NEURODEGENERATIVE DISEASES
Neuro

- 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

Enhancement of Production

Loss of Clearance
Intra-neuronal deregulation:
- Autophagy
- Unfolded protein stress response

Extra-neuronal deregulation:
- Interaction among neurons, astrocytes, and microglia
- Phagocytic clearance
- Autoimmunity
- BBB/CSF transport

Intra- and Extra-neuronal
Misfolded Protein Precipitation

PROTEINOPATHIES

PROTEIN MISHFOLDING MECHANISMS

PROTEIN MISHFOLDING MECHANISMS

MISFOLDED PROTEINS

Frontotemporal Lobar Degeneration

Amyotrophic Lateral Sclerosis

Multiple System Atrophy

Parkinson’s Disease

Lewy Body Dementia

Alzheimer’s Disease

Aβ
Tau

α-Synuclein

Tau
TDP-43
FUS

TDP-43
FUS
SOD1

Amino acid hydrophobicity
Ubiquitination (HSP)
Selective Vulnerability

Alzheimer’s disease (AD)

Neuronal degeneration of the nucleus basalis of Meynert, hippocampus and cortex - with non-uniform neuronal loss in various brain structures
Selective Vulnerability

Parkinson’s disease (PD)
Degeneration of dopaminergic neurons of the substantia nigra in the midbrain
Selective Vulnerability

Huntington’s disease (HD)
Degeneration of neurons of caudate-putamen (striatum)

https://www.openaccessgovernment.org/hunttings-disease-hd-research/107601/
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
Multiple Sclerosis (MS)

Chronic autoimmune disease characterized by demyelination of neurons of CNS

https://www.beaumont.org/conditions/multiple-sclerosis
Alzheimer’s Disease (AD)
3 November 1906 would be the first time the pathology and the clinical symptoms of presenile dementia would be presented together
Franz Nissl
## Alzheimer’s Disease Symptoms

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Behavioral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory loss</td>
<td>Agitation / anxiety</td>
</tr>
<tr>
<td>Absence of logical thoughts</td>
<td>Delusions, hallucinations</td>
</tr>
<tr>
<td>Confusion</td>
<td>Depression</td>
</tr>
<tr>
<td>Disorientation</td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Poor attention</td>
</tr>
</tbody>
</table>

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
<table>
<thead>
<tr>
<th>Maximum Score</th>
<th>Patient's Score</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5</td>
<td>“What is the year? Season? Date? Day? Month?”</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>“Where are we now? State? County? Town/city? Hospital? Floor?”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient’s response is used for scoring. The examiner repeats them until patient learns all of them, if possible.</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“I would like you to count backward from 100 by sevens.” (93, 86, 79, 72, 65, ...) Alternative: “Spell WORLD backwards.” (D-L-R-O-W)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Earlier I told you the names of three things. Can you tell me what those were?”</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Repeat the phrase: ‘No ifs, ands, or buts.’”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Take the paper in your right hand, fold it in half, and put it on the floor.” (The examiner gives the patient a piece of blank paper.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please read this and do what it says.” (Written instruction is “Close your eyes.”)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please copy this picture.” (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)</td>
</tr>
<tr>
<td>30</td>
<td>TOTAL</td>
<td></td>
</tr>
</tbody>
</table>
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
Amyloid precursor protein (APP) & production of Aβ42

https://www.cellsignal.com/science-resources/amyloid-beta-protein
Tau Protein & AD Pathology

Tau Protein & AD Pathology

https://doi.org/10.1016/j.ijbiomac.2020.07.327
1. Inhibition β secretase (BACE 1)
2. Inhibition γ secretase
3. Augment α secretase
4. Augment elimination amyloid Aβ42
Alzheimer’s Disease and Acetylcholine
Acetylcholine Life-Cycle & Synapse

1. Acetylcholine (ACh) is made from choline and acetyl CoA

2. In the synapse, ACh is rapidly broken down by the enzyme acetylcholinesterase (AChE)

3. Choline is transported back into the axon terminal and used to make more ACh

Alzheimer’s Disease Therapy

Lack of drugs that lead to regression of the disease

β secretase inhibition
Y secretase inhibition
Increased α secretase
Increased elimination Aβ42

Symptomatic therapy

SPECIFIC DRUGS (AChE inhibitors)

ASPECIFIC DRUGS

-NOOTROPICS (Piracetam, Ginko)

-ANTIPSYCHOTICS
# TABLE 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proprietary name (date approved)</th>
<th>Indications</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholinesterase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept (1996), generics available</td>
<td>Mild to moderate disease (5–10 mg), moderate to severe disease (10–23 mg)</td>
<td>Tablets, disintegrating tablets</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon (2000), generics available</td>
<td>Mild to moderate disease</td>
<td>Tablets, oral solution, transdermal patch</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne (2001), generics available</td>
<td>Mild to moderate disease</td>
<td>Immediate-release tablets, oral solution, extended-release tablets</td>
</tr>
<tr>
<td><strong>N-methyl-D-aspartate receptor antagonist</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>Namenda (2003), generics available</td>
<td>Moderate to severe disease</td>
<td>Tablets, oral solution</td>
</tr>
<tr>
<td><strong>Combination drug</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil + memantine</td>
<td>Namzaric (2014), generics available</td>
<td>Moderate to severe disease</td>
<td>Extended-release capsules</td>
</tr>
<tr>
<td>Dementia category</td>
<td>Global Deterioration Scale (stages 1–7)</td>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Not demented</td>
<td>1 No cognitive impairment</td>
<td>No indication for cognitive enhancers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Very mild decline: age-associated cognitive impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Mild cognitive impairment, minor neurocognitive decline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild dementia</td>
<td>4 Decreased knowledge of current and recent events</td>
<td>Cholinesterase inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased ability to travel, handle finances, and manage basic activities of daily living</td>
<td></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 many years, or the names of close family members</td>
<td>Cholinesterase inhibitors with or without an NMDA receptor antagonist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basic activities of daily living begin to be impaired</td>
<td></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 without an NMDA receptor antagonist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unaware of all recent events and experiences in their lives</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most basic activities of daily living impaired</td>
<td></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>
<td></td>
</tr>
</tbody>
</table>

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

<sup>a</sup>Dose-related.
NMDA = N-methyl-D-aspartate
**Memantine**
- NMDA non-competitive antagonist
  - Side effects: dizziness, vomiting, increased blood pressure, epilepsy

**Donepezil**
- Selective inhibitor of AChE in the CNS (does not act on butyrylcholinesterase)
  - Long half-life
  - Improvement of cognitive symptoms

**Rivastigmine & Galantamine**
Similar effects to donepezil (shorter duration of action)

**Tacrine**
- First of the anticholinesterase agents approved for use but removed from US market due to liver toxicity.
Directions

• Do not use AChE inhibitors in combination, with memantine only
• Slow titration of AChE inhibitors needed to minimize side effects in patients
• AChE inhibitors used in mild and moderate forms AD
• Patients assessed every 3-6 months & continued only if stable or improved
OTHER DRUGS

Anxiolytics, Antidepressants, Antipsychotics (symptoms)

Dihydroergotamine, Hydergine (Ergoloid): brain blood flow

Piracetam (Nootropil), Aniracetam - Nootropics (improve memory), increase glutamate release: little effect in AD
AD Drug Development - 2021

<table>
<thead>
<tr>
<th></th>
<th>No. trials (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 3</td>
</tr>
<tr>
<td>North America (US &amp; Canada)</td>
<td>15 (37%)</td>
</tr>
<tr>
<td>Non-North America</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>Both</td>
<td>14 (34%)</td>
</tr>
</tbody>
</table>

*TABLE 8: Global distribution of trials (ClinicalTrials.gov accessed January 5, 2021)*

FIGURE 4  Mechanisms of action of disease-modifying agents in all phases of clinical trials grouped according to the Common Alzheimer’s Disease Research Ontology (CADRO). Figure: J Cummings; M de la Flor, PhD, Illustrator
AD Drug Development - 2021

2021 Alzheimer’s Drug Development Pipeline

**Mechanism of Action**
- Amyloid
- Tau
- Synaptic Plasticity/Neuroprotection
- Metabolism/Bioenergetics
- Inflammation/Infection/Immunity
- Vasculature
- Growth Factor/Hormone
- Epigenetic
- Proteostasis/Proteinopathies
- Other
- Symptomatic - Cognition
- Symptomatic - Neuropsychiatric

**Disease-Modifying Biologic**
- Phase 1
  - AAV-hTERT
  - Lu AF67508
  - LY3882993
- Phase 2
  - AL003
  - AAV-10hLFP12
- Phase 3
  - Aducanumab
  - Bexarotene
  - Solanezumab
  - Cilostazol

**Symptom-Reducing Small Molecule**
- Phase 1
  - AAV-hTERT
  - Lu AF67508
  - LY3882993
- Phase 2
  - AL003
  - AAV-10hLFP12
- Phase 3
  - Aducanumab
  - Bexarotene
  - Solanezumab

**Subject Characteristics**
- Healthy Volunteers
- Preclinical
- Prodomal/Prodromal - Mild
- Mild - Moderate Dementia
- Severe Dementia
AD Drug Development - 2021

86% Disease-Modifying Therapies
- 74 Agents in Phase 2
- Neuropsychiatric Symptoms (5%), Symptomatic Cognitive Enhancers (8%), Other (4%)

61% Disease-Modifying Therapies
- 28 Agents in Phase 3
- Neuropsychiatric Symptoms (18%), Symptomatic Cognitive Enhancers (21%), Other (6%)

64 DMTs in Phase 2
- Amyloid (17%)
- Synaptic plasticity/Neuroprotection (19%)
- Tau (14%)
- Inflammation/Infection/Immunity (19%)
- Oxidative stress (6%)
- Gut brain axis (6%)
- Amyloid (n=11)
- Synaptic plasticity/Neuroprotection (n=12)
- Tau (n=9)
- Inflammation/Infection/Immunity (n=12)

17 DMTs in Phase 3
- Amyloid (29%)
- Synaptic plasticity/Neuroprotection (18%)
- Metabolism/Bioenergetics (12%)
- Inflammation/Infection/Immunity (12%)
- Oxidative stress (12%)
- Gut brain axis (6%)
- Amyloid (n=5)
- Synaptic plasticity/Neuroprotection (n=3)