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Main Title: An argument for simple tests of treatment of Alzheimer's Disease

Running Title: Validation before combination of treatments

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Author declarations

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Abstract

Two potential disease-modifying approaches for dementia are being vigorously tested: the early targeting of the neuropathology of Alzheimer's Disease (AD), and multi-domain lifestyle interventions to promote resilience to neuropathology. We apply the “web of information” model of clinical translation to both approaches to argue firstly that tests of treatments aiming to achieve clinically meaningful outcomes should remain simple. Secondly, that building clinically-meaningful treatments should be kept separate from public health policy which means promoting wide-reaching action against risk factors now with available information.

Keywords: dementia, Alzheimer's disease, clinical trials, treatment, innovation, public health

There is a major need for “clinically meaningful outcomes ... [which] produce a clear and sustainable benefit, while altering the disease trajectory” of AD [1]. Two international working groups argue that the early targeting of hallmark AD pathology (ADP)—including beta-amyloid (A β) and tau proteins—before the arrival of the symptoms of dementia may represent the best disease-modifying treatment option available [2, 3]. Conversely, members of two Lancet Commissions focus on the discrepancy between the accumulation of AD pathology and dementia and argue that 40% of cases of dementia might be preventable if society can take lifelong action against 12 risk factors including lower education as well as poor physical, mental and social health across the lifetime [4, 5]. These epidemiological risk factors are not “targets” in the same way as ADP provides targets, since they have low specificity for AD and thus are not considered causes of the disease. Nevertheless, recent initiatives are directly testing their therapeutic value in randomized clinical trials and researchers are indeed in favour of “targeting” lifestyle risk factors [6]. Other approaches beyond targeting ADP and risk reversal also exist from within basic biology

but there is a lack of expert consensus on how to choose between the “long list of disease-causing options” [7].

Jeffrey Cummings regularly publishes updates on the “drug development pipeline” for treatments of AD [8]. But Kimmelman and London [9] argue that “the so-called drug pipeline is not really about drugs and is not much like a pipeline ... [translation] is really about ... information ... a web ... between exploratory studies, confirmatory studies, clinical practice, and theory” (pp. 27, 32, *ibid*) which requires finding the “optimal values of various variables ... dose, timing of drug administration, or diagnostic scores ... at which [the intervention] achieves the most favorable risk-benefit balance ... [and] defining the boundaries on dimensions beyond which [treatment] ceases to be clinically useful ... clarifying the minimal effective and maximum tolerated doses, the earliest and latest a drug can be applied in disease course, and so on” (p. 29, *ibid*).

Meaningful outcomes or endpoints involve necessarily different disease stages, stakeholders, and measures of meaningfulness [1]. Broadly, we understand a treatment producing a clinically meaningful outcome as a *setup* containing safety (*s*) and efficacy (*e*) instructions to make some thing (*t*) useful (*u*) with respect to some end point (*p*). We use the loose term “thing” because it can be applied to *anything* in a proposed treatment (from treadmill running to taking aspirin) and because the same thing can have multiple clinical uses. (High-dose aspirin is used for alleviating pain and inflammation whereas low-dose aspirin is used as an antiaggregant agent for the secondary prevention of stroke. Same *thing*, different *treatment*.) This is why drugs have approved “labels” for use.

We apply this information model to both life-style interventions and drug strategies before discussing the prospects of combination therapies for dementia. There is still no fully-approved treatment setup (i.e. drug plus label) based on targeting ADP. The question of “whether the negative clinical trials of putative disease-modifying interventions have been true failures ... of

the hypothesis; negative outcomes deserve to be trusted) or false failures (failure of the trial methodology; hypotheses deserve another chance)” (p. 482, [10]) is currently dividing the AD community [6].

The evidence for specific treatment setups is also scarce on the side of risk reversal. “Little evidence exists for any single specific activity protecting against dementia” (p. 413, [5]). The Finnish Geriatric “FINGER” study, a 2-year multi-domain physical and cognitive interventional trial that led to “a small group reduction in cognitive decline” (p. 426, *ibid*) in a treatment group aged 60-77 of approximately 600 cognitively at-risk people vs. controls [11], has not been replicated by other similar tests of multi-domain intervention.

Beyond these two approaches, there is a generalized mismatch between converting possible targets with promising data and therapeutic rationale into a disease-modifying treatment for AD, including NSAIDs like naproxen [12]. Given the current failure of any one thing (drug or activity) to have some meaningful disease-modifying impact on AD, there are calls for combination therapies. Salloway et al. [13] offer biological, pharmacological and regulatory arguments to “support the development of combination disease-modifying therapies for AD” (Table 1, *ibid*). Karl Herrup [7] argues that there is a “long list of disease-causing options ... choose them all ... each treatment will make a difference” (p. 797, *ibid*). His call is being heeded. There is a “more diversified” AD pipeline in 2021 than in previous years [8]. Though Herrup indeed argues for “small and incremental” victories against this disease (p. 797, [7]), we are concerned that “choose them all ...” might be interpreted as “simultaneously.” For example, certain researchers defend an “integrated approach” of resilience promotion and pharmacology [14], whilst others are exploring a “silver buckshot” approach based on multiple targets [15].

When simple treatments get combined they become a complex intervention ensemble, whose elements may interact. This is what Salloway et al. [13] cite as “additive or synergistic effects” (p.

2, *ibid*). There are famous instances of useful combination therapies like antiretroviral therapy (ART) in HIV. But these work so well because they were essentially improvements on therapies acting at already-validated targets, offering multi-pronged attacks on different aspects of the same virus [16]. This is not the case for dementia research since even the most hopeful target ($A\beta$) may not deliver on its promise and most other targets are very diverse and not specific to AD [7]. Just as drug interactions in the elderly are a major cause for concern, interactions between aspects of lifestyle intervention for the purpose of building and validating clinically meaningful treatments should be studied further. This is because risk factors may themselves be part of dementia, offer little direct therapeutic value, and also interact [17]. We are concerned that for a disease with no currently-validated therapeutic targets, combining treatments may lead to interactions that may be more numerous and clinically significant than individual target engagement itself (Table 1). This would make interpreting the origin of treatment effects very difficult, with serious issues for generalisability for a disease with millions of sufferers waiting for a treatment.

N. of items in the ensemble	Informational representation of the complex ensemble	Number of hypothetical interactions	Possible contributions to treatment effect
1	= Safety, Efficacy Instructions + Thing (SET) ₁	0	1 item + 0 interactions = 1

2	= Set1 + Set2 + Interaction ₁₋₂	1	2 items + 1 interaction = 3
3	= Set1 + Set2 + Set3 + I ₁₋₂ + I ₁₋₃ + I ₂₋₃	3	3 items + 3 interactions = 6
4	= Set1 + Set2+ Set3 + Set4 + I ₁₋₂ + I ₁₋₃ + I ₁₋₄ + I ₂₋₃ + I ₂₋₄ + I ₃₋₄	6	4 items + 6 interactions = 10

Table 1 – The informational complexity of complex treatments for diseases like Alzheimer’s disease. Items in complex treatments may interact. In treatment-resistant dementia it is vital for the first therapies to be as informationally simple as possible. This same reasoning can be applied equally to drug cocktails and multi-domain lifestyle interventions.

For a disease with different stages, stakeholders, and outcome measures, providing a meaningful disease-altering benefit is a tall order. We argue to keep the tests of treatments simple, but also to distinguish research into treatments (building and validating them) from health policy, which should be wide-reaching so as to maximise its impact. New platform trial methodology should accelerate trials with simple drug treatments [18]. Conversely, policymakers must act on the best

evidence available to them to promote health despite uncertainty and revise their decisions with new evidence. This involves encouraging wide-reaching action against risk factors, while being careful to respect individual autonomy and avoid stigmatising language of the sick [19]. On the treatment side we must keep the stringent requirements of validation for full authorization and registration so as to avoid the propagation of unvalidated treatments for dementia [15]. By keeping these activities separate, policymakers can act now while researchers make meaningful victories.

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