

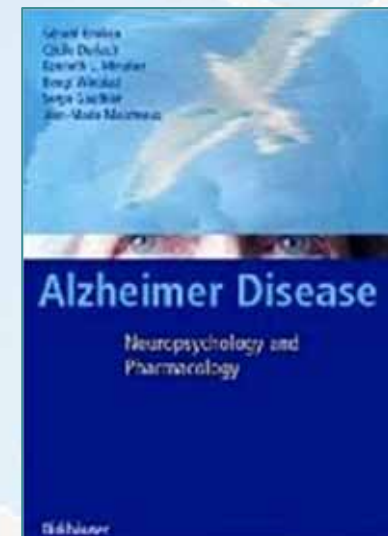
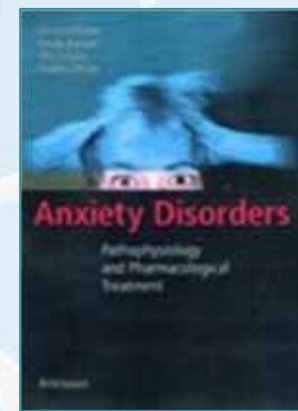
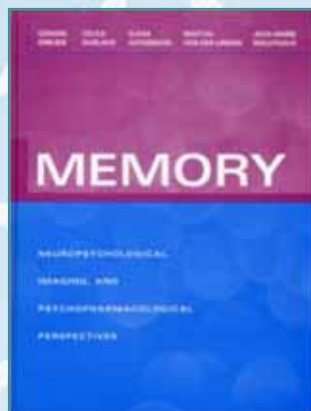
Treatment of Alzheimer's Disease: An update

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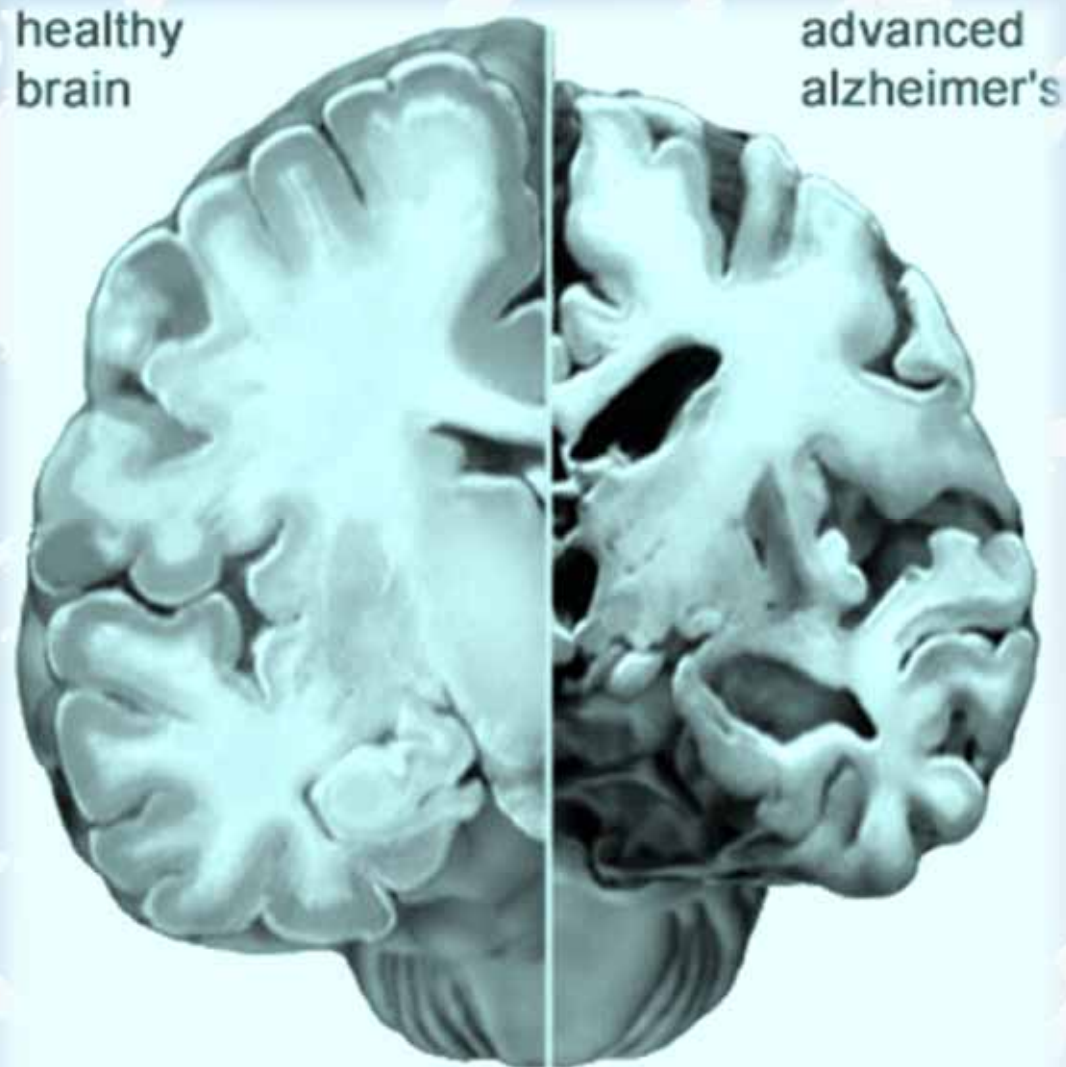
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Agenda

- 1. Alzheimer's Disease**
- 2. Main goals of treatment for AD**
- 3. Conclusions**

1. What is Alzheimer's Disease?



What is Alzheimer's Disease (AD)?

- A brain disorder named after German physician Alois Alzheimer who first described it in 1906
- A progressive and fatal brain disease
 1. Destroys brain cells, causing problems with memory, thinking and behavior severe enough to affect work, lifelong hobbies or social life
- No current cure
- An accelerating worldwide effort to find better ways to treat the disease, delay its onset, or prevent its development
- High Medical costs in the billions estimates



Natural history of AD



Gauthier (1996)

DIAGNOSTIC CRITERIA FOR PROBABLE AD IN 1984

Dementia established clinically, eg deficit in memory and one or more areas of cognition, interfering with daily life, progressing gradually

No disturbance of consciousness

Onset between 40 and 90 (below 65: early onset)

Absence of other brain or systemic disease that could account for the dementia

DIAGNOSTIC CRITERIA FOR PROBABLE AD IN 2011

Dementia established clinically, eg deficit in two or more areas or cognition, interfering with daily life, progressing gradually

No disturbance of consciousness

Any age

Absence of other brain or systemic disease that could account for the dementia

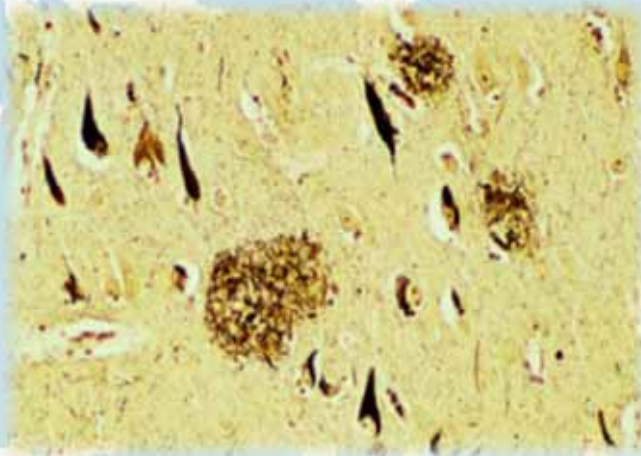
Optional evidence of AD pathophysiology using biomarkers

BIOMARKERS IN AD

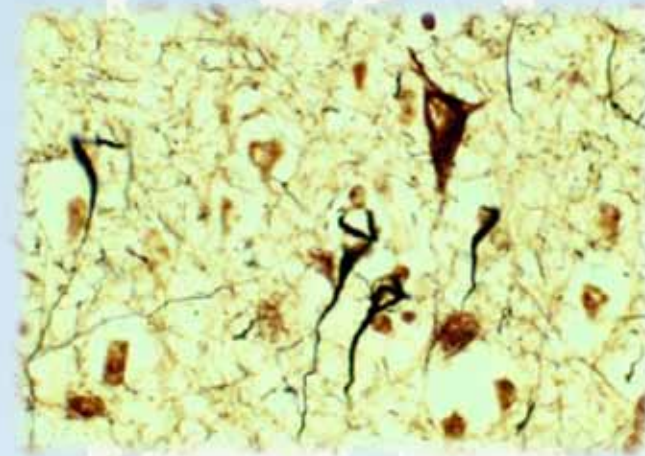
- Biomarkers of A β deposition
 - * spinal fluid A β levels (low)
 - * PET amyloid imaging (high)
- Biomarkers of neuronal injury
 - * spinal fluid tau levels (high)
 - * MRI looking at hippocampus, temporal lobe or whole brain (smaller)
 - * FDG-PET (areas of reduced metabolism)
 - * SPECT (areas of reduced blood flow)

Histological Hallmarks of AD

SENILE PLAQUES

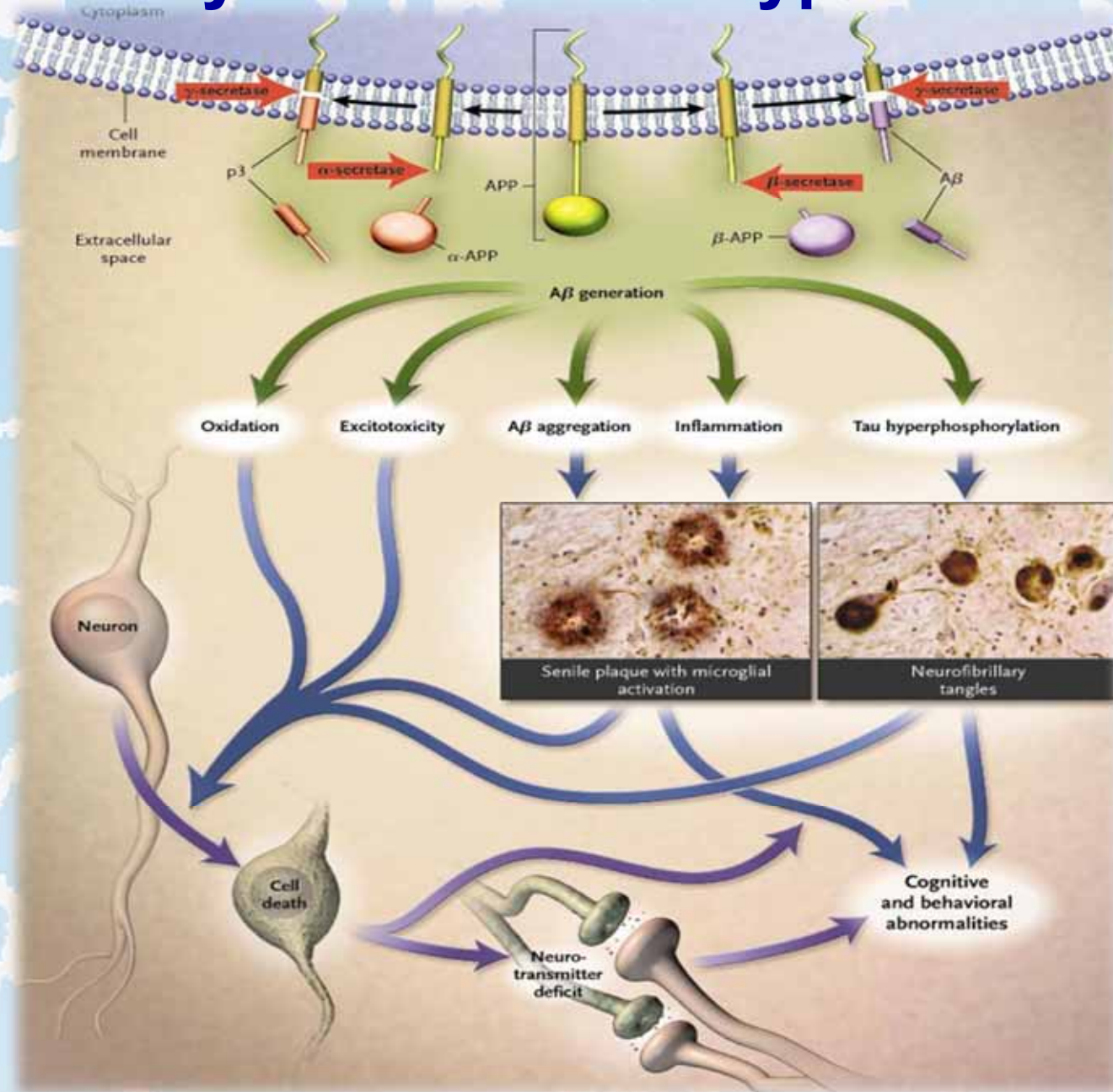


NEUROFIBRILLARY TANGLES



- In 1907, in the first report, Alois Alzheimer described senile plaques (SP) and neurofibrillary tangles (NFT)
- SP are found in neocortex, hippocampus and in several subcortical areas
- NFT density correlates with disease duration and severity of dementia

Amyloid Cascade Hypothesis



The A β cascade, which progresses from the generation of the A β peptide from the APP, through multiple secondary steps, to cell death, forms the foundation for current and emerging options for AD treatment.

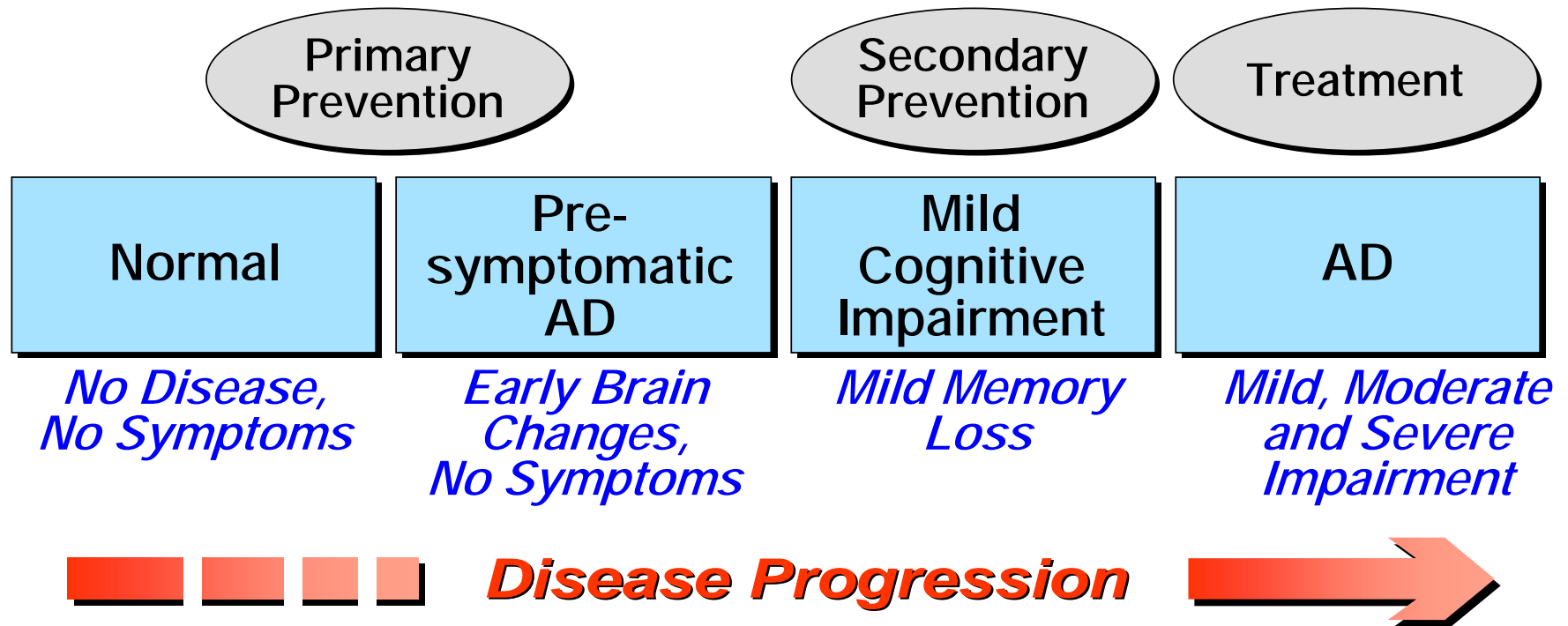
Case Example: Why Amyloid Matters

- Plaques are a hallmark of the illness
- The major (rare) causes of familial Alzheimer's all involve abnormal processing of the amyloid protein
- Leads to highly toxic intermediates
- Can we block this cascade?

2. Main Goals of Treatment for AD



AD Prevention Initiative



Goals for the Treatment of AD

- Improve memory
- Improve functional status
- Improve behavioral symptoms
- Slow progression
- Delay or prevent onset

Current Drug Treatments for AD

- Acetylcholinesterase inhibitors for mild to moderate AD
 - Tacrine (Cognex)
 - Donepezil (Aricept)
 - Rivastigmine (Exelon)
 - Galantamine (Reminyl)
- Neuroprotective agent for moderate to severe AD
 - Memantine (Namenda)

ONCE-A-DAY
ARICEPT
(donepezil HCl)
5-MG AND 10-MG TABLETS



NDC 0578-9929-18 Rx only
EXELON[®] PATCH
(rivastigmine transdermal system)
Each System Delivers 9.5 mg/24 hours
Contains 30 Systems NOVARTIS



Disease-Modifying Strategies

<u>Therapeutic Strategies</u>	<u>Approaches</u>
A β Production	<ul style="list-style-type: none">-γ secretase inhibitor-γ secretase modulators-α secretase modulators
A β Degradation	<ul style="list-style-type: none">- Somatostatin agonists
A β Aggregation	<ul style="list-style-type: none">- Aβ fibrillation inhibitors
Immunotherapy	<ul style="list-style-type: none">- Anti Aβ antibody- Immunisation against a fragment of Aβ
Protein Tau	<ul style="list-style-type: none">- GSK3β inhibitors
Inflammation	<ul style="list-style-type: none">- Nonsteroidal antiinflammatory

Anti Amyloid Therapy: Conclusions

- Many medications and immunotherapies exist that can alter the processing of amyloid in the lab and in animal models
- They have shown at least some ability to alter blood, spinal fluid, PiB, and pathological measures of different types of amyloid in normals and/or people with AD
- Effects on MRI, FDG PET, other biomarkers in humans unclear/unknown
- Dose ranges not established in all cases
- Clinical significance of encouraging proof of concept biomarkers remain unknown