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Anti-dementia medications – *fighting a losing battle?*

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Summary

Alzheimer's disease (AD), the most common cause of dementia, is growing health, social and economic issue because of the increasing number of sufferers, limited efficacy of available treatment options, and high total healthcare costs. It is clinically characterized by cognitive and behavioral impairments, both of which need to be treated appropriately to improve patients' quality of life and their caregivers as well. Currently, available anti-dementia medications provide only modest and transient cognitive benefits. Donepezil, rivastigmine and galantamine (cholinesterase inhibitors) are indicated for the symptomatic management of mild to moderately severe AD, while memantine (NMDA glutamate receptors antagonist) is recommended for moderate-to-severe AD. A special focus on behavioral symptoms (e.g. anxiety, depression, aggression) management is required as they cause great suffering in patients/caregivers. The use of medications that can impair cognitive function, such as drugs with anticholinergic activity, should be avoided in patients with dementia. Additionally, interventions that could delay or prevent dementia onset in some subjects are focused on minimizing modifiable risk factors (hypertension, diabetes, depression) and maximizing protective factors (physical activity, healthy diet, leisure, and social activities). The treatment of AD remains a challenge.

Key words: Alzheimer's disease, donepezil, rivastigmine, galantamine, memantine, pharmacist-led interventions

Introduction

To fight a losing battle is not a promising beginning, but it aims to draw attention to one of the biggest challenges facing modern medicine, that is the increasing number of dementia sufferers on the one hand, and very limited therapeutic options on the other (1,2). Thus, raising dementia awareness and implementing measures for its prevention/treatment are within the scope of practice of all healthcare professionals.

It is very important to make a difference between key terms that partially overlap and are misused as synonyms. Dementia is a clinical syndrome characterized by progressive loss of cognitive abilities that significantly impairs the performance of daily living. While memory impairment is the most common in dementia patients, other cognitive domains such as language, visuospatial ability, and executive functions are also affected. Behavioral disorders such as depression, hallucinations, delusions and agitation, also develop in many dementia syndromes. Symptoms of dementia usually develop gradually and tend to get worse over time. It is estimated that dementia develops in 6-10% of the population aged 65 and above, so an increasing number of sufferers and costs worldwide are driven by increased longevity (2-4). Alzheimer's disease is the most common cause of dementia (60-70%), followed by vascular, Lewy bodies, and frontotemporal dementias. Mixed dementias in which more than one type of dementia occur simultaneously are also common (3,4). The crucial issue in all dementia syndromes is that cognitive impairments are sufficiently pronounced to disrupt daily living activities and social functioning. Mild cognitive impairment is an acquired cognitive deficit without significant impairment of daily living activities (3,4). Nearly half of people with this cognitive impairment will progress to dementia, usually of Alzheimer's type, in 3 years. It is still unknown why some subjects develop dementia and others do not (2,4).

Altogether, dementia syndromes (especially Alzheimer's disease) are highly prevalent conditions, adversely affect patient quality of life, burden caregivers, increase institutionalization, and are costly to families and society. Additionally, there are stigmatising beliefs attached to dementia, which can cause people to avoid diagnosis. Therefore, in this work available and potentially novel treatment options for Alzheimer's disease will be discussed.

Alzheimer's disease

Alzheimer's disease (AD), the most common dementia type, is a progressive, irreversible neurodegenerative disease followed by a mental decline of patients. The prevalence of AD is rising and reaching epidemic proportions (5,6). Usually, symptomatic AD lasts about 8-10 years. Some patients with AD show a steady decline in cognitive functioning while others have extended plateaus with no significant clinical deterioration (4,7). AD is associated with high patients' care costs, while the emotional

toll for family members and caregivers is immeasurable (4,8). According to the World Health Organization, AD and other dementias are the fifth global cause of death (9). Thus, AD is a growing health, social, and economic problem.

Risk factors for AD development can be classified as unmodifiable (age, genotype, female sex) and potentially modifiable (vascular risk factors, depression, hearing loss, head injury, lack of physical activity, environmental factors), either by pharmacological measures or lifestyle modification. The single most important risk factor for AD is increasing age (> 65 years). In this regard, it needs to be emphasized that AD and other dementias are not a part of normal aging. A positive family history of dementia implies a genetic contribution to AD, but autosomal dominant inheritance occurs only in 2,5-5% of patients. Female sex is another unmodifiable risk factor that is not related to the general greater longevity of women (3,4). It is estimated that about a third of AD cases worldwide could be attributed to potentially modifiable risk factors (9), but no convincing data on beneficial effects of risk factors control have been reported in clinical settings (2,3,11). However, interventions to minimize risk factors and maximize protective factors may be considered justified in light of their overall health benefits (2,3,11). Interventions to minimize risk factors for AD include appropriate management of vascular risk factors (hypertension, diabetes, insulin resistance, and dyslipidemia - especially in midlife age) and depression, smoking cessation, caution with exposure to proposed environmental risk factors (aluminium, mercury, and viruses) (2,3,7). On the other side, certain lifestyle habits are linked to lower risk for AD and are recognized as protective factors. These include a higher level of education (formation of „cognitive reserve"), physical activity (positive effects on plasticity and cerebral circulation), Mediterranean-like diet (antioxidant and anti-inflammatory properties), leisure (reading, playing board games/musical instruments, dancing – serve as cognitive training) and social activities (1-3, 12-14).

Drug-induced dementia symptoms

„*Any new symptom in an older patient should be considered a possible drug side effect until proved otherwise"*.

This frolicsome statement seems to be appropriate in the case of AD, as many commonly used medications may cause undesirable effects that mimic dementia symptoms, especially in older adults. As AD is associated with a deficiency in brain acetylcholine levels, centrally acting anticholinergic medications particularly negatively impact cognition. First-generation antihistamines (e.g. diphenhydramine, dimenhydrinate, promethazine), tricyclic antidepressants (e.g. amitriptyline, doxepin, imipramine), and bladder antimuscarinics (e.g. oxybutynin, tolterodine) are the most commonly prescribed anticholinergic drugs and should be ruled out first when drug-induced dementia is suspected (15). Certain antipsychotics (e.g. chlorpromazine,

olanzapine, clozapine) and antiparkinsonian drugs (e.g. trihexyphenidyl, biperiden) with anticholinergic properties are also often used (15,16). Some over-the-counter (OTC) medications (e.g. dimenhydrinate, diphenhydramine; regimens vary by country) used in self-medication to treat colds and allergies, as well as sleep aids, are linked to cognitive impairment in older adults. Anticholinergic drugs-induced cognitive impairment is considered to be reversible upon medication discontinuation, but there is also evidence that anticholinergic treatment may be associated with a higher risk of dementia development. Nonetheless, some drugs without anticholinergic potentials, such as benzodiazepines, non-benzodiazepine sedative-hypnotics, and anticonvulsant drugs, have also been associated with cognitive and/or behavioral impairment (15,16). Therefore, the use of drugs that could negatively impact cognition should be limited or discontinued (if possible) in subjects with high risk for dementia, and dementia patients as well.

Rationale for the pharmacological treatment of Alzheimer's disease

Compelling data support the amyloid cascade hypothesis in the pathogenesis of AD, by which slow and progressive accumulation of aggregates of the toxic β-amyloid peptide (Aβ) in the brain triggers a complex pathological cascade leading to neurodegeneration and dementia symptoms (17). Aβ production depends on the proteolytic processing of the amyloid precursor protein (APP) by enzymes β- and γ-secretases. Aβ exists in various lengths, including the non-toxic Aβ40 and the toxic Aβ42 forms. Non-toxic Aβ and APP probably have a protective role, while Aβ42 aggregates form oligomers, fibrils, and ultimately insoluble extraneuronal amyloid plaques (a neuropathological hallmark of AD). Aβ42 oligomers promote hyperphosphorylation of the tau protein and its deposition into neurofibrillary tangles intracellularly (a neuropathological hallmark of AD). There is a strong correlation between tau pathology and neuronal loss and consequently disease severity (17,18).

In a functional sense, the amyloid cascade causes synaptic dysfunction, neuronal dysfunction, and loss, primarily in the neocortex, associative regions of the hippocampus, amygdala complex, and nucleus basalis Meynert (NBM), i.e. in brain structures that are important for cognition. The NBM is the major source of cholinergic innervation of the cerebral neocortex. Degeneration of these neurons results in a decreased acetylcholine level, which correlates with the severity of the cognitive deficit. Disorders in glutamatergic, serotonergic, and noradrenergic transmission also occur (7,17).

Thus, the amyloid hypothesis provides the rationale for therapeutics designed to (5,18):

- target production/accumulation of toxic Aβ peptides, Aβ aggregates (especially oligomeric soluble forms) and hyperphosphorylated tau proteins, their

excretion and/or intracellular signaling cascades leading to nerve degeneration => potential disease-modifying based therapy

- target levels of neurotransmitters (to increase cholinergic/noradrenergic/serotonergic and decrease glutamatergic transmission) => symptomatic based therapy.

Pharmacological treatment for Alzheimer's disease

The treatment of AD is still a great challenge. Currently, available medicines for AD cannot slow down or stop disease progression but can ease symptoms for a while and improve life quality for both patients and their carers. As AD progresses, neurons die and cell connections are lost, causing worsening of cognitive symptoms. Thus, treatment should be initiated without delay. Dementia treatment could address problems with cognition and behavior as well (1,3,19). Thus, we will discuss the management of cognitive and behavioral symptoms associated with AD.

Management of cognitive symptoms

Currently available drugs, cholinesterase inhibitors and memantine, provide only modest and transient cognitive benefits. Therefore, it is important to have realistic expectations regarding therapy, especially by the patient's family and caregiver(s).

Donepezil, rivastigmine and galantamine

Cholinesterase inhibitors (ChEI), donepezil, rivastigmine, and galantamine, are indicated for the symptomatic management of mild to moderately severe AD (20,21). Rivastigmine is also licenced for the treatment of mild to moderately severe dementia associated with idiopathic Parkinson's disease (20,21). ChEIs appear beneficial for dementia with Lewy bodies, which may be considered an „off-label" indication (19).

Clinical efficacy. Cognitive and overall benefits of ChEIs, although modest, have been confirmed in numerous clinical studies in patients with mild to moderate AD (1,22). Some reputable sources state that ChEI (particularly donepezil) could also help people in the later stages of AD, so physicians may continue to prescribe one of these drugs for longer if they realize it is still having a beneficial effect (23,24). From the patients' perspective, about 40–70% of those taking a ChEI find it helps them (6). So far, no difference in the effectiveness between ChEIs has been shown, but some people may respond more favorably to one ChEI than another. Some guidelines (e.g. NICE guidance) suggest that the cheapest drug (currently donepezil) should generally be tried first (6,19). If no response is achieved with one of the ChEIs, it should be replaced by another, and if that attempt does not lead to results, a third ChEI should not be tried. After 6 to 12 months (possibly longer with donepezil) the beneficial effect of ChEIs on cognition usually wears off, so symptoms gradually get worse over time, even though

the patient is still taking medications. Therefore, as the disease progresses, therapy will need to be re-evaluated (1,3,7). Discontinuation of ChEI treatment can lead to the loss of beneficial cognitive and functional effects that may not have been evident. Because limited data on their long-term biological and clinical effects are available, there is no clear consensus of how long ChEIs should be prescribed. Therefore, the decision about whether to continue therapy should be individualized. If a patient is still having beneficial effects to ChEI therapy, treatment is generally continued as long as the patient/his caregiver is willing to continue with the medication, remains reasonably adherent, and does not have intolerable adverse drug effects. The treatment goals should be agreed upon with the patient (his caregiver), with monitoring of the patient over time, for both drug-related beneficial and adverse effects (6,25).

Mechanism of action. Donepezil, rivastigmine, and galantamine work in a similar way by preventing the enzyme acetylcholinesterase from breaking down acetylcholine. As stated previously, decreased cortical acetylcholine levels in dementia patients are in correlation with an increase in cognitive symptoms. Accordingly, ChEIs by increasing the amount of acetylcholine and most likely activating muscarinic M_1 receptors (play a crucial role in cognitive functions like learning and memory), improve the communication between nerve cells in cholinergic synapses and consequently diminish cognitive impairment (3,7,17,26). The dosing and titration schedule of the ChEIs is presented in Table 1.

Undesirable effects. Most patients tolerate ChEIs well. The most common side effects of donepezil, rivastigmine, and galantamine are diarrhoea, muscle cramps, fatigue, nausea, and vomiting. Side effects are less likely to occur when treatment is started with lower doses (1,20,21). Some patients taking donepezil complain of vivid dreams and nightmares and in these cases morning dosing may be preferred. There is an evidence that patients who do not tolerate one ChEI may tolerate another, so changing one ChEI with another seems to be appropriate (1).

Table I Pharmacological management of cognitive symptoms of Alzheimer's disease (20,21)

Tabela I Farmakološko lečenje kognitivnih simptoma Alzheimer-ove bolesti (20,21)

Drug (generic name)	Brand names	Dosage form (strength)	Titration	Comments on dosing
Donepezil	**Aricept®** **Aricept Evess®** **Donecept®** **Donepezil Alvogen®** **Tregona®** **Yasnal®** **Yasnal® Q-Tab®**	• tablets • oral dispersible tablets (5 and 10 mg)	• treatment is started with 5 mg/day (*once-a-day* dosing) • following a one-month clinical assessment of treatment at 5 mg/day, the dose can be increased to 10 mg/day (maximum recommended daily dose)	• donepezil is taken usually at bedtime, but if insomnia occurs morning dosing could be preferred
Rivastigmine	**Exelon®** **Nimvastid®** **Rexit ®**	• capsules (1.5, 3, 4.5 and 6 mg) • transdermal patches (4.6mg/24h, 9.5mg/24h)	<u>oral dosage forms</u> • treatment is started with 1.5 mg twice a day • if well tolerated; after a minimum of two weeks, the dose should be increased to 3 mg twice a day, and subsequently up to 6 mg twice a day (maximum recommended daily dose) <u>transdermal patches</u> • treatment is started with 4.6 mg/24 h • if well tolerated, after a minimum of four weeks, the dose should be increased to 9.5 mg/24 h, the daily recommended effective dose	• patches may be better for people who can not take medication by mouth • only one patch should be used at any one time • new patch should be put on a different area of the skin, to avoid a rash
Galantamine	**Alzamin®**	• prolonged release capsules (8, 16 and 24 mg)	• treatment is started with 8 mg/day for four weeks, increasing to 16 mg/day for another four weeks, and then kept at a dose between 16 mg and 24 mg daily (maximum recommended daily dose)	• galantamine is taken once a day in the morning, preferably with food • capsules must not be chewed or crushed
Memantine	**Memando** **NEMDATINE** **YMANA**	• tablets (10 and 20 mg)	• treatment is started with 5 mg/day, increasing the dose every week by 5 mg, up to 20 mg/day after four weeks (recommended maintenance dose is 20 mg/day)	• memantine is usually given in the morning to avoid sleep disturbance

Memantine

Memantine is approved for the treatment of moderate to severe AD (20,21). Memantine monotherapy could be recommended as an option for patients with moderate AD who do not tolerate or have a contraindication to ChEIs (19). It could be also offered to people with Lewy body dementia if ChEIs are not tolerated or are contraindicated (19). Research is underway to learn more about whether memantine might be beneficial for people with other forms of dementia.

Clinical efficacy. Like ChEIs, memantine represents symptomatic therapy of AD. Memantine can improve cognitive symptoms, but there is an evidence that it may also help with behavioral symptoms such as delusions, aggression, and agitation (1). There is an important difference in the efficacy of memantine depending on the stage of the disease. The notable clinical benefit of memantine in patients with moderate-to-severe AD was observed, while patients with mild AD have no beneficial effect (27). A consensus has been reached that memantine and ChEIs combination in patients with moderate-to-severe AD shows small but significant improvement of overall functioning, cognitive and behavioral symptoms with acceptable tolerance, in comparison to ChEIs alone (28). This observation is pharmacologically expected because these drugs have complementary mechanisms of action.

Mechanism of action. Memantine blocks NMDA glutamate receptors thereby interrupting excessive glutamatergic activity. Excessive glutamate production, which results in the excessive flow of calcium into neurons through NMDA receptors, plays an important role in the pathogenesis of AD (17,27). Thus, the clinical actions of memantine are likely to be associated with a decrease in this excitotoxicity (27).

Undesirable effects. The most frequently occurring adverse reactions to memantine are dizziness, headaches, constipation, somnolence, and hypertension. These effects are usually only temporary. Concomitant use of memantine and amantadine (chemically related NMDA-antagonist), L-dopa or dopamine receptor agonists (e.g. pramipexole, ropinirole) may result in clinically relevant interactions due to an increased risk of CNS toxicity. Thus, caution or avoidance (in the case of amantadine) is needed with mentioned comedications (1,20,21).

Many other treatments, such as cerebrolysin, nicergoline, piracetam, pentoxyfylline, selegiline, and vinpocetine are used in some countries as treatments for AD. There are no convincing data for the efficacy of these drugs in AD management and they should not be recommended to patients (1).

Management of behavioral symptoms

Behavioral symptoms, such as anxiety, depression, aggression, paranoia, sleep, and appetite disorders, are very common (occur in 80-90% of patients) in AD. These symptoms cause much suffering to patients and their carers, sometimes more than cognitive impairment. Clinical evidence indicates a high placebo response, thus safe nonpharmacological measures should be, wherever possible, firstly tried as some symptoms may resolve over time. Pharmacotherapy should be reserved for more severe cases, as it is often associated with unfavorable outcomes. Selective serotonin reuptake inhibitors and trazodone may be useful for anxiety and depression treatment in dementia because they are devoid of anticholinergic properties. Antipsychotics, conventional and atypical, may reduce agitation, paranoid and aggressive behavior, but may also increase the risk for fatal outcomes due to stroke and cardiovascular events, and the risk of infections such as pneumonia. Therefore, antipsychotics should be used with caution after careful assessment of risk and benefit. Anticonvulsives, carbamazepine or oxcarbazepine, are considered helpful for agitation/aggression („off-label" use), and may be used in combination with atypical antipsychotics as needed (1,7,29).

(Lack of) Efficacy of pharmacological treatments in the prevention of Alzheimer's disease

Several pharmacological treatments have been tested to reduce the risk of AD development. It was found that vitamin supplementation (B, E, or multi-complex), nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, statins, menopause hormone therapy (estrogen and estrogen-progestin) do not reduce the risk of subsequent AD development in cognitively normal subjects and should not be recommended. No treatment (cholinesterase inhibitors, vitamin E, NSAIDs, aspirin, statins, menopause hormone therapy) has been shown to be effective in preventing/delaying the development of AD in subjects with mild cognitive impairment and should not be recommended (1,3,11).

The inconsistent pattern of benefit associated with *Ginkgo biloba* was observed in subjects having normal basal cognition or mild cognitive impairment. Further evidence is needed to clearly establish the efficacy of Gingko (1,2).

Research into new treatments

„Nihil novum sub sole"

Although great strides have been made in understanding AD pathophysiology, there are no approved disease-modifying medications for AD and no new drugs have been licensed for the management of cognitive symptoms since memantine in 2002 (in Europe). However, there is a lot of research into new drug treatments.

When it comes to disease-modifying therapy, the majority of drugs tested in the past 15 years have targeted the accumulation and deposition of the Aβ peptide. Despite the evident Aβ clearance and/or attenuation of neuropathological changes in certain brain regions, anti-amyloid drugs tested so far failed to provide meaningful clinical benefits in patients with prodromal, mild, and moderate AD (18,30). Unexpectedly, some drugs such as verubecestat, a β-secretase inhibitor, were found to worsen cognition (31), while Aβ immunotherapy (i.e. vaccination with Aβ oligomers, which induces an immune response against Aβ oligomer aggregation and promotes its clearance) caused meningoencephalitis (32). These disappointing results have raised the possibility that Aβ is a byproduct of the AD pathology, rather than its cause, casting doubt on the prevailing amyloid hypothesis of AD. To overcome this problem, research efforts are currently focused on the most neurotoxic species, Aβ oligomers, and monoclonal antibodies directed against these oligomers such as aducanumab, solanezumab which are (were) in phase 3 clinical trials (30). Further, drugs are now being tested in asymptomatic stage of AD (i.e. in cognitively intact subjects at risk of AD), having in mind that Aβ accumulation in the brain starts 15–20 years before the clinical onset of dementia (5,30). Approaches directed against tau aggregation, CNS inflammation, and brain insulin resistance, are also in the focus of ongoing clinical studies (18).

Something very unusual happened recently. The company that developed aducanumab announced that this anti-amyloid antibody failed futility analyses in phase 3 clinical trials in patients with prodromal or mild AD, and discontinued the study and further drug development (March 2019). A little bit later (October 2019), the same company disclosed that they were applying for US Food and Drug Administration (FDA) marketing approval of aducanumab. After they reanalyzed the data it was found that aducanumab given at high doses actually reduced clinical decline in patients with early AD (33). We will find out soon if the first disease-modifying therapy will be approved.

Role of the pharmacist in dementia treatment

Pharmacists could certainly play a more important role in the care of patients with dementia than they currently have. Due to their accessibility and expertise in the appropriate utilization of prescription and OTC medications, and dietary supplements as well, pharmacists are uniquely positioned to help dementia patients at all stages of the disease (asymptomatic, prodromal, and symptomatic). As dementia occurs in older people, when comorbidity and comedication are common, pharmacists by having access to patient medications list, can timely recognize the adverse impact of concomitant treatment on cognition and unwanted drug interactions (34,35).

Community pharmacist-led interventions in prevention/treatment of AD could include (34-36):

- identifying subjects with risk factors for AD => suggest healthy lifestyle habits
- identifying subjects with early symptoms of cognitive decline associated with AD (subtle short-term memory changes, difficulty finding the right words and completing normal tasks, mood changes, disorientation in time or space, misplacing items, being repetitive) => refer subjects with suspected dementia symptoms to physicians for follow up
- screening patients' medication list for drugs that could impair cognition, especially with the increased anticholinergic burden (including those available as OTC medicines**)** => consider minimizing the use of such medicines, and, if possible, look for alternatives in consultation with prescribers
- educating and counseling patients and their caregivers about the disease course, the efficacy and safety of available treatment options to improve treatment adherence and maintain patients' independence
- therapy monitoring to determine problems such as medication failure, non-adherence, and side effects => continue with counseling and look for interventions that may overcome the problem (alternative medication/formulation/delivery method/regimen) in consultation with prescribers.

Conclusion

Let us hope we have not lost the battle with dementia yet. It is probably more prudent and rational not to fight the battle, but to adopt healthy lifestyle habits from early life and to control modifiable risk factors, as the current treatment options provide only modest clinical benefit and novel treatments are still uncertain. The role of pharmacists in dementia treatment is indisputable but underused in our healthcare system.

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Lekovi u lečenju demencija – *unapred izgubljena bitka*?

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Kratak sadržaj

Alzheimer-ova bolest (AB), najčešći oblik demencije, rastući je zdravstveni, socijalni i ekonomski problem zbog sve većeg broja obolelih, nedovoljne efikasnosti postojećih terapijskih mera, kao i velikih ukupnih troškova nege. Klinički se manifestuje smanjenjem kognitivnih funkcija i poremećajima ponašanja, koje treba adekvatno lečiti kako bi se popravio kvalitet života obolelih i njihovih negovatelja. Raspoloživi lekovi za lečenje demencija ostvaruju umereno i prolazno poboljšanje kognitivnih funkcija. Donepezil, rivastigmin i galantamin (inhibitori holinesteraza) su indikovani kao simptomatska terapija blage do umereno teške forme AB, dok se memantin (antagonist glutamatergičkih NMDA receptora) preporučuje za lečenje umerene do teške AB. Poseban aspekt lečenja predstavlja terapija bihejvioralnih simptoma (anksioznost, depresija, agresivnost), koji su veliki problem za pacijente i negovatelje. Trebalo bi izbegavati primenu lekova koji nepovoljno utiču na kogniciju, kao što su lekovi sa antiholinegičkim dejstvom, kod pacijenata sa demencijom. Dodatno, kontrola promenljivih faktora rizika (hipertenzija, dijabetes, depresija) i usvajanje protektivnih faktora (fizička aktivnost, zdrava ishrana, socijalne aktivnosti i aktivnosti u slobodno vreme) možda može da spreči ili odloži pojavu demencije kod izvesnih ljudi. Lečenje AB i dalje je veliki izazov.

Ključne reči: Alzheimer-ova bolest, donepezil, rivastigmin, galantamin, memantin, uloga farmaceuta