

# Anti-dementia medications: current prescriptions in clinical practice and new agents in progress

Florindo Stella, Márcia Radanovic, Paulo Renato Canineu, Vanessa J. R. de Paula and Orestes V. Fortenxa

**Abstract:** Almost three decades after the publication of the first clinical studies with tacrine, the pharmacological treatment of Alzheimer's disease (AD) remains a challenge. Randomized clinical trials have yielded evidence of significant – although modest and transient – benefit from cholinergic replacement therapy for people diagnosed with AD, and disease modification with antidementia compounds is still an urgent, unmet need. The natural history of AD is very long, and its pharmacological treatment must acknowledge different needs according to the stage of the disease process. Cognitive and functional deterioration evolves gradually since the onset of clinical symptoms, which may be preceded by several years or perhaps decades of silent, presymptomatic neurodegeneration. Therefore, the pharmacological treatment of AD must ideally comprise both a symptomatic effect to preserve or improve cognition and a disease-modifying effect to tackle the progression of the pathological process. Primary prevention is the ultimate goal, should these strategies be delivered to patients with preclinical AD. In this article, we briefly address the pharmaceutical compounds that are currently used for the symptomatic treatment of AD and discuss the ongoing strategies designed to modify its natural course.

**Keywords:** Alzheimer's disease, cognitive impairment, dementia, treatment, pharmacology

## Introduction

In the past two decades, the body of knowledge on pathophysiological mechanisms of Alzheimer's disease (AD) has increased substantially. Pathological cascades including extracellular amyloid plaques, intracellular neurofibrillary tangles, inflammatory mechanisms, synaptic degeneration and loss of neuronal cells have been extensively investigated [Braak and Del Tredici, 2011; Winblad *et al.* 2014; Sperling *et al.* 2014]. Convergent findings strongly suggest that these neurobiological mechanisms start long before clinical manifestations, although it is debatable how, where and when the neurodegenerative process actually begins [Dubois *et al.* 2014; Sperling *et al.* 2014; Jack *et al.* 2014]. A better understanding of pathological mechanisms of the disease allows the proposal of new effective and safe treatment strategies.

Currently, there are three acetylcholinesterase (AChE) inhibitors – donepezil, galantamine and

rivastigmine – available for AD treatment, as well as the glutamatergic antagonist memantine. Despite being widely prescribed, these drugs have only limited and transient symptomatic effects when compared with placebo, without a definite impact on the long-term neurodegenerative process [O'Brien and Burns, 2011].

Other pharmaceutical compounds were designed to attenuate or interrupt the progression of neurotoxic events subsequent to overproduction of the amyloid-beta peptide (A $\beta$ ), with potential effects in animal models. However, clinical trials with most of these agents have not so far provided any conclusive evidence of clinical benefit for human patients, in spite of promoting A $\beta$  clearance and/or attenuation of neuropathological changes within the brain.

Converging efforts toward the development of pharmacological agents with properties to effectively prevent or interrupt the earliest stages of the

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