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Editorial

The Time for Combination Therapy Research in Alzheimer's Disease is Now[1]

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By far, Alzheimer's disease (AD) is the most common neurodegenerative process, and we have so far failed to manage it effectively, with only a handful of symptomatic therapies and questionable newer disease modifying agents. AD is uniformly fatal and needs to be compared to other serious diseases such as cancer or HIV with an otherwise progressive irreversible course. AD pathology is multifactorial. Most symptomatic and potential disease modifying agents in development have narrow molecular targets. Most are tested alone versus placebo. It is only practical to expand our portfolio of combination trials, now, testing multiple pathological targets simultaneously. Similar research modalities have been successfully deployed in other multifactorial diseases such as HIV, diabetes, tuberculosis, and various oncological conditions [1]. Combination therapy may trigger a synergistic effect. Combination therapy may allow us, in theory, to improve tolerability of treatment by giving lower doses of medications. Adaptive combination treatments may prove helpful in various stages of AD. Of course, combination trials are complicated and demand a special design and a higher level of cooperation between the pharmaceutical industry, academic institutions, advocacy groups, and the federal government [2]. The reliance on multiple biomarkers to assess outcome may be complicated, and may demand development of novel outcome measures, corresponding with functional stabilization with benefit to patients and their families.

I call for the Federal governmental agencies to take on the urgent need to address and adjust the regulatory hurdles pertaining safety and efficacy for combination therapy research in AD.

The CTAD EU/US task force discussed combination trial therapy in AD in 2018 [3] and needs to meet again now, to readdress the topic with the newer disease modifying agents on the market. Updated guidelines are needed now.

I call for advocacy groups to prioritize the role of mediators between the pharmaceutical companies to allow combination therapies from separate development processes to work together, to devise the proper design of combination therapy research, and to solve issues of reimbursement, as well as mediate for a combined effort regarding post research monitoring of long-term effects of polypharmacy.

The time to do this is now, with more than 6 million patients with AD in the United States today, with a projection of more than 13 million patients in 2050, any delay in the evolution of combination therapy research could lead to expansion of suffering and the

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death rate of millions of projected patients in a decade or two.

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