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NEW TREATMENT STRATEGIES AND DRUG DEVELOPMENT FOR THE ALZHEIMER'S DISEASE

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ABSTRACT

The discussion in this research paper will explore the major reasons behind the Alzheimer's disease and what kind of clinical treatments are available till now. This irreversible and progressive impairment of brain activities is a serious concern among the scientists worldwide for slowly destroying the behavioral, cognitive, and physical skills with eventually causing death. Statistical evidence is also presented to provide the significant evidence of the prevalence of the Alzheimer's among the ageing populations worldwide. Hence it has been trying to focus on significant investments that should be made for the development of efficacious treatments for the AD patients. This research paper also covers the brief overview of the drug development and recent clinical trials to find out how the disease-modifying therapies (DMTs) are trying to improve the outcomes by changing the way of treating the Alzheimer's patients, rather than depending on mere symptom management. It also emphasizes on building strong support group to assist the caregivers in overcoming the challenges.

INTRODUCTION

Throughout the world prevalence of the Alzheimer's patients is causing a serious concern among the scientists as this irreversible and progressive cognitive impairment of brain is affecting the behavioral, cognitive, and physical skills with eventually causing death to the patients. Further, by causing devastating and debilitating neurodegenerative condition, it has been affecting the lives of the majority of the demented individuals worldwide. Irrespective of the development status of the countries the prevalence of this disease is expected to increase in the future years due to the steady growth of ageing population (Winslow et al., 2011). Instead of a single disease, AD may be considered as a combined one with overlapping pathogenetic mechanisms and clinical manifestations. However, statistically it has been found that these conditions are responsible for an estimated 60-70% out of all dementing disorders in the ageing population (Swerdlow, 2007). Besides, due to prevalence of dementia, itis expected that between 5% and 10% of the population aged 65 years and older as well as up to 50% of those older than 85 years of age are going to be affected by this disease in the forthcoming years. On the basis of the World Health Organization (WHO) projections, it has been found that by the year 2025, the majority of the estimated 1.2 billion ageing population of the world will be living in the developing and less developing countries.

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It is also found that in most of the Asian and Latin American countries, the prevalence of this disease among ageing populations is quite high (above 5%). In India and sub-Saharan Africa, however, the prevalence of dementia seems to be comparatively lower (1-3%) (Swerdlow, 2007).

On the basis of the above analysis, it can be stated that significant investments should be made for the development of efficacious treatments for the AD patients. Till now only symptomatic therapies are available for the patients and as such they cannot be considered as significant steps to check the evolution of this disease. Currently, the available ones, only help in improving the symptoms like cognitive decline and memory loss, but not in addressing the key issues, such as underlying pathology of the condition (Brookmeyer et al., 2007). Hence, in this paper the discussion will be around the new treatments and development of drugs for the AD patients (Winslow et al., 2011).

LITERATURE REVIEW

The disease is named after Alois Alzheimer, the neuropathologist and psychiatrist, in 1906 after discovering the brain impairment of a demented patient. The Alzheimer's disease is the degenerative changes affecting the areas of brain controlling thought, memory, and language. As in this disease, physical, behavioral, and mental functions of a person are affected, therefore throughout the world scientific quest for new treatments to either slow or eventually eliminating the root causes of this disease is gaining momentum. However the recent treatment strategies include the development of target microscopic clumps of the protein beta-amyloid (plaques), as these plaques are the characteristic sign of this disease (Brookmeyer et al., 2017). Most of the recent drugs emphasize on this beta-amyloid as by proper therapeutic use, it will reduce the production of beta-amyloid in the brain, boost immune system, and prevent destruction, all of which are very essential in the treatment of this disease. As of now the U.S. Food and Drug Administration (FDA) approved five Alzheimer's drugs for treating the symptoms of this disease. In spite of a sixth drug is going to be available globally, yet it can be stated that these medications cannot be able to eliminate the root causes of this disease or slow its progression (Winslow et al., 2011). So, the research is going to intervene on the changes occurring in the brain with the new medications or treatment processes. Hence, it is believed that the new drugs will potentially target the slowing or stopping the progress of this disease by a combination of medications. The future drug therapies will include several targets, like keeping tau from tangling, reducing inflammation, and blocking the 5HT6 receptor (Winslow et al., 2011).

It has been observed that Alzheimer's disease generally consists of three stages- mild, moderate, and severe. During all these stages within an average range of 2-20 years, the cognitive and functional decline is stretching over 5-8 years (Brookmeyer et al., 2017). The following table will give an overview of the various phases this global cognitive impairment of the brain.

Table 1.Global measurement of cognitive impairment of different stages of AD patients

		Measure		
Stage	**Duration (years)**	**Global Deterioration Scale (score)***	**Mini-Mental State Exam (score)†**	**Global Autonomy**
Mild	2–3	3–4	26–18	Independent living
Moderate	2	5	17–10	Supervision required
Severe	2–3	6–7	9–0	Total dependence

* Scale measures progressive need for assistance in daily activities (e.g., choosing clothes, dressing); scores range from 1–2 (normal) through 6–7 (severe dysfunction (219).
† This 22-item scale measures cognitive function; scores range from 30 (excellent function) to 0 (severe dysfunction) (220).
Note: Reprinted with permission of Dr. S. Gauthier and *Can Med Assoc J*. 2002;166 (Reference 12).

Source: https://www.researchgate.net/publication/324936192_Alzheimer's_disease_drug_development_pipeline_2018

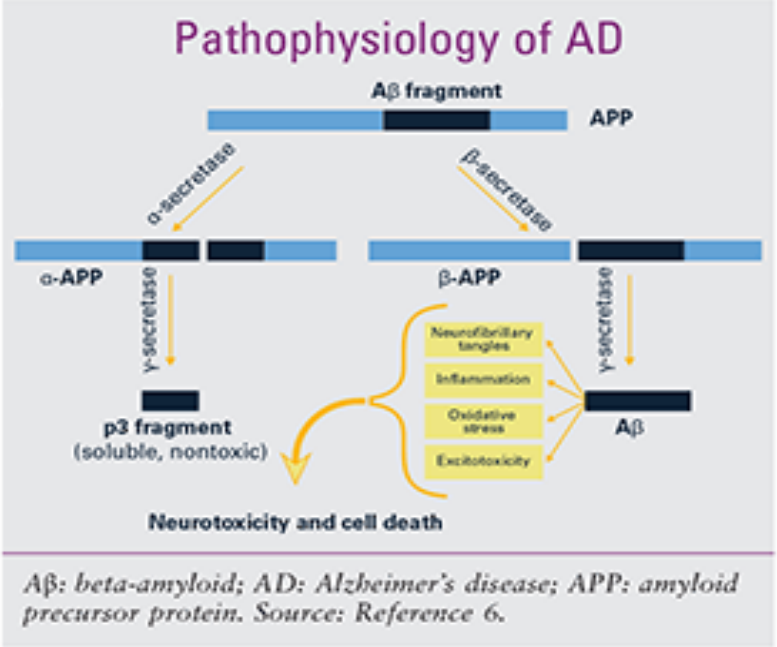
However, the recent studies indicate a far grimmer prognosis that especially AD patients with age of above 85 years, often die within about 3 years of diagnosis, which contradicts the previous assumption that they would exist. Due to lack of effective treatment, the initial and mid-stage patients usually survive for 2-3 years and during this period the symptoms of short-term memory impairment, anxiety and depression are observed (Cummings et al., 2018). In the moderate stage all these symptoms are replaced with dominance of neuropsychiatric symptoms, like sleeping disorders, hallucinations, and others, become more significant. In the severe and final stage the condition of AD patients is majorly characterized by the motor disorder signs, like rigidity and other prominent cognitive disorders. Although the cognitive and functional decline appears to be linear during all the 3 stages of the AD, yet the severe stage requires total care for the AD patients due to the major physical care burden and the considerable neuropsychiatric care burden (Cummings, Morstorf, & Zhong, 2014). In the next section discussion will be around the research for new strategies for Alzheimer's treatments and development of medications that will either stop or significantly delay the progression of this disease.

RESEARCH FOR NEW TREATMENTS AND DEVELOPMENT OF MEDICATIONS FOR AD PATIENTS

Till today, no effective treatment has been available for the cure or prevention of the Alzheimer's disease. Most of the pharmacological drugs are targeting the symptom management with anti-dementia therapy. Hence, only temporary clinical benefits have been observed in respect of physical, behavioral, and cognitive symptom management. This strategy mainly relies on the increment inhibition of acetyl-cholinesterase in combination of donepezil, galantamine or rivastigmine for achieving the effect (Massoud & Gauthier, 2010). However, it has been observed that memantinecan become a crucial factor in preventing the excessive release of glutamate, which generally happens in this disease due to the damage of the neurons. As such, for mild, moderate or even severe AD patients, the clinical use of cholinesterase inhibitors is prescribed. Further the memantine can also be used for moderate and severe AD

patients, preferably in combination with cholinesterase inhibitors. Quite obviously, the urgent development of new drugs for AD is perceived to be the foremost priority for the scientists to stop or even slow the progression of this disease (Kumar, Singh, &Ekavali, 2015).

Despite being unable to explore the underlying causes till now, still the amyloid plaques and neurofibrillary tangles are presumed to be the root causes of this disease. Further, the generation and inhibition of plaques and tangles are supposed to be associated with this neurodegenerative functional disorder, which distinctively result in a slowly progressive brain impairment with ultimately affecting the functional, cognitive, and behavioral skills. Amyloid plaques are primarily composed of beta-amyloid proteins, which generally derive from a parent protein called amyloid precursor protein (APP) (Massoud & Gauthier, 2010). This beta-amyloid is the key factor working behind the brain abnormality of the AD patients. The scientists have understood the detailed layout of how this protein fragment, the chief component of plaques, is clipped from the APP, by the two enzymes- beta-secretase and gamma-secretase- to form the beta-amyloid proteins. In the brains of the AD patients, however, the significant high presence of this component is considered as quite abnormal(Cummings, Morstorf, &Zhong, 2014). The following figure will give a clear overview about the inappropriate cleaving of APP by the above two enzymes-



Source: https://www.uspharmacist.com/article/alzheimers-disease-current-treatments-and-potential-new-agents

Figure 1.Pathophysiology of AD

Hence, the current research is aimed at developing medications which majorly target the every point of beta-amyloid processing techniques. As such the researchers are considering almost every option, including blocking activity of the beta-secretase enzyme, preventing the beta-amyloid fragments from clumping into plaques, and using antibodies against beta-amyloid to clear the toxic changes taking place in the brain (Cummings et al., 2018). However, by targeting the beta-amyloid, the current research drugs are undergoing through rigorous clinical trials. The investigational research drugs are now targeting the beta-amyloid, which can be segregated in the following way to give a detailed overview of the recent research progress.

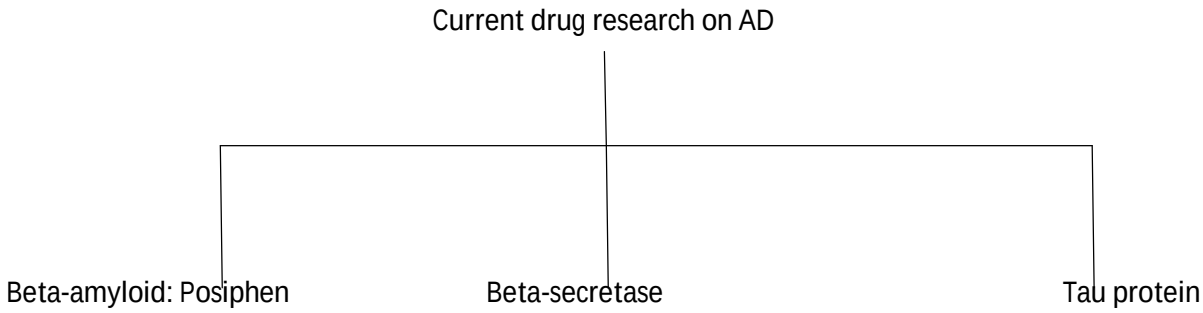


Figure 2.Layout on current drug research

POSIPHEN

The posiphen may delay the onset of this disease process or even slowing the progress of brain impairment among the AD patients by inhibiting the production of APP. As it helps in amyloid buildup, therefore the clinical study is aimed at evaluating the efficacy of the safe usage of the posiphen dosages in elderly patients with early-onset of this disease (Brookmeyer et al., 2017). In spite of too early to comment, in the clinical studies, it has been observed that posiphen can easily enter the brain and the cerebrospinal fluid (CSF) tests have also indicated that after receiving the drug it will significantly lower the levels of amyloid, tau and inflammation. Reducing the inflammation is a significant part of the treatment of this disease as it causes chronic as well as low-level brain cell inflammation (Brookmeyer et al., 2007).

Hence the researchers are significantly trying for treating inflammation processes, despite all the investigational drugs are in very early phase of clinical trials. For example, the drug sargramostim (Leukine) is currently in the research process as it presumes to protect the brain from the harmful proteins by stimulating the immune system (Cummings et al., 2018). However, previous clinical research trial on the diabetes drug pioglitazone (Actos) was negative, despite initially it was supposed to lessen beta-amyloid and inflammation in the brain.

In case of second research study on beta-secretase (BACE) it has been found that BACE helps in forming the beta-amyloid on the basis of evidence that it is one of the two enzymes that can clip the APP. By therapeutic use of this drug it may interrupt this process and ultimately helps in reducing the excesses of this protein in the brain. Hence it can be emerged as a comparatively advanced way of treating the AD patients (Brookmeyer et al., 2017). In the recent research studies, it has been revealed that JNJ-54861911can inhibit the ability of the beta-secretase enzyme in forming the beta-amyloid. This drug isnowinthe phase 3 of the clinical trial to investigate whether it can be able to slow down the cognitive decline in the people with no AD symptoms, but at the same time with elevating levels of beta-amyloid in the brain (Cummings et al., 2018).

As the chief component of tangles, the tau protein can be defined as another hallmark for brain abnormality in this disease. This protein helps in managing the neuron structure, including the microtubules, the tiny-tube like structures, in delivering the nutrients throughout the neuron (Brookmeyer et al., 2007). However the research is going on to prevent the collapsing and twisting of tau protein into tangles, a vital mechanism that can destroy the microtubules and ultimately the neuron (Hudson, Lauer, & Collins, 2016). In this regard the AADvac1 is currently in the research process as this vaccine has the ability to stimulate the body immunity system by attacking the abnormal form of tau protein which works for destabilizing the neuron structure. If this trial will be successful, then it is expected to eliminate the

progress of this neurodegenerative disease (Cummings, Morstorf, & Zhong, 2014).

Another significant finding is the 5HT6 receptor on some brain cells that can lock the chemicals called neurotransmitters. This 5HT6 receptor can decrease the available amount of neurotransmitters in the brain, which generally uses for communications between the neurons. As the only neuron-to-neuron communication can help the individuals to think and function normally (Brookmeyer et al., 2017). AD patients generally have lower levels of acetylcholine and by blocking the 5HT6 receptor can significantly increase the level of this neurotransmitter. If this clinical trial proves to be successful, then it is expected to help the neurons in managing the normal communication. Currently Pimavanserin, an inverse agonist for the 5-HT2A receptor, is under clinical trial as to observe whether it can be able to reduce the symptoms of dementia-related psychosis (Cummings, Morstorf, &Zhong, 2014).

Further, in the preventative research process the effectiveness of several drugs is examined, like solanezumab, a drug targeting beta-amyloid, on high risk individuals to find out whether early intervention can be able to prevent the cognitive decline (Winslow et al., 2011).Besides current research process is also testing the drugs, gantenerumab and solanezumab, to find out whether they can be able to reduce the abnormal levels of beta-amyloid in the brain (Cummings, Morstorf, &Zhong, 2014). In the DIAN-TU the experimental drugs are used for AD patients, who have developed this disease due to mutations of three genes, APP, PS1, and PS2.Out of the three genes, PS1 mutations are majorly accountable for early onset of hereditary Alzheimer's disease, while the rest two are rarer(Winslow et al., 2011). In this kind of AD patients, brain changes are almost similar to those of the more common sporadic form of AD patients. It is expected that if the clinical trial under the DIAN-TU will be successful, then it can also help in slowing or stopping the progress of the disease among the high-risk group of the sporadic form of AD patients.

Another significant research study is going on through the prevention clinical trials, API, as it covers both the Autosomal Dominant Alzheimer's Disease (ADAD) trial and the Generation Study. In the API, like the DIAN-TU, therapeutic tests are carried out on the people, with the gene mutation causing the Alzheimer's, but not yet develop the symptoms (Massoud& Gauthier, 2010). In the ADAD trial the effects of an immune-based therapeutic drug, have been investigated to study whether by antibodies it can eliminate the negative consequences of the beta-amyloid (Hudson, Lauer, & Collins, 2016). Where as in the Generation Study it studies the high risk group of healthy ageing population with two copies of the APOE-e4. In this research study, however, the focus has been on CAD106 and CNP520, to find out whether they can be able to prevent or delay the onset of AD symptoms (Winslow et al., 2011).

NEW WORK COMPARISON ANALYSIS

From the above, it can be stated that increased path physiology-oriented research on AD has effectively resulted in the testing of many new agents for treating the AD patients. However, in 2018, 112 agents of the developmental phases were in different 3 stages of the clinical trials. Out of them 63% can be labeled as disease-modifying therapies (DMTs) which are significantly trying to improve the outcomes by changing the pattern of treating the AD patients, rather than managing the symptoms (Massoud& Gauthier, 2010). About one-quarter of the drugs, under the research process, are testing for investigating their ability to enhance cognition, which may ultimately result in improving memory, language, thinking, and judgment ability (Cummings, Morstorf, & Zhong, 2014). While approximately 10% of the drugs are investigated to observe their effects on decreasing the behavioral dysfunctions.

Within the course of a clinical trial, many drugs are studied to investigate their effects on alleviating the behavioral symptoms of the AD patients, with having previous approval. Sometimes these repurposed drugs are moved from preclinical investigation to phase II clinical trials, to lessen the timeline in the drug pipeline. Some of the examples of these kinds of repurposed drugs belong to antidepressants, anticonvulsants, mood stabilizing, and stimulant categories (Massoud & Gauthier, 2010). In this regard it can be stated due to slow and painstaking process of the development of new medications, the AD patients and their families, are suffering from the frustrations. However, due to not being able to find out the distinctive reasons behind this disease till now, the scientists are facing the challenges of providing an effective disease-modifying therapies (DMTs) to AD patients. Although requirement for combination therapies has been presumed, yet the current research strategies are emphasizing on the single-entity therapies (Cummings, Morstorf, & Zhong, 2014). Further, the usage of new therapies on animals cannot be able to provide any predictive results for humans and sometimes with huge side-effects. Besides, due to the huge costs of launching a new drug into the market, an advanced funding strategy is required to ensure safe and efficacious treatments for the Alzheimer's group.

CONCLUSION

The complexity of the Alzheimer's disease has compelled the current treatment strategy to target the symptom management instead of merely delaying the disease progression. Although the current medication therapies are emphasizing on the symptomatic therapies, yet the approved ones by the FDA can only reduce the symptoms with eliminating the behavioral problems to some extent. All these drugs are effective only to a limited extent for some groups as they are not able to change the underlying disease process. As such, new clinical studies are shifting their focus to the disease-modifying therapies (DMTs). But before deducing any conclusion more studies are necessary to collect the necessary data. Under the ongoing clinical trials, the scientists are investigating several possible interventions to achieve a variety of targets. They are also considering nondrug interventions, like physical activity, diet, cognitive training, and combined approaches to completely eliminate the root causes of this disease. However, to achieve the target strong support group is necessary to assist the caregivers in overcoming the challenges.

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