Review Paper

ISSN: 3139-3683

JOURNAL OF HEALTH SYNAPSE (JHS)

Peer Reviewed Refereed Open Access International Multidisciplinary Journal

Publisher: *Scientistic Era Private Limited*
Journal Hompage: *https://healthsynapse.org*

Advances and Challenges in Alzheimer's Disease: a Comprehensive Review of Treatment Strategies, Diagnostic Tools, and Future Directions

Running Title: A Comprehensive Review on Alzheimer's Disease

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ARTICLE INFO

KEYWORDS:
Acetylcholinesterase Inhibitors (AChE Inhibitors), Nanoparticle-Mediated Delivery, Blood-Brain Barrier (BBB), Drug Formulation, Nanomedicine, Neurodegenerative Disorders, Cognitive Decline, Amyloid-Beta Plaques, Neurofibrillary Tangles

ARTICLE HISTORY
Received Date: 25 July 2026
Revised Date: 08 August 2026
Accepted Date: 18 August 2026
Published Date: 25 August 2026

CITATION
Sushma, Dubey, R., 2026 Review of Treatment Strategies, Diagnostic Tools, and Future Directions. *Journal of Health Synapse (JHS), 1(3), 41-50. https://doi.org/10.67529/jhs.v1i3.4*

A B S T R A C T

"Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss, primarily caused by the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain". Current therapeutic strategies focus on symptomatic relief, with acetylcholinesterase (AChE) inhibitors being a mainstay in treatment. However, the efficacy of these inhibitors is limited by their poor "bioavailability and inability to effectively cross the blood-brain barrier (BBB)".
"Recent advances in nanotechnology have shown promise in overcoming these challenges through the development of nanoparticle-mediated delivery systems". These systems offer enhanced drug stability, targeted delivery, and controlled release, potentially improving the therapeutic outcomes for AD patients. This study explores the formulation of nanoparticle-based delivery systems for AChE inhibitors, evaluating their physicochemical properties, BBB permeability, and therapeutic efficacy.
The include optimizing nanoparticle "size, surface charge, and composition to enhance BBB" penetration and drug release profiles. "In vitro and in vivo studies are conducted to assess" the biocompatibility, neuroprotective effects, and cognitive benefits of the formulated nanoparticles. Preliminary results indicate that nanoparticle-mediated delivery significantly enhances the bioavailability and efficacy of AChE inhibitors compared to conventional delivery methods. This research contributes to the growing field of nanomedicine, providing a foundation "for the development of more effective therapeutic strategies for Alzheimer's disease". The potential of nanoparticle-mediated delivery systems to revolutionize AD treatment underscores the importance of continued innovation in this area, paving "the way for improved patient outcomes and quality of life".

I. Introduction

Alzheimer's disease is a progressive, degenerative disorder that attacks the brain, leading to a decline in cognitive abilities, memory loss, and changes in behavior. It is the most common form of dementia, accounting for 60-80% of all dementia cases [4][5]. Alzheimer's disease is not a normal part of aging, and it affects people of all ages,

though it is more prevalent in older adults. The greatest known risk factor is increasing age, with most people with Alzheimer's being 65 and older [4]. The disease is characterized by the presence of amyloid plaques and tau tangles in the brain, which are abnormal structures that damage and kill nerve cells. These plaques and tangles disrupt communication between nerve cells, leading to memory failure, personality changes, problems carrying out daily activities, and other symptoms of Alzheimer's disease [4]. Alzheimer's disease progresses in stages, with symptoms gradually worsening over time. The early stages of the disease may be marked by mild memory loss, while the later stages can result in severe cognitive decline and the inability to carry on a conversation or respond to one's environment [4]. The average lifespan of a person with Alzheimer's disease is 4 to 8 years after diagnosis, but some people can live as long as 20 years, depending on other factors [4]. Currently, there is no cure for Alzheimer's disease, but certain medications and therapies can help manage symptoms temporarily. Researchers worldwide are working to find better ways to treat the disease, delay its onset, and prevent it from developing [4]. Alzheimer's disease is a devastating condition that affects millions of people around the world. It is essential to understand the signs and symptoms of the disease, seek medical advice if you notice any issues with your memory, and support ongoing research to find better treatments and ultimately a cure for Alzheimer's disease. Alzheimer's disease is a chronic and progressive neurological disorder that primarily affects older adults and is the leading cause of dementia worldwide. The condition is characterized by cognitive decline, memory loss, and changes in behavior and personality. As the disease progresses, it can severely impact a person's ability to perform daily activities and interact with others. Although it is most commonly diagnosed in individuals over the age of 65, Alzheimer's disease can also occur in younger people, known as early-onset Alzheimer's.

Sign and symptoms:

Alzheimer's disease typically progresses through several stages, each with its own set of symptoms:

- **Mild Cognitive Impairment (MCI):** This early stage often involves subtle changes in memory and cognitive function, which may go unnoticed by others.
- **Mild Alzheimer's Disease:** Memory loss becomes more noticeable, particularly in recent events and conversations. Individuals may experience difficulty with planning and organizing, and may struggle with language and spatial orientation.
- **Moderate Alzheimer's Disease:** As the disease progresses, individuals may struggle with more complex tasks such as managing finances and personal care. Behavioral changes such as aggression, depression, and anxiety may become more pronounced.
- **Severe Alzheimer's Disease:** In the final stages, individuals may lose the ability to communicate and perform basic daily tasks such as dressing, bathing, and eating. They may require full-time care and support.

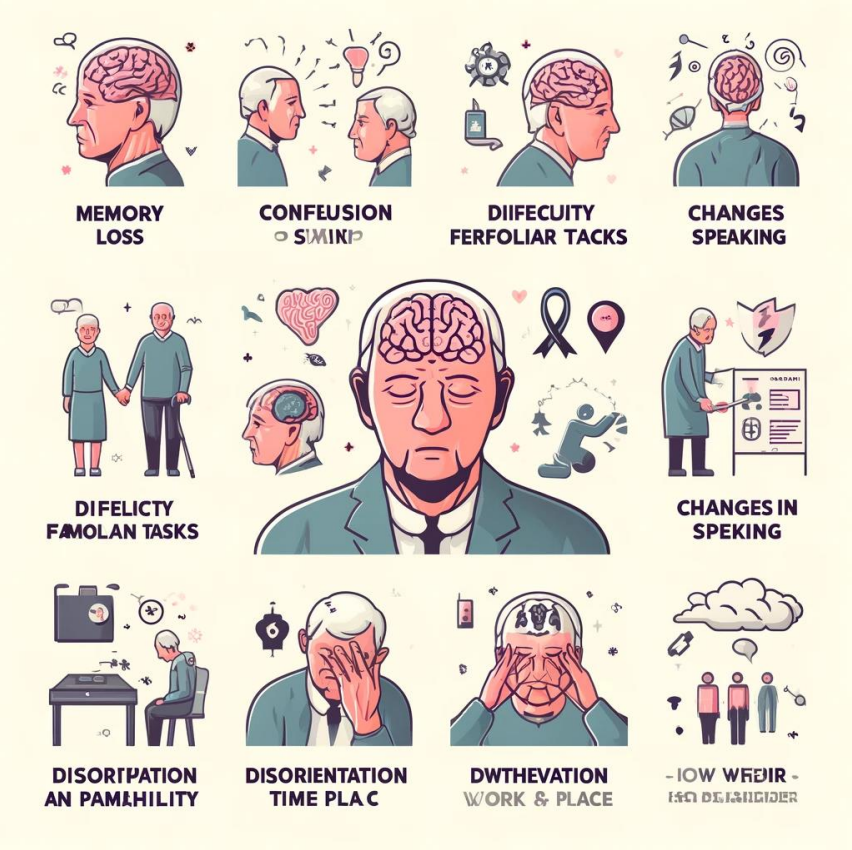

Figure 1: Sign and symptoms of Alzheimer's Disease
(Source: This Image is created by author.)

Pathophysiology

The two hallmark pathological features of Alzheimer's disease are the accumulation of amyloid plaques and neurofibrillary tangles in the brain.

- **Amyloid Plaques:** These plaques are composed of beta-amyloid protein, which accumulates in sticky clusters between nerve cells. These clusters interfere with cell communication and can trigger inflammation, ultimately leading to cell death.
- **Neurofibrillary Tangles:** These tangles form inside neurons and consist of twisted tau proteins. In a healthy brain, tau proteins stabilize microtubules in the cell. In Alzheimer's, tau becomes abnormally phosphorylated, causing tangles that disrupt cell function and contribute to neuronal death.

The destruction of neurons and the disruption of communication between them lead to progressive cognitive decline and memory loss.

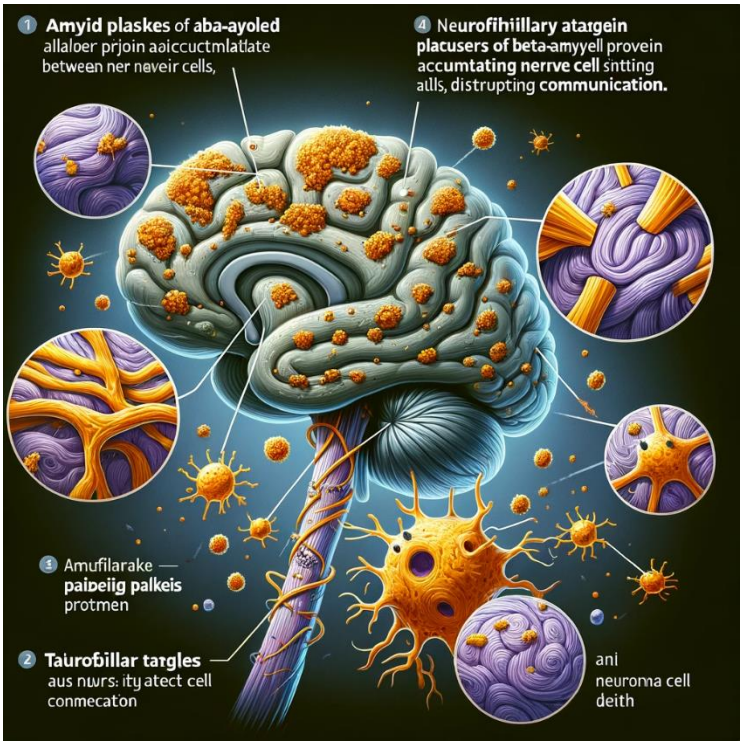

Figure 2: Pathophysiology of AD (Source: This Image is created by author.)

Another context of Pathophysiology

- **Neuronal Loss**: The accumulation of amyloid plaques and neurofibrillary tangles leads to the progressive degeneration and loss of neurons, particularly in regions of the brain associated with memory and cognition such as the hippocampus and cerebral cortex.
- **Inflammation**: Amyloid plaques trigger inflammatory responses in the brain. The activation of microglia (brain's immune cells) and the release of pro-inflammatory cytokines can contribute to further neuronal damage.
- **Synaptic Dysfunction**: Synapses (connections between neurons) are essential for communication in the brain. Both amyloid plaques and tangles can disrupt synaptic function, impairing the brain's ability to process information.
- **Vascular Factors**: Reduced blood flow to the brain and the presence of vascular risk factors (such as high blood pressure and diabetes) are also associated with Alzheimer's disease. These factors may exacerbate the disease's progression.

These pathological features lead to the characteristic symptoms of Alzheimer's disease, including memory loss, cognitive impairment, difficulty with language, disorientation, and changes in mood and behavior.

Diagnosis

Diagnosing Alzheimer's disease can be challenging due to its overlap with other forms of dementia and age-related cognitive decline. A comprehensive evaluation typically involves:

- **Medical History:** Gathering information about the individual's symptoms, medical history, and family history of dementia.
- **Cognitive Testing:** Assessing memory, problem-solving, language, and other cognitive functions.
- **Physical Examination:** Checking for other possible causes of cognitive decline such as infections or vitamin deficiencies.

- **Brain Imaging:** Techniques such as MRI and PET scans can provide information about structural changes and amyloid deposits in the brain.

While a definitive diagnosis can only be made post-mortem, these assessments help rule out other conditions and provide a probable diagnosis.

Treatment

Currently, there is no cure for Alzheimer's disease, but treatments are available to manage symptoms and improve quality of life.

- **Medications:** Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) can help slow cognitive decline, particularly in the early to moderate stages. Memantine, an NMDA receptor antagonist, may be prescribed in the later stages to help with memory and cognitive function.
- **Non-Pharmacological Approaches:** Cognitive stimulation, physical activity, and social engagement can all contribute to maintaining cognitive function and improving well-being.
- **Supportive Care:** Managing behavioral symptoms with therapies such as music, art, or pet therapy can help improve mood and reduce agitation.

Risk Factors

In addition to age, there are several other risk factors for Alzheimer's disease:

- **Genetics:** Certain genes, such as the APOE4 allele, increase the risk of developing Alzheimer's.
- **Family History:** Individuals with a family history of Alzheimer's have a higher risk of developing the disease.
- **Health Conditions:** Cardiovascular disease, diabetes, obesity, and high blood pressure can increase the risk of Alzheimer's.
- **Lifestyle Choices:** A healthy diet, regular exercise, and mental stimulation may help lower the risk of developing Alzheimer's.

Prevention and Research

Preventing Alzheimer's disease remains a challenge, but ongoing research is exploring potential strategies.

- **Lifestyle Changes:** Healthy habits such as regular exercise, a balanced diet, and cognitive stimulation may help delay the onset of Alzheimer's.
- **Medications:** Research is underway to develop drugs that target beta-amyloid and tau proteins to slow or prevent the progression of the disease.
- **Genetic and Biomarker Research:** Understanding genetic risk factors and identifying biomarkers could lead to earlier diagnosis and targeted treatments.

Recent Advances in Alzheimer's Disease Treatment

Recent advances in the treatment of Alzheimer's disease focus on a multifaceted approach, encompassing the introduction of new drugs targeting amyloid beta plaques, the use of non-pharmacological interventions, and the development of personalized treatment plans based on genetic factors. These approaches aim to slow the progression of the disease and improve the quality of life for individuals affected by Alzheimer's.

New Drugs Targeting Amyloid Beta Plaques

One of the key pathological features of Alzheimer's disease is the accumulation of amyloid beta plaques in the brain. Recent advances in drug development have led to the introduction of therapies specifically targeting these plaques:

- **Aducanumab:** Aducanumab is a monoclonal antibody that targets amyloid beta plaques in the brain. In 2021, it became the first drug approved by the U.S. Food and Drug Administration (FDA) to address the underlying cause of Alzheimer's disease by reducing amyloid plaque levels. Its approval sparked debate within the medical community due to mixed clinical trial results.
- **Lecanemab and Donanemab:** These are other monoclonal antibodies being investigated for their potential to target amyloid beta plaques. Both have shown promise in clinical trials by reducing plaque levels and slowing cognitive decline, though further research is needed to confirm their efficacy and safety.

Use of Non-Pharmacological Interventions

Non-pharmacological interventions play a crucial role in managing symptoms and improving the well-being of individuals with Alzheimer's disease. These approaches include:

- **Cognitive Training:** Cognitive training, such as puzzles, memory exercises, and problem-solving tasks, can help maintain cognitive function and delay the progression of symptoms.
- **Physical Exercise:** Regular physical exercise is beneficial for overall health and may help improve cognitive function. Aerobic exercises, strength training, and balance exercises can contribute to better physical and mental health.
- **Social Engagement:** Participating in social activities and maintaining relationships can improve mood and reduce feelings of isolation.
- **Creative Therapies:** Activities such as music therapy, art therapy, and reminiscence therapy can provide emotional support and improve quality of life.

Development of Personalized Treatment Plans Based on Genetic Factors

Personalized treatment plans based on genetic factors are becoming increasingly important in Alzheimer's disease research and management. By understanding an individual's genetic makeup, researchers and clinicians can tailor treatments to the specific needs of the patient:

- **Genetic Testing:** Identifying genetic risk factors, such as the APOE4 allele, can help determine an

individual's susceptibility to Alzheimer's disease and guide treatment decisions.

- **Precision Medicine:** This approach aims to provide targeted treatments based on an individual's genetic profile, potentially leading to more effective interventions.
- **Pharmacogenomics:** Understanding how an individual's genetic makeup influences their response to medications can help optimize drug therapies and minimize adverse effects.

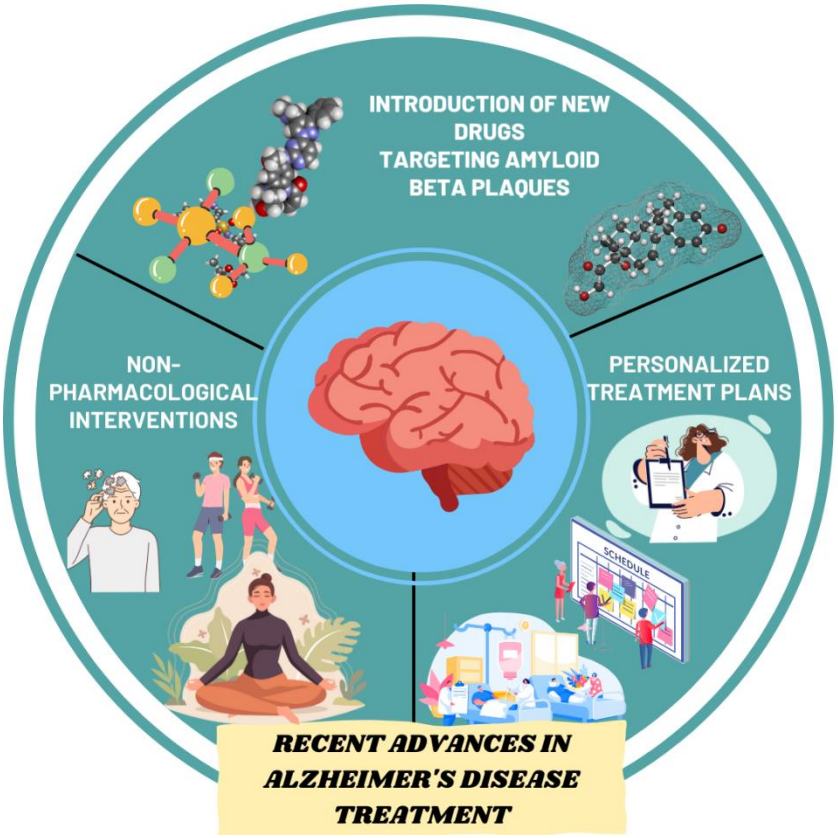

Figure 3: Recent Advances in treatment of AD
(Source: This Image is created by author.)

Diagnostic Tools for Alzheimer's Disease

Neuroimaging Techniques

Neuroimaging plays a crucial role in diagnosing and understanding the progression of Alzheimer's disease. These techniques help visualize the structure and function of the brain, providing insights into the changes associated with the disease.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) uses powerful magnetic fields and radio waves to create detailed images of the brain's structure. It is particularly useful in diagnosing Alzheimer's disease because it can visualize and quantify specific changes in the brain associated with the disease.

- **Identify Brain Atrophy**: MRI can detect atrophy (shrinkage) in specific regions of the brain, such as the hippocampus and entorhinal cortex, which are associated with memory and are typically affected in Alzheimer's disease. This atrophy is often one of the earliest signs of the disease and can be used to distinguish Alzheimer's from other types of dementia.
- **White Matter Changes**: MRI can identify changes in white matter integrity, such as white matter hyperintensities, which have been associated with an increased risk of Alzheimer's disease and other types of cognitive decline.
- **Rule Out Other Conditions**: MRI can help rule out other causes of cognitive impairment, such as stroke, tumors, or hydrocephalus. This is important because other conditions can mimic the symptoms of Alzheimer's disease and must be differentiated for proper diagnosis and treatment.
- **Monitor Disease Progression**: MRI can be used to track the progression of brain atrophy over time, providing valuable information for disease management and research. Repeated MRI scans can help clinicians assess the effectiveness of treatments and interventions.

Positron Emission Tomography (PET)

Positron emission tomography (PET) scans involve injecting a small amount of radioactive tracer into the body, which binds to specific molecules in the brain. PET

scans can provide functional information about the brain, offering insights into the molecular and cellular changes associated with Alzheimer's disease.

Amyloid PET scans use tracers that bind to amyloid plaques, allowing clinicians to visualize their distribution and density. Similarly, tau PET scans use tracers that bind to tau tangles, providing information on the extent of tau pathology.

- **Assess Brain Metabolism**: Fluorodeoxyglucose (FDG) PET scans measure glucose metabolism in the brain, revealing areas of reduced activity commonly seen in Alzheimer's patients. Hypometabolism in certain brain regions, such as the posterior cingulate cortex and precuneus, is indicative of Alzheimer's disease.
- **Differentiate Types of Dementia**: PET scans can help differentiate Alzheimer's disease from other types of dementia based on patterns of protein accumulation and metabolic activity. For example, in frontotemporal dementia, tau pathology and hypometabolism may be present in different regions compared to Alzheimer's disease.

Computed Tomography (CT) Scans

Computed tomography (CT) scans use X-rays to create cross-sectional images of the brain. While CT scans are not as sensitive as MRI or PET scans for diagnosing Alzheimer's disease, they do have some clinical utility.

- **Rule Out Other Conditions**: CT scans can help identify other potential causes of cognitive impairment, such as stroke, tumors, or hemorrhages. This is important for distinguishing Alzheimer's disease from other conditions that may present with similar symptoms.
- **Provide a Baseline**: CT scans may serve as a baseline for comparison in subsequent imaging studies. Although MRI and PET scans are more sensitive for detecting Alzheimer's-related changes, CT scans can be useful for establishing a reference point in some cases.
- **Accessibility and Cost-Effectiveness**: CT scans are often more accessible and less expensive than MRI or PET scans, making them a practical option in some clinical settings. However, their sensitivity and specificity for Alzheimer's disease are lower than other imaging modalities.

Cognitive Assessments

Cognitive assessments are used to evaluate a patient's cognitive abilities, which can provide important clues about the presence and severity of Alzheimer's disease. These assessments are non-invasive and relatively quick to administer, making them valuable tools for screening and monitoring cognitive decline.

Mini-Mental State Examination (MMSE)

- **Detect Amyloid and Tau Proteins**: PET can identify the accumulation of amyloid and tau proteins in the brain, which are hallmarks of Alzheimer's disease.

The Mini-Mental State Examination (MMSE) is a widely used cognitive screening tool that assesses various cognitive domains, including orientation, memory, attention, language, and visuospatial skills. The test consists of 30 items, with a maximum score of 30. A lower score indicates greater cognitive impairment.

- **Orientation**: The MMSE assesses a patient's awareness of their surroundings by asking questions about the date, location, and other aspects of orientation.
- **Memory**: The MMSE includes tasks that evaluate short-term memory, such as recalling a list of words after a brief delay.
- **Attention and Calculation**: Patients are asked to perform simple arithmetic tasks and other activities that assess their attention and ability to concentrate.
- **Language**: Language skills are evaluated through tasks such as naming objects, repeating phrases, and following written instructions.
- **Visuospatial Skills**: Patients are asked to draw simple shapes or copy geometric figures, which assesses their ability to perceive and reproduce visual information.

The MMSE provides a general overview of cognitive function and is quick to administer. However, it may not be sensitive enough to detect early-stage Alzheimer's disease or mild cognitive impairment (MCI).

Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) is a more comprehensive cognitive assessment tool compared to the MMSE. It evaluates multiple cognitive domains, including executive function, memory, attention, language, and visuospatial skills. The test consists of 30 items, with a maximum score of 30. A score of 26 or above is considered normal.

- **Executive Function and Visuospatial Skills**: The MoCA includes tasks that assess complex cognitive processes such as planning, problem-solving, and abstract thinking. Visuospatial skills are evaluated through tasks such as drawing a cube or a clock face.
- **Memory**: Memory tasks in the MoCA include delayed recall of words and other activities that assess episodic memory.
- **Attention and Concentration**: The MoCA includes tasks that assess attention, such as serial subtraction and vigilance tasks.
- **Language**: Language skills are evaluated through tasks such as naming objects, repeating phrases, and verbal fluency tasks.

The MoCA is more sensitive than the MMSE for detecting mild cognitive impairment and early-stage Alzheimer's disease. It provides a more detailed assessment of cognitive function and is useful for monitoring changes over time.

Clock Drawing Test

The Clock Drawing Test is a simple cognitive assessment tool that evaluates visuospatial and executive function. planning, organization, and visuospatial skills, which are common in Alzheimer's disease.

- **Clock Drawing**: Patients are instructed to draw a circle and then fill in the numbers and hands to represent a specific time. The ability to accurately draw the clock face and position the numbers and hands correctly is assessed.
- **Visuospatial and Executive Function**: The Clock Drawing Test requires patients to integrate visual and spatial information with planning and organization skills. Errors in clock drawing can indicate impairments in these cognitive domains.

Patients are asked to draw a clock face showing a specific time (e.g., 10:10). The test can reveal difficulties in

The Clock Drawing Test is often used as part of a broader cognitive assessment, such as the MMSE or MoCA. It is a quick and easy test to administer and can provide valuable information about a patient's cognitive abilities.

Diagnostic Tool	Method	Use Cases
Neuroimaging	**MRI**	Identifies brain atrophy, Rules out other conditions and Monitors disease progression.
	PET	Detects amyloid and tau proteins, assesses brain metabolism and Differentiates types of dementia.
	CT	Rules out other conditions and provides a baseline for comparison.
Cognitive Assessments	**MMSE**	Assesses orientation, memory, attention, and language skills.
	MoCA	Sensitive to mild cognitive impairment and evaluates executive function, memory, attention, language, and visuospatial skills.
Clock Drawing Test		Evaluates visuospatial and executive function and quick and easy assessment of planning and organization skills

Alzheimer's Disease Treatment Methods

Alzheimer's disease is a progressive neurological disorder that affects memory, thinking, and behaviour. Treatment approaches include both pharmacological and non-pharmacological methods.

A. Pharmacological Treatments

1. **Cholinesterase Inhibitors**:

- Cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, work by increasing acetylcholine levels in the brain.
- These drugs are used to treat mild to moderate Alzheimer's symptoms and can improve memory, thinking, and communication.

2. **Memantine**:

- Memantine is an NMDA receptor antagonist that helps regulate the activity of glutamate, a chemical involved in learning and memory.
- It is used for moderate to severe Alzheimer's symptoms and may help slow the progression of cognitive and functional decline.

3. **Antipsychotic Medications**:

- Antipsychotic medications, such as risperidone and olanzapine, may be used to manage symptoms like aggression, agitation, and psychosis.
- These medications should be used with caution due to potential side effects and limited efficacy.

B. Non-Pharmacological Treatments

1. **Cognitive Stimulation Therapy**:

- Cognitive stimulation therapy (CST) involves engaging individuals in activities that stimulate cognitive functions.
- Activities may include puzzles, memory games, and discussions that challenge memory, attention, and problem-solving skills.

2. **Art Therapy**:

- Art therapy uses creative activities, such as painting, drawing, and sculpting, to help individuals express themselves and improve mood and cognitive function.
- It can provide a sense of accomplishment and enhance well-being.

3. **Music Therapy**:

- Music therapy involves using music to evoke memories, emotions, and positive responses in individuals with Alzheimer's.
- Listening to familiar music can improve mood, reduce anxiety, and encourage social interaction.

Figure 4: Non-Pharmacological Treatment of AD (Source: This Image is created by author.)

Treatment Method	Type	Benefits
Cholinesterase Inhibitors	Pharmacological	Improve memory, thinking, and communication
		Treat mild to moderate symptoms
Memantine	Pharmacological	Regulate glutamate activity
		Treat moderate to severe symptoms
Antipsychotic Medications	Pharmacological	Manage aggression, agitation, and psychosis
		Used with caution due to side effects
Cognitive Stimulation Therapy	Non-Pharmacological	Stimulate cognitive functions
		Engage in memory games and discussions
Art Therapy	Non-Pharmacological	Promote expression and creativity
		Enhance well-being and mood
Music Therapy	Non-Pharmacological	Evoke memories and emotions
		Improve mood and encourage interaction

Table: Treatment of AD

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