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Editorial

Perspective on Failed Trial Re: Efficacy of Nutritional Supplement to Prevent Cognitive Decline

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In the realm of science, the ratio between success and failure of experiment normally is very small. This scarcity of positive findings is especially true in the field of therapeutics for dementia-Alzheimer syndrome, where 'failure of clinical trials' is a frequent outcome.

A longstanding puzzle for the field of therapeutic research on interventions for dementia is the reason[s] for the frequency of mismatches between the positive findings of observational studies or the promising results from animal model and negative results from randomized control trials [RCT].

Some of the plausible variables that might account for the discordance between the results from different approaches [e.g., observation or epidemiological and RCT] might include:

- Methodological difference; such as assumptions, outcomes measures, instruments, criteria for inclusion-exclusion of subject.
- RCT are necessarily of short duration; they cannot test interventions for biological processes that have evolved over decades. For example, those conditions that have begun at mid-life, such as post-stroke cognitive impairment, change-deteriorate is very slow, over several years. So, in populations where the rate of cognitive decline is very slow, time frame for RCT needs to be longer.
- RCT subjects are often enriched for the probability of some specified outcome; consequently, the results may not be generalizable more broadly as in people in observational studies.
- The categorical outcome measures, particularly the sensitivity to change, may differ between observational study and RCT.
- Difference in process of randomization to control for x, y or z variables. For example, in trials like the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability [FINGER] that are considered multi-modal interventions, several modifiable factors are addressed at the same time, where the focus is on the overall impact rather than the effect of any one specific factor.

Consequently, the negative results of a year-long clinical study reported in the current issue of the Journal is not a surprising outcome (1) . Nonetheless, the analysis of this failed experiment has didactic value by offering important lessons for future research on therapeutics for complex chronic brain disorders such as dementia-Alzheimer syndrome.

The specific aim of the 'Noland Trial' by Giudici et al was to test, via secondary analysis, the hypothesis that '…nutritional supplementation could be a possible intervention pathway to prevent cognitive decline and Alzheimer's disease (AD)…'. The intent was to test the efficacy of a nutritional blend on plasma p-tau181 and glial fibrillary acidic protein (GFAP) levels in community-dwelling older adults. The study design was based on the assertion [or assumption] that positron emission tomography (PET) measurements /or/ cerebrospinal fluid (CSF) analyses of amyloid-β and tau pathophysiology may represent the plasma versions of biomarkers that are more accessible and may have '…comparable capacity of predicting cognitive impairment…'.

Although the rationale for this study was well-grounded, the findings did not support [nor disprove] the central premise of the study. The results showed that the '…increase in plasma p-tau181 and GFAP levels was not different...' among the supplementation groups at the end of one-year intervention. In short, the central hypothesis regarding a functional relationship between nutritional supplement and behavior/cognitive performance still remains to be tested and validated via a more adequate clinical trial. So, the question is what the lessons are to be gleaned from the failed trial for improving the next generation of studies.

In recent years, in the wake of successive failures to demonstrate efficacy of treatments, the enigma , 'what' is broken in clinical trial and 'how' to fix these problems has been the topic of extensive discussion at various meetings. These stocktaking excercises have identified several potential shortcomings of previous trials that may account for the failure of any particular study. Although some of these plausible explanations may account for some of negative results reported, such as errors in study design /or / flaws in methods /or / data analysis /or / in target selection and/ or mistakes in drugs tested / or mistakes in subject selection /or / trial duration and other explanations, there are other factors that have been overlooked. Among these, the adequacy or accuracy of the conceptual framework for the polygenic origins of

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the 'disease' or the validity of the assumptions about the causal mechanistic putative links between are sufficiently explored. For example, it is very likely the widely accepted ideas or assumptions about the pathogenesis of dementia Alzheimer syndrome which provide the mechanistic foundation for current therapy development, may not be sufficient or accurate. The recent succession of failed trials for efficacy of interventions provide further weight to the growing recognition for a different novel conceptual models that take into account the 'complexity' of the condition and one that would address the major gaps in understanding the multi-facetted biology of dementia.

One of the vital shortcomings of prevailing theories on pathogenesis, the fatal flaw for most paradigms for clinical trials, is the deficiency to account fully for the cascade of mechanistic [cause-effect] relationships between the putative biological underpinnings of the disease and the expression of its behavioral-clinical features or phenotypes. So, the main challenge for a prospective novel conceptual model is to a) identify the multiple key components [.e., signaling paths], and b) explain the non-linear interactions among these variables that underlie the pathogenesis of this complex brain disorder.

The lingering challenge for the field, which might provide a plausible explanation for the negative results of the present study, is the inconsistent relationship between biological phenotypes of the disease [vis-à-vis pathogenesis and associated putative biomarkers] and clinical/behavioral features such as cognitive impairments. The association between hallmark brain lesions [e.g., amyloidosis, tauopathy, and various 'biomarkers' such as plasma p-tau181, glial fibrillary acidic protein (GFAP), positron emission tomography (PET) measurements, or cerebrospinal fluid (CSF) levels of amyloid-β and tau] and the disease have been known for some time, along with various hypothesis about the putative mode of action or toxicity. However, the precise cascade of signaling path or the specific molecular mechanism of how such misfolded proteins effect neuronal function-dysfunction remain unknown. Thus, the details of multiple interwoven signaling pathways triggered by various biological signals, leading to massive loss of synapses – the most proximal neurobiological events associated with cognitive impairments, remain poorly understood.

In summary, 'Noland Trial' by Giudici et al once again underscores the lessons that:

- although a 'biomarker' might be used as an index of the disease, it might even potentially predict a clinical benefit, but alone it is not a measure of clinical benefit
- the negative results do not negate or speak for the putative benefits nutritional supplements as intervention to maintain brain health or delay cognitive impairment
- there are gaps in knowledge about the functional or mechanistic relationships between biomarkers, the biology of the disease, and the neural mechanisms that underlie the expression of the behavioral-clinical features of dementia-Alzheimer syndrome.

Conflict of interest: Zaven S. Khachaturian, Ph.D. is an Officer and director of the Campaign to Prevent Alzheimer's Disease (PAD 20/20) and; director and employee of Khachaturian and Associates; Founding editor-in-chief of Alzheimer's & Dementia, The Journal of the Alzheimer's Association (retired).

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