Patrícia da Silva Azevedo

The role of drugs in modulating synaptic plasticity associated with aging diseases: Alzheimer's disease

Faculdade de Ciências da Saúde

Universidade Fernando Pessoa

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Atesto a originalidade do trabalho,

Patrícia da Silva Azevedo

(Patrícia Azevedo)

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Orientador: Professor Doutor Henrique Silva

RESUMO

O processo fisiológico do envelhecimento é regulado por uma variedade de mecanismos bioquímicos e genéticos, que estão intimamente ligados à longevidade e à causa de todos os distúrbios relacionados à idade. O surgimento das doenças neurodegenerativas aumenta exponencialmente com a idade, sugerindo que o cérebro é particularmente suscetível ao processo de envelhecimento (Grimm *et al.*, 2017; Li *et al.*, 2021).

A Organização Mundial de Saúde relata que a incidência de Alzheimer, uma das doenças neurodegenerativas associadas ao envelhecimento, está a aumentar a cada ano, levando à hipótese de que, em 2050, poderá haver três vezes mais pacientes com Alzheimer (Askarova *et al.*, 2020).

Como o Alzheimer se destaca em número a todas as outras doenças neurodegenerativas, este será o foco principal deste manuscrito. A doença de Alzheimer começa com um estágio assintomático e evidentes biomarcadores da condição patológica. Progride expressando anormalidades cognitivas e/ou neurocomportamentais leves até atingir o estado de demência (Porsteinsson *et al.*, 2021).

Dada a complexidade da doença, várias hipóteses etiológicas para descrever o percurso da patologia têm sido propostas, salientando-se entre elas a aglomeração de vários tipos de proteínas, que causam neuroinflamação, stress oxidativo, disfunção mitocondrial, desregulação dos sistemas enzimáticos e morte neuronal (Askarova *et al.*, 2020).

Perturbações como as mencionadas acima causam perda sinática e neuronal e ainda neurodegeneração. O hipocampo, essencial na regulação da aprendizagem e memória, é a estrutura cerebral mais afetada pela doença de Alzheimer, tornando-o um dos principais objetos de estudo. Este exibe incrível plasticidade estrutural e funcional em resposta às mudanças ambientais, o que suscita especial interesse no combate à neurodegeneração causada pela doença (Zhang et al., 2022).

Para muitos pacientes com Alzheimer, o padrão da terapia farmacológica inclui o uso de inibidores da colinesterase e o antagonista do recetor de N-metil-D-aspartato, a memantina. A *Food and Drug Administration* autorizou o aducanumab, um tipo de anticorpo monoclonal humano, para tratar pacientes com Alzheimer a 7 de junho de 2021 (Scheltens *et al.*, 2021; Vaz *et al.*, 2022).

Devido à sua notória eficácia em reduzir drasticamente a o péptido amiloide-β no cérebro, um dos marcadores da doença de Alzheimer, o aducanumab destacou-se como o tratamento mais promissor para esta doença (Vaz *et al.*, 2022).

Embora haja falta de mais estudos relativos à eficácia de outras terapias não farmacológicas, a terapia com células estaminais e a oxigenoterapia hiperbárica são dois potenciais candidatos para ajudar a prevenir e/ou tratar a doença de Alzheimer.

Esta dissertação foi elaborada com o objetivo de realizar uma revisão bibliográfica de artigos relacionados com a prevenção de doenças neurodegenerativas com vista em melhorar a qualidade de vida no envelhecimento, para compreender bem os mecanismos de neuroplasticidade e neurogénese e conhecer o atual estado da arte das terapêuticas e medidas preventivas existentes com a finalidade de prevenção em especial da doença de Alzheimer, que é a doença neurodegenerativa com maior impacto na população idosa.

Por fim, este manuscrito destaca a importância do diagnóstico precoce do Alzheimer, pois permite o acesso a opções de tratamento que não curam a doença, mas reduzem o declínio cognitivo e funcional em um estágio inicial da doença. Também abre novos horizontes para que as pessoas mudem o seu estilo de vida para prevenir doenças neurodegenerativas e se manterem saudáveis por mais tempo.

A pesquisa bibliográfica utilizada no presente artigo científico foi efetuada no período compreendido entre setembro de 2021 e setembro de 2022, através das bases de dados PubMed e B-On, e também entidades reguladoras da saúde como a Organização Mundial de Saúde, *The National Institutes of Health* e *National Center for Complementary and Integrative Health*.

Palavras-chave: neuroplasticidade, envelhecimento, fármacos, modulação sinática, doenças neurodegenerativas e Alzheimer

ABSTRACT

The physiological process of aging is regulated by a variety of biochemical and genetic mechanisms, which are closely linked to longevity and the cause of all age-related disorders. The onset of neurodegenerative disorders has increased exponentially with age, suggesting that the brain is particularly susceptible to the aging process (Grimm *et al.*, 2017; Li *et al.*, 2021).

The World Health Organization reports that the incidence of Alzheimer’s Disease (AD), a neurodegenerative disease linked to aging, is rising each year, leading to the hypothesis that by 2050, there may be three times as many Alzheimer’s patients (Askarova *et al.*, 2020).

As Alzheimer's outnumbers all other neurodegenerative diseases, it will be the main focus of this manuscript. Alzheimer's disease starts with an asymptomatic stage and biomarker evidence of the condition and progresses by expressing mild cognitive and/or neurobehavioral abnormalities until it reaches the state of dementia (Porsteinsson *et al.*, 2021).

Given the complexity of the disease several etiological hypotheses to describe the pathology course have been proposed, highlighting among them clustering several types of proteins, which cause neuroinflammation, oxidative stress, mitochondrial dysregulation of enzymatic systems and neuronal death (Askarova *et al.*, 2020).

Disturbances such as those mentioned above cause synaptic and neuronal loss as well as neurodegeneration. The hippocampus, essential in the regulation of learning and memory, is the brain structure most affected by Alzheimer's disease, making it one of the main research targets. It exhibits incredible structural and functional plasticity in response to environmental changes, which is of particular interest in combating neurodegeneration caused by the disease. (Zhang *et al.*, 2022).

For many Alzheimer's patients, the standard of pharmacological therapy includes the use of cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist memantine. The Food and Drug Administration authorized aducanumab, a kind of human monoclonal antibody, to treat Alzheimer's patients on June 7, 2021 (Scheltens *et al.*, 2021; Vaz *et al.*, 2022).

Due to its obvious efficacy in dramatically reducing the amyloid-β peptide in the brain, one of Alzheimer’s disease (AD)'s markers, aducanumab has emerged as the most promising treatment for AD during the past ten years (Vaz *et al.*, 2022).

Although there is a lack of further studies regarding the effectiveness of other non-pharmacological therapies, stem cell therapy and hyperbaric oxygen therapy are two potential candidates to help prevent and/or treat Alzheimer’s.

This manuscript was written with the goal of conducting a literature review of articles related to the prevention of neurodegenerative diseases with a view of improving quality of life in aging, to understand well the mechanisms of neuroplasticity and neurogenesis, and know the current state of the art of existing therapies and preventive measures with the aim at preventing aging related disease in particular of Alzheimer’s disease, which is the neurodegenerative disease with the greatest impact on the elderly population.

Finally, this manuscript highlights the importance of early diagnosis of AD, as it allows access to treatment options that do not cure the disease but reduce cognitive and functional decline at an early stage of the disease. It also opens new horizons for people to change their lifestyle to prevent neurodegenerative diseases and stay healthy longer.

The literature search used in this manuscript was conducted between September 2021 and September 2022, using the PubMed and B-On databases, as well as health regulatory agencies such as the World Health Organization, The National Institutes of Health, and National Center for Complementary and Integrative Health.

Keywords: neuroplasticity, aging, drugs, synaptic modulation, neurodegenerative diseases and Alzheimer's

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ABBREVIATION INDEX

5-HT: Serotonin

Aβ: Amyloid-β peptide

ACh: Acetylcholine

AChE: Acetylcholinesterase

AChEIs: Acetylcholinesterase Enzyme Inhibitors

AD: Alzheimer's Disease

ALS: Amyotrophic Lateral Sclerosis

AN: Adult Neurogenesis

ANS: Autonomous Nervous System

APP: Amyloid Precursor Protein

BBB: Blood Brain Barrier

BChE: Butyrylcholinesterase

bvFTD: behavioral variant of Frontotemporal Dementia

ChAT: Choline Acetyltransferase

CHT1: Choline Transporter 1

CNS: Central Nervous System

CT: Combination Therapy

DA: Dopamine

DG: Dentate gyrus

DLB: Dementia with Lewy Bodies

DNA: Deoxyribonucleic Acid

E: Epinephrine

EC: Endothelial Cells

FDA: Food and Drug Administration

FDG-PET: Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)

GAL: Galantamine

GCL: Granule Cell Layer

Hcy: Homocysteine

HBOT: Hyperbaric Oxygen Therapy

HD: Huntington's Disease

INs: Immature Neurons

IV: Intravenous

MCI: Mild Cognitive Impairment

MRI: Magnetic Resonance Imaging

mRNA: Messenger Ribonucleic Acid

MS: Multiple Sclerosis

NDs: Neurodegenerative Disorders

NE: Norepinephrine

NFTs: Neurofibrillary Tangles

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association

nm: Nanometers

NMDA: N-methyl D-aspartate

NMDAR: N-methyl D-aspartate Receptor

NPCs: Neural Progenitor Cells

NSCs: Neural Stem Cells

PD: Parkinson's Disease

PHF: Paired Helical Filaments

PNS: Peripheral Nervous System

PPA: Primary Progressive Aphasia

SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2

SGZ: Subgranular Zone

SSRIs: Selective Serotonin Reuptake Inhibitors

SVZ: Subventricular Zone

TDP-43: Transactive DNA binding protein 43

TJs: Tight-Junctions

VAChT: Vesicular Acetylcholine Transporter

WHO: World Health Organization

XR: Extended Release

I. INTRODUTION

All living things age over time, and it has the greatest impact on the decline of physical and mental abilities, as well as contributing to the onset of several disorders, neurodegeneration being one of them (Fitzgerald *et al.*, 2021).

The nervous system is anatomically divided into two parts: the central nervous system (CNS) and the peripheral nervous system (PNS) (Almeida, 2018).

The chronic gradual loss of the structure and functions of neuronal components, resulting in functional and mental deficits, characterizes CNS degeneration. This behavior occurs in neurodegenerative diseases (ND) such Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), which mainly affect elderly people (Chen *et al.*, 2016).

Continuing to focus on the CNS, we can find, within our skulls, the human brain, a sophisticated three-dimensional structure (Hernández-Aceituno *et al.*, 2022).

The hippocampus, is prominent in the paramedial area of the temporal lobe of the brain and is essential for learning, memory formation and consolidation, as well as for controlling emotions such as fear, worry, and stress (Bartsch *et al.*, 2015; Almeida, 2018).

Hippocampus is the main part of the brain where neuroplasticity occurs. Neuroplasticity is the ability to adapt and remodel brain structure or function in response to internal or external stimuli (Bartsch et al., 2015).

There are different types of neuroplasticity mechanisms, such as synaptic plasticity (changes in neuronal connections caused by the development and removal of synapses) and adult neurogenesis (AN) (creation of new neurons in the postnatal brain by stem cells) (Bonfanti *et al.*, 2021).

It is expected that diseases such as AD and PD will continue to gradually increase in the coming decades, as a result of the large increase in human life expectancy.

AD is the most common cause of dementia and is characterized as a degenerative brain disease involving cell death, which leads to loss of cognitive function.

A variety of risk factors impact the disease, including advancing age, genetic factors, head trauma, vascular abnormalities, infections, environmental variables and lifestyle habits. Furthermore, approved medications are only effective in treating the symptoms of the disease and do not cure or prevent it (Breijyeh *et al.*, 2020).

II. AGING

Aging is an inevitable and irreversible process that occurs biologically as a result of the accumulation of several types of molecular and cellular damage over time and it is accompanied by obvious and recognizable changes in the physical characteristics and functions of an organism. In addiction to biological changes, aging is often linked to other life transitions including retirement, moving to a more suitable home, and losing friends and companions (Hou *et al.*, 2019; WHO, 2021a).

As a result of aging, physical and mental abilities gradually deteriorate, the risk of disease increases, and eventually death occurs. These changes are neither linear nor consistent, and correspond only tangentially to an individual's age expressed in years. It is important to note that, people who have the same chronological age may exhibit organs with varying age-related deterioration trajectories. So, we need to distinguish between biological and chronological ages when assessing individuals (Khan *et al.*, 2017; WHO, 2021a).

The ability of tissues and organs to repair and regenerate decreases with biological age, so, the rate at which an individual’s biological age has a direct impact on their vulnerability to disease and death (Khan *et al.*, 2017; Liu *et al.*, 2019).

For the first time in human history, there are expected to be more elderly people than adolescents and young adults combined in 2050. A significant portion of the world's population will be very old individuals (Figure 1) (Zhang *et al.*, 2020).

Given these sobering statistics, it is imperative to ensure the elderly's quality of life as they make up a significant portion of the global population and are more prone to disease due to senescence, which is a natural part of aging.

For example, speaking of the current outbreak issue responsible for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel form of human coronavirus, in December 2019, the elderly showed severe consequences from being infected with this virus, and it led to an alarming number of deaths when compared to other age groups.

One of the reasons was due to an age-related loss of proteostasis, the process that regulates proteins within the cell, which leads to fewer proteins being dissolved and forming aggregates that have been accumulated in the body over time. Aggregates are a hallmark of multiple age-related disorders, such as neurodegeneration (Lippi *et al.*, 2020).

The World Health Organization (WHO) defines healthy aging as being functionally able to maintain wellbeing in old age. (Rudnicka *et al.*, 2020).

To understand what elderly people define as "Successful aging", 23 studies were made between 2010-2020 that included 13 countries across Asia, the Middle East, North America, Oceania, and Western Europe (Reich *et al.*, 2020).

Older folks place a great priority on social interaction and a positive outlook on aging. Secondly, they show concern when it comes to independence and having enough money to afford to live alone and keep their home forever (Reich *et al.*, 2020).

When it comes to physical health, as long as they can deal with their daily tasks, they will not make it a priority (Reich *et al.*, 2020).

Ethnic minority groups were more prone to discuss spiritual matters, making this topic the second less important for elders (Reich *et al.*, 2020).

And finally, the lack of attention to cognitive health in this study is justified by the fact that this matter is taken for granted in people who are still cognitively intact to join this study (Reich *et al.*, 2020).

Cognitive health assures the ability to think effectively, learn new things, and remember things, which is a crucial part of socialization and performing daily tasks. Although cognitive health is not the first place in the elderly's priority, it is crucial to achieve what they prioritize the most.

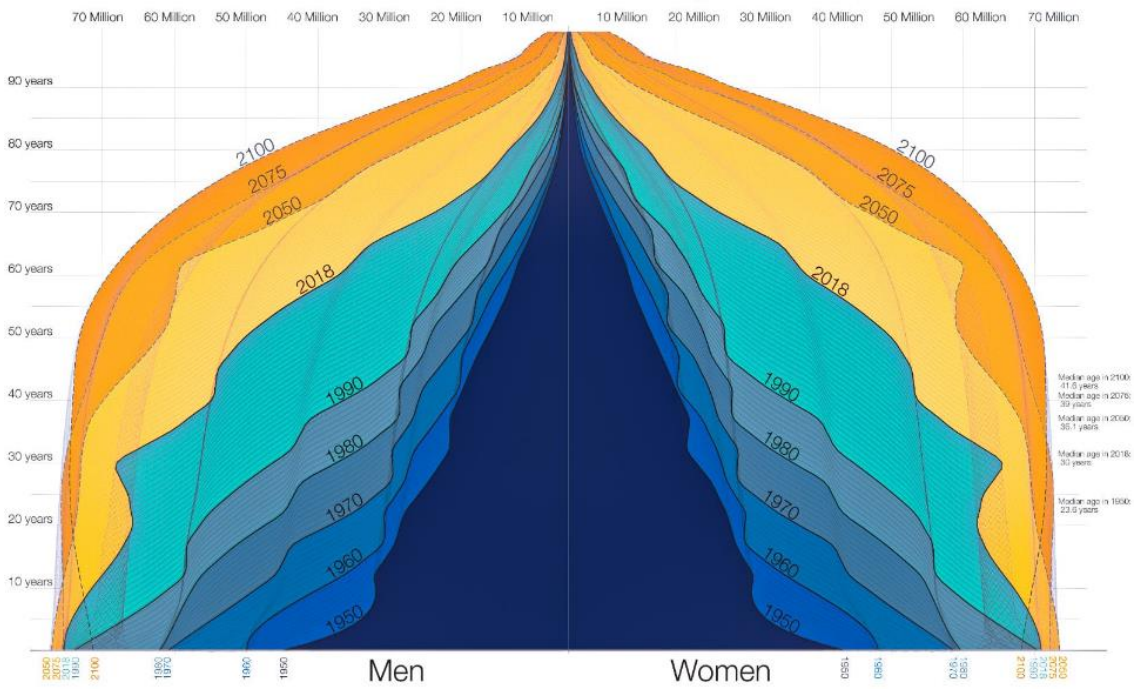

Figure 1 The World Population Demographics – by sex – from 1950 to 2018 and the UN Population Division projection to 2100 - Adapted from (Ritchie *et al.*, 2019)

2.1. Factors that impact aging

Multiple behavioral lifestyle variables, such as nutrition, exercise, moderate alcohol consumption, and sleeping habits, as well as intrinsic variables such as gender, family, social structure, economic status, and education and even the environment in which we live are major variables for unraveling the intricate interactions that are responsible for aging and longevity (Quach *et al.*, 2017).

An important aspect to take into consideration is the immune system. It is clear that the immune system of older people functions differently than younger people. This notion leads to a greater vulnerability to infections as well as the onset of several degenerative illnesses. Immunosenescence is the word used to describe the decreasing function of the immune system, where the levels of inflammatory mediators in the blood are typically slightly higher in elderly individuals ("inflammaging") and have been linked to mortality and frailty (Pawelec, 2018).

The brain is particularly susceptible to stress and immunological difficulties throughout adolescence and adulthood, which can lead to long-lasting neurodegenerative problems.

For example, changing diet has the potential to reduce the chance of developing age-related diseases, since there is a strong link between gut dysbiosis and neurodegeneration (Quach *et al.*, 2017; Yahfoufi *et al.*, 2020).

Nutritional practices for preserving good health include foods such as grains and dietary fiber, fish and omega-3 fatty acids, and fruits and vegetables (Quach *et al.*, 2017).

In addition to nutrition, a healthy lifestyle, competence of the metabolic cycle, and the circadian rhythm integrity are essential for maintaining brain homeostasis and may delay the onset of immunosenescence. Sufficient rest strengthens the immune system, while lack of sleep makes it more difficult for the body to clear clogged proteins, a major potential mediating factor in AD. On the other hand, stress may injure the brain and damage the immune system (Costantini *et al.*, 2018; Lananna *et al.*, 2020).

When it comes to exercise, it can be assumed that aerobic exercise training might have positive health consequences, including reducing cognitive decline (Costantini *et al.*, 2018).

A minimum of 30 minutes of daily activity, at least five days a week, at an intensity level between 60 and 80 percent of perceived maximal effort was recommended as part of a study on lifestyle recommendations for reversing epigenetic aging (Fitzgerald *et al.*, 2021).

Speaking of epigenetic aging, the genetics of human longevity has shown that the human body and the environment are not static but instead have undergone and continue to undergo complicated reciprocal remodeling. Such dynamics significantly affect the rate of aging, quality of life, and length of life (Giuliani *et al.*, 2018).

Genetic modification provides enormous contributions to the scientific understanding of the systems underlying aging (Snell *et al.*, 2018).

Now that whole-exome and whole-genome sequencing data from human populations, including centenarians, are more widely available, it is now possible to quickly identify unusual coding variations that alter healthy aging phenotypes, so, gene-based anti-aging therapies are being developed to extend the span of human health (Zhang *et al.*, 2020).

Finally, pharmaceutical interventions have shown a remarkable advantage when compared to other interventions for preventing aging, and that would be the ability to precisely control their dosage. They can also be used as a complement to other non-pharmacological therapies to enhance the anti-aging process (Snell *et al.*, 2018).

Drugs can bind to a larger number of protein targets, resulting in effects other than from their main pathway that cannot be predicted or are yet unknown. That said, therapeutics already established to treat other chronic diseases in the elderly population that have shown different interactions between the active principle and proteins is a crucial field of study because it offers a wide range of opportunities for low risk, especially if they are already approved by Food and Drug Administration (FDA) because that way we know their safety is already established, and faster drug development (Snell *et al.*, 2018; Wang *et al.*, 2018).

III. THE NERVOUS SYSTEM & HUMAN BRAIN

The nervous system is the body's main monitoring, regulating, and communicative system. All mental activity, including memory, learning, and cognition, is centered there (NIH, 2016).

The nervous system is divided anatomically into two parts: the CNS and the PNS. The fundamental anatomical difference between these two compartments is that the first has a meningeal coating, which meaning that it is bordered by three parallel membranes that isolate the neural parenchyma from the cranial and vertebral bone compartments (Almeida, 2018).

The autonomic nervous system (ANS) is a functional division of the nervous system that includes the central nervous system (CNS) and the peripheral nervous system (PNS). Nearly every organ system in the body is deeply innervated by the ANS. The ANS, which is frequently thought as controlling the "fight or flight" and "rest and digest" functions, contains a complex web connection that allow it to precisely regulate the body's reaction to almost any event. The enteric nervous system is now seen as a third part of the ANS, once only divided into sympathetic and parasympathetic systems (Gibbons, 2019).

The human brain belongs to the CNS and is considered the most sophisticated organ in the human body. This three-pound organ serves as the seat of intellect, the body's primary movement controller, the senses' translator, and the source of thought. The brain, which is covered by a fluid that serves as protection and is inside a bone shell, is where all the characteristics that make us human originate (NIH, 2022).

There are two cerebral hemispheres that are connected by the massive white commissure known as the corpus callosum. The frontal, parietal, occipital, and temporal lobes correspond to each of the four parts that make up the cerebral hemispheres (Figure 2). Prominent in the innermost area of the temporal lobe of the brain there’s hippocampus, a structure that will be discussed later on (Almeida, 2018).

Brain vascular health affects brain health. Given its specific metabolic requirements, the brain requires one of the body's most heavily perfused organs. Stroke, prenatal

neurological disorders, and age-related neurodegenerative illnesses are all influenced by brain vascular dysfunction. (Yang *et al.*, 2022).

The blood-brain barrier (BBB) is an extremely selective barrier that separates blood from the brain. It consists of a continuous layer of non-fenestrated endothelial cells (ECs) associated by tight junctions (TJs), along with pericytes, astrocytes, microglia, and the surrounding basement membrane. It is crucial for the CNS to operate properly and to maintain homeostasis. Without the BBB, the CNS is susceptible to invasion by infections, immune cells, poisons, or other substances, which might result in neuronal dysfunction and aging. Deterioration in BBB form and function is a feature of healthy aging but is exacerbated in many neurodegenerative illnesses and is a sign of cognitive impairment (Kang *et al.*, 2020; Knox *et al.*, 2022).

Despite being essential for normal neuronal function, the BBB thwarts pharmacological therapy of almost all brain illnesses. As a result, intense research is being done to identify targets on the human BBB that would improve drug delivery (Yang *et al.*, 2022).

Notably, older mice may have damaged BBBs, but cognitive deterioration shows no evidence until an inflammatory stimulus uprise (Wen *et al.*, 2020).

Understanding possible therapeutic methods to preserve and improve BBB integrity is more important as the world's population ages. It will be intriguing to include and utilize these connections for the purpose of treatments to either repair or protect against BBB disintegration (Knox *et al.*, 2022).

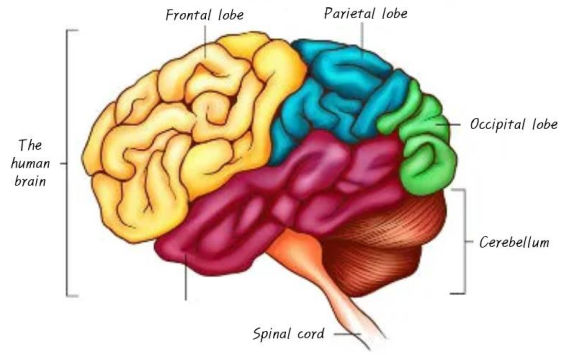

Figure 2 The Human Brain - Adapted from (Educação, 2016)

3.1. Hippocampus and its central role in memory

Now that we have a better understanding of the human brain, let's focus on the hippocampus. The hippocampus is a component of the so-called limbic system, the one that controls our behavior and feelings, such as fear, worry and stress. The ability to connect events, learn, and make sense of our life is precisely what memory enables. In other words, it helps us develop our life story (Camina *et al.*, 2017; Almeida, 2018).

Sensory memory, short-term memory, and long-term memory are the three main categories of memory that the scientific community currently studies. Sensory memory is the ability to recall information obtained from the senses and it allows to store information from the environment around us, making it possible to access this information later. The information processed by a person in a short period of time is referred to as short-term memory. We can keep knowledge in our long-term memory for a very long time (Camina *et al.*, 2017).

Age-related cognitive impairment is linked to changes in synaptic plasticity or its loss, and also to reduced neurogenesis (a type of neuroplasticity characterized by the formation of new neurons), which makes older people more susceptible to neurodegenerative diseases like Alzheimer's Disease and Parkinson's Disease. (Khan *et al.*, 2017).

In Alzheimer's patients, hippocampal degradation is linked to a loss of short-term memory and cognition that leads to impairment of daily activities (Sheppard *et al.*, 2020).

It has been demonstrated that the hippocampus of adult mammal may generate new neurons and glial cells; these new cells may play a significant role in plasticity mechanisms of learning and adaptation throughout life (Bartsch *et al.*, 2015).

3.2. Neuroplasticity & Neurogenesis

The structural plasticity of the mature brain is an exceptional tool that allows it to adapt to environmental changes, learn, heal itself after injury or disease, and halt aging (La Rosa *et al.*, 2020)

Most plasticity is the retention of "embryonic" or "immature" features, some of which persist into postnatal years. As people age, their flexibility and immaturity gradually decline (Bonfanti *et al.*, 2021).

Structural changes occur on a variety of "types and scales," ranging from microscopic adjustments that only affect discrete sections of pre-existing cells (glia, neurons) to more macroscopic adjustments that affect entire populations of cells (adult neurogenesis) (Bonfanti *et al.*, 2021).

A lengthy history of neuroscience studies has resulted in exciting findings about many forms of plasticity, such as synaptic plasticity, neuron and glial production, post-neurogenetic maturation, and more (Bonfanti *et al.*, 2021).

Synaptic plasticity refers to changes in neuronal connections caused by the development and removal of synapses. Such plasticity affects connections between pre-existing neuronal connections (Bonfanti *et al.*, 2021).

Adult neurogenesis (AN) refers to the creation of new neurons in the postnatal brain by stem cells. Neurogenesis in the adult brain requires both active stem cells and a favorable environment (niche). (Bonfanti *et al.*, 2021).

It is limited to two brain locations in mammals: the olfactory bulb and the hippocampus, where neurons are created by neural stem cells throughout adult life. AN in humans is assumed to be limited to the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus (Bartsch *et al.*, 2015).

Radial glial stem cells located in the SGZ, which is a region just between the granule cell layer (GCL) and the hilus, divide significantly asymmetrically to start the process. These cells have the ability to self-renew and can produce astrocytes or neurons. Radial glial stem cells give rise to neuroblasts via their highly proliferating daughter cells.

Following a brief migration from the SGZ into the GCL, the cell bodies of these new neurons start to differentiate into granule neurons. After their integration into the circuits of the hippocampus, these granule neurons can then affect behavioral function (Cope *et al.*, 2019).

Some findings imply that the neurogenesis of the human hippocampus has changed in the aging human brain at key developmental stages.

Stage 1 is known as the proliferation phase and occurs 1-3 days after birth. During this time, neural progenitor cells (NPCs) are able to proliferate and differentiate into a variety of cell types, but are unable to self-renew. Stages 2-4, commonly referred to as the differentiation stage, take place around a week after birth. During this period, neural progenitors end the cell cycle and commit to the neuronal lineage. The immature neurons enter stage 5, often known as the migration stage, following the commitment, to go to their final location. This takes place two to three weeks after delivery. Stage 6 of adult neurogenesis, which is the synaptic integration stage, begins about four weeks after birth and is when the newly formed neurons begin to form synaptic connections with those of the pre-existing circuits. In general, it takes 2-4 months for adult-born neurons to properly integrate with their surroundings and become part of the hippocampus circuits. (Niklison-Chirou *et al.*, 2020).

These stages are suitable for drug development to restore neurogenesis and, as a result, potentially support cognitive function (Mathews *et al.*, 2017).

Although the role for neurogenesis in the human hippocampus is still under discussion, continuous proliferation by neural stem cells (NSCs), defined as multipotent cells with unlimited self-renewal, in the hippocampus contributes to the maintenance of hippocampal plasticity and hippocampus-dependent learning, memory, and mood function (Vogel *et al.*, 2018).

Additionally, neuronal loss is observed in non-neurogenic parts of the brain in neurodegenerative diseases such as like Alzheimer's disease, making it much more challenging to replace lost neurons by relying exclusively on the inherent neurogenic potential of these endogenous cells (Matsubara *et al.*, 2021).

As the AN is extremely sensitive to environmental cues, new neurons may serve as a crucial substrate for experience-dependent transformation. Several pleasurable events for rats, such as voluntary physical activity, environmental enrichment, and sexual encounter, significantly increase the number of new neurons. In some of these circumstances, such as physical activity, data shows that acts at various stages of the AN process boost the number of new neurons, resulting in increase in neuroblast production (Cope *et al.*, 2019).

Stress appears to impair AN by suppressing radial stem cells proliferation and amplifying progenitors, resulting in a decrease in neuroblasts. Stress may also have an unfavorable effect on the survival of young neurons (Cope *et al.*, 2019).

3.3. Neurons, Glia cells & Stem cells

As mentioned earlier, various types of neuroplasticity are responsible for the generation of cells that belong to the CNS, like neurons and glia.

While glial cells conduct crucial interactions with neurons, such as providing support, nourishment, removing neurotransmitters, forming myelin, immunological surveillance, and participating in the transmission of CNS signals, neurons have the unique ability to communicate with one another through synapses (Rego *et al.*, 2017).

Neurons are morphological, trophic, and functional unit of the nervous system. These cells have a remarkable ability to capture and transmit impulses or nerve inputs via their cellular extensions (Almeida, 2018).

Immature neurons are created by dividing stem cell, and these cells undergo a long maturation process that involves the development of axons, dendrites, and synaptic connections. Within two weeks of their creation, young neurons start to morphologically resemble adult granule cells, developing a single dendritic tree that extends into the molecular layer and the development of dendritic spines, which serve as the main sites of excitatory synapses (Cope *et al.*, 2019).

The neuron has a unique structure that allows for remarkable functions. It has two types of cell branching. The dendrites are short arm-like structures and often multiple, whereas the axon terminals at the end are single and much longer. This neural extension

is capable of carrying out intracellular transport of chemicals and organelles across long distances along its broad course (Holford, 2005; Almeida, 2018).

Adult CNS neurons are post-mitotic cells, which means they cannot duplicate the quantity of deoxyribonucleic acid (DNA) they carry. They lack centrioles, which are tubular organelles involved in mitosis. In circumstances where nuclear chromatin is attacked, these properties render it unable to divide and regenerate. The dentate gyrus of the hippocampus and the olfactory epithelium are now known to have an outstanding ability for neurogenesis (Almeida, 2018).

Neuron cell membranes are excitable, which means that they can create action potentials, something that only neurons and muscle cells can accomplish. Nerve cells can thus receive inputs, such as electrical signals from other neurons and receptor organs (Almeida, 2018).

The ability of a neuron to produce action potentials is one of its distinctive features. This ability appears quite rapid (within a week) post-mitotic, according to electrophysiological investigations of newly formed cells in the adult dentate gyrus (Cope *et al.*, 2019).

Mammalian neurons are completely glucose dependent, and energy consumption is tightly controlled during both neuronal development and degeneration.

To meet their energy needs, neurons rely on oxidative phosphorylation (OXPHOS). Through OXPHOS, neurons metabolize one glucose molecule to produce 30-32 ATP molecules. As a result, mitochondria are essential for cytoskeletal remodeling, the formation of axons, dendrites, and synaptic activity throughout neurodevelopment and adult neurogenesis (Niklison-Chirou *et al.*, 2020).

The primary immune cells in the adult brain, known as microglia, descended from primitive macrophages, and are mononuclear phagocytes that make up to 10% of the total number of brain cells. They come from the mesoderm, appear in the early stages of brain development, and last throughout maturity. Primitive macrophages enter the developing CNS when blood circulation is established (Kang *et al.*, 2020; Matsubara *et al.*, 2021).

Microglia are initial responders that are triggered and change their phenotype from resting microglia to active microglia in response to immunological stimulation and brain damage. The microglial cells that are activated control neuroinflammation, a significant cause of secondary cell death. These cells gather at sites of injury and become the main cell type in the glial scar (Kang *et al.*, 2020; Matsubara *et al.*, 2021).

Microglial interactions with dendrites cause spine development in hippocampus cultures, indicating that microglia may contribute to the remodeling of postsynaptic sites to build more effective synapses (Weinhard *et al.*, 2018).

Microglial aging and malfunction in AD patients cause a buildup and lack of peripheral immune response, which aids in disease progression. Moreover, the interaction of age and a gradually declining immune response in both AD and PD points to a propensity for neurodegeneration (Costantini *et al.*, 2018).

In fact, cerebral amyloid angiopathy (a disease in which amyloid protein is deposited in the walls of the arteries of the brain) results by microglial depletion. Vascular cells do not, however, multiply as effectively as microglia. Therefore, continued exposure to vascular debris such as β-amyloid (a peptide known to be as the leading cause of AD) causes cell death, malfunction, and decreased cerebral spinal fluid and blood flow (Yang *et al.*, 2022).

Astrocytes are the most abundant form of neuroglia in the brain and have a strong impact on the cerebrovascular system (Cohen-Salmon *et al.*, 2021).

Astrocytes in the adult hippocampus regulate stem cell proliferation, commitment to a neuronal phenotype, and survival. Mature astrocytes also help adult-born neurons mature and integrate into hippocampal circuitry. Blocking vesicular release from astrocytes has been shown to decrease new neuron survival and dendritic maturation by decreasing dendritic branching and the number of dendritic spines in new neurons, indicating that astrocytes play a key role in adult neurogenesis at many stages (Cope *et al.*, 2019).

After brain trauma, astrocytes, become reactive and eventually aid in the development of glial scars. Due to their abundance in the brain, astrocytes are one of the best sources

for neuronal conversion in vivo, as there is less concern about depletion of the initial cells after conversion (Matsubara *et al.*, 2021).

Stem cells are undifferentiated human cells that show the ability to self-renewal and can evolve into any cell type in the body (Zakrzewski *et al.*, 2019).

Although stem cells offer a great promise for brain repair, mammals have a limited supply and a limited ability for endogenous regeneration (Bonfanti *et al.*, 2021).

NSCs stop proliferating in most areas of the brain and undergo terminal differentiation or enter a quiescent state (period of inactivity) after CNS development is complete with the required populations of different cell groups. Thus, only a small portion of the CNS has active NSCs capable of producing neurons, astrocytes, and oligodendrocytes during the postnatal and adult periods (Vogel *et al.*, 2018).

As a possible treatment for neurological diseases, transplantation of exogenous NSCs made from human induced pluripotent stem cells has been investigated. In animal studies, transplanted NSCs can survive, multiply, and regenerate new neurons in infarct (a tiny, localized region of dead tissue caused by a lack of blood flow), however there are still significant risks of immune rejection and tumor formation. By directly inducing the fate conversion of non-neuronal cells remaining in the injured brain into neurons through a process known as direct reprogramming, a novel method for replacing damaged neurons. Direct reprogramming provides a number of benefits over exogenous cell transplantation, including a rapid induction time, efficient conversion, a lower risk of cancer, and the absence of the need for ex vivo culture (Matsubara *et al.*, 2021).

3.4. Neurotransmitters & Synapses

Neurotransmitters are the small-molecule chemical messengers that control the neurological system and regulate emotions like happiness, fear, despair, and insomnia as well as cravings for sugary foods, narcotics, and alcoholic beverages. A common symptom of a number of neurological illnesses is fluctuation levels of neurotransmitters. Neurotransmitters are formed through the metabolism of amino acids or their precursors in the brain by enzymes (Holford, 2005; Sinha *et al.*, 2020).

However, the amino acid homocysteine (Hcy) is known that predicts the likelihood of memory, mood, and attention problems, making it a significant molecule for Alzheimer's research (Holford, 2005).

Hcy is shown to have an impact on normal mitochondrial structure and function, including energy generation, mitochondrial dynamics, and cell survival and death, according to the data compiled in a study done to understand the Hcy impact on mitochondrial structures in the cardiovascular and cerebrovascular systems. Numerous vital cellular processes are carried out by mitochondria, and mitochondrial abnormalities are linked to the onset of numerous diseases. (Kaplan *et al.*, 2020).

Dopamine (DA), serotonin (5-HT), epinephrine (E), and norepinephrine (NE) are monoamine neurotransmitters that stand out among the rest because they are crucial in the development of a number of mental illnesses, including schizophrenia, migraine, depression, and diseases like AD, PD, Huntington's disease (HD), prion disease and multiple sclerosis (MS) (Sinha *et al.*, 2020).

Another crucial neurotransmitter that regulates the ANS is acetylcholine (ACh). AD and other memory-related issues are caused by ACh dysregulation and imbalance (Sinha *et al.*, 2020).

The main excitatory neurotransmitter, DA, is linked to many of the typical physiological processes of the brain (Sinha *et al.*, 2020).

The primary cause of PD pathogenesis is abnormal DA concentration, which has been connected to the pathophysiology of many diseases. 5-HT has a significant function in anxiety, depression, decision-making, learning, memory, maturity, mood, and tranquility. It has also been shown to be associated with a number of physiological functions, including the regulation of hunger and digestion, and play a significant role preserving chemical balance and proper functioning of the CNS (Sinha *et al.*, 2020).

Additionally, there is a clear link between the imbalance in 5-HT concentration and numerous neurological and psychiatric disorders as well as suicidal tendencies (Sinha *et al.*, 2020).

In order to control neuronal transmembrane potential, neurotransmitters are essential. Upon synaptic connection, they are released, allowing impulses to travel from one nerve fiber to another and to various tissues throughout the nervous system (Cover *et al.*, 2021).

The synapse, which is defined by where neurotransmitters are released, connects two neurons (Holford, 2005).

Synapses are located mostly at the ends of the numerous nerve cell processes, and the rate of electrical transmission is consistent across all cells (Almeida, 2018).

Synapses have two strands, which are known as presynaptic and postsynaptic in terms of information flow. The presynaptic strand is normally the axon terminal, whereas the postsynaptic strand can be a dendritic or the cell body of another neuron. The synaptic cleft is the gap between the presynaptic and postsynaptic membranes (Almeida, 2018).

The primary method of communication between neurons in the CNS is the chemical synapse. Axo-dendritic synapses and axo-somatic synapses are formed by the presynaptic axon endings on postsynaptic dendrites or the cell body of the neuron, respectively (Cover *et al.*, 2021).

Electrical synapses allow the direct transmission of ionic current, that is, the passage of ions from one cell to another. They are located in specialized locations, the so-called interconnection spaces, where the pre and postsynaptic membranes are very close together, with only a space of about 3 nanometers (nm) covered by special proteins that form channels to allow the direct passage of ions from the cytoplasm of one cell to another (Almeida, 2018).

As the electrical current can pass through these channels, cells that have them are said to be electronically coupled. At the electrical synapse, transmission is very rapid and an action potential in the presynaptic neuron can almost instantaneously produce another action potential in the postsynaptic one. Electrical synapses are located mainly in very specialized areas of the CNS, where function requires special synchronization of activity with that of neighboring neurons. (Almeida, 2018).

IV. NEURODEGENERATIVE DISEASES

Neurodegenerative Diseases (NDs) are a widespread and growing source of death and morbidity, especially among the elderly. Although they often share similar characteristics, distinct neurodegenerative illnesses differ in their clinical manifestations and underlying physiology. Accurate diagnosis is essential because it facilitates a more reliable prognosis and often guides specific management and therapy (Erkkinen *et al.*, 2018).

CNS degeneration is characterized by chronic and gradual loss of the structure and functions of neuronal components, resulting in functional and mental deficits. The frequency of neurodegeneration increases with age, peaking in middle adulthood, although the reasons for neuronal degeneration are still poorly understood. This behavior occurs in neurodegenerative disorders such AD, MS, PD, and ALS, which mainly affect the elderly (Chen *et al.*, 2016).

In the present day, dementia, defined as a decline in cognitive performance beyond what can be anticipated from the typical effects of biological aging, is one of the leading causes of handicap and dependency among older people and the sixth largest cause of mortality among all diseases. Dementia affects people physically, psychologically, socially, and economically, as well as their caregivers, families, and society at large (WHO, 2021b).

Although most cases of senile dementia are caused by Alzheimer's (a specific disease in contrast with dementia), other significant types of dementia include frontotemporal dementia-associated diseases, dementia with Lewy bodies (abnormal protein clumps that occur within nerve cells), and vascular dementia (degeneration of the frontal lobe of the brain) (WHO, 2021b).

While anatomic vulnerability and specific protein accumulations serve to characterize NDs, many fundamental processes that contribute to progressive neuronal dysfunction and death also occur in NDs, including oxidative stress, programmed cell death, and neuroinflammation. Most geriatric diseases, including infections, cancer, autoimmune conditions, and chronic inflammatory diseases, are thought to be the result of

immunosenescence and inflamm-aging working together (Dugger *et al.*, 2017; Fulop *et al.*, 2017).

Immunosenescence (the act of the immune system getting old) is the word for the most of of these changes. Because it often results in the subclinical buildup of pro-inflammatory chemicals and inflamm-aging, immunosenescence has long been viewed as harmful. (Fulop *et al.*, 2017).

Neuro-inflamm-aging, also known as chronic aseptic CNS inflammation, is the result of immune and neurological system interactions (de Souto Barreto *et al.*, 2021).

These processes include proteotoxic stress and the abnormalities it causes in the ubiquitin-proteasomal and autophagosomal/lysosomal systems. These systems are responsible for regulating protein quality in cells (Dugger *et al.*, 2017).

Given the proven connection of the immune system to the brain, neurodegeneration might result from age-related immunel dysregulation, although it has been proven that inflamm-aging associated with immunosenescence is required but insufficient to produce age-related neurodegenerative disorders (Costantini *et al.*, 2018).

Amyloidoses, tauopathies, α-synucleinopathies, and proteinopathies involving transactivation response DNA binding protein 43 (TDP-43) are the most common NDs (Dugger *et al.*, 2017).

Tau in neurofibrillary tangles (NFTs) or Pick bodies, α-synuclein in Lewy bodies, and TDP-43 in neuronal cytoplasmic and neuronal intranuclear inclusions are a few examples of protein accumulations inside neurons (Dugger *et al.*, 2017).

It is difficult to effectively treat neurological disorders because they are difficult to definitively diagnose. For example, while some natural resources, natural amino acids, and peptide-based compounds can be used as treatment options, most of them are largely ineffective due to a number of drawbacks (Sinha *et al.*, 2020).

4.1. Alzheimer’s Disease

Alzheimer’s disease (AD), one of the currently incurable brain diseases, can cause a patient's cognitive and memory abilities to deteriorate continuously, eventually leading to an abnormal existence. Named after Alois Alzheimer, a German psychiatrist, this disease is distinguished by its gradual onset and continuous progression that leads to the decrease of independence in daily tasks associated with a decreased cognition caused by cell loss in the brain and is the leading cause of dementia, about 60% to 80% of all dementia cases (Erkkinen *et al.*, 2018; Breijyeh *et al.*, 2020; Jia *et al.*, 2021).

Although it can affect younger people, the elderly are the main demographic group for this condition. With age, the prevalence of AD increases noticeably; between 65 and 85, it is believed to increase more than 15-fold (the ratio of an increased number to the original number) (Erkkinen *et al.*, 2018).

The diverse neuroanatomical distribution of disease and its impact on the functionality of neural networks are reflected in the astonishing heterogeneity of the clinical presentations of AD (Erkkinen *et al.*, 2018).

Several processes, including inappropriate tau protein metabolism, amyloid-β (Aβ), inflammatory response, cholinergic and free radical damage, cholesterol and lipid metabolism, and endocytosis mechanisms active in neurons and glia have been postulated to explain the pathophysiology of AD in order to change its course and create effective therapies. Changes in the BBB have also been identified as early indicators of this neurodegenerative condition (Breijyeh *et al.*, 2020; Ishii *et al.*, 2020; Yang *et al.*, 2022)

Significant memory concerns (SMC) are thought to be a precursor to moderate cognitive impairment (MCI) and Alzheimer's disease (AD). Poor memory function is clearly a clinical sign (Jia *et al.*, 2021).

MCI is characterized as a condition in which people lose memory more frequently than would be expected given their age but do not fulfill the criteria for dementia. They initially proposed five specific clinical criteria for MCI: not demented, relatively retained general cognition, subjective memory complaint, objective memory impairment for age, and relative memory preservation. Later, this categorization system was

expanded to include "amnestic MCI" or "non-amnestic MCI" subtypes, as well as "single domain" or "multiple domain" situations to denote the number of cognitive areas affected (Bondi *et al.*, 2017).

Memory loss with other cognitive deficits—often visuospatial and executive function deficits —begins slowly and progresses over time in typical AD (also known as amnestic or limbic type), which results in a loss of functional independence, as mentioned earlier. Declarative episodic memory, which refers to autobiographical memories connected to particular times, places, and feelings, is predominantly affected by the amnesia observed in typical AD. It is often most noticeable for recent memories early in the disease. Numerous manifestations of this type of memory loss are caused by mesial temporal structure malfunction. People may miss things, repeat inquiries or discussions, or have difficulty remembering dates and appointments. Memory processes outside of the hippocampal structures, such as procedural memory, are often spared in AD. (Erkkinen *et al.*, 2018).

As the pathogenesis of AD is complex, adopting a multimodal treatment intervention that addresses numerous molecular targets of AD-related degenerative processes appears to be the most feasible strategy to alter the course of AD development (Kabir *et al.*, 2020).

Combination therapy (CT) outperforms no treatment or monotherapy in terms of clinical efficacy (Kabir *et al.*, 2020).

The management of behavioral issues particularly benefits from environmental and behavioral approaches. Maintaining a familiar environment, staying comfortable, offering security items, refocusing attention, eliminating doorknobs, and avoiding confrontation are all simple methods that can be quite effective in controlling behavioral disorders (Kumar *et al.*, 2022).

Mild sleep problems can be mitigated to lessen the burden on caregivers by getting exposure to sunlight and engaging in daytime activities. The anticipated benefits of treatment are not great. If there are no discernible benefits or unacceptably severe adverse effects, treatment should be discontinued or changed. It has been shown that regular aerobic exercise can slow the course of Alzheimer's disease (Kumar *et al.*, 2022).

Due to the complicated and poorly known pathomechanism of AD and the multiple clinical failures of anti-amyloid and anti-tau medications, it is important to consider methods that incorporate dietary or lifestyle modifications that could prevent the onset of neurodegenerative alterations or slow the course of AD. Coffee, tea, and yerba mate are considered sources of caffeine, has been associated with a lower risk of MCI and AD in the past (Gardener *et al.*, 2021; Londzin *et al.*, 2021).

Stages of Alzheimer's Disease

Currently, AD stages can be classified as Preclinical or Presymptomatic, MCI and Dementia. It is also possible to subdivide Dementia into Mild Dementia, Moderate Dementia and Severe Dementia (Table 1).

For advanced care planning and prognosis, a proper diagnosis in the early stages of a disease is essential. A late diagnosis of AD delays the start of advanced care planning and non-pharmacological therapies including cognitive stimulation, psychological treatment, and lifestyle modifications that can maintain cognitive function or improve quality of life, even if an authorized drug is not yet available for the early stages of AD that can slow disease progression. Reduced caregiver stress, a delay in institutionalization, and lower healthcare expenses may result from lifestyle changes and improved social support (Galvin *et al.*, 2020).

Presymptomatic AD is a phrase used to describe people who will eventually acquire AD due to a fully penetrant genetic mutation but who do not yet exhibit any AD symptoms. Typically, we refer to these people as having familial AD. The only situation that currently satisfies this condition is that of a carrier of a familial autosomal genetic mutation causing dominant AD. Amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) are the three proteins that are encoded by genes that are mutated in familial AD (FAD), which accounts for 5% of AD cases. The majority of sporadic types of AD appear beyond the age of 65; the etiology of these cases is unclear. To distinguish these individuals with known autosomal dominant or other well-characterized single-gene alterations from non-genetic family aggregations of the illness, we now advocate the use of the term "monogenic AD." Preclinical AD patient cohorts are expected to gain increasing attention for intervention studies to prevent AD (Dubois *et al.*, 2010; Londzin *et al.*, 2021).

Mild cognitive impairment (MCI) is the deviation of cognitive processes in populations, but without loss of functional abilities and skills in daily social and occupational life. In fact, magnetic resonance imaging (MRI) research has revealed that hippocampus shrinkage corresponds to the degree of cognitive dysfunction at the time of MCI diagnosis and can occur years before cognitive impairment. (Broadhouse *et al.*, 2020; Zhuang *et al.*, 2021).

The prefrontal cortex still maintains compensatory mechanisms in MCI, delaying the transition to AD and relying on strong synaptic plasticity. Aβ viable strategy to improve compensation in MCI and stop the progression to AD is to increase prefrontal cortex plasticity in vivo and, in turn, prefrontal cortical function in individuals with MCI (Rajji, 2019).

Increased synaptic plasticity in MCI is believed to decrease Aβ load. According to research, there is a tendency for extracellular clearance of Aβ and its load is reduced during MCI, with a balance between the creation of Aβ by synaptic activity and its disruption by synaptic activity (Rajji, 2019).

Predictably, the onset of dementia brings with it a new set of management concerns for clinician, such as those relating to patient autonomy, such as driving ability, financial ability, and care. The diagnosis of typical AD now requires the presence of an amnestic condition of the hippocampal type. This syndrome is based on patient and informant reports of memory loss and objective evidence of episodic memory loss on tests that are responsible for accurately recording things that need to be remembered and probing the response to suggestion as a measure of the storage capacity and associative function of the hippocampus (Dubois *et al.*, 2010).

Since the development of drugs that are specifically directed against the pathogenic processes of AD requires high diagnostic specificity, patients with typical AD are of interest for pharmacological trials (Dubois *et al.*, 2010).

There are specific clinical phenotypic variation AD presentations that do not fit the above-mentioned pattern. It is now conceivable to classify these clinical conditions as atypical AD if the biomarker evidence is strong enough. An amnestic impairment may

not manifest in certain illnesses until later in the course of the illness (Dubois *et al.*, 2010).

As these clinical symptoms might possibly be caused by other degenerative processes, we suggest that only the diagnostic designation atypical AD be used for well-characterized clinical presentations such as primary progressive aphasia (language disorder caused by damage in a specific area of the brain), logopenic aphasia (a type of dementia characterized by language disturbance), posterior cortical atrophy, and frontal variation. Because the specific clinical presentations in these situations are much less normal than the amnestic appearance, the word "atypical" is used to describe them (Dubois *et al.*, 2010).

Mixed Alzheimer's is a diagnostic term for the co-existence of different biologically based causes of cognitive loss, most often cerebrovascular illness or Lewy body pathology. These coexisting disorders might manifest as diseases with overlapping clinical features. Elderly people living in the community often have mixed diseases, thus any diagnostic plan must take into account how existing diseases affect cognitive decline (Dubois *et al.*, 2010).

Table 1 The stages of AD - Adapted from (Kumar et al., 2022)

Preclinical or Presymptomatic	**Mild Cognitive Impairment**	**Dementia**
Individuals are asymptomatic with clear test evidence at this stage. Finding the biomarkers can aid in this stage of AD diagnosis. As a biomarker, low amyloid and elevated tau proteins in cerebrospinal fluid (CSF) are useful, although they are not exclusive to AD. According to a different analysis, the progression to MCI can be predicted by several different factors, including ApoE4 positivity, results on the paired associates immediate recall test and the digits symbol substitution test, elevated tau protein in CSF, right entorhinal cortex thickness, and right hippocampal volume on MRI.	Patients in this stage exhibit either memory impairment or impairment in non-memory areas, such executive function or language function. These people continue to engage in autonomous jobs, social interactions, and functioning. 10% of patients with MCI develop dementia each year. Along with the other risk factors for AD, the degree of impairment at the time of diagnosis is a risk factor for dementia progression.	Patients at this stage have severe memory impairment. In 20–40% of patients, suffer from vhallucinations, predominanly the visual one's. Anomia (unable to recall the names of everyday objects), paraphasic mistakes (wrong sound or words) and a decline in spontaneous verbal production are symptoms of language alterations. Motor vehicle accidents are increased in these patients. Patients also have interrupted sleep and lose their regular circadian sleep-wake rhythm..

Alzheimer's Disease Etiology

Although numerous hypothesis have been pointed out as causes of AD, two are considered to be the most significant: some feel that cholinergic dysfunction is a significant risk factor for AD, while others believe that a change in amyloid-protein synthesis and processing is the main starting factor. (Breijyeh *et al.*, 2020).

As for familial AD the main causes are thought to be AD inducing mutations in the presenilin genes (PSEN1 and PSEN2) and the amyloid precursor protein gene (APP) (Dugger *et al.*, 2017).

Several proteinopathies are associated with impaired clearance of protein aggregates, and lysosomal instability is a feature of brain aging that reduces clearing efficiency and disrupts the balance between protein synthesis and protein degradation/recycling. This imbalance raises the risk of AD and associated dementias because aberrant accumulations of tau and Aβ-peptide occur before symptoms of memory loss (Almeida *et al.*, 2020).

As lysosome, autophagosome, and autolysosome levels are altered in AD, familial AD and polymorphisms associated with sporadic AD show signs of endo-lysosomal and autophagic abnormalities, respectively. The delayed breakdown of microtubule-based transport mechanisms, slow deposition of pathogenic protein species, and cumulative synaptic loss are all caused by gradual age-related lysosomal instability (Almeida *et al.*, 2020).

i. Amyloid hypothesis

Amyloids are fibrous, insoluble proteins with unique structural properties. Amyloid plaques can take on a variety of morphologies, and they can also be classified as diffuse, dense-cored, classical, or cotton-wool plaques. The most prevalent form of amyloidosis is caused by a proteolytic byproduct of the amyloid precursor protein, also known as amyloid-β (Aβ), which is encoded by a gene on chromosome 21 (Dugger *et al.*, 2017).

Filamentous amyloid-like aggregates are mainly seen in the cytoplasm of neurons and glia in ND. Extracellular amyloid deposits can appear as plaques in the brain parenchyma or as amyloid angiopathy in the blood vessel walls (Dugger *et al.*, 2017).

The amyloid hypothesis was developed when it was realized for many years that dementia and atypical β-sheets deposition in the central nervous system are strongly correlated. However, it was discovered that with age, amyloid plaques (AP) also accumulate in healthy, normal brains, raising the question of whether or not AP deposition is the cause of AD development (Breijyeh *et al.*, 2020).

The amyloid hypothesis, which holds that Aβ deposits in the form of senile plaques play a significant role in the pathogenesis of AD, is the most widely accepted theory. Currently, extracellular neuritic plaques made up of Aβ-peptide deposits and intraneuronal neurofibrillary tangles (NFTs) made up of hyperphosphorylated, aggregated, and often truncated tau protein are the neuropathological hallmarks of AD (Londzin *et al.*, 2021).

According to the amyloid hypothesis, aging or pathological circumstances impair the ability of β- and γ-secretase's to break down Aβ, which results in the buildup of Aβ peptides (Aβ40 and Aβ42). An increase in the Aβ 42/ Aβ 40 ratio causes the creation of Aβ amyloid fibrils (senile plaques), which evokes neurotoxicity and the development of tau pathology, ultimately ending in the death and degeneration of neuronal cells. Senile plaques cause inflammation and microglial cell activation (Breijyeh *et al.*, 2020; Londzin *et al.*, 2021).

Aβ catabolism and anabolism were discovered to be affected by AD risk factors and mutations of multiple genes, including transmembrane amyloid precursor protein (APP), PSEN1, and PSEN2, which quickly lead to a buildup of Aβ and a rapid onset of neurodegeneration (Breijyeh *et al.*, 2020).

Following the development of these plaques across the forebrain, a series of processes culminate in the loss of synapses and neurons, which underlies the memory deficits associated with the illness (Spangenberg *et al.*, 2019).

ii. Tau Hypothesis

Tau is a microtubule-associated protein that is heat-stable and encourages microtubule stability and assembly. It is often found in axons and is strongly expressed in neurons (Gallardo *et al.*, 2019).

Under typical circumstances, the microtubule-binding protein tau is mostly found in the axons of neurons. In a variety of tauopathies, which include AD and other NDs, tau produces paired helical filaments (PHF). Strong evidence supports the idea that tau hyperphosphorylation plays a crucial role in tau pathogenesis by releasing tau from microtubules, allowing it to consolidate and go to the neuronal processes or cell body.

In AD, the tau protein detaches from the microtubules, clusters into tangles, and prevents microtubular transport. This intraneuronal neurofibrillary tangles (NFT), consisting of hyperphosphorylation and aggregation of tau protein results in axonal injury and dysregulation of the neural system (Laurent *et al.*, 2018; Londzin *et al.*, 2021).

NFTs are pathological intraneuronal structures made mostly of the microtubule-associated protein tau (Gallardo *et al.*, 2019).

iii. Cholinergic Hypothesis

The cholinergic system plays a more important role in the development of neuronal plasticity and is crucial for neuronal function in memory, learning, and other crucial elements of cognition, where ACh plays an important role in the brain as it is a substance that nerve cells utilize to interact with each another. Inflammation, neurofibrillary tangles, amyloid-β plaques, oxidative stress, and vascular insufficiency are some of the key pathophysiologic features of AD that combine with dysfunction in cholinergic networks originating from the basal forebrain to impair cognition. The advantages of improving cholinergic function in AD using cholinesterase inhibitors are abundantly documented in clinical literature. Additionally, new MRI-based research is showing evidence of hippocampal protection and, possibly, changes in disease

progression in people who take cholinesterase inhibitors for extended periods of time (Hampel *et al.*, 2018; Kumar *et al.*, 2022).

The production of ACh is carried out by the enzyme choline acetyltransferase (ChAT) in the cytoplasm of cholinergic neurons. The vesicular acetylcholine transporter transports it to the synaptic vesicles (VAChT). Finally, at the synaptic cleft, the opening of the slow channels in the pre-synaptic membrane, which is regulated by depolarization, results in the inflow of calcium ions, which is what causes the release activity. (Stanciu *et al.*, 2019; Breijyeh *et al.*, 2020).

Acetylcholine is released through exocytosis of synaptic vesicles. The slow channels of the presynaptic membrane open as a result of depolarization, which triggers the influx of calcium ions and causes the release activity. This is how the neurotransmitter content of the presynaptic membrane is released into the synapse cleft. The ACh is responsible for the activation both muscarinic and nicotinic receptors on the postsynaptic membrane. (Stanciu *et al.*, 2019).

Acetylcholinesterase (AChE) rapidly breaks down ACh at the synaptic cleft into acetate and choline, which is then reintroduced into the presynaptic nerve terminal via the high-affinity choline transporter (CHT1). AD causes a significant loss of cholinergic neurons in the *nucleus basalis* of Meynert and other basal regions of the forebrain (Ferreira-Vieira *et al.*, 2016).

Cholinesterase inhibitors are one of the few medication treatments that have been shown to be clinically effective in treating AD dementia, establishing the cholinergic system as a key therapeutic target in the disease. They increase the availability of acetylcholine at synapses in the brain (Hampel *et al.*, 2018).

Early diagnosis and its importance

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) first used amnestic symptoms as part of their diagnostic criteria. The criteria were amended in 2011 to incorporate a broader range of clinical phenotypes due to the relatively poor sensitivity of the previous criteria when contrasted with underlying pathology and the

growing awareness of "atypical" non-amnestic presentations of Alzheimer's disease, all depicted in the charts shown in figure 3, 4 and 5 (McKhann *et al.*, 2011).

With the appearance of amyloid PET imaging, a significant fraction of elderly people who are still cognitively healthy and symptom-free (referred to as "asymptomatic at risk for AD") can now be identified as having fibrillar amyloid, one of the neuropathological markers of the disease. Similarly, asymptomatic, functional people have been shown to have lower levels of cerebrospinal fluid (CSF) Aβ and can be classified as healthy, meaning that they may or may not continue to meet the clinical diagnostic criteria for AD (Dubois *et al.*, 2010).

Individual susceptibility may affect this development, including genetic variables (such as the APOE genotype), other risk or protective factors (such as vascular factors, nutrition, etc.), and comorbidities (eg, diabetes). The risk of AD in asymptomatic people with Aβ positive and tau-biomarkers will be clarified by broader follow-up investigations (Dubois *et al.*, 2010).

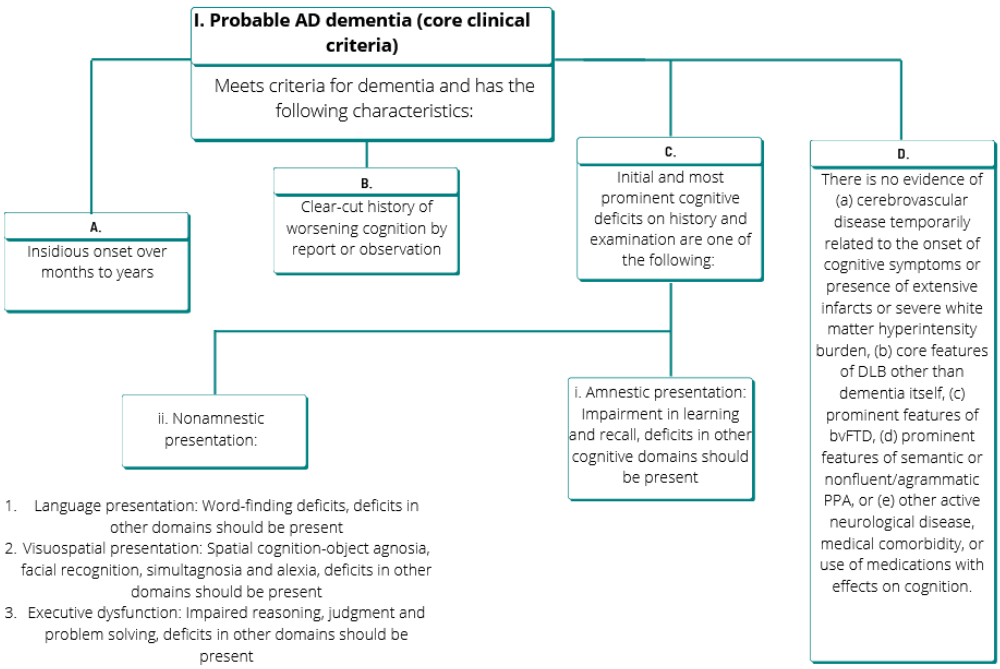

Figure 3 Clinical diagnostic criteria for Alzheimer's disease (part 1) - Adapted from (McKhann et al., 2011); Note: DLB: Dementia with Lewy Bodies, bvFTD: behavioral variant of Frontotemporal Dementia, PPA: Primary Progressive Aphasia (language disorder)

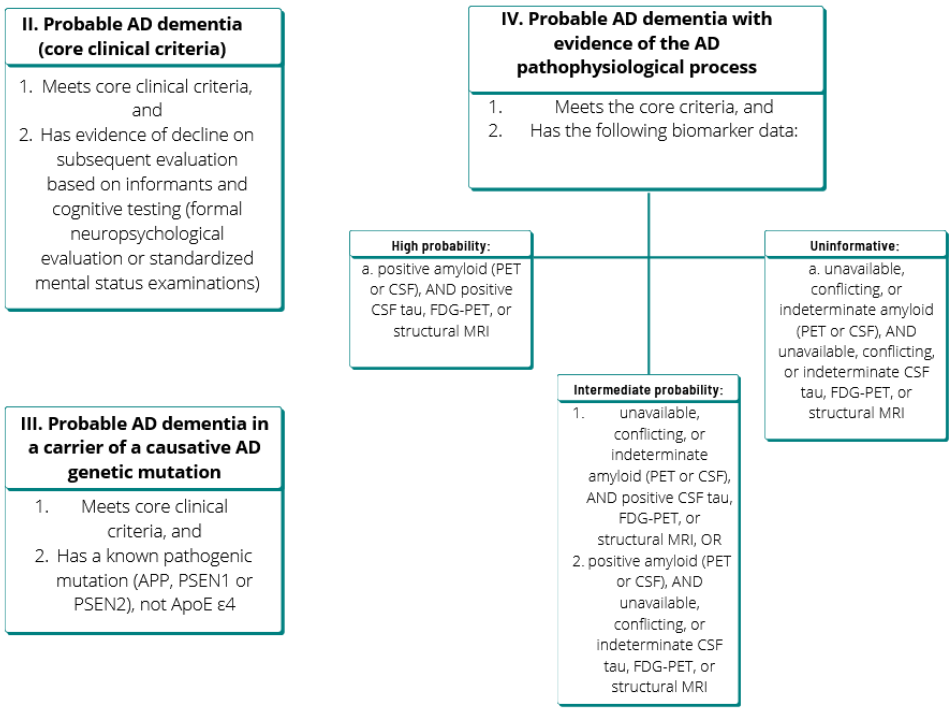

Figure 4 Clinical diagnostic criteria for Alzheimer's disease (part 2) - Adapted from (McKhann et al., 2011); Note: CSF: Cerebrospinal Fluid, FDG-PET: Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET), MRI: Magnetic Resonance Imaging

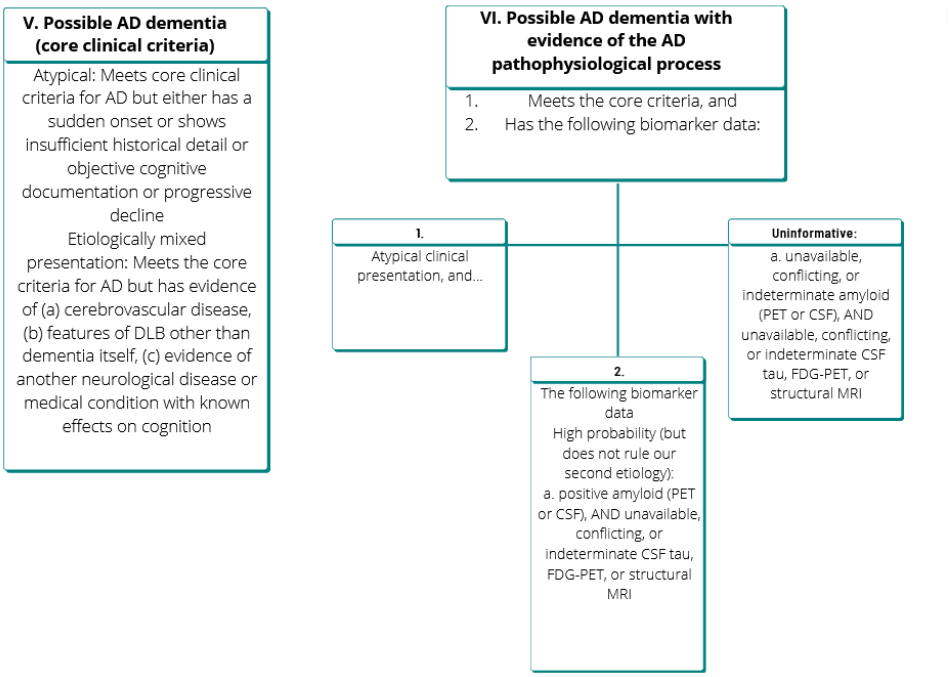

Figure 5 Clinical diagnostic criteria for Alzheimer's disease (part 3) - Adapted from (McKhann et al., 2011) Note: CSF: Cerebrospinal Fluid, FDG-PET: Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET), MRI: Magnetic Resonance Imaging

Pharmacological therapies

Currently, there are no pharmacological treatments for AD that have been shown to effectively change the course of the disease. Therefore, the goal of medical therapy of AD is to reduce patient symptoms and maximize both patients and caregivers' quality of life (Erkkinen *et al.*, 2018; Breijyeh *et al.*, 2020).

As previously noted in the chapter "The Nervous System & Human Brain," the BBB poses a significant barrier to effective delivery of therapeutic substances at the brain level by imposing size and biochemical restrictions on the flow of molecules. Numerous methods have been tested over the years to cross the BBB, but all have been severely restricted by a lack of specificity, safety concerns, and an inability to deliver sufficient concentrations of released chemicals to the right amounts of brain tissue. Furthermore, according to the vascular hypothesis of AD, the fundamental insult is the degeneration of the blood arteries, which results in the malfunction of BBB and decreased brain perfusion, which in turn causes neuronal injury and the accumulation of Aβ in the brain (Stanciu *et al.*, 2019).

The BBB functions as a dynamic interface between the CNS and peripheral tissues, and drugs are now being developed with the goal of targeting this barrier as a therapeutic target to treat neuropsychiatric disorders such as AD. As a result, controlling BBB function may be a potential therapeutic focus for the treatment of AD (Stanciu *et al.*, 2019).

Only two groups of drugs have been authorized for this purpose: cholinesterase enzyme inhibitors (AChEIs) and N-methyl D-aspartate receptor (NMDAR) antagonists. Recently there has been a new authorized drug called, aducanumab, a monoclonal antibody that targets Aβ (Breijyeh *et al.*, 2020; Padda *et al.*, 2022).

Typically, cholinesterase inhibitors (donepezil, rivastigmine patch, or galantamine) should be the first pharmaceutical treatment. These are recommended for the treatment of AD in the early and moderate stages; since the effect is less obvious in the more advanced condition (Soria Lopez *et al.*, 2019).

Patients with AD have lower levels of acetylcholine (ACh), a neurotransmitter that is extensively distributed and is thought to improve cognition. The destruction of ACh

producing cells by a series of physiological mechanisms in AD decreases cholinergic transmission in the brain. ACh levels in the synaptic cleft are elevated as a result of cholinesterase enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) being prevented from degrading ACh by AChEIs, which are categorized as reversible, irreversible, and pseudo-reversible. Drugs such as donepezil, rivastigmine, and galantamine belong to the AChEIs category and are linked to cognition improvement (Erkkinen *et al.*, 2018; Breijyeh *et al.*, 2020).

On the other hand, excessive NMDA activity increases Ca^{2+} influx, which encourages synaptic dysfunction and cell death. The NMDAR antagonists restores normal activity of NMDA-type glutamate receptors, preventing overactivation, which in turn reduces Ca^{2+}influx. In moderate to severe AD, memantine is authorized as a stand-alone therapy or as a supplement to cholinesterase inhibitors. It can be used as a first-line therapy for severe diseases and may be useful in the managing behavioral problems (Erkkinen *et al.*, 2018; Soria Lopez *et al.*, 2019; Breijyeh *et al.*, 2020).

For mood, behavior, and sleep, SSRIs (selective serotonin reuptake inhibitors) or certain tricyclic antidepressants are recommended. It is best to avoid medications with potent anticholinergic effects. As a first line of treatment, the use of pure SSRIs such as escitalopram is suggested; however, the sedative effects of other SSRIs such as trazodone or mirtazapine may be useful in treating mood and sleep problems concurrently (Soria Lopez *et al.*, 2019).

In general, neuroleptics and antipsychotics should be avoided. Traditional drugs are more recommended than atypical ones such as quetiapine, risperidone, and olanzapine as well as benzodiazepines should be avoided (Soria Lopez *et al.*, 2019).

Table 2 Summary of currently available symptomatic therapies in Alzheimer's disease - Adapted from (Soria Lopez et al., 2019); Note: XR: extended-release

Name	Metabolism	Starting dose	Min dose	Max dose	Benefits
Donepezil	Hepatic	5 mg once daily	5 mg once daily	23 mg once daily	Cognitive, functional, and behavioral
Rivastigmine (oral)	Renal	1.5 mg twice daily	3 mg twice daily	6 mg twice daily	Cognitive, functional, and behavioral
Rivastigmine (transdermal)	Renal	4.6 mg/day	9.5 mg/day	13.3 mg/day	Cognitive, functional, and behavioral
Galantamine XR	Hepatic	8 mg once daily	16 m once daily	24 mg once daily	Cognitive, functional, and behavioral
Memantine	Renal	5 mg daily	10 mg daily	20 mg daily	Cognitive, functional, and behavioral
Memantine XR	Renal	7 mg once daily	14 mg once daily	28 mg once daily	Cognitive, functional, and behavioral

Cholinesterase Inhibitors

One of the treatment approaches that improves cognitive and neural cell performance is considered to be increasing cholinergic levels by suppressing AChE. Decreased ACh levels at synapses are prevented by AChEIs, leading to a continuous accumulation of ACh and cholinergic receptor activation. Tacrine, which works by increasing ACh in muscarinic neurons, was the first cholinesterase inhibitor drug approved by the FDA for the treatment of AD but was removed from the market shortly after its introduction due to a high incidence of side effects such as hepatotoxicity and a lack of benefits, which were observed in several trials. Later, several AChEIs were developed, including donepezil, rivastigmine, and galantamine, and these are now used to treat AD symptoms (Breijyeh *et al.*, 2020).

Increasing choline reuptake and, as a result, the production of ACh at presynaptic terminals, may be another method to treat AD. This can be done by targeting the choline transporter (CHT1), which provides choline for the production of ACh. The future of

AD treatment may lie in creating drugs that can raise CHT1 in the plasma membrane (Breijyeh *et al.*, 2020).

ChEIs are dosed in two stages during AD therapy: the first dose-escalation phase, which is used to achieved a therapeutic dose, and the maintenance phase, which is used to maintain the therapeutic level for the duration of treatment. In individuals with mild to severe AD, ChEIs may subtly postpone the loss of brain function.

Donepezil is effective at treating AD at all stages. MCI and dementia stages are authorized for treatment with galantamine and rivastigmine. Galantamine and donepezil are AChEIs that work rapidly and reversibly. Rivastigmine inhibits AChE and BChE slowly and irreversibly. Due to its single dose, donepezil is typically recommended above all others. The extended-release capsule or twice-daily tablet forms of galantamine are both readily accessible. In cases of severe liver failure or end-stage renal disease, it cannot be utilized. Both transdermal and oral forms of rivastigmine are available. With cholinesterase inhibitors most frequent adverse effects are gastrointestinal nausea, vomiting, and diarrhea. With donepezil, sleep disturbances are more frequent. Patients with significant heart conduction problems should not use these drugs (Kumar *et al.*, 2022).

Due to cholinergic activation in various areas of the brain and the periphery, these substances can also cause a range of adverse effects. All ChEIs with the dual AChE and BuChE activity fall into the category of centrally mediated acute gastrointestinal events, which are typically reported during the dose-escalation phase of treatment. Instead, by administrating them with food and employing moderate dosage escalation with mild dose gradations, adverse effects can be reduced (Stanciu *et al.*, 2019).

Adverse effects of ChEIs include central nervous system events, extrapyramidal events, sleep problems and cardiorespiratory disruption associated to cholinergic action in the cortex, caudate nucleus of the basal ganglia, brainstem, and medulla, cardiorespiratory symptoms, and urine incontinence in relation to peripheral cholinergic activity (Stanciu *et al.*, 2019).

Going on detail of the cholinesterase inhibitors (donepezil, rivastigmine and galantamine):

i. Donepezil

The most effective drug for treating AD is donepezil, a member of the second generation of AChEIs. A higher concentration of ACh is present at the synapses as a result of donepezil's reversible binding to acetylcholinesterase and inhibition of acetylcholine hydrolysis. The drug is well-tolerated, with only minor and temporary cholinergic side effects that affect the neurological and gastrointestinal systems. Notably, donepezil is utilized to treat AD symptoms including cognition and behavior improvement without affecting how AD develops (Breijyeh *et al.*, 2020).

Once we understand the mechanism by which cholinesterase inhibitors (donepezil, rivastigmine patch, or galantamine) work, let's talk about each of the drugs individually.

ii. Rivastigmine

Rivastigmine is a butyrylcholinesterase (BChE) and AChE pseudo-irreversible inhibitor. It works by binding to the two active sites of AChE (anionic and estearic sites), which stops ACh metabolism. In the healthy brain, BChE is mostly located in glial cells, where AChE activity is only 10%. However, in the AD brain, BChE activity is elevated to 40–90% while ACh activity is simultaneously decreased, suggesting that BChE activity may be a sign of mild to severe dementia. The medication is used in situations of mild to severe AD (Breijyeh et al., 2020).

Most AD patients have difficulty to swallow and remembering things, which makes it difficult for them to take their oral medications on time. Therefore, the best way to deliver the medication to AD patients is through transdermal patches (Breijyeh *et al.*, 2020).

iii. Galantamine

For mild to severe AD patients, galantamine (GAL) is regarded as a conventional first-line medication. AChE is competitively inhibited by the selective tertiary isoquinoline alkaloid GAL, which also has the ability to bind allosterically to a specific subunit of nicotinic acetylcholine receptors and activate them. Similar to other AChE inhibitors, GAL has high effectiveness and tolerability and can reduce behavioral symptoms and enhance daily activities, cognitive performance, and mood (Breijyeh *et al.*, 2020).

N-*methyl D-aspartate Antagonists*

NMDAR is thought to play a prominent role in the pathophysiology of AD. Ca^{2+} influx caused by NMDAR activation promotes signal transduction, which in turn causes gene transcription necessary for the development of a long-term potentiation (LTP), which is crucial for synaptic neurotransmission, plasticity, and memory formation. The main excitatory amino acid in the CNS, glutamate, is overstimulated by excessive NMDA receptor activation, which leads to excitotoxicity, synaptic malfunction, neuronal cell death, and loss of cognitive abilities. Numerous NMDAR uncompetitive antagonists have been created and tested in clinical trials, however most of them were ineffective and had undesirable side effects (Breijyeh *et al.*, 2020).

i. Memantine

Memantine is a low-affinity, non-competitive antagonist of the NMDA-type glutamate receptor that inhibits overactivation of the glutaminergic system, which is a contributing factor to neurotoxicity in AD patients. Memantine is used alone or in combination with AChEI to treat mild to severe AD. Due to memantine's low affinity, which is rapidly displaced from the NMDAR by high glutamate concentrations, the drug is safe and well-tolerated and blocks the excitatory receptor without interfering with normal synaptic communication, preventing a chronic blockage. The latter is linked to serious adverse effects, particularly those affecting memory and learning (Breijyeh *et al.*, 2020).

Aducanumab (Aduhelm™)

A monoclonal antibody of human immunoglobulin gamma 1 (IgG1), aducanumab is a recently authorized immunotherapeutic drug. Through the BBB, it specifically targets and binds aggregated soluble oligomers and insoluble fibrils conformations of Aβ plaques in the brain, hence exerting its mode of action. Aducanumab has changed from the previous one, in which it was recommended for all patients with AD. Whether it is safe or effective to introduce β-amyloid antibody-directed early in the disease course has not been investigated or documented. Based on patients who had moderate cognitive impairment or mild dementia associated with AD and showed a decrease in Amyloid-β plaques, the FDA granted an expedited clearance for aducanumab in 2021 (Padda *et al.*, 2022).

With regard to single-dose vials for intravenous (IV) infusion delivery, aducanumab is now offered as a clear to opalescent and colorless to yellow solution. Aducanumab should be diluted with 100 mL of 0.9% sodium chloride injection before being administered as an infusion based on the subject's body weight per kilogram (kg). Additionally, it is advised that the diluted agent solution be warmed to room temperature before therapy initiation and delivered immediately. After administration of aducanumab, unused diluted parts should be discard (Padda *et al.*, 2022).

Non-Pharmacological therapies

Stem cell therapy

Alzheimer disease and others neurodegenerative diseases currently have no cure but new research shows that, stem cell transplantation has great potential to replace damaged brain cells with healthy cells, differentiating into neurons and glia or releasing cellular cytokines that stimulate endogenous neurogenesis. Few trials have so far yielded encouraging results, indicating that many elements of stem cell need to be taken. Therefore, in addition to gaining a deeper understanding of the processes behind the pathophysiology of AD that control the survival, proliferation, migration, differentiation, and functionality of transplanted stem cells, we also need to apply the findings of animal research to human clinical trials (Han *et al.*, 2020).

Hyperbaric oxygen therapy

A pressurized treatment chamber is pressurized to a pressure higher than absolute atmospheric pressure in order to deliver 100% oxygen. This procedure is known as hyperbaric oxygen therapy (HBOT) (Somaa, 2021).

By saturating hemoglobin and plasma with oxygen, stimulating angiogenesis, and attracting progenitor cells to areas of injured tissue, HBOT exerts mechanical and physiological effects that lead to tissue hyperoxia. The main mechanism of action of HBOT is through an increase in neuroprotection and a decrease in neuroinflammation, oxidative stress, and neuronal apoptosis. Through decreased tau protein phosphorylation and a general decrease in amyloid load, HBOT induces changes at cellular level. The improvement of memory, cognitive, and motor abilities in human patients as well as

memory and cognitive ability in animal models are examples of therapeutic effects (Somaa, 2021).

Dietary supplements

Omega-3 Fatty Acid Supplements

The most reliable positive results from research into the nutritional and dietary components examined to preventing cognitive decline in older people are for omega-3 fatty acids, which are often assessed on the amount of fish is eaten in the diet. Omega-3 polyunsaturated fatty acid supplements have not been shown to be significantly more effective than placebo in treatment of mild to moderate AD, according to multiple high-quality evaluations (NCCIH, 2022).

Curcumin

Curcumin directly affects amyloid aggregation, as well as inflammatory and antioxidant mechanisms, according to preclinical research. However, the small number of clinical studies that have looked at how curcumin affects AD are inconsistent, making it difficult to draw conclusions about possible benefits (NCCIH, 2022).

B vitamins

Studies conducted over a short period of time showed that B vitamin supplements (B12, B6, and folic acid) had no positive effects on cognitive performance in people aged 50 years or older, with or without dementia. However, a meta-analysis of 95 longer-term (more than 12 months) trials found a possible link between taking more B vitamins and slowing cognitive aging (NCCIH, 2022).

A vitamin B-like component called choline is present in many daily meals and is crucial for a number of cellular processes. Acetylcholine also has choline as a precursor. In animal models, lifetime choline supplementation significantly reduced the amount of amyloid plaques and improved spatial memory. This was mainly due to less amyloid processing of APP and less disease-related microglial activation (Velazquez *et al.*, 2019).

4.2. Other Neurodegenerative Diseases

Parkinson’s disease

The only neurodegenerative disease that is more common than Parkinson’s disease is Alzheimer’s disease. Its motor symptoms, such as tremor, bradykinesia (slow movements), and akinesia (absence of movement), are what most distinguish it, but it can also show non-motor symptoms such dysautonomia (ANS failure), depression, anxiety, and cognitive deterioration. Dopaminergic drugs or, more recently, deep brain stimulation are the main methods to treat motor symptoms (Hayes, 2019).

Lewy Body Disorders

Parkinson’s disease dementia and dementia with Lewy bodies are the two clinical conditions that constitute Lewy Body Dementia (LBD). Dementia, psychosis, and parkinsonian symptoms are all characteristics of this progressive degenerative brain disease. Symptoms change over time and vary from person to person. After Alzheimer's disease and vascular dementia, it is the third most prevalent kind of dementia. It is distinguished by the accumulation of Lewy bodies, which are intraneuronal cytoplasmic inclusion bodies with alpha-synuclein and ubiquitin aggregates, in the brain.

Multiple Sclerosis

MS is a demyelinating autoimmune disease of the CNS characterized by the infiltration of immune cells from the periphery into the CNS as well as activation of the microglia and astrocytes, which together promote neuroinflammation and neurodegeneration (Piancone *et al.*, 2021)

Prion Diseases

Prion diseases, also known as transmissible spongiform encephalopathies, are a group of uncommon, progressive NDs that can affect both people and animals (CDC, 2021).

The name "prions" refers to aberrant, pathogenic substances that are contagious and have the ability to cause the improper folding of specific normal cellular proteins known as prion proteins, which are mostly present in the brain. Prion diseases often progress rapidly and are invariably deadly (CDC, 2021).

Chronic traumatic encephalopathy

As a main tauopathy, chronic traumatic encephalopathy is distinguished from other tauopathies by the fact that its etiology has been linked to repeated concussions or sub concussions. As it is linked to recurrent brain trauma from contact sports and can cause dementia, this disorder has gained more and more attention (Dugger *et al.*, 2017).

V. CONCLUSION

Our life expectancy has been increased due to research on healthy aging and longevity, which also promises to lessen the burden of degenerative diseases, which will have significant social and economic repercussions.

Important aging pathways have been found, and several aging hypotheses have been put forth. It is still unclear in most of neurological diseases whether these abnormalities in cell death are the true cause of the disease, or at least a significant contributing factor, or if they are merely the result of some tissue injury, in which case even effectively blocking this cell death would not improve treatment.

Neuroplasticity is a ongoing process that includes learning and memory functions. It involves the complex response of neurons to endogenous and external stimuli. Changes in synaptogenesis, remodeling of the synaptic, axonal, and dendritic structures, and the production of new neurons are all examples of the morphological and functional exchanges that make up neuroplasticity (neurogenesis).

The hippocampus, neocortical regions, and cholinergic basal forebrain neurons, which are involved in the regulation of higher brain functions, such as learning, memory, and cognition, maintain a high level of plasticity throughout all life stages. All brain tissues are associated with neuroplasticity.

The restoration of synaptic circuitry by the adult CNS is limited, but successful, and its effects on cognition are still debatable. Furthermore, NDs appear to include processes that control neuroplasticity.

The most frequent cause of dementia, a term that encompasses memory loss and other cognitive impairments severe enough to interfere with daily life, is Alzheimer's disease. Why is Alzheimer’s disease such an important issue? No other disease is experiencing such a steep increase in population.

There is now neither a cure nor a drug to slow the course of Alzheimer’s disease. The most significant feature of the disease is neuronal death and loss of cognitive abilities, which are likely the result of various degenerative processes in the brain, including changes in synaptic activity, inflammation, and energy metabolism.

It has been extensively researched how nutrition, exercise, and other lifestyle choices affect cognitive performance, and there is growing evidence that these variables play a part in the onset of dementia and cognitive decline.

Furthermore, the design of various pharmacological drugs has been long-established to counteract the worsening effects of AD on a person's cognitive and memory abilities.

Among the ChEIs with standard drug approval to block the hydrolytic action of AChE on ACh and improve the cholinergic system are galantamine, rivastigmine, and donepezil. Memantine, on the other hand, specifically targets the NMDA glutamate receptor to block intracellular calcium (Ca2+) influx and the ensuing excitotoxicity that results in AD-related neuronal degeneration.

The most promising drug for AD during the past ten years has been aducanumab. Despite the controversies surrounding this drug, it is undeniable that aducanumab considerably decreases brain levels of amyloid plaques, a feature of AD. The results also showed that aducanumab reduces the amount of tau in the brain, the second trait of AD. The most efficient method to develop a truly disease-modifying drug for this epidemic of our century may be to target AD in several routes.

Despite having great potential, stem cell treatment of AD is still in the research and development stage. Preclinical research now reveals the underlying treatment processes and provides proof of concept. Clinical trials have examined stem cell treatment. The basis for the next therapeutic treatment of AD patients has been set by the collection of research data. In a therapeutic approach that includes cell alteration, gene manipulation, and pharmaceutical intervention, perhaps the synergy of many approaches can be used. More time will be needed before any judgments can be made about the efficacy of stem cell treatment in AD patients.

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