DRUG TREATMENTS IN DEVELOPMENT FOR ALZHEIMER'S DISEASE

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Translational Research & Clinical Interventions

RESEARCH ARTICLE

Alzheimer's disease drug development pipeline: 2021

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Abstract

Introduction: The number of individuals worldwide with Alzheimer's disease (AD) is growing at a rapid rate. New treatments are urgently needed. We review the current pipeline of drugs in clinical trials for the treatment of AD.

Methods: We interrogated ClinicalTrials.gov, the federal registry of clinical trials to identify drugs in trials.

Results: There are 126 agents in 152 trials assessing new therapies for AD: 28 treatments in Phase 3 trials, 74 in Phase 2, and 24 in Phase 1. The majority of drugs in trials (82.5%) target the underlying biology of AD with the intent of disease modification; 10.3% are putative cognitive enhancing agents; and 7.1% are drugs being developed to reduce neuropsychiatric symptoms.

Discussion: This pipeline analysis shows that target biological processes are more diversified, biomarkers are more regularly used, and repurposed agents are being explored to determine their utility for the treatment of AD.

KEYWORDS

Alzheimer's disease, amyloid, biomarkers, clinical trials, Common Alzheimer's Disease Research Ontology (CADRO), drug development, inflammation, National Institutes of Health, pharmaceutical companies, repurposed drugs, tau

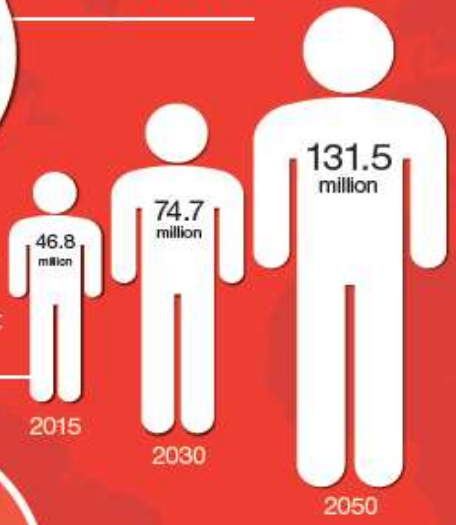
INTRODUCTION

- Alzheimer's disease (AD) is the sixth leading cause of death in the United States and the fifth leading cause among those over age 65.
- The current number of those with AD dementia is 5.8 million and this is anticipated to grow to 13.8 million in 2050 if effective interventions are not found.
- Based on 2018 death certificate data, 122,019 individuals succumbed from AD dementia that year, indicating an average daily death toll of 334.

The global impact of dementia

Around the world, there will be 9.9 million new cases of dementia in 2015,

one every 3 seconds



46.8 million people worldwide are living with dementia in 2015.

This number will almost double every 20 years.

Much of the increase will take place in low and middle income countries (LMICs): in 2015, 58% of all people with dementia live in LMICs, rising to 63% in 2030 and 68% in 2050.

The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to

US$ 2 trillion by 2030

If global dementia care were a country, it would be the

18th largest economy

in the world exceeding the market values of companies such as Apple and Google

(source: Forbes 2015 ranking).

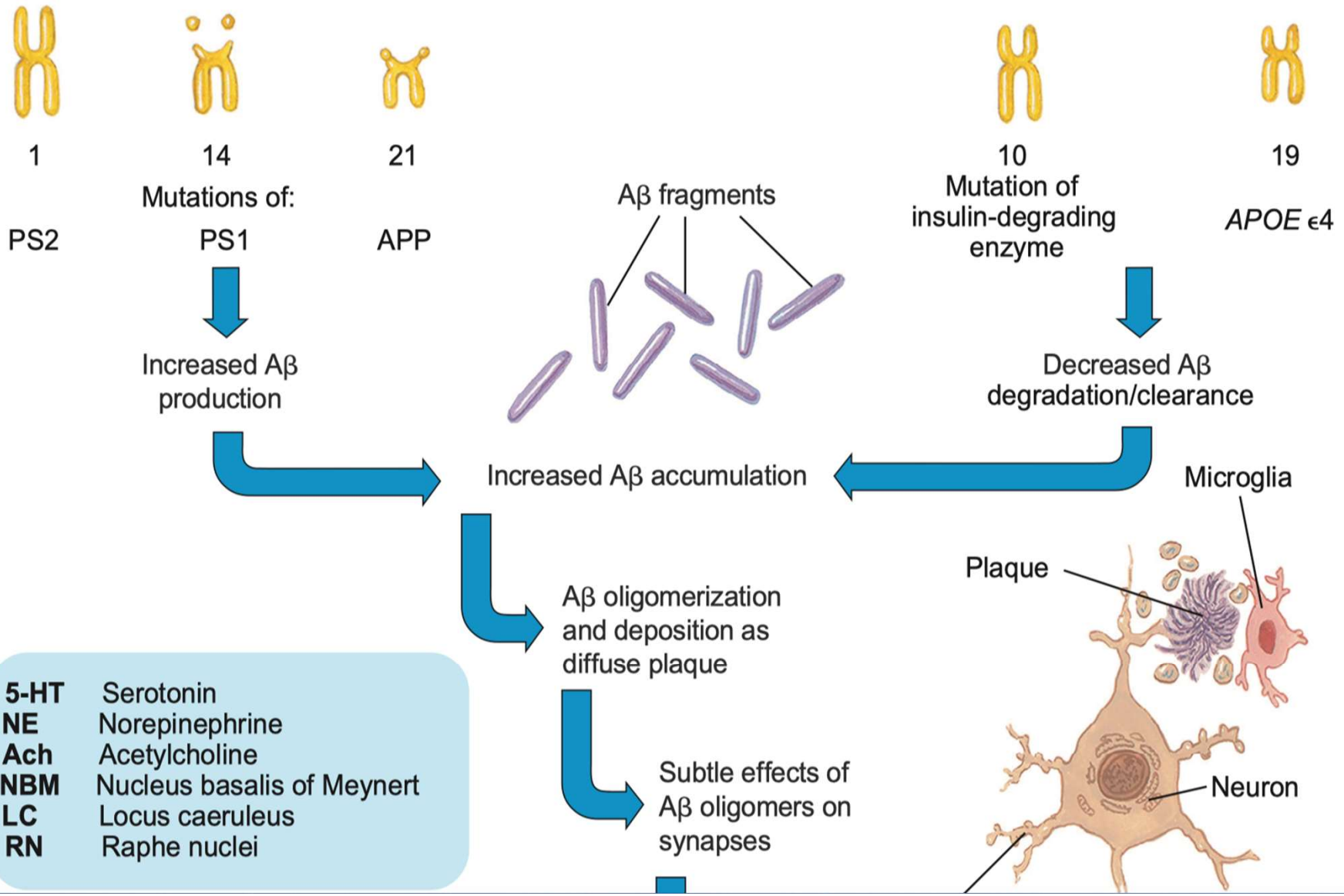
This map shows the estimated number of people living with dementia in each world region in 2015.

We must now involve more countries and regions in the global action on dementia.

The World Alzheimer Report 2015 was independently researched by King's College London and supported by Bupa.

Alzheimer's Disease International

The global voice on dementia


1
14
21
10
19
Mutations of:
PS2
PS1
APP
Mutation of insulin-degrading enzyme
APOE ϵ4
Aβ fragments
Increased Aβ production
Decreased Aβ degradation/clearance
Increased Aβ accumulation
Microglia
Plaque
Aβ oligomerization and deposition as diffuse plaque
Neuron
Subtle effects of Aβ oligomers on synapses
5-HT Serotonin
NE Norepinephrine
Ach Acetylcholine
NBM Nucleus basalis of Meynert
LC Locus caeruleus
RN Raphe nuclei

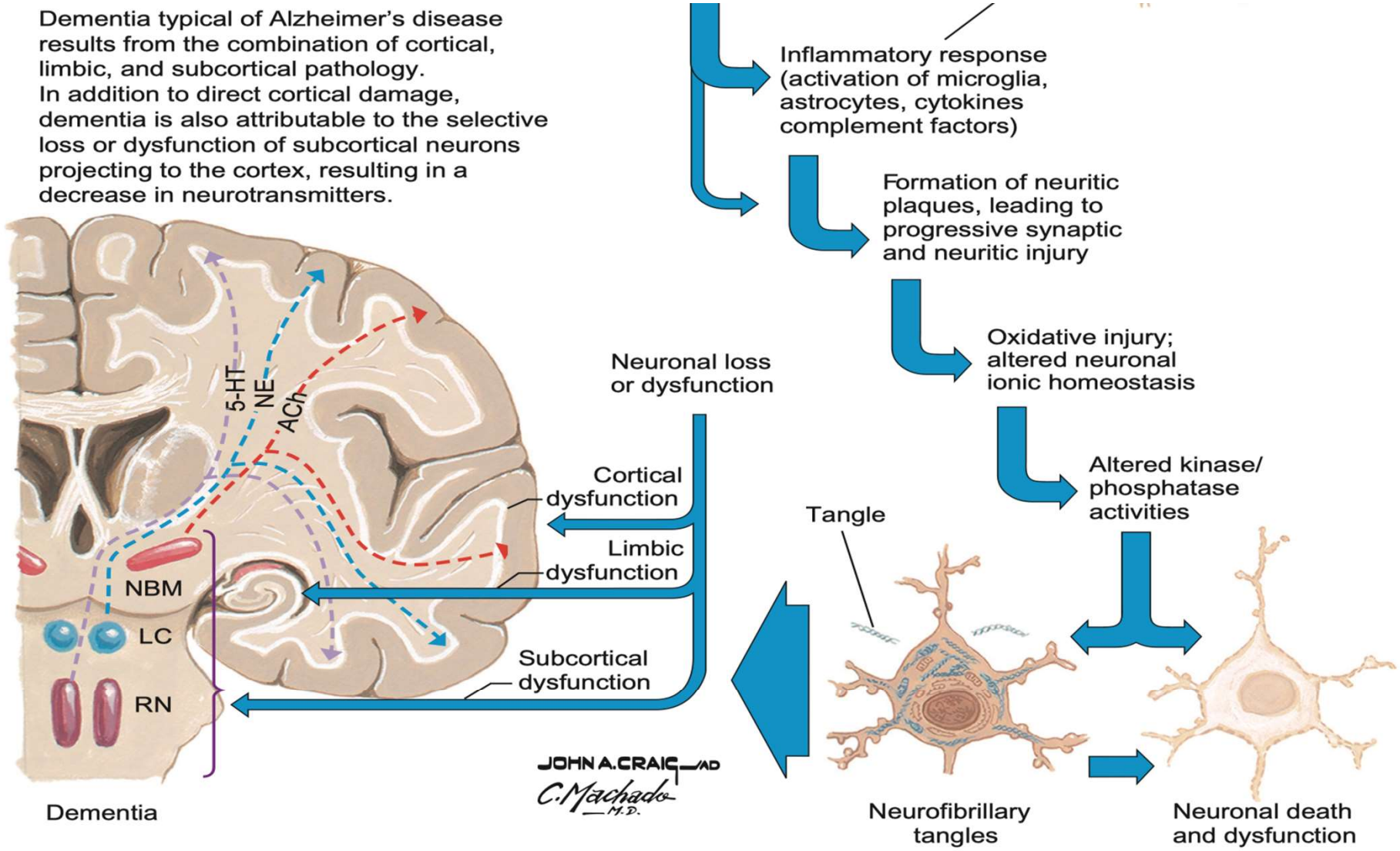


FIGURE 4-9 The amyloid cascade hypothesis in Alzheimer's disease. (Netter illustration from www.netterimages.com. Copyright Elsevier Inc. All rights reserved.)

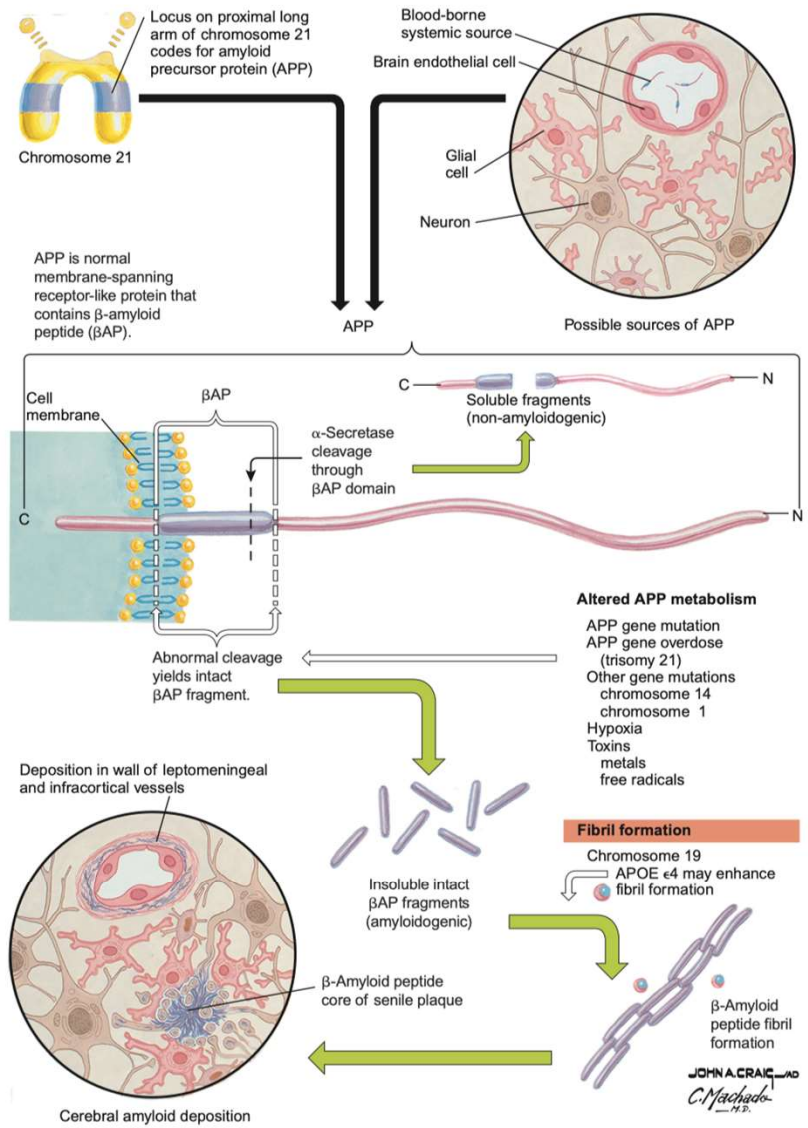
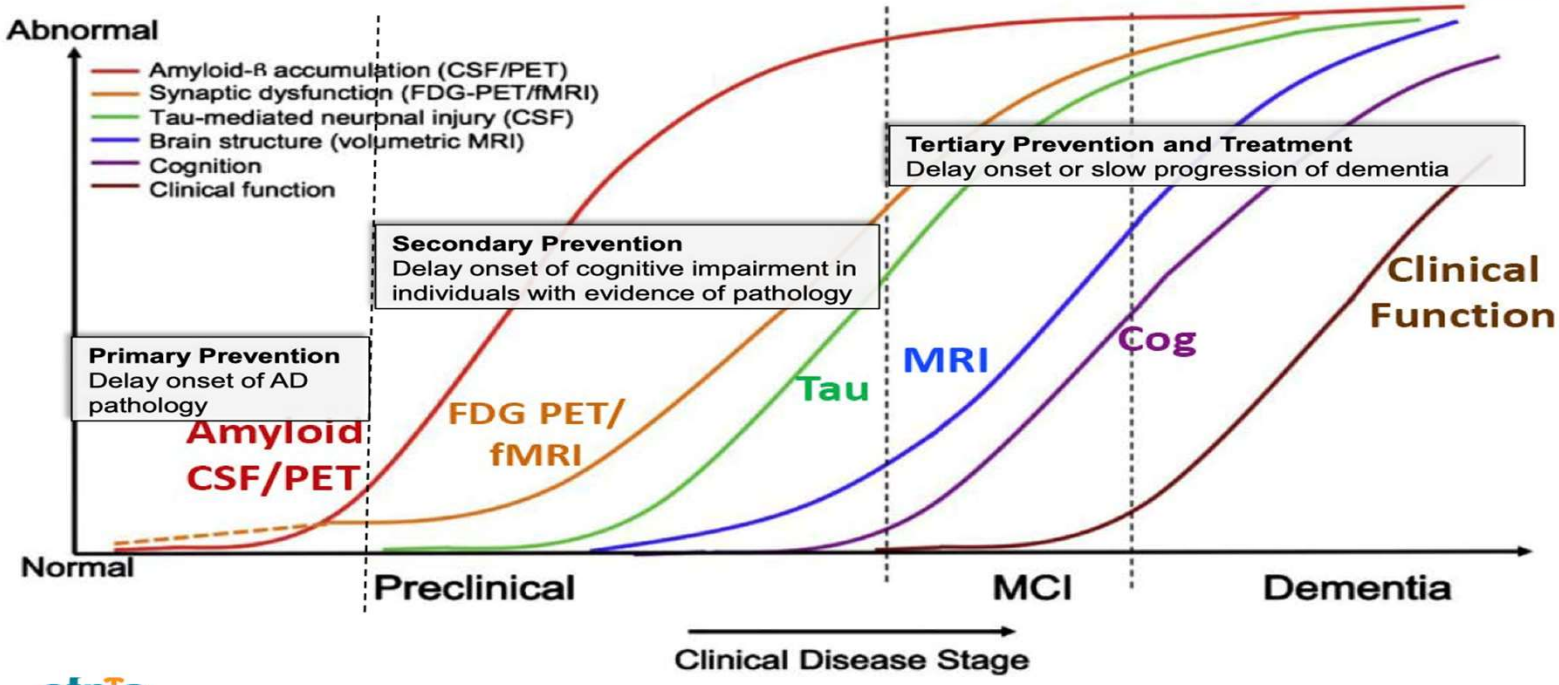


FIGURE 4-11 Possible pathways for normal and pathological Aβ processing. (Netter illustration from www.netterimages.com. Copyright Elsevier Inc. All rights reserved.)

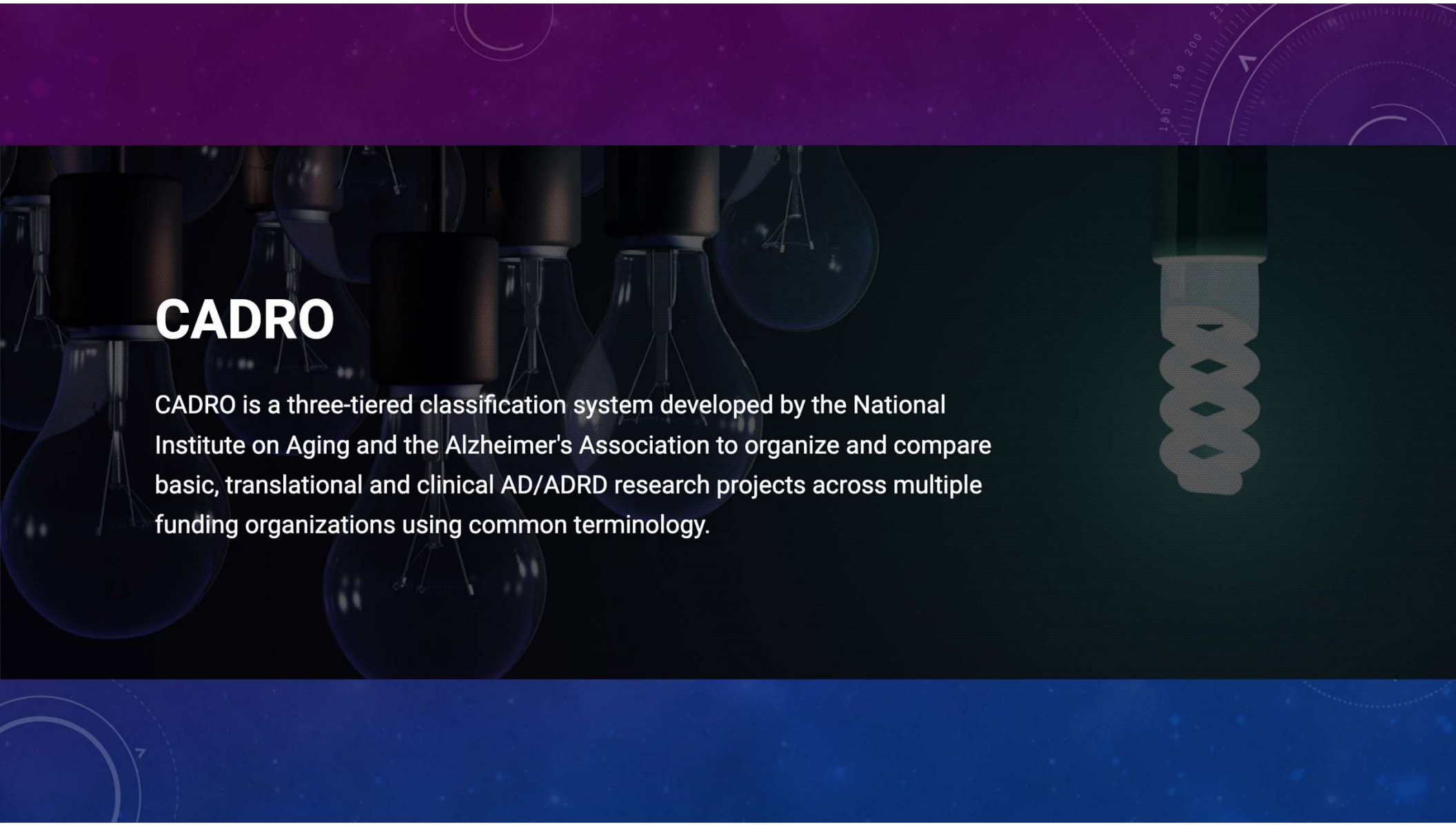
AD pathology begins prior to the onset of clinical symptoms



Clifford Jack et al. Lancet. Neurol. 2010 January; 9(1): 119.
Reisa Sperling, Clifford R Jack, Paul S Aisen Science translational medicine Nov 2011

- AD dementia is preceded by a preclinical phase that may last for 15 to 20 years and a prodromal period that persists for 3 to 6 years prior to onset of dementia.

- the US Food and Drug Administration (FDA) has provided guidance on defining AD populations from preclinical to late-stage dementia to facilitate clinical trials and drug development across the continuum of AD.
- The Common Alzheimer's Disease Research Ontology (CADRO) provides a means of classifying targets for drug development relevant to AD.



CADRO

CADRO is a three-tiered classification system developed by the National Institute on Aging and the Alzheimer's Association to organize and compare basic, translational and clinical AD/ADRD research projects across multiple funding organizations using common terminology.

Category A. Molecular Pathogenesis and Physiology of Alzheimer's Disease and Alzheimer's Disease-related Dementias (AD/ADRDs) +

Category B. Diagnosis, Assessment, and Disease Monitoring +

Category C. Translational Research and Clinical Interventions +

Category D. Population Studies +

Category E. Dementia Care and Impact of Disease +

Category F. Research Resources +

Category G. Consortia and Public Private Partnerships +

Category H. Brain Aging and Common Mechanisms Related to Dementias +

Category B. Diagnosis, Assessment, and Disease Monitoring

This category includes research focused on the discovery, development, testing and validation (including through Autopsy) of tools and methods for diagnosing and monitoring individuals with AD and ADRDs from the preclinical phase of the disease through advanced dementia, including post-mortem analyses. These methods and tools include all types of novel and established biomarkers.

1. **Fluid Biomarkers**
   - A. CSF Biomarkers
   - B. Blood-based Biomarkers
   - C. Urine Biomarkers
   - D. Saliva-based Biomarkers
   - E. Multi-fluid Biomarkers

2. **Imaging Biomarkers**
   - A. PET Amyloid Imaging
   - B. PET Tau Imaging
   - C. PET Other Imaging
   - D. Functional MRI
   - E. Structural MRI
   - F. Diffusion Tensor Imaging
   - G. Retinal Imaging
   - H. SPECT
   - I. MR Microscopy
   - J. Multiple Imaging
   - K. Other Imaging Modalities

3. **Traditional assessments (including cognitive, behavioral, functional reflecting changes in affective, social, decision-making, language/ speech, sensory and motor functions)**

4. **Personal assessments (using wearable and mobile technology including cognitive, behavioral, functional reflecting changes in affective, social, decision-making, language/ speech, sensory and motor functions)**

5. **Re-Purposed Biomarkers**
   - A. Cardiovascular
   - B. Hormonal
   - C. Genetic (Micro-RNAs)
   - D. White Matter Lesions/Damage
   - E. Other

6. **Emerging Biomarkers**
   - A. Genomic
   - B. Proteomic
   - C. Metabolomic
   - D. Multi-omics
   - E. Other

7. **Multimodal Biomarkers**

8. **Novel Analyses, Methodologies and Techniques for Biomarker Discovery and Validation**

9. **Other**

Category C. Translational Research and Clinical Interventions

This category aims to capture projects focused on the identification, validation and development of potential targets (including small molecule, natural products, and biologics) for AD and ADRDs from early therapeutic discovery through late stage preclinical development and all stages of clinical testing. Also, included are projects focused on repurposing pharmacological agents already in use for other conditions as well as non-pharmacological interventions.

1. **Research Resources and Enabling Technologies to Accelerate Therapy Development**
   - A. Enabling Technologies (ex. iPS cells)
   - B. Translational Bioinformatics and Multi-scale Modeling (ex. Drug repurposing)
   - C. Translational Infrastructure (ex. Model AD, ACTC)

2. **Identification and Validation of Novel Targets**

3. **Drug Discovery (small molecules and biologics), including assay development**
   - A. Amyloid beta
   - B. Tau
   - C. ApoE, Lipids and Lipoprotein Receptors
   - D. Neurotransmitter Receptors
   - E. Neurogenesis
   - F. Inflammation
   - G. Oxidative Stress
   - H. Cell death
   - I. Proteostasis/Proteinopathies
   - J. Metabolism and Bioenergetics
   - K. Vasculature
   - L. Growth Factors and Hormones
   - M. Synaptic Plasticity/Neuroprotection
   - N. Gut-Brain Axis
   - O. Circadian Rhythm
   - P. Environmental Factors
   - Q. Epigenetic Regulators
   - R. Multi-target
   - S. Unknown target
   - T. Other

4. **Non-clinical Drug Development (small molecules and biologics), including toxicology studies**

A. Amyloid beta
B. Tau
C. ApoE, Lipids and Lipoprotein Receptors
D. Neurotransmitter Receptors
E. Neurogenesis
F. Inflammation
G. Oxidative Stress
H. Cell death
I. Proteostasis/Proteinopathies
J. Metabolism and Bioenergetics
K. Vasculature
L. Growth Factors and Hormones
M. Synaptic Plasticity/Neuroprotection
N. Gut-Brain Axis
O. Circadian Rhythm
P. Environmental Factors
Q. Epigenetic Regulators
R. Multi-target
S. Unknown target
T. Other

5. **Non-clinical Proof of Concept for Non-Pharmacological Interventions**

A. Exercise
B. Diet
C. Environmental Enrichment
D. Sleep-related
E. Combination therapy
F. Other

6. **Clinical Trial Design, including Recruitment/ Retention Strategies**

7. **Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials)**

A. Amyloid beta
B. Tau
C. ApoE, Lipids and Lipoprotein Receptors
D. Neurotransmitter Receptors
E. Neurogenesis
F. Inflammation
G. Oxidative Stress
H. Cell death
I. Proteostasis/Proteinopathies
J. Metabolism and Bioenergetics
K. Vasculature
L. Growth Factors and Hormones
M. Synaptic Plasticity/Neuroprotection
N. Gut-Brain Axis
O. Circadian Rhythm
P. Environmental Factors
Q. Epigenetic Regulators
R. Multi-target
S. Unknown target
T. Other

8. **Late-stage Clinical Drug Development (Phase II/III and III Clinical Trials)**

A. Amyloid beta
B. Tau
C. ApoE, Lipids and Lipoprotein Receptors
D. Neurotransmitter Receptors
E. Neurogenesis
F. Inflammation
G. Oxidative Stress
H. Cell death
I. Proteostasis/Proteinopathies
J. Metabolism and Bioenergetics
K. Vasculature
L. Growth Factors and Hormones
M. Synaptic Plasticity/Neuroprotection
N. Gut-Brain Axis
O. Circadian Rhythm
P. Environmental Factors
Q. Epigenetic Regulators
R. Multi-target
S. Unknown target
T. Other

9. **Non-Pharmacological Interventions**

A. Exercise

B. Diet

C. Cognitive Training

D. Sleep-related

E. Neurostimulation

F. Combination therapy

G. Other

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10. **Clinical Therapy Development for the Neuropsychiatric Symptoms of Dementia**

A. Pharmacological

B. Non-Pharmacological

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11. **Clinical Ethics**

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12. **Other**

MAIN DRUG PIPELINES:

- There is an urgent need to develop new therapies for
  - Disease modification of AD
  - Cognitive impairment
  - Neuropsychiatric symptoms

INTRODUCTION

- Suvorexant had a successful Phase 3 trial for insomnia in AD and safety and efficacy data have been added to the package insert allowing clinicians to use this agent for sleep disturbances in AD using evidence-based guidance.

INTRODUCTION

- Pimavanserin is under review by the FDA for treatment of dementia-related psychosis
- Aducanumab is under review for treatment of progression of AD.

INTRODUCTION

- For mechanism of action (MOA), we classified agents using the CADRO approach.
- Some agents have more than one mechanism of action and, in these cases, we noted both mechanisms and depended on the available literature to identify a dominant mechanism.

SOURCE OF INFORMATION:

- FDA/US National Library of Medicine of the National Institutes of Health (NIH) clinical research registry, *ClinicalTrials.gov*
- The “common rule” governing ClinicalTrials.gov:
  - registration is required for studies that meet the definition of an “applicable clinical trial” ***(ACT)***
    - initiated after September 27, 2007
- trials present on ClinicalTrials.gov as of ***January 5, 2021;***

DEFINITIONS

- *"symptomatic"* treatments:
  - cognitive enhancement or
  - Control of neuropsychiatric symptoms
- *"disease-modifying" treatments:*
  - change the biology of AD and produce neuroprotection
    - often through a variety of intermediate mechanisms such as effects on amyloid or tau

DEFINITIONS

- disease-modifying therapies (DMTs)
  - biologics
    - Biologics are generally derived from living organisms and include antibodies, vaccines, antisense oligonucleotides (ASOs), and therapeutic proteins.
  - small molecules
    - drugs typically taken orally that are <500 daltons in size and can regulate a biological process.

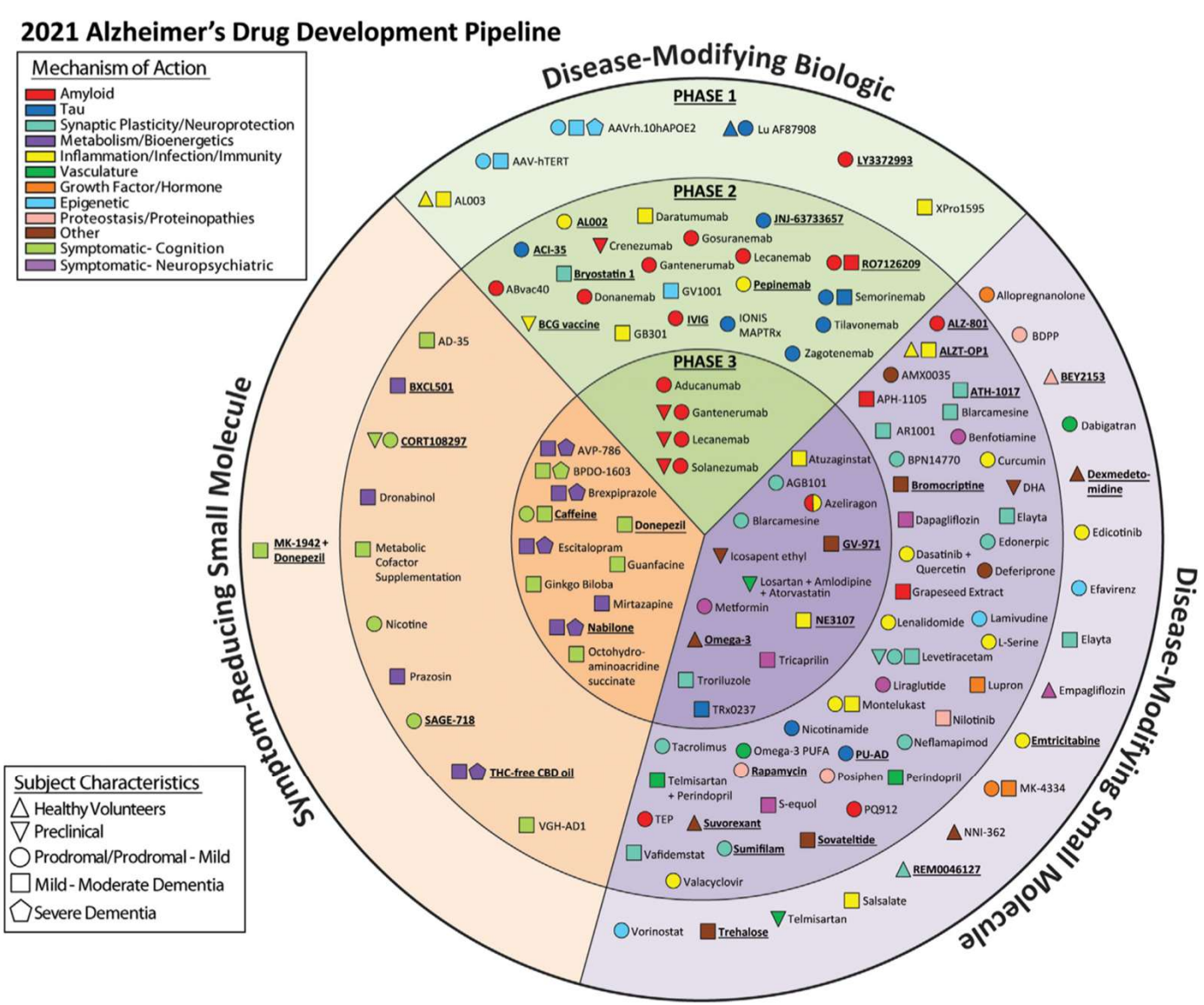
DEFINITIONS

- AD has preclinical, prodromal, and dementia phases,
  - ***Prevention trials*** including participants with preclinical AD;
  - ***Prodromal trials*** with participants with mild cognitive impairment (MCI) who have biomarker evidence indicative of AD pathology; or have
  - ***Dementia trials*** mild, moderate, or severe AD dementia.

PHASE 1, 2 & 3:

- ***126 agents*** in ***152 trials***
  - January 5, 2021
  - 28 agents in 41 Phase 3 trials,
  - 74 agents in 87 Phase 2 trials,
  - 24 agents in 24 Phase 1 trials.

2021 Alzheimer's Drug Development Pipeline



126 AGENTS IN 152 TRIALS:

- ***DMTs*** are the most common agents being studied
  - 104; 82.5% of the total number of agents in trial
    - 16 (15.4%) have amyloid target
    - 11 (10.6%) have tau target
- 13 (10.3%) agents in trials target cognitive enhancement
- 9 (7.1%) are intended to treat neuropsychiatric and behavioral symptoms.

PHASE 3

- ***28 agents*** in ***41 trials***
- 10 repurposed agents

- 11 (39.3%) symptomatic agents
  - six (21.4%) cognitive enhancers
  - five (17.9%) targeting behavioral symptoms.

PHASE 3

- 17 DMTs
  - 4 biological therapies => Amyloid Target
  - 13 oral agents/small molecule therapies
    - 1 receptor for advanced glycation end products (RAGE) antagonist => Amyloid Target

- Amyloid Target 29.4% of DMTs
- Four (23.5%) of the DMT agents => repurposed agents approved

OTHER CADRO MECHANISMS REPRESENTED AMONG PHASE 3 DMT THERAPIES:

- 1 tau (5.9%)
- 2 inflammation/infection (11.8%)
- 2 oxidative stress (11.8%)
- 2 metabolism and bioenergetics (11.8%)
- 1 vascular factors (5.9%),
- 3 Synaptic plasticity/neuroprotection (17.6%),
- 1 gut–brain axis (5.9%)

PHASE 3

- 5 prevention trials enrolling cognitively normal participants known to be at risk for AD (preclinical AD).
  - 2 monoclonal antibodies (solanezumab, gantenerumab)
  - 1 vaccine trial (CAD106)
  - 2 small molecules (icosapent ethyl and a combination of losartan, amlodipine, and atorvastatin).

PHASE 3

- 1 trial enrolling both preclinical patients and patients with MCI to mild AD dementia (DIAN-TU trial);
- 13 trials in patients with prodromal AD/MCI or prodromal/mild AD dementia;
- 11 trials of patients with mild to moderate AD
- 11 trials of patients with mild-to-severe AD

PHASE 3

- A mean of 619 participants per trial
- total of 25,373 participants were needed for enrollment.
- Prevention trials
  - a mean of 684 participants and had a mean duration of 335 weeks

PHASE 3 – DMT TRIALS

- focusing on prodromal AD or prodromal AD/mild AD dementia:
  - a mean of 772 participants
  - mean duration of 240 weeks
- Enrolling mild-to-moderate AD dementia participants:
  - an average of 504 participants
  - a mean duration of 177 weeks

PHASE 3 – EXPOSURE PERIOD

- 154 weeks for prevention trials
- 87 weeks for prodromal AD or prodromal AD/mild AD dementia trials
- 31 weeks for mild-to-moderate AD dementia trials

PHASE 3

- cognitive enhancer trials was
  - a mean duration of 161 weeks (22 treatment weeks)
  - an average of 367 participants.
- agents for behavioral symptoms had
  - a mean duration of 210 weeks (15 treatment weeks)
  - a mean of 447 subjects.

- Calculated recruitment periods for trials were:
  - Prevention (172 weeks)
  - Prodromal AD and prodromal AD/mild AD dementia (120 weeks)
  - AD dementia trial (123 weeks)

- Two thirds of Phase 3 trials took longer to complete than originally planned as recorded on ClinicalTrials.gov.
- The time required for recruitment of the patient population typically exceeded the treatment period by up to two- to five-fold.

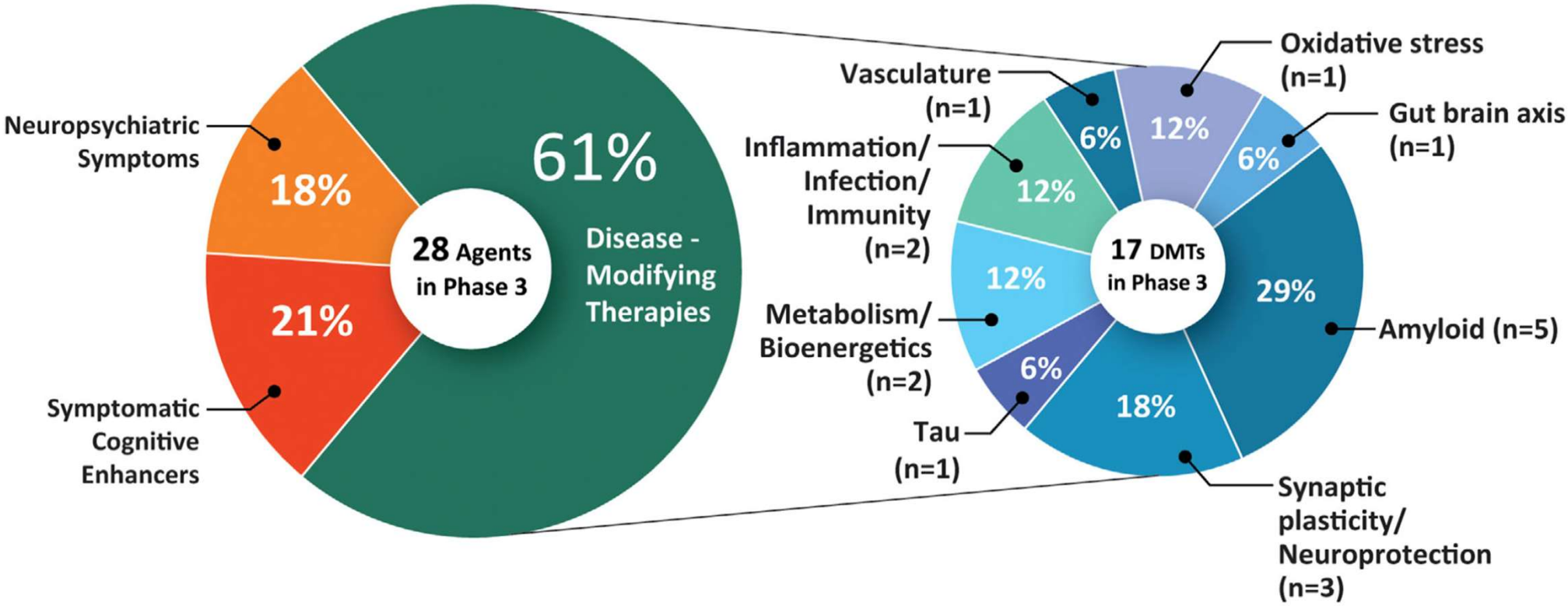


FIGURE 2 Mechanisms of action of agents in Phase 3 (as classified using the Common Alzheimer's Disease Research Ontology approach).
Figure: J Cummings; M de la Flor, PhD, Illustrator

PHASE 2

- ***74 agents*** in ***87 trials***
  - 30 (40.5%) of the agents are repurposed
  - 64 potential DMTs
  - 6 cognitive enhancing agents
  - 4 drugs targeting behavioral symptoms

PHASE 2 - DMTS

- DMTs in Phase 2 there are
  - 21 biologics => 7 amyloid Target
  - 43 small molecules => 4 amyloid Target
- Amyloid target in 17.2% of DMTs

OTHER CADRO MECHANISMS REPRESENTED AMONG PHASE 2 DMT THERAPIES:

- 9 tau (14.1%)
- 12 inflammation/infection/immunity (18.8%)
- 2 transmitter systems and receptors (3.1%)
- 1 oxidative stress (1.6%)
- 2 cell death (3.1%),
- 4 proteostasis (6.3%)
- 4 metabolism and bioenergetics (6.3%)

OTHER CADRO MECHANISMS REPRESENTED AMONG PHASE 2 DMT THERAPIES:

- 3 vascular factors (4.7%)
- 1 growth factors and hormones (1.6%)
- 11 synaptic plasticity/neuroprotection (17.2%)
- 1 epigenetic regulators (1.6%)
- 1 neurogenesis (1.6%)

PHASE 2

- 6 trials involving cell therapies.
- 26 of the Phase 2 DMT agents are repurposed

PHASE 2

- 2 prevention trials involving participants with preclinical AD (assessing crenezumab and levetiracetam)
- 49 trials involved patients with prodromal or prodromal/mild AD dementia
- 30 trials for mild-to-moderate AD
- 1 trial included patients with mild, moderate, or severe AD
- 1 trial included preclinical patients and patients with prodromal/mild AD
- 1 trial was for mild-to moderate AD or healthy participants

PHASE 2

- trials for DMTs included
  - an average of 147 participants
  - average 197 weeks in duration
    - 52 weeks of treatment
    - 121 weeks for recruitment
- trials for cognitive-enhancing agents
  - average of 117 participants
  - average 103 weeks in duration
    - including an average of 31 weeks of treatment.

PHASE 2

- trials for agents targeting behavioral symptoms included
  - mean 104 participants
  - average 145 weeks
    - including an average of 8 weeks of treatments
- Of Phase 2 trials 78.6% took longer to complete
- All types of trials took between two and three times longer to recruit patients to the trial than to assess the effects of the treatment during the exposure period.

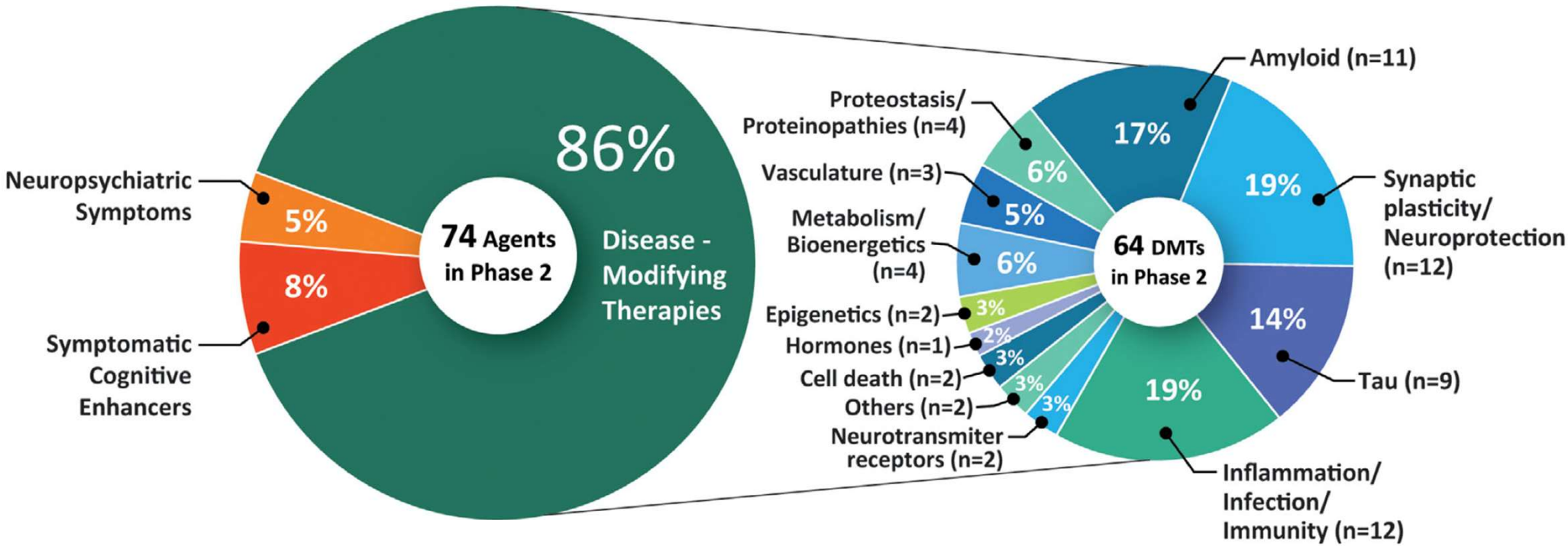


FIGURE 3 Mechanisms of action of agents in Phase 2. Figure: J Cummings; M de la Flor, PhD, Illustrator

PHASE 1

- ***24 agents*** in ***24 trials***
  - 10 Repurposed agents (41.6%)
  - 23 potential DMTs
    - 6 biologics
      - 1 amyloid target (4.3% of DMTs)
    - 17 small molecules
  - 1 cognitive enhancing agent
  - no agents targeting behavioral symptoms

OTHER CADRO MECHANISMS REPRESENTED AMONG PHASE 1 DMT THERAPIES:

- 1 tau (4.3%)
- 5 inflammation (21.7%)
- 1 cell death (4.3%)
- 2 proteostasis (8.7%)
- 1 metabolism and bioenergetics (4.3%)
- 2 vascular factors (8.7%)
- 2 growth factors and hormones (8.7%)

OTHER CADRO MECHANISMS REPRESENTED AMONG PHASE 1 DMT THERAPIES:

- 2 synaptic plasticity/neuroprotection (8.7%)
- 2 epigenetic regulators (8.7%)
- 1 circadian rhythm (4.3%)
- 1 neurogenesis (4.3%)

PHASE 1

- 3 trials involving stem cell therapies
- average duration of 127 weeks
- a mean of 43 participants

BIOMARKERS IN PHASE 3 AS ENTRY CRITERIA

- Of the 24 Phase 3 DMT trials:
  - 4 trials (17%) used amyloid positron emission tomography (PET) as an entry criterion,
  - 1 (4%) used cerebrospinal fluid (CSF) amyloid, and
  - 6 (25%) used either amyloid PET or CSF-amyloid.
  - 13 (54%) of trials did not use biomarkers for study entry.
- 1 cognitive enhancer trial uses CSF amyloid or CSF tau for entry.

BIOMARKERS IN PHASE 2 AS ENTRY CRITERIA

- 11 (14%) DMT trials used amyloid PET as an entry criterion
- 9 (12%) used CSF amyloid
- 11 (14%) used either amyloid PET or CSF amyloid
- 2 (3%) of the Phase 2 DMT trials used tau PET as an entry criterion
- 2 (3%) used either CSF amyloid or CSF tau
- 1 (1%) used either amyloid PET or CSF tau
- 40 (53%) of the Phase 2 trials did not require biomarker confirmation for study entry.

BIOMARKERS

- Of Phase 3 DMT trials, 15 (63%) use biomarkers as supportive outcomes.
- In Phase 2, nine DMT trials (12%) have biomarkers as primary outcomes and 29 (38%) have biomarkers as supportive outcomes.
- Three (13%) of the Phase 3 DMT trials include tau PET imaging as an outcome and nine (12%) of Phase 2 DMT trials include tau PET imaging as an outcome.

Biomarker role in trial[a]	N of trials (%)	
	Phase 3 DMTs	Phase 2 DMTs
Biomarker as an outcome measure[a]		
CSF amyloid	15 (25%)	10 (48%)
CSF tau	17 (28%)	9 (43%)
FDG-PET	7 (11%)	1 (5%)
vMRI	8 (13%)	8 (38%)
Plasma amyloid	7 (11%)	2 (10%)
Plasma tau	2 (3%)	1 (5%)
Amyloid PET	5 (8%)	7 (33%)
Tau PET	4 (7%)	3 (14%)
Biomarker as an entry criterion[a]		
Amyloid PET	4 (17%)	11 (14%)
CSF amyloid	1 (4%)	9 (12%)
Amyloid PET or CSF amyloid	6 (25%)	11 (14%)
Tau PET	0	2 (3%)
CSF amyloid or CSF tau	0	2 (3%)
Amyloid PET or CSF tau	0	1 (1%)

Abbreviations: CSF, cerebrospinal fluid; DMT, disease-modifying therapy; FDG, fluorodeoxyglucose; PET, positron emission tomography; vMRI, volumetric magnetic resonance imaging.

[a]Percentages refer to the percent of trials that used any biomarker as an outcome or the percent that used biomarkers as an entry criterion.

CONCLUSION

The AD drug development pipeline comprises 126 agents in 152 trials (Figure 1).

There are 28 agents in Phase 3, 74 in Phase 2, and 24 in Phase 1. One hundred four putative DMTs are being assessed (17 in Phase 3, 64 in Phase 2, 23 in Phase 1).

DMTs represent 83% of the pipeline of agents. There are 13 cognitive enhancers and nine drugs targeting neuropsychiatric symptoms in the pipeline.

CONCLUSION

Using the CADRO classification, review of the pipeline reveals a proliferation of mechanistic approaches to the treatment of AD (Figure 4).

Phase 2 has both more agents in trials and a greater diversity of targets than other phases; this may reflect a more diversified approach to treatment targets in Phase 2 or a reduction of targets in Phase 3 because of the lack of success in Phase 2 outcomes.

Amyloid and tau protein are important targets; inflammation, synaptic plasticity, neuroprotection, and bioenergetics/metabolism account for most of the rest of the current pipeline of agents.

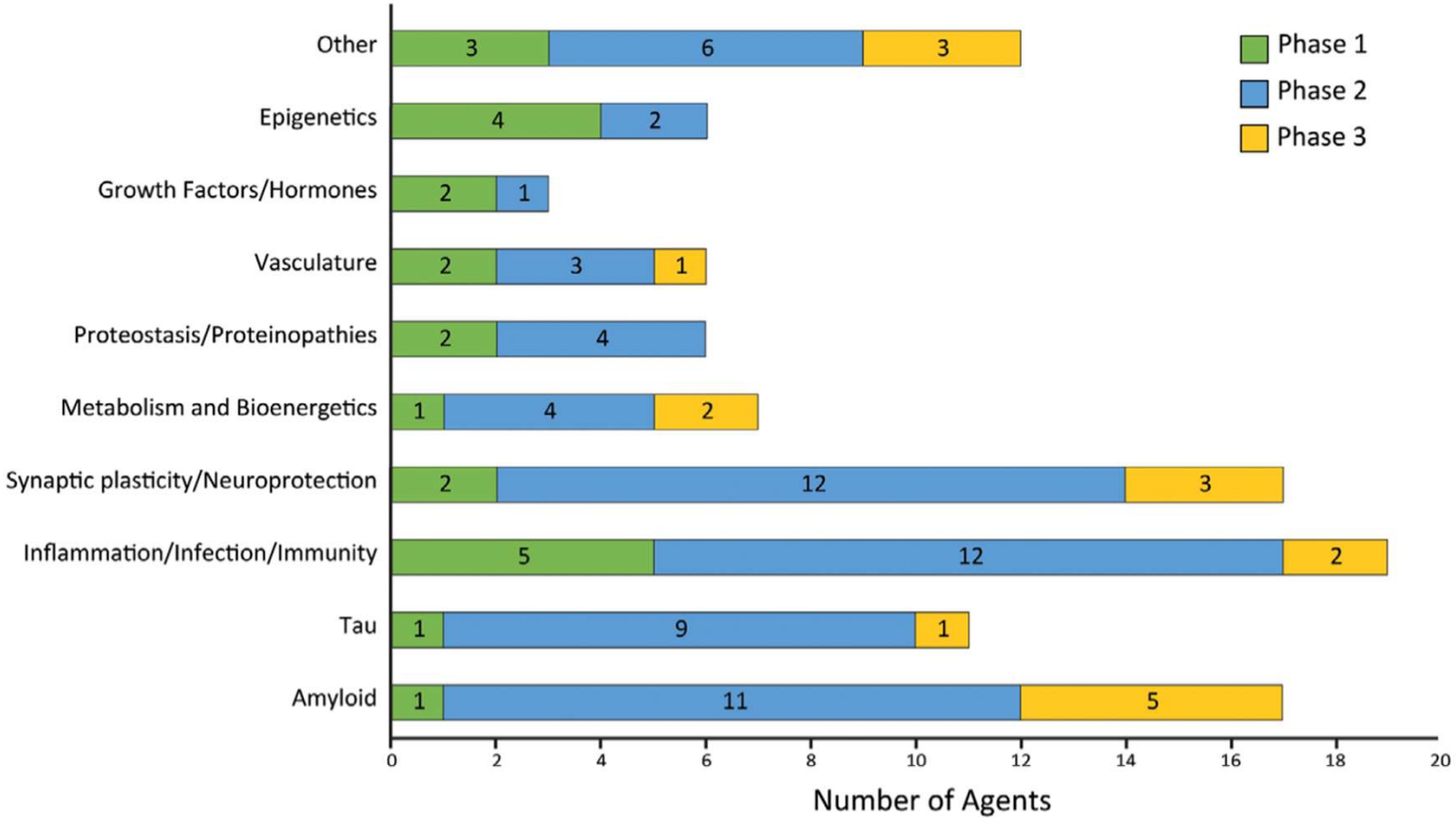


FIGURE 4 Mechanisms of action of disease-modifying agents in all phases of clinical trials grouped according to the Common Alzheimer's Disease Research Ontology (CADRO). Figure: J Cummings; M de la Flor, PhD, Illustrator

CONCLUSION

Biomarkers play an increasing role in drug development and use the amyloid (A), tau (T), neurodegeneration (N)—A/T/N—biomarker framework.

Biomarkers are integrated into development programs for diagnostic confirmation (e.g., amyloid PET, CSF amyloid), analytic stratification (e.g., apolipoprotein E genotype), prognostic anticipation (e.g., tau PET, CSF phosphorylated tau [p-tau]), assessment of neuroprotection and disease modification (magnetic resonance imaging, fluorodeoxyglucose [FDG] PET, CSF total tau, neurofilament light [NfL], neurogranin), or for safety monitoring in monoclonal antibodies and possibly other therapies.

CONCLUSION

The rapid evolution of blood-based biomarkers may have a significant impact on patient screening and diagnosis and is expected to eventually act as entry criteria or outcomes in some circumstances.

Plasma amyloid beta protein (Aβ) 42/40 correlates highly with amyloid PET 27 and is commercially available for clinical application (PrecivityAD).

Plasma p-tau-181 and plasma p-tau 217 are elevated as AD advances and may be useful in trials to assess impact on tau pathology of trial participants.

Plasma NfL, a measure of neuronal degeneration, is increasingly elevated as AD progresses.

THE ADUCANUMAB CONTROVERSY

THE ADUCANUMAB CONTROVERSY

Aducanumab has been FDA-approved for mild cognitive impairment and mild dementia due to Alzheimer disease despite controversy over the research findings to date.

Careful consideration of appropriate use is needed.

THE ADUCANUMAB CONTROVERSY

The clinical trials of aducanumab focused on those with mild cognitive impairment (MCI) or mild dementia due to AD with increased β-amyloid on positron emission tomography (PET) imaging.

PRIME, a phase 1b, 12-month, double blind randomized controlled trial, showed a significant reduction of β-amyloid plaques on amyloid PET scans; the 10-mg/kg dose was most efficacious (NEJM JW Psychiatry Nov 2016) and Nature 2016; 537:50. T

he main side effect, amyloid-related imaging abnormalities (ARIA), also was dose-dependent (41% with 10 mg/kg), more common in apolipoprotein E Ɛ4 carriers (ApoE Ɛ4), and reduced if the medication was titrated.

THE ADUCANUMAB CONTROVERSY

Two subsequent phase 3 clinical trials (ENGAGE and EMERGE) with identical designs were conducted.

Approximately 2200 participants total received aducanumab (FDA 2020 Nov 6; [e-pub]. opens in new tab).

The primary outcome included change in Clinical Dementia Rating (CDR) Sum of Boxes score, an integrated metric of cognitive and functional status.

Secondary outcomes included reduction of β-amyloid on PET imaging.

Participants were divided into high- and low-dose groups based on ApoE Ɛ4 carrier status.

THE ADUCANUMAB CONTROVERSY

Initially, ApoE Ɛ4 carriers received 6 mg/kg or 3 mg/kg. After the PRIME study showed that ApoE Ɛ4 carriers could be titrated safely to 10 mg/kg, a protocol amendment allowed the 6-mg/kg dose ApoE Ɛ4 carrier group to receive 10 mg/kg in the clinical trials.

To reduce risk for ARIA, doses were titrated to the maximum allowed dose in each group.

THE ADUCANUMAB CONTROVERSY

In a pre-planned futility analysis, ENGAGE showed no significant changes in clinical outcomes, while EMERGE showed significant improvement in clinical outcomes versus placebo. Both trials showed significant reduction in β-amyloid levels.

ARIA with edema was the most common adverse effect, seen in 35% of aducanumab recipients.

The conflicting clinical efficacy results led the manufacturer to stop the trials (NEJM JW Neurol 2019 Jun).

But after further post-hoc analyses, the manufacturer determined that those who received 14 doses of 10 mg/kg in both studies had a significant reduction (−23%) in CDR Sum of Boxes score versus placebo recipients, leading to the manufacturer submitting an application for FDA approval of the medication.

THE ADUCANUMAB CONTROVERSY

Others reported that different placebo effects in the two studies also may explain the post-hoc analysis findings and stated that a third phase 3 trial with high-dose aducanumab was needed (Alzheimers Dement 2021; 17:696).

While the FDA's Peripheral and Central Nervous System Advisory Council voted against FDA approval (2020 Nov), the FDA approved aducanumab use through an accelerated pathway based on reduction in β-amyloid as a surrogate endpoint (FDA 2021 Jun 7; [e-pub]. opens in new tab).

THE ADUCANUMAB CONTROVERSY

Given the controversy, careful consideration is essential in determining whether a patient may be a candidate for aducanumab. FDA approval initially was for all AD stages but eventually was revised to target those with MCI or mild dementia due to AD, similar to the phase 3 clinical trial participants. An expert panel has published the following appropriate-use recommendations and guidelines (J Prev Alz Dis 2021; [e-pub].

THE ADUCANUMAB CONTROVERSY

1. Patients should meet the clinical criteria for MCI due to AD or mild AD dementia. Cognitive scores on validated scales should support the clinical diagnosis. Patients can be on cholinesterase inhibitors or memantine.

2. Amyloid status should be confirmed with an amyloid PET scan (visually interpreted by properly trained radiologists) or cerebrospinal fluid (CSF) biomarkers.

3. ApoE Ɛ4 genotyping should be discussed with the patient/care partner, given the risk for ARIA.

THE ADUCANUMAB CONTROVERSY

4. A brain MRI should be obtained within 1 year before initiating aducanumab treatment.

5. Cardiovascular, medical, and psychiatric status should be stable before initiating treatment. Patients who are pregnant, on anticoagulant medications, or have evidence of significant cerebrovascular disease on brain MRI should be excluded from treatment.

6. Patients and care partners should understand the requirements of therapy.7. Clinicians may need to collaborate with or refer to specialists with expertise in these assessments.

THE ADUCANUMAB CONTROVERSY

Aducanumab infusions should be given every 4 weeks (at least 21 days apart) and titrated to 10 mg/kg, i.e., 1 mg/kg for infusions 1 and 2, 3 mg/kg for infusions 3 and 4, 6 mg/kg for infusions 5 and 6, and 10 mg/kg/month thereafter.

THE ADUCANUMAB CONTROVERSY

Brain MRI should be done prior to initiating treatment and before infusions 5, 7, and 12 or for symptoms of ARIA (e.g., seizures or stroke-like episodes).

Those with symptomatic or moderate-to-severe ARIA should discontinue treatment and be reassessed both clinically and with an MRI after 1 month.

Consider resuming treatment with resolution of ARIA due to vasogenic edema or stabilization of ARIA due to hemorrhage on MRI and improvement of symptoms.

THE ADUCANUMAB CONTROVERSY

The clinical efficacy of the medication can be tracked by following clinical status.

Our institution regularly uses the CDR scale and comprehensive neuropsychological testing to monitor clinical status, which also will be used to track clinical efficacy of aducanumab.

We also routinely use CSF studies to determine AD biomarker status, including β-amyloid and tau levels.

In addition to following appropriate-use parameters, we are only offering this treatment to patients without elevated CSF tau levels and those adequately treated for obstructive sleep apnea. We also are monitoring CSF biomarker levels with MRI at weeks 5, 7, and 12 after initiating aducanumab therapy.

THE ADUCANUMAB CONTROVERSY

The debate on whether reduction of β-amyloid correlates clinical stabilization or improvement in AD continues. There is a clinical trial currently enrolling participants to determine clinical safety and efficacy, but the timeline to complete it is 9 years. The cost of the medication is high (>$50,000 annually), and the Centers for Medicare and Medicaid Services is still determining whether it will be covered.

THE ADUCANUMAB CONTROVERSY

Further studies are needed to assess if aducanumab is appropriate for those with atypical presentations of AD, such as posterior cortical atrophy and logopenic primary progressive aphasia, or those with AD and concomitant conditions such as Lewy body disease.

Because many questions remain, fully informing the qualifying patients about what's unknown is the best way to address the uncertainty. While aducanumab may offer hope, we also need to practice discernment and caution.

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THANKS