

## Modification to Trial-Ready Alzheimer's Therapy

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### Short Communication

Early onset Alzheimer's Disease (AD) had been found to be caused by a genetic abnormality affecting metabolism of the small Beta-amyloid peptide. This peptide, found in early onset AD, is also found in the senile plaques present in patients suffering from late onset AD. From this it has been concluded that the pathology of early onset AD was also occurring in late onset disease but from differing genetic mutations. Enzymes important in generating amyloid Beta were identified and efforts made to inhibit the function of these enzymes. However clinical trials of such therapies have not been shown to improve patient cognition. This despite the fact that all patients with Alzheimer's Disease have innumerable amyloid plaques in their brains.

It is the authors belief that abnormal AB precursor protein metabolism is in fact a significant cause of AD. But there are three other major etiologies of the disease which must be considered and which contribute to death of neuronal cells. Presuming their continued destructive activities while the AB pathology is being treated, a failure of the latter to significantly inhibit the disease progression is understandable due to ongoing damaging effects of the other pathologic processes of the disease. With this hypothesis of multiple etiologies of AD it is reasonable to expect that four different disease etiologies would require the treatment of all four pathologies at the same time to show an effective therapy. This means a combination of agents used together, effective against all four etiologies, is necessary to treat the disease.

There are many scientific reports of the importance of all four of the identified etiologies of AD with major reports discussed and referenced in the literature. These all should be seriously considered in reviewing how to deal with the disease, particularly the use of a combination therapy to treat all of the etiologies,

Previously the author had an article published in Medical Hypothesis [1] suggesting a unique combination therapy for the treatment of Alzheimer's Disease. The article includes references for the rationale of the hypothesis, as well as methodology for treatment. Documentation that AD is a disease of four major causes is presented and therefore the most effective therapy would be one which addresses all etiologies simultaneously. The four major causes are mitochondria dystrophy, damaging protein inclusions, oxidative stress, and pro-inflammatory processes. The specific therapeutic combination includes the drugs Trental, nicergeline, methylene blue, nilotinib and pyridoxamine, a B6 vitomer. The four drugs have all been shown in clinical studies to ameliorate dementia. All five have been shown in non-clinical studies to inhibit one or more of the four pathologic processes leading to the disease, and together inhibiting all of them.

Nilotinib however has two problems associated with its usage: its high cost at \$1000 per month and side effects as it is a chemotherapeutic agent, even used at 1/4th of its standard dosage for

leukemia. It is one purpose of this report to point out that there are two alternatives to using nilotinib in the therapeutic combination: not using it or using lithium carbonate at a dosage of 150mg per day to substitute for it.

It has been suggested in an article by Lee [2], found subsequent to the Medical Hypothesis article that mitochondria inhibition promotes the formation of aggregates of alpha-synuclein (a protein inclusion) in cells. Accordingly, the first cause of AD, mitochondria dystrophy, would lead to the second cause, damaging protein inclusions. Two of the treatments for mitochondria dystrophy are included in our proposed combination therapy, these being methylene blue, which has a direct benefit on mitochondria function, and pyridoxamine, which aids mitochondria secondarily by reducing oxidative stress. It is conceivable that by enhancing mitochondria function nilotinib would not be required as a cleansing agent of damaging protein inclusions and the therapeutic combination without nilotinib would be effective with lesser possible side effects and at a much lesser cost while still treating all four etiologies. It is recommended that the nilotinib free combination be tried for six to 12 months reserving the addition of nilotinib, or lithium carbonate, to the combination in case the four member combination without nilotinib fails. However, although the dose of lithium carbonate is significantly lower than the usual therapeutic dosages for bipolar disorder and although lithium induces autophagy so as to remove inclusions by inhibiting inositol monophosphatase [3], even the low dose has side effects in the AD age group.

The three alternative combinations which can thus be considered as an AD therapy are (1) the original five agents, (2) four of the combination without nilotinib, and (3) substituting lithium carbonate for the nilotinib. The combination without nilotinib would be preferred but only if it works clinically at least as well as the other two alternatives which directly remove protein inclusions.

It was the purpose of the original Medical Hypothesis article to first offer an explanation for the failure to find an effective Alzheimer's therapy. Evidence presented in that article showed that AD is caused by four multiple pathologic processes and that previous failed research was directed against only single etiologies. Accepting this, a hypothesis that an effective therapy requires treating all four etiologies is reasonable. The Medical Hypothesis article presented a specific combination therapy to do exactly that, while explaining the rationale for the usage of the members of the combination. The purpose of this article is to suggest a modest modification of the suggested combination. Its use would decrease the projected cost and reduce the likelihood of side effects of the therapy. It is recommended that this proposed combination be tried as a treatment for intermediate stage Alzheimer's. It is based on good scientific evidence and has a reasonable chance of success. If ineffective the risk of harm to patients is minor. Considering the terrible consequences of AD and the

millions of affected people it is felt that trials of this simple and relatively safe treatment should be carried out in the near future.

## References

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