



Editorial

Treatment and Preventive Measures of Alzheimer's Disease: Current Perspective

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Alzheimer's disease (AD) is an age-related, progressive, and irreversible neurodegenerative disorder characterized by cognitive and memory impairment, and it is the most common cause of dementia in older adults. The estimated prevalence of this disease in 2015 was 44 million people throughout the world and it is estimated that this figure will double by 2050¹. Most people with AD (over 95%) have sporadic or late-onset AD (LOAD), a multifactorial disease in which environmental factors and genetic predisposition contribute to the pathology². The other form of AD, familial or early-onset AD (EOAD), corresponds to less than 5% of the AD population³ and is due to mutations in any of the three genes⁴ which are the amyloid precursor protein (APP) gene on chromosome 21, presenilin 1 (PSEN-1) gene on chromosome 14, and presenilin 2 (PSEN-2) gene on chromosome 1. The classification of AD is based on clinical criteria including medical history, physical examination, laboratory tests, neuroimaging, and neuropsychological evaluation⁵⁻⁶.

Due to the aging of the global populations, chronic disorders are becoming increasingly prevalent⁷. This includes dementia, which in 2015 affected 47 million people worldwide and is expected to affect twice as many people 20 years from now⁸. Most late-onset dementia cases are related to Alzheimer disease (AD) pathology, but mixed etiologies are more prevalent in older populations. Amyloid- β ($A\beta$) plaques and tau neurofibrils, the two pathological hallmarks of AD, have less impact on cognitive performance in the oldest-old compared with younger individuals⁹ and "pure" AD cases are also less frequent in older patients, who mostly have additional neuropathological lesions, including vascular changes. Also, significant $A\beta$ pathology is not only found in individuals with dementia but is also prevalent in cognitively intact individuals, and

age is a main predictor of $A\beta$ plaques, even in the absence of relevant cognitive decline¹⁰.

In neuropsychiatric tradition, AD was conceptualized as a clinicopathological duality, ie, a diagnosis was only possible in the presence of an amnesic-type progressive dementia syndrome and the exclusion of alternative etiologies. This simple set of criteria is not particularly sensitive for early changes nor is it specific enough for AD pathophysiology. Therefore, in the last 10 years evolving sets of new AD criteria were proposed by different international expert groups, aiming to steer the dementia field towards a more biologically oriented disease concept, similar to other areas of medicine, such as cancer, where biomarkers are used to define diseases¹¹. This paradigm shift is fueled by the urgent desire to develop more effective, ie, disease-modifying rather than purely symptomatic, treatment options. Being able to identify a disease in its pre-symptomatic or prodromal stage would open new opportunities to prevent or slow pathophysiological processes rather than merely trying to retard the worsening of symptoms. The development of biomarkers which are more sensitive for the early stages of AD is a prerequisite for a successful transformation of the diagnostic approaches¹².

Individuals at risk of cognitive deterioration and dementia, who are still asymptomatic, would probably benefit most from intervention strategies aimed at prevention of further neuronal loss¹³. If no or only minimal symptoms are present, effective disease modification could help the target population to maintain their independence, fulfilment of social roles, and ability to work for a longer period of time. Alzheimer's disease requires precise diagnosis, early if possible, and adequate etiological treatment, and,

as an incurable age-related neurodegenerative disorder, its particular pathophysiology needs to be considered. The therapeutic options have focused on ameliorating the symptoms as well as reducing the rate of progression of damage, although this has not significantly reversed the disease, so prevention is a better solution for this public health problem¹⁴.

The toxic conformations of A β or tau in the brain are thought to spread the disease, and blocking the generation of these peptides may be part of useful treatments. Nevertheless, the current treatments of this disease are based on cholinesterase inhibitors and a glutamate antagonist, providing only symptomatic relief, while evidence for the complexity and multicausality of this dementia is recognized in basic and clinical studies¹¹. Efforts in etiology-based treatment are currently underway in clinical trials, as well as complement preventive treatments such as physical activity, proper diet, cognitive stimulation, and the management of comorbidity³.

Effective treatment for AD is achieved with cholinesterase inhibitors, which corresponds well to Davies and Maloney's early cholinergic deficit hypothesis explaining AD pathophysiology. Tacrine, donepezil, rivastigmine, galantamine, xanthostigmine, para-aminobenzoic acid, coumarin, flavonoid, and pyrrolisoxazole analogs have been developed and studied for the treatment of AD¹¹. Rivastigmine, donepezil, and galantamine are the approved drugs that promote higher ACh levels and improve the brain's cholinergic function by inhibiting the enzyme acetylcholinesterase which degrades the neurotransmitter⁹. In general, acetylcholinesterase inhibitors (except tacrine) are well tolerated and adverse effects are dose-related⁴. The acetylcholinesterase inhibitor ladostigil (TV3326) is in phase II clinical trials and it also produces antidepressant effects for the inhibition of monoamine oxidases A and B^{7,11}.

Memantine can protect neurons by attenuating tau phosphorylation through a decrease in glycogen synthase kinase 3 β (GSK-3 β) activity¹¹. This noncompetitive glutamatergic NMDA receptor antagonist can be administered alone or in combination with an acetylcholinesterase inhibitor although there may be few significant favorable changes in the combination therapy⁷.

in 2018 the current AD drug development pipeline across all study phases encompasses 112 compounds, including 23 agents in 25 phase 1 trials, 63 agents in 75 phase 2 trials, and 26 agents in 35 phase 3 trials¹. This includes eight new drugs in

phase 1, 14 in phase 2, and four in phase 3 compared with an analysis conducted in 2017⁷. Biomarkers, mainly indicating A β status, are increasingly being used as study entry criterion, particularly for studies on disease-modifying agents. There is also a trend towards targeting earlier disease stages, ie, prodromal or preclinical AD. Most studies (14 phase 3 trials in 2018) target A β , but an increase of non-A β mechanisms of action of compounds in earlier stages of development is noted⁵.

Among the different approaches targeted at A β , immunotherapy remains the best developed strategy, particularly passive immunization with monoclonal antibodies. Other strategies are being explored, including efforts to inhibit the activity of the APP cleaving enzymes β - and γ -secretase or A β aggregation, amongst others. Immunization trials had an ill-fated start with AN1792 (active immunization with full-length A β 42), for which the development was terminated prematurely because of T cell mediated meningoencephalitis in 6% of the treated study population⁹. Second-generation active vaccines use antibodies restricted to the N-terminus of A β , avoiding T cell epitopes at the C-terminus. So far only CAD106 has advanced to phase 3 clinical developments and is being studied in the Alzheimer Prevention Initiative study in homozygous carriers of the apolipoprotein E (*APOE*) $\epsilon\epsilon$ risk allele¹⁴.

Aducanumab is intravenous infusion therapy is the first drug of its kind to be approved for Alzheimer's disease¹. It is approved only for patients with mild cognitive impairment and mild dementia due to Alzheimer's disease. The FDA approved aducanumab under an accelerated approval provision because it reduced brain beta-amyloid, a protein that is thought to be a key part of the Alzheimer disease pathway. Another Alzheimer's medicine, lecanemab, has shown promise for people with mild Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease³.

It could become available in 2023. A phase 3 clinical trial found the medicine slowed cognitive decline in people with early Alzheimer's disease by 27.0% cases. Lecanemab works by preventing amyloid plaques in the brain from clumping^{3,7}. This was the largest study so far to look at whether clearing clumps of amyloid plaques from the brain can slow the disease. Lecanemab is under review by the FDA. Another study is looking at how effective the medicine may be for people at risk of Alzheimer's disease, including people who have a close relative with the disease.

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