The Journal of Prevention of Alzheimer's Disease 12 (2025) 100211

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Not a slam dunk (or Free Lunch): The complex future of Alzheimer's combination therapy

In clinical practice, it is common to treat chronic complex diseases with combination therapy. However, every medical student learns early on that the best practice is to initiate treatment for individuals with a disease using a single therapeutic intervention and to monitor their progress. In reality, combination therapy rates vary, but they are estimated to be higher than 30 % for people with schizophrenia [1], rheumatoid arthritis [2], and for epilepsy [3]. Most of these combinations are used empirically, without a robust evidence base. Furthermore, cases of schizophrenia and epilepsy involve symptomatic treatments where improvements in clinical phenomenology serve to monitor treatment response. Meanwhile, combinations that delay disease progression are much more difficult to evaluate clinically, even in trials, because the slowing of progression tends to be elusive.

Angioni et al. [4] discuss the development of combination therapies for Alzheimer's disease as part of the US-EU CTAD task force. This forum brings together academics, industry professionals, and regulators or former regulators to identify gaps and solutions for pressing issues in Alzheimer's disease drug development. A similar discussion was held in 2024 by the Alzheimer's Drug Discovery Foundation (ADDF) [5]. The complex and multifactorial nature of AD pathogenesis suggests potential benefits from targeting multiple mechanisms simultaneously. The relatively modest clinical benefit—despite the significant reduction in amyloid plaques (approximately 30 % less progression as measured by CDR-SB)—observed in the pivotal trials supporting the recent approval of anti-amyloid drugs [6,7], raises the hypothesis that a single mechanism of action may be insufficient to achieve a clinically meaningful effect and that combining treatments with different mechanisms could produce additive or even synergistic effects.

This is a plausible hypothesis, but not a slam dunk. There are reasons to believe that, depending on the disease stage and the degree of irreversible changes at the molecular, cellular, and circulatory levels, the ability to improve the disease course may be limited by a threshold. The existence of such a threshold is unknown; likewise, the benefit-risk of combination therapy, although logical and intuitive, also remains uncertain. Angioni et al. describe different scenarios for scientifically evaluating the therapeutic value of combination therapies. Questions to be answered are: 1) What to combine? 2) When to combine? 3) How to combine? 4) Who is more likely to benefit?

Regarding what to combine, Angioni et al. state that anti-amyloid and anti-tau therapies are emerging as a central focus, while anti-inflammatory agents combined with anti-amyloid or other therapies show promise. It is crucial to acknowledge that neither anti-tau therapies nor anti-inflammatory agents (such as GLP-1 agonists) have yet demonstrated benefit in randomized trials, which are currently ongoing. Several other ongoing trials involve combinations targeting senolytics, neuroinflammation, and bioenergetic agents. Until these trials conclude, it is premature to assume the future configuration of combination therapy.

Aside from the mechanistic challenge of combining therapies, there is also a mathematical combinatorial issue. Without a technical triage of potential combinations and considering just three classes (each containing two different drugs)—anti-amyloid, anti-tau, and anti-inflammatory—the theoretical number of combinations of 2 or 3 drugs amounts to 20. Given the complexities and logistical demands of clinical trials, testing all these combinations is unfeasible. Therefore, it is essential to utilize technologies like AI within the context of "network medicine" to predict the best candidates for combination, as proposed by Cummings et al. [8].

Then there is the question of when, i.e., at which stage of the disease drug combinations should be used; this is tied to the question of who should be treated with which combination. To paraphrase Angioni, "[if it is established that tau seeding is the primary driver of cognitive decline and occurs early in the disease course, it may be reasonable to initiate anti-tau therapy first… if it proves to be highly effective." Once again, there is a pressing need for robust evidence!

There is also the question of how. Combination therapy may be started simultaneously; that is, two or more interventions can be initiated concurrently, or the different components of the treatment may be administered sequentially in a non-arbitrary order, with variations in sequencing: a) First, treatment is initiated and stabilized, and the second treatment is later added. b) First, treatment is initiated and maintained for a yet-to-be-established period, after which the treatment is interrupted, and the second treatment is initiated.

The authors discuss trial designs to address these different scenarios, including the factorial design, which is theoretically the best solution to provide the evidence needed on a combination's value, but is usually impractical due to the large sample sizes required. There is no free lunch!

Angioni et al. are correct to emphasize the importance of using biomarkers as endpoints in combination clinical trials, particularly when the interventions are deployed early in the disease course. However, such use must be coupled with an understanding of the relationship between those biomarkers and the pathophysiology of AD. In the long run, they should also be predictive of clinical outcomes.

Combination therapy is expected to become the standard treatment for Alzheimer's disease in the reasonably near future. However, before payers support it, the benefits and risks of each treatment must be better defined, and the economic value of the combinations established.

https://doi.org/10.1016/j.tjpad.2025.100211
Received 19 May 2025; Accepted 20 May 2025
Available online 31 May 2025

A further consensus discussion, like the one described in the Angioni et al. paper, is warranted in the coming years as more data accrue. This follow-up discussion will help narrow the number of possible designs and combinations to be tested.

During the preparation of this work the author(s) used [NAME TOOL / SERVICE] in order to [REASON]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Conflict of interest

CS is an employee of CHDI Management, Inc. advisors for CHDI Foundation. and has received consultancy honorarium from Pfizer, Kyowa Kirin, vTv Therapeutics, GW pharmaceuticals, Neuraly, Neuroderm, Neuroxpharm, Inflictis, Biocodex, Thelonious Mind, Novartis, Biogen, Green Valley Pharmaceuticals, and Pinteeon Pharmaceuticals.

CRediT authorship contribution statement

Cristina Sampaio: Writing – review & editing.

Cristina Sampaio
Chief Medical Officer
CHDI Management, Inc. for CHDI Foundation, Princeton, USA
Professor Clinical Pharmacology, Faculdade de Medicina de Lisboa, Lisboa, Portugal

E-mail address: Cristina.Sampaio@chdifoundation.org

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