Time to rethink the pharmacological treatment of Alzheimer's disease

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The understanding of the physiopathological bases of Alzheimer's disease (AD) is rapidly increasing and a variety of possible pharmacological treatment modalities have emerged thanks to these improved mechanistic hypotheses. However, it remains unclear how to develop novel disease modifying drugs and several problematic issues have been raised. In particular, these relate to: the definition of AD, the participation of patients with mild cognitive impairment in clinical studies, the very definition of modification of the course of disease, potential impediments to the satisfaction of patients on disease-modifying drugs, the importance of add-on therapy with symptomatic medications, the optimal design of clinical trials to demonstrate the modification of course of the disease, the best strategy to minimize the time spent in phase II during the development of drugs, the potential role of adaptive designs in clinical studies, the role of biomarkers, the treatment of patients with disease at an advanced stage, the definitive distinction between modification of the course and disease prevention. These and other relevant issues need to be appropriately addressed if we are to develop novel molecules for a better pharmacological treatment of AD.