DRUG DEVELOPMENT IN ALZHEIMER'S DISEASE

BRAIN LOVES CIRCUITS

THE DRUG DEVELOPMENT PATH

PHASE 1

Testing for Safety

This is generally the first time drugs are tested in a small number of normal and disease-affected people. Phase 1 follows rigorous laboratory and often animal studies. At this stage, the drug is evaluated for safety and possible side effects. Sometimes, biomarkers can be included at this phase to determine participants' reaction to the treatment's effects.

PHASE 2

Testing for Drug Effect

Drugs that succeed in phase 1 move to this "proof-of-concept" stage. Researchers continue to evaluate safety and evaluate a drug's efficacy in larger numbers of people. Phase 2 trials may also use biomarker tests to begin to evaluate target engagement, that is, to determine whether a drug interacts with its biological target (e.g., reducing inflammation or clearing misfolded proteins in the brain).

PHASE 3

Proof of Efficacy in Larger Trials

Drugs that succeed in phase 2 are then tested in large groups of patients over a longer time. These trials can include thousands of patients at multiple sites and last for many years. Alzheimer's phase 3 trials are more rigorous than ever and most measure both clinical outcomes such as changes in people's memory and cognitive functions, as well as biomarker outcomes such as neuroimaging, spinal fluid and blood tests. Once this phase is complete, a drug can be submitted for FDA approval.

https://www.alzdiscovery.org/research-and-grants/clinical-trials-report/2021-report

RECENT ALZHEIMER´S DRUG APPROVAL HISTORY

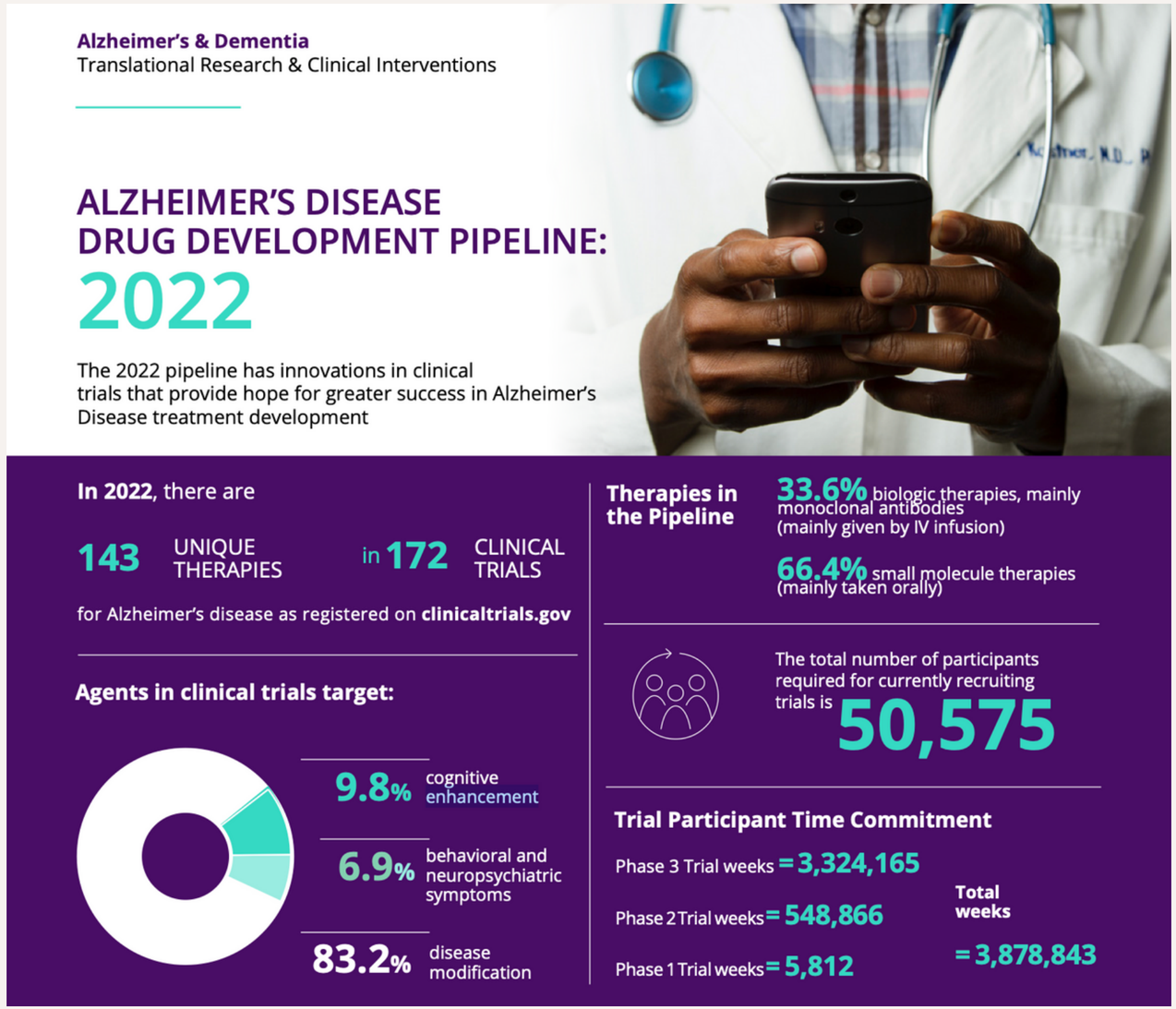
- The Food and Drug Administration (FDA) provided accelerated approval of Aducanumab (Aduhelm®) for mild cognitive impairment and mild dementia.
- The EMA refused the marketing authorization, which is why people living in Europe with Alzheimer´s Disease are waiting for an effective treatment for **more than 20 years** since the last medication was approved by the EMA in 2002.

WHY ARE ALZHEIMER´S DISEASE TRIALS ARE FAILING?

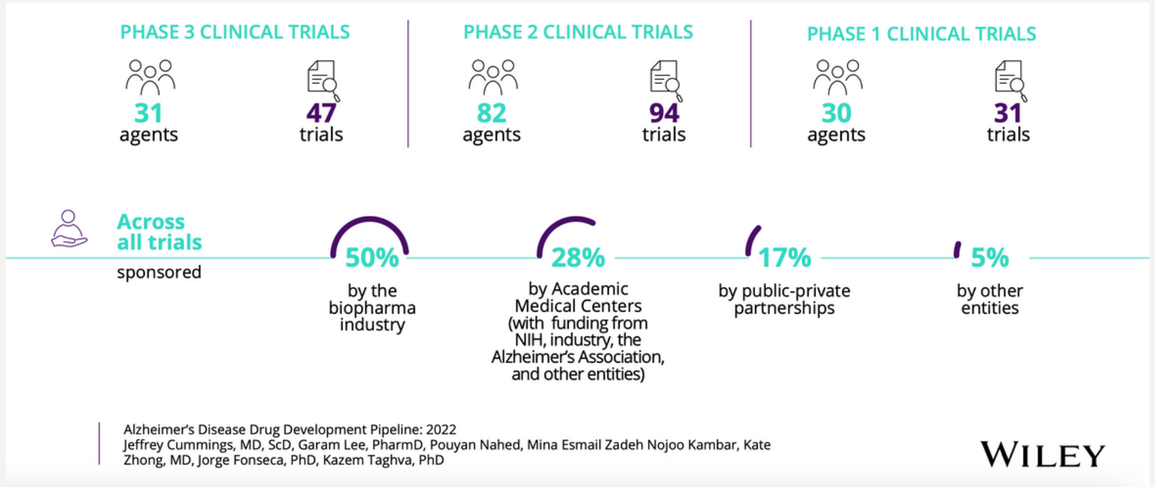
- 99% of Alzheimer´s Disease clinical trials do not show a difference between the drug and the placebo.
- Clinical trials fostered a one-size-fits-all approach which is not working in a disease that manifests differently in the different types of patients.
- Alzheimer´s disease is incredibly complex and its pathology includes most known biological pathways.
- Clinical Research has been focused on amyloid plaques and tangles but we cannot conclude that plaques and tangles cause Alzheimer's disease.

https://www.frontiersin.org/articles/10.3389/fnagi.2022.846902/ful
https://www.eneuro.org/content/9/1/ENEURO.0530-21.2021l
https://www.beingpatient.com/

BUT THERE IS HOPE AND THE DRUG DEVELOPMENT PIPELINE CROWDED



The Food and Drug Administration granted priority review of Lecanemab in Jul 2022. Like Aducanumab (Aduhelm®), lecanemab targets the amyloid protein and is designed to modify the disease.



https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/trc2.12295

AND THERE ARE NOVEL AND EXCITING NONAMYLOID ALTERNATIVES

- Diversification of drug targets is increasing with the major targets shown on the right side.
- 37% of the agents in the pipeline are repurposed drugs approved for other indications.
- MCI due to AD and mild AD dementia comprise the most common population included in current clinical trials accounting for 36% of Phase 3 trials and 52% of Phase 2 trials.

Type of Target

This is the primary biological process the drug is designed to target. The seven biological targets described below are all part of the "biology of aging"—biological changes that are more common with aging and that contribute to Alzheimer's.

Genetics & Epigenetics: Specific genetic traits, such as inheriting the APOE4 gene, can increase risk of Alzheimer's disease. Epigenetics are processes that regulate how active each gene is (i.e., the level of "gene expression"). Epigenetics can act like a volume control that can make genes quieter or louder, or as an "on/off switch."

Inflammation: Chronic (long-term) inflammation in the brain can accelerate Alzheimer's disease and may be a trigger for the disease. Most inflammation in the brain is regulated by special cells called microglia.

Misfolded Proteins: The three-dimensional folding of a protein is critical to its function. In Alzheimer's, proteins like amyloid, tau and others can misfold and become toxic. These misfolded proteins accumulate into plaques, tangles, and other forms in the brain if they are not cleared by the brain's self-repair mechanisms.

Mitochondria & Metabolic Function: All cells need energy to maintain healthy function, and neurons are among the highest energy users. As we age, mitochondria—the internal energy centers of our cells—can become impaired, as can the way our cells use external energy, such as glucose and oxygen (metabolism).

Neuroprotection: As Alzheimer's progresses, neurons in the brain lose their connections and begin to die, causing the loss of memory and other cognitive functions. Neuroprotective strategies protect brain cells from multiple causes of damage and death.

Synaptic Activity & Neurotransmitters: Synapses are the connections between neurons and are important for communication between these cells, creating circuits. Neurotransmitters carry signals across these connections. In Alzheimer's, synapses can become damaged and their ability to send or receive neurotransmitters and transmit messages is often impaired.

Vascular: Healthy blood flow is required for optimal brain function. Blood vessel damage can affect how misfolded proteins and toxins are removed from the brain and can limit the ability of neurons to get sufficient oxygen, glucose and vital nutrients.

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