The Evolving Concept of Alzheimer's Disease

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Epochs of AD Research

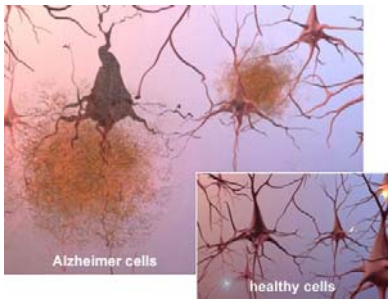
Epoch	Years	Key Event	Principles
Clinical Observation	1906-1960s	Alzheimer: links dementia to plaques & tangles	• "Strange Disease of the Cerebral Cortex" • Pre-senile dementia
Human Pathology	1960s-1990s	Blessed et al: Plaques & tangles are common in senile dementia	• Collapse of the age dichotomy • Convergence of Alzheimer's disease (pathology) and dementia of the Alzheimer type (clinical)
Animal models	1980s-current	Glenner et al: Amyloid is sequenced	• Amyloid biology is clarified • Genetics of autosomal dominant AD
Human Biomarkers	2000s-curent	Klunk et al: *in vivo* amyloid imaging	• Disease process has long silent period

Diagnostic schemes have evolved with the research

- DSM (1952) – Organic Brain Syndrome
- DSM-III (1980) Primary Degenerative Dementia
  - Senile vs. Presenile
- NINDS-ADRDA (1984) – Possible/Probable/Definite
- DSM-IV (1987) – Dementia of the Alzheimer Type
- NIA-AA (2011) – Separated pathology from dementia
  - Preclinical AD can now be defined
- DSM 5 (2013) – Major Neurocognitive Disorder
- Revised NIA-AA (2018) – Separate staging of pathology and clinical features (A-T-N)

Traditional view

Amyloid plaque damages brain cells



http://flippies.com/adflipoff/wp-content/plugins/RSSPoster_PRO/cache/5ccdd_cells.jpg

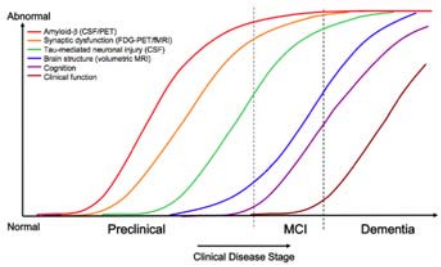
Newer view:

*Amyloid damage begins **before** the plaque forms*

http://www.sciencenews.org/pictures/031211/alzheimers_illustration_zoom.jpg

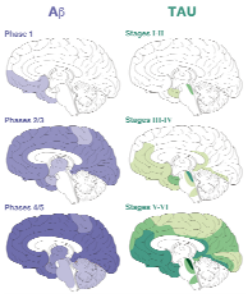
Preclinical Alzheimer disease

Amyloid and tau are temporally dissociated



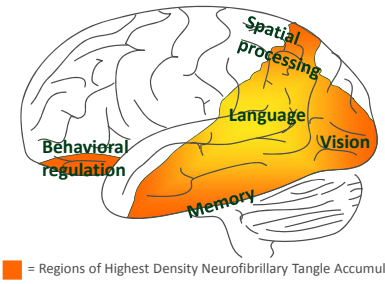
Sperling et al. Alzheimer's and Dementia, 2011;7:280-92.

Amyloid and tau are spatially dissociated



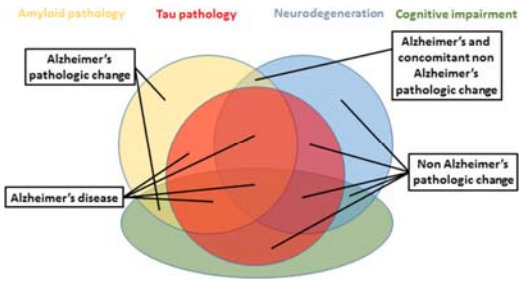
Brain. 2016;140(2):266-278

Tau distribution better explains symptom progression



= Regions of Highest Density Neurofibrillary Tangle Accumulation

The A-T-N schema



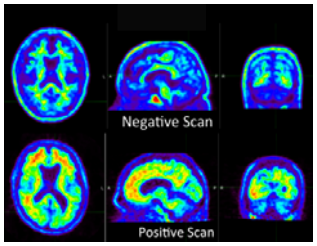
Jack CR et al, Alzheimer's & Dementia 2018;14:535-562.

Detecting the biomarkers

Amyloid PET

Evidence for Aβ pathophysiology

- Detects amyloid plaques
- In early onset autosomal dominant AD, becomes positive decades before symptoms
- FDA approved
- Essentially no insurance coverage
- Meaningful effect on therapeutic decision making (IDEAS study)



Next steps

Tau imaging

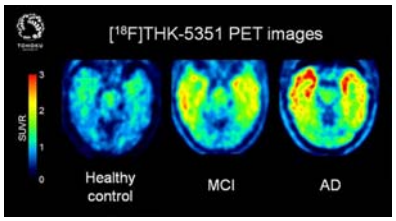
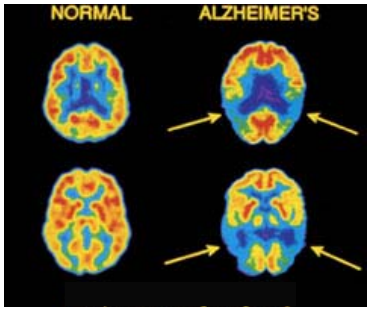


Image by Nobuyuki Okamura, Tohoku University via Alzforum.org

FDG-PET in AD

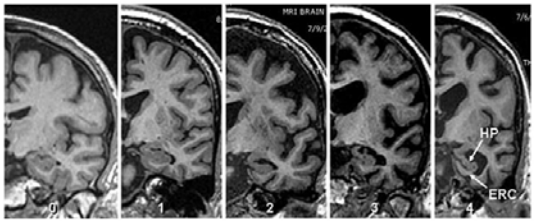
Evidence of neuronal injury

- Measures brain glucose metabolism
- FDA approved
- Very limited insurance coverage



Hippocampus Atrophy in AD

Evidence of neuronal injury



Duara R, et al *Front Aging Neurosci*. 2013;5:47

What about genetics?

Alzheimer genetics and amyloid

- Early onset AD is caused by autosomal dominant, highly penetrant, deterministic mutations
  - All result in amyloid overproduction
  - These mutations are found in less than 1% of all AD cases
    - Only 50% of Early onset, autosomal dominant AD
  - Onset in these cases is almost always before age 50
- Late onset AD has been linked to more than 30 genes
  - Most of these affect amyloid removal, not production
  - None contribute more than 20% of the variance
    - Most contribute <3% of the variance
- Thus, no genetic test can reliably predict most AD

Common "software" issues that mimic AD

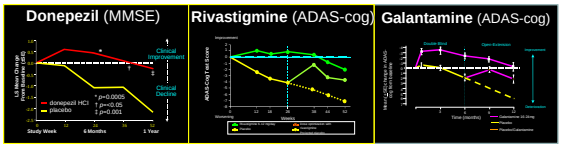
- Depression/Anxiety
- Sleep issues including OSA
- Pain/Pain medications

- These all tend to have bigger mismatches between
  - Complaints and scores
  - Complaints and daily function

Alzheimer Therapeutics in 2018

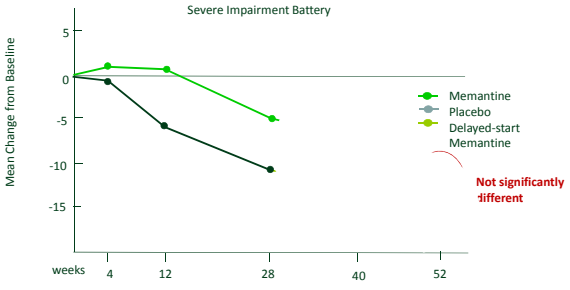
Cholinesterase Inhibitors

Stabilize cognition over one year



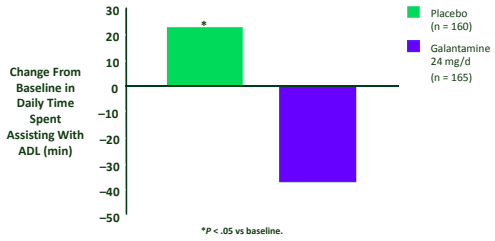
Among people with mild and moderate AD, treatment with any of the three drugs results in reduced loss of ability over one year.

Memantine in Moderate-Severe AD



Observed Cases; Reisberg et al. *Arch Neurol*. 2006;63:49-54

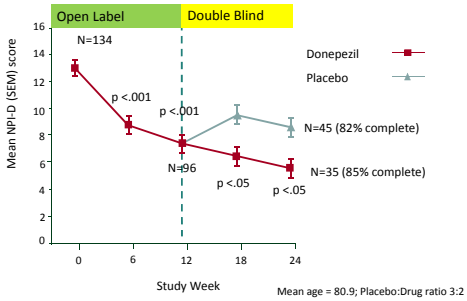
Drug Treatment Effects on Caregiver Time



Sano et al. *Int J Geriatr Psychiatry*. 2003;18:842-850 (I).

Drug Treatments and Caregiver Distress

Behavioral Symptoms



Mean age = 80.9; Placebo:Drug ratio 3:2

Holmes et al. *Neurology*. 2004;63:214-219 (I).

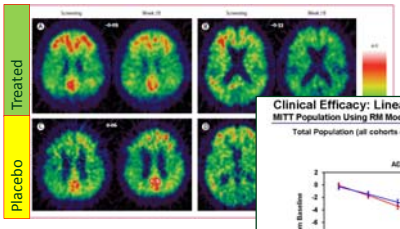
Delay to Nursing Home Placement (NHP)

- Eight (of 9) published studies report delayed admission or reduced risk for NHP with drug treatment
  - Risk is lowered by 28% at 1 year, 21% at 2 years, but there is no difference after three years[2]
- Caregiver support also delays NHP, but does not add to the medicine's effects[3]
- All delayed NHP results probably reflect access to high quality dementia care and good family support

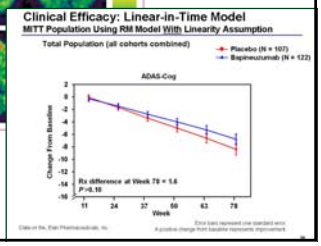
[1] Lopez et al. *JNNP* 2002;72:310-314 (II-2)
[2] Becker M. et al *ADAD* 2006;20:147-52 (II-2)
[3] Brodaty H. *Am J Geriatr Psychiatry*. 2009 ;17:734-43

Removing brain amyloid in AD dementia

Good News/Bad News



Anti-aβ antibodies successfully removed Aβ from the brain

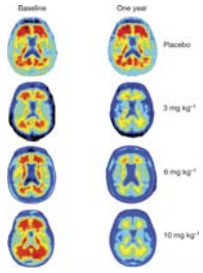


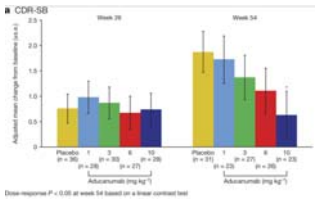
No clinical effectiveness
Substantial adverse effects

Rinne et al, *Lancet Neurology* 2010;9:363-72

Tantalizing hints of anti-Aβ success

Aducanumab treatment in early AD/MCI





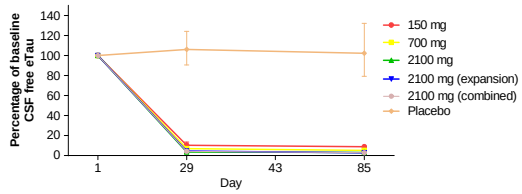
nature

September 1, 2016

Dose-related response in early AD

And now, preliminary indications of anti-τ efficacy

in patients with Progressive Supranuclear Palsy



Mean suppression of CSF free eTau by Biogen BIIB092 was ~90–96% (Day 29) and 91–97% (Day 85) at doses of 150–2100 mg (n = 31)

Boxer et al, AAN Annual Meeting presentation, 2018

Primary Prevention

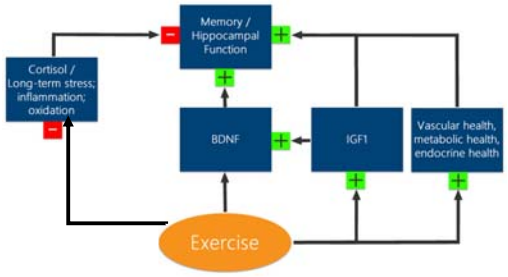
Lifestyle approaches to cognition and AD

Target	Observational Studies	Controlled Trials
Diet*	↓ Risk with high antioxidant and PUFA intake	Improved cognition and lower AD risk
Cognitive activity	↓ Dementia risk with high education and more cognitive engagement	Improved cognition and less decline
Physical* activity	↓ AD risk with high activity in mid & late life	Improved cognition with exercise

*Middleton & Jaffe, *Arch Neurol* 2009;66:1210-5

Exercise is the best supported lifestyle approach*

Multiple pathways for exercise to benefit



AAN Practice Parameter (MCI) 2017

Summary

- Alzheimer's disease definitions have been a moving target based on research successes (and failures)
- Current treatments are meaningful, but not sufficient to fully address patient or public needs
- Future treatments will likely need to start very early in the course
  - Treat amyloidosis and tauopathy to prevent neurodegeneration.
  - Biologics can provide proof of concept, but cost will likely limit long-term wide-ranging utility
- Risk-lowering lifestyle approaches offer promise