New Standards in Alzheimer's Disease Trial Design

It is expected that between 2010 and 2050, the number of patients diagnosed in the US with Alzheimer's disease will roughly double, from approximately 5 million to 10 million individuals, with a worldwide population approaching 40 million[1]. The economic and social impact is tremendous, with billions of dollars in lost productivity, increased healthcare cost and increased family burden. Thus the effort to find a viable treatment for the prevention or symptomatic relief of Alzheimer's continues with great fervour.

Over the last decade the only new treatment for Alzheimer's that has hit the market is memantine (Namenda™). The number of failed drug programmes in that span provides a roadmap of scientific approaches that initially appear promising, but flame out in late stage development. Most recently, two promising drugs, bapineuzimab (Pfizer/Janssen) and solanezumab (Lilly), completed large Phase III programmes, only failing to meet designated endpoints necessary for approval[2]. This begs the question: Is there a better way?

The Profile

Drugs developed for treatment of Alzheimer's disease usually fall into two categories: disease-modifying or symptomatic. Currently, all approved drugs are categorised for symptomatic. These include the acetylcholinesterase inhibitors (AChEI; donepezil, galantamine, rivastigmine) as well as an NMDA antagonist (memantine). Though pursuit of symptomatic agents continues, Alzheimer's research has shifted focus more upstream and sought to find a disease-modifying drug that either prevents or delays disease progression. Tremendous progress has been made in building a profile of the prospective Alzheimer's patients, based on use of imaging and other biomarkers[4-7]. Clifford Jack[5,6] provided solid guidance for the potential relationship between β-amyloid plaque deposition in the brain, structural MRI imaging, neurodegeneration as detected by PET scanning, and cerebrospinal fluid (CSF) levels of amyloid-β_{42} peptide and *tau*. Others[4,7,8] have extended this work to create a representative profile of a pre- or early dementia subject, but for whom likelihood of disease increases. In addition, certain genetic markers, namely ApoE4[9], have also shown correlation in patients to develop dementia later in life. Finally, vast amounts of research has been derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to further define an Alzheimer's patient profile, both prior to and post disease onset. Thus, researchers now have a more defined way of targeting the best patients to participate in their trials.

The Outcomes

Both FDA and EMA guidance ask that any efficacy claims for Alzheimer's be accompanied by data supporting both cognitive and functional improvement. Historically, researchers sought to target a mild to moderate Alzheimer's population looking for statistically significant changes in a cognitive endpoint (normally the ADAS-cog) and some other functional or global measure, e.g., ADCS-ADL, CGI, CIBIC, etc. Successive failed programmes have been unable to meet the defined endpoint criteria, and have found no significant differences between patients treated with study drug and those with placebo. The reasons are varied and controversial, though population heterogeneity, data variability and error from subjective rating scales are likely culprits. By defining patients through use of biomarkers, it is hoped that such endpoints will become more sensitive. Recently, the FDA issued guidance for developing drugs for treatment of early stage Alzheimer's, providing direction for use of biomarkers as a way to design a more practical trial, but not for use as primary endpoints themselves. Kozauer and Katz[3] state that it remains unclear whether the effect of a drug on one or more such biomarkers can actually predict a meaningful clinical benefit. However, the FDA has provided guidance for use of a single endpoint, the Clinical Dementia Rating- sum of boxes (CDR-sb), as a scale that may be used to combine cognitive and functional measure for better longitudinal sucess[10]; this also has support within the Alzheimer's research community[11]. Between building a solid patient profile, and determining the right endpoints, the final challenge is tactical execution of a successful clinical trial.

Conclusions

Drug development in Alzheimer's disease requires significant investment in time and money. Consider that a Phase III programme could take three to four years to complete and cost over $200M. Thus, setting up the trials correctly the first time through proper patient selection, appropriate endpoints and study design is critical. Likewise, realistic expectations for the number of investigative sites, a global approach and regulatory

and enrolment timelines should be factored in the planning stages. It is always recommended to stay attuned to the current regulatory guidance and competitive climate to know where one's study fits and how the research community will respond to it. A careful merging of science, strategy and tactics provide for the best opportunity to address the conundrum plaguing Alzheimer's research today.
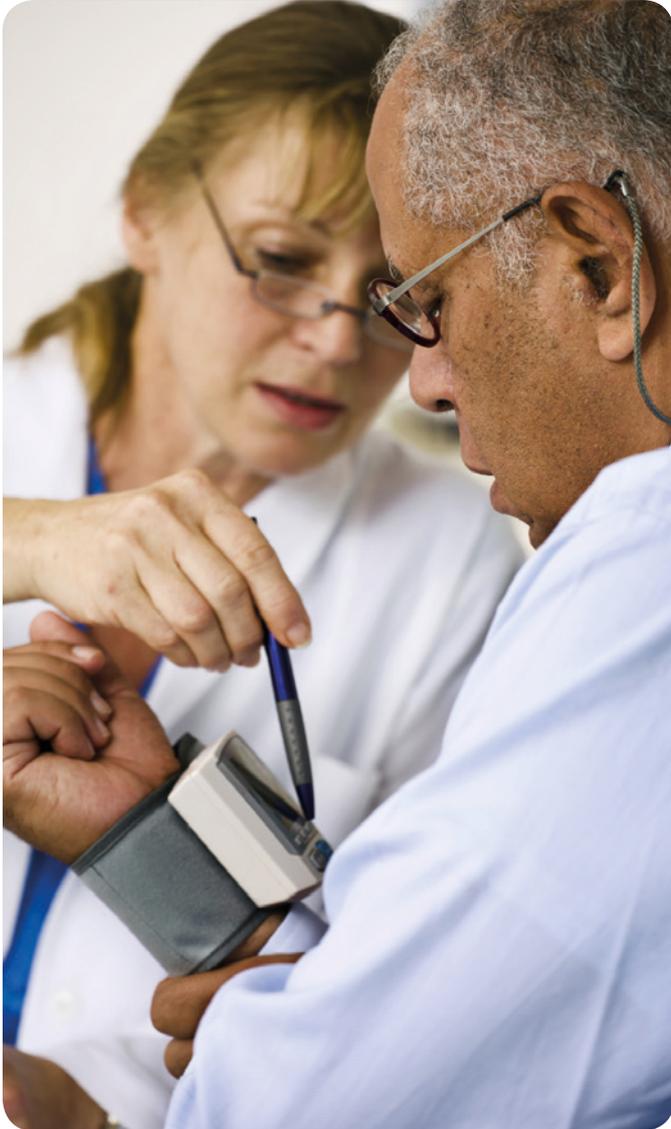
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