- **Alzheimer’s disease (AD)**
- **Parkinson’s disease (PD)**
- **Huntington’s disease (HD)**
- **Amyotrophic Lateral Sclerosis (ALS)**
- **Multiple Sclerosis (MS)**

  - **Common features:**
    - Progressive & irreversible loss of neurons
    - Characterized by protein aggregation
    - Selective vulnerability of neuronal populations
    - Role of genetics, environment
    - Current therapies address symptoms but do not affect disease processes
Proteinopathies
Accumulation of cellular proteins as aggregates
“Misfolding” of proteins

Correct folding
Maintain partial denaturation
Stabilize damaged proteins (chemical or physical stress)
Facilitate degradation
Selective Vulnerability

**ALZHEIMER:**
neuronal degeneration of the nucleus basalis of Maynert, of the hippocampus and of the cortex (non-uniform neuronal loss in various brain structures)
Selective Vulnerability

**PARKINSON**: degeneration of dopaminergic neurons of the substantia nigra
Selective Vulnerability

**HUNTINGTON** Disease:

degeneration of

Caudate-Putamen

neurons
Selective Vulnerability

Multiple Sclerosis (MS)

Chronic autoimmune disease characterized by demyelination of neurons

https://www.beaumont.org/conditions/multiple-sclerosis
Selective Vulnerability

Amyotrophic Lateral Sclerosis (ALS)

Degeneration of upper motor neurons (brain) & lower motor neurons (spinal cord)

Also know as: Lou Gehrig’s disease & Charcot’s disease

alsa.org/site/PageServer?pagename=ALSA_Disease_Process_ALS
Alzheimer Disease
Alois Alzheimer

Birth: Jun. 14, 1864
Death: Dec. 19, 1915

3 November 1906 would be the first time the pathology and the clinical symptoms of presenile dementia would be presented together Franz Nissl

Mrs. Auguste Deter
Alzheimer’s Disease Symptoms

Cognitive
- Memory loss
- Absence of logical thoughts
- Confusion
- Disorientation

Behavioral
- Agitation / anxiety
- Delusions, hallucinations
- Depression
- Insomnia
- Poor attention

GRADUAL ONSET AND CONTINUING PROGRESS
Mini-Mental State Exam (MMSE)

Exam consists of questions referring to seven different cognitive areas:
- orientation in time
- orientation in space
- word registration
- attention and calculation
- recalling
- language
- constructive praxia (finalized gestures)

**Scoring**
- 30 normal
- Slight 21-26
- Moderate 10-20
- Moderate-Severe 10-14
- Severe < 10
Origin of Alzheimer Disease
Origin of the disease

1. Mutation in APP gene-presenelin 1, presenelin 2 or Apolipo protein (APOE4) gene
   - Amyloid precursor protein (APP)
   - sAPP
   - Change in cleavage pattern by secretase
   - Aβ 1-42 (easily aggregate)

2. Immunal response
   - Release cytokines and microglia on identifying plaque
   - Hyperphosphorylation of tau
   - Neuron infected by spirochetes, Chlamydia and HSV-1

3. Mutation in tall gene or dysregulation of kinase-overexpression of Denticelless (DTL) encoding protein CD2, activates CDK (cyclin dependent kinase)
   - Hyper phosphorylation of Tau
   - Decrease affinity to microtubule.
   - Tau form Neuro Fibrillary Tangles and deposit in cytosol.

4. ROS, inflammation & degeneration.
   - Increase in cytotoxic bile acid (deoxycholic acid) which crosses BBB
   - Distubance in gut micro flora
   - Metal ions bind to Aβ plaque
   - Oxidative changes
   - Zn, Cu
Alzheimer’s Disease Pathology

Accumulation of protein aggregates outside & inside neurons

**Amyloid plaques** (senile) located outside neurons; composed of amyloid beta protein (A-beta) derived from processing **amyloid precursor protein (APP)** by secretases; gene chromosome 21

**Neurofibrillary tangles** located inside neurons; composed of **Tau protein**, which normally interacts with microtubules; gene chromosome 17
1. Inibizione secretasi β
2. Inibizione secretasi γ
3. Aumento secretasi α
4. Aumento eliminazione amiloide Aβ42
Importance of microglia and astroglia

Figure 1. Signaling pathways of microglia modulators and astrocyte modulators. (A) Signaling pathways in microglia; (B) signaling pathways in astrocytes. Created with BioRender.com. *TREM2—triggering the receptor expressed on myeloid cells 2, TLR—Toll-like receptor, CSF1R—colony-stimulating factor-1 receptor, JAK—Janus kinase, STAT3—signal transducer and activator of transcription 3, NFAT—nuclear factor of activated T cells, NFκB—nuclear factor-kB, NLRP3—nod-like receptor family pyrin domain containing 3, MAPK—mitogen-activated protein kinase, P2Y1R—P2Y1 purinoreceptor.
I microtubuli forniscono un supporto strutturale e rappresentano la via lungo la quale vengono trasportate sostanze nutritive e altre molecole. Sono costituiti da tubulina, una proteina a cui TAU si lega.

Nella malattia di Alzheimer la quantità e il tipo di TAU prodotti sono in qualche modo alterati oppure si modifica il tipo di legame fra TAU e tubulina. Il risultato è che si accumulano filamenti di TAU attorcigliati, che danneggiano i microtubuli cambiandone la forma e bloccandone il funzionamento. Questi aggregati soffocano anche i neuroni.
Alzheimer Disease and Acetylcholine
Acetylcholinesterase (AChE)

1. Acetylcholine (ACh) is made from choline and acetyl CoA.
2. In the synaptic cleft, ACh is rapidly broken down by the enzyme acetylcholinesterase.
3. Choline is transported back into the axon terminal and is used to make more ACh.

Butyrylcholinesterase (BuChE)

It increases with the progress of the disease, while it is low in physiological conditions.

Cholinesterase enzymes carry out a peptidase action of APP, contributing to the formation of plaques.
THERAPY

SYMPTOMATIC therapy

- SPECIFIC DRUGS (ACE inhibitors, NMDA antagonists)
- ASPECIFIC DRUGS
  - NOOTROPICS (Piracetam, Ginko)
  - ANTIPSYCHOTICS

Lack of drugs that lead to regression of the disease

B secretase inhibition

Y secretase inhibition
Increased α-secretase
Increased amyloid elimination Aβ42
Memantine
- NMDA non-competitive antagonist
  Side effects: dizziness, vomiting, increased blood pressure, epilepsy

Donepezil
- Selective inhibitor of ACE in the CNS (does not act on butyrylcholinesterase)
- Long half-life, Improvement of cognitive symptoms
  **Low side effects** (ulcer, disturbance conduction Atrio-Ventricular, respiratory disturbance)

**RIVASTIGMINE AND GALANTAMINE**
They have similar effects to donepezil (shorter duration of action)
Side effects: vomiting, diarrhea, ulcer

Tacrine
- Side effects: abdominal cramps, nausea, anorexia, increased transaminases, hepatotoxicity, short duration of action
### TABLE 3
Adverse effects of cognitive enhancers: Percent of patients affected

<table>
<thead>
<tr>
<th></th>
<th>Cholinesterase inhibitors</th>
<th>NMDA receptor antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donepezil</td>
<td>Galantamine</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>3%–19%*</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>5%–15%*</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td>2%–8%</td>
<td>7% (decreased appetite)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>3%–9%*</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td>2%–14%</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>3%–10%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>2%–8%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>1%–8%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Bradycardia</strong></td>
<td>≥ 1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>11%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

* *Dose-related.*

*NMDA = N-methyl-d-aspartate*
<table>
<thead>
<tr>
<th>Dementia category</th>
<th>Global Deterioration Scale (stages 1–7)</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not demented</td>
<td>1 No cognitive impairment</td>
<td>No indication for cognitive enhancers</td>
</tr>
<tr>
<td></td>
<td>2 Very mild decline: age-associated cognitive impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Mild cognitive impairment, minor neurocognitive decline</td>
<td></td>
</tr>
<tr>
<td>Mild dementia</td>
<td>4 Decreased knowledge of current and recent events</td>
<td>Cholinesterase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Decreased ability to travel, handle finances, and manage basic activities of daily living</td>
<td></td>
</tr>
<tr>
<td>Moderate dementia</td>
<td>5 Unable to recall a major relevant aspect of their current life, an address or telephone number of</td>
<td>Cholinesterase inhibitors with or without an</td>
</tr>
<tr>
<td></td>
<td>many years, or the names of close family members</td>
<td>NMDA receptor antagonist</td>
</tr>
<tr>
<td></td>
<td>Basic activities of daily living begin to be impaired</td>
<td></td>
</tr>
<tr>
<td>Severe dementia</td>
<td>6 Occasionally forgets the name of the spouse or caregiver on whom he or she is entirely dependent</td>
<td>Cholinesterase inhibitor (donepezil) with or</td>
</tr>
<tr>
<td></td>
<td>Unaware of all recent events and experiences in their lives</td>
<td>without an NMDA receptor antagonist</td>
</tr>
<tr>
<td></td>
<td>Most basic activities of daily living impaired</td>
<td></td>
</tr>
<tr>
<td>Advanced dementia</td>
<td>7 Cannot speak or walk, has incontinence and difficulty swallowing</td>
<td>No randomized controlled trials in stage 7</td>
</tr>
</tbody>
</table>

NMDA = N-methyl-D-aspartate
Directions

- Do not use AchE inhibitors in combination (memantine only)
- Titration of the drug in the patient
- AchE inhibitors in mild and moderate forms
- After 3 months it is continued only if stable or improved patient
OTHER DRUGS

Anxiolytics, Antidepressants, Antipsychotics (symptoms)

DIHYROERGOTAMIN, IDERGINE: Brain vasodilator

PIRACETAM, ANIRACETAM
Nootropics increase glutamate release (little effective in AD)
Side Effects of dell’acetylcholinesterase (AchE) inhibitors

CYP 3A4, 2D6

**Inhibitors:**
- Itraconazole
- Erythromycin
- Fluoxetine

**Inductors:**
- Rifampicin
- Phenytoin
- Carbamazepine
- Alcohol

Fatigue
Insomnia
New therapies for Alzheimer Disease
Strategies In Treatment

- Peptidomimetics
- Immuno Therapy
- FDA approved medicine
- Gene Therapy
- Metal chelators
- Prebiotics, probiotics & exercise.

Strategies In Early Detection

- Biomarkers
- Blood and Urine
- CSF Proteins
- Genetic Materials
- MCI Biomarkers
- Brain Lipids Biomarkers

ALZHEIMER

Brain Imaging
Artificial Intelligence
Theranostics
eg. NIR
Beta-site APP cleaving enzyme 1 (BACE1)

- Amyloid plaques, cell death, other features of Alzheimer's disease
- Aβ oligomer
- Alternate BACE1 proteins
- BACE1 mRNA
- BACE1 micro-RNA gene
- BACE1 antisense gene
- Cell membrane
- Cytoplasm
- Nucleus

Receptor of advanced glycation end products (RAGE)

- BBB
- AGES
- Aβ
- RAGEs
- Senile plaques
- Activated Microglia
- IL-1, 6
- TNF-α
- ROS
- Tau
- Neurofibrillary tangles (NFTs)

Glycogen Synthase Kinase (GSK)

Beta Amyloid Protein (AB)
Peroxisome Proliferator-Activated Receptors (PPARs)
<table>
<thead>
<tr>
<th>Name of the Drug</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Clinical Trial</th>
<th>Reason for Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verubecestat</td>
<td>Merck</td>
<td>β-site amyloid precursor protein-cleaving enzyme 1 (BACE 1) inhibitors</td>
<td>EPOCH trial APECS trial</td>
<td>No effect on slowing the progression of AD</td>
</tr>
<tr>
<td>Lanabecestat</td>
<td>Astra Zeneca &amp; Eli Lilly</td>
<td>BACE 1 inhibitors</td>
<td>AMARANTH and DAYBREAK-ALZ</td>
<td>Failure of interim futility analysis</td>
</tr>
<tr>
<td>Atabecestat</td>
<td>Janssen</td>
<td>BACE 1 inhibitors</td>
<td>EARLY</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td></td>
<td>Eli Lilly</td>
<td></td>
<td></td>
<td>nativé decline</td>
</tr>
<tr>
<td>Azeliragon</td>
<td>vTv Therapeutics</td>
<td>Receptor for Advanced Glycation End products (RAGE) inhibitor</td>
<td>STEADFAST (Phase III)</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Takeda and Zinfandel</td>
<td>Peroxisome Proliferator-Activated Receptor γ (PPAR-γ)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Idalopirdine</td>
<td>Lundbeck &amp; Otsuka</td>
<td>5HT6 antagonist</td>
<td>STARSHINE, STARBEAM, STARBRIGHT (Phase III)</td>
<td>Did not improve cognition</td>
</tr>
</tbody>
</table>
Immunotherapy
Active or Passive Immunization

- **Active immunization**: $A\beta$-42 can stimulate B-cells, T-cells and microglia for immune response

- **Passive immunization**: administration of monoclonal antibodies (mAb)
<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism</th>
<th>Phase of Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACI-24</td>
<td>Cause production of antibodies against Aβ without activating inflammatory cells.</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ACI-35</td>
<td>Liposome based vaccine which generates antibodies against phosphorylated tau.</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ABvac40</td>
<td>Targets C-terminus of Aβ40</td>
<td>Phase 2</td>
</tr>
<tr>
<td>AADvac-1</td>
<td>Consist of Peptide (KDKNKHKVPGGGS) which generate antibodies against tau.</td>
<td>Phase 3</td>
</tr>
<tr>
<td>CAD106</td>
<td>Virus based active vaccine which target Aβ without activating T cells.</td>
<td>Phase 2</td>
</tr>
<tr>
<td>LuAF20513 (engineered mixed peptide antigen)</td>
<td>Generate anti Aβ antibodies without microglial activation.</td>
<td>Phase 1</td>
</tr>
<tr>
<td>DNA based vaccine</td>
<td>Translation of Aβ based DNA leads to generation of antibodies.</td>
<td>Early stage of development</td>
</tr>
</tbody>
</table>

### Passive Immunotherapeutic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Phase of Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>Monoclonal antibody against Aβ</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Crenezumab</td>
<td>Humanised monoclonal antibody which mainly identifies polymorphic form of Aβ</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>Binds to Aβ and induce phagocytosis by activating microglia.</td>
<td>Phase 3</td>
</tr>
<tr>
<td>BAN2401</td>
<td>Preferentially binds to soluble photosfibrils of Aβ</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Bapineuzumab (Humanised form of murine monoclonal antibody)</td>
<td>Target N- terminal region of Aβ</td>
<td>Failed in clinical trials</td>
</tr>
<tr>
<td>Solancumab</td>
<td>Targets monomeric and non-fibrillary form of Aβ peptides</td>
<td>Phase 3</td>
</tr>
<tr>
<td>BIIB092</td>
<td>Targets N terminal fragment of tau</td>
<td>Phase 2</td>
</tr>
<tr>
<td>C2N 8E12</td>
<td>Targets extracellular tau aggregates.</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>