

Editorial

Commentary for Sequential Therapy Based on Evolvement of Patterns: A New Model for Treatment of Alzheimer's Disease



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It has been accepted for many years that Alzheimer's disease (AD) is the main cause of dementia in most if not all parts of the world. It is a very complex disorder and its underlying pathological mechanisms are still poorly understood. There are a number of risk factors. These include increasing age, apolipoprotein E ε 4 genotype, a number of different autosomal dominant genetic mutations that especially affect younger people, and a host of medical risk factors such as hypertension, diabetes mellitus, hypercholesterolaemia, lack of exercise and obesity to name but a few. Modestly effective symptom treating drugs such as the cholinesterase inhibitors and memantine, and N-methyl-D-aspartate receptor antagonist, have been available for many years but despite fifteen to twenty years of research endeavour we still do not have any AD targeted disease modifying drug treatments that delay or prevent the pathology. All of the trials of the latter have failed so far despite many different underlying strategies. This could be the result of all the trials being of a monotherapy, or targeting the wrong pathological process, or trying to develop a single "magic bullet" approach that would benefit all patients with AD, or a combination of these factors acting alone or together with intrinsic risks factors such as those mentioned above.

It is clear that the time to examine alternative strategies is already upon us, and it is in this context that we should be looking outside our existing boxes, and consider what we can learn from other avenues in medicine, including other cultures, for instance

Chinese medicine. The latter differs significantly from what we are used to apply in the context of Western medical practice and constructs, but that is part of its attraction. The ethnopharmacological approach to understanding the use of Chinese herbal medicine for AD is important and discussed by Howes, et al.⁽¹⁾

Traditional medical treatment is a pattern-based treatment model, adopting different therapies with the evolution of patterns (also called Zheng or syndrome) defined by Chinese medicine. It includes multi patterns-targeted treatment which may be better than single-target therapy in AD. Tian, et al's model proposes a treatment regimen for the whole process of AD.⁽²⁾ A multi-targeted approach is also under consideration by others, e.g. the recent paper by Cummings, et al⁽³⁾ which broaches the need for us to widen our horizons, including different types of combination therapy.

Whether or not the concept of disease-pattern combination treatment for AD, i.e. disease-targeted therapy combining with patterns-targeted therapy, with multiple targets and temporal characteristics stands up to further evaluation remains to be seen, but it deserves consideration. We should take a look at hypotheses originating outside our own understanding of science, such as those emanating from this paper, despite the fact that the science is very different to our own, and some is difficult to understand for those of us not schooled in Chinese medicine.

The results quoted e.g. that when the STEP regimen is combined with conventional therapy for AD cognitive and behavioural stability was maintained for at least 12 months with cognitive enhancement after

6 months, and also longer term benefits, deserves further scrutiny. The concepts inherent in the STEP process, for instance in relationship to the Shen (Kidney) deficiency cascade, blood stasis therapy and the other components are difficult to understand for those steeped in Western medicine, although there may be some overlap in some of these at a conceptual level. For instance we would not put Shen deficiency at the heart of AD. How robust is the evidence that these phenomenae are related to AD, what is the evidence linking them directly to the A β cascade that the authors place centrally in the AD process, and how are they diagnosed? Nevertheless, as the authors suggest, it is reasonable to change the treatment strategy according to different stages in AD, and this concept may also be relevant to chronic disease entities other than AD.

We also need to accept a number of trial design issues at face value, e.g. the accuracy of the diagnosis of AD—as the paper does not provide the diagnostic criteria, and whether the subjects in both treatment groups were randomly allocated, and whether both groups had an equal distribution of important characteristics. However the data is still of interest.

Chinese medicine has a long and honourable history and has been practiced for at least 2000 years.



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The pathogenesis of Alzheimer's disease is complex. Successful treatment would have to reverse amyloid deposition extra-neuronally, neurofibrillary tangle accumulation intra-neuronally, the loss of neurones and synapses as well as changes in neurotransmitters and inter-neuronal connectivities. Moreover, Alzheimer's disease is an evolving process over time. Thus, monotherapy aimed at amyloid deposition or cholinergic deficits will inevitably meet with limited success. It is therefore appropriate to adopt multiple approaches.

The study of Tian, et al⁽¹⁾ describes the adoption

Research scientists have identified compounds of interest that may improve dementia with relatively few adverse effects although none have so far yielded concrete evidence of disease modifying properties. Despite this the paper by Tian, et al should act as a stimulus for us to give careful consideration to alternative hypotheses from different backgrounds for treating AD, especially when our own attempts to develop disease modifying strategies have not been successful.

Whether or not the hypotheses intrinsic to the STEP process as described in this paper lead to treatment benefits when evaluated in appropriate confirmatory trials, many working in this field may be stimulated to carry on looking for potential therapeutic constructs outside our usual comfort zone.

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of a staged approach, involving the administration of a number of Chinese medicine (CM) agents over the course of the disease. The results indicate a superior therapeutic outcome when sequential CM is combined with conventional prescription of donepezil compared to the effects of placebo or donepezil alone. A crucial aspect of the study is that it examines the CM therapy systematically in the context of a controlled clinical trial, involving a direct comparison between the combined therapy and a standard Western medicine treatment. It is important that Western clinical practitioners become informed of these CM practices, particularly because of the dearth of effective pharmaceutical or immunological interventions that are currently available for Alzheimer's disease.

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