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Review Article

Alzheimer's disease drug development pipeline: 2017

Jeffrey Cummings[a,*], Garam Lee[a], Travis Mortsdorf[b], Aaron Ritter[a], Kate Zhong[c]

[a]Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA
[b]Touro University Nevada, Henderson, NV, USA
[c]Global Alzheimer Platform, Washington, D.C., USA

Abstract

Introduction: There is an urgent need to develop new treatments for Alzheimer's disease (AD) and to understand the drug development process for new AD therapies.

Methods: We assessed the agents in the AD pipeline as documented in clinicaltrials.gov for phase I, phase II, and phase III, accessed 1/5/2017.

Results: There are 105 agents in the AD treatment development pipeline, of which 25 agents are in 29 trials in phase I, 52 agents are in 68 trials in phase II, and 28 agents are in 42 trials in phase III. Seventy percent of drugs in the AD pipeline are disease-modifying therapies (DMTs). Fourteen percent are symptomatic cognitive enhancers, and 13% are symptomatic agents addressing neuropsychiatric and behavioral changes (2% have undisclosed mechanisms). Most trials are sponsored by the biopharmaceutical industry. Trials include patients with preclinical AD (cognitively normal with biomarker evidence of AD), prodromal AD (mild cognitive symptoms and biomarker evidence of AD), and AD dementia. Biomarkers are included in many drug development programs particularly those for DMTs. Thirteen of 46 phase II DMT trials have amyloid imaging as an entry criterion, and 10 of 28 phase III trials incorporate amyloid imaging for diagnosis and entry. A large number of participants are needed for AD clinical trials; in total, 54,073 participants are required for trials spanning preclinical AD to AD dementia. When compared with the 2016 pipeline, there are eight new agents in phase I, 16 in phase II, and five in phase III.

Discussion: The AD drug development pipeline has 105 agents divided among phase I, phase II, and phase III. The trials include a wide range of clinical trial populations, many mechanisms of action, and require a substantial number of clinical trial participants. Biomarkers are increasingly used in patient identification and as outcome measures, particularly in trials of DMTs.

Keywords: Alzheimer's disease; Phase I; Phase II; Phase III; Biomarkers; Preclinical AD; Prodromal AD; AD dementia

Alzheimer's disease (AD) is increasing rapidly in frequency as the world's population ages and more people enter the major risk period for this age-related disorder. From the 5.3 million US citizens affected now, the number of victims will increase to 13 million or more by 2050; worldwide the total number of affected individuals will increase to a staggering 100 million [1]. The cost of care in the US, currently more than $200 billion annually, will grow to an unsupportable $1 trillion annually by 2050 [1].

New therapies are urgently needed to treat affected patients and to prevent, defer, slow the decline, or improve the symptoms of AD. It has been estimated that the overall frequency of the disease would be decreased by nearly 50% if the onset of the disease could be delayed by 5 years [2]. Symptomatic

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*Corresponding author. Tel.: +1-702-483-6029; Fax: +1-702-722-6584.

E-mail address: cumminj@ccf.org

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treatments are drugs aimed at cognitive enhancement or control of neuropsychiatric symptoms and typically work through neurotransmitter mechanisms; disease-modifying therapies or treatments (DMTs) are agents that prevent, delay, or slow progression and target the underlying pathophysiologic mechanisms of AD [3].

To understand the progress of drug development, describe the timelines regarding when drugs could become available, and interrogate the current drug development approaches for AD treatments, we examined the AD drug development pipeline as currently revealed in clinicaltrials.gov. We present our findings as a means of understanding and ultimately improving AD drug development. This paper continues the themes developed in our 2016 pipeline report [4] and impacts the understanding of the likelihood of reaching the national goal of having meaningful therapy for AD by 2025 [5].

1. Methods

Clinicaltrials.gov includes a comprehensive list of all clinical trials of AD and describes the trial features in text form. The "Common Rule" governing clinicaltrials.gov was updated in 2016 [6,7]. Registration is mandated for all trials from sponsors with an Investigational New Drug or Investigational New Device. Trials must be submitted to the site within 21 days of the enrollment of the first trial participant. Results must be submitted to clincaltrials.gov within 12 months of completion of final data collection for the prespecified primary outcome measures; clinicaltrials.gov can be regarded as a comprehensive resource for the study of clinical trials governed by the US Food and Drug Administration (FDA) or the National Institutes of Health (NIH). Not all non-US trials are registered on clinicaltrials.gov—especially phase I trials. We also cannot attest to compliance with the rule governing clinicaltrials.gov, and some agents may not be registered or sponsors may not adhere to required timelines.

We examined clinicaltrials.gov as of January 5, 2017. We captured all trials of all agents in phases I, II, and III. In a comprehensive database, we entered the trial title, beginning date, projected end date, calculated duration, number of subjects planned to be enrolled, number of arms of the study (usually a placebo arm and one or more treatment arms with different doses of the experimental agent), whether a biomarker was described, and sponsorship by a biopharma company, NIH, academic medical center, "other" entity such as a consortium or a philanthropic organization, or a combination of the aforementioned sponsors. We included trials that were recruiting, active but not recruiting (e.g., trials that have completed recruiting and are continuing as the efficacy or safety of the agent is being determined), enrolling by invitation, and not yet recruiting. We did not include trials listed as completed, terminated, suspended, or withdrawn. Information on these trials or the reasons for suspension or termination is often incomplete. The choice of types of trials included was informed by our intention of understanding the currently active pipeline and to know what agents could evolve in the near term. We did not include trials of nonpharmacologic therapeutic approaches such as devices, cognitive therapies, and medical food. We did not include trials of biomarkers.

The mechanism of action (MOA) of each agent was determined from the information on clinicaltrials.gov (e.g., the mechanism is often noted in the title of the trial or in a description of the trial) or from a comprehensive search of the literature if the mechanism was not provided on the federal website. In a few cases, the mechanism is undisclosed and could not be identified in the literature. We grouped the mechanisms into symptomatic agents or DMTs. We divided the symptomatic agents into those that are putative cognitive enhancing agents or those that address neuropsychiatric and behavioral symptoms. DMTs were divided into those that target amyloid-related mechanisms, those that have tau-related MOAs, and those with "other" mechanisms such as anti-inflammatory MOAs, growth factors, or metabolic effects. Stem cell therapies were included in the "other" category.

2. Results

2.1. Overview

Fig. 1 provides an overview of all agents currently in the AD pipeline. The circles reveal the stages of development (I, II, and III), the colors pertain to the MOA of the agent, and the shape denotes the population in which the agent is being tested (normal volunteers, cognitive normal at-risk individuals, prodromal AD, and AD dementia).

In all, there are 105 agents in the pipeline as shown on clinicaltrials.gov, of which 25 are agents in 29 trials in phase I, 52 agents are in 68 trials in phase II, and 28 agents are in 42 trials in phase III. Across all stages, 70% are DMTs, 14% are symptomatic cognitive enhancers, 13% are symptomatic agents addressing neuropsychiatric and behavioral changes, and 2% have undisclosed MOAs.

Of all trials, 65.5% are sponsored by the biopharma industry, 16.6% by Academic Medical Centers, 3.6% by Academic Medical Center-NIH collaborations, and 10.8% by the collaborations between consortiums/philanthropic organizations and one or more of the following: biopharma, NIH, and Academic Medical Centers. One trial is sponsored by NIH, one trial by biopharma-NIH collaboration, and one trial by a biopharma-NIH-Academic Medical Center collaboration.

2.2. Phase I

Phase I first-in-human trials are generally conducted in healthy volunteers unless they are assessing immunotherapies where the potential long-term modification of the immune system makes participation of normal controls impermissible. These trials generally progress from single ascending dose trials where increasing doses are administered once in supervised settings to assess tolerability and establish a maximum tolerated dose to multiple ascending dose trials where individuals receive doses for 14 to