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Featured Article

Alzheimer's drug-development pipeline: 2016

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Abstract

Background: Alzheimer's disease (AD) is growing in frequency and new therapies are urgently needed.

Methods: We assessed clinicaltrials.gov (accessed 1-4-2016) to determine the number and characteristics of trials in phase I, phase II, and phase III for treatment of AD.

Results: There are currently 24 agents in 36 trials in phase III of AD drug development. Seven of these 24 agents are symptomatic cognitive-enhancing compounds, and 17 are disease-modifying treatments (DMTs). Most DMTs are currently targeting amyloid-related targets (76%). There are 45 agents in phase II being assessed in 52 clinical trials. Phase II trials include 30 DMTs, including 26 small molecules and 4 immunotherapies. There are 24 agents in the first phase of AD drug development.

Discussion: There are relatively few agents in clinical trials for AD suggesting a need to amplify the drug discovery ecosystem.

Keywords: Alzheimer's disease; Drug development; Phase I; Phase II; Phase III; Biomarkers; Amyloid; Tau; Cognitive enhancement

Alzheimer's disease (AD) is rapidly becoming a major public health threat with increasing numbers of affected individuals as the world's population ages. There are currently 5.3 million Americans and 35 million people worldwide with AD dementia, and the number will increase to nearly 15 million in the United States and over 100 million globally by 2050 if solutions to treatments are not found [1,2].

New therapies are needed for this burgeoning population of affected and at-risk persons that improve the symptoms of patients with memory and cognitive decline, prevent or delay the onset of AD in individuals who are at-risk for the disease, or slow progression in those with declining cognition. New therapies are being assessed in clinical trials but the success rate of AD drug development has been low with the last new novel agent approved in 2003 [3].

To gain insight into the current AD treatment pipeline, we reviewed all trials registered in clinicaltrials.gov (accessed 1/4/2016), the US government website that lists all US and most global clinical trials. Registration of new trials on the site is required for trials approved by the US Food and Drug Administration (FDA) since 2007 [4]. We reviewed this comprehensive website for all agents in clinical trials for AD dividing them into those in phase I, phase II, and phase III. The purpose of the study was to understand the

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landscape of AD drug development and determine evolutions occurring in AD drug development from historical practices. The goal is to assess the state of AD drug development, anticipate the emergence of new therapies, review emerging pharmacologic mechanisms and clinical trial approaches, and derive lessons possibly helpful in the drug development process.

1. Methods

We interrogated clinicaltrials.gov with the information summarized here accessed on January 4, 2016. We used the search features of the site to capture all agents listed for AD in phase I, II, and III. We captured the trial title, beginning date, anticipated ending date, anticipated duration, number of subjects to be enrolled, number of arms of the study (usually a placebo arm and one or more treatment arms with different doses of the test agent), whether a biomarker was described, and whether the sponsor was a biopharma company, the National Institutes of Health (NIH), a combination of biopharma and NIH, or "other." We included trials that were recruiting, active but not recruiting—trials that have completed recruiting and are continuing as the efficacy or safety of the agent is being determined—and enrolling by invitation. We did not include trials listed as not yet recruiting, completed, terminated, suspended, or withdrawn. These exclusions were based on the currently active pipeline and to what agents could evolve in the near term. Reasons for terminating, suspending, or withdrawing trials are often not provided, and we could not draw conclusions about these trials or the agents involved. The agents and trials reviewed comprise a comprehensive list of agents currently in trials. The list is not exhaustive because not all non-US trials are registered on clinicaltrials.gov, and there is sometimes a delay in registering trials. The mechanism of action 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. We grouped the mechanisms into symptomatic or disease modifying. We further divided the symptomatic agents into those that were putative cognitive-enhancing agents or those that addressed neuropsychiatric symptoms. Disease-modifying therapies (DMT) were divided into those that targeted amyloid-related targets, those that aimed at modifying tau-related mechanisms and those with "other" mechanisms such as neuroprotection or metabolic effects [5]. The definitions of disease-modification and neuroprotection are controversial and evolving [6,7]; the terminology is used here to conveniently classify the types of mechanisms for agents in current AD drug-development programs. We did not include nonpharmacologic therapeutic approaches such as devices, cognitive therapies, and medical foods.

2. Results

There are currently 93 agents in some phase of drug development for AD. Fig. 1 provides a comprehensive overview of the agents currently in clinical trials for AD.

2.1. Phase III

There are currently 24 agents in 36 trials in phase III of AD drug development. Eight agents are in two or more clinical trials. Of the agents in trials, seven are symptomatic treatments targeting neurotransmitter pathways with cognitive enhancement (3) or neuropsychiatric (4) effects. Encenicline, a nicotinic cognitive-enhancing agent, was put on clinical hold by the FDA pending the review of gastrointestinal effects seen in some trial participants. Of the 17 DMTs in phase III, 12 are small molecules, and 5 are immunotherapies. All the immunotherapies and 8 of the 12 small molecules are directed at amyloid-related targets. There are four beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitors in phase III trials. Amyloid-targeting agents comprise 76% of the late-stage DMT pipeline. There is one antitau agent in phase III—TRx0237.

The mean duration of trials of symptomatic agents was 23.3 weeks; the mean duration of DMT trials was 114.1 weeks. In these phase III trials, the mean number of subjects per arm for symptomatic trials is 392.2 and for trials of DMT agents is 516.1.

Eighty-eight percent (32 of 36) of trials are sponsored by the biopharma industry, 2 are jointly sponsored by NIH and industry, and 2 are sponsored by "other" entities.

Table 1 shows the agents in phase III with their mechanism of action.

2.2. Phase II

There are 45 agents in phase II AD drug development being assessed in 52 clinical trials. The pipeline includes 12 symptomatic cognitive-enhancing agents and three agents addressing neuropsychiatric symptoms. There are 30 DMTs being studied in phase II drug development programs; 26 of these are small molecules and four are immunotherapies. Amyloid-related targets comprise the mechanism of action of nine of the 26 small molecules and all four of the immunotherapies. Forty-three percent of phase II DMTs have amyloid-targeting mechanisms of action. Sixteen agents have "other mechanisms" including ten putative neuroprotective agents and six addressing metabolic problems. There is one antitau agent in phase II and one stem cell program (with two trials) in phase II of development.

Phase II trials of symptomatic agents have a mean duration of 19.1 weeks and trials of DMTs in phase II have a mean duration of 49.5 weeks. On average, there are 67.1 subjects per arm in phase II trials of symptomatic treatments and 76.9 subjects per arm in trials of DMT agents.

Of the 52 trials for the 45 agents, 29 are industry-sponsored, four are sponsored by NIH, and 18 are sponsored