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Featured Article

Alzheimer's disease drug development pipeline: 2018

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Abstract

Introduction: Treatments for Alzheimer's disease (AD) are needed by the growing number of individuals with preclinical, prodromal, and dementia forms of AD. Drug development for AD therapies can be examined by inspecting the drug development pipeline as represented on ClinicalTrials.gov.
Methods: ClinicalTrials.gov was assessed as of January 30, 2018, to determine AD therapies represented in Phase I, II, and III.
Results: There are 113 agents in the current AD treatment pipeline. There are 26 agents in 35 trials in Phase III, 64 agents in 76 trials in Phase II, and 23 agents in 25 trials in Phase I. A review of the mechanisms of actions of the agents in the pipeline shows that 73% are disease-modifying treatments, 11% are symptomatic cognitive enhancers, and 13% are symptomatic agents addressing neuropsychiatric and behavioral changes. Trials in Phase III are larger and longer than those in Phase II or Phase I, particularly those involving disease-modifying agents. Comparison to the 2017 pipeline shows that there are four new agents in Phase III, 14 in Phase II, and eight in Phase I. Inspection of the use of biomarkers as revealed on ClinicalTrials.gov shows that amyloid biomarkers are used as entry criterion in 25 Phase III disease-modifying agent trials and 11 disease-modifying agent trials in Phase III. Thirty-one trials in Phase II did not require biomarker confirmation for AD at trial entry.
Discussion: The AD drug development pipeline is slightly larger in 2018 than in 2017. Trials increasingly include preclinical and prodromal populations. There is an increase in nonamyloid mechanisms of action in earlier phases of drug development. Biomarkers are increasingly used in AD drug development but are not uniformly employed for AD diagnosis confirmation.

Keywords: Alzheimer's disease; Pipeline; ClinicalTrials.gov; Biomarkers; Drug development; Clinical trials; Monoclonal antibodies

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with cognitive, functional, and behavioral alterations [1,2]. AD is age related and is becoming markedly more common with the aging of the world's population. It is estimated that by 2050, one in every 85 people will be living with AD [3]. Nearly eightfold as many people have preclinical AD or symptomatic AD and are at risk for progressing to manifest the disease [4]. Disease-modifying treatments (DMTs) that will prevent or delay the onset or slow the progression of AD are urgently needed. A modest 1-year delay in the onset by 2020 would result in 9.2 million fewer cases in 2050 [3]. Similarly, medications to effectively improve cognition or ameliorate neuropsychiatric symptoms of patients in the symptomatic phases of AD are needed to improve memory and behavior [5].

In this update of our annual review of the AD drug development pipeline, we provide a summary of the current state of progress in developing new therapies for AD [6,7]. We discuss each Phase of the AD pipeline (I, II, III) and describe DMTs, cognitive enhancing agents, and treatments for behavioral disturbances in AD that are in development. We note the use of biomarkers in clinical

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trials. We discuss evolving targets of the agents in the pipeline. We discuss trial infrastructure changes that may accelerate clinical trials and drug development. Our goal is to provide insight into the drug development process and to help drug developers and clinical trialists learn from the current pipeline experience.

2. Methods

This annual review is based on clinical trial activity as recorded in ClinicalTrials.gov, a comprehensive US government database. United States law requires that all clinical trials conducted in the United States be registered on the site. The "Common Rule" governing ClinicalTrials.gov was recently updated and mandated registration for all trials from sponsors with an investigational new drug or investigational new device [8,9]. Trials must be registered within 21 days of the enrollment of the first trial participant. Results for the primary outcome measures must be submitted to ClinicalTrials.gov within 12 months of completion of final data collection. Compliance with trial registration is high [10–12]; compliance with results reporting is lower [13]. ClinicalTrials.gov can be regarded as a comprehensive and valid data source for the study of clinical trials conducted in the United States. Not all non-US trials are registered on ClinicalTrials.gov—especially Phase I trials—and our findings may underrepresent the agents populating global Phase I efforts.

Results reported here are based on trials registered on ClinicalTrials.gov as of January 30, 2018. We include all trials of all agents in Phase I, II, and III; some trials are presented as I/II or II/III in the database, and we use that nomenclature in the review. In our trial database, we entered the trial title; beginning date; projected end date; calculated duration; planned enrollment number; number of arms of the study (usually a placebo arm and one or more treatment arms with different doses); whether a biomarker was described; subject characteristics; and sponsorship by a biopharma company, National Institute of Health, academic medical center, "other" entity such as a consortium or a philanthropic organization, or a combination of these sponsors. Using the ClinicalTrials.gov classification, we included trials that were recruiting, active but not recruiting (e.g., trials that have completed recruiting and are continuing with the exposure portion of the trial), enrolling by invitation, and not yet recruiting. We did not include trials listed as completed, terminated, suspended, unknown, or withdrawn because information on these trials is often incomplete. We included all pharmacologic trials listed in the database; we did not include trials of nonpharmacologic therapeutic approaches such as devices, cognitive therapies, caregiver interventions, supplements, and medical foods. We did not include trials of biomarkers although we noted whether biomarkers were used in the trials of interest.

Drug targets and mechanism of action (MOA) of treatments are important aspects of this review. MOA was determined from the information on ClinicalTrials.gov or from a comprehensive search of the literature. In a few cases, the mechanism is undisclosed and could not be identified in the literature, and we note these agents as having an "unknown" MOA. 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 targeting amyloid-related mechanisms, those that have tau-related MOAs, and those with "other" mechanisms such as neuroprotection, anti-inflammatory activity, growth factors, or agents with metabolic effects. Stem cell therapies were included in the "other" category.

3. Results

3.1. Overview

Fig. 1 provides an overview of all agents identified in the current AD pipeline. The main circles of the figure reveal the stage of development (I, II, 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, cognitively normal at-risk individuals, prodromal AD, and AD dementia).

In total, there are 113 agents in the pipeline as shown on ClinicalTrials.gov. We identified 26 agents in 35 trials in Phase III, 64 agents in 76 trials in Phase II, and 23 agents in 25 trials in Phase I. Review of the MOAs of pipeline agents showed that 73% are DMTs, 11% are symptomatic cognitive enhancers, 13% are symptomatic agents addressing neuropsychiatric and behavioral changes, and 3% have undisclosed MOAs.

3.2. Phase III

Phase III of the 2018 AD pipeline has 26 agents in 35 trials. There were 17 DMTs, one cognitive enhancing agent, and eight drugs for behavioral symptoms (Figure 1; Table 1). Among the DMTs, 14 addressed amyloid targets, one involved a tau-related target, one involved neuroprotection, and one had a metabolic MOA. The DMTs include six immunotherapies (all addressing amyloid). Of the DMTs, two are repurposed agents approved for use in another indication (insulin, albumin plus immunoglobulin). Of the drugs with amyloid targets, there were six β-site amyloid precursor protein cleavage enzyme inhibitors, six immunotherapies, and two antiaggregation agents. Figure 2 shows the MOAs of agents in Phase III.

There is a movement toward treating patients with milder forms of AD, including cognitively normal individuals with evidence of amyloid pathology (by cerebrospinal fluid [CSF] measures or amyloid positron emission tomography [PET]), or who have genetic profiles that place them at high risk for developing AD (Table 2). In Phase III, there were six prevention trials enrolling cognitively normal