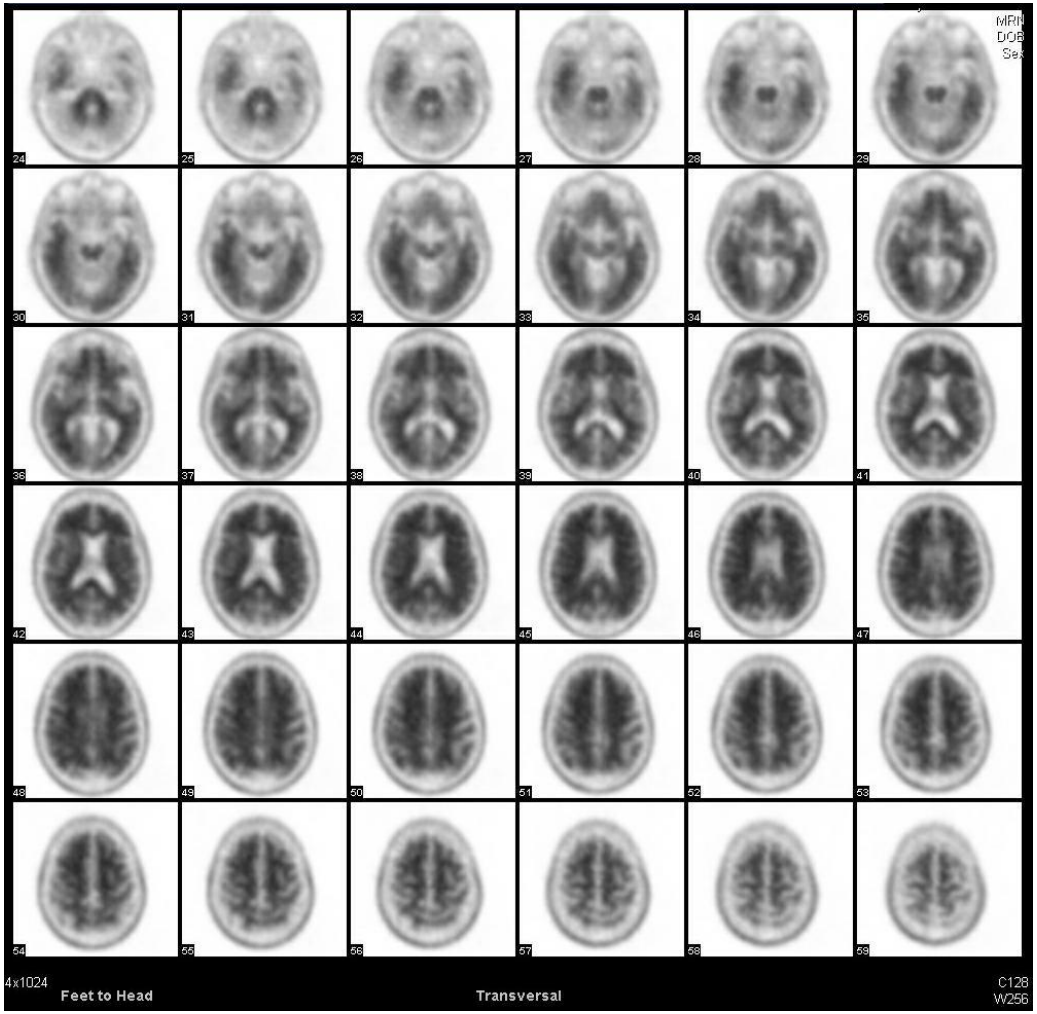
JAMA. 2003;289(16):2094-2103

Atypical/ Young-onset Dementia-Amyloid PET

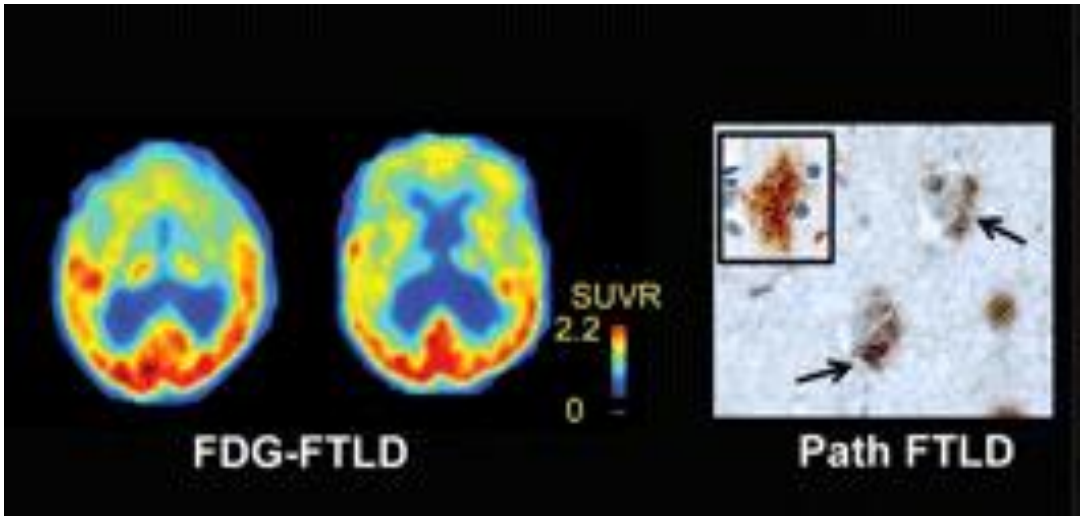


Atypical/ Young-onset Dementia-Amyloid PET

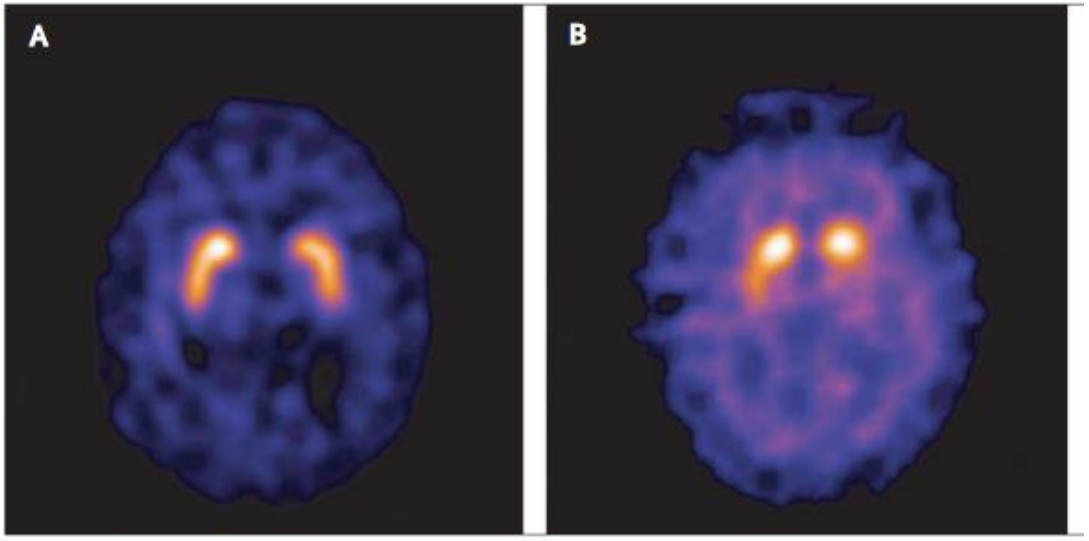
Florbetapir



Atypical/ Young-onset Dementia-FDG/DaT

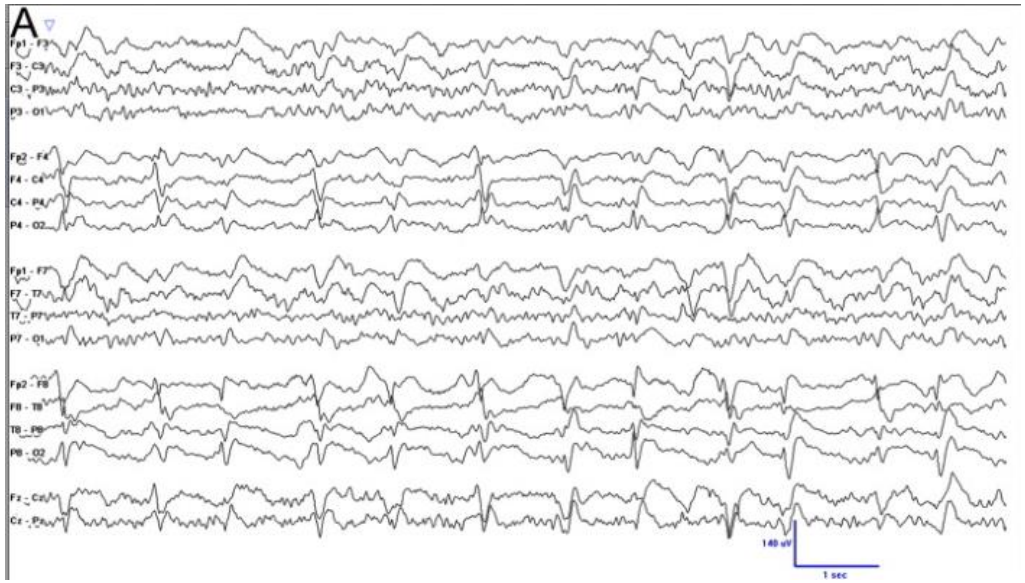


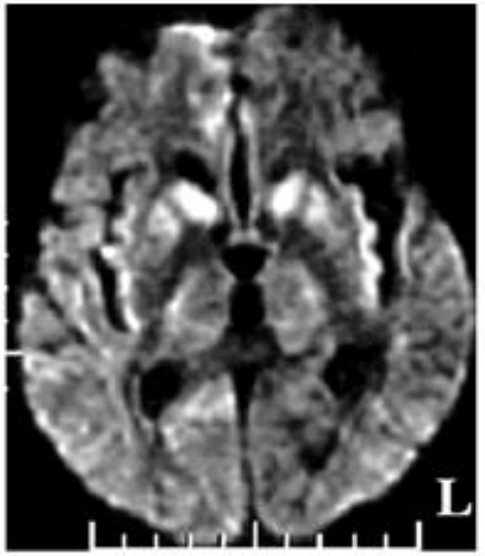
FDG PET in FTLD
Rabinovici et al, Neurology

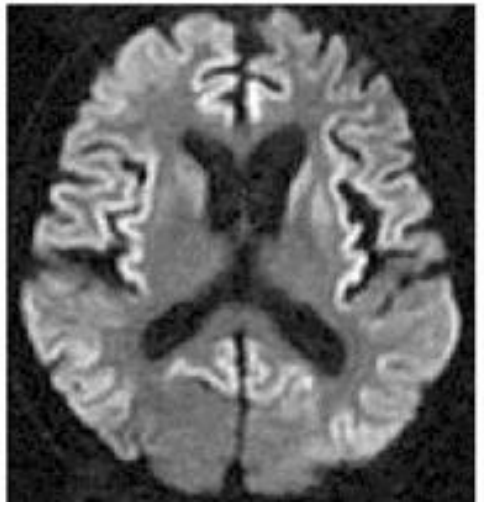


DaT in Dementia with Lewy Bodies
McKeith et al, Lancet Neurology

Atypical/ Young-onset Dementia-EEG







CJD

Chung et al Neurology

An MDT approach

- Neuroradiologists and nuclear medicine physicians with neurologists, psychiatrists, geriatricians
- Discuss the case of each request and review MRI imaging
- Review PET imaging post scan and also discuss utility of other investigations

Conclusions

- Investigations support clinical diagnosis
- Investigations can be

-used to rule out non-degenerative/potentially treatable causes of cognitive impairment

-to support diagnosis of AD in typical patients and may also suggest other common causes

e.g. Vascular Disease, FTLD

In atypical, young-onset cases, investigations can be used, in tandem with detailed clinical assessment, to make specific diagnosis and, most importantly, look for treatable causes of dementia.

Hype or hope?

Will we ever be able to treat Alzheimer's Disease?

Dr Richard Perry

Imperial College Healthcare NHS Trust

Imperial College


ET OK! MAGAZINE FOR JUST £1
ALZHEIMER'S
CURE IS CLOSE
perts hail new
g breakthrough
Don't call her Duchess... Why Kate really is a Princess


WHAT DO WE WANT?
A CURE FOR ALZHEIMERS!
WHEN DO WE WANT IT?
WANT WHAT?


The Daily Te
National
shame of
dementia
diagnosis


Pomegranate
Compound
Could Help
Fight
Alzheimer's


Global actio
against dem
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PLUS: FREE replica of royal WWI Xmas Box
CUT ALZHEIMER'S
RISK BY WALKING


5p DAILY
BURIED ALIVE: COUPLE FOUND DEAD IN CAR TEN DAYS AFTER LANDSLIDE
BRITAIN'S ECONOMY BOOSTED AT LAST
PILL TO BEAT ALZHEIMER'S
New treatment


5p DAILY EXPRESS
EVERLEY CALLARD
FRIENDS ABANDONED
E WHEN I TOLD THEM
I HAD DEPRESSION
UN SAYS
OPEN ALL
BORDERS T
MIGRANTS


Alzheimer's Treatment
vs.
GRAPES FIGHT
MEMORY LOSS
Experts say they are key to giving your brain a boost

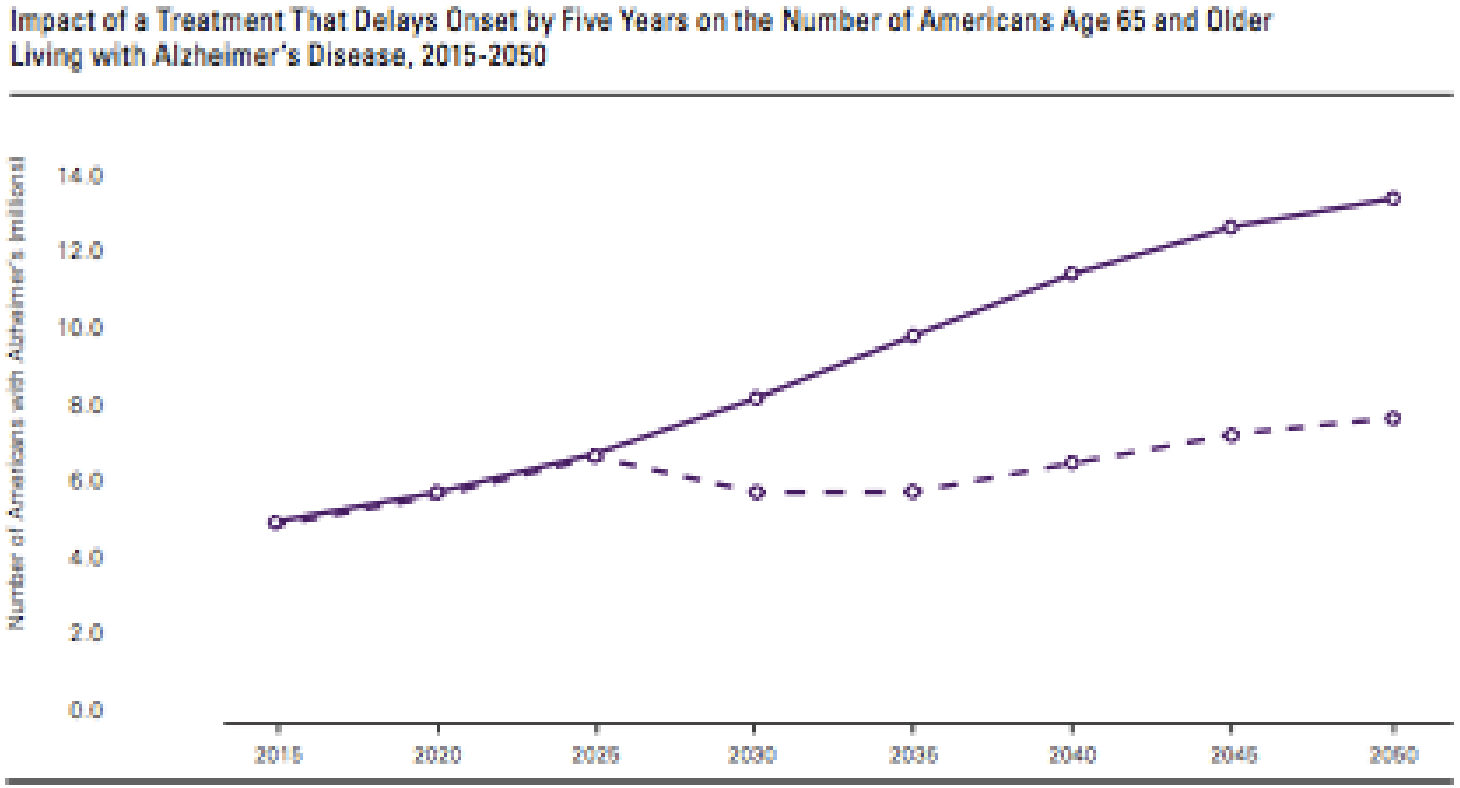

KEEP
CALM
AND
CURE
ALZHEIMER'S

Overview

- The scale of the problem
- Challenges
- Targets
- Track record
- The future

It’s a big problem

Effect of disease modification



Challenges

- Drug pipeline in CNS disorders
- Incomplete understanding of mechanisms
- Finding patient populations
  - Heterogeneity
  - Therapeutic nihilism
- What to measure?
  - Cognitive scales, activities of daily living
  - Measuring change in chronic conditions
- Duration of trials

Clinical Trials

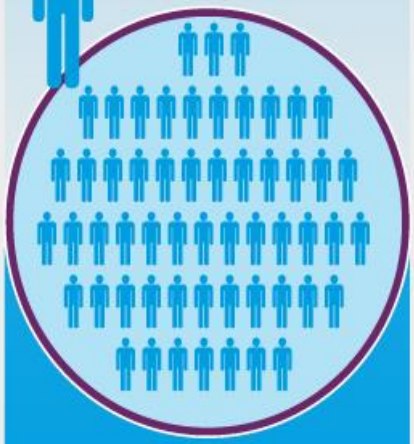
There are three main phases of clinical trials

Alzheimer's Research UK

The Power to Defeat Dementia

Phase I

Young healthy people
Small group size
(about 50)

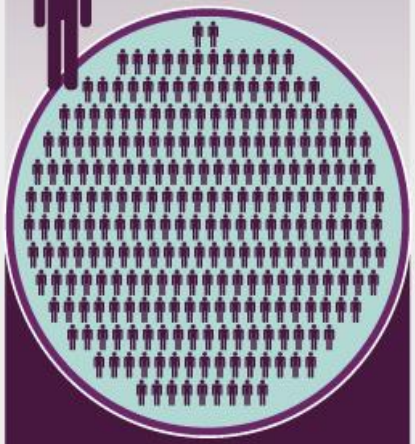


Tests

- Possible harm
- Side effects
- Dosage

Phase II

People affected by the disease
Larger group size
(up to 500)

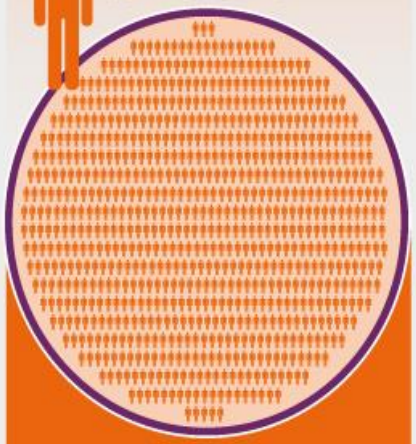


Tests

- Whether treatment is effective in patients
- Side Effects
- Against a dummy treatment (called a placebo)

Phase III

People affected by the disease
Larger group size
(up to thousands)



Tests

- Whether treatment is effective in patients
- Over longer periods over many different countries
- Often against other possible existing treatments

Treatment deemed safe / effective

Licensing

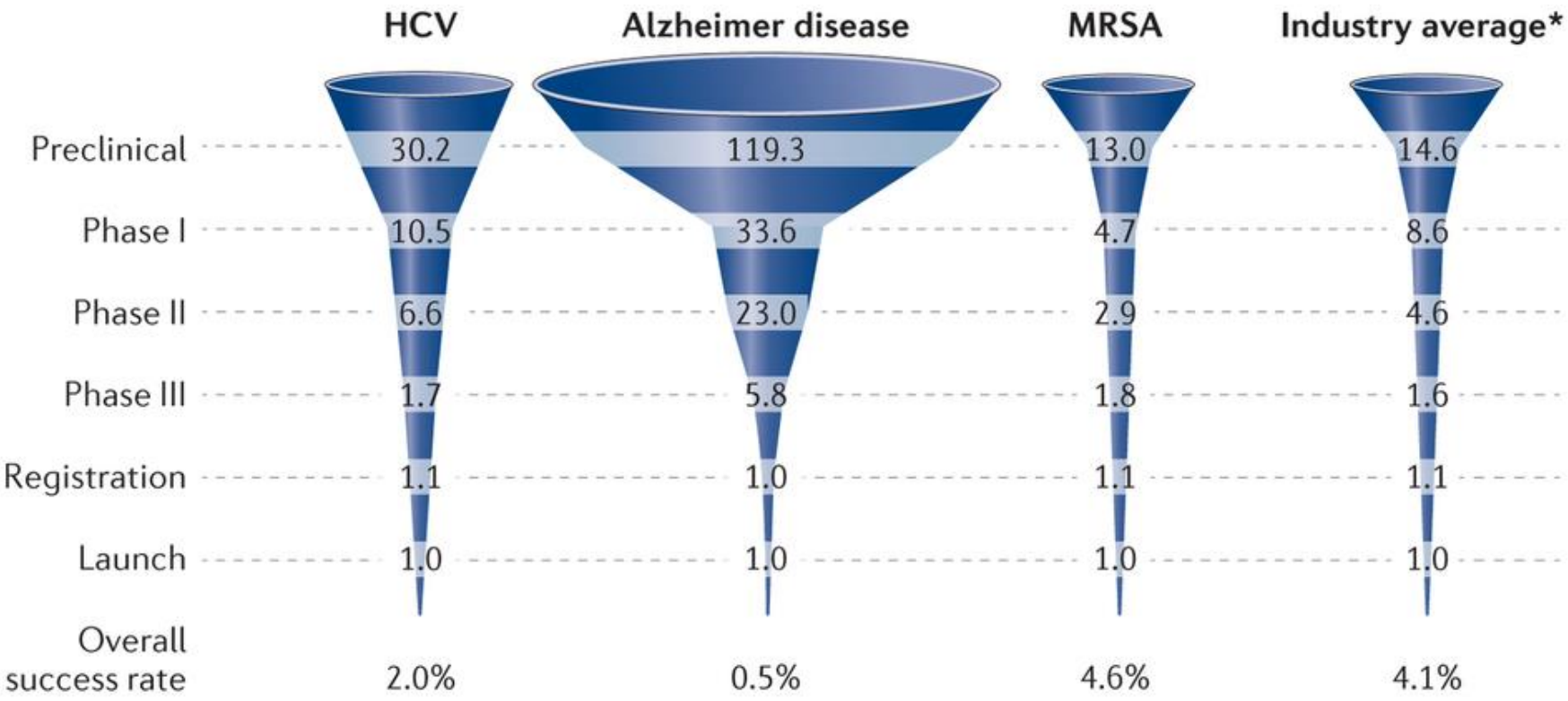
Treatment licensed, and benefits weighed up by NICE against costs and limitations to help guide use in the NHS

Phase IV

Tests over longer periods of time, in different groups of people and/or in combination with other treatments

Ten to fifteen years later

Pipeline, or funnel?



Nature Reviews | Drug Discovery

Challenges

- Drug pipeline in CNS disorders
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  - Therapeutic nihilism
- What to measure?
  - Cognitive scales, activities of daily living
  - Measuring change in chronic conditions
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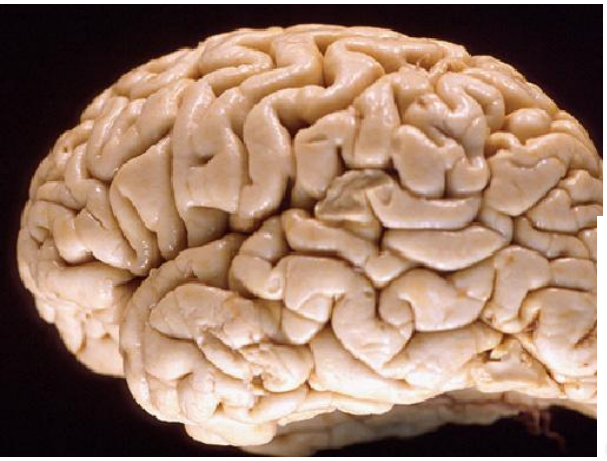
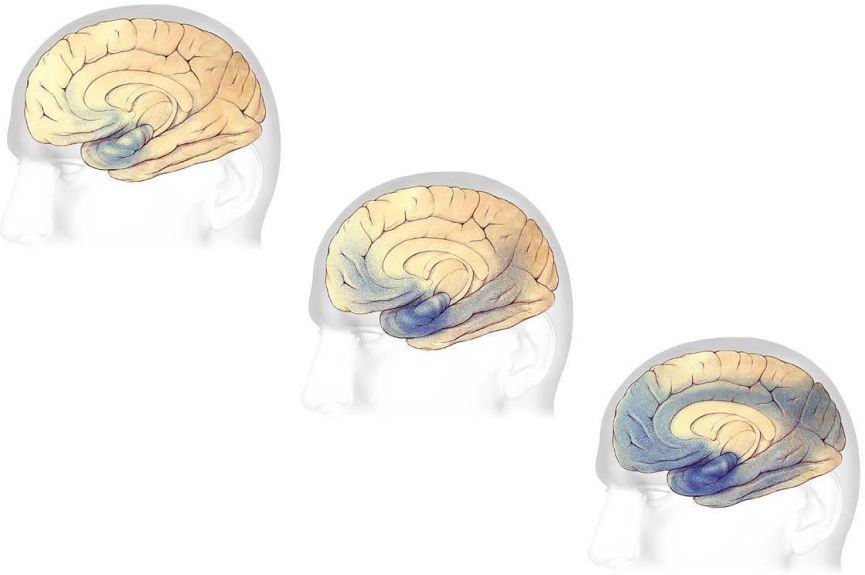
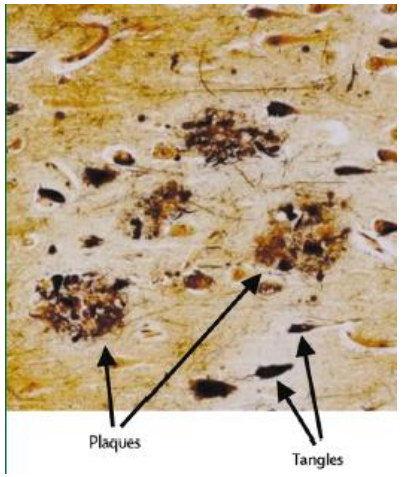
Pathology of Alzheimer's Disease

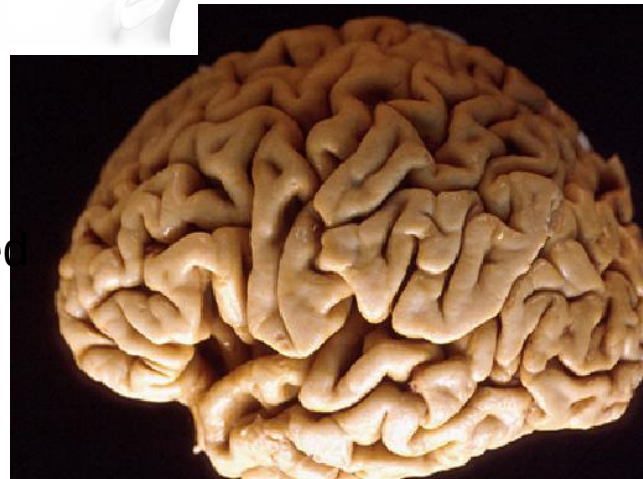






β Amyloid – plaques, extracellular
Tau – abnormally hyperphosphorylated tau → neurofibrillary tangles

Plus neuronal and synaptic loss



Alzheimer pathology

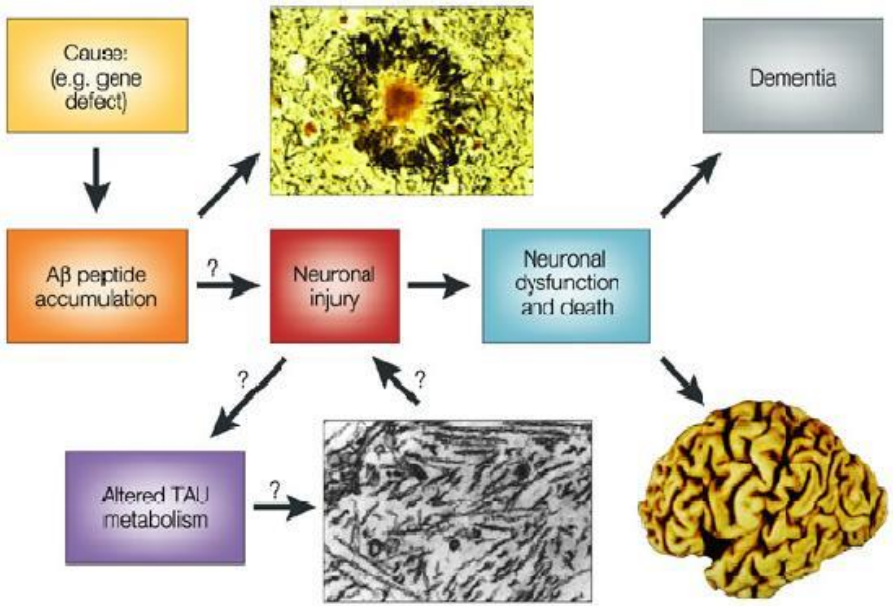
Tauists vs βAPtists

For the Tauists

Tangles correlate with dementia better than plaques

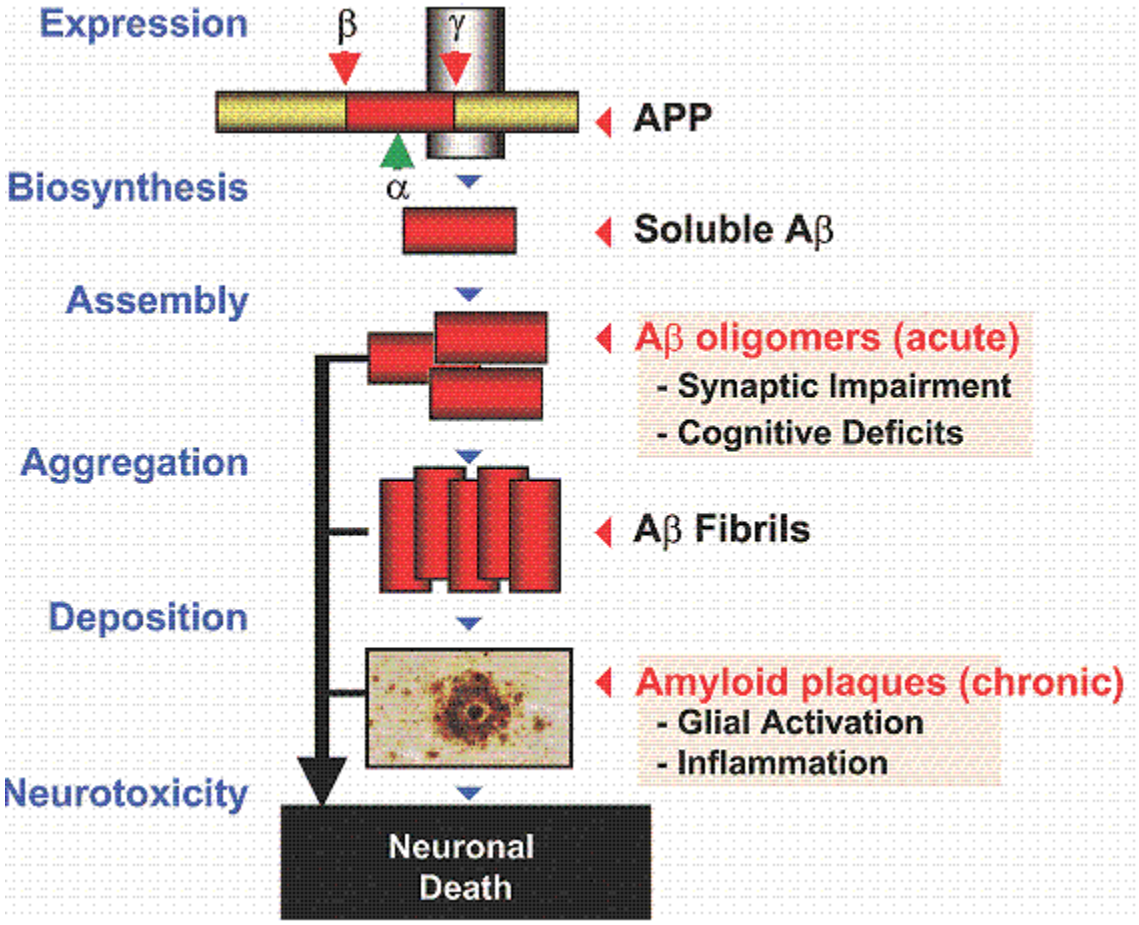
For the βAPtists

All familial AD mutations affect β- amyloid



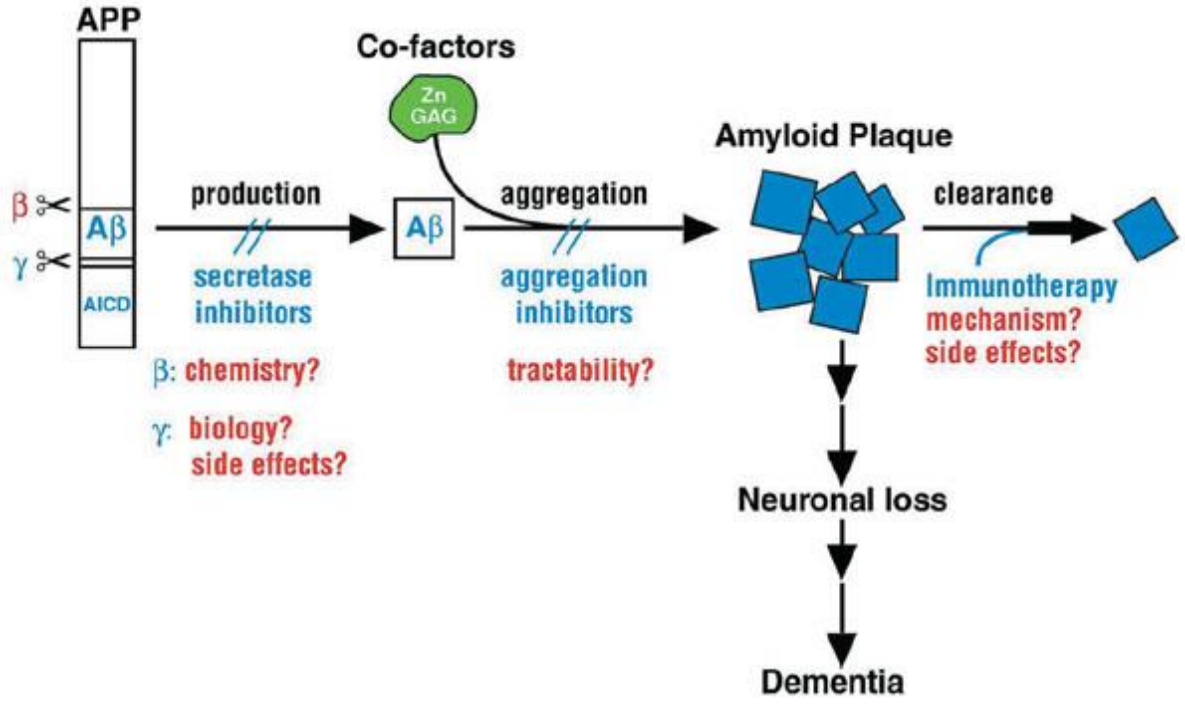
Alzheimer's disease

The amyloid cascade



Over the last decade, most of the money has been on amyloid

Therapeutic drug targets in AD



1. Decrease production of Aβ – secretase inhibitors
2. Prevent aggregation of toxic oligomers
3. Increase removal of toxic amyloid

Challenges

- Drug pipeline in CNS disorders
- Incomplete understanding of mechanisms
- Finding patient populations
  - Heterogeneity
  - Therapeutic nihilism
- What to measure?
  - Cognitive scales, activities of daily living
  - Measuring change in chronic conditions
- Duration of trials

Finding patient populations

- Do they have the disease that the drug is aimed at?
  - Pathology studies of MCI trial populations show > 30% don't have the disease
- Medical co-morbidities and caregivers
- Insight and capacity
- Long trials with complex assessments

Measuring change

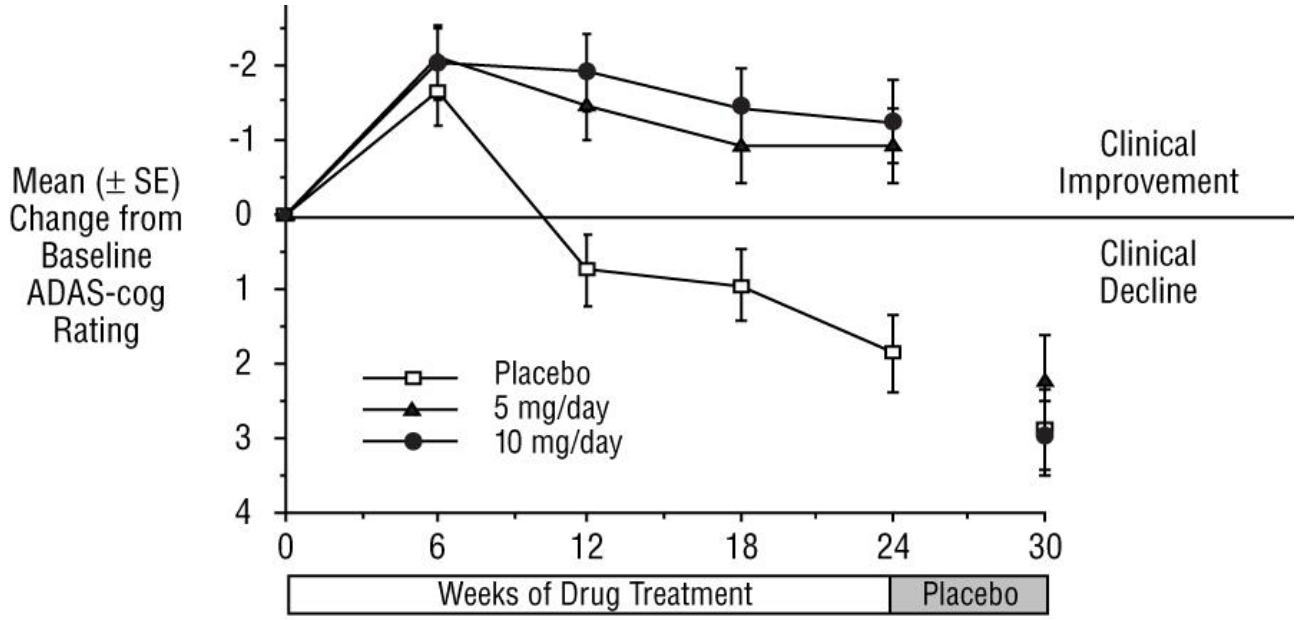


Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients

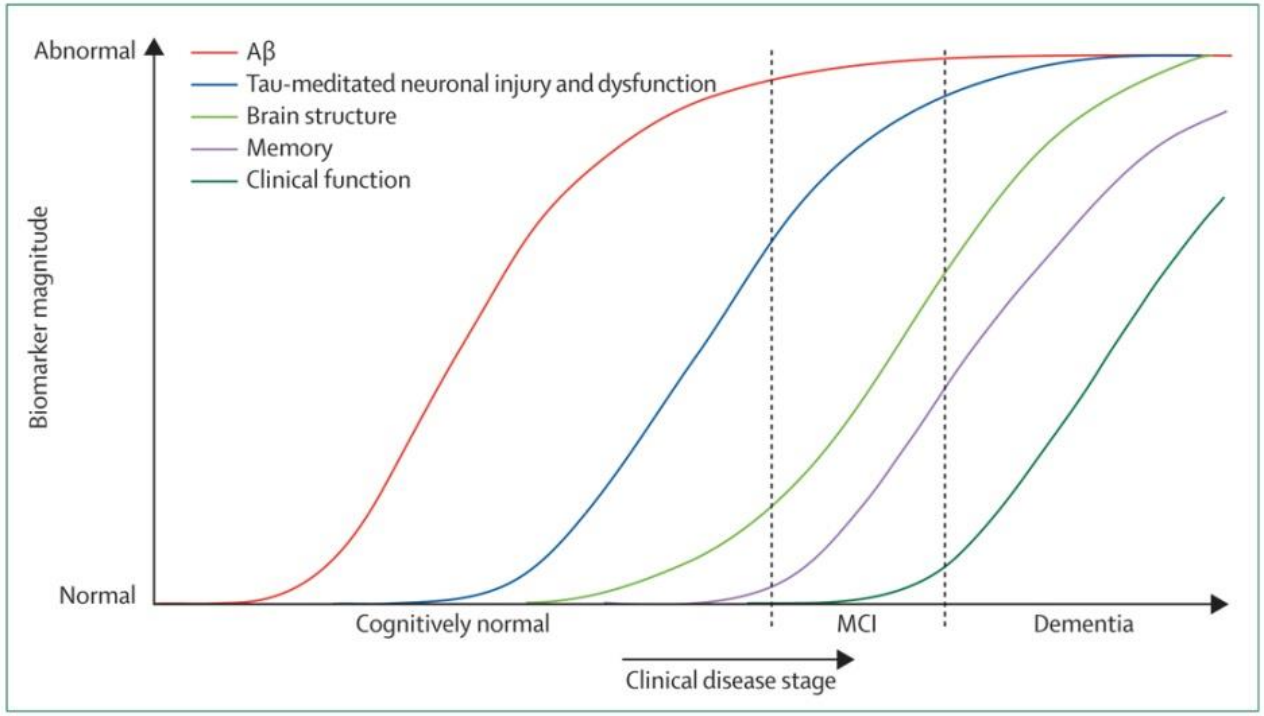
For acetyl cholinesterase inhibitor studies, change measured over 24 weeks with ADAS-cog.

Measuring change in disease modifying trials

- Earlier in course of disease, change is slower
  - Longer trials
  - Larger numbers
- For proof of disease modifying effect need cognitive and functional change as well as change in biomarker
  - Markers of neuronal loss e.g. MRI, FDG PET
  - Markers of amyloid e.g CSF, amyloid PET
  - Markers of tau e.g CSF, tau PET

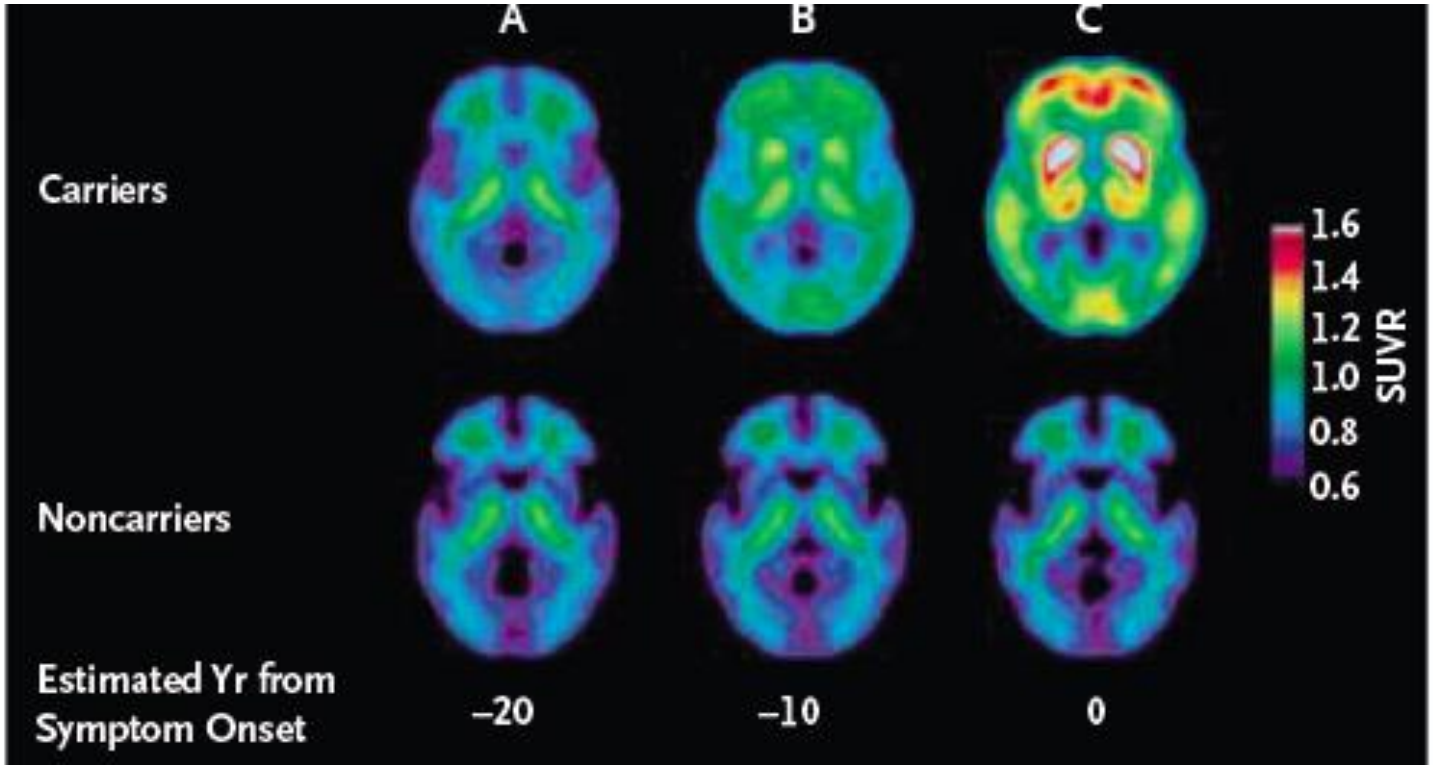
When does Alzheimer's Disease start?

- Amyloid deposition may occur 10-15 yrs before manifestation of dementia
- Tangle deposition probably later



Jack et al 2010

When does Alzheimer's Disease start?



Fibrillar amyloid deposition as measured by PET imaging in carriers of autosomal dominant AD mutations

Bateman et al NEJM 2012

Challenges

- Drug pipeline in CNS disorders
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  - Heterogeneity
  - Therapeutic nihilism
- What to measure?
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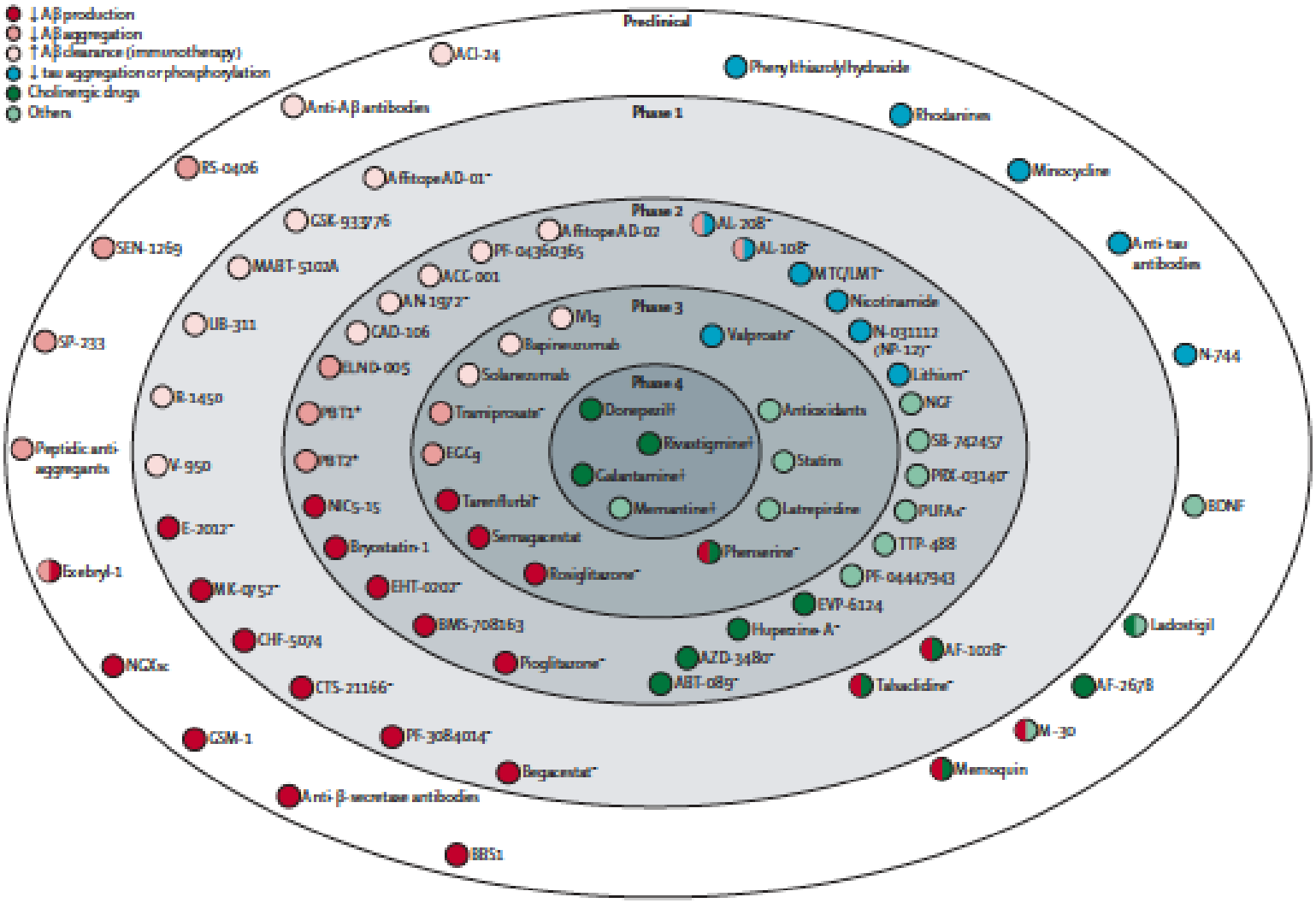
Drug development in Alzheimer's Disease



Track record

Agent	Target/Mechanism	Outcome
Non-Aβ		
Atorvastatin; Simvastatin	Cholesterol (HMG CoA reductase inhibitor)	Negative
NSAIDs	Inflammation	Negative
Rosiglitazone	Insulin (PPAR gamma agonist)	Negative
Latrepirdine	Mitochondrial function	Negative
Aβ		
AN1792	Amyloid immunoRx	Negative (AEs)
Tramiprosate	Amyloid aggregation	Negative
Tarenflurbil	Gamma secretase	Negative
Semagacestat; Avagacestat	Gamma secretase	Negative
Bapineuzumab	Amyloid immunoRx	Negative
Solanezumab	Amyloid immunoRx	Negative (+/-)
IVIG	Nonselective immunoRx	Negative
LY2886721	Beta secretase	Negative (AEs)

AE = adverse event

Table 1. Failure of AD Candidate "Disease Modifying" Therapeutics. Modified with permission from a presentation by Laurie Ryan, PhD, Division of Neuroscience, National Institute on Aging, Bethesda, Maryland.

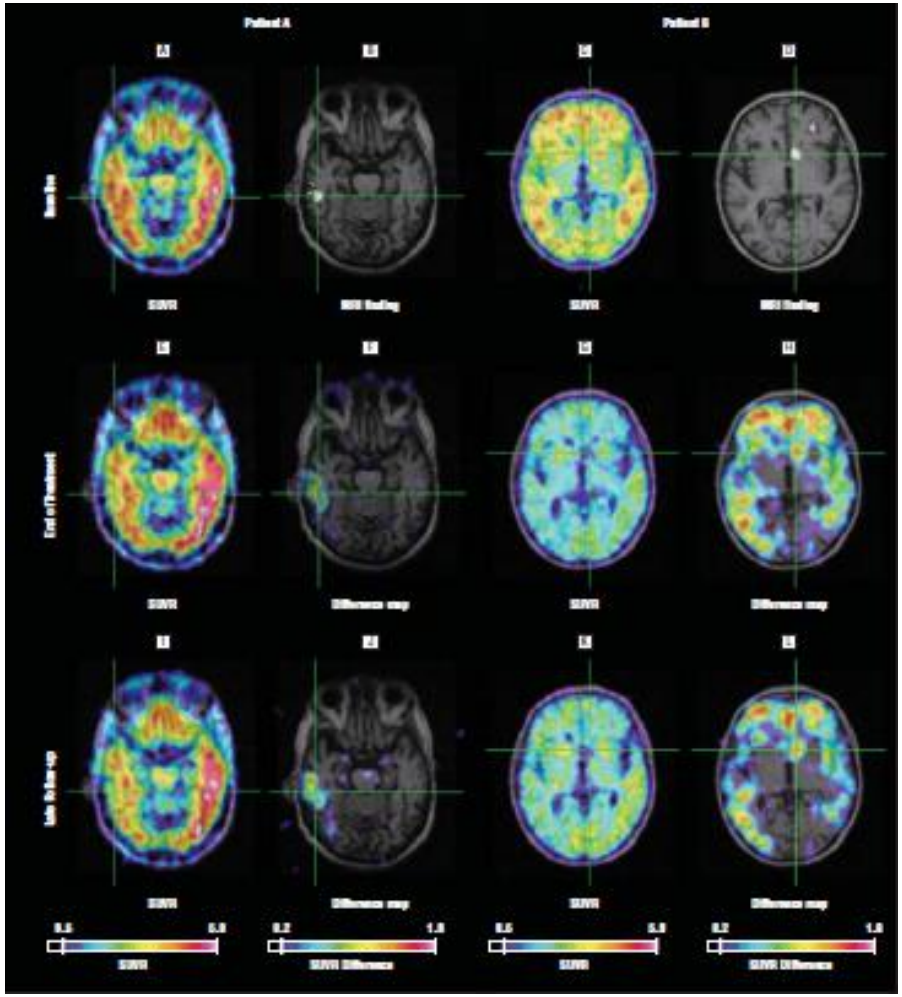
Main ongoing studies

Table 1 | **Current status of selected Alzheimer disease agents in development**

Drug	Developer	Mechanism of action	Indication	Highest stage
Gantenerumab (RO4909832)	Roche/Genentech	Aβ-specific mAb	Prodromal or mild AD	Phase III
Solanezumab (LY2062430)	Eli Lilly	Aβ-specific mAb	Mild AD	Phase III
Aducanumab (BIIB037)	Biogen Inc.	Aβ-specific mAb	Prodromal or mild AD	Phase III
Crenezumab	Roche/Genentech/ AC Immune	Aβ-specific mAb	Mild-to-moderate AD	Phase II
AAB-003 (PF-05236812)	Janssen/Pfizer	Aβ-specific mAb	Mild-to-moderate AD	Phase I
N3pG-Aβ (LY-3002813)	Eli Lilly	Aβ-specific mAb	Mild-to-moderate AD	Phase I
MEDI1814	AstraZeneca	Aβ-specific mAb	Mild-to-moderate AD	Phase I
CAD106	Novartis	Aβ vaccine	Mild AD	Phase II
ACI-24	AC Immune	Aβ vaccine	Mild-to-moderate AD; AD with Down syndrome	Phase I/II
ACI-35	Janssen/AC Immune	Anti-tau vaccine	Mild-to-moderate AD	Phase I
MK-8931	Merck & Co.	BACE1 inhibitor	Prodromal or mild-to-moderate AD	Phase III
AZD3293 (LY3314814)	AstraZeneca/ Eli Lilly	BACE1 inhibitor	Prodromal or mild AD	Phase II/III
E2609	Eisai	BACE1 inhibitor	Prodromal or mild-to-moderate AD	Phase II
JNJ-54861911 (ALZ2002)	Janssen	BACE1 inhibitor	Prodromal or mild AD	Phase II
TRx0237 (LMTX)	TauRx Therapeutics	Tau-aggregation inhibitor	Mild or mild-to-moderate AD; dementia	Phase III
Azeliragon (TTP488)	vTv Therapeutics	RAGE inhibitor	Mild AD	Phase III
Circadin (melatonin)	Neurim Pharmaceuticals	Unknown	Mild-to-moderate AD; sleep disturbances	Phase II
Resveratrol	ADCS/NIA	Unknown	Mild-to-moderate AD	Phase II

Why is it so difficult?

- No effect on target?
- Wrong target?
- Too late?
- Wrong dose?



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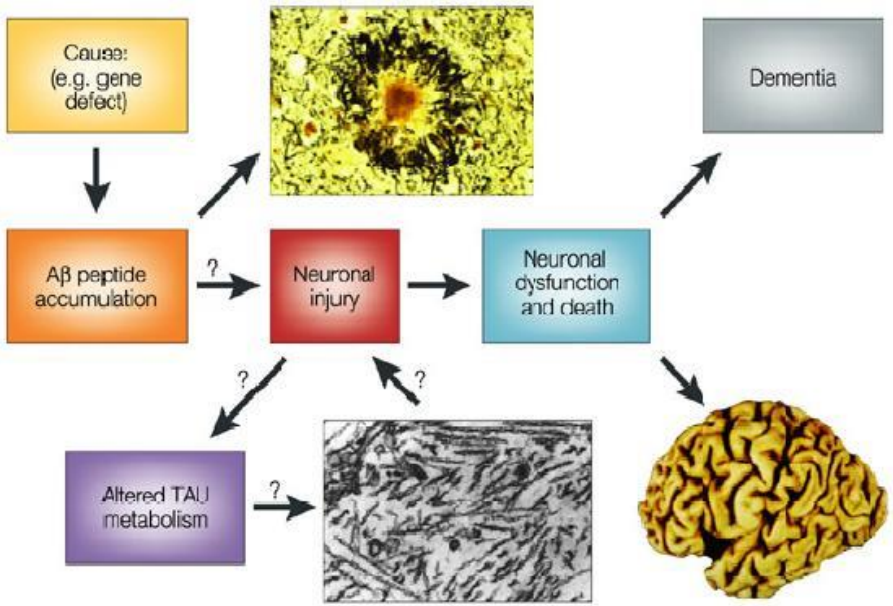
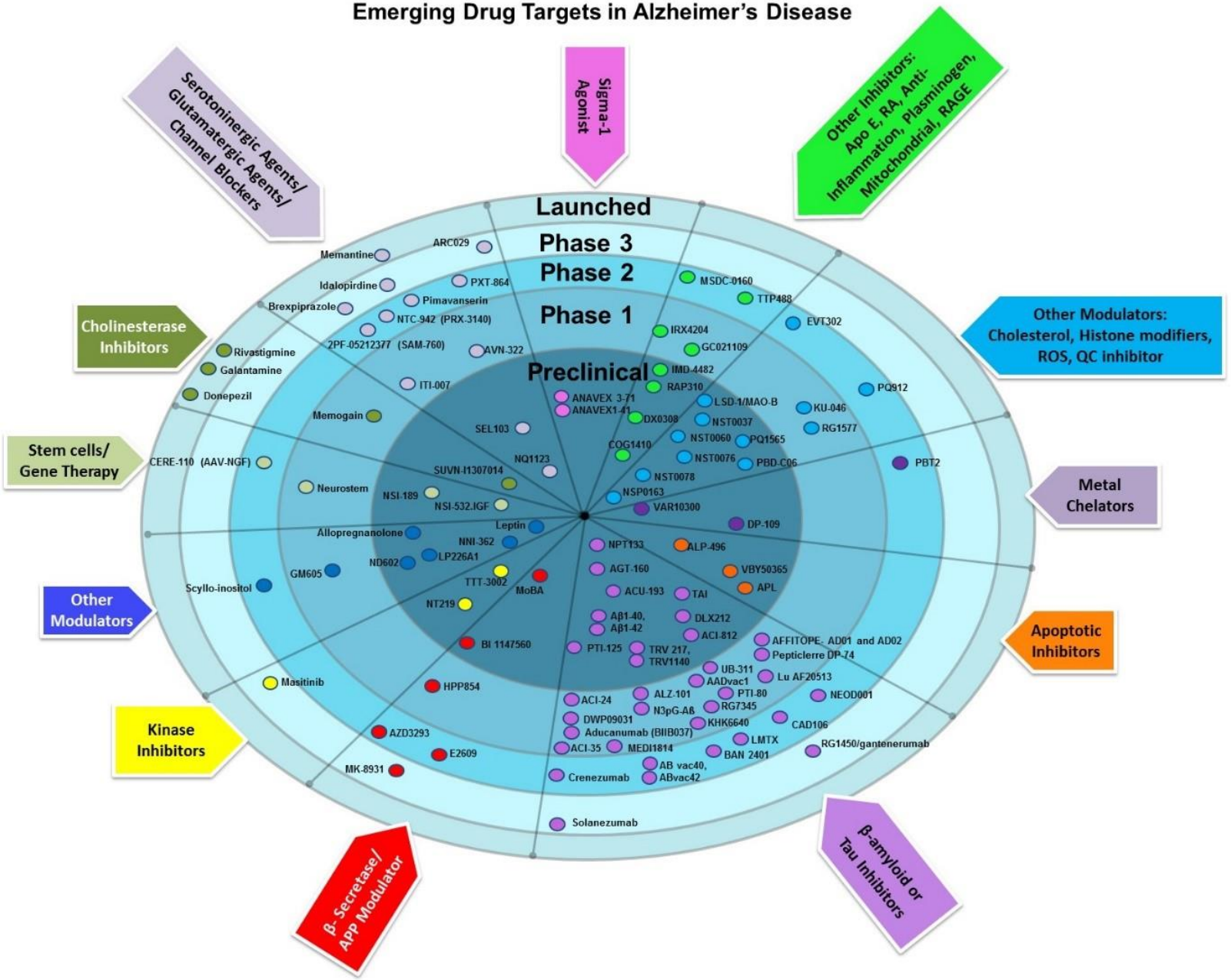
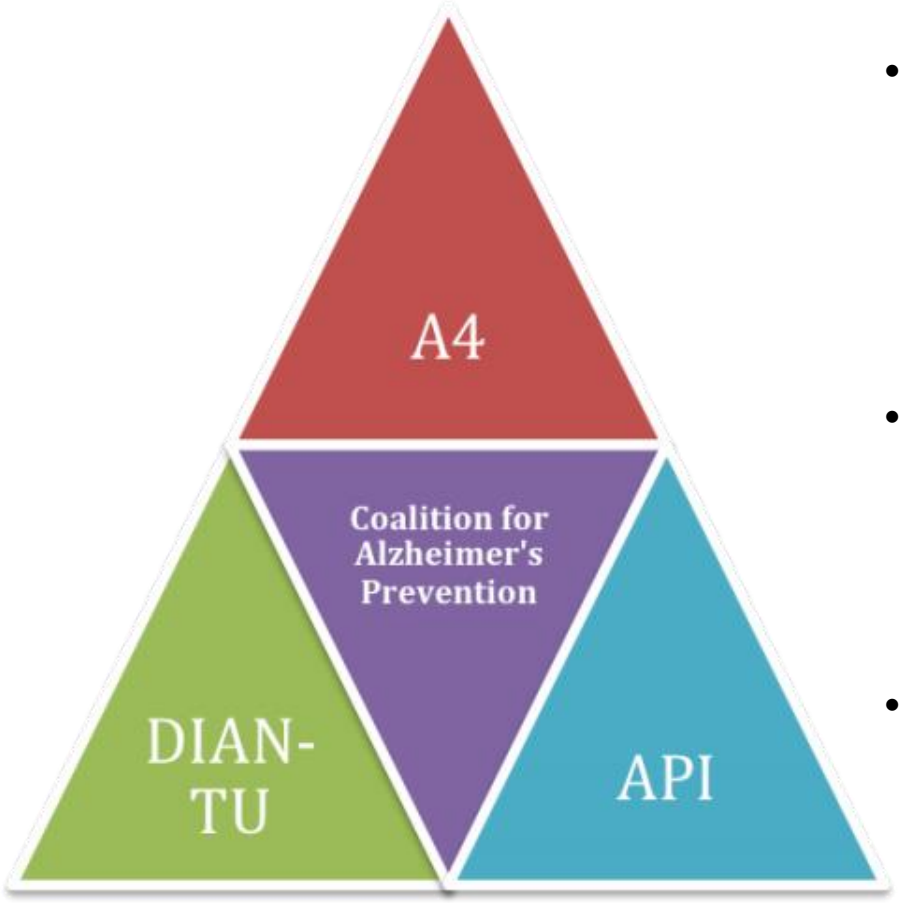


Emerging Drug Targets in Alzheimer's Disease



Preclinical trials



- DIAN
  - Dominantly Inherited Alzheimer Network
  - Monoclonal Abs in asymptomatic or mildly symptomatic carriers
- A4
  - 65-85, asymptomatic amyloid positive on amyloid PET
  - Monoclonal Ab for 3 years
- API – Apo E 4 trial. Apo E4 homozygotes have active abeta vaccine for 5 years

Why is it so difficult?

- No effect on target?
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- Too late?
- Wrong dose?

Why is it so difficult?

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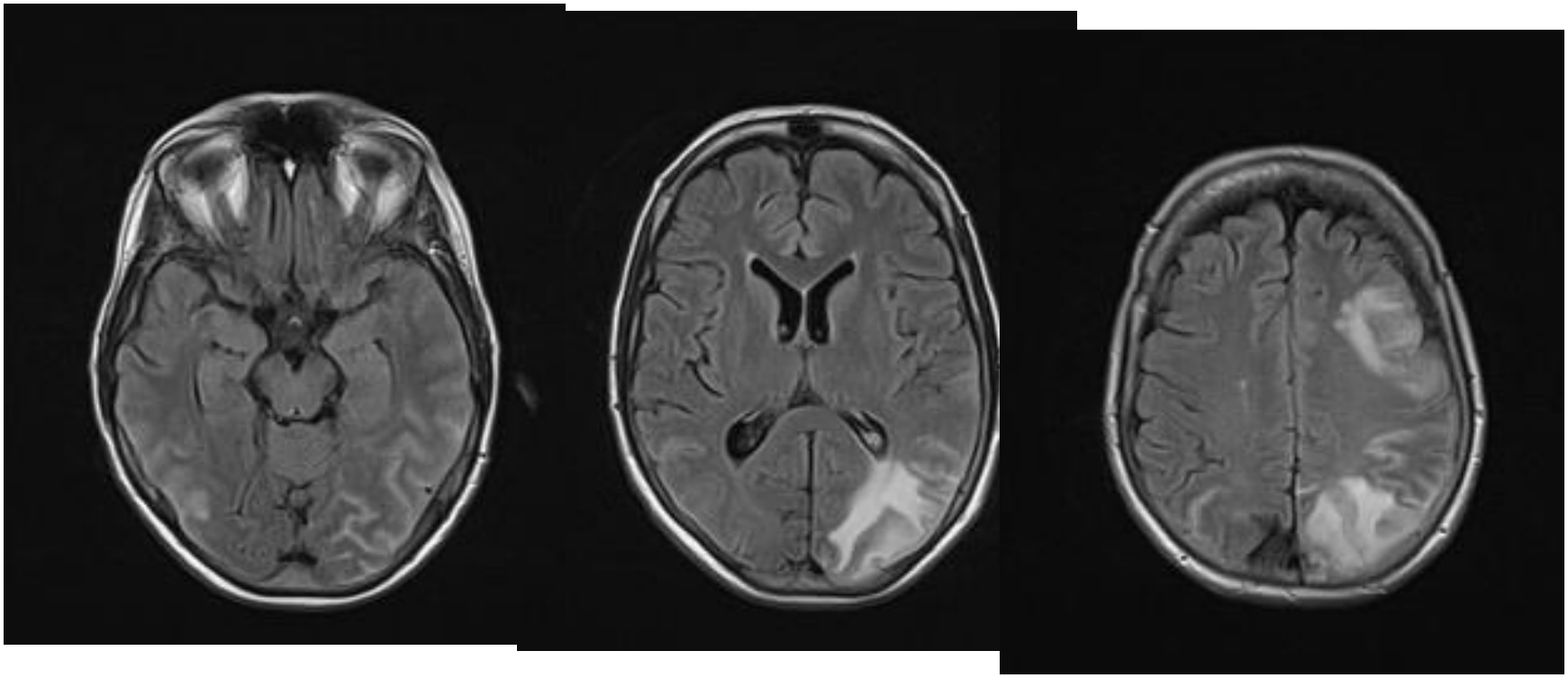
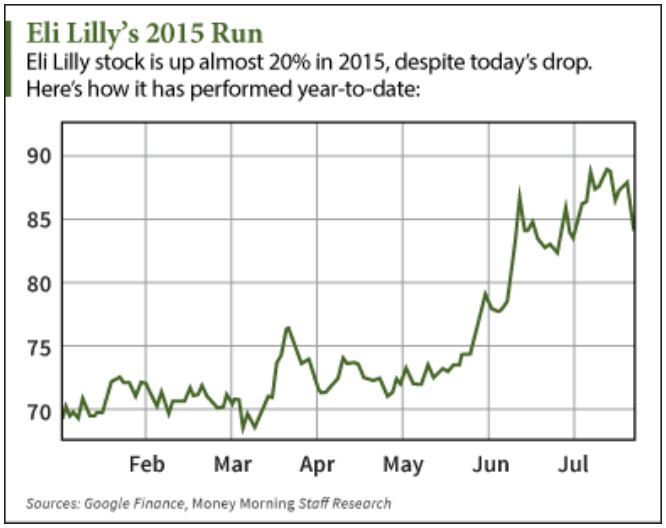
- Wrong target?
- Too late?
- Wrong dose?

ARIA

Amyloid Related Imaging Abnormalities

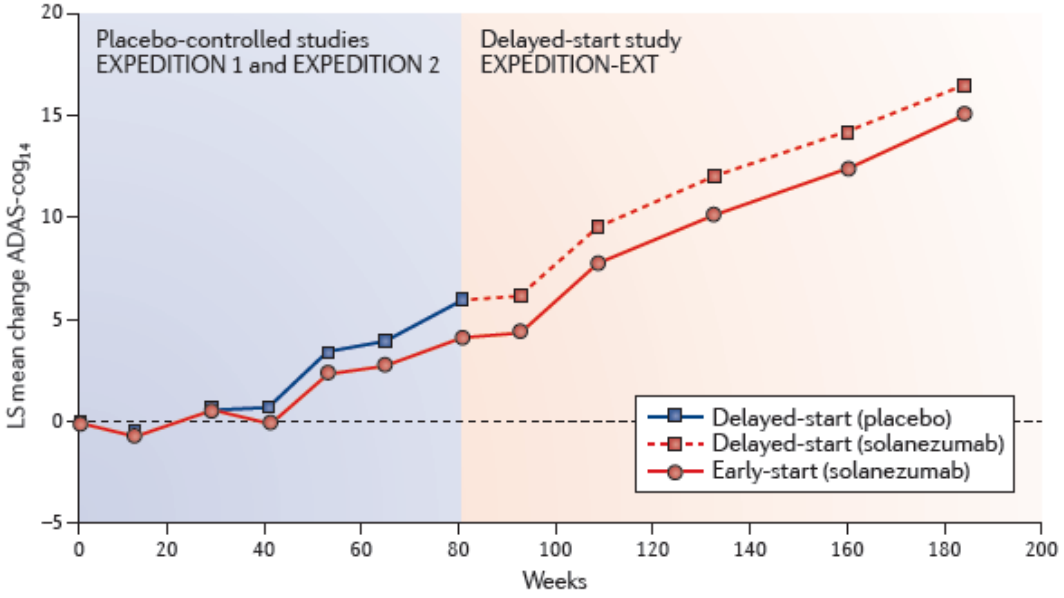


Glimmers of hope



The Telegraph

Solanezumab, the first drug to slow Alzheimer's Disease unveiled in landmark breakthrough



theguardian

Scientists appear to have broken a decades-long deadlock in the battle against Alzheimer's disease after announcing trial results for the first drug that appears to slow the pace of mental decline.

Reardon Nat Rev Drug Discovery 2015

Aducanumab

Treatment	MMSE Score Change at 54 Weeks	CDR-SB Score Change at 54 Weeks	Average Composite SUVR Change at 54 Weeks
Placebo (n = 40)	-2.81	1.87	"Virtually unchanged"
1 mg/kg (n = 31)	-2.18	1.72	-0.055
3 mg/kg (n = 33)	-0.70 (P < .05)	1.37	-0.135 (P < .001)
6 mg/kg (n = 30)	-1.96	1.11	-0.210 (P < .001)
10 mg/kg (n = 32)	-0.56 (P < .05)	0.63 (P < .05)	-0.268 (P < .001)