INVITED REVIEW

A new direction for Alzheimer's research

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Abstract
Despite decades of research, at present there is no curative therapy for Alzheimer's disease. Changes in the way new drugs are tested appear to be necessary. Three changes are presented here and will be discussed. The first change is that Alzheimer's disease must be considered a disease of four major pathological processes, not one. The four processes are: 1) vascular hypoperfusion of the brain with associated mitochondrial dysfunction, 2) destructive protein inclusions, 3) uncontrolled oxidative stress, and 4) proinflammatory immune processes secondary to microglial and astrocytic dysfunction in the brain. The second change recommended is to alter the standard cognitive measurement tools used to quantify mental decline in test patients. Specifically the Dementia Severity Rating Scale (DSRS) should supersede Mini-Mental State Examination (MMSE) and other popular tests, and a measurement scale developed in research should be used to produce a linear and non-irregular baseline. Finally, accepting the concept that four etiologies cause Alzheimer's disease leads to the last necessary change, that new therapies must be employed directed against all four causes, likely as a combination. There are drugs ready to be employed in such a combinations which are available and used clinically for other purposes so can be used "off label" and one such combination is suggested.

Key Words: *Alzheimer's disease etiologies; combination therapy; cognitive testing; failed research; off-label use; Dementia Severity Rating Scale*

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Introduction

Although billions of dollars have been spent for research on Alzheimer's disease (AD), little progress has been made in finding an effective therapy. Numerous drugs, having failed over years of research, suggest the need for a reevaluation of how the research is now being done. To that end, three changes in current AD research methodology are offered.

First, we must acknowledge that AD is a disease of four etiologies rather than coming from a single primary cause. These four should be treated simultaneously for an effective therapy. Second, combination therapies to deal with these multiple etiologies is recommended and a specific combination, used off label, is proposed. Finally, relying on the Dementia Severity Rating Scale and a consistent rate of decline as defined in referenced research will improve the efficiency and accuracy of drug trials.

The Four Pathological Processes Causing AD

The myriad of AD drugs which failed have been aimed primarily at dealing with amyloid pathology. Some of them succeeded in their designs but still failed to slow dementia. Why? There is more to AD than merely amyloid pathology. There are in fact four major pathologic processes working simultaneously in AD, and to cure the disease all four must be addressed together. These are the four:

(I) Mitochondrial dysfunction is manifested primarily by reduction of energy metabolism which in turn negatively affects all cellular functions. There is an excessive production of reactive oxygen species (ROS) which produces oxidative stress if compensating mechanisms are inadequate. The pathologic process producing mitochondrial dysfunction appears to be associated with aging, from maternally transmitted mitochondrial DNA mutations or spontaneous genetic mutations (Swerdlow and Khan, 2004). Cerebrovascular hypoperfusion appears to be an important cause for the initiation of mitochondrial dysfunction (Aliev et al., 2010).

(II) Abnormal protein deposits (inclusions) are damaging to neural elements. Familial AD is associated with hereditary mutations which affect critical regions of amyloid-β protein precursor (AβPP). Amyloid pathologies also increased in

late onset AD where coalesced inclusions ultimately form senile plaques. Many different damaging effects of amyloid abnormalities have been reported. Other misfolded protein inclusions present in the brains of AD patients are found in other primary diseases, specifically fronto-temporal neuro degeneration, Parkinson's dementia, amyotrophic lateral sclerosis (ALS), and chronic traumatic encephalopathy (CTE). Neurofibrillary tangles, made up of pathologic tau proteins, are found in all later stages of the disease. Lewy bodies made up of alpha-synuclein and found in Parkinson's dementia are present in 50% of Alzheimer's victims (Hamilton, 2000). A more recently identified inclusion, TAR DNA-binding protein 43 (TDP-43, transactive response DNA binding protein 43 kDa), seen in fronto-temporal degeneration, is also estimated to be present in 50% of Alzheimer's patients (Arai et al., 2009).

(III) Oxidation can be destructive to any structures whose components may be oxidized. Structure and component elements of cells, including membranes, organelles and DNA can be oxidized and in the process lose their structural integrity and physiologic function. In this process of oxidative stress ROS are not neutralized. This can occur when ROS are increased and overwhelm the defensive elements or when there is a decrease in the latter, as with aging. Advanced glycation end products (AGE) and receptor for AGE (RAGE) is a process seen in aging, but is shown to be present in AD to a much greater degree than in unaffected individuals (Gella and Durany, 2009). The effect from this glycation of proteins results in significantly increased, perhaps by 50 times, production of ROS with secondary oxidative stress effects.

(IV) Neuroinflammation can occur in association with microglia or astrocytic dysfunction. These cells tend increasingly to convert from anti-inflammatory to pro-inflammatory activity with aging. The abnormalities may be created by release of pro-inflammatory immune cytokines (*e.g.*, interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α)), with immunological deficiencies promoting neurodegeneration (Blasko et al., 2004). This may include a stimulation of late tau pathology. Activation of microglia (rather than dystrophy) may lead to a cascade of events leading to destructive inflammatory processes. This is theoretically mediated by the pro-inflammatory interleukin-1 overexpressed by activated microglia. Neuronal death occurs, activating more microglia, and destroying more neurons.

Combination Therapies

A single drug will likely not be able to treat all four AD etiologies. A combination therapy addressing the various causes is necessary, despite the difficulty inherant in testing them. In order to cure other diseases, combination therapies have been required, and this approach should be employed as the path to success with AD.

The creation of new drugs is another expensive and time consuming process. But right now drugs already exist which might work in combination to successfully treat AD. Because we have now simplified the testing procedure of new therapies and recognize that there are multiple etiologies to deal with, drugs which were left behind or ignored might now be viable as part of a successful therapy. They should be selected from drugs which have been shown to modulate dementia in patients, as well as found in preclinical studies to inhibit the activities of the various pathologic etiologies which produce AD.

It is true that the number of possible combinations of therapies available to try is in fact almost infinite, considering the mathematics of combinations, varying dosages, and the question of which etiologies might require more than one of a test combination to address. However, the lead investigators making selections can choose from hundreds tried in prior test experiments, as well as drugs suggested in the literature or new drugs as they are offered. The fact that there are so many possible combinations to try does not mean that the selection of a combination is random, and does not preclude the selection of an ultimately successful combination where knowledgeable and careful choices are made from possible therapies available.

One example of such a combination previously published meets the suggested criteria and uti-

lizes the altered methodology (Weinstein, 2017). The combination consists of Trental, Nicergoline, Methylene blue, Nilotinib and Pyridoxamine (vitamin B6 vitomer). Trental (pentoxifylline) is effective in enhancing cerebral circulation (No authors listed, 1996) and preventing mitochondrial dysfunction. It has also been shown to inhibit oxidative stress which develop from advanced glycation end products. A third Trental function may be the inhibition of pro-inflammatory effects from microglia and astrocytes. Nicergoline is also used to increase blood flow to the brain and also inhibits pro-inflammatory cytokines (Winblad et al., 2008). Methylene blue, used to treat methglobinemia, enhances mitochondial function by enhancing ATP (energy production) and reducing production of ROS (Atamna et al., 2008). It also may inhibit phosphorylated tau production. Nilotinib, a chemotherapeutic agent, is used at 1/4 of chemotherapeutic dosage for removal of the damaging protein inclusions (Lonskaya et al., 2014). Its mechanism of action is by stimulating the formation of Parkin, a protein which enhances the removal of these protein inclusions. The Pyridoxamine inhibits oxidative stress (Voziyan and Hudson, 2005) (**Figure 1**).

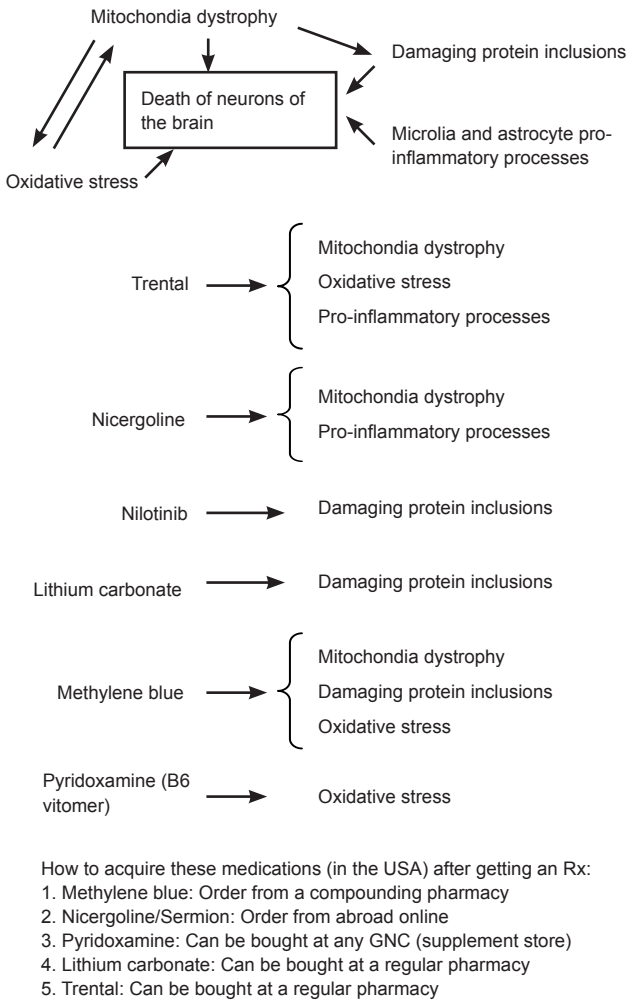

Figure 1 Multiple causes and combintion therapy for Alzhemer's disease.

Changing Testing Methods

Given the multitude of failures during the latter phases of drug trials, a more consistent evaluation of the efficacy of new treatments during the initial phases is necessary. The latter stage studies require a significant investment of time, money and effort and it is extremely damaging to the research process that so many ineffective drugs make it so far when they do not work. Drug companies like Pfizer are giving up their Alzheimer's efforts entirely because of this continuing lack of success. Currently the Mini-Mental State Examination (MMSE), Montreal Congnitive Assessment (MoCA) and Alzheimer's Disease Assessment Scale (ADAS-cog) and some others are the primary instruments used to measure dementia in research studies. However, these tools do not show a linear measure of decline throughout different stages of the disease. There are also large variations of the measured results within the placebo groups (Schneider and Sano, 2009). Therefore, it is difficult to ensure that a treatment is really working without testing a large number of patients where accurate statistics can be applied.

The Dementia Severity Rating Scale is much more reliable and consistent. Xie et al. (2009) showed an increase of ~4.5 points per year in 702 patients over seven years and that remains steady for every patient throughout the entire range of severity. Furthermore, there is only a slight deviation from the average score. This is a firm definition of AD decline that can then be compared to treated patients, and it will be clear with even a small cohort if a drug works.

Discussion and Conclusions

Its impossible to deny that something needs to change in AD research. Hugely expensive failures continue with almost no affect in AD prognosis. The three alterations in research methodology proposed will help to solve this problem. First, it must be accepted that AD is a disease of not one but multiple etiologies. Second, an effective therapy requires treating not one but all of the four causes simultaneously using a combination therapy. Promising combination therapies from available drugs can be tried right away, especially the specific one mentioned. Finally, the most popular AD measuring tools used in testing are not accurate and consistent enough and many ineffective drugs make it too far into the pipeline. The Depression Self-Rating Scale (DSRS) and the Xie measurements should be made the standard. For the millions suffering, this new direction for AD research is one that ought to be taken.

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Open peer review report:
Reviewer: *Debra Toiber, Ben-Gurion University of the Negev, Israel.*
Comments to author*: This article presents an interesting suggestion regarding how clinical trials should be done, and what should be measured, such as an end point. I think it is a valid and interesting suggestion that should be analyzed in depth. The author presents a compact and to the point review on the different aspects of AD pathology, moving the focus from Amyloid beta, to several important points that are less studied. The author summarizes phenotype and mechanisms that are affected in AD, and possible causing AD. In addition, the author proposes a novel paradigm about the way clinical trials should be performed, although I do not completely agree on all of this suggestion (like the end point to measure, and some other details). I think it is a valid and interesting point that is worth raising in the AD comunity.*

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