Pharmacological treatment of Alzheimer’s disease

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The mainstay of treatment for Alzheimer’s disease is supportive care from family and other caregivers.
The nucleus basalis of Meynert shows a profound reduction of cholinergic neurons in Alzheimer’s disease

Whitehouse et al. Science 1982;215:1237
Cholinesterase inhibitors are a symptomatic treatment for Alzheimer’s disease

Mean change from baseline CDR-SB

Weeks of therapy

Placebo washout

Donepezil
Rivastigmine
Galantamine
Memantine

Approved therapies in AD (only used for the treatment of the dementia phase)

Cholinesterase inhibitors
NMDA receptor antagonist
Plaques rich in Aβ42 and neurofibrillary tangles rich in 3/4R tau aggregates are pathological hallmarks of Alzheimer’s disease.
In two phase 3 double-blind trials, anti-amyloid therapy with solanezumab failed to improve cognition or functional ability.

Caveats:
- Treatment started too late in the disease course
- AD diagnosis was clinical
- Drug not potent enough?

An effective treatment for Alzheimer’s disease will ideally target the earliest possible detectable abnormality.

Alzheimer’s disease biomarkers aid in patient selection for clinical trials

Brain MRI

Brain amyloid PET

Brain amyloid PET

Technical Results

<table>
<thead>
<tr>
<th>biomarker</th>
<th>concentration (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ42</td>
<td>230.95</td>
</tr>
<tr>
<td>T-Tau</td>
<td>910.5</td>
</tr>
<tr>
<td>P-Tau</td>
<td>115.1</td>
</tr>
<tr>
<td>ATI</td>
<td>0.18</td>
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</tbody>
</table>

Aβ42, tau and p-tau in CSF
A number of anti-amyloid therapies have failed to show benefits in clinical trials

Anti-amyloid treatments are focusing on reducing brain amyloid before AD symptoms begin.
Emerging anti-amyloid trials: press release May 10, 2019

• **A45** (pre-symptomatic AD)
  - Cognitively normal individuals with positive amyloid PET
  - BAN2401 (anti-amyloid monoclonal antibody) followed by elenbecestat (BACE inhibitor)

• **A3** (primary prevention)
  - Cognitively normal individuals with *negative* amyloid PET at risk of amyloid accumulation
  - Elenbecestat (BACE inhibitor) vs. placebo

• **Enrollment to begin in early 2020**

https://www.a3a45.org/
Treatment of Alzheimer’s disease: thinking out of the box

- Anti-tau monoclonal antibodies
- Anti-sense oligonucleotides

COR388: anti-gingipain protease inhibitor

Intensive blood pressure control

Transcranial photobiomodulation

Intensive blood pressure lowering prevents mild cognitive impairment and possible dementia and slows development of white matter lesions in brain: the SPRINT Memory and Cognition IN Decreased Hypertension (SPRINT MIND) study

https://www.alzforum.org/therapeutics/bib080
Kaba S, et al. Clinical Trials on Alzheimer’s Disease October, 24-27,2018
Chao LL. Photobiomodul Photomed Laser Surg 2019;37:133-141
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Conclusion

• Therapy development in Alzheimer’s disease is challenging, but it is an active field of research.
• Current approaches pursue early intervention.
• Novel emerging strategies will likely accompany anti-amyloid and anti-tau approaches in the future.