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# What are the latest advancements and challenges in the comprehensive understanding and treatment of Alzheimer's Disease?

**Can Pasinler**

Year 13 | Jumeirah College, Dubai, United Arab Emirates

**ABSTRACT**

**Alzheimer's disease (AD), a very complex neuro-degenerative disease, presents a serious public health concern, especially with the growing number of aged population. This paper provides an overview of this neuro-degenerative disease with special focus on its epidemiology, its pathophysiological and clinical characteristics, available tools for diagnostic and management, and the emergent trends in the area of research. A review of the available literature suggests an upwards surge in the incidences of AD in the developing countries. For example, China is expected to have the largest patient population by 2050, followed in India. Alzheimer's disease includes cholinergic disfunction, deposition of amyloid-beta, hyperphosphorylation of tau protein, stress on oxidative functions and inflammation in neurons. The clinical symptoms of AD includes gradual but increasing loss of cognitive functions, behavioural changes and growing inability to perform daily routine.**

**While evaluation tools and biomarkers focus on cholinesterase, current treatments also focus on alleviating the symptoms through cholinesterase inhibitors and glutamate regulator like memantine. Besides these medicinal tools, there are ongoing researches focussed on modifying the disease. The research areas include therapeutic intervention at personal level, treatments based on combinations drugs and screening of patients at early stages of the disease. This paper also discusses the challenges faced by caregivers, the wide range of burden caused on AD and the ethical considerations while providing care to an AD patient. The ongoing researches and clinical practices for AD emphasize upon the need for early intervention based on clinical symptoms, where the interventions need to be cost-effective yet impactful.**

**Keywords: Alzheimer's disease, dementia, diagnosis, treatment, gene therapy, personalized medicine, ethical considerations, clinical trials, early detection, combination therapies**

## INTRODUCTION

### *A Brief Overview*

Alzheimer's disease has become the most prevalent form of neurodegenerative illness. Among all the cases of dementia affecting the elderly population at the global level, AD accounts for over 80% cases and leads to increasing decline in mental abilities including the ability to learn, gradual loss of physical functions or capabilities and behavioural changes [1]. While dementia connotes a generalized symptom of progressive decline in memory, speech abilities, problem solving abilities and other cognitive and functional abilities, Alzheimer's disease remains its most common cause [2]. Based on current projections on Alzheimer's disease and the cases of demential caused by it, by 2050 over 2/3$^{rd}$ of these cases are likely to occur in low to mid-income countries while virtually all the research works are based on high income countries.

This underlying problem in existing researches is further amplified when we look into the global distribution of population where majority of population lies in low to mid-income countries, with India alone accounting for around 18% with roughly 1.4 billion population. The limited researches conducted in India, estimating prevalence of dementia, have picked a handful of population samples that fails to represent the demographic diversity across the different regions of the country. India has staked its claim to being the most populous country in the world, overtaking china, and the improving healthcare system has also resulted in significant improvement in average life span.

From a lowly average life span of 49.2 years in year 1960, India has shown remarkable improvement with an average life span of 70.4 years. Increased average life span also implies an increase in the percentage of elderly population, and the elderly population is expected to reach around 20% by year 2050. As the occurrence of Alzheimer's disease and dementia shows a positive correlation with aging population, these cases are expected to rise in india and an understanding of its level of prevalence in country's population can allow a better estimation of challenges in the near future [3].

***Historical Context***

Alzheimer's Disease gets its name from a renowned doctor involved with the study of neurosyphilis and multi-infarct dementia. This doctor presented the first case of this type in the academic circles and the disease gets its name from him. It was the year 1901 when Alois Alzheimer first encountered a female patient named Auguste Deter, who was 51 years old. She was taken to a mental hospital by her husband Karl because of her progressively strange behaviour. She would hide things, threaten her neighbours and even accuse Karl of cheating. On the other hand, her functional abilities deteriorated as she was unable to perform domestic chores like cooking or cleaning. She was admitted to the Frankfurt Mental Hospital. Alois Alzheimer was a doctor at that hospital and Auguste was under his care. Alzheimer closely observed her behaviour. He found many peculiarities like her ability to talk coincided with her inability to write her own name, her ability to name general objects like a pen or pencil with her inability to name her own food, and her shifting behaviour between polite and loud and rude.

Alzheimer initially came up with the diagnosis of presenile dementia. Auguste died in 1906, allowing Alzheimer to examine her brain. This examination revealed cortical atrophy widely spread through the brain and cell clusters that had undergone specific changes. He also observed that nerve fibres contained plaques and tangles- phenomena recognised by the later researchers in 1980's as beta amyloid plaques and tau neurofibrillary tangles. The findings from his observation of Auguste's behaviour and the examination of her brain were presented by Alzheimer at a German Psychiatry conference, where he linked the clinical symptoms with the changes in her brain. The very next year these findings were published as a paper and in 1910 he wrote a textbook that first named this particular condition of dementia as Alzheimer's Disease. In 1984, standardized diagnostic criteria for Alzheimer's disease was finalized in the USA. There were subsequent updates in the criteria in 2011, followed by in 2018. These updates created distinction between mild cognitive impairment stage and the dementia stage, presenting distinct diagnostic criteria for both. Besides making these distinctions, these updates also included the important role of biomarkers while diagnosing for the disease [4].

***Epidemiology***

With an estimated number of 57.4 million people being affected by this disease, it poses a major health concern on the global scale. Better healthcare system has resulted in increased lifespan and decline in the birth rates, leading to an increasing size of elderly population. it is expected that this demographic shift will persist in the future, resulting in even larger percentage of elderly population. With an observed positive correlation between old age and incidence of dementia, such cases are also expected to increase. Global Burden of Disease Study 2019 projects an increase of 166% in the number dementia cases between the years 2019 and 2050. This projected increase puts the number of affected individuals around 152.8 million, a figure that is very close to the projections of WHO as well. Countries with low socio-demographic index, India being a key example, are expected to witness an even faster increase in the incidences of dementia and AD, reaching upto 330%. While india ranked fourth in terms of contributing to the global number of individuals suffering from dementia in 2019, it is expected to become the second largest contributor following china [5]. Besides age, this increasing trend in the incidences of AD is also resulting from diet, pollution, factors affecting vascular health and genetics [6].

***Impact on Global Health***

Two noteworthy global studies have projected the direct and indirect cost of dementia care to increase to 2 trillion USD by 2030. This figure is expected to reach 9.12 trillion USD by 2050. These figures are projected on the basis of the statistical value of life, calculated at national, regional and global levels up to year 2050. This reliance on statistical value of life to calculate the estimated economic cost of Alzheimer's Disease and Related Dementia (ADRD) remains the first such attempt. The research data points to a significant increase in the economic cost of ADRD at the global level, while also pointing to a shift where a larger percentage of burden will fall upon the low to mid-income countries. as the low to mid-income countries are likely to experience higher burden of ADRD, it becomes imperative to increase investment in the erstwhile underfunded research and development activities to provide better prevention, treatment and care [7]. The investments in preventive measures or improved treatment services for ADRD need to be evaluated with due consideration for informal care based economic loss. Based on available projections, the total burden on the global economy due to Alzheimer's disease and other dementia for the period between 2020 and 2050 will be approximately 14.513 trillion USD, which is equal to the total global expenditure on health in the year 2020. Currently that larger share of this burden fall upon the high-income countries [8].

Based on a report by Alzheimer's Disease Internation, a new case of dementia is reported at the global level every three seconds and Alzheimer's disease constitutes around 60 to 70% of these total cases of dementia. Researches into the factors influencing vulnerability to dementia reveal genetic factors, individual lifestyle and the environment as the potential factors that increase the risk of developing dementia and its progression. Hence, there has been a shift away

from single treatment based approach and a shift towards studying individual or group based variations in the cases of Alzheimer's Disease and Other Dementia [9].

**PATHOPHYSIOLOGY**

Loss or damage at the level of neurons is primarily concentrated in hippocampus- located in medial temporal lobe- that plays an important role in memory formation and learning, amygdala- deep inside the temporal lobe- that plays important role in emotional processes and also contributes to the functions of memory and motivation, entorhinal cortex- a region within the temporal lobe- that plays important role in memory formation and navigation in a spatial context, and various association areas located within the frontal lobe, parietal lobe and the temporal lobe. These neural losses and damages primarily affect different parts of the subcortical regions. Formation of neural tangles starts from the cortex and reaches the association areas. All the three lobes-frontal, temporal and parietal- are affected by these tangles. The magnitude and placement of these tangles shows a closer correlation with how severe dementia is, as compared to the influence of amyloid plaques. Decline in cognitive functions and cerebral atrophy shows a positive association with Tau accumulation, especially in the Hippocampus [10] , [11] .

A number of hypotheses have been proposed based on pathophysiological premises. Some these hypotheses are worth mentioning at this point. Cholinergic hypothesis proposes adverse effect of anticholinergic medicines on the memory of older patients. Amyloid Hypothesis postulates increased formation of aggregated amyloid proteins in the place of breakdown of amyloid precursor protein, due to the actions of Aβ42 [12]. Another hypothesis has been proposed, based on Hyperphosphorylated tau protein and Amyloid β, that links pathology of alzheimer's disease with defunction at cholinergic level, toxicity of amyloid and tau protein, and oxidative stress. There is another hypothesis pertaining to oxidative stress, linking lower level of glutathione in neurons to injuries caused by oxidative stress [13]. Neuroinflammation focussed hypothesis argues that neurons undergo changes at functional and structural levels caused by continuous activation of microglia and exposure to pro-inflammatory cytokines, leading to eventual degradation or degeneration [14].

**Alzheimer's disease and Genetics:**

While genetic factors are known to influence susceptibility to Alzheimer's disease, they cannot be pointed as the sole causal factor. APOE gene is responsible for synthesis of protein that transports cholesterol and has multiple alleles. There are other genes as well, for instance APP, PSEN1 AND 2, that are linked with Alzheimer's disease. However, there is no definitive proof linking genetics with Alzheimer's disease as a sole reason. Researches are looking into both genetic and environmental factors. While genetic testing provides an option, it is usually not prescribed in Alzheimer's disease because of its inability to provide definite prediction about someone getting Alzheimer's disease [15].

**Clinical Symptoms**

Cognitive Symptoms: Alzheimer's Disease affects the cognitive function of individuals. Such patients show progressive loss of memory. Their linguistic abilities degrade or diminish and they also face problems with depth perception and spatial awareness. Such individuals have shorter attention span, limited reasoning ability and face challenges with executive functioning as well [17].

Besides the decline of cognitive functions, there are symptomatic changes at behavioural and psychological level as well. It becomes highly important to compile patient's history in order to categorize the symptoms on the basis of type and urgency, and prioritize intervention for specific symptom. This history also enable proper description of symptoms and identify factors that can make the symptoms even worse and can be reversed. These factors include but are not exclusive to environmental factors, medicines being used, discomfort level of the patient, history of substance abuse and any past mental ailment [18].

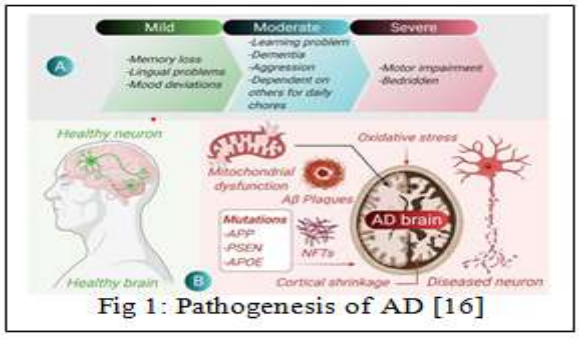

Fig 1: Pathogenesis of AD [16]

**Fig 2. Conceptual Framework [19]**

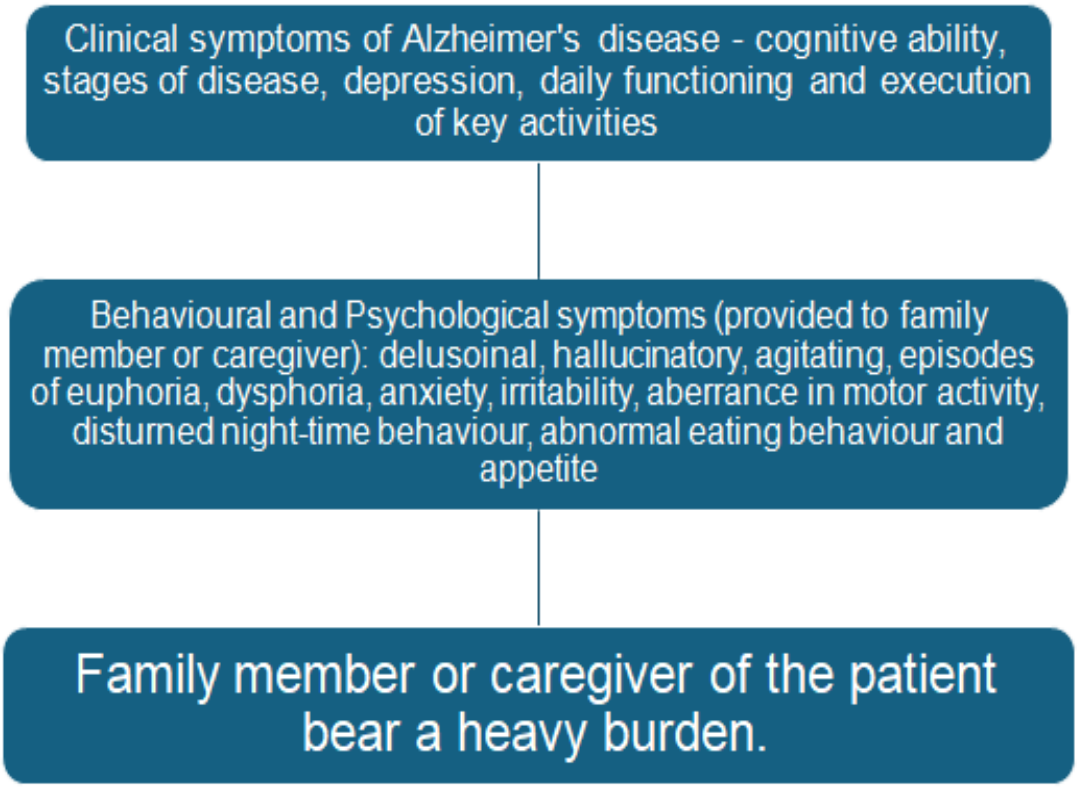


**Fig 2. Conceptual Framework [19]**

Based on the symptoms, a Global Deterioration scale has been prepared that identifies seven stages of Alzheimer's disease. The stage-wise listing of symptoms is as follows:

Stage 1: while the individual shows mental normalcy, there are changes in the brain.

Stage 2: This stage shows the onset of memory loss, but it is at a very slight level that may be confused with common forgetfulness.

Stage 3: At this stage the individual experiences mild level of cognitive loss, resulting in problems like getting lost or facing difficulty with finding the right words to express themselves.

Stage 4: A moderate level of dementia sets on as the patient finds difficulty with their short term memory and may also forget some bits and pieces from their individual history.

Stage 5: There is progressive decline of cognitive functions and the patient faces difficulty carrying out their daily activities. Feeling confused and partial forgetting of personal details are other key symptoms. Now they need help to carry out their daily functions.

Stage 6: At this stage the patient experiences sever onset of dementia with a need for constant supervision. Loss of ability to recognize family members or friends, personality changes are some other key developments at this stage.

Stage 7: This is the final stage where the patient is generally bed ridden with severe motor issues, may lose control over passing the waste, face difficulty with communicating and need assistance with feeding [20].

**DIAGNOSIS**

There are many criteria to diagnose a case of Alzheimer's disease. These criteria may range from assessment of cognitive impairment to neuropsychological tests, use of imaging methods or test for presence of certain bio-markers. The clinical criteria focusses on the onset and increasing loss of memory and cognitive abilities. The assessment or diagnosis criteria helps to identify probability of Alzheimer's disease, possibility of the disease and the certainty of the disease. While these criteria are in use, they are subject to changes or modifications with the growing size of information and understanding [21].

**Cognitive assessments**:

i) Mini-Mental State examination is a generally used 10 minutes test for Alzheimer's disease that tests various cognitive domains like memory of the individual, spatial orientation, mathematical skills, attention span, linguistic and visual skills.
ii) Montreal Cognitive Assessment is on thinking ability in different areas that includes tasks like clock-drawing or skills like putting numbers in sequence and planning, or awareness of setting and space. This assessment determines the need for any further assessments.
iii) Memory impairment screen is usually performed at the initial stage and in a supplementary role with other tests. This screening is based on performance of some tasks like putting words into different categories, reading those words out loud and then recall of those words.
iv) Mini-cog is a test that is performed at community level healthcare to assess cognitive health of elderly people and provides understanding of their memory condition and their thinking ability.
v) 7-Minutes screen test uses activities like asking questions, giving prompts to test memory recall and drawing a clock to identify onset of Alzheimer's disease. This test usually lasts for 7 to 8 minutes and identifies potential loss of cognitive functions.
vi) Saint Lous University Mental Status Exam serves a set of eleven questions that seek to assess cognitive status, linguistic skills, ability to recognize shapes and identify animals.
vii) AD8 Informant Interview uses a brei set of questions that assesses changes in cognitive functions of an individual and this test is performed by someone closely familiar with the patient.
viii) General practitioner assessment of cognition provides a range of tasks like repeating a selective list of information, telling the data, drawing a clock and recalling a news story in a period of two to give minutes.
ix) SAGE test is performed at home and then brought to a specialist in dementia for evaluation purposes. This test focusses on assessment of linguistic ability, memory of the patient, ability to perform executive functions and naming objects, and demonstration of orientation and visual-spatial skills [22].

**Biomarkers based diagnosis**:
Biomarker refers to organic molecules present in body fluids or tissues that may indicate absence or presence of health conditions through their normal or abnormal quantity. These biomarkers also help with monitoring bodily response to treatments for a particular physical ailment [23], [24]. Cerebrospinal fluid (CSF) contains a key set of biomarkers that can be used to determine risks or possibility of alzheimer's disease. Beta amyloid 42, Tau and phosphor-tau and GAP-43 are some examples of biomarkers present in CSF. Technological tools available for diagnosis include NeuroFilament Light, Neuroimaging, PET scan, DTI. [25], [26].

**Differential Diagnoses:**
This approach is used because many health conditions can have symptoms that are similar to Alzheimer's disease. For instance, certain types of dementia can also present similar symptoms like Lewy Body, Frontotemporal or vascular dementia. There are many other conditions to be kept in consideration like the effects of aging process, deficiency of vitamin B12, increased level of sodium in the body, Parkinson's disease, side effect of certain medications, substance abuse and so forth. Hence, a reliable diagnosis of Alzheimer's disease requires combined use of diagnostic tools, patient's previous records and any other useful information. The diagnostic tools available to the doctors include neurological exams, assessment of cognitive functions, different imaging techniques used for brain and tests for different biomarkers present in the cerebro-spinal fluid or blood [27]. A specialized criteria for diagnosing Alzeimer's Disease caused dementia (NIA-AA criteria) focusses on the clinical signs of the disease and keeps the biomarkers in a supporting role [28].

**Identifying Risk Factors and Preventive Measures**

Based on existing research, Alzheimer's disease can be caused by a number of risk factors. These risk factors can be genetic in nature, it can be due to ageing of the individual, behaviour of the individual and their habits. While the genetic aspect, ageing of the individual or family history of Alzheimer's disease are unalterable factors, behavioural, environmental or habit related factors can be modified to reduce the possibility of losing cognitive functions [29].

Among the unalterable factors, age plays a crucial role. Based on research data, once an individual reaches the age of 65, the probability of Alzheimer's disease increases by 100 percent per five years. Genetics, another unalterable factor, also plays a crucial role. People with family history of Alzheimer's disease are more likely to develop this disease as compared to people with no such history.

Behavioural and environmental factors, on the other hand, are modifiable and can be altered to reduce likelihood of developing Alzheimer's disease. Among the behavioural factors unhealthy dietary habits, sedentary lifestyle,

unattended chronic diseases are some of the key factors. Pollution level, particularly air and noise pollution, isolated existence, mentally unstimulating life are some of the environmental factors. Heart problems, stroke, hypertension, diabetic condition, obesity, head injury resulting in concussion and chronic depression are some other contributing actors. Unlike genetic and ageing related factors that are unchangeable, these behavioural and environmental factors can be modified to reduce the risk of reduced cognitive functions or Alzheimer's [30].

**Strategies for potential prevention**
Individuals can adopt and practice certain strategies to prevent, reduce the likelihood or delay the onset Alzheimer's disease. They can make it a habit to stay active. They should engage in activities that stimulate cognitive faculties, eat healthy food and develop community engagement to avoid social isolation. Managing diabetes and hypertension, stopping smoking, limiting consumption of alcohol, preventing injuries to the brain and taking proper minerals and vitamins are some other measures that can help with prevention or , at least, lower the risk for the same [31].

**Treatments Currently in Use**:
Pharmacological- There is a limited range of options available for the treatment of dementia in general and Alzheimer's disease in particular, but they demonstrate the ability to alleviate the symptoms [32]. The medicines that are approved to be used in the treatment of dementia include-
Donepezil
Rivastigmine
Galantamine
Memantine

Among these, the first three come in the category of cholinesterase inhibitors. Memantine has a different way of working as it affects secretion of glutamate[33]. These inhibitor based medicines are not found to offer complete cure of dementia, but offer some help with alleviation of some symptoms in the early stages of the disease. The use of memantine has been tested in certain types of dementia cases like Lewy body and Parkinson's disease and the results do not provide any conclusive evidence of its effectiveness [34]. However, it has approval for usage in the case of moderate to severe cases of Alzheimer's disease and often in combination with inhibitors. Rivastigmine patches have potential applications in the severe cases of dementia.

**Non-Pharmacological:**
Besides medicinal treatment, there are many other treatment methods being used for Alzheimer's disease. Using activities to stimulate cognitive functions, leading physically active lifestyle, using light therapy, music as a therapeutic tool, reminiscence, animal assistance based therapy and aromatherapy are some of the non-pharmacological interventions being used to alleviate the symptoms of Alzheimer's disease. As for alleviating the cognitive degradation, exposure to nature, playing board games or doing needlework are recommended interventions. However, these therapeutic interventions need to be tailored to suit the individual requirements. [35].

**Emergent Treatment Methods and Researches**

Besides the already approved and practices list of treatments available, there has been some new developments in the field of detection and treatment of Alzheimer's disease. One such approach is the use of immunotherapy. This approach focusses on using antibody drug-conjugates that combine precision of delivery with potency of drugs, regenerative medicine that repairs and restores target tissues, transfer of genes to counter genetic factor behind the disease, therapy focussed on lowering lipid and some off-label therapies as well [36].

Gene therapy combined with stem cell technology has presented itself as a promising way forward. Gene therapy or gene transfer introduces new DNA into a cell as a way to replace or repair a faulty gene and correct a genetic disorder. While there are many methods or ways for gene transfer, stem cell-based method is generally employed for this purpose. In this method, stem cells are extracted rfom the body, modified in a laboratory and then reintroduced into the body. Hematopoietic, Mesenchymal and Neural stem cells are generally used for this purpose of gene transfer [37].

These emerging treatment methods are also complemented with identifying new biomarkers that can help with early detection of Alzheimer's disease. Some of these new markers include Amyloid-β peptide, which is derived from amyloid precursor protein and its accumulation in brain form plaques; Tau protein, where its abnormal phosphorylation causes deposition in neurofibrillary tangles that is a key indicator of alzheimer's disease; and Cerebrospinal fluid levels that indicate any possible infections in the neurons. Besides these, technique of neuroimaging and the innovation of Plasma neurofilament light can also provide much help with diagnosis. Creating a combination of these bio-markers and other technological innovations can provide a better individually customized diagnosis [38].

**Challenges with Research and Care in Alzheimer's Disease**

Research into treatment and care for the patients of Alzheimer's disease face numerous challenges:

- Recruiting patients for clinical trial becomes a challenge due to paucity of time, limited tools for diagnosis and the risks for the patients.

- Adhering to a medical regimen also becomes a challenge because the cognitive deterioration makes it difficult for the elderly patients and if the drug is to be administered via transdermal process, it would result in added pressure for the caregiver.

- Disclosing the diagnosis results is another challenge. The frequency at which the symptoms appear is not uniform or fixed and some symptoms may have appeared before the diagnosis takes place.

- Progression of the disease itself is a challenge. Brain changes, that are precursor to the Alzheimer's disease, take place much before the clinical symptoms start showing up.
- People suffering from dementia are more prone to infections their declining cognitive functions also means their reduced ability to understand public health advisories.

- Observations in the cases of Alzheimer's disease have shown inflammation which may also be symptomatic of another serious ailment and cognitive problem. However, use of anti-inflammatory medications or therapies have not yielded positive trial results.

- Majority of treatment approved or used for Alzheimer's disease are focussed on alleviating the symptoms instead of treating the underlying causes[39].

Alzheimer's disease still remains a mysterious challenge due to lack of clarity over how it works. We still haven't developed very precise and accurate marker to track it. Given the complications associated with this disease, designing and running a clinical trial is very difficult. These factors collectively cause the failure many drug development efforts [40].

**Clinical Trial Design Challenges**:

- Finding patients of Alzheimer's disease who are suitable for the trial is a key challenge. Patients with advanced level of disease and significant decline in cognitive functions are easier to find but do not provide a reliable assessment of the treatment.
- When the treatment outcome is measured through subjective evaluation of patient's cognitive functions, it introduces the scope for individual variations that would complicate the interpretation process.
- When the trials are conducted with smaller groups, there is not sufficiently robust data point to differentiate between the actual treatment and placebo groups [41].

**Lessons from Drug Development Failures**:

- It is important to focus on identification of Alzheimer's disease in its early stages, which can be done through the use of biomarkers that indicate the disease risk level, in order to have better and observable treatment outcomes.

- Greater focus and investment in identifying biomarkers that provide reliable tracking of how the disease is progressing and reliable prediction of how a treatment will affect the patient.
- A better customization of treatment is needed. It can be done by classifying patients on the basis of their genetic traits and physical traits and observe the effectiveness of different treatment methods on different groups.
- Trial design needs to be improved through more careful selection of patients to ensure standard homogeneity in the group.
- Assessment of cognitive functions should be standardized and effective enough to identify even small changes.
- Trials should have sufficiently large sample size to draw meaningful inferences and conclusions.
- There is also need for better collaboration and data sharing among different researchers' groups, companies and the institutions functioning as different regulatory bodies to facilitate aster drug developments.
- Researchers should validate the effectiveness of drugs in terms their interaction with the targeted part of the brain before taking up clinical trials.

Thus, drug development efforts to treat Alzheimer's disease require comprehensive changes in the areas of trial design, sample selection, biomarker selection, information sharing and intervention timing to improve their chances of success [42].

**Caregiver Burden and Support Systems**

One of the biggest problems with researches in Alzheimer's disease and its care is the burden it exerts upon the caregivers. Individuals responsible for providing care to such patients often experience substantial stress at emotional level, at physical level and even at financial level. This constant stress adversely affects the caregivers, making them depressed, anxious and unhealthy because this is a long -term and very demanding burden, and often with insufficient support [43].

- In the case of Alzheimer's disease, the caregivers experience stress at emotional and physical levels, their financial resources are strained, they become isolated in the society because of the demanding nature of care and they also lack knowledge about the disease and appropriate care [44].

- Providing support to caregivers has its own share of challenges. Identifying the needs of these caregivers, ensuring accessibility to the support system, providing training to the caregivers and accommodating the cultural differences are some of the key challenges [45].

- Some of the ways to reduce the stress level of caregivers include formation of support groups, providing counselling services through trained professional, aiding them with technology based tools and further researches into caregiver stress [46], [47].

**Ethical Considerations in Diagnosis and Treatment**

While dealing with researches in the field of Alzheimer's disease and its care, it is important to consider the ethical aspects as well. Some of these ethical considerations are as follows:

While there is increasing emphasis on early diagnosis o the disease, it also comes with challenges like chances of classifying the disease incorrectly or not having suitable treatment, which can adversely affect the future course of the disease. However, early diagnosis also offers the patients an opportunity to make their choices in an informed way when their cognitive abilities still sufficient for the purpose.

Genetic testing has the potential to diagnose the onset of disease or predict its probability. As the family is also affect by these results along with the patient, counselling services is essential for both.

While designing trials for AD in preclinical stage, it is imperative that the risks for the participants is clearly outweighed by its benefits.

In trials focussed on preventive measures, the participants are likely to be tested for various risk factors, like genetic factors or other biological factors, that are generally not provided or available in standard clinics. Hence, the disclosure of these information must be considered with due carefulness.

Delivering the news of dementia can be challenging for the clinicians due to the its massive impact on the lives of the patients and their families and the already high pressure atmosphere in the hospitals or clinics.

The psychological impact upon receiving the diagnosis of Alzheimer's disease poses another ethical consideration. While some may respond with experience of relief or clarity for understanding their symptoms, others may experience fear and anxiety about their future or may go in depression [48].

Some other ethical issues may emanate from the following factors:

**Table 1 [49]**

| | | |
|---|---|---|
| Financial impact | Impact on caregivers | Socio-economic impact on patient and caregiver |
| Chances of abuse faced by patients of dementia | Racial/ethnic identity | Cultural identity |

**Future Directions**

Personalized medical intervention can be developed based on the genetic, environmental and lifestyle related uniqueness of the individuals, and such treatment approaches promising to be more impactful. Some potential initiatives in this direction are as follows:

- Research projects like ABOARD can be promoted that focus on personalized and enhanced methods of diagnosing or predicting the disease, offering ways of preventing the disease, and suitable care for the patient.
- Individually tailored lifestyle habits can be developed for individuals vulnerable to such diseases, focussing on micronutrients intake to prevent or slowdown decline in cognitive functions.
- Researching into genetic factors like APOE and MTHFR can help with more effectively personalized treatment for AD. For example, methylated vitamin B is more effective as compared to standard vitamin B when administered to individuals with certain variations of MTHFR.
- Use of artificial intelligence in combination with biomarkers can yield better results in the areas of neuroimaging, study of biomarkers and development of medicines or the disease.
- Light therapy has the potential to positively affect sleeping pattern and neurotoxicity [50].

With the projected rise in the incidences of alzheimer's disease, the burden on healthcare system and expenses is also going to increase. In this scenario, personalized treatment approaches has the potential to alleviate the burden [51].

**Combination Therapies and its Scope**

Since the Alzheimer's disease is a result of complexly interwoven factors, combination therapies promise to be a more effective approach to treating the disease. These combination therapies can try targeting a combination of areas, using a combination of delivery methods or applying a combination of functions within a single treatment. Some of these potential combinations are as follows:

- Either pick a combination of targets like amyloid and tau protein or pick just one target and use different ways of tackling it.
- They can use a combination of delivery systems like combining oral delivery method with intravenous delivery .
- Multifunctional molecules can be put into use. Rasagiline can be seen as an example. Its primary function is as inhibitor of monoamine oxidase B, but it also provides protection to the neurons and influences the processing of amyloid.
- Treatments can also create a sequence of targets that are tackled in that order. For example, removal of amyloid plaques can be set as the first target, tackled using a monoclonal antibody, followed by the application of BACE 1 inhibitor.
- Combining two well proven molecules can be another option. For example, donepezil can be applied in combination with memantine. Patients without any clinical symptoms but having biomarkers that suggest presence of Alzheimer's disease are ideal candidates for the application of combination therapies. [52].

**Advancements in Early Detection and Prevention**

The ongoing researches in the area of Alzheimer's disease have shown many promising techniques that can help with early detection of AD and its prevention. Some of these are as follows:

- Blood tests to find presence of Alzheimer's disease linked proteins like amyloid or tau.
- Imaging methods like PET scans or fMRI to find the presence of amyloid protein or tau protein can help with early finding of risk factors, thus helping early detection.
- Identifying biomarkers that help with risk identification, like finding blood exospores and examining neuroretina.

- Variability of heart rate can also be refined as a marker to indicate development of Alzheimer's disease.

- Artificial intelligence and deep learning models can be used in combination with imagining techniques like MRI and PET scans to provide early warning of Alzheimer's disease [53].

These advancements in the field of early detection have been complemented by progress in treatments as well. These treatments focus on amyloid beta peptides and tau proteins. There are anti-amyloid beta medicines that are showing promises of improved treatment. Some therapies have shown effectiveness in slowing down progress of the disease [54]. Besides these therapeutic progresses, there have been focus on risk management as well. These risk management processes ocus on cardiovascular, cognitive and environmental risks [55].

## CONCLUSION

It can be concluded at this point that Alzheimer's disease is a massive challenge for the global health, particularly with the ageing population across the world and increasing prevalence of this disease in the highly populated low to middle income group countries. A proper understanding of this disease requires combining historical background of the disease with its biochemical and pathophysiological indicators, clinical symptoms, biological and non-biological risk factors, methods and tools for diagnosis, prevailing approaches of treatment and the merging trends in the field of diagnosis and treatment. The complex nature of disease requires a multi-pronged approach in researches that understand the urgency of increasing awareness about the disease, need for early diagnosis and the importance of support system that both the patients and their caregivers.

As the current researches establish future upward surge in cases of Alzheimer's disease, it becomes imperative that the policymakers collaborate and cooperate with the medical communities and, by extension, the wider society to promote researches in this field through better funding, improving the strategies for patient care and developing impactful protocols for the prevention and treatment of the disease. Investment in personalized treatment and care for the patients is the way forward for alleviating the living condition of people affected by the disease. It becomes a collective responsibility to strive for a framework of comprehensive care, alleviation of stress experienced by caregivers and breakthroughs in diagnosis and treatment that can eventually provide a cure for the disease.

**Recommendations for future researches and care:**

There is an urgent need for developing therapies with better effectiveness and accessibility, and can be used in early stage.
It is important to find trial subjects who have early stage of the disease in order to find more relevant data and results.

The treatment and care therapies need to be more affordable, especially with greater number of cases occurring in low to mid-income countries. A sustainable and effective support system is needed for both the patients and the caregivers. Improvement in diagnosis methods and tools is needed to detect the disease at early stage. For improving research quality, trial criteria for the participants must be set in advance, followed by group formation and screening. Clinical trial infrastructure needs improvement for better speed and efficiency. Therapies can focus on understanding the biological mechanism behind the disease and modifying it. The tools used for clinical assessment need to be validated and key information should be accessible for the patients [56].

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