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Investigation for Novel Pharmacological Target for Dementia of Alzheimer's Type

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Abstract: *Dementia of the Alzheimer type is a progressive, fatal neurodegenerative condition characterized by deterioration in cognition and memory, progressive impairement in the ability to carry out activities of daily living, and a number of neuropsychiatric symptoms.[38] This narrative review summarizes the literature regarding descriptive epidemiology, clinical course, and characteristic neuropathological changes of dementia of the Alzheimer type. Although there are no definitive imaging or laboratory tests, except for brain biopsy, for diagnosis, brief screening instruments and neuropsychiatric test batteries used to assess the disease are discussed.*

Insufficient evidence exists for the use of biomarkers in clinical practice for diagnosis or disease management, but promising discoveries are summerised. Optimal treatment requires both non-pharmacological and pharmacological interventions, yet none have been shown to modify the diseases clinical course. This review describes the current available options and summarizes promising new avenues for treatment.

Issues related to the care of persons with dementia of the Alzheimer type, including caregiver burden, long-term care, and the proliferation of dementia special care units, are discussed. Although advances have been made, more research is needed to address the gaps in our understanding of the disease. At least half of the patients who present with progressive decline in their memory, cognitive, and intellectual abilities will eventually be diagnosed as having Alzheimer's disease. The diagnosis is reached by clinical and ancillary evaluation and exclusion of all other causes of dementia. Recently, considerable advances have been made in our understanding of the neuro biologic features of Alzheimer's disease.

Cortical neurons contain paired helical filaments with a very specific electron microscopic appearance. These filaments contain proteins with unusual properties. A severe decline in cholinergic activity in the cortex is related to a marked loss of cholinergic neurons in deep cerebral structures, such as the nucleus basalis of Meynert in the substantia innominata. No specific treatment is available for Alzheimer's disease. Patients and the relatives who take care of them require substantial help and assistance in coping with the disease.

Alzheimer's disease is the most common form of dementia and the most common neurodegenerative disease. It manifests as a decline in short-term memory and cognition that impairs daily behavior. Most cases of Alzheimer's disease are sporadic, but a small minority of inherited forms allow gene identification which, together with neuropathology, yields important clues about the wider causes. Environmental and metabolic risk factors, including inflammation and vascular impairment, play a role in disease onset and progression. While neuronal atrophy and a loss of synapses occur throughout the cerebral cortex, we lack a full understanding of how this arises. The known hallmarks of Alzheimer's disease include amyloid-β plaques and neurofibrillary tau tangles and while extensive research has been carried out throughout the past few decades, the exact role of these protein aggregates in the disease remains elusive. In this chapter, we discuss mechanisms that have been implicated, including inflammation, mitochondrial dysfunction, oxidative stress and changes in protein clearance.

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Keywords: Fatal neurogenerative, epidemiology, neuropsychiatric test,filaments, amyloid beta plaques, etiology of Alzheimer's disease, dementia,neurodegeneration in Alzheimer's disease, neurofibrillary tau tangles

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes memory loss and other cognitive impairments, such as deterioration in language, learning, memory, visual-spatial abilities, reasoning, and behavior.[1] The decline in cognitive abilities can become severe enough to interfere with daily activities. AD is the most prevalent form of dementia, contributing to at least two-thirds of dementia cases among individuals aged 65 and older. [2,3]

Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. In most people with the disease- those with the late-onset type- symptoms first appear in their mid-60s. Early- onset Alzheimer's occurs between a person's 30s and mid-60s and is very rare. Alzheimer's disease is the most common cause of dementia among older adults. The disease is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. Her symptoms included memory loss, language problems, and unpredictable behaviour. After she died, he examined her brain and found many abnormal clumps (now called amyloid plaques) and tangled bundles of fibres (now called neurofibrillary, or tau, tangles). These plaques and tangles in the brain are still considered some of the main features of Alzheimer's disease. Another feature is the loss of connections between nerve cells (neurons) in the brain. Neurons transmit messages between different parts of the brain, and from the brain to muscles and organs in the body. Many other complex brain changes are thought to play a role in Alzheimer's too. This damage initially appears to take place in the hippocampus, the part of the brain essential in forming memories. As neurons die, additional parts of the brain are affected. By the final stage of Alzheimer's, damage is widespread, and brain tissue has shrunk significantly. Memory problems are typically one of the first signs of Alzheimer's, though initial symptoms may vary from person to person. A decline in other aspects of, such as finding the right words, vision/spatial issues, and impaired reasoning or judgment, may also signal the very early stages of Alzheimer's disease. Mild cognitive impairment (MCI) is a condition that can be an early sign of Alzheimer's, but not everyone with MCI will develop the disease.

History

In 1906, Alois Alzheimer, a German doctor, published his now-famous case study. He carefully detailed the symptoms of a 51-year-old woman named Auguste Deter, who was in his care at the state asylum in Frankfurt, Germany.[4] The neuropathologic analysis of Alzheimer's patients revealed widespread brain degeneration and specific changes in cortical cellular bundles. He presented his research titled "On the peculiar disease process of the cerebral cortex".[5] Since then, progress has been made in our understanding of the disease that bears his name, along with its neuropsychological effects [6]. In 1984, Dr. George Glenner and Dr. Cain Wong identified amyloid protein as the primary constituent of extracellular plaques.[7] In 1986, researchers discovered that the abnormal hyperphosphorylation of tau protein results in the neurofibrillary tangles characteristic of Alzheimer's. Tau protein is a type of protein that maintains microtubules and is released during neurodegeneration.[8,9] In 1993, Tacrine (Cognex) became the first drug authorized by the FDA to address the cognitive symptoms of Alzheimer's, such as thinking and memory.[10] It is essential to note that the clinical diagnostic criteria for AD were updated in 1984, 2011, 2018, and 2024 to reflect the growing availability of biomarkers and improved ability to identify preclinical disease episodes.[11,12,13,14] In the most recent update in 2024, AD as described as beginning as an asymptomatic biological process with AD neuropathologic changes (ADNPC), progressing to clinical symptoms as the neuropathologic burden increases.[15] Early-changing Core 1 biomarkers, such as amyloid PET, cerebrospinal fluid, and plasma biomarkers, reflect ADNPC and are sufficient for diagnosis and clinical decision-making

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In the coming decades, Alzheimer's care will likely remain a significant public health concern. Due to this ongoing and future concern, increasing knowledge and research about AD could be effective through various approaches, such as identifying and managing risk factors, and updating methods for early diagnosis and appropriate treatment. Gaining further insight into the aging process and alterations in brain function, along with evaluating strategies to halt disease progression, could lead to improved approaches to this challenging disease.

In this study, we aim to present a comprehensive review of AD, examining its epidemiology, genetics, underlying environmental factors, symptoms, various diagnostic techniques, treatment, challenges, and concerns.[16]

Dementia is a general term used to describe a significant decline in cognitive ability that interferes with a person's activities of daily living. Alzheimer disease (AD) is the most prevalent type of dementia, accounting for at least two-thirds of cases in individuals aged 65 and older. AD is a neurodegenerative condition with insidious onset and progressive impairment of behavioral and cognitive functions. These functions include memory, comprehension, language, attention, reasoning, and judgment. While AD does not directly cause death, it substantially raises vulnerability to other complications, which can eventually lead to a person's death.

According to Centers for Disease Control and Prevention (CDC) data, AD is ranked as the seventh leading cause of death in the United States in 2022, while COVID-19 ranked fourth. Before the COVID-19 pandemic, AD was the sixth leading cause of death stroke. AD typically manifests after age 65, referred to as late-onset AD (LOAD). However, early-onset AD (EOAD), occurring before 65, is less common and seen in about 5% of AD patients. EOAD often exhibits atypical symptoms, and its diagnosis is usually delayed, leading to a more aggressive disease course.

Significant progress has been made in developing biomarkers for specific and early diagnosis of AD over the past decade. These biomarkers include neuroimaging markers obtained through amyloid and tau PET scans, cerebrospinal fluid (CSF), and plasma markers, such as amyloid, tau, and phospho-tau levels.There is no cure for AD, although there are treatments available that may alleviate and manage some of its symptoms. In recent years, there have been significant advancements in the development of medications that aim to moderate the progression of the disease, particularly with the discovery of new disease biomarkers.

The symptoms of AD can vary depending on the stage of the disease. AD is classified into different stages based on the level of cognitive impairment and disability experienced by individuals. These stages include the preclinical or presymptomatic stage, mild cognitive impairment, and dementia stage. The dementia stage is further divided into mild, moderate, and severe stages (see Graph. AD Stages from Preclinical to Severe Disease). This staging system is distinct from the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) for AD. Episodic short-term memory loss is the initial and most common presenting symptom of typical AD. Individuals may have difficulty retaining new information while still recalling long-term memories. Individuals may experience problem solving, judgment, executive functioning, and organizational skills impairments following short-term memory loss.

They may struggle with tasks that require multitasking and abstract thinking. In the early stages of the disease, executive functioning impairments can range from subtle to significant. Instrumental activities of daily living such as driving, financial management, cooking, and detailed activity planning are affected relatively early in their dementia.

These early signs of cognitive decline are followed by language disorder and impaired visuospatial skills. Neuropsychiatric symptoms like apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are also common in the moderate to late stages. Difficulty performing learned motor tasks (dyspraxia),

olfactory dysfunction, sleep disturbances, and extrapyramidal motor signs like dystonia, akathisia, and Parkinsonian symptoms occur late in the disease.

How Long Can a Person Live with Alzheimer's disease?

The time from diagnosis to death varies—as little as 3 or 4 years if the person is older than 80 when diagnosed, to as long as 10 or more years if the person is younger. Alzheimer's disease is currently ranked as the sixth leading cause of death in the United States, but recent estimates indicate that the disorder may rank third, just behind heart disease and

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cancer, as a cause of death for older people. Although treatment can help manage symptoms in some people, currently there is no cure for this devastating disease.

Symptoms:

Memory loss is the key symptom of Alzheimer's disease. An early sign of the disease is usually difficulty remembering recent events or conversations. As the disease progresses, memory impairments worsen and other symptoms develop.

At first, a person with Alzheimer's disease may be aware of having difficulty with remembering things and organizing thoughts. A family member or friend may be more likely to notice how the symptoms worsen.

Brain changes associated with Alzheimer's disease lead to growing trouble with.

Memory:

Everyone has occasional memory lapses. It's normal to lose track of where you put your keys or forget the name of an acquaintance. But the memory loss associated with Alzheimer's disease persists and worsens, affecting the ability to function at work or at home.

People with Alzheimer's may:

- Repeat statements and questions over and over
- Forget conversations, appointments or events, and not remember them later
- Routinely misplace possessions, often putting them in illogical locations
- Eventually forget the names of family members and everyday objects
- Have trouble finding the right words to identify objects, express thoughts or take part in conversations.

Thinking and reasoning:

Alzheimer's disease causes difficulty concentrating and thinking, especially about abstract concepts such as numbers. Multitasking is especially difficult, and it may be challenging to manage finances, balance checkbooks and pay bills on time. These difficulties may progress to an inability to recognize and deal with numbers.

Making judgments and decisions:

The ability to make reasonable decisions and judgments in everyday situations will decline.

For example, a person may make poor or uncharacteristic choices in social interactions or wear clothes that are inappropriate for the weather.

It may be more difficult to respond effectively to everyday problems, such as food burning on the stove or unexpected driving situations.

Planning and performing familiar tasks:

Once-routine activities that require sequential steps, such as planning and cooking a meal or playing a favorite game, become a struggle as the disease progresses. Eventually, people with advanced Alzheimer's may forget how to perform basic tasks such as dressing and bathing.

Changes in personality and behavior:

Brain changes that occur in Alzheimer's disease can affect moods and behaviors. Problems may include the following:

- Depression
- Apathy
- Social withdrawal
- Mood swings
- Distrust in others
- Irritability and aggressiveness
- Changes in sleeping habits
- Wandering
- Loss of inhibitions

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- Delusions, such as believing something has been stolen

Preserved skills:

Many important skills are preserved for longer periods even while symptoms worsen. Preserved skills may include reading or listening to books, telling stories and reminiscing, singing, listening to music, dancing, drawing, or doing crafts. These skills may be preserved longer because they are controlled by parts of the brain affected later in the course of the disease. Alzheimer's disease is thought to be caused by the abnormal build-up of proteins in and around brain cells. One of the proteins involved is called amyloid, deposits of which form plaques around brain cells. The other protein is called tau, deposits of which form tangles within brain cells.

Dementia vs Alzheimer's disease:

The terms "dementia" and "Alzheimer's" are sometimes used interchangeably. However, these two conditions aren't the same. Alzheimer's is a type of dementia. Dementia is a broader term for conditions with symptoms relating to memory loss such as forgetfulness and confusion. Dementia includes more specific conditions, such as Alzheimer's disease, Parkinson's disease, traumatic brain injury, and others, which can cause these symptoms. Causes, symptoms, and treatments can be different for these diseases.

Alzheimer's disease (AD) is the most frequent cause of dementia. In most cases the progression of the disease is slow with disease duration of approximately 10 years while rapid progression is observed in some cases. Rapid progression can be defined by decline on psycho-metric tests such as the Mini Mental State Examination score, e.g. 5 points/year, or on a basis of survival time, e.g. less than 4 years.

Alzheimer's disease (AD) pathology is characterized by abnormal aggregation of the proteins amyloid- (A) and hyper phosphorylated tau accompanied by brain inflammation in the form of microglial activation. No effective disease-modifying therapies are currently available for AD. To date, immunotherapy trials, with both passive anti amyloid and anti tau antibodies and vaccines, while proving effective in lowering the abnormally aggregated protein load, have generally proved ineffective in improving cognitive status with one possible exception (aducanumab) though further trials are currently running in mild cognitive impairment and amyloid positive elderly subjects without cognitive symptoms.

Considerable evidence suggests that the pathogenetic process of Alzheimer's disease includes a long latent (asymptomatic) stage before mild cognitive problems appear as a prodrome of dementia. Although later interventions may retard symptomatic progression, the latent stage appears to be the ideal time for application of a prevention strategy. Several candidate agents for this strategy have been identified. These include postmenopausal oestrogen replacement, consumption of red wine, use of histamine H2 blockers and use of aspirin.

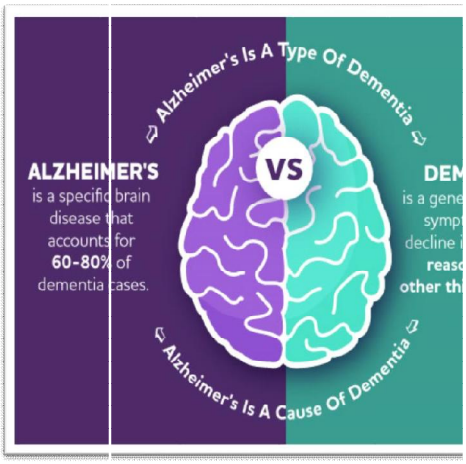

FIG NO.01

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Background:

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and impaired reasoning. It is the leading cause of dementia in older adults, marked by the pathological accumulation of amyloid-beta plaques and neurofibrillary tangles. These pathological changes lead to widespread neuronal damage, significantly impacting daily functioning and quality of life.

Dementia of Alzheimer's Type (DAT) is the most common form of dementia and is caused by progressive degeneration of brain cells. It mainly affects memory, thinking, behavior, and the ability to perform daily activities.

The disease was first described in 1906 by Alois Alzheimer after observing abnormal brain changes in a woman with severe memory loss and confusion.

SYMPTOMS:

I. The First Stage: Mild Alzheimer's Dementia

A person experiencing the earliest symptoms of Alzheimer's disease may still be able to work, drive, take part in social activities, and otherwise live independently. But they may begin to experience problems with memory or concentration. They may have trouble retaining new information- remembering the name of someone they've just met, for instance, or recalling material they've just read. Unfortunately, this symptom is often dismissed as a normal part of ageing or the result of stress, delaying diagnosis and treatment.[61,62]

Other common symptoms of mild Alzheimer's include:

- Misplacing items.
- Language problems, such as having trouble coming up with the right words.
- Trouble planning, organizing, or solving problems.
- Losing a sense of time.
- Vision-related problems, such as with depth perception and color contrast.
- Increasingly poor judgment leading to bad decisions
- Mood and personality changes, such as becoming confused, anxious, irritable, or depressed.
- Difficulty completing familiar home, work, or leisure tasks, such as managing a budget.
- Withdrawal from work or social engagements.

II. The Second Stage: Moderate Alzheimer's Dementia

In most cases of moderate Alzheimer's dementia, the disease has spread to areas of the brain that control language, reasoning, sensory processing, and conscious thought, causing previous symptoms to become more pronounced. Damage to the brain can make it difficult for people to say what they're thinking or complete basic tasks, such as paying bills. But they may still remember important details about their personal history. This is typically the longest stage, potentially lasting for many years.

Symptoms of this period may include:

- Increased memory loss and confusion, including forgetting names or personally significant events
- Trouble recognizing family and friends
- Inability to learn new things or cope with new situations
- Hallucinations, delusions, and paranoia
- Loss of impulse control, such as undressing at inappropriate times or using vulgar language
- Repetitive statements or movements, such as hand-wringing or tissue- shredding
- Trouble carrying out activities that require multiple steps, such as getting dressed
- Difficulty reading, writing, or working with numbers
- Incontinence
- Behavioral problems, such as moodiness or inappropriate anger outbursts

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 Restlessness, agitation, anxiety, tearfulness, and increased risk of wandering, especially in the late afternoon or evening (a condition called sun downing)

III. The Third Stage: Severe Alzheimer's Dementia:

People with severe Alzheimer's dementia are completely dependent on others for around-the-clock care. They become increasingly unable to respond to their environment, communicate, and perform basic daily activities, such as dressing, eating, or bathing. They become bedridden or chair-bound. Eventually, they become unable to control movement. This stage may last from several weeks to several years. Other symptoms of advanced Alzheimer's may include[16-18]

 Seizures
 Weight loss
 Increased risk of infections, including skin infections and pneumonia
 Failure to recognize family and friends
 Increased sleeping
 Groaning, grunting, and moaning
 Difficulty swallowing
 Loss of bowel and bladder control

Researchers have not found a specific gene that directly causes the late-onset form of the disease. However, one genetic risk factor— having one form of the Apolipoprotein E (APOE) geneon chromosome 19—does increase a person's risk. APOE comes in several different forms, or alleles.

APOE ε2 is relatively rare and may provide some protection against the disease. If Alzheimer's disease occurs in a person with this allele, it usually develop later in life than it would in someone with the APOE ε4 gene.

APOE ε3, the most common allele, is believed to play a neutral role in the disease—neither decreasing nor increasing risk.

APOE ε4 increases risk for Alzheimer's disease and is also associated with an earlier age of disease onset.

A person has zero, one, or two APOE ε4 alleles. Having more APOE ε4 alleles increases the risk of developing Alzheimer's. APOE ε4 is called a risk-factor gene because it increases a person's risk of developing the disease. However, inheriting an APOE ε4 allele does not mean that a person will definitely develop Alzheimer's.

Some people with an APOE ε4 allele never get the disease, and others who develop Alzheimer's do not have any APOE ε4 alleles.

IV. EARLY-ONSET ALZHEIMER'S DISEASE:

Early-onset Alzheimer's disease occurs between a person's 30s to mid-60s and represents less than 10 percent of all people with Alzheimer's. Some cases are caused by an inherited change in one of three genes, resulting in a type known as early-onset familial Alzheimer's disease, or FAD. For other cases of early-onset Alzheimer's, research suggests there may be a genetic component related to factors other than these three genes. A child whose biological mother or father carries a genetic mutation for early-onset FAD has a 50/50 chance of inheriting that mutation. If the mutation is in fact inherited, the child has a very strong probability of developing early-onset FAD. Early-onset FAD is cause by any one of a number of different single gene mutations on chromosomes 21, 14, and 1. Each of these mutations causes abnormal proteins to be formed. Mutations on chromosome 21 cause the formation of abnormal amyloid precursor protein (APP). A mutation on chromosome 14 causes abnormal presenilin 1 to be made, and a mutation on chromosome 1 leads to abnormal presenilin 2. Each of these mutations plays a role in the breakdown of APP, a protein whose precise function is not yet fully understood.[https://www.alz.org/alzheimers-dementia/stages]

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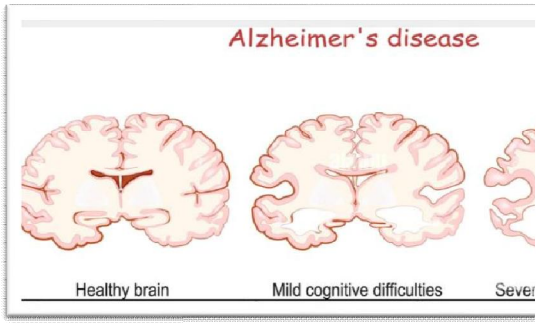

FIG NO.02

Objectives:

- To study the basic concept and clinical features of Alzheimer's disease.
- To understand the pathophysiology and progression of Dementia of Alzheimer's Type.
- To evaluate the role of amyloid plaques and neurofibrillary tangles in neuronal degeneration.
- To identify the risk factors associated with Alzheimer's disease.
- To study the cognitive, behavioral, and functional impairments seen in patients.
- To understand the diagnostic methods used for Alzheimer's disease.
- To review available pharmacological and non-pharmacological treatment approaches.
- To investigate novel therapeutic targets and recent research developments in Alzheimer's disease.
- To study preventive measures and strategies for improving quality of life in affected patients.

Causes of Dementia:

Dementia of the Alzheimer's type is caused by the abnormal, progressive accumulation of two proteins in the brain: amyloid plaques and tau tangles. These protein buildups damage healthy neurons, disrupt brain cell communication, and eventually cause brain cells to die, leading to cognitive decline.

The exact trigger for this protein buildup isn't fully understood, but experts attribute the disease to a combination of three main factors:

1. Protein Abnormalities

• Amyloid Plaques: Fragments of a protein called beta-amyloid clump together between brain cells (neurons), disrupting the electrical signals the brain needs to function.[44]

• Tau Tangles: Another protein called tau twists into abnormal fiber-like strands inside the neurons, destroying the cell's internal transport system. [43]

2. Genetics:

• Late-Onset Alzheimer's: The most common form (appearing in a person's mid-60s) is influenced by gene variations, such as the APOE gene.

• Early-Onset Alzheimer's: In very rare cases (usually developing between ages 30 and 60), the disease is caused by specific, direct genetic mutations that are inherited.

3. Lifestyle, health and environment:

Scientists believe a lifetime combination of health, lifestyle, and environmental factors can accelerate the disease process. Key risk factors include:

• Cardiovascular health issues: High blood pressure, high cholesterol, diabetes, and obesity.

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• Head trauma: Severe or repeated traumatic brain injuries.
• Lifestyle factors: Physical inactivity, smoking, poor diet, depression, and social isolation.

Diagnosis of dementia:

There is no one test to determine if someone has dementia. Doctors diagnose Alzheimer's and other types of dementia based on a careful medical history, a physical examination, laboratory tests, and the characteristic changes in thinking, day-to-day function and behavior associated with each type. Doctors can determine that a person has dementia with a high level of certainty. But it's harder to determine the exact type of dementia because the symptoms and brain changes of different dementias can overlap. In some cases, a doctor may diagnose "dementia" and not specify a type. If this occurs, it may be necessary to see a specialist such as a neurologist, psychiatrist, psychologist or geriatrician.[33]

II. REVIEW OF LITERATURE

1.1 Circadian Rhythm, Sleep, and Alzheimer's Disease from Clinical Perspective:

Circadian alterations occur both during healthy aging and in age-related diseases such as AD. However, some data suggest circadian rhythm disruption in AD is more pronounced and could be a useful additional indicator of the disease development. Some of the changes that seem to occur are related to sleep and involve nocturnal sleep fragmentation, increased wakefulness, and decreased levels of daytime activity with diurnal napping . Although additional research is needed to fully understand the diagnostic significance of circadian disruption in preclinical AD, it would be beneficial to include sleep pattern related questions in medical history examination. These sleep disturbances have a significant impact on patients and their caregivers, and present a major risk factor for early institutionalization.

Specific sleep alterations include loss of slow-wave sleep (SWS) and REM sleep. Some studies suggest that the REM phase stays unaffected during the early stages of the disease, but starts decreasing in later stages. Slow-wave sleep, which represents stage three of non-REM (NREM) sleep and is often called deep sleep, has also shown decreased duration in patients affected with AD. Electroencephalograms (EEGs) of patients with AD, compared to healthy controls and patients suffering from MCI, display a decreased density of K- complexes (KC), which are one of the hallmarks of NREM sleep. It should also be noted that KC density was in positive correlation with Mini Mental State Examination (MMSE) scores, acknowledging the fact that sleep disruption parallels severity of dementia. It has been long known that sleep has a restorative function in the brain and is involved with memory retention. Slow-wave sleep specifically has proven to be especially significant for memory retention . The mechanism behind this phenomenon has been proposed by Tononi and Cirelli in 2006. Slow waves found in EEG stand for lower neuronal energy, which is more sustainable and favorable for synaptic plasticity and memory consolidation.

Elderly people are known to have decreased SWS, a characteristic which is even more emphasized in AD, further aggravating already existing memory problems. Other circadian changes were also observed in AD patients. Most et al. reported that AD patients have higher proximal skin temperature in comparison with age- matched controls. Volicer et al. observed AD patients have higher amplitude of the fitted cosine temperature curve, and later temperature acrophase (time of peak) than the healthy subjects did. In AD and sleep deprived patients, SWS is diminished, meaning neurons spend less time in a hyperpolarized state and more in energized states, producing even more Aβ protein. A bidirectional link between these two exists, although it is still unclear which one holds the causative role.

Alzheimer's disease patients experienced less diurnal motor activity, a higher percentage of nocturnal activity, lower inter-daily stability of motor activity, and a later activity acrophase than did the healthy individuals. Moreover, higher levels of regular nocturnal motor activity are in correlation with aggressive behavior, agitation and restlessness occurring during the late afternoon or early evening often referred to as sundowning and diagnosed in 13–66% of patients. Circadian disruption presenting as excessive night-time activity and wakefulness also seems to be an important risk factor for early institutiom.

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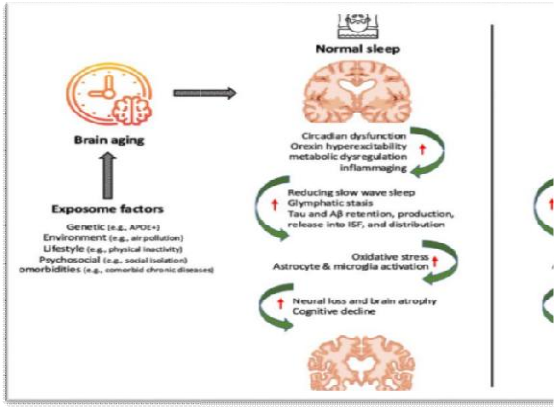

FIG NO.03

1.2 Circadian rhythm sleep-wake disorders and their impact on AD: Disruptions in circadian rhythms and sleep-wake cycles, such as fragmented sleep and insomnia, are preceded by AD pathology, suggested as a potential early symptom or risk factor for AD6. Microtubule-associated protein tau (MAPT), aβ, levels, and other metabolic by-products like lactate fluctuate diurnally in the brain, peaking during wakefulness and decreasing during sleep, this fluctuation is linked to the glymphatic system's efficiency7. Glymphatic system refers to the synergistic function of both astrocytes and lymphatic system, where astrocytic water channel aquaporin-4 (AQP4) supports the cerebrospinal fluid-interstitial fluid exchange in the brain and supports aβ clearance7. Chronic circadian misalignment leads to increased aβ production, which in turn promotes the degradation of clock proteins like BMAL1, CREB-binding protein (CBP), and PER1, thereby accelerating plaque formation and reducing clearance34. In AD patients, arrhythmic Bmal1 methylation correlates with abnormal tau phosphorylation, night wakeup, and decreased cognitive functions35.

Meta-analysis and community-based, cohort longitudinal studies with many participants revealed that shift workers, particularly those working during the night times, were more prone to dementia and AD36,37. Recent reseahrch highlights a bidirectional relationship between the disruption of sleep and circadian rhythms to the pathogenesis and progression of AD. A 15-year longitudinal study with 1401 older adults (median age: 81.8 years, IQR: 76.3–85.7 years, both genders) revealed a bidirectional link between circadian dysregulation and Alzheimer's progression38. Familial Natural Short Sleepers are associated with mutations in DEC2 (P384R) and NPSR1 (Y206H), genes regulating sleep duration and circadian rhythms. These mutations promote efficient sleep with reduced duration and no cognitive decline. In Alzheimer's mouse models, DEC2-P384R; 5XFAD and female Npsr1-Y206H; 5XFAD mice exhibited reduced tau pathology in the hippocampus and significantly fewer amyloid plaques at six months, suggesting enhancing sleep quality may protect against neurodegeneration in AD39. Another FNSS mutation, Adrb1-A187V, alters β1-adrenergic receptor signaling in brain regions responsible for sleep regulation, reduces tau pathology, and improves random eye moment (REM) sleep in a mouse model of tauopathy40. A double- blind, randomized, placebo-controlled trial evaluated the efficacy and safety of trazodone (50 mg, administered daily at 10:00 P.M.) for improving sleep disturbances in 30 community-dwelling patients with AD. Over a 2-week treatment period, trazodone significantly enhanced sleep, with participants sleeping an additional 42.5 min per night and increasing nighttime sleep percentage by 8.5% compared to the placebo group. This highlights the significance of circadian rhythm and the quality of sleep in AD pathology.

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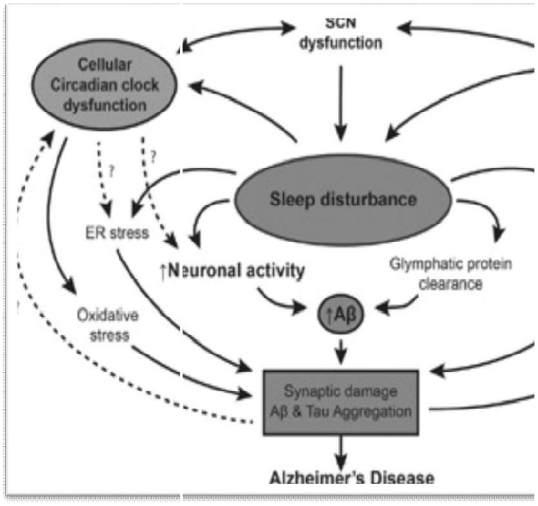

. FIG NO.04

1.3 Circadian resetting by serotonergic pathway:

The serotonergic pathway originating from the midbrain raphe nuclei provides crucial arousal-dependent signals that help reset the SCN and synchronize the body's internal clock. The Serotonergic System & The Biological Clock.

The actions of serotonin on target cells, including glutamate and GABA neurons, are mediated by seven receptor subtypes (5-HT1–7) in the central nervous system (CNS), peripheral nervous system (PNS), and blood vessel cells of the cardiovascular system (CVS). Most of them are G-coupled ones and only 5- HT3 receptors are ion channels permeable to sodium and potassium cations.

The 5-HT1R and 5-HT5R subtypes couple with the Gi/o protein, leading to the inhibition of adenylyl cyclase (AC) activity and a reduction in cyclic adenosine monophosphate (cAMP) levels. 5-HT2R couples with the Gq/11 protein, stimulating phospholipase C, which leads to elevated levels of inositol triphosphate and calcium ions. The 5-HT4, 5-HT6, and 5-HT7 receptors couple with the Gs protein to enhance AC activity and elevate cAMP levels. Notably, 5-HT4R can bind to both Gs and Gi proteins with a preference for Gs over Gi.

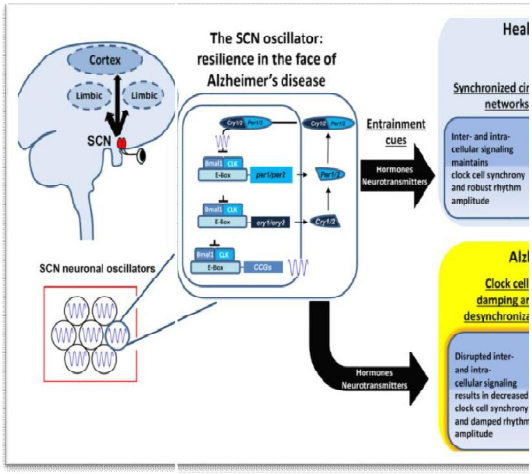

FIG NO.05

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1.3 Coupling of rhythm:

This includes uncoupled circadian clocks and misaligned brain waves during sleep (e.g., disrupted slow oscillation-spindle coupling).

These breakdowns correlate with amyloid/tau buildup, medial prefrontal cortex atrophy, and faster cognitive decline.

Changes in rhythm coupling in Alzheimer's disease:

• Sleep-wake disturbances: patients may experience – insomnia, daytime sleepiness, frequent nighttime awakening, sundowning (confusion & agitation in evening).

• Altered brain rhythm: brain electrical activities becomes abnormal- reduced alpha & beta waves, increased slow-wave activity.

• Harmonal rhythm disturbance: abnormal secretion of- melatonin, cortisol.

• Reduced synchronization: normally, body systems work in coordinated timing. In Alzheimer's disease: internal clocks become desynchronized, communication between brain regions weakness.

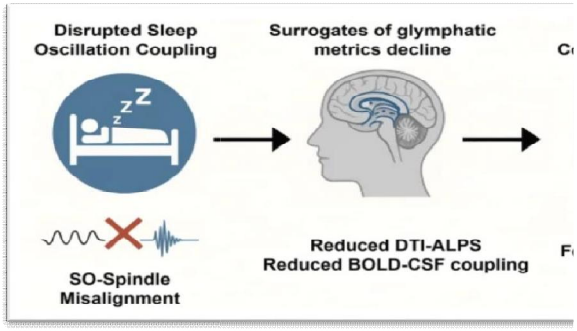

FIG NO.06

1.4 Transcription translation feedback loop:

In Alzheimer's disease, the "transcription-translation feedback loop" (TTFL) refers to the core molecular mechanism that drives your internal circadian rhythms. In a healthy brain, a primary TTFL coordinates rest and wake cycles, sleep, and cellular health.

1.5 The Breakdown of the TTFL in Alzheimer's:

In Alzheimer's disease, the molecular feedback loop within brain cells (neurons) breaks down, directly causing cognitive and behavioral symptoms.

1.6 How the Loop Works:

In a healthy brain, specific transcription factors (activators like CLOCK and BMAL1) bind together to drive the transcription of clock genes into messenger RNA (mRNA). This mRNA is then translated into repressor proteins (like PER and CRY). Over a roughly 24-hour cycle, these repressors turn off the activators, creating a continuous feedback loop.

Alzheimer's Interference:

Pathological Alzheimer's hallmarks, such as Amyloid-beta plaques and Tau tangles, disrupt this feedback loop. The expression of key activators like BMAL1 is severely reduced, which blunts the healthy rhythmic expression of genes responsible for sleep, memory, and clearing cellular waste.

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The Vicious Feedback Loop:

The disruption of this genetic loop creates a vicious cycle that accelerates neurodegeneration:

TTFL Breakdown: The collapse of the TTFL leads to severe disruptions in your sleep-wake cycle and internal body clock.

Toxic Protein Accumulation: Because your brain's waste clearance mechanisms (such as the glymphatic system) operate most efficiently during deep, synchronized sleep, this TTFL breakdown impairs the brain's ability to flush out Amyloid-beta.

Amplified Toxicity: The accumulation of Amyloid-beta and Tau further degrades the clock mechanism, trapping the brain in a downward spiral that worsens both Alzheimer's pathology and cognitive decline.

Broader Transcription/Translation Dysregulation:

Beyond the circadian TTFL, Alzheimer's triggers aberrant gene expression via master transcription factors like SP1. In advanced stages of the disease, widespread gene dysregulation occurs, impairing protein translation, mitochondrial function, and increasing neuroinflammation

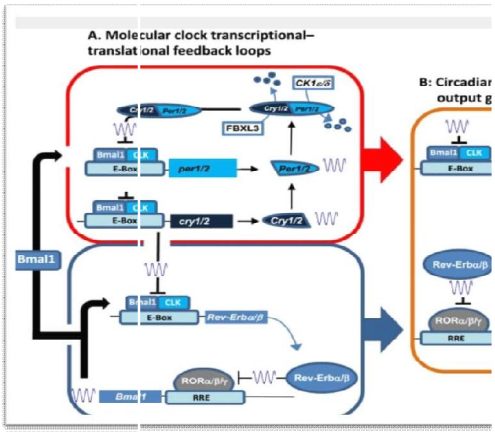

FIG NO.07

Non-Transcriptional Oscillators:

In Alzheimer's disease (AD), the brain's circadian system relies on two cogs: a classic transcriptional clock and a non-transcriptional oscillator. While the transcriptional mechanism relies on gene activation, the non-transcriptional oscillator depends on rhythmic metabolic changes, primarily redox oscillations and cytoplasmic peroxiredoxin (PRX) oxidation cycles.

The Two Circadian Cogs in AD:

All cells, including neurons and those in the suprachiasmatic nucleus (SCN), regulate their daily rhythms using this dual system.

The Transcriptional Cog (TTFL): Relies on the transcription-translation feedback loop of core clock genes (such as (Bmal1), (Clock), (Per), and (Cry)). In Alzheimer's, this master clock system often degenerates and dysregulates.

The Non-transcriptional Cog (Metabolic): Operates independently of DNA transcription. It is primarily driven by the cyclic production of reactive oxygen species (ROS) that naturally cause redox oscillations within the cytoplasm.

Non-Transcriptional Oscillators and Dementia:

The primary non-transcriptional oscillator is the cyclic oxidation and reduction of PRX proteins. PRX enzymes act as crucial antioxidant defenses that neutralize harmful ROS in the brain.

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The Pathology: In dementia, the accumulation of toxic amyloid-beta (A\(\beta \)) and tau proteins creates severe, self-reinforcing oxidative stress in the brain.
The Breakdown: As this oxidative damage cascades, the metabolic non- transcriptional machinery becomes overwhelmed. The rhythmic redox cycles are dampened or desynchronized, meaning cells can no longer properly track time metabolically.
Feedback Loop: This loss of PRX and non-transcriptional rhythmicity creates a vicious cycle. The disruption of these metabolic pacemakers accelerates the misfolding of A (beta) and tau proteins, directly exacerbating the neurodegeneration that defines Alzheimer's.

Transcription and Translation in the Circadian Clock:

Our understanding of the role of transcription and translation in the circadian oscillator began with research using invertebrate models including the marine mollusk Aplysia californica, the fruit fly Drosophila melanogaster and the bioluminescent dinoflaggelate Gonyaulax. The isolated Aplysia eye provided the first in vitro system to model the circadian clock using measurements of rhythmic compound action potentials as an output of the circadian clock. Phase specific shifts were observed when either reversible inhibition of transcription or translation was pharmacologically induced, suggesting that the circadian oscillator mechanism was dependent upon these processes. Intriguingly, the effects of translation inhibitors were dependent upon the time of day, with distinct phases identified in which phase advances, phase delays or even no effect on the circadian rhythm were observed. Subsequent studies of time of day effects on post- translational processes suggested that post-transcriptional regulation was key to both circadian oscillator function and the timing of circadian outputs. Further evidence for circadian regulation of translation was provided through studies in the bioluminescent marine alga Gonyaulax. Bioluminescence is dependent upon luciferin binding protein and the abundance and activity of the enzyme luciferase. The circadian clock modulates the translation of the luciferin binding protein, rather than its transcription, to regulate, at least in part, the rhythm in bioluminescence. Circadian rhythms in the translation and transcription of core circadian oscillator genes were first demonstrated in Drosophila with the analysis of mRNA and protein rhythms in the period gene. These pioneering studies using invertebrate models uncovered the fundamental principles of transcriptional regulation and negative feedback through which the core circadian oscillator is organized and demonstrated that circadian outputs were also regulated through circadian modulation of translation.

Molecular Pathogenesis of Alzheimer:

Core Molecular Targets:

Scientific literature and reviews highlight several primary targets in AD pathogenesis:
 Amyloid-beta Production and Clearance: Focuses on the modulation of beta-secretase (BACE1) to prevent the generation of neurotoxic Abeta peptides, as well as clearance mechanisms via anti-amyloid immunotherapies.
 Tau Protein: Investigates the inhibition of tau hyperphosphorylation by specific kinases to halt the formation of neurofibrillary tangles (NFTs) and stabilize neuronal microtubules.[33]
 Neuroinflammation: Targets microglial receptors (like TREM2) and inflammatory cytokines (e.g., TNF-alpha, IL-1beta) to downregulate chronic immune responses that exacerbate neuronal damage.[66]
 Mitochondrial Dysfunction and Oxidative Stress: Explores therapeutic molecules designed to reduce reactive oxygen species (ROS) and restore metabolic homeostasis in brain tissue.
Molecular biology throws a significant light in studying the pathogenesis of any disease condition and AD is no exception to it. A deep insight into the understanding of the disease pathogenesis helps to develop a successful treatment regimen and realizes the existing flaws in the prevailing paradigms. Pathophysiologically, AD is complex, multifactorial, and of heterogeneous condition indicating the accumulation of amyloid cerebral plaques and neurofibrillary tangles of abnormal tau protein, presence or absence of germ line mutations, presence or absence of polymorphic susceptibility alleles, and so forth. The two major biochemical features related to the neuropathogenesis of

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AD are the neurofibrillary tangles containing phosphorylated tau protein in soluble intermediate form leading to synaptic toxicity (lack of definitive therapeutic intervention further leads to neurodegeneration) and senile plaques containing amyloid-β-peptide (Aβ) which is a soluble intermediate and inherently deleterious to synapses. Aβ is formed after sequential cleavage of the amyloid precursor protein (APP), a transmembrane glycoprotein of undetermined function. APP can be cleaved by the proteolytic enzymes α-, β- and γ-secretase; Aβ is generated by successive action of the β- and γ-secretases. The γ-secretase, which produces the C-terminal end of the Aβ, cleaves within the transmembrane region of APP and can generate a number of isoforms of 30–51 amino acid residues in length. Apart from these two major proteins; oxidative stress, genetic, epigenetic, and viral hypothesis have also been put forward to explain the pathophysiology of AD.

According to the "amyloid hypothesis," missense mutations in the APP gene promote generation of Aβ by favoring proteolytic processing of APP by β- or γ- secretase. Furthermore, APP mutations internal to the Aβ sequence heighten the self-aggregation of Aβ into amyloid fibrils. part from these, the cloning of the presenilin (PS) proteins and AD-causing mutations in PS1 and PS2 also promote the processing of APP to form amyloidogenic Aβ . During AD, there is enhanced formation of Aβ which hastens the process of neuronal loss and thus it can be hypothesized that components of apoptotic machinery have a direct or indirect contribution to the complex proteolytic processing. The neuritic plaques and neurofibrillary tangles consisting of hyperphosphorylated protein tau are the major neuropathologic hallmark of AD; hence, AD is also known as "tauopathy".

Depending on the type of secretases that cleave it, APP can undergo amyloidogenic or no namyloidogenic processing. On being cleaved by β-secretase, APP via amyloidogenic pathway produces a soluble secreted form of APP (s APPβ) and a C-terminal fragment (βAPP-CTF) which is further cleaved by γ-secretase to yield Aβ peptide and amyloid precursor protein intracellular domain (AICD). Following the nonamyloidogenic pathway, APP is first cleaved by α-secretase to generate the soluble secreted sAPPα fragment and αAPP-CTF which is further cleaved by γ- secretase resulting in Aβ and AICD.

Multitransmembrane proteins, known as presenilins (two homologues PS1 and PS2), are catalytic components of γ-secretase complex having diverse biological activity and contribute to AD pathogenesis via "amyloid hypothesis." APP and Notch (type I transmembrane cell surface receptors) are important γ-secretase substrates where PS plays a significant γ-secretase dependent role in the sequential cleavage in the processing of APP and Notch and stabilizes the β-catenin in Wnt signaling pathway which are γ-secretase independent actions. PS mutations cause impairment in the Notch signaling pathway which has significant role in neurogenesis. The genetic inactivation of presenilins in hippocampal synapses has been shown to selectively affect the long-term potentiation caused by theta burst stimulation with the inactivation in presynapse but not the postsynapse impairing short-term plasticity and synaptic facilitation. The release of glutamate was also reduced in presynaptic terminals by processes that involve modulation of intracellular Ca2+ release. This has been suggested to represent a general convergent mechanism leading to neurodegeneration.

From the genetic point of view, the three early onset genes, namely, the APP and the two presenilins, and the late onset gene apolipoprotein E (ApoE) significantly increase the accumulation of amyloid plaques in AD brains. ApoE, a 299-amino- acid glycoprotein with a molecular mass of 34200 Da, is a polymorphic protein. Its three isoforms (ApoE2, ApoE3, and ApoE4) in humans are all products of the same gene, which exists as three alleles (ϵ2, ϵ3, and ϵ4) at a single gene locus. It has been demonstrated that ε4 allele of ApoE gene is a major genetic risk factor for late onset and sporadic AD. ApoE isoforms influence Aβ aggregation, modulate neurotoxicity and tau phosphorylation, play role in synaptic plasticity and neuroinflammation, elevate neurotoxicity, and retard neuroprotection. Therapeutic strategies modulating ApoE protein levels and its physiological and protective actions can serve as effective target in counteracting AD.

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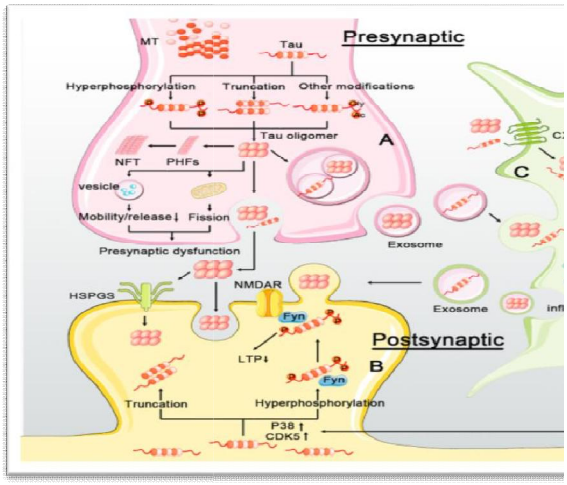

FIG NO.08

IV. MATERIALS AND METHODS

Drugs used in Alzheimer's disease:

Drug treatment for Alzheimer's disease is important, but the benefits are small, and drugs should only be one part of a person's overall care. Nondrug treatments, activities and support are just as important in helping someone to live well with Alzheimer's disease.

Many drugs have at least two names. The generic name identifies the substance. The brand name varies depending on the company that manufactures it. For example, a familiar painkiller has the generic name paracetamol and is manufactured under brand names such as Panadol and Calpol, among others. Occasionally, a drug with a very well-known generic name (such as paracetamol) will also be manufactured and sold using just this name.

What are the main drugs used?

There are two types of medication used to treat Alzheimer's disease: acetylcholinesterase inhibitors (often shortened to just 'cholinesterase inhibitors') and NMDA receptor antagonists. The two types work in different ways. These are explained below.

 The generic names for the cholinesterase inhibitors are donepezil, rivastigmine and galantamine:

 Donepezil was originally patented as the brand name Aricept, but is more widely available now as just generic donepezil.

 Rivastigmine was patented as Exelon and is now also available as other brands, as well as generic rivastigmine.

 Galantamine was patented as Reminyl and is now also available as generic galantamine and the brands Reminyl XL, Acumor XL, Galsya XL and Gatalin XL.

 The NMDA receptor antagonist is memantine. It was originally patented as Ebixa and is now also available as generic memantine. Other UK brand names for memantine include Maruxa and Nemdatine.

How do they work?

Cholinesterase inhibitors (donepezil, rivastigmine and galantamine) In the brain of a person with Alzheimer's disease, there are lower levels of a chemical called acetylcholine. Acetylcholine helps to send messages between certain nerve cells. In Alzheimer's there is also a loss of the nerve cells that use acetylcholine. Falling acetylcholine levels and progressive loss of these nerve cells are linked to worsening symptoms.

Donepezil, rivastigmine and galantamine all prevent an enzyme called acetylcholinesterase from breaking down acetylcholine in the brain. As a result, an increased concentration of acetylcholine leads to increased communication between nerve cells. This may temporarily alleviate or stabilise some symptoms of Alzheimer's disease.

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All three cholinesterase inhibitors work in a similar way, but one might suit a certain individual better than another, particularly in terms of side effects experienced.

Guidance on the use of drugs in the NHS is issued by the National Institute for Health and Care Excellence (NICE). NICE reviews drugs and decides whether they represent good enough value for money to be available as part of NHS treatment. Drugs considered by NICE will also have been through the UK or European licensing process for new medicines. This means the medicine has been tested and met rigorous standards of safety, quality and effectiveness. The licence will be granted for treatment of a particular health condition.

For the cholinesterase inhibitors, the NICE guidance (2011) suggests that the cheapest drug (currently donepezil) should generally be tried first. See 'NICE guidance: a summary'.

Memantine:

The action of memantine is different from that of donepezil, rivastigmine and galantamine. Glutamate is another chemical that helps to send messages between nerve cells. Glutamate is released in excessive amounts when brain cells are damaged by Alzheimer's disease. This causes the brain cells to be damaged further. Memantine protects brain cells by blocking the effects of excess glutamate.

Are these drugs effective for everyone with Alzheimer's disease? (Donepezil, rivastigmine and galantamine)

The guidance from NICE (2011) recommends that donepezil, rivastigmine or galantamine is offered as part of NHS care for people with mild- tomoderate Alzheimer's disease. There is good evidence (strongest for donepezil) that these cholinesterase inhibitors also help people with more severe Alzheimer's disease (see 'Stopping treatment'). Between 40 and 70 per cent of people with Alzheimer's disease benefit from taking a cholinesterase inhibitor. In cases where the treatment shows benefit, symptoms improve temporarily (for between six and 12 months in most cases) and then gradually worsen over the following months. People taking a cholinesterase inhibitor can experience: reduced anxiety; improvements in motivation, memory and concentration; and improved ability to continue daily activities (eg personal care, shopping, dressing). It is not clear whether the cholinesterase inhibitors also bring benefits for behavioural changes such as agitation or aggression. Trials in this area have given mixed results.

Memantine

The NICE guidance (2011) recommends use of memantine as part of NHS care for severe Alzheimer's disease (see 'NICE guidance: a summary'). NICE also recommends memantine for people with moderate Alzheimer's disease who cannot take the cholinesterase inhibitor drugs (this is usually because of side effects).

Memantine is licensed for the treatment of moderate-to-severe Alzheimer's disease. In people in the middle and later stages of the disease, it can slow down the progression of symptoms, including disorientation and difficulties carrying out daily activities. There is some evidence that memantine may also help with symptoms such as delusions, aggression and agitation. For more information see factsheet 408, Drugs for behavioural and psychological symptoms in dementia, and factsheet 509, Dementia and aggressive behaviour.

How are these drugs prescribed?

NICE guidance (2011) states that, in the first instance, these drugs can only be prescribed by a specialist in dementia care. This will often be a consultant old-age psychiatrist, geriatrician or neurologist. A GP will generally refer a person with suspected dementia to a memory service for a specialist assessment. A consultant-led team at the clinic will carry out a series of tests to determine whether the person has dementia and, if so, which type. For more about the diagnosis of dementia see factsheet 426,

Assessment and diagnosis:

If the diagnosis is Alzheimer's disease, the consultant will offer the drugs and write the first prescription. (In some parts of the country arrangements allow for the consultant to write to the GP to ask them to start prescribing.) Once the person has started on the drugs and is stable at the optimum dose (see 'Taking the drugs'), the specialist will usually ask the GP to take over routine prescribing. The person will then generally have regular reviews of how well their medication is working, either with a specialist at the memory clinic or with the GP. (This divided responsibility between the consultant and GP is sometimes called shared care prescribing.)

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Are these drugs effective for other types of dementia?

The cholinesterase inhibitors were developed specifically to treat Alzheimer's disease. There has been relatively little research into whether they (or memantine) are helpful for people with other types of dementia.

There is evidence that the cholinesterase inhibitors are effective in people with dementia with Lewy bodies, and dementia due to Parkinson's disease. Rivastigmine is licensed for Parkinson's disease dementia. Acetylcholine levels are often even lower in people with dementia with Lewy bodies than in those with Alzheimer's disease.

NICE guidelines recommend that a cholinesterase inhibitor is offered to a person with dementia with Lewy bodies or Parkinson's disease dementia if they have distressing symptoms (eg hallucinations) or challenging behaviours (eg agitation, aggression). For more information, see factsheet 403, What is dementia with Lewy bodies (DLB)? and factsheet 442, Rarer causes of dementia. For memantine, one trial showed benefits for people with dementia with Lewy bodies and Parkinson's disease dementia, but there is not enough evidence to draw any firm conclusions.

Several trials have looked at the treatment of vascular dementia with a cholinesterase inhibitor or memantine. The benefits for either are very small (if any), and seen mainly for mental abilities of people with a combination of both Alzheimer's disease and vascular dementia (known as mixed dementia). NICE guidelines recommend cholinesterase inhibitors for treatment of mixed dementia when Alzheimer's is the main cause, but not for the treatment of pure vascular dementia. For more information see factsheet 402.

From the few trials carried out, there is no good evidence that the cholinesterase inhibitors or memantine are of benefit for people with frontotemporal dementia, including Pick's disease. In some people they may make symptoms worse. These drugs are not licensed for frontotemporal dementia and will not generally be prescribed for it. For more information see factsheet 404.

Taking the drugs:

NICE guidelines (2011) say the specialist should seek the views of the carer on the condition of the person with dementia, before treatment and during follow-up appointments. They should also seek the views of the person with dementia.

The person should take the drugs as prescribed and the doctor should try to ensure this is done. The person may benefit from using a pill box with different compartments for each day of the week, containing the prescribed dose. The pharmacist may be able to supply drugs pre-packed like this.

If the person misses a dose of any of these drugs, they should take it as soon as they remember, as long as it is on the same day. If it is the next day, the person should not take two tablets, but should simply continue with their normal dose.

Doses vary. Usually a person with Alzheimer's disease will start on a low dose, which will be increased later to make the treatment more effective. Some people may not be able to take the highest dose because of side effects. The doctor will prescribe the best dose for each individual. Information about doses is given below.

Donepezil is available in 5mg or 10mg tablets. It is taken once a day, usually at bedtime. Treatment is started at 5mg a day and then increased to 10mg a day after one month if necessary. The maximum licensed total daily dose is 10mg.

Rivastigmine comes in capsules or a solution to drink. It is taken twice a day, with morning and evening meals. People start with 3mg a day in two divided doses, which will usually increase (at intervals of at least two weeks) to between 6mg and 12mg a day. The maximum licensed total daily dose for oral rivastigmine is 12mg. Rivastigmine patches are also available. These deliver daily doses of 4.6mg, 9.5mg or 13mg, with fewer side effects than the capsules. Patches are suited to people who struggle with taking medication by mouth; they are popular with carers. Only one patch should be applied at any one time and it should be put on different parts of the skin each time, to avoid the person getting a rash.

The recommended starting dose for galantamine is 8mg each day for four weeks, increasing to 16mg a day for another four weeks, and then kept at a dose of between 16 and 24mg daily. Galantamine is made in a variety of forms including a 4mg/ml (twice-daily) oral solution, and tablets of 8mg and 12mg. Slow-release (XL) capsules are available in doses

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of 8mg, 16mg and 24mg. These are popular because they only need to be taken once a day. The maximum licensed total daily dose for galantamine is 24mg.

Memantine comes in two forms: as 10mg and 20mg tablets, and as 10mg oral drops. The 10mg tablets can be broken in half (into 5mg doses) and taken with or without food. The recommended starting dose is 5mg a day, increasing every week by 5mg, up to 20mg a day after four weeks. The maximum licensed total daily dose for memantine is 20mg.

It is important that the person takes the doses that have been prescribed.

Stopping treatment:

Medication should be reviewed regularly, and continued for as long as the benefits outweigh any side effects. If the person with Alzheimer's decides to stop taking a drug, they should speak to the doctor first if possible, or as soon as they can after stopping treatment. Treatment may also be stopped by agreement with the doctor if the person becomes unable to take the medicines in the prescribed way, even with support. If someone stops taking their prescribed drug, their condition may get worse more quickly. If someone has stopped and thinks they should restart their medication, it is important that they contact their doctor as soon as possible.

For someone who is taking a cholinesterase inhibitor, a decision will need to be made when their Alzheimer's disease becomes severe. There is now good evidence that cholinesterase inhibitors continue to bring benefits even when someone's Alzheimer's is severe. Many doctors therefore continue to prescribe a cholinesterase inhibitor for severe Alzheimer's until the above criteria for stopping treatment are met, if ever.The issue of whether to add memantine to the cholinesterase inhibitor for someone with severe Alzheimer's disease (known as combination treatment) is less clear cut. The two drugs work in different ways and there is research evidence that, for someone who is already on donepezil, adding memantine might bring additional benefit.

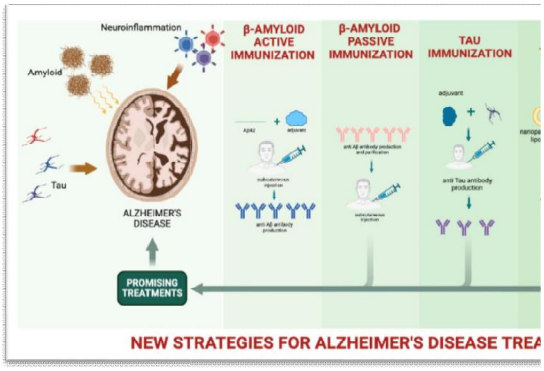

FIG NO.09

Research into new treatments:

No new drugs have been licensed in the UK for Alzheimer's disease since memantine in 2002. However, there is a lot of research into new drug treatments. These aim either to give better relief from symptoms or – if possible – to slow down or stop the underlying disease in the brain.

More information about taking part in research is available from memory services or the Join Dementia Research website (see 'Other useful organisations').

Research on Alzheimer's disease and related Dementia's:

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FIG NO.10

Alzheimer's disease and related dementias are a series of complex brain disorders that affect millions of Americans and many more people worldwide. These disorders have an enormous impact on individuals and their families, long-term care facilities, health care providers, health care systems and infrastructure, and the communities in which we all live. As the economic, social, and personal costs of these diseases climb, the research community is working to discover solutions that will improve the lives of those with dementia, their caregivers, and their communities.[88]

The federal government's Alzheimer's and related dementias research strategy focuses on engaging a cross-disciplinary team of geneticists, epidemiologists,

gerontologists, behavioral scientists, disease and structural biologists, pharmacologists, clinical researchers, and others to bring the greatest and most diverse expertise to the field. This includes training new generations of researchers and clinician-scientists and engaging in innovative partnerships with private industry, nonprofit groups, and more to foster collaboration and broaden access to research resources and data.

Critically, the government's research strategy includes the search to find treatment and prevention strategies, as well as interventions, services, and supports to improve quality of life for those already living with these diseases and their families.

Advances in Alzheimer's and Related Dementias Research:

As the nation's biomedical research agency, NIH supports research ranging from basic biology to drug development and from clinical studies to evaluating public health outcomes. Within the past several decades, researchers have made great strides toward better understanding what causes Alzheimer's and related dementias and discovering approaches that may prevent, diagnose, and treat them. Some highlights of these efforts include:

Drug discovery and drug repurposing:

Thanks to the substantial investment in Alzheimer's and related dementias research over the past decade, NIH has increased drug discovery significantly. Of the many compounds in NIH-supported drug development programs for Alzheimer's and related dementias, 18 new dementia drug candidates have now matured through the pipeline, from discovery in the lab all the way through preclinical development, to reach the stage of human testing. NIA currently supports more than 60 clinical trials testing drug candidates that target many different aspects of the disease.

Several of these drug candidates are intended to stop or slow the disease process rather than only treat symptoms. For example, some target amyloid plaques and tau tangles in new ways. Researchers are also exploring multiple ways to repurpose drugs for the potential treatment of dementia, including FDA-approved drugs used to treat epilepsy and diabetes.

Early detection and diagnosis:

Researchers have made significant progress in developing, testing, and validating biomarkers that detect signs of the disease process. For example, in addition to PET scans that detect abnormal beta-amyloid plaques and tau tangles in the

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brain, NIH- supported scientists have developed the first commercial blood test for Alzheimer's. This test and others in development can not only help support diagnosis but also be used to screen volunteers for research studies. Other discoveries are leading to the development of potential biomarkers for other dementias. These include the detection of abnormal TDP-43 protein, found in frontotemporal dementias, and a cerebrospinal fluid test to help diagnose. Researchers are also studying behavioral and social indicators, including problems with paying bills and a combined decline in memory and walking speed, that may be early signs of these diseases. Other early markers are also under study.

Risks factors, genetics, and disease pathways:

NIH's research investments to identify the biological mechanisms that lead to Alzheimer's and related dementias are fundamental for the discovery of potential drugs that target them. There are many biological pathways that scientists can target with investigational drugs. For example, several recent studies have further revealed how components of the immune system, brain inflammation, vascular disease, and possibly viruses and bacteria — including the many tiny organisms that live in the digestive system, known as the gut microbiome .

Scientists are also exploring genetic variations that may contribute to or prevent disease. Recent research has revealed that the genetic risk for Alzheimer's differs between ethnic and racial groups, highlighting the need for more diversity in genetic research studies. Scientists are also discovering genetic variants that may help protect against Alzheimer's. Other studies are identifying the genetic underpinnings of related dementias, including new gene variants linked to the development of Lewy body dementia.

Population studies and precision medicine:

By studying large, diverse groups of people, researchers are identifying which genes, behaviors, and lifestyle choices are linked with dementia. Population studies have shown that sedentary behavior, low socioeconomic status, low level of education, and living in a poor neighborhood may increase the risk of developing dementia. These observational discoveries, along with knowledge of genetic and other factors, can be used to advance the development of methods for diagnosis, prevention, and treatment at an individualized level.

Health disparities and dementia risk:

NIH-funded researchers are examining the biological, social, and environmental factors that contribute to the higher prevalence of dementia in Hispanic Americans and Black Americans compared with other White Americans. Since dementia is also underdiagnosed in these populations, researchers are studying approaches to improve diagnoses in underserved communities. NIH is also investing in strategies to increase diversity in research study participants.

Lifestyle interventions:

Researchers are investigating interventions around exercise, healthy eating, cognitive training, preventive health care, and management of chronic conditions, such as high blood pressure, that — if made early in life — may be able to prevent or delay disease symptoms. Emerging areas of study include interventions to enhance cognitive reserve — the mind's ability to cope with the effects of aging — and interventions to potentially compensate for premature cognitive decline and dementia linked to adverse exposures in early life, such as abuse and malnutrition. NIA currently supports more than 150 trials testing behavioral and lifestyle interventions.

Dementia care and caregiver support:

NIH has significantly expanded research on how to improve dementia care and support for care partners. Researchers are investigating new dementia care models and strategies to equip family caregivers with tools and knowledge to manage the challenges of caring for a loved one with dementia. Studies are also underway to examine ways to improve quality of life for people with dementia and their caregivers. Other studies aim to understand the costs and challenges

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of dementia including lost wages and paying for long-term care. NIA currently supports more than 200 studies on dementia care and caregiving.

Dementia care and caregiver support involve tailored daily management and strong emotional networks. Essential strategies include establishing safe, predictable routines, using clear communication, and utilizing respite services. Since caregiving is emotionally demanding, accessing peer support and professional help is vital to preventing burnout. Managing dementia and supporting those who care for loved ones requires a mix of practical caregiving techniques and dedicated mental health resources.

Practical Care Strategies:

 Routine & Environment: Maintain a consistent daily schedule for waking up, meals, and activities to reduce confusion and anxiety. Simplify the home environment to minimize clutter and potential hazards (like wandering).

 Communication: Speak slowly and clearly. Use short, simple sentences, and ask one-step questions. Offer reassurance and avoid arguing over lost memories.

 Behavioral Management: Wandering and agitation are common. Gentle redirection, offering favorite activities, playing calming music, and utilizing tactile objects like fidget blankets can help.

Caregiver Support & Well-being:

 Caregiver burnout is a major risk, making emotional support and respite (temporary relief) critical.

 Support Groups: Sharing experiences with peers facing similar challenges combats the severe isolation often felt by caregivers.

 Professional Help: Hiring trained in-home caregivers or utilizing adult day centers provides necessary breaks, allowing the primary caregiver to rest and tend to their own health.

Infrastructure development:

NIH is continually investing in research infrastructure to advance Alzheimer's and related dementias research. Efforts in this area include launching a consortium for Alzheimer's clinical trials, a collaboratory to test interventions to improve care of people with dementia in real-world settings, research efforts to validate cognitive tests in a primary care setting, and centralized data-sharing platforms and other technologies.

Clinical Research Into Alzheimer's and Related Dementias:

No major advance in Alzheimer's and related dementias treatment, prevention, or care will be possible without robust clinical research. Clinical research includes studies that involve people so scientists can learn more about disease progression, how behavior and lifestyle factors may affect health, and the safety and effectiveness of an intervention. Advances made through clinical research rely on the volunteers who participate in these types of studies. NIA is working on multiple initiatives to enhance recruitment and retention of diverse populations in clinical research. View some of those resources below.

NIA-funded clinical research includes both observational studies through which researchers gather important information, and clinical trials in which researchers test interventions to treat or prevent disease, improve care and caregiver support, and enhance quality of life for people living with dementia. NIA is currently funding more than 400 active clinical trials.

NIA also fund Alzheimer research centres across the country. Scientists at these centers conduct clinical research to improve diagnosis and care for people with dementia and their families, and to find a treatment or increase prevention.

ETIOLOGY:

Both genetic and environmental risk factors play a role in the manifestation of AD. The greatest risk factor is age. At age 65, the likelihood of having AD is about 3%, rising to over 30% by age 85. The incidence of AD under the age of

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65 is less certain, but estimates suggest that this age group accounts for around 3% of AD cases. Although overall numbers are increasing with the ageing population, age- specific incidence appears to be falling in several countries.[71]

AD can be classified by when the disease manifests, and whether it is inherited. Early-onset Alzheimer's disease (EOAD) occurs before age 65, whereas late-onset Alzheimer's disease (LOAD) accounts for over 95% of cases and manifests beyond age 65. Familial AD shows Mendelian (usually dominant) inheritance, while sporadic AD shows no simple familial link. Nearly all EOAD are familial as these cases are due to mutations in APP, PSEN1 or PSEN2, and a vast majority of LOAD are sporadic. Genome wide association studies (GWAS) and sequencing have now provided more than 20 risk loci in total that contribute to sporadic cases, but often there is no identifiable genetic cause.

Aβ precursor protein:

Aβ precursor protein (APP) was the first gene shown to have autosomal dominant mutations causing AD. As the precursor of the aggregated peptide in amyloid plaques, its discovery in 1991 by John Hardy and colleagues led to the "amyloid hypothesis," which states that the toxic build-up of Aβ starts a cascade of events, leading to neuronal death and disease. There are now over 50 known APP mutations, accounting for approximately 10% of familial cases. Widely studied ones include the London (V717I), Swedish (KM670/671NL), Indiana (V717F) and Artic (E693G) (mutations, and most cluster around cleavage sites for β and γ-secretase. Research suggests that many of these mutations increase Aβ production, or the Aβ 42:40 ratio, leading to increased amyloid accumulation. In very rare instances, APP duplication or promoter mutations can cause AD. Interestingly, studies have also found that there is an APP mutation (Icelandic— A673T) which lowers Aβ and protects against AD.

Presenilins:

Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) encode the catalytic components of γ-secretase, an enzyme complex involved in APP processing. Presenilin mutations cause autosomal dominant AD, with PSEN1 variants being the most commonly known Mendelian genetic cause, estimated to account for around 30– 50% of familial EOAD cases . Research shows that PSEN1 and PSEN2 mutations alter Aβ production, similar to APP mutations but paradoxically tend to confer loss of function, raising questions as to how this fits the amyloid hypothesis.

Other genetic risk factors:

Other genes known to have variants associated with AD risk include TREM2, APOE, CLU, SORL, BIN1 and PICALM.APOE (apolipoprotein E) is a protein involved in fat metabolism, and its E4 allele is the most common genetic risk factor for AD with an allele frequency of ~13.7%. Heterozygosity for this allele increases the risk 3-fol.

Although rarer, the variant TREM2R47H (triggering receptor expressed on myeloid cells 2) has a similar effect size. TREM2 is a receptor expressed on multiple cell types of the immune response, and its association supports a role for inflammation in AD pathogenesis.

Down syndrome:

By age 65, up to 80% of Down syndrome (DS) individuals develop dementia. As with other instances of EOAD, amyloid and tau pathology begin much earlier than in LOAD, even at <40 years of age. DS results from the trisomy of chromosome 21, where the APP gene is located, and having three copies of this gene is sufficient to increase Aβ levels. However, the increased risk of developing the disease may also be due in part to triplication of other genes on chromosome 21.

Inflammation:

Sporadic AD often results from a combination of genetic and environmental risk factors, with cerebral hypoperfusion and inflammation being among the most common. Inflammation due to trauma, sepsis and infection has been linked to both short- and long-term cognitive impairment. Traumatic brain injury, and even bone fractures in the elderly, are implicated in dementia risk. Higher levels of inflammatory markers such as interleukin 6 (IL-6) associate with greater risk of AD and vascular dementia. AD patients often have higher levels of certain inflammatory markers and activated microglia and astrocytes in the brain, which tend to surround plaques and tangles. Finally, higher levels of these markers are associated with faster cognitive decline.

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Cerebral, cardiovascular disease and diabetes:

There is a strong link between vascular disease and dementia. Cardiovascular disease, including high blood pressure and heart attack, and cerebrovascular disease such as ischemia are associated with increased risk of AD. Metabolic and lifestyle risk factors for developing vascular diseases, including poor diet, obesity, high cholesterol and sedentary lifestyle, are also risk factors for dementia. Poor diet and high cholesterol can produce metabolic changes both systemically and in
the brain, and alter oxygen levels. Additionally, type 2 diabetes approximately doubles the risk for dementia.

Other environmental risk factors:

The list of environmental and metabolic risk factors discussed here is not intended to be comprehensive, especially as the nature of epidemiology in populations with diverse genetics and lifestyle means that important mechanisms will not always generate conclusive evidence. Other risk factors implicated include pollution, stress and heavy metal exposure. Many of these risk factors share some common characteristics with one another which can thus make it difficult to determine how their presence affects the brain. Some may act through similar mechanisms, such as inflammation or oxidative stress, which will be discussed later in this chapter.

Abstract:

Dementia as a public health priority:[89]

- Dementia, human rights and equitable society
- Dementia policy and plans
- Economics and value of dementia
- Ethics, finances and laws of dementia NEW
- Engaging people with dementia and carers in policy
- Healthcare system readiness

Dementia awareness:

- Attitudes, awareness and stigma
- Dementia friendliness and inclusivity
- Diverse populations: solutions around inclusion and equality
- Environment, architecture and design for dementia
- The work of national dementia associations

Dementia risk reduction:

- Brain health for life NEW!
- Campaigns shaping the future of dementia prevention
- Risk factors (Physical inactivity, smoking, excessive alcohol consumption, air pollution, head injury, infrequent social contact, less education, obesity, hypertension, diabetes, depression, hearing impairment, untreated vision loss, elevated LDL levels)
- Risk factors beyond the Lancet Commission (e.g. sleep, vitamins etc.) NEW!
- Risk reduction and prevention (including clinical trials and lifestyle interventions)

Dementia diagnosis, treatment, care and support:

- Behavioural and psychological symptoms of dementia
- Biomarkers
- Dementia therapies (music, dance, art etc.)
- Diagnosis, diagnostic tools and cognitive assessments
- End of life and palliative care

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- Living alone with dementia: research, innovation and support NEW!
- Models of care (including residential, end of life and day care)
- Post diagnostic support for people with dementia and carers
- Psychosocial interventions
- Rehabilitation
- Support for people living with dementia
- Treatment experiences of people living with dementia, carers and clinicians NEW!
- Well being and quality of life

Support for dementia carers:

- Education and training for informal carers
- Education and training for professionals and formal carers
- Informal carers support: pre, during and post
- Migration and the importance of cultural context for carers/providers
- Young carers.

Information systems for dementia:

- The Global Dementia Observatory (GDO), international collaboration on data sharing and registries

Dementia research & innovation:

- AI and innovation
- Assistive technology (including adaptive and rehabilitative devices) NEW!
- Clinical trials
- Dementia beyond the amyloid hypothesis (including oral hygiene, new genes, gut microbiome, autoimmune diseases and neuroinflammation) NEW!
- Epidemiology
- International collaborations
- Less common dementias and syndromes (including Down Syndrome and childhood dementia)
- LGBTQI+ and dementia
- Mild Cognitive Impairment (MCI) NEW!
- New and future approaches and treatments
- Non-pharmacological interventions
- Stages of dementia
- Underrepresented populations and dementia: exploring sex, gender,diversity, equity and inclusion in dementia research.

V. CONCLUSION:

Alzheimer's disease is one of the top listed causes of death in the world. The mortality rate of AD over a period has increased, and so as the concerns for treating the infected population too. The cure for AD is still in finding since the first report of the Disease. The strategy of Alzheimer's research is finding better biomarkers that could reasonably identify the risk of the disease and finding therapeutic agents that control the disease or the symptoms. There were only a few drugs that were approved to treat the disease which targets the symptoms. Decades of research concluded multiple causes of the disease. With no dubiety, certainly, there is a demand for superior therapy to treat the patients. Several drug molecules are in different stages of clinical trials that target other causes of the disease apart from improving memory. Another therapeutic concern of the disease is to identify the early stage AD and treat it. In support of Alzheimer's research and understanding the criticality, USFDA lowers the bar for clinical trial success (Feb- 2018) of drugs that treat the early stages of Alzheimer's. This states the necessity for the new molecules or new plant

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constituents to control the estimated statistics of AD deaths in the future. Furthermore, the success of components extracted from natural sources like curcumin and the very recent GV-971 obtained from a seaweed brown alga gives a scope and hope for the emerging researchers, to consider natural components to elicit certain pharmacological action and could be proved as potential drugs for the future

VI. FUTURE SCOPE

Alzheimer's disease (AD) is a slow progressive, irreversible disease of the brain that is characterized by impairment of memory and other intellectual abilities. It's most common form is dementia, a general term for memory loss and enough to interfere with daily life. Alzheimer's disease accounts for 60 to 80 percent of dementia cases. Alzheimer's disease is currently ranked as the sixth leading cause of death in the United States, but recent estimates indicate that the disorder may rank third, next to heart diseases and cancer as a cause of death for older people.6

Although the disease was first identified more than 100 years ago, research into its symptoms, causes, risk factors and treatment have gained momentum only in the last 30 years. Most of the medications

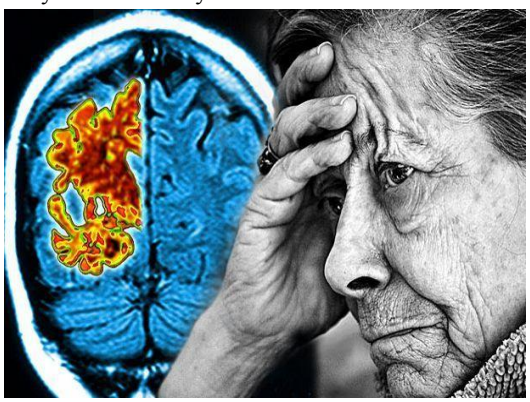

FIG NO.11currently approved

to treat Alzheimer's are for early to moderate stages. These include cholinesterase inhibitors and Memantine drug. Cholinesterase inhibitors treat symptoms related to memory, thinking, language, judgment and other thought processes. Glutamate helps to send messages between nerve cells. Glutamate is excessively released during Alzheimer's. Memantine drug protects the brain cells by blocking the effects of excess glutamate.

There is a vigorous drug development for Alzheimer's disease. Many compounds are under clinical testing, most of which intend to slow down the progress of the disease. Several of these drugs are under Phase III trials, which is a final phase before approval for general use.

Developing new treatments for Alzheimer's has proven challenging, however, scientists still need to know more about how the brain functions. Scientists are working on better ways to diagnose Alzheimer's disease in its earlier stages, before symptoms initially start appearing. These include brain scan techniques that can track amyloid beta or detect changes in brain function, size, or blood use. Spinal tests that detect abnormal amounts of amyloid and tau proteins could help track disease progress in those with mild cognitive impairment or Alzheimer's disease. One of the new Alzheimer's treatments is developing target microscopic clumps of the protein beta-amyloid (plaques). Plaques have long been considered as a sign of Alzheimer's disease. Two strategies aimed at beta-amyloid include immunization against it and blocking its production.

Studies also continue on the kinds of exercises, mental activities, diets, and lifestyle choices that seem to minimize the risk of developing Alzheimer's disease, or reduce the severity and progression of symptoms.

Although current Alzheimer's treatments cannot stop Alzheimer's from progressing, they can temporarily slow down the worsening of dementia symptoms and improve quality of life. Today, there is a worldwide effort to find better ways to treat the disease, delay its onset and prevent it from developing.

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