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Editorial

A Paradigm Shift in Drug Development for the Treatment of Alzheimer's Disease

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Alzheimer's disease (AD) and other dementias are progressive neurodegenerative diseases that affect nearly 44 million people worldwide. The number of AD patients is expected to rise in coming decades reaching a threshold of epidemic proportions with the increasing age of the general population. Today, AD and other dementias are the leading cause for disabilities in later life without a way to prevent, cure, or even slow their progression. The estimated global cost is around $605 billion, which is equivalent to 1% of the entire world's gross domestic product.

Despite considerable gains in knowledge and understanding of neuropathological mechanisms of AD in recent years, effective therapeutic options remain elusive. The identification of new relevant pharmacological targets has not led to a success in drug development. Nearly 200 new compounds progressed to at least Phase 2 in development during the past 20 years but ultimately failed to demonstrate their safety and efficacy in clinical trials. Despite this massive research effort, since 2003, only four acetylcholinesterase inhibitors (e.g., tacrine, donepezil, rivastigmine, galantamine) and memantine, a partial antagonist of glutamate at NMDA receptors have gained formal approval for the treatment of AD. The development of these therapeutic agents has been largely based on the conceptual framework for AD as a cholinergic disease. Hence, the approved drugs modify different aspects of cholinergic neurotransmission with only limited clinical effectiveness as they failed to prevent progression or alter the course of the illness. Arguably, no practical advancements in pharmacological treatments of AD have been achieved over the past quarter of a century.

With this understanding, the new approach to the drug development required a radical change in thinking and identification of different types of potential therapeutic targets. The amyloids cascade hypothesis has provided a methodical foundation in these efforts and led to the development of new classes of molecular entities aimed at disrupting the amyloid-β (Aβ) peptide deposition that also drives tau phosphorylation, neurofibrillary tangle formation and neuronal death.

Today, all of the disease-modifying agents have fallen short of validating the amyloid-β as a therapeutic target. This setback called for changes in the selection of patients eligible for clinical trials participation. The participants of on-going clinical trials reflect evolving understanding of heterogeneity AD from a perspective of severity: from asymptomatic individuals with biological vulnerability, to prodromal and mildly symptomatic, to moderately affected, and to severe AD dementia. New more stringent inclusion criteria for clinical trial participation requires a validation of diagnosis of AD by biological markers in order to select those individuals who most likely will be responsive to the anti-amyloid therapeutic approach.

The neurobiology of AD is inherently complex. Therefore, the stalemate in the drug development of the novel therapies for AD is unlikely to be broken while utilizing interventions with a single therapeutic agent. To understand better the process of drug development, it is important to acknowledge that commonly used the add-on approach of anti-amyloid therapies to the standard of care does not provide the same outcome data as the rational combinations of different therapeutics aimed to address multiple disease pathways. The preponderance of clinical evidence from a combination therapy of acetylcholinesterase inhibitors and NMDA antagonists support the short-term benefit of this approach on symptomatic level. However, these therapeutics are not expected to modify or slow down the progression of AD. Therefore, another important step for advancing the process of drug development will be to simultaneously initiate the drug combinations of therapy that target the amyloid cascade including anti- Aβ peptide antibodies and secretase inhibitors.

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