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# Evaluation of Amyloid Plaques in the Nervous System of Alzheimer's Patients with Reference to Non-Pharmacological Treatments in Patients

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## Abstract

In this study, the assessment of amyloid plaques in the nervous system of Alzheimer's patients has been investigated. Alzheimer's disease is the most common cause of dementia and is associated with high mortality in the elderly. In the current study, by reviewing more than 70 articles and searching for the words amyloid plaques, nervous system, Alzheimer's, non-drug treatments, it was concluded that swelling is caused by the accumulation of lysosomes. Lysosomes are small garbage bag-like compartments made by cells to break down waste products and hold them until they can be eliminated. These lysosomes attach to spherical structures along the axons of brain cells. These swellings are thought to disrupt the ability of brain cells to conduct electrical signals that are essential for forming and consolidating memories. Today, 47 million people worldwide are suffering from this disease, 13% of people over 65 years old and 45% of people over 85 years old are in this group. It is predicted that by 2050, one person will be diagnosed with this disease every 33 seconds and the total number of new cases will reach one million people every year. The main (and now controversial) hypothesis is that amyloid plaques (protein deposits) in the brain play a major role in the development of this disease; But the drugs that target these plaques have given uncertain results in clinical trials. Amyloid beta is a protein of 36 to 43 peptides and the main builder of amyloid plaques found in the brains of people with Alzheimer's disease. Also, the results showed that a protein called PLD3 (the protein encoded by the PLD3 gene) is highly expressed in globular proteins. Mice engineered to lack the PLD3 gene did not produce lysosome accumulation and had less swelling on their neurons. High levels of PLD3 occasionally lead to lysosomal swelling even in healthy mice. However, it was more pronounced in globular proteins located near amyloid plaques in Alzheimer's mice, indicating that the process of swelling is associated with amyloid plaques.

**Key words:** Amyloid Plaques, Nervous System, Alzheimer's Patients, Less Swelling.

## Introduction

Although the cause of Alzheimer's disease has not been fully identified, the amyloid cascade hypothesis seems to be the main cause of this disease [1-3]. It is believed that the imbalance between the production and clearance of amyloid beta proteins in the brain and the subsequent disruption of synaptic function and degeneration of neurons is the main cause of progressive and irreversible memory impairment and affects the power of speech, personality and cognition [4].

A newly published study suggests that this condition may be directly linked to circadian rhythms. This finding may lead to a new preventative treatment, one that this time might actually work. Jennifer Hurley of Rensselaer Polytechnic Institute, who led the study, said in a press release that it may be possible to understand how our circadian rhythm can regulate cell-surface heparin levels to control the build-up of amyloid beta led to the development of a new treatment that reduces the symptoms of Alzheimer's disease as well as other inflammatory diseases [5]. Their study showed that the immune cells responsible for clearing a key protein that accumulates in the brains of Alzheimer's patients operate in accordance with daily circadian rhythms, the same 24-hour cycles that control many elements of human physiology [6-8].

This key finding may lead to a potential explanation for the link between Alzheimer's disease and disruption of a person's sleep cycle [9], as previous studies have shown that sleep disturbances can be early signs of Alzheimer's, starting years before symptoms appear, and a sign of higher risk. The new study evaluated the activity of immune cells responsible for clearing proteins called amyloid beta, which build up as plaques in the brains of people with Alzheimer's [10-12]. Scientists have discovered that immune cells clear "Amyloid-beta" in a cycle determined by the circadian rhythm. Any defect in this rhythm leads to the disappearance of this daily



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cycle, resulting in an increase in the accumulation of dangerous "Amyloid-beta" proteins in the brain. Therefore, the scientists deduced that there is a molecular mechanism that is potentially responsible for the connection between Alzheimer's disease and circadian rhythms and plays a key role in the development of this disease [13-15]. Amyloid beta, abbreviated as "Aβ" or "Abeta", is a 36 to 43 amino acid peptide and the main constituent of amyloid plaques found in the brains of people with Alzheimer's disease. These peptides are derived from "amyloid-beta precursor protein" (APP), which is broken down by "Beta-secretase 1" and "Gamma-secretase" enzymes, and amyloid-beta is obtained. Aggregation of amyloid beta molecules forms a type of flexible soluble oligomer that can be found in various forms [16-18]. It is now believed that some misfolded oligomers, called "Seeds" or "Microbeads," cause another amyloid-beta molecule to miss fold, and a chain reaction similar to that seen in prion infections occurs [19]. These oligomers are toxic to nerve cells. Another protein involved in the development of Alzheimer's disease, which is called "Tau protein", forms prion-like misfolded oligomers, and there is even evidence that misfolded amyloid beta can cause tau protein to fold and miss fold [20-22]. According to a 2013 study, it is possible that the origin of the amyloid-beta precursor protein is very ancient and dates back to the early Domian period [23]. The research is still in its early stages, but the findings already show the potential. If the daily clearance of "Amyloid beta" proteins can be maintained and stabilized, patients will be less likely to develop this disease, or at least avoid experiencing more severe symptoms [24].

Amyloid plaques are composed of the accumulation of amyloid beta proteins, which are derived from a parent protein called amyloid precursor protein [25]. Three types of secretase enzymes (alpha, beta and gamma) break down the amyloid precursor protein into soluble components. In case of inappropriate breakdown of this protein by beta and gamma secretase enzymes, insoluble beta amyloid proteins are formed [26], which accumulate in the brain and lead to the formation of amyloid plaques, brain toxicity and cell death. Intra neuronal interwoven filaments consist of filaments containing the phosphorylated form of tau proteins [27]. Tau proteins naturally contain phosphate molecules [28]. In Alzheimer's disease, these proteins are excessively phosphorylated and this leads to their twisting around each other and the formation of insoluble tangles, and as a result of this, the presence of macrophages and mononuclear cells in the cerebral cortex and the activation of microglia in the parenchyma [29]. Dementia and atrophy of the frontal-temporal cortex follows. Although neuropathology experts believe that amyloid plaques and inter-neuronal entwined fibers are the most important cause of Alzheimer's disease [30], there are other predisposing factors that will be discussed below;

- In some families, genetic mechanisms have been identified for the occurrence of this disease, among which we can refer to the e-4 allele of Apo lipoprotein E [31]. Apo lipoprotein E plays an important role in breaking down and cleaning the amyloid precursor protein, and it seems that e-4 carriers do not have the necessary ability to clean the products resulting from the breakdown of this main protein [32], and as a result, the production and accumulation of beta proteins in the body increases [33].
- Inflammation of the nerve is an important factor as the cause of the disease as well as the result of the disease. Probably, the production of plaques and interwoven threads occurs to some extent in connection with the inflammatory process caused by aging [34]. The production of plaques and interwoven threads causes inflammation and accelerates the formation of subsequent plaques and deterioration of cognition [35].

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n the current study, by reviewing more than 70 articles and searching for the words amyloid plaques, nervous system, Alzheimer's, non-drug treatments, it was concluded that swelling is caused by the accumulation of lysosomes. Lysosomes are small garbage bag-like compartments made by cells to break down waste products and hold them until they can be eliminated. These lysosomes attach to spherical structures along the axons of brain cells. These swellings are thought to disrupt the ability of brain cells to conduct electrical signals that are essential for forming and consolidating memories.

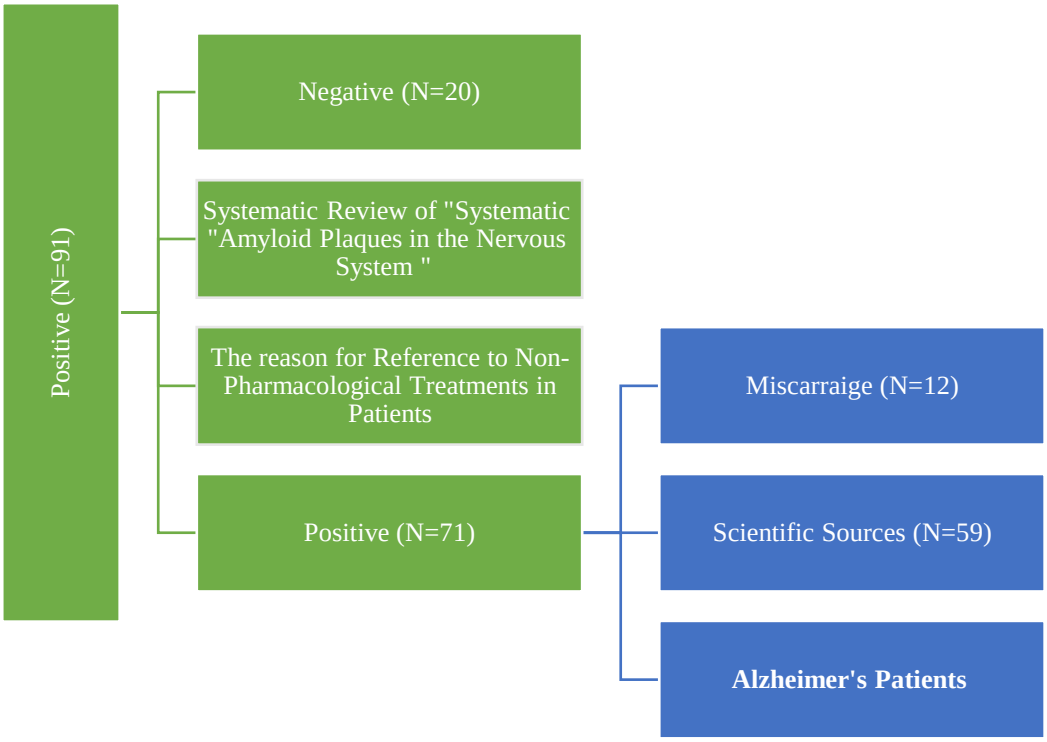


**Figure 1. Flow chart of included subjects**

**Acquired risk factors**

In a third of the known cases of the disease, in a statistical analysis, factors such as diabetes, high blood pressure, obesity [36], physical inactivity [37], depression [38], smoking [39], and low education level are modifiable risk factors that predispose a person to Alzheimer's disease [40]. have been reported. Different genetic and acquired factors can increase the risk of Alzheimer's disease, among which we can mention lipid disorders, cerebrovascular disease, changes in sugar metabolism, and brain trauma [41-43]. Many of these risk factors are more related to the occurrence of Alzheimer's when they occur in middle age. Strict management of vascular factors in middle age is a key strategy to reduce the risk, progression and severity of Alzheimer's disease and other forms of dementia [44].

**High blood pressure**

In cross-sectional studies and long-term cohort studies, high blood pressure in middle age is always associated with the risk of Alzheimer's disease and dementia. This risk is caused by cerebrovascular diseases and the long-term effect of high blood pressure, and this risk increases in the presence of diabetes and smoking. This relationship is stronger in women than in men, although this is not true in all cases. Arterial stiffness and blood pressure fluctuations play an important role in the relationship between blood pressure and the risk of Alzheimer's disease [45]. Arterial stiffness increases with age and blood pressure levels, diabetes and smoking. In a case cohort study, arterial stiffness (independent of blood pressure level and Apo lipoprotein E genotype) was directly associated with amyloid-beta plaque deposition. While observational studies show that hypertension treatment reduces the risk of dementia, clinical trials of hypertension treatment do not always report a reduction in this risk, but it is noteworthy that most of these trials have examined short-term outcomes and Long-term treatment of high blood pressure (especially in middle age) may alter the risk of developing Alzheimer's disease later in life [46].

**Fat disorders**

Although some epidemiological studies have suggested a relationship between the level of total cholesterol and low-density lipoprotein cholesterol with the risk of Alzheimer's disease, these studies are difficult to interpret [47]. Low-density lipoprotein cholesterol in the peripheral blood does not have the ability to cross the blood-brain barrier unless this barrier is damaged by factors such as vascular diseases. Most of the cholesterol in the brain is made by stellate cells and neurons and is supplied to brain cells by high-density lipoprotein, and low-density lipoprotein cholesterol in the brain is either very little or absent [48]. However, observational data

support an association between total cholesterol and low-density lipoprotein cholesterol levels and the risk of Alzheimer's disease [49].

In a long-term cohort study, there was a three-fold increase in the risk of Alzheimer's disease in middle-aged patients with high total cholesterol levels, with a mean age of approximately 50 years, independently of Apo lipoprotein E genotype, education level [50], smoking, and alcohol consumption [51]. Regarding the relationship between total blood cholesterol levels in old age and the possibility of Alzheimer's disease, there are conflicting data available, and in some studies, there is a direct relationship, in some studies, an inverse relationship between these two variables, and in some studies, there is no clear relationship [52]. Also, in Alzheimer's patients, increased levels of total cholesterol and low-density lipoprotein cholesterol have been associated with more cognitive disorders [53]. It is thought that cholesterol in the brain increases the risk of Alzheimer's disease by increasing the formation or deposition of amyloid beta proteins or by affecting other non-amyloid factors such as cerebrovascular problems, local inflammation and the metabolism of tau proteins. Based on these data, research has led to the use of blood cholesterol-lowering drugs to prevent Alzheimer's disease [54]. Randomized trials have not been successful in proving the protective effects of statin drugs on cognition in cardiovascular patients or in people at high risk of cardiovascular disease. Oral statin drugs have not had a positive effect in reducing the rate of cognitive decline in patients with mild-moderate Alzheimer's disease [55].

**Cerebrovascular diseases**

This group of diseases is associated with Alzheimer's disease, and the simultaneous presence of Alzheimer's disease with vascular problems is called mixed dementia. Cerebral small vessel diseases are more common in old age and are related to factors such as high blood pressure, diabetes, smoking, obesity, low physical activity, and lipid disorders [56]. Decreased blood flow before the deposition of amyloid beta protein has been shown in Alzheimer's mouse models, and human studies confirm the accumulation of amyloid proteins as a result of their clearance disorder. In a cohort case study, it was shown that decreased cerebral blood flow and white matter disorders were associated with an increased risk of Alzheimer's disease [57]. In autopsies performed on patients with Alzheimer's disease, vascular pathology is found in 35-50% of patients with Alzheimer's disease. On the other hand, one third of patients with a definitive diagnosis of vascular dementia at autopsy show disorders related to Alzheimer's disease [58]. If the pathological findings do not confirm Alzheimer's disease, the presence of large strokes and lacunas with a higher probability can confirm the diagnosis [59].

The genotype e-4 of Apo lipoprotein E is associated with an increased risk of Alzheimer's disease and cardiovascular problems [60]. In one study, in Apo lipoprotein E allele-4 carriers, the severity of coronary artery disease was clearly related to the increased density of neurological-pathological findings of Alzheimer's disease. In another study, the association of the e-4 allele of Apo lipoprotein E with capillary changes in the subcortical area in patients with Alzheimer's disease was proven [61], but these changes were not in favor of extensive cerebrovascular damage. Cerebrovascular disease is associated with worse cognitive function in patients with Alzheimer's disease, and clinical-pathological studies show that these diseases reduce the threshold of dementia in patients diagnosed with Alzheimer's disease [62].

**Medicines**

Many studies have confirmed the existence of a relationship between the use of different drug categories such as benzodiazepine drugs, drugs with anticholinergic effects or side effects, antihistamine drugs and opioid drugs and the occurrence of cognitive disorders in the elderly. But in most cases, it has been mentioned that these effects are transient and reversible. Long-term exposure to these drugs has been associated with an increased risk of Alzheimer's disease and other types of dementia in many studies [63]. These studies also state that the cognitive effects caused by drugs may not be reversible in some patients, or that this long-term exposure may cause the progression of Alzheimer's disease from the asymptomatic or initial stage of symptoms to the symptomatic stage. Some of these types of drugs are mentioned below [64].

**Benzodiazepine drugs**

Conflicting data are available regarding the relationship between the use of this drug class and the risk of dementia. In a case-control study including 2000 elderly people, after adjusting for several intervening variables such as anxiety, depression and insomnia, receiving benzodiazepine drugs for more than 180 days was associated with an increased risk of Alzheimer's disease by 1.5 times, on the other hand, the relationship dose-response, an increase in the rate of complications with an increase in the duration of receiving the drug and an increase in the incidence of complications with an increase in the half-life of the drug were also reported [65]. It is possible that benzodiazepine drugs are used to treat the early symptoms of Alzheimer's disease. Therefore, the

researchers set the condition of entering the study on people who have been prescribed this drug class at least 5 years before the diagnosis of Alzheimer's disease. Other large studies failed to show a link between long-term use of benzodiazepines and the occurrence of dementia [66].

**Drugs with anticholinergic effects or side effects**

In a prospective study, including a seven-year review of more than 3400 elderly patients who did not have dementia at the beginning of the study, high cumulative doses of anticholinergic drugs increased the risk of dementia. The most common anticholinergic drugs used by patients included tricyclic antidepressants, first-generation antihistamines, and anti-muscarinic effective in the bladder [67].

**Proton pump inhibitors**

As with benzodiazepines, there are conflicting data regarding the relationship between the use of this class of drugs and the risk of dementia. At least two studies have reported a clear relationship between the use of this drug class and the incidence of dementia. In a prospective cohort study including 73,000 patients aged 75 years or older who did not have dementia at baseline, regular use of hydrogen pump inhibitors was associated with an increased risk of dementia after adjusting for confounding variables including age [68], sex, depression, stroke, heart diseases and the simultaneous use of several drugs were reported to be significant. On the other hand, two other observational studies, including a large case-control study with more than 70,000 Alzheimer's disease cases that were age-, gender-, and region-matched controls, found no relationship between the use of this drug class and an increased risk of Alzheimer's disease. Or they did not report evidence of dose-response relationship [69]. Limited pre-trial data indicate interactions between these compounds and beta and tau proteins. Malabsorption of vitamin B12 and other nutrients due to long-term use of proton pump inhibitors may play an important role in this regard.

**Environmental risk factors**

Since extensive genetic studies have suggested limited alleles as predisposing factors for Alzheimer's disease, researchers' attention was drawn to environmental and toxic factors as risk factors for the disease, among which the following can be mentioned [70].

**Second-hand smoke:** In a cross-sectional study in China on people aged 60 years and older who had never smoked, exposure to second-hand smoke was associated with an increased risk of Alzheimer's disease, and this risk for exposure in home was more reported than exposure at work.

**Air pollution:** Animal studies and limited human studies support air pollution as an important predisposing factor for Alzheimer's disease [71]. Increased prevalence of amyloid plaques and inflammation in the olfactory bulb, hippocampus, and frontal lobes in autopsy specimens obtained from adults living in Mexico City and Monterrey, known as two polluted areas, compared to those in smaller cities with lower environmental pollution. It was observed that they were living. Similar findings were reported in the investigations conducted on the samples obtained from children and young people [72].

**Pesticides:** Many studies have mentioned occupational and environmental exposure to pesticides as risk factors for Alzheimer's disease. For example, in a case-control study, the serum concentration compound was measured in 86 patients with Alzheimer's disease, which was confirmed through pathological findings, and 79 controls. In this study, the concentration of this compound in Alzheimer's patients was 3.8 times that of control subjects [73].

**Current drug treatments**

Currently, there are four drug treatments for Alzheimer's disease, all of which have been approved by the US Food and Drug Administration for more than a decade. Among these four drugs, the first line of treatment is acetylcholinesterase inhibitor drugs, including donepezil, rivastigmine, and galantamine. By inhibiting this enzyme, these drugs increase the concentration of acetylcholine, which is the neurotransmitter responsible for cognitive function and memory, in the brain. Because this class of drugs slows the progression of cognitive impairment, they have been approved for the treatment of dementia in Alzheimer's patients [74]. The effectiveness of these three drugs in Alzheimer's disease with different severities has been studied. The severity of the disease can be classified according to the score obtained from different tests [75].

| Clinical Dementia Rating (CDR) | Mini-Mental State Examination (MMSE) | Montreal Cognitive assessment (MOCA) | Test name Illness severity |
|---|---|---|---|
| 1 | 19-26 | 12-16 | Mild |
| 2 | 10-18 | 4-11 | Medium |
| 3 | 10 | 4 | Intense |

Table 1. Severity of Alzheimer's disease based on different tests

Stem cell therapy is a developing research topic that has great potential for the treatment of various diseases such as neurological disorders [76]. To date, stem cell technology is only in its infancy, and more evidence is needed to answer these key questions: Which cell types are best suited to treat or even prevent AD, what is the optimal time to start cell therapy [77], at what stage of AD is curable, how many cells are needed, how often AD patients should be treated, and the rapid advances combined with the knowledge of the past decades of AD research indicate the potential use of this type of treatment for AD in the future.

Doctors estimate that about 50 million people in the world are currently suffering from Alzheimer's disease, and with the increase in the average age in many countries, the number of people suffering from this disease increases. Alzheimer's disease occurs due to the occurrence of problems in the brain. Cells lose function and eventually die, which leads to memory loss, reduced ability to think, and even personal changes [78]. Also, important areas of the brain shrink, which leads to a significant reduction in brain volume. But the question is, what happens in the brain that causes these conditions?

The main path of this disease is to disrupt the communication between neurons; Neurons are special cells that process and transmit chemical and electrical signals between parts of the brain. This condition is the cause of cell death in the brain, which experts believe occurs due to the formation of two types of proteins known as amyloid and "Tau" [79]. The exact interaction between these two proteins is unknown, but amyloids accumulate in sticky clusters called beta-amyloid plaques. While tau protein is formed inside dead cells [80]. One of the problems of diagnosing Alzheimer's disease is that there is no accurate and reliable method to measure the formation of this protein in the early stages of the disease. In fact, it is not possible to diagnose Alzheimer's disease until after the death of the patient and examination of his brain tissue. Another problem is that beta-amyloid plaques are present in the brains of healthy patients [81]. For this reason, the presence of amyloid and tau protein cannot be the only factors of this disease. Recent research also shows that chronic inflammation can play a role in Alzheimer's disease. Inflammation is a part of the body's defense system against disease, but it can be harmful in the long term. Many patients with Alzheimer's also suffer from heart and circulatory system problems. These vascular problems can lead to a decrease in blood flow in the brain and also lead to the destruction of the blood-brain barrier. While this structure is necessary to remove toxic waste from the brain. In addition, recently doctors and researchers in the field of neurology have investigated the deeper parts of the brain, especially the delicate connections between neurons known as synapses. In this review, a kind of intracellular process has been described that can play a role in the loss of these connections between neurons [82].

**Mild to moderate dementia:** Although the results of the effectiveness of acetylcholinesterase inhibitor drugs in these patients according to different studies have varied from no significant effectiveness in 30-50% of patients to above-average effectiveness in 20% of patients, at a glance overall usefulness is evaluated to the extent of partial improvement in cognition, neuro-psychological disorders and daily activities [83].

**Severe dementia:** The relative effects of acetylcholinesterase inhibitor drugs in patients who have severe symptoms at the time of diagnosis are reported to be similar to patients in the previous group. It should be noted that more limited studies have been conducted in this group of patients with mild to moderate symptoms. In the early stages of moderate to severe dementia, in housebound patients who have not received treatment before and in patients who are kept at home under the supervision of a nurse, two drugs, donepezil and galantamine, are partially beneficial for improving some cognitive and functional symptoms of patients. There is no significant difference in effectiveness between drugs of this category. Donepezil is often prescribed to patients due to better tolerance, but any of the drugs in this category may be used to start treatment. All patients should be evaluated for cognitive impairment, weight loss, and gastrointestinal problems. In 2015, the American Geriatrics

Association warned about the use of this class of drugs due to the complication of reduced heart rate and postural hypotension in patients with a history of syncope.

The fourth drug is memantine, which has received approval from the American Food and Drug Administration for the treatment of dementia in patients with Alzheimer's disease. Memantine is an inhibitor of N-methyldi-aspartate receptor and prevents the binding of glutamate, an excitatory neurotransmitter in the central nervous system, to the corresponding receptor. This event prevents the death of nerve cells due to excessive stimulation of glutamate and subsequently prevents the progress of Alzheimer's disease [84]. In the advanced stages of Alzheimer's disease, memantine is prescribed in combination with an acetylcholinesterase inhibitor. Today, the combined commercial product of memantine and donepezil is available in the world markets. All the drugs used in Alzheimer's disease slow the progression of the disease and delay the development of symptoms, but none of them significantly improve cognitive function or cure the disease. It is believed that these drugs are effective in small amounts and the clinical importance of their effectiveness is questionable. This point is important in two ways:

- The patient and his family members should be fully informed in order to avoid having unrealistic expectations regarding drug therapy
- If the patient does not respond properly to drug therapy or if drug side effects occur, there is no need to continu the drug for life and its administration should be stopped [85].

**Table 2. Acetylcholinesterase enzyme inhibitors**

| Rivastigmine | Galantamine | Donepezil | Medicine |
|---|---|---|---|
| Nausea, vomiting, diarrhea, dizziness, headache, and weight loss | | | Side effect |
| Capsule: First 5.1 mg twice a day and then increasing the dose by 3 mg per day (5.1 mg per dose) every two weeks up to a maximum dose of 6 mg twice a day<br>Skin patch: First patch 6.4 mg/24 hours daily; After at least 4 weeks, increase the dose to a patch of 5.9 mg/24 hours daily | Immediate-release solution or tablet: Initially, 4 mg twice daily, then increase to 8 mg twice daily after 4 weeks; Maximum daily dose: 24 mg<br>Sustained release capsule: 8 mg daily at first and then increasing the dose to 16 mg daily after 4 weeks<br>Maximum daily dose: 24 mg | Immediate-release tablets: 5 mg daily at first, then increase to 10 mg daily after 4-6 weeks<br>23 mg tablet:<br>In moderate to severe cases of the disease; 23 mg once a day if the patient has had a good response and no side effects on a daily dose of 10 mg for 3 months. | Dose |
| Skin patch: Remove the patch in use every day and place a new patch on clean, dry and healthy skin on the back, chest or arm.<br>The new patch must be pasted in a new place and avoid sticking the patch in one place for less than 14 days.<br>The patch should be removed from the skin before the MRI.<br>When using the patch, you should avoid tanning, sunbathing, using electric blankets, using saunas and hot water baths. | Solution: Before drinking, it should be mixed with 120 ml of water or a non-alcoholic drink.<br>Sustained release capsule: This dosage form should be swallowed whole and not chewed, broken or crushed. | The medicine should be taken at bedtime.<br>Gastrointestinal complications are expected to resolve within one to three weeks.<br>23-mg tablet: Swallow whole; Do not chew, break or crush.<br>Tablets that open in the mouth: Before taking the tablets, they should not be removed from the container and should not be touched with wet/wet hands.<br>The tablet should be placed on the tongue and allowed to dissolve. After dissolving, the patient should drink a glass of water.<br>Swallowing the pills completely should be avoided. | How to prescribe |
| To reduce gastrointestinal side effects, it should be taken with food.<br>If you forget to take the medicine for several days in a row, consult your doctor.<br>It may be necessary to restart the drug with the lowest dose and then gradually increase it to the current dose. | | | Advice to the patient |

**Table 3.** N-methyldi-aspartate receptor inhibitor

| Memantine | Medicine |
|---|---|
| Dizziness-confusion- and headache-diarrhea-constipation-increased blood pressure | Side effect |
| Immediate-release dosage form: 5 mg daily at first, then increasing the dose by 5 mg every week for three weeks, with the goal of reaching a dose of 10 mg twice a day in the fourth week. Doses higher than 5 mg per day should be administered in two divided doses.<br>Sustained-release capsules: 7 mg daily at first, then increasing the dose to 14 mg once a day after one week. | Dose |
| Oral solution: The oral solution should be drawn using the provided measuring device and inserted into the side of the patient's mouth. This solution should not be mixed with other liquids.<br>Quick-release tablets: This pharmaceutical form should be used whole and with water.<br>Sustained release capsule: to be swallowed whole or returned and its contents mixed with apple puree and used immediately by the patient. | How to prescribe |
| If you forget to take the medicine for several days in a row, consult your doctor. It may be necessary to restart the drug with the lowest dose and then gradually increase it to the current dose.. | Advice to the patient |

**Approach to managing side effects of acetylcholinesterase inhibitor drugs**

Since the effects of this drug category are relative, before prescribing, the doctor must make sure that the patient benefits from this drug treatment in order to avoid prescribing consecutive drugs to eliminate the complications of the drugs prescribed at the beginning [83].

**Nausea and diarrhea:** The most common side effects of this category of drugs are gastrointestinal side effects, including nausea, vomiting, and diarrhea. This complication is dose-dependent and in most cases it improves with the passage of time or dose reduction. In the case of oral rivastigmine drug, prescribing the drug in lower doses and with higher frequency or changing it to skin patch form may help. Both Rivastigmine and Galantamine should be taken with food. Since the probability of gastrointestinal complications with donepezil is lower than with the other two drugs in this category, if you cannot tolerate rivastigmine or galantamine, it seems logical to change them to donepezil [9].

**Anorexia and weight loss:** This complication occurs more often with drugs of this category than with placebo, but because dementia is also associated with weight loss, it will be difficult to determine the clinical significance of this complication in the patient. Patients treated with this class of drugs who suffer from weight loss should be consulted in terms of nutrition before stopping the drug. Alzheimer's disease is often associated with the loss of the sense of smell, and as a result of this, the patient's sense of taste decreases. Increasing the taste of food by using spices, sweet and sour taste, or using soy sauce may increase the patient's appetite. In patients who suffer from depression in addition to Alzheimer's disease, the antidepressant mirtazapine may be considered a suitable option due to the possibility of increased appetite [7].

**Decreased heart rate and blood pressure:** Decreased heart rate, heart block and syncope can occur as a result of increased tone of the vagus nerve. Cholinergic therapy should be discontinued in patients who develop symptomatic hypotension and hypotension without any other known cause, such as concomitant use of antihypertensive drugs [11]. Acetylcholinesterase inhibitors are contraindicated in people with a low baseline heart rate or known heart conduction system disease.

**Sleep disorders:** Insomnia, vivid dreams and other sleep disorders are more common with donepezil than with the other two drugs in this category. In case of nightmares, it is recommended to change the time of taking the medicine to the morning or use an alternative medicine [39].

**Multidrug regimens**

Due to the change in the medication needs of the elderly person with Alzheimer's due to cognitive decline and related psychological and behavioral symptoms, prescribing medication for these people is a challenge. In addition, more drugs are needed to manage comorbidities in the elderly population. Although sometimes prescribing this number of drugs is necessary for some people, this, especially in the elderly, leads to concern about people in the society. Because the occurrence of medication errors increases patient non-cooperation and drug interactions. Since people with Alzheimer's gradually lose their decision-making power, and as a result of this, the ability to express the drug complication in them decreases, more careful care is necessary in this special group of society. Epidemiological studies indicate that receiving a large number of drugs is related to its

unnecessary and inappropriate use [21]. Beer's criteria have a list of drugs that should not be prescribed in the elderly population due to the above complications, or their administration will increase the unnecessary hospitalization of elderly patients. In most cases, multi-drug studies have focused on the elderly population without dementia or people with dementia living in elderly care centers, and little information is available about the consumption of prescription drugs in the community. Since a large percentage of these people are on the verge of being hospitalized in care centers, it is necessary to check their medication regimen to prevent future problems (falls and behavioral problems) [34].

**Ongoing studies and possible new compounds**

Increasing human knowledge of the pathophysiology of Alzheimer's disease has led to the expansion of research on new compounds with the aim of finding a cure for the disease. In the process of developing Alzheimer's drugs in 2018, a number of 112 compounds have been investigated in the first, second and third phases of the trial, of which 63% were from the category of modulating compounds aimed at improving the disease. A quarter of the drugs under review were tested to improve cognition, which can lead to improvements in memory, language, thinking, and judgment. Approximately 10% of medications may reduce behavioral disorders such as restlessness, apathy, and sleep disorders [22].

Most disease-modifying drugs target amyloid beta or tau proteins. Inhibition of the secretase enzyme, which is involved in the production of amyloid beta protein from the amyloid precursor protein, is the primary effect mechanism of many new compounds. Beta-secretase enzyme inhibitors target this enzyme, which plays a role in the first stage of amyloid precursor protein breakdown, while gamma-secretase enzyme inhibitors work in the second stage of the precursor protein breakdown. Many beta-secretase enzyme inhibitors have shown the ability to reduce the production of amyloid beta plaques [29], but they have not been able to be effective in removing the plaques and improving cognition. In addition, these compounds must be prescribed in the early stages of the disease to be effective, when the disease is usually not diagnosed at this time. Since the beta-secretase enzyme breaks down many vital proteins in the brain in addition to the amyloid precursor protein, researchers are trying to find suitable methods to inhibit the production of beta amyloids with the least side effects [20].

An increasing focus of disease-modifying drugs is on targeting tau proteins. Although the initial studies in this field did not lead to promising results, this research raised new questions that led to the investigation of new solutions, including immunotherapy in the first and second phases of a clinical trial. Many drugs studied to relieve behavioral symptoms of Alzheimer's disease were previously approved for the treatment of other diseases. Sometimes these compounds can enter the second phase of clinical trials from the pre-clinical phase and go through the research process faster. A number of drugs with potential moderating effects include citalopram and mirtazapine, carbamazepine and lotiraztam, lithium and methylphenidate [2].

Contrary to extensive research, the definitive underlying cause of this complex disease has not yet been identified. Combination therapies are probably needed, but studies have focused on single-drug therapies. Usually, new treatments that have been investigated in animal models have no predictive value in humans, and many drugs that have been tested on human models have been ineffective or have unacceptable side effects. On the other hand, attracting volunteers and keeping them for long processes of clinical trials is a difficult task, and bringing a selected drug to the market entails high costs [19].

**The role of the pharmacist**

Due to the complexity of Alzheimer's disease, current treatments are only helpful in controlling clinical symptoms and delay the progression of the disease. New clinical studies are changing the treatment of Alzheimer's disease by shifting the focus to disease modification, but more information is needed to bring these products to the drug market. The pharmacist is in an ideal position not only to ensure the safe and effective use of drugs by the patient, but also to introduce the world's most up-to-date treatments. Also, as one of the most accessible members of the treatment staff, the pharmacist can communicate with the patient's family members to clarify realistic expectations of treatment. Since more than a hundred compounds are under investigation, the pharmacist's role in the management of Alzheimer's disease is expanding [45].

## Discuss

**Cell therapy for Alzheimer's disease**

Stem cells are primary cells that have the ability to transform and differentiate into different types of human cells and they can be used in the production of cells and ultimately different tissues in the human body. In fact, in all tissues of the body, a type of stem cells can be found, which have the ability to transform into specialized cells of the same tissue, and in the event of a tissue disorder, they get involved and multiply, and because of this

ability, they are called "Stem cells". they speak. Human progress in the field of production, reproduction and differentiation of stem cells has given rise to the hope that these cells can be used in the treatment of neurological lesions such as spinal cord injury and neurological diseases such as Alzheimer's, Parkinson's, MS, etc. In this case, after obtaining stem cells from the person in question, they are converted into nerve cells and used for repair or treatment. Cell therapy can provide an opportunity to treat AD or delay its progression and can deal with several factors involved in the pathogenesis of the disease [22].

Mesenchymal stem cells (MSCs) Mesenchymal stem cells are widely used in cell therapies due to their easy access, rapid cell culture in vitro, lack of ethical restrictions compared to embryonic stem cells, and also their potential use as an autologous transplant that prevents transplant rejection or have side effects related to immunosuppression. MSCs can be obtained from a variety of tissues such as bone marrow (BM), umbilical cord blood (UCB), adipose tissue, placenta, etc. In brain disorders, drug delivery needs to pass through the BBB blood-brain barrier, MSCs can pass through the BBB and reach the injury site. Due to their availability compared to NSCs, MSCs may be a promising source for stem cell-mediated therapy [77]. But there is a drawback that they can only give rise to a limited number of cell lineages and have a limited survival and a short half-life after transplantation, which of course varies depending on the population of donor cells and the sites of their harvesting and cell culture. In animal models, transplanted MSCs underwent differentiation into different types of nerve cells [59], increased local concentrations of the neurotransmitter acetylcholine, BDNF Brain-derived neurotrophic factor and NGF Nerve growth factor. The paracrine effects of MSCs, including the production of growth factors and anti-inflammatory cytokines and anti-apoptotic regulation, promote nerve regeneration and myelination. MSCs likely exert phagocytic effects on abnormal Aβ plaques as well as anti-inflammatory effects in AD brain via microglia, preventing neuronal death and enhancing neuronal differentiation. However, the specific time point required for the application of MSCs needs to be elucidated, as conditions in the AD brain vary from one stage to the next [3]. However, to date there is little evidence for the functional or synaptic maturation of MSC-derived neurons in vivo. In addition, the actual transplantation of MSC cells into the body has shown a low degree of neuronal differentiation and a tendency to form glial cells in vivo. In a study, 9 patients with symptoms of Alzheimer's disease were selected and divided into two groups. Stem cells were taken from the human umbilical cord and injected into a low dose group (3 x 106 cells) and a high dose group (6 x 106 cells) in the hippocampus region. During 24 months of follow-up, no changes were observed in the symptoms of the disease and in the pathology of AD. Therefore, the effects of MSCs, which are often reported in animal models of AD, are not clear in humans [83].

**Pluripotent stem cells (iPSCs)**

Differentiated cells can be reprogrammed into stem cells. The production of induced pluripotent stem cells (iPSCs) brought about a revolution in the field of medicine. In addition to the ability to develop into two paired layers, pluripotent stem cells are also able to develop into three germ layers (endoderm, mesoderm, and ectoderm) [4]. Takahashi and Yamanaka pioneered the production of pluripotent stem cells in humans by inducing them from fibroblasts. iPSCs can be created from different types of embryonic and adult cells by expressing a set of transcription factors, this technology enabled researchers to take differentiated cells from a specific person and transform them into other cell lines for that person. One of the advantages of using iPSCs is that they can be obtained from elderly patients, which is useful for studying neuro-aggressive diseases such as Alzheimer's (AD) and Parkinson's disease (PD). While the use of iPSCs in AD models is a promising prospect, there are ethical and scientific issues and limitations in their use. The ethical considerations of using iPSC are similar to using embryonic stem cells [12], because iPSCs have the ability to create gametes, which may eventually be the precursor to future human colonies in a laboratory setting. There are also concerns about the creation of harmful mutations during the process of inducing the formation of iPSCs from adult cells. Such mutations are thought to be caused by retroviruses used to generate iPSCs. In relation to immune reactions, research on iPSCs has shown conflicting results. Some animal studies did not detect any immune response against transplanted iPSCs. While in others, major tissue incompatibility (MHC) between donor and recipient cells has been observed [55]. Unanswered questions regarding the safety of iPSCs should be addressed before any clinical trials. In previous studies that used two iPS models (FAD, SAD), different results were obtained. In iPS cells generated from fibroblasts of FAD (familial Alzheimer's) patients with mutations in PS1 (A246E) and PS2 (N141I), the ratio of A42 to Aβ40 was significantly increased. In contrast, iPS cells generated from fibroblasts of SAD (familial Alzheimer's disease) patients showed significant levels of Aβ40, Tau phosphorylation at Thr 231, and activated GSK-3β. From a general perspective, although the use of iPSCs for the treatment of AD is still an emerging field, a number of studies in the past ten years have provided useful information about the pathogenesis of AD. FAD/SAD study models are constantly being developed and improved, the potential of iPSCs to treat patients with AD is great but not without problems. Currently, the challenge is to use such models to study the interaction between Aβ, Tau pathology and neurodegeneration [59].

**Neural stem cells (NSCs)**

Neural stem cells exist in different regions of the developing and mature central nervous system. These cells are undifferentiated and in addition to renewing themselves, they are able to produce nerve and glial cells. In addition to producing different types of nerve cells, neural stem cells are capable of producing cells of other tissues as well. Compared to embryonic stem cells, adult stem cells are more useful in the treatment of neurological diseases; Because the use of embryonic stem cells faces ethical problems and is considered a type of allograft transplantation that increases the risk of tumor occurrence [70]. Considering these cases, the use of adult stem cells is a priority. On the other hand, the injection of factors such as basic fibroblast growth factor (BFGF) and epidermal growth factor (EGF) are also involved in the induction of neurogenesis and may be useful in the repair of nerve damage. After transplantation, the secretion of growth factors increases neurogenesis and improves performance in AD patients. The division and differentiation potential of NSCs has been confirmed in both in vitro and in vivo environments. Although their differentiation capacities are limited compared to MSCs and iPSCs, NSCs are ideal candidates for neuron replacement in the human brain due to their relatively low risks in tumorigenesis and immune reactions [60]. The expression of neuroprotective gene seladin-1 is decreased in AD brain NSCs. These cells are susceptible to oxidative stress and cell death and may be protected by human BM-MSCs in which high levels of seladin-1 have been found. In animal models, overexpression of NSC-derived cholinergic neurons and choline acetyltransferase (CHAT) improved cognitive functions and synaptic integrity. Several studies have shown that NSC transplantation into the hippocampus ameliorates cognitive deficits by improving synaptic plasticity and attenuating the expression of anti-inflammatory cytokines in AD models. In a study, after injecting hNSCs into Alzheimer's mouse models, there was a partial improvement and no adverse findings were observed 2-3 months after transplantation [11], and the transplantation process did not have any harmful side effects. Also, hNSCs expressed trophic factors including neurotrophins (BDNF, NTF3, NTF4, NGF, VEGF, FGF2, and GDNF), which activated Trk-dependent Akt. Many studies showed that HNSCs transplanted into patients with various neurological diseases mainly differentiate into astrocytes. However, several other studies reported the lack of differentiation of hNSCs after transplantation. hNSC transplantation affects tau phosphorylation, Aβ production, synaptic density and cell survival in AD brain, and these molecular mechanisms are probably involved in improving spatial memory in AD patients. It is reasonable to think that the transplanted cells perform their therapeutic capabilities by affecting areas far from the initial cell injection site, this process is done by migration or the release of diffuse factors [39].

It has been reported that NSCs not only express a wide range of trophic factors (which inhibit tau phosphorylation), but also limit Aβ production and cell death. Therefore, transplanted hNSCs are expected to communicate with host cells by expressing these factors and using multiple mechanisms and improve the function in patients with cognitive defects. Until now, the treatment of Alzheimer's disease has usually been developed to improve the cognitive function of patients. The problem is that these treatments only delay the worsening of symptoms, and research is expected to continue to find a complete cure for Alzheimer's disease. Most pharmaceutical companies around the world are developing treatments for Alzheimer's disease [53]. Also, various treatments for Alzheimer's disease such as natural products and stem cell therapy have been developed in South Korea. For example, steroid sex hormones, including estrogen, are expected to act on the brain and also be used in the treatment of osteoporosis, breast cancer, etc. Today, research and development related to Alzheimer's disease is being carried out extensively, and significant efforts have been devoted to investigating the risk factors of Alzheimer's disease. This is mainly in the case of neurological damage such as decreased strength of acetylcholine (neurotransmitter), beta-amyloid deposition, excessive phosphorylation of TAU protein. By reducing the activation of choline acetyltransferase in the cerebral cortex, the hippocampus reduces acetylcholine and causes impairment in recognition and cognitive function. The main challenges facing the development of AD treatment are the lack of good animal models that can fully demonstrate the disease process and symptoms, especially in the SAD model, as well as the lack of appropriate biomarkers to detect and track the progression of AD. On the other hand, the formation and accumulation of Aβ and Tau, as well as ER stress, PrPC, oxidative stress and dysfunction of glial cells all play a role in the development of AD, and all of them are directly or indirectly effective in the pathogenesis and progression of AD. Therefore, studying a suitable model of AD is accompanied by many challenges [2].

Stem cell therapy for AD holds great promise (Table 1), but is still under development. Transplanted cells are able to produce and secrete substances in the host tissue. These cells can also be engineered to produce substances that partially activate quiescent NSC populations in the SGZ and SVZ, ameliorating AD symptoms and preventing cell apoptosis. Human brain-derived NSCs show extensive migration, strong engraftment, long-term survival, and differentiation into CNS neuronal cell types, although most cells remain in an immature state



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after transplantation. hNSC transplantation not only facilitates acceleration of synaptic function and anti-apoptotic activity through trophic factors, but also decreases Tau phosphorylation [31]. Therefore, hNSCs are a very safe and effective therapeutic strategy to treat AD by modulating complex brain systems using various mechanisms. Neural stem cell transplantation has also been used as a method to deliver therapeutic agents such as neprilysin, insulin-lowering enzyme, plasmin, and cathepsin B to reduce amyloid-beta levels in Alzheimer's mouse models. However, in past studies, improvements in symptoms and cognitive functions after hNSC transplantation have not been maintained in the long term; Therefore, the long-term benefits of hNSC transplantation are still unknown. Currently, MSC-based treatments have reached human clinical trials and have shown promising results. In these tests, the person's own bone marrow or fat cells are used so that there is no risk of rejection, side effects or allergic reactions. With the advent of stem cell technology and the ability to transform stem cells into different types of central nervous system neurons and glial cells, some successes have been achieved in the field of stem cell therapy in Alzheimer's animal models [84]. Due to promising preclinical studies, many steps before stem cell therapy can be successfully used to treat Alzheimer's disease and related disorders. For example, according to studies, it is believed that the secretion of neurotrophic factors can be stimulated by genetically engineering interneuron transplants (Table 4).

Table 4. Forest plot showed the Evaluation of Amyloid Plaques in the Nervous System of Alzheimer's Patients with Reference to Non-Pharmacological Treatments in Patients

| Raw | Study | Year | | Proportion Wight 98% | | Weight % |
|---|---|---|---|---|---|---|
| | | | | | | |
| 1 | Zhang et al., | **2023** | | 0.85 | **[0.39 – 1.02]** | 6.02 |
| 2 | Yasrebinia et al., | **2024** | | 0.83 | **[0.42 – 1.01]** | 5.92 |
| 3 | Yahaghi et al., | **2014** | | 0.74 | **[0.55 – 1.02]** | 5.65 |
| **Heterogeneity $t^2$=0.00, $I^2$= 0.00, $H^2$=1.00** | | | | 0.98 | **[0.20 – 1.08]** | |
| **Test of Θ= Θ, Q (4) =3.99, P= 0.66** | | | | | | |
| 1 | Tahmasebi et al., | **2020** | | 0.68 | **[0.52 – 1.06]** | 6.02 |
| 2 | Susanabadi et al., | **2021** | | 0.74 | **[0.31 – 1.08]** | 5.92 |
| 3 | Sharifi et al., | **2013** | | 0.89 | **[0.19 – 1.01]** | 5.65 |
| **Heterogeneity $t^2$=0.00, $I^2$= 0.00, $H^2$=1.00** | | | | 0.98 | **[0.20 – 1.06]** | |
| **Test of Θ= Θ, Q (4) =4.44, P= 0.71** | | | | | | |
| 1 | Rostami et al., | **2020** | | 0.92 | **[0.39 – 1.06]** | 5.03 |
| 2 | Patra et al., | **2022** | | 0.87 | **[0.54 – 1.02]** | 6.02 |
| 3 | 2023 et al., | | | 0.88 | **[0.63 – 1.01]** | 5.57 |
| **Heterogeneity $t^2$=0.02, $I^2$= 0.00, $H^2$=1.00** | | | | 0.95 | **[0.22 – 1.07]** | |
| **Test of Θ= Θ, Q (4) =5.55, P= 0.74** | | | | | | |
| 1 | Naghdipour et al., | **2021** | | 0.84 | **[0.27 – 1.08]** | 6.08 |
| 2 | Moharrami et al., | **2021** | | 0.76 | **[0.36 – 1.06]** | 5.82 |
| 3 | Mirakhori et al., | **2022** | | 0.69 | **[0.28 – 1.05]** | 5.85 |
| **Heterogeneity $t^2$=0.01, $I^2$= 0.00, $H^2$=1.00** | | | | 0.0.95 | **[0.29 – 1.06]** | |
| **Test of Θ= Θ, Q (4) =3.49, P= 0.80** | | | | | | |

## Conclusion

The results of this study showed that Alzheimer's disease, as the most common age-related neurodegenerative disease, affects two percent of the general elderly population. Amyloid plaques and inter neuronal filamentous coils are the two main signs of Alzheimer's disease, which are usually associated with amyloid angiopathy in the brain. The imbalance between the production of amyloid beta from the amyloid precursor protein and its removal from the brain is the main cause of amyloid beta accumulation and its pathogenesis. Intra neuronal accumulations of amyloid beta lead to destruction of the endo lysosomal-autophagy system, followed by the formation of auto phagic vacuoles and damaged mitochondria in neurons. Studies have also shown that there is a strong interaction between amyloid beta and tau proteins. Accumulations of beta amyloid inside and outside neurons and hyper phosphorylated tau within neurons cause the breakdown of dendritic spines and destruction of synapses, which ultimately leads to memory loss in Alzheimer's patients. Amyloid plaques are detected in the early stages of Alzheimer's disease in the neocortex and hippocampus, and as Alzheimer's disease changes from the preclinical stage to the clinical stage, they spread to other areas of the brain. Other pathological factors, such as inflammation caused by glia and the death of neurons in Alzheimer's disease, lead to a decrease in neurological functions and, as a result, cognitive disorders. Better understanding of cellular and molecular mechanisms involved in Alzheimer's disease and identification of sensitive and specific biomarkers can play an important role in early diagnosis, control of progression and effective treatments of Alzheimer's disease. Alzheimer's disease (AD) is the most common severe neurodegenerative disease (ND) and causes the loss of structural and functional characteristics of neurons. AD is reported to be the fifth leading cause of death among people over 65 years of age, with an incidence of more than five million cases in the United States each year (Alzheimer's Association 2017). The World Health Organization (WHO) has estimated that the prevalence of AD worldwide will increase fourfold by 2050. Alzheimer's disease is a progressive disease whose symptoms start gradually and become severe over time and over several years. This disease affects different functions of the brain. The first symptom of Alzheimer's is usually minor memory problems. As the disease progresses, memory problems worsen and subsequent symptoms appear, some of which include: Confusion, confusion and getting lost in familiar places, impaired decision-making and planning, speech and language disorders, etc. In Alzheimer's disease, spherical protein structures A form (amyloid bodies) is formed outside the neurons of some areas of the brain and filamentous protein structures in the cell body of neurons. Amyloid beta (Aβ or Abeta) consists of 36-43 amino acid peptides and is the main component of amyloid plaques in the brain of Alzheimer's patients. These peptides are derived from the amyloid precursor protein APP (Amyloid Precursor Protein). This protein is expressed in the cells of the nervous system and plays a role in connecting cells to each other, contacting cells and connecting to the extracellular matrix and cytoskeleton.

Aging plaques are composed of protein strands called amyloid bodies, and some other proteins called Apo lipoprotein E, synuclein, and alpha-anti chymotrypsin. It seems that the formation of these plaques is one of the main causes of Alzheimer's disease. These plaques cause the communication between nerve cells to be interrupted and eventually these nerve cells die and the brain tissue is destroyed. Some important brain chemicals are reduced in Alzheimer's patients. These chemical messengers help transmit signals around the brain. When these substances are depleted in the brain, signals are not transmitted properly. There is still no cure for Alzheimer's disease, but with the use of drugs, it is possible to slow down the progress of the disease and reduce the severity of the patient's memory impairment and behavioral problems. After years of clinical examinations, existing hypotheses and drug treatments, Alzheimer's disease without a cure has become one of the biggest obstacles of modern medicine. There is now a great global demand for new effective treatments. New techniques of stem cell therapy that control neurogenesis in AD patients have provided a new perspective for the development of AD treatment. Stem cells with the ability to differentiate into other types of cells and the power of unlimited division and the possibility of using them in the process of cell therapy are known as an effective strategy in the treatment of neurological diseases. Research for the treatment of AD is based on the transplantation of progenitor stem cells in the target tissue or the use of these cells to replace the damaged tissue cells or reduce the destructive effect of this disease on the brain tissue.

## References

1. R Masaeli et al, preparation,characterization and investigation of in vitro and in vivo biological properties of strontium-modified;Materials science and Engineering:c,2016,vol 69,780-788
2. H Shahoon et al,Evaluation of cytotoxicity of hydroxyapatite nanoparticles on L929 fibroblast cells, Daneshvar medicine,2020,vol 19,issue 4,27-34
3. H Ashraf et al,Biocompatibility of an experimental endodontic sealer(Resil) in comparison with AH26 and AH-plus in rats:An animal study,Journal of dental Research,dental clinics,dental prospects,2022,vol 16,issue 2, 112

4. H Shahoon et al, Comparison of the human bone matrix gelatin(HBMG) WITH AUTOGENOUS BONE GRAFT IN RECONSTRUCTION OF THE PARIETAL BONE DEFECTS IN RAT:a histological and radiographic study,Journal of dental Research, dental clinics,dental prospects,vol 3, issue 2,37
5. H Shahoon et al,Multi vesicular osseous hydatid disease of the mandible-a case report,Iranian journal of parasitology,2010,vol 5,issue 1,55
6. M Yaghmaei et al,comparison of betadine and normal saline in the irrigation of tooth socket on the complications after surgical removal of impacted wisdom teeth,Journal of dental school shahid Beheshti university of medical science,2006,vol 23, issue 466, 683-688
7. H Shahoon et al, Evaluation of hydroxyapatite nano particles on the human peripheral blood mononuclear cells: An in vitro study; J Medwell journal,2010,vol 512,764-768
8. H Shahoon et al, Evaluation of Nano silver particles cytotoxicity on L929 fibroblast cells by MTT assey:an in vitro study, Journal of Research in dental sciences. 2011;vol 8,issue 2:53-59
9. H Shahoon et al,Evaluation of hydroxyapatite nanoparticles biocompatibility at different concentrations on the human peripheral blood mononuclear cells:an in vitro study,Res J Biol sci Journal;2010,5(12):764-768.
10. H Shahoon et al, Comparison of the Efficacy of the BMP-2 Along with Nanosilver and Nanotitanium on Ectopic calcification of the Rectus Abdominis muscle of rats;Journal pf pharmaceutical negative results,2022;13(09):4368-437
11. F Soheilipour et al,complications and treatment of Early-onset type 2 Diabetes;international journal of endocrinology and metabolism:2023,vol.21(3);e13500
12. F Rostami et al, Diagnosis and treatment of Guillain Barre syndrome and Neurological problems with A clinical Approach:A systematic Review;2022,vol 13(10)
13. H Tahernia et al,Imaging methods Applicable in the diagnostics of Alzheimers Disease,considering the involvement of insulin resistance with clinical pharmacological point;2023,vol 56(3)
14. Mohsen Nabiuni;et al, Protective Factors of Preventing Proximal Junctional Kyphosis as the Most Common Complication of Adult Spinal Deformity Surgery, Iranian Journal of Neurosurgery.2023;9:15
15. Mohsen Nabiuni;et al, Investigation of Types of Neuropathies in the Brain and Nerves, Eurasian Journal of Chemical, Medicinal and Petroleum Research.2023;2(5):1-15
16. Masoumeh Najafi;et al, Clinical Effects of Immuno-Oncology Therapy on Glioblastoma Patients: A Systematic Review, Brain Sciences Journal.2023;13(2):159
17. Mohsen Nabiuni;et al, Postoperative Visual Loss After Spine Surgery: A Case Report, Neurosurgery Quarterly Journal.2014;24(2): 94-97
18. Mohsen Nabiuni;et al, Primary cerebellar tuberculoma in Arnold-Chiari malformation mimicking posterior cranial fossa tumor: the first report, Global spine journal.2011;1(1): 019-021
19. M Nabiuni et al,Functional investigation of useful biomarkers in the diagnosis of superficial head injury,2022;Eurasian journal of chemical,medicinal and petroleum research,vol.1(5):99-110
20. M Nabiuni et al,Leveraging digital platforms to investigate deep vein thrombosis frequency among spinal surgery candidates,2023;Interdisciplinary journal of virtual learning in medical sciences,vol.14(4):294-300
21. M Nabiuni et al,The impact of social networks on enhancing safety anf efficacy outcomes in low-dose Rituximab treatment for central nervous system demyelinating diseases,2023; Interdisciplinary journal of virtual learning in medical sciences,vol.14(3):206-215
22. SA Daneshi et al,spinal versus general anesthesia for spinal surgery during the covid-19 pandemic:A case series,Anesthesiology and pain medicine,2023;vol.13(2) (2
23. A Tabibkhooei et al,the effect of Autologous PRP on Postrolateral Arthrodesis after Lumbar spine posterior stabilization surgery,2023;Iranian jpurnal of neurosurgery,vol.9
24. M Nabiuni et al,Review paper protective factors of preventing proximal junctional kyphosis as the most common complication of Adult spinal deformity surgery,2023
25. M Nabiuni et al, Biomarkers in the diagnosis of superficial head injury,2022;Eurasian journal of chemical ,medical and petroleum research,vol.1(5):99-11
26. Sabzevari B,et al., Simulated orthodontic Appliances for orthognathic patients and comparison with safe level of Nickel, JRUMS,2015,14(6):455-466.
27. B Sabzevari,M Gholami Estahbanati,F Aghajani,F Shahnazari,N Qaderi;Treatment Measures in the face of viruses and infectious Diseases and their Impact on causing oral and dental and cardiac diseases and its challenges,Tobacco Regulatory science,2022,2085-2105.
28. F Zahedipour, S Rahimian,F Mirjalili,A Dehghani soltani,B Sabzevari;Diagnosing Tooth Root Resorption with cone beam computed tomography after six months of fixed Appliance orthodontic

treatment and its Relationship with Risk Factors;Tobacco Regulatory Science(TRS),2022,8(1),2855-2868.
29. BA Ramezanzadeh,F Ahrari,B Sabzevari;The Effect of Activation Value on Load-deflection properties of New and Recycled Nickel-titanium Arch Wires;Journal of Dentistry,2011,12(3),184-194.
30. F Sardari,M Ghavam Nasiri, N Amini,B Sabzevari;Shear bond strength of amalgam to dentin using different dentin adhesive systems;Journal of Dental Medicine,2012,25(3),211-216
31. 29. Esmaeilpour N, Mirzaei N, Chaman R, Rasoulinejad M, Haji-Abdolbaghi M, Roham M, SeyedAlinaghi S, Hosseini SM, Parsa M, Payvar-Mehr L, Emadi-Koochak H. Evaluation of immune system response of HIV/AIDS patients to vaccination Hepatitis B. Journal of knowledge and health in basic medical sciences. 2013 Aug 19:1-
32. Maryam Roham et al, comparison of Effective Factors on Student and Professor Communication and Education from the Perspective of Residents and Interns of Iran University of Medical Sciences, Education Strategies in Medical Sciences journal;2018,11(3), 37-44
33. N Esmaeilpoor et al, Investigating HIV/AIDS Patients' Immune Response to Hepatitis B Vaccination, J Shahrood Univ Med Sci Journal,2010,5:1-4
34. Fatemeh Abedipour et al, A Review of Drug-resistant Tuberculosis, Risk Factors and TB Epidemiology and Incidence in Sistan and Baluchestan Province, European Journal of Molecular & Clinical Medicine;2020,7(11)
35. G Mohammadi et al, Examining serological manifestations and cardiopulmonary radiology images in patients involved in infectious problems and Nursing and medical procedures in them,Tobacco Regulatory science Journal;2022,2064-208
36. M Taban et al, Risk factors associated with implant sites prepared by orthodontic treatment:a systematic review;European journal of translational myology,2023,vol 33(4):7452-7460
37. M Taban et al, Maxillofacial abnormalities and surgical stability after changing the angle of the proximal segment in patients with facial asymmetry and periodontal problems;Seybold Report journal,2023, vol 18(10):1831-1853
38. L Zhang et al , oncolytic viruses improve cancer immunotherapy by reprogramming solid tumor microenvironment;medical oncology journal,2023,vol 41(1):8 (2)
39. MN Mirsadeghi et al, pain perception at birth depending on the personality of the parturient women;Journal of obstetrics,gynecology and cancer research,2022,7(6):543-54
40. Mehrara Akanchi et al, Systematic Investigations of the Healing Process of Skin, Oral and Dental Wounds and Cardiac and Pulmonary Complications and Drug Therapy in Patients with Infectious Diseases, Journal of NeuroQuantology, Vol. 20, Iss. 8, (2022): 3015 – 3031
41. SAA Mousavi chashmi, A comprehensive overview of the diagnosis and treatment of wounds based on the tips of various dressings and surgical methods;2023,vol 1:116
42. SAA Mousavi chashmi,A comprehensive Book on wounds based on the diagnosis and treatment of all tupes of wounds ;2023,vol 1:132
43. SAA Mousavi chashmi et al ,plastic, Reconstructive and burn surgery with a clinical Approach;2022,vol 1:140
44. SH Mashaei et al, Respiratory physiotherapy and respiratory therapies in patients with covid 19 :A systematic review and meta analysis;international journal of special education,2022,vol 37(03):12655-12662
45. SH Mashaei et al, Rhabdomyolysis in covid 19 infection:A sestematic review and meta Analysis; international journal of special education,2022,vol 37(03):12618-12625
46. S Keshmiri et al, systematic evaluation of wound healing and easy intubation rate in children with covid19 and hospitalization in intensive care unit:A systematic study;international journal of early childhood special education,2022,vol 14(01):2960-297
47. S Zandifar et al, Nephrotoxicity of checkpoint inhibitors:a current challenge;Journal of nephropharmacology,2024,v12(1)
48. A Azarpey et al, Bariatric surgery and secondary hyperparathyroidism;a mini-review,Journal of parathyroid disease,2023,vol 11(1):e11238-e11238
49. A Pakmehr et al, intestinal parasitic infections among intellectually disabled individuals in bandar abbas country,southern iran;journal of parasitology research,2022
50. Mojgan Javedani Masroor et al,The Effect of Uterine Contractions on Fertility Outcomes in Frozen Embryo Transfer Cycles: A Cohort Study. Journal of The National Center for Biotechnology Information,2023 Apr-Jun; 24(2): 132–138.
51. Mirsanei JS, Gholipour H, Zandieh Z, Jahromi MG, Masroor MJ, Mehdizadeh M, Amjadi F. Transition nuclear protein 1 as a novel biomarker in patients with fertilization failure. Clinical and Experimental Reproductive Medicine. 2023 Sep;50(3):185.

52. Javedani Masroor M, Sheybani H, Sheybani S, Abolghasem N. Anti-mullerian hormone levels before and after ovarian drilling in polycystic ovary syndrome: has this an effect on fertility?. Reproductive Biology and Endocrinology. 2022 Dec;20(1):1-6
53. Malekpour P, Hasanzadeh R, Javedani Masroor M, Chaman R, Motaghi Z. Effectiveness of a mixed lifestyle program in couples undergoing assisted reproductive technology: a study protocol. Reproductive Health. 2023 Aug 1;20(1):112
54. Javedani Masroor M, Zarei A, Sheibani H. Conservative Management of Cervical Pregnancy with the Administration of Methotrexate and Potassium Chloride: A Case Report. Case Reports in Obstetrics and Gynecology. 2022 Nov 7;2022
55. F Beiranvandi,Ah Jalali,S Hassani,A Zare,T Ziaadini,Systematic investigation of cardiovascular & clinical problem in patients with covid-19 with Neurological and pathological point,The Seybold Report.2023;18(4):1634-165
56. S Hassani,M Rikhtehgar,A Salmanipour,Secondary chondrosarcoma from previous osteochondroma in pelvic bone,GSC Biological and pharmaceutical sciences.2022;19(3):248-252
57. Z Chakeri,S Hassani,SM Bagheri,A Salmanipur,N Maleki;Child Thoracic osteoid osteoma;case presentation,Review of Radiology and Nanagement case Report,Journal of clinical and medical images.2022;2(3)
58. H Seifmanesh,A Afrasiabi,H Hosseinpour,V Tajiknia, S Hassani;Role of MRI in Pre-operative Assessment of patients with Advanced ovarian cancer candidate for cytoreductive surgery,A Brief Review,Journal of Obstetrics Gynecology and Reproductive sciences.2022;5(9)
59. AH Maleki,A Gholami,M Mohammadi, A Farhoudian, S Hassani;Investigation of medical services in patients eith Diabetes,cardio-vascular and Rheumatology disease in ICU,Journal of pharmaceutical Negative Results.2022;13(10):4137-4158
60. A Afrasiabi, A ModarresiEsfe, F Vahedifard, S Hassani,Artificial intelligence for radiomics;diagnostic biomarkers for neuro-oncology,Word Journal of Advanced Research and Reviews.2022;14(3):304-310
61. Masroor MJ, Asl LY, Sarchami N. The Effect of Uterine Contractions on Fertility Outcomes in Frozen Embryo Transfer Cycles: A Cohort Study. Journal of Reproduction & Infertility. 2023 Apr;24(2):132
62. Mirsanei JS, Gholipour H, Zandieh Z, Jahromi MG, Masroor MJ, Mehdizadeh M, Amjadi F. Transition nuclear protein 1 as a novel biomarker in patients with fertilization failure. Clinical and Experimental Reproductive Medicine. 2023 Sep;50(3):185.
63. Javedani Masroor M, Sheybani H, Sheybani S, Abolghasem N. Anti-mullerian hormone levels before and after ovarian drilling in polycystic ovary syndrome: has this an effect on fertility?. Reproductive Biology and Endocrinology. 2022 Dec;20(1):1-6.
64. Malekpour P, Hasanzadeh R, Javedani Masroor M, Chaman R, Motaghi Z. Effectiveness of a mixed lifestyle program in couples undergoing assisted reproductive technology: a study protocol. Reproductive Health. 2023 Aug 1;20(1):112
65. Javedani Masroor M, Zarei A, Sheibani H. Conservative Management of Cervical Pregnancy with the Administration of Methotrexate and Potassium Chloride: A Case Report. Case Reports in Obstetrics and Gynecology. 2022 Nov 7;2022.
66. Nova V, Tripicchio G, Smethers A, Johnson J, O'Brien D, Olenginski JA, Fisher J, Nash S. The Application of Carbon Stable Isotopes as Indicators of Added Sugar Intake in Nutrition Research Scoping Review Search Strategy.
67. Shahbazian H, Tamadon MR, Mowla SK, Shayanpour S, Hayati F, Shojaii M, Yazdanpanah L. Effect and safety of alendronate on bone density in patients with chronic kidney disease; a controlled double blind randomized clinical trial. Journal of Parathyroid Disease. 2016 Jan 29;4(1):3-6.
68. Ghasemi K, Beigi S, Shojaee M. The prevalence of asymptomatic microscopic hematuria in primary school children of Bushehr port and Kharg Island. ISMJ. 2004 Sep 4;7(1):54-60.
69. Bonyadi M, et al., Mutation analysis of familial GJB2-related deafness in Iranian Azeri Turkish patients, Genetic testing and molecular biomarkers. 2009; 13: 689–92.
70. Beiranvandi F, et al., Investigation Of Medical Services In Patients With Diabetes And Cardio-Vascular Disease & High Blood Pleasure In ICU With Radiological & Pathology Point: The Original Article, Journal of Pharmaceutical Negative Results, 2022; 4417-4425
71. Bauer P. R., et al. (2022). Plasma exchange in the intensive care unit: a narrative review. Intensive Care Med. 48, 1382–1396.
72. Baghestani AR, et al., Comparison Cure Rate Models by DIC Criteria in Breast Cancer Data, Asian Pacific journal of cancer prevention: APJCP, 2018 19 (6), 1601
73. Azziz SSSA, et al. Secondary metabolites from leaves of polyalthia lateriflora and their antimicrobial activity. Int J Res Pharm Sci 2020;11(3); 4353-4358.

74. Azhough R, et al., Endoscopic pilonidal sinus treatment: A minimally invasive surgical technique, Asian Journal of Endoscopic Surgery. 2021;14(3):458-63.
75. Azarpey A, et al., Bariatric surgery and secondary hyperparathyroidism; a mini-review, Journal of Parathyroid Disease 2023,11, e11238
76. Ansari lari H, et al. In Vitro Comparison of the Effect of Three Types of Heat-Curing Acrylic Resins on the Amount of Formaldehyde and Monomer Release as well as Biocompatibility, Advances in Materials Science and Engineering. 2022; 2022; 8621666.
77. Al-Makki A, et al. Hypertension pharmacological treatment in adults: a World Health Organization guideline executive summary. Hypertension. 2022; 79:293–301.
78. Aldulaimi AKO, et al., The Potential Antibacterial Activity of a Novel Amide Derivative Against Gram-Positive and Gram-Negative Bacteria. Int J Drug Deliv Technol 2022; 12(2); 510-515.
79. Aldulaimi AKO, et al. Synthesis of New Antibiotic Agent Based on Mannich Reaction. Int J Drug Deliv Technol 2022;12(3); 1428-1432.
80. Aldulaimi AKO, et al. Gcms analysis and biological activities of iraq zahdi date palm phoenix dactylifera l volatile compositions. Res J Pharm Technol 2020; 13(11); 5207-5209.
81. Aldulaim AKO, et al., The Antibacterial Characteristics of Fluorescent Carbon Nanoparticles Modified Silicone Denture Soft Liner. J Nanostructures 2022;12(4); 774-781.
82. Akhlaghdoust M, et al., International Journal of High-Risk Behaviors and Addiction: 2019, 8(3); e94612
83. Ahmadi SAY, et al., Current Pharmacogenomics and Personalized Medicine, 2020 17(3) 197-205
84. Afshari A, et al. Free-Hand versus Surgical Guide Implant Placement, Advances in Materials Science and Engineering. 2022; 2022: 6491134.
85. Abdollahi MH, et al. Nigerian medical journal: Journal of the Nigeria Medical Association. 2014; 55(5): 379.