


**NEURO DEGENERATION OF ACETYLCHOLINE IN SYNAPTIC CLEFT CAUSE
ALZHEIMER DISEASE**
Dibyendu Dutta*, Jaydeep Roy, Falguni Dutta, Rahul Kumar Singh, Rishav Banerjee and Dhrubo Jyoti Sen

School of Pharmacy, Techno India University, Salt Lake City, Sector-V, EM-4/1, Kolkata-700091, West Bengal, India.


***Corresponding Author: Dibyendu Dutta**

School of Pharmacy, Techno India University, Salt Lake City, Sector-V, EM-4/1, Kolkata-700091, West Bengal, India.

Article Received on 21/07/2024

Article Revised on 11/08/2024

Article Accepted on 01/09/2024

ABSTRACT

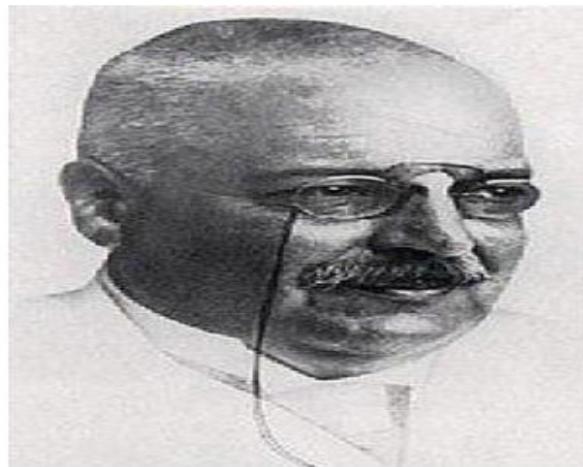
As brain cells become affected, there's also a decrease in chemical messengers (called neurotransmitters) involved in sending messages, or signals, between brain cells. Levels of one neurotransmitter, acetylcholine, are particularly low in the brains of people with Alzheimer's disease. Acetylcholine (ACh), a neurotransmitter essential for processing memory and learning, is decreased in both concentration and function in patients with Alzheimer's disease. There is widespread loss of acetylcholine and other neurotransmitters in Alzheimer's disease and vascular dementia. Alzheimer's disease damages cells that produce and use acetylcholine. Certain medications can increase levels of acetylcholine. They do this by blocking the action of enzymes that break down the neurotransmitter. Acetylcholine is a neurotransmitter that plays a role in memory, learning, attention, arousal and involuntary muscle movement. Medical conditions associated with low acetylcholine levels include Alzheimer's disease and myasthenia gravis.

KEYWORDS: Acetylcholine, Synaptic cleft, Neurotransmitter, Alzheimer disease, Dementia, Tau protein.

INTRODUCTION

Alzheimer's disease is thought to be caused by the abnormal build-up of proteins in and around brain cells. One of the proteins involved is called amyloid, deposits of which form plaques around brain cells. The other protein is called tau, deposits of which form tangles within brain cells. Modifiable risk factors such as sleep,

smoking habits, hypertension or diabetes can further increase the risk. Emil Kraepelin (1856–1926), a doctor in Germany, classified dementia into senile dementia and presenile dementia in 1910. He was the first to name the disease as 'Alzheimer's disease', after Alois Alzheimer (1864–1915), who discovered pathological features of presenile dementia while his student.^[1,2]


Figure 1: Alois Alzheimer [Inventor].

As Alzheimer's worsens, people experience greater memory loss and other cognitive difficulties. Problems can include wandering and getting lost, trouble handling

money and paying bills, repeating questions, taking longer to complete normal daily tasks, and personality and behaviour changes.^[3,4]

Symptoms often include

- Inability to communicate.
- No awareness of recent experiences or surroundings.
- Weight loss with little interest in eating.
- Seizures.

- General physical decline, including dental, skin, and foot problems.
- Difficulty swallowing.
- Groaning, moaning, or grunting.
- Increased sleeping.
- Forgetfulness

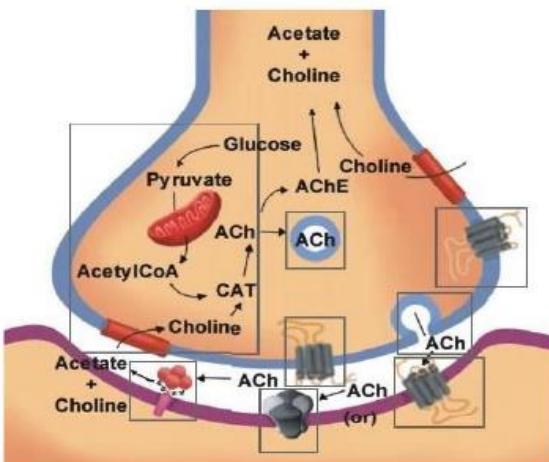
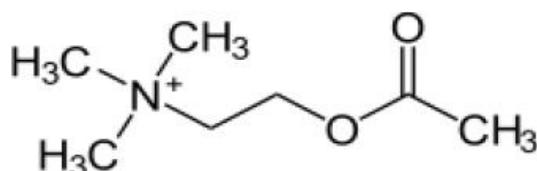


Figure 2: Acetylcholine as neurotransmitter.

It may be possible to reduce your risk of Alzheimer's disease and other types of dementia by:

Reading.

Learning foreign languages.

Playing musical instruments.

Volunteering in your local community.

Taking part in group sports, such as bowling.

Trying new activities or hobbies.

Maintaining an active social life.

There's no cure for Alzheimer's, but there are treatments that may change disease progression, and drug and non-drug options that may help treat symptoms. Understanding available options can help individuals living with the disease and their caregivers to cope with symptoms and improve quality of life. Most people with

Alzheimer's develop the disease when they are 65 or older, with less than 10% of cases occurring before then. As a person ages past 65, their risk of Alzheimer's increases. About one in 13 people 65 to 84 and one in three people 85 and older live with Alzheimer's. Alzheimer disease usually affects people older than 65. A small number of people have "early-onset" Alzheimer disease, which starts when they are in their 30s or 40s. Alzheimer's disease is a brain disorder that gets worse over time. It's characterized by changes in the brain that lead to deposits of certain proteins. Alzheimer's disease causes the brain to shrink and brain cells to eventually die. In the final stages of Alzheimer's, a person may not be able to tell you that they are in pain.^[5,6]

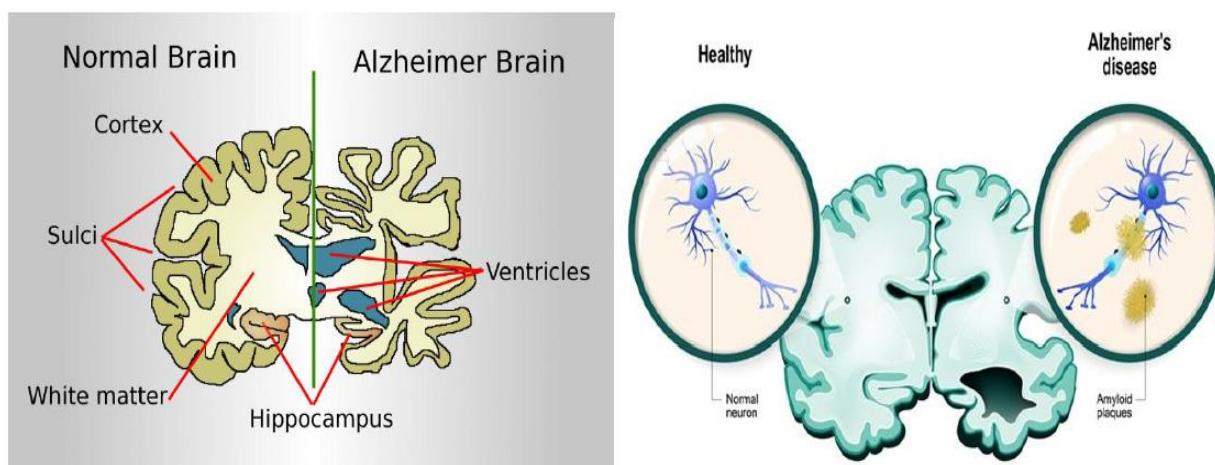


Figure 3: Normal Brain and Alzheimer brain.

Instead, people with Alzheimer's may express pain with groans or sighs and may grimace when touched. They may become upset or aggressive and may sit in unusual positions to guard the part of their body that hurts.

The average life expectancy figures for the most common types of dementia are as follows: Alzheimer's disease – around eight to 10 years. Life expectancy is less if the person is diagnosed in their 80s or 90s. A few people with Alzheimer's live for longer, sometimes for

15 or even 20 years. Only rare instances of Alzheimer's disease are inherited or familial, accounting for less than five percent of all cases. Three familial Alzheimer's disease genes have been discovered so far: two presenilin genes (PSEN1 and PSEN2), and an amyloid precursor protein (APP) gene. Very early stages of Alzheimer's can look like normal-aged forgetfulness. Your loved one might have memory lapses, including forgetting people's names or where they left their keys, but they can still drive, work and be social.^[7,8]



Figure 4: Dementia and Loss of memory.

Misplacing your car keys, calling your neighbour by the wrong name or forgetting to buy bread at the grocery store are common memory lapses. But with age, forgetfulness happens more often, and it's easy to begin questioning what's normal — like if it's a sign of Alzheimer's disease.

Alzheimer's disease is the most common form of dementia, which is a term to describe the loss of cognitive functioning. Over time, Alzheimer's can lead to an inability to carry out daily activities, such as getting dressed, having conversations. If someone you care

about is experiencing signs of Alzheimer's, knowing the signs of each stage can help you assist in managing the disease.^[9,10]

Donepezil, Galantamine and Rivastigmine can be prescribed for people with early- to mid-stage Alzheimer's disease. Rivastigmine can also be applied as a patch. The latest guidelines recommend that these medicines should be continued in the later, severe, stages of the disease. Three cholinesterase inhibitors are commonly prescribed:



Figure 5: Donepezil, Galantamine and Rivastigmine.

Donepezil (Aricept) Donepezil is a medication that treats symptoms of Alzheimer's disease like memory loss and confusion. This medication works by improving your attention, memory and ability to engage in your daily activities. It isn't a cure for Alzheimer's disease or dementia. [CAS: 120014-06-4; (RS)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one] is approved to treat all stages of the disease. It's taken once a day as a pill.^[11]

Galantamine is an acetylcholinesterase inhibitor used to manage Alzheimer disease by elevating acetylcholine levels in the brain, thereby improving cognitive function and memory. This activity reviews galantamine's indications, mechanism of action, contraindications, and adverse events. [CAS: 357-70-0; (4aS,6R,8aS)-5,6,9,10,11,12-Hexahydro-3-methoxy-11-methyl-4aH-[1]benzofuro[3a,3,2-ef] [2]benzazepin-6-ol] is approved to treat mild to moderate Alzheimer's disease.

Rivastigmine [CAS: 123441-03-2; (S)-3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate] is a medication used to manage and treat neurodegenerative disease, specifically dementia, in patients with Alzheimer and Parkinson disease. It is in the cholinesterase inhibitor class of drugs. is approved for mild to moderate Alzheimer's disease. The timing and severity may be different for each person, and it can be difficult to determine which stage your loved one is in because stages may overlap and are only meant to be a guideline.^[12,13]

Stage 1: Before symptoms appear

Just like with many diseases, changes in the brain that are related to Alzheimer's begin before symptoms are noticeable. Currently, there is no treatment for this pre-clinical stage, but we hope in the future that we will have medicines that can halt the progress before people have symptoms and prevent the disease. Because the risk of

Alzheimer's increases with age, it's important to keep up with regular primary care visits to allow for screening to detect the earliest signs of disease. If you notice your loved one's cognitive abilities beginning to slip, that may mean they're entering the second stage of Alzheimer's disease.^[14]

Stage 2: Basic forgetfulness

Everyone can be forgetful from time to time, and that's likely to happen more often with age. Very early stages of Alzheimer's can look like normal-aged forgetfulness. Your loved one might have memory lapses, including forgetting people's names or where they left their keys, but they can still drive, work and be social. However, these memory lapses become more frequent. You will probably notice this before your loved one does — and you may be able to get them treatment sooner to slow the progression.^[15]

Stage 3: Noticeable memory difficulties

For many, this stage brings noticeable changes, and it will become harder to blame age. It's common to be diagnosed in this stage, because this is when a person's daily routine becomes more disrupted. Common difficulties in this stage go beyond forgetting names and misplacing objects. Your loved one may: Have trouble remembering recently read material, such as books or magazines Find remember plans and organizing increasingly difficult Have more difficulty retrieving a name or word Experience challenges in social settings or at work.

This stage may bring about more anxiety for your loved one, and some people may even deny that anything is wrong. These feelings are normal, but not talking to a physician will only allow symptoms to get worse. The best way to keep symptoms at bay is to talk to your loved one's physician about treatment options, including medications, and care planning.^[16]



Figure 6: Brain anatomy of Alzheimer disease.

Stage 4: More than memory loss

In this stage, damage to the brain often involves other aspects of cognition outside of memory, including some difficulty with language, organization, and calculations.

These problems can make it more challenging for your loved one to perform daily tasks. During this stage — which can last for many years — your loved one will experience major difficulties with memory. They may

still remember significant details about their life, such as who they are married to or what state they live in. Their memory of the distant past will usually be significantly better than their memory of day-to-day information, such as what they saw on the news or a conversation from earlier in the day.^[17]

Other challenges during this stage include:

Confusion about what day it is and where they are
Increased risk of wandering off or getting lost
Changes in sleep patterns, such as restlessness at night and sleeping during the day
Difficulty choosing appropriate clothing for the weather or the occasion.

During this stage, situations that require a lot of thinking, such as being at a social gathering, can be very frustrating, and it's common to feel moody or withdrawn. Because of the damage to the brain cells, your loved one may also experience other personality changes, such as feeling suspicious of others, having less interest in things, or feeling depressed.

Stage 5: Decreased independence

Until now, your loved one may have been able to live on their own with no significant challenges. You may have dropped in to check on them every so often, but for the most part, they were able to function without your regular assistance. In this stage, your loved one will likely have trouble remembering people that are important to them, such as close family and friends. They may struggle with learning new things, and basic tasks like getting dressed might be too much for them.

Emotional changes are also common during this stage, including:

Hallucinations: Seeing things that aren't there
Delusions: False beliefs that you believe to be true
Paranoia: The feeling that others are against you

Stage 6: Severe symptoms

Living on your own requires you to be able to respond to your environment, like knowing what to do if the fire alarm goes off or the phone rings. During stage 6, this becomes difficult for people with Alzheimer's. Your loved one will be experiencing more significant symptoms at this time, which impact his or her ability to manage their own care and they will be more dependent on others. Communicating may also become difficult during this stage. Your loved one may still use words and phrases, but communicating about specific thoughts, such as where they're experiencing pain, can be challenging.

Significant personality changes may continue to occur, including increased anxiety, hallucinations, delusions and paranoia. As their independence continues to decrease, your loved one may become more frustrated with you. There are both medicines and behavioural strategies that may help in these instances which you can discuss with your care team.

While the above behavioural changes are not universal and some patients may be content throughout the course of the disease. However, when they do occur, one should remember that they are unaware of what they're doing at this point, so don't take it personally.^[18]

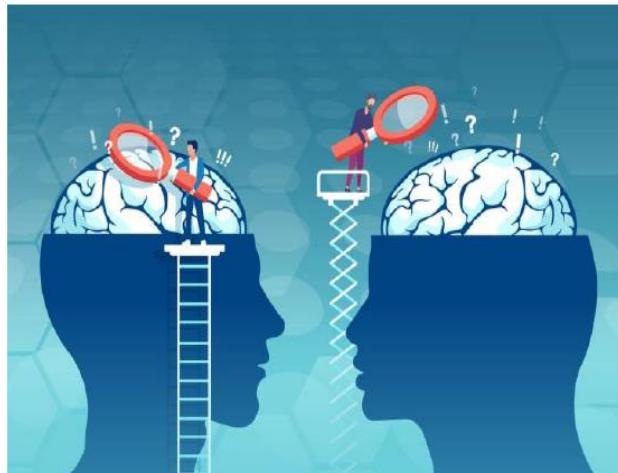
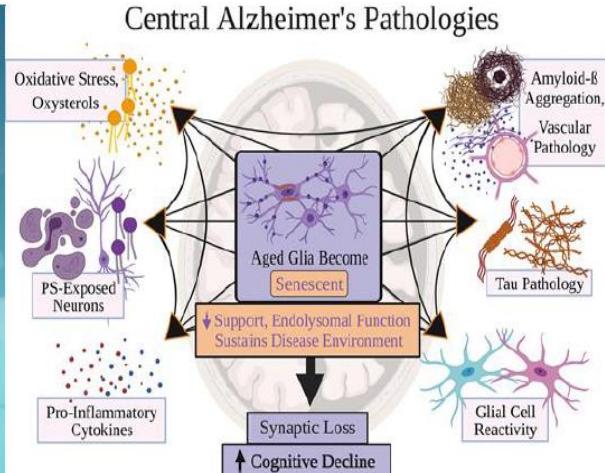


Figure 7: Alzheimer steps.



Stage 7: Lack of physical control

Alzheimer's destroys brain cells, and eventually, this can cause severe mental and physical impairment. Your loved one's body may begin to shut down as their mind struggles to communicate and delegate tasks effectively. At this point, your loved one's needs will significantly increase. They may need round-the-clock care for help with walking, sitting and eventually swallowing. Because of their reduced mobility, their body can also

become vulnerable to infections, such as pneumonia. To help avoid infections, keep their teeth and mouth clean, treat cuts and scrapes with an antibiotic ointment right away, and make sure they get their flu shot each year.^[19]

Participants are given a set of 5 random words to remember for a short duration before being asked to recall them. This seemingly rudimentary exercise is underlined by intricate cognitive processes, and it can be

a vital tool in the early detection of impaired cognitive function. Alzheimer's disease in humans is associated

with the deficiency of acetylcholine.^[20]



Figure 8: MRI of Alzheimer brain.

CONCLUSION

Alzheimer's disease is a brain disorder that gets worse over time. It's characterized by changes in the brain that lead to deposits of certain proteins. Alzheimer's disease causes the brain to shrink and brain cells to eventually die. Alzheimer's disease is the most common cause of dementia — a gradual decline in memory, thinking, behaviour and social skills. These changes affect a person's ability to function. About 6.5 million people in the United States age 65 and older live with Alzheimer's disease. Among them, more than 70% are 75 years old and older. Of the about 55 million people worldwide with dementia, 60% to 70% are estimated to have Alzheimer's disease. The early signs of the disease include forgetting recent events or conversations. Over time, it progresses to serious memory problems and loss of the ability to perform everyday tasks. Medicines may improve or slow the progression of symptoms. Programs and services can help support people with the disease and their caregivers. There is no treatment that cures Alzheimer's disease. In advanced stages, severe loss of brain function can cause dehydration, malnutrition or infection. These complications can result in death. Memory loss is the key symptom of Alzheimer's disease. Early signs include difficulty remembering recent events or conversations. But memory gets worse and other symptoms develop as the disease progresses. At first, someone with the disease may be aware of having trouble remembering things and thinking clearly. As symptoms get worse, a family member or friend may be more likely to notice the issues. Brain changes associated with Alzheimer's disease lead to growing trouble with:

Memory: Everyone has memory lapses at times, but the memory loss associated with Alzheimer's disease persists and gets worse. Over time, memory loss affects the ability to function at work or at home.

People with Alzheimer's disease may:

Repeat statements and questions over and over.
Forget conversations, appointments or events.

Misplace items, often putting them in places that don't make sense.

Get lost in places they used to know well.

Eventually forget the names of family members and everyday objects.

Have trouble finding the right words for objects, expressing thoughts or taking part in conversations.

Thinking and reasoning: Alzheimer's disease causes difficulty concentrating and thinking, especially about abstract concepts such as numbers. Doing more than one task at once is especially difficult. It may be challenging to manage finances, balance check books and pay bills on time. Eventually, a person with Alzheimer's disease may be unable to recognize and deal with numbers.

Making judgments and decisions: Alzheimer's disease causes a decline in the ability to make sensible decisions and judgments in everyday situations. For example, a person may make poor choices in social settings or wear clothes for the wrong type of weather. It may become harder for someone to respond to everyday problems. For example, the person may not know how to handle food burning on the stove or decisions when driving.

Planning and performing familiar tasks: Routine activities that require completing steps in order become a struggle. This may include planning and cooking a meal or playing a favourite game. Eventually, people with advanced Alzheimer's disease forget how to do basic tasks such as dressing and bathing.

Changes in personality and behaviour: Brain changes that occur in Alzheimer's disease can affect moods and behaviours. Problems may include the following: Depression, Loss of interest in activities, Social withdrawal, Mood swings, Distrust in others, Anger or aggression, Changes in sleeping habits, Wandering, Loss

of inhibitions, Delusions, such as believing something has been stolen.

REFERENCES

1. Jignesh B. Patel, Kiran M. Patel, Divyang H. Shah, Jimit S. Patel, Charoo S. Garg, Kinjal J. Brahmbhatt and Prof. Dr. Dhrubo Jyoti Sen; Functional magnetic resonance imaging: a new diversion in medical diagnosis: *Research Journal of Pharmacy and Technology*, 2011; 4(8): 1169–1178.
2. Divyang H. Shah, Kiran M. Patel, Jignesh B. Patel, Jimit S. Patel, Charoo S. Garg and Prof. Dr. Dhrubo Jyoti Sen; Interface between neuroimaging and brain mapping in cognitive psychology: *International Journal of Drug Development and Research*, 2016; 3(2): 51–63.
3. Shivani J. Patel, Krupa K. Patel, Mona S. Patel, Md. Abdullah Hil Baky Rupak, Yash B. Patel, Astha P. Sanyal, Charmi P. Patel and Prof. Dr. Dhrubo Jyoti Sen; Neuro stimulants cognitive enhancers as nootropics in multi task hectic schedule: *World Journal of Pharmaceutical Research*, 2016; 3(5): 570–590.
4. Dr. Dhrubo Jyoti Sen; Galantamine as benzofuro-benzazepine alkaloid used in cognition and dementia: *World Journal of Pharmaceutical Sciences*, 2017; 5(4): 1–5.
5. Mendez MF "Early-onset Alzheimer's disease: nonamnestic subtypes and type 2 AD". *Archives of Medical Research*, 2012; 43(8): 677–685.
6. Khan S, Barve KH, Kumar MS "Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease". *Curr Neuropharmacol*, 2020; 18(11): 1106–1125.
7. Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, et al. "Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline". *Annals of Internal Medicine*, 2008; 148(5): 379–397.
8. Kandiah N, Ong PA, Yuda T, Ng LL, Mamun K, Merchant RA, et al. "Treatment of dementia and mild cognitive impairment with or without cerebrovascular disease: Expert consensus on the use of Ginkgo biloba extract, EGb 761". *CNS Neuroscience & Therapeutics*, 2019; 25(2): 288–298.
9. McKeage K, Lyseng-Williamson KA "Ginkgo biloba extract EGb 761 in the symptomatic treatment of mild-to-moderate dementia: a profile of its use". *Drugs & Therapy Perspectives*, 2018; 34(8): 358–366.
10. Yang G, Wang Y, Sun J, Zhang K, Liu J. "Ginkgo Biloba for Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials". *Current Topics in Medicinal Chemistry*, 2015; 16(5): 520–528.
11. Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, et al. "The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial". *The Lancet. Neurology*, 2009; 8(2): 151–157.
12. Declercq T, Petrovic M, Azermi M, Vander Stichele R, De Sutter AI, van Driel ML, et al. "Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia". *The Cochrane Database of Systematic Reviews*, 2013; 3(3): CD007726.
13. Gitlin LN, Corcoran M, Winter L, Boyce A, Hauck WW. "A randomized, controlled trial of a home environmental intervention: effect on efficacy and upset in caregivers and on daily function of persons with dementia". *The Gerontologist*, 2001; 41(1): 4–14.
14. Gitlin LN, Hauck WW, Dennis MP, Winter L. "Maintenance of effects of the home environmental skill-building program for family caregivers and individuals with Alzheimer's disease and related disorders". *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 2005; 60(3): 368–374.
15. Dunne TE, Neargarder SA, Cipolloni PB, Cronin-Golomb A "Visual contrast enhances food and liquid intake in advanced Alzheimer's disease". *Clinical Nutrition*, 2004; 23(4): 533–538.
16. Dennehy C. "Analysis of patients' rights: dementia and PEG insertion". *British Journal of Nursing*, 2006; 15(1): 18–20.
17. Chernoff R "Tube feeding patients with dementia". *Nutrition in Clinical Practice*, 2006; 21(2): 142–146.
18. Shega JW, Levin A, Hougham GW, Cox-Hayley D, Luchins D, Hanrahan P, et al. "Palliative Excellence in Alzheimer Care Efforts (PEACE): a program description". *Journal of Palliative Medicine*, 2003; 6(2): 315–320.
19. Dominguez LJ, Barbagallo M. "Nutritional prevention of cognitive decline and dementia". *Acta Bio-Medica*, 2018; 89(2): 276–290.
20. Zanetti O, Solerte SB, Cantoni F. "Life expectancy in Alzheimer's disease (AD)". *Archives of Gerontology and Geriatrics*, 2009; 49(1): 237–243.