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## Combination of psycho- and pharmacotherapy as a modern method of treatment of Alzheimer's disease.

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### Abstract

**Introduction:** Alzheimer's disease is a degenerative disease of the brain, caused by the deposition of beta-amyloid and tau protein. It is characterized by progressive memory and behavior disorders which, over time, completely prevent the patient from functioning properly in everyday life, performing work and disrupting social contacts. Communication problems arise and patients forget more and more words. Unfortunately, we are not able to completely stop the progression of this disease, but we can only delay its development. To delay the progression of the disease, pharmacotherapy includes acetylcholinesterase inhibitors and NMDA receptor antagonists.

**Materials and methods:** This article, based on a PubMed review of available research, examines the impact of rivastigmine, donepezil, memantine and psychotherapy on delaying disease progression.

**Results:** A number of studies have investigated the effect of 6-12 milligrams of rivastigmine, 10 milligrams of donepezil and 20 milligrams of memantine on patients' ability to communicate. The results were checked using the MMSE, ADAS or SIB scales and interviews conducted regularly by clinicians. In addition, patients were subjected to various forms of psychotherapy, including reminiscence therapy and cognitive therapy. All groups experienced significantly less deterioration in their functional stage of disease compared to the placebo groups.

**Conclusions:** The best results in the treatment of Alzheimer's disease can be obtained by combining pharmacological therapy with non-pharmacological effects. Thanks to this form of treatment, the progression of the disease is delayed, and patients retain their communication abilities for longer.

**Keywords:** Alzheimer's disease; pharmacotherapy; psychotherapy; communication.

## **Introduction**

Alzheimer's disease is a degenerative disease of the brain. It is characterized by progressive impairment of memory and behavior, impaired ability to learn new information, aphasia (disorders of speech), apraxia (impairment of the ability to produce locomotor activity despite intact physical properties), agnosia (inability to recognize or distinguish objects despite normal sensory functions), and disturbances in activities such as planning and organization. This causes serious problems in the social and professional life of the sick person, as well as leads to a significant deterioration compared to previous levels of functioning. [1]

## **Pathogenesis**

In the course of the disease, proteins with a pathological structure are deposited in the brain - mainly beta-amyloid and excessively phosphorylated tau protein. Abnormal deposits cause the death of nerve cells, most often by apoptosis. Neuronal atrophy leads to a significant deficiency of acetylcholine and, to a lesser extent, other neurotransmitters such as serotonin and norepinephrine. [1]

## **Etiology**

95% of all cases are sporadic, unrelated to familial occurrence. Both genetic and environmental factors are believed to play a role in the development of the disease, but it has not been precisely determined which of these influence the development of the disease and to what extent they contribute to it. The only genetic risk factor that has been documented is polymorphism in the APOE gene (encoding apolipoprotein E). [1] About 1.5-5% of Alzheimer's disease runs in families. The first symptoms then usually appear earlier than in the typical form of the disease and usually progress faster. The likelihood of developing Alzheimer's disease increases with age and is more common in women. If there is any dementia syndrome in the family, the risk of developing this disease is about doubled. Its development is favored by the occurrence of hypertension, type 2 diabetes or heart failure, as well as low physical activity and lack of social contacts. [2]

## **Disease stages and changes in Communications**

There are three stages of Alzheimer's disease, depending on the severity of symptoms: mild, moderate and advanced.

In the early stage of the disease, seniors do not show any major communication problems. They generally understand well what is going on around them and what is said to them, they are able to articulate their needs and express their own opinion. However, the first signs of problems with short-term memory appear. The patient more and more often forgets about everyday events, but remembers events from the past well, even the distant one. There may also be problems remembering certain words, specifying thoughts, and performing complex and focused activities, such as writing or counting. During this period, the patient is often apathetic and depressed, he makes contacts with other people worse, he is less self-confident. At this stage, the role of the caregiver should be limited primarily to discreetly supporting the ward in everyday life and to encouraging him to be active and train his memory regularly. [3]

In the second, medium-advanced stage of the disease, difficulties in communicating with the environment are very clear. Gradually increasing behavioral disorders dominate, such as aimless walking, making the same movements, restlessness, wandering, sudden outbursts of anger, verbal, but often also physical aggression. Patients have serious problems with both short-term and long-term memory. They forget more and more words, confuse concepts, express themselves in an incoherent, chaotic way, stop sentences they start. At this stage, patients begin to have trouble recognizing family members. In addition, there are serious problems with orientation in time and space. Seniors may also forget what basic objects are for, they do not remember to perform everyday activities, such as the need to dress or eat. Their personality may change. In this situation, the patient requires round-the-clock care. [2]

In the advanced stage of the disease, the damage to the brain is so great that the senior almost loses contact with reality and falls into a state of dementia. Not only does he not recognize people around him, but also his own face in the mirror. The patient's ability to communicate verbally disappears. He is unable to form a simple sentence, speaks completely in slurred words, and sometimes stops speaking altogether. The lifestyle becomes more and more sedentary, gradually shifting to permanent bed rest in the terminal phase of the disease. There are visual, auditory hallucinations and delusions. At this stage, the patient is completely dependent on the caregiver, and establishing contact with him or her is very difficult. [2]

### **Rules in communication with patients**

Communicating with people with Alzheimer's is very difficult. They often do not understand the sentences spoken by their carers, but they are very sensitive to non-verbal messages: tone of voice, facial expressions, gestures or body posture. Therefore, when talking to patients, we should adopt the so-called "open attitude", expressing our interest in what patients want to convey. This is, for example, leaning towards the patient during a conversation, maintaining eye contact or nodding with understanding. It is equally important to observe the non-verbal messages sent by the patient, because in the advanced stage of the disease, seniors are not able to verbalize their needs. However, they can convey a lot with gestures alone. If you want to make contact with the patient, you should limit other stimuli, such as the TV or radio on, as this can distract their attention. If he has problems understanding messages, we should speak a little slower and louder. However, do not raise your voice unnecessarily or speak too slowly. When addressing patients, we should use simple, short sentences and avoid asking open-ended questions. If the patient has speech difficulties, the questions should be phrased in such a way that they do not force him to articulate a longer utterance. It's best if he can point to the thing we're asking about. Use words that are understandable to the patient and avoid diminutives and manner of speaking characteristic of contact with a child. During the conversation, we should focus on one issue and not take up other threads. In communicating with patients suffering from Alzheimer's disease, physical contact is also important: a gentle touch, stroking the hand or holding it during a conversation. A great facilitation in communication with patients can be leaving him some information and hints in the form of notes stuck on equipment and furniture containing their names or a brief description of the content. If the patient has a reading problem, the information on the cards may be in the form of pictograms. [2,4]

### **Pharmacotherapy**

In the pharmacotherapy of Alzheimer's disease, only symptomatic treatment is used, there is no causal treatment. Two groups of drugs are used for this. In mild and moderate disease, acetylcholinesterase inhibitors are used, which, by delaying the breakdown of the neurotransmitter (acetylcholine) in the synaptic clefts, increase cholinergic neurotransmission in the relevant areas of the brain. These are donepezil, galantamine and rivastigmine. In the moderate and severe stage, memantine, an NMDA receptor antagonist, is used. In addition, antidepressant treatment with selective serotonin reuptake inhibitors, such as sertraline, venlafaxine or citalopram, can be used. [1]

A series of studies were conducted that examined the effect of these drugs on patients' communication skills. The formal assessment of language proficiency covers the following areas: naming, repetition of words or sentences, comprehension, reading and writing. The Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale (ADAS) were used for mild and moderate disease, and the Severe Impairment Battery (SIB) for severe disease. [5]

### **Rivastigmine**

Four different randomized controlled trials were conducted over a period of twenty-six weeks evaluating the effects of rivastigmine on cognition in patients with mild to moderate Alzheimer's disease. [6] 5,121 people were enrolled in the study, and their age ranged from 68 to 84 years. Exclusion criteria were cardiovascular or pulmonary diseases, unregulated diabetes, peptic ulcers within the last 5 years, alcohol or substance abuse, use of anticholinergics, acetylcholine precursor dietary supplements, nootropics, insulin or psychotropic drugs. The subjects took 6-12 milligrams of rivastigmine daily, and the control group received a placebo. In the group treated with this acetylcholinesterase inhibitor compared to the placebo group, an improvement in cognitive functioning (assessed by ADAS and MMSE), a greater chance of achieving overall clinical improvement as assessed by the CIBIC-Plus scale (Clinician Interview Based Impression of Change) and an improvement in coping with activities of daily living. The participants' communication skills and language understanding improved.

## **Donepezil**

A number of studies in patients with moderate to severe Alzheimer's disease looked at the therapeutic effects of a dose of 10 milligrams of this medicine a day for six months on specific cognitive domains, including language. [7] Based on the SIB analysis using placebo-controlled data, patients treated with donepezil showed improvement in eight out of nine SIB domains. On the other hand, the communicativeness of patients receiving placebo deteriorated.

## **Memantine**

It is an antagonist of glutamatergic N-methyl-D-aspartate (NMDA) receptors, the excessive stimulation of which causes the death of neurons in the mechanism of excitotoxicity, i.e. toxicity from excessive excitation. This leads to the accumulation of degenerative changes in the central nervous system. Memantine binds to them non-competitively, with moderate strength. Thanks to this, it normalizes their functioning - it prevents the effects of excessive stimulation with glutamate in pathological conditions, without completely blocking physiological activity. Patients with moderate to severe Alzheimer's disease were randomized to receive placebo or 20 milligrams of memantine daily for twenty-eight weeks. [8] The main variables regarding the drug's effectiveness were interviews conducted regularly by clinicians - they assessed the degree of communication of patients using the CIBIC-Plus scale and the MMSE. Those in the memantine group showed significantly less deterioration in their functional stage of the disease. A particularly large improvement in communication was observed in patients with severe Alzheimer's.

## **Combination therapy**

Combination therapy – a combination of memantine with cholinesterase inhibitors is also becoming more and more popular. Regardless of their basic neurotransmitter mechanism of action, both groups of drugs are suspected of affecting processes directly related to pathological changes typical of Alzheimer's disease, such as amyloidogenesis, tau protein phosphorylation, apoptosis activation or microglial activity. The toxic effect of elements of the amyloid cascade on neurotransmission has been proven, leading to cholinergic hypofunction and glutamatergic hyperactivity. The use of cholinesterase inhibitors may reduce the severity of amyloidogenesis through a beneficial effect on the metabolism of amyloid precursor protein (APP), while memantine may counteract the adverse consequences of excessive activity of NMDA receptors. Drugs from both groups also have anti-inflammatory effects. [9] Moreover, memantine probably reduces the severity of excessive tau phosphorylation. [10] Data from experimental studies suggest that the cholinergic and glutamatergic systems may interact with each other, and subjecting these interactions to pharmacological modulation may have a beneficial effect on the condition of patients. The safety of combining both therapies has also been tested. Memantine is not metabolised by the hepatic cytochrome P450 enzyme system and is therefore not expected to have any pharmacokinetic interactions with these cholinesterase inhibitors. These theoretical assumptions were confirmed in vivo studies with donepezil, galantamine and rivastigmine - memantine did not change concentrations of any of these drugs and vice versa. [11-13]

The short-term effectiveness of the two-therapy strategy was evaluated in a randomized controlled trial. [14] It involved 404 patients with moderate to severe Alzheimer's disease, taking stable doses of donepezil. In addition, the inclusion criterion was to obtain a score between 5 and 14 on the MMSE test. Patients were randomized to memantine (up to 20 mg/day) or placebo. The study lasted 24 weeks. The basic criteria for measuring the effectiveness of treatment were the scales evaluating the efficiency of cognitive functions - SIB and CIBIC-Plus, as well as scales of the severity of behavioral disorders and psychiatric symptoms (NPI and BGP). Statistically significant benefits of adding memantine over placebo were observed in all scales used. In terms of behavioral effects, combination therapy was found to significantly reduce the severity of such NPI categories as agitation, aggression, irritability, emotional lability, and eating disorders. In patients who did not show signs of aggression at the start of the study, memantine significantly delayed their onset, extending the period of relatively lower care burden. Combination treatment also had a positive effect on patients' independence in terms of daily activities, conversation and the possibility of being left alone by a carer. The addition of memantine also significantly improved the cognitive functions of patients, both in terms of memory and language functions. In addition, the cost-effectiveness analysis showed that the combined use of memantine with donepezil significantly reduced the total cost of care, so in addition to numerous clinical advantages, it also turned out to be economically justified.

The long-term effect of the therapy was assessed by dividing 382 patients into 3 groups. One hundred and sixteen patients were treated with a combination of cholinesterase inhibitors and memantine, one hundred and twenty-two received inhibitors alone, and one hundred and forty-four received no medication. Follow-up visits were held every 6 months, cognitive function was assessed using the BDS (Blessed Dementia Scale) and functioning of patients using the ADL (Activities of Daily Living) scale. The mean follow-up time was 30 months and the mean

cumulative treatment time was 22 months. [15] The pace of disease progression in both analyzed aspects was by far the slowest in patients receiving combination therapy. It is also worth emphasizing that the advantage of using cumulative therapy was more and more evident with the duration of treatment.

## **Psychotherapy**

Pharmacological treatment of Alzheimer's disease should be supported by various methods of rehabilitation, occupational therapy and psychotherapy, because the slowing down of cognitive and functioning disorders is primarily facilitated by constant intellectual stimulation, a variety of mental and emotional stimuli as well as social and physical activity. [1]

There are several types of psychotherapy. Cognitive therapy is an active form of therapy aimed at improving memory and intellectual performance. It consists in getting used to specific exercises or tasks, most often selected individually by a psychologist, which are to strengthen the patient's cognitive efficiency. This division also includes reality orientation training. Its main task is to strengthen the auto-allopsychic orientation (directed to ourselves and to time and place). It is carried out by repeated repetition in short intervals of basic biographical information, the patient's location, date or time. For this purpose, a calendar with large, tear-off sheets and an electronic clock are placed in a place visible to the patient. Patients are also advised to keep diaries and schedules, which they are later taught to use properly. Part of this type of therapy is also actively watching news programs, listening to radio broadcasts or talking about current events. [16]

Reminiscence therapy, also known as memory therapy, involves the use of pleasant memories and events from the patient's past in the treatment. This is achieved by looking at photos, family heirlooms, browsing the press from the old days or talking about the patient's experiences and experiences. For this purpose, own memory boxes or individual albums containing the most important autobiographical events are also constructed. What else we can use during reminiscence therapy are smells. It can be described as aromatherapy, but in this case the scents should have positive associations with the person. It can be the smell of the forest, the smell of garden flowers or your favorite perfume. We can also use elements of music therapy. In its application, it is important that the music comes from the times when the patient felt the happiest. These are usually the times when he was at his most physically fit and uninhibited. [16,17]

The aim of occupational therapy is to maintain normal functioning, fulfill existing social roles and strengthen the sense of "usefulness" among the family and relatives. For this purpose, music therapy, painting, communing with art, treatment with the use of animals (animalotherapy) or light therapy are used. This type of treatment allows to preserve the activities that the sick person is still able to perform properly and to recreate those whose performance has been limited by the progress of the disease. [17]

Environmental therapy consists in adapting the immediate environment to the needs of the sick person in such a way that it supports their independence for as long as possible. For this purpose, minor changes are made in the apartment - the removal of thresholds, the installation of smoke detectors or bathroom handles. Thanks to this, it becomes friendly and safe for the patient. This makes it possible to reduce his fear and normalize relations with the environment, prevents alienation and abandonment of the current social roles. [18]

The last form of non-pharmacological treatment is validation therapy. It has a different goal from other interventions, as it focuses on the mood of a person with dementia. It involves accepting her emotional experiences and listening carefully, affirmatively, to make her feel better and lessen her anxiety. Its task is also to stimulate appropriate social behavior. It consists in confirming the patient's observations, even if they are unrealistic. Thanks to this, people suffering from this disease have a chance to feel that they are understood and accepted. [16]

## **Conclusions**

To sum up, the best results in the treatment of dementia-related disorders, such as Alzheimer's disease, can be obtained by combining pharmacological therapy with non-pharmacological effects. This should be an integral part of the overall concept of treating cognitive disorders. Thanks to this form of treatment, patients retain their communication abilities for longer. Unfortunately, we are not able to completely stop the progression of this disease, but we can only delay its development.

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