Review

CHOLINOMIMETIC TREATMENT FOR ALZHEIMER'S DISEASE

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INTRODUCTION

Alzheimer's Disease (AD) is a progressive disease involving the loss of several cognitive functions. In the etiology there are mutation deficits in some genes and resultant mutational changes in amyloid precursor protein, presenilin 1 and 2, apolipoprotein E and low-density-lipoprotein-bound receptor protein (1).

AD is the most common cause of dementia; 50-60% of all dementia cases and more than 50% of institutionalized patients have been diagnosed with AD. It is a disease of the elderly, its prevalence doubles every 5 years after the age of 65 years (2), and its incidence reaches 8% per year from age 85 onward (3).

Major risk factors for AD are age, family history and apolipoprotein E4 type while minor risk factors are Down's syndrome, head trauma, myocardial infarction, hyperthyroidism, vitamin B_{12} deficiency, exposure to toxins, low educational status and female gender. Tobacco consumption has been determined as a factor lowering the risk of AD.

AD can have many different etiologic, clinical and pathologic presentations, which makes the differential diagnosis of AD important. Although the most common cause of dementia after AD is vascular dementia (3), its first rank in the differential diagnosis is replaced by Parkinson's disease as a result of improved imaging techniques. See Table I for a summary of dementia causes other than AD. The treatable causes of dementia should be ruled out before a diagnosis of AD is established.

Table I.: Causes of dementia other than Alzheimer's disease.

Vascular dementia	Creutzfeldt-Jacob disease
Binswanger's disease	Sydromes of focal cortical atrophy
Thalamic dementia	Metabolic or toxic encephalopathies
Amyloid angiopathy	Vitamin B_{12} deficiency
Lewy body dementia	Hypothyroidism
Frontal lobe dementia	Wernicke-Korsakoff syndrome
Pick's disease	Organic solvents
Frontotemporal dementia	Renal impairment
Normal pressure hydrocephalus	Hepatic disturbance
Subcortical degenetrative dementia	Infections
Progressive supranuclear palsy	Viral encephalitis
Huntington's disease	AIDS dementia
Corticobasal ganglion dementia	Neurosyphilis
ALS-PD complex	Whipple's disease
Hallervorden-Spatz disease	Tumors
Progressive subcortical gliosis	Subdural hemorrhage
Prion diseases	Mutiple sclerosis
	Trauma

ALS, Amyotrophic lateral sclerosis; PD, Parkinson's disease; AIDS, Acquired Immunodeficiency Syndrome.

The criteria of three different classifications are available for use in the diagnosis of AD: (a) International Classification of Diseases [ICD-10] (4), (b) Diagnostic and Statistical Manual of Mental Disorders ed. 4 [DSM-IV] (5), (c) National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and

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Related Disorders [NINCDS-ADRDA] (6). Of these, the use of DSM-IV enables the physician to achieve a high rate of accuracy in his diagnoses (7). The presence of normal cerebrospinal fluid, electroencephalogram within normal limits, the detection of remarkable atrophy in computerized tomography or magnetic resonance imaging of the brain are findings that may support the diagnosis of AD (7, 8).

The goal of this review is giving recent information on the cholinomimetic drug group and each drug, discussing the pathologic and pathogenetic properties of AD, which shape the rationale for the pharmacotreatment. Different strategies for the AD treatment will also be mentioned.

PATHOLOGY AND PATHOGENESIS OF AD

The important points in the pathology of AD may be summerized as (a) loss of big-sized neurons, especially in the association areas and some nuclei of the brain, (b) accumulation of the Aβ protein, especially in some locations called "plaques" in the cortex, leptomeninges and in the walls of arteries, (c) accumulation of "tau" as intraneuronal tangles and (d) proliferation of astrocytes and microglia (9, 10, 11).

Macroscopic pathology is characterized by remarkable diffuse atrophy concentrated in the frontal, parietal and temporal regions (3, 12). Atrophy involves the association areas in particular, while preservation of precentral and postcentral gyri is typical. The sulci are presented as enlarged due to the atrophy of the gyri; the cerebral ventricles are presented as enlarged as well (3, 8, 12).

The AD pathogenesis is also related to pathology of molecular level, possibly linked to genetic factors. Beta-amyloid (Aβ), is formed of 40 or 42 amino acid residues and is a small portion of a big transmembraneous molecule named amyloid precursor protein (APP) (3). It is coded on the long arm of chromosome 21, and this may be an explanation of why the people with this syndrome have (early-onset) AD (3, 11). Aβ of 40 amino acid residues (Aβ 1-40) is found in the brains of healthy individuals while Aβ of 42 amino acid residues (Aβ 1-42) is pathologic. Both forms are present in the brains of patients diagnosed with AD and furthermore Aβ is found in the body fluids of these patients (11).

APP is a big molecule crossing the cytoplasmic membrane once and is degraded by enzymatic activity. APP is degraded into so-called "nexins" by alpha-secretase activity, and meanwhile the Aβ molecule is also divided. Beta- and gamma-secretase activity degrades the APP from the amino- (extraneuronal) and carboxy-terminal (intramembranous), respectively. As the amount of Aβ is increased in the AD brain, the alpha-secretase enzyme and nexins are not attributed any role in the AD pathogenesis (11, 12).

Another substance possibly related to the AD pathogenesis is the tau protein, which is involved in the structure of cytoskeleton and micrutubuli. This protein has six isoforms and any one or more may be present in the brain, depending on the age and neuronal subpopulation (11). In AD patients' brains, all of these forms are hyperphosphorylated, and thus their ability to bind the microtubuli is decreased (13). As a result, they are found as double-helical filaments intracellularly. Among the substances mentioned so far, the amount of tau correlates the most with the AD patient's clinical condition (11). Tau localizes to three regions in AD patients' brains: (a) Neurofibrillary tangles, (b) dysmorphic neurites around the senile plaques and (c) neuropil filaments.

Neurofibrillary tangles (NFTs), which are accumulations of intraneuronal cytoplasmic filaments, are one of the two pathologic hallmarks of AD. On the other hand, NFTs are not specific, they may even be found in a healthy brain. In AD brains NFTs are more diffuse than in a healthy brain, and the lesions are also more numerous. NFTs are also seen in aging brains and in degenerative brain diseases (3). They contain the posttranslational hyperphosphorylated form of tau, as mentioned above, as double helical filaments (13). Aluminium is shown to increase tau phosphorylation but as it is found in other diseases in which NFTs are observed, it is rather accepted as a contributing factor in the formation NFTs (3, 13). After two animal experiments in which tau and amyloid proteins are reported to cause NFTs, it is proposed that the interaction of these two molecules could lead to the formation of NFTs (14, 15).

Senile plaques, which are the second of the two pathologic hallmarks of AD, are 50 – 200 μm in size and contain extracellular Aβ 1-40 and Aβ 1-42 centrally and glial filaments, dysmorphic neurites and microglia around this core (3). Other lesions named "diffuse plaques", which cannot be stained with Congo red and can only weakly be stained with hematoxylin-eosin stain, form the earliest pathologic sign of AD, appearing even before the clinical findings develop. They can be demonstrated by strong anti-Aβ 1-42 staining (11, 13).

Some changes in AD pathology points to the possible role of genetic mechanisms in the etiology of the disease. The people with sporadic late-onset AD, which is the most common clinical form of the disease, have three times the ratio of the ε4 of the three different alleles on chromosome 19 for apolipoprotein E, than the healthy population (12). Moreover, it is eight times more common for people with this allele to have AD (3). In the less common early-onset form of the disease mutations are detected at (a) Aβ-coding region of the APP gene or around, (b) presenilin-1 region on chromosome 14 and (c) presenilin-2 region on chromosome 1. Presenilin-1 and 2 proteins are considered to be identical to gamma-secretase (11). These make up only less than 2% of the AD cases and therefore other genes and genetic changes are thought to take part in the pathologic process.

The AD pathogenesis, which begins with the changes in APP metabolism related to genetic and nongenetic factors, continues with nonfibrillary and fibrillary Aβ deposition. These Aβ accumulations are directly neurotoxic even in small concentrations and it is proposed that they also lead to a chronic inflammatory process through the activation of the classical compliment pathway, resulting in neurofibrillary degeneration, synapse loss and neuronal loss, which contribute to the symptomatology of the disease (13).

Cholinergic Hypothesis of AD

Changes in the amounts of certain neurotransmitters are the main cause of AD symptoms (2, 3, 8, 16, 17). Certain neurotransmitter systems, the cholinergic system in particular, are selectively affected in AD.

The presence of acetylcholine in the synapse depends on the activity of the enzymes choline acetyltransferase and acetylcholinesterase. In the presynaptic neuron, choline acetyltransferase transfers one acetyl from acetyl coenzyme-A to choline and thus acetylcholine is formed. These molecules are stored in the specialized presynaptic vesicles which empty into the synaptic cleft upon the arrival of a neuronal impulse (8). Most of the acetylcholine molecules emptied into the vesicle bind the postsynaptic receptors to carry the impulse while some cannot bind and are deactivated by acetylcholinesterase. The bound molecules leave the receptor after the impulse is conducted, are cleaved by acetylcholinesterase and the remaining choline is returned to the presynaptic neuron for recycling (2, 8).

The cortex and hippocampus of an AD brain have considerably low levels of acetylcholine and acetylcholinesterase (3). The neocortex and hippocampus have low activity of choline acetyltransferase, and large amounts of neuronal loss is present in these regions and in the amygdala. The neurons in these regions originate from cholinergic forebrain systems such as the medial septum, nucleus basalis of Meynert and diagonal band of Broca, and there is excessive neuronal loss in these regions as well (17). On the other hand, the enzyme butyrylcholinesterase, which is found in very low concentrations in healthy brains, is found in increased amounts and is more diffuse (18, 19). The presence of the enzyme in senile plaques in high concentrations points to the possible role of this enzyme in the formation of these lesions.

CHOLINOMIMETIC TREATMENT FOR AD

Parameters Used for Quantifying Response to Treatment in AD

Some criteria have been determined in order to detect the condition of the disease and the effect of treatment in the individual patient, for use in the third and fourth phase clinical trials. As they are not in routine use, most physicians are not familiar with these criteria (16). Tests used for the evaluation of the cognitive ability of the AD patient are Alzheimer's disease assessment scale – cognitive subscale (ADAS-Cog),

Clinicians' interview-based impression of change (CIBIC), Clinical global impression of change (CGIC) and Clinical dementia rating scale (CDR) (8, 16, 17). Of these, ADAS-Cog has become the main tool for the cognitive evaluation of the AD patient, considering the recent studies (20). It evaluates the memory, language, orientation, praxis and logic functions of the patient by way of a 11- or 12-part test of 30 minutes, and in the end the patient is given a score between 0-70, a higher score indicating more serious disease. A middle-stage AD patient has 6-12 ADAS-Cog points of cognitive function loss per year (8). CIBIC evaluates the general condition, cognitive ability, behavior and daily activities of the patient by way of information from the patient and his/her care giver (8). CIBIC has been developed from its previous form, CGIC. CDR is a parameter integrating the six main functional domains (memory, orientation, decision-making, social relations, home and hobbies, personal care) and enables the clinician to grade the illness as mild, moderate or severe (21).

In contrast to the presence of standardized tests for evaluating the cognitive functions, there are lots of tests which quantify a patient's ability to manage daily activities and his/her life quality, for which there is no consensus. Mini mental state examination (MMSE), activities of daily living (ADL), geriatric evaluation by relatives rating instrument (GERRI) and progressive detoriation scale (PDS) are examples. There is no consensus on the evaluation of behavior either. Some scales, including ADAS Noncognitive score, Neuropsychiatric inventory (NPI), Behavioral pathology in Alzheimer's disease (BEHAVE-AD), are being used (16).

The criterion for the promotion of drugs to phase III and IV trials has been set by the European Medical Evaluation Agency as the development of 4 points or more in the ADAS-Cog scale in a setting designed to assess a possible clinical effect (16). This is equivalent to a 6-month delay in the decrease of the brain functions, but it may be equivalent to a greater clinical difference when the heterogeneity of the disease is considered. On the other hand, the psychological condition of the patient, behavioral and functional changes have become less important in the evaluation of the drugs as a result of the above mentioned criterion (16).

Basics of Cholinomimetic Treatment

The cholinergic hypothesis of AD, which may be summarized as decreased synaptic acetylcholine leading to AD symptoms, is the basis of symptomatic treatment of AD. The previous strategies, including the trials of (a) agonists of the preserved postsynaptic muscarinic receptors such as arecholine, pilocarpine and (b) precursors of acetylcholine such as choline, phosphatydylcholine, lecithin, have failed due to side effects and discouraging trial results, respectively (2). More selective muscarinic receptor agonists (xanomeline, milameline, civimeline) are under trial. The most effective cholinomimetic treatment today is the use of acetylcholinesterase inhibitors, which have received the approval of the US Food and Drug Administration (FDA) (16). The drugs approved or investigated by the FDA are listed in Table II. These drugs increase the acetylcholine amount in the synaptic cleft by inhibiting the hydrolysis of the acetylcholine molecules secreted into the synaptic cleft (2). Tertiary amino compounds

Table II.: Drugs for Alzheimer's disease treatment.

Drugs which are approved for use in AD by FDA	Selegiline
Donepezil (Aricept™)	Valproate
Rivastigmine (Exelon™)	Drugs under phase II trials for FDA approval
Galantamine (Reminyl™)	AF-102B (Evoxac)
Tacrine (Cognex™)	AIT-082 (NeoTrofin)
Drug with a withdrawn application for an FDA approval	Ampalex (CX-516)
Metrifonate	AN-1792 (AIP-001)
Drugs under phase III trials for FDA approval	Cerebrolysin
ALCAR	Dapsone
Estrogen replacemant therapy	Lipitor
Ibuprofen	Nefiracetam
Memantine	Phenserine
Naproxene	Rofecoxib (Vioxx™)

AD, Alzheimer's disease; FDA, United States Food and Drug Administration.

such as donepezil and tacrine lead to allosteric inhibition by binding the hydrophobic regions in the α and β zones of the acetylcholinesterase surface, while carbamate compounds such as rivastigmine form a complex with a serine residue and deactivate the enzyme (17).

The goal of such AD treatment is improvement in memory, cognition, mood, behavior and as a result, in the activities of daily living. Greater enzyme inhibition leads to more clinical benefit, although this may also lead to greater insight and resultant depression. On the other hand, the efficacy of these drugs is limited due to their side effects. As well as peripheral side effects such as nausea, vomiting, anorexia, diarrhoea, bradycardia, muscle cramps or weakness, facial flushing, rhinorrhea, central side effects such as insomnia, nightmares, irritability and panic state may be observed. Such effects are observed more commonly in low-body-weight patients, higher drug doses, and during upward titration of the drug doses. Slower upward titration of the drug doses has been related to lower frequency of side effects. Adverse effects are usually transient. It is advised that these drugs should be carefully used in patients with peptic ulcers, chronic diarrhea, bradycardia and/or bundle branch block and should be stopped if adverse effects occur or no significant therapeutic effect develops. This effect is usually assessed by the physician considering the MMSE and the care givers' report (2).

There are usually no drug interactions involving the use of acetylcholinesterase inhibitors. It is known that tacrine inhibits the cleavage of teophylline and increases the anesthetic agents succinylcholine muscle relaxants through the cytochrome P450 mechanism (22). The plasma levels of tacrine were found to be increased by 50% when used simultaneously with cimetidine (2).

Tacrine (Cognex™)

Tacrine, known as "first generation acetylcholinesterase inhibitor", was the first to receive an FDA approval among the drugs of this group. Daily dose is 50-100 mg. This drug, which is not strongly marketed abroad, is not commercially available in Turkey.

The efficacy of tacrine has been investigated in numerous studies on thousands of patients. Although number of small studies have yielded discouraging results, two multicenter and large-scale trials have shown the efficacy of the drug (23, 24). At the end of these studies, patients receiving the highest dose of tacrine (80 mg/d and 160 mg/d, respectively) had ADAS-Cog score improvements 4 or 5 points higher than those receiving placebo (In the study by Knapp et al., $p<0,002$ for ADAS-Cog, $p<0,04$ for CIBIC and $p<0,01$ for GDS). According to ADAS-Cog and CIBIC, 160 mg/d of tacrine has been observed to be superior to lower doses (80 and 120 mg/d) and placebo. After a 30-day use of tacrine at 160 mg/d and a 2-year follow-up with tacrine at 120 mg/d, the patients were demonstrated to be less institutionalized compared to patients on lower doses of tacrine. On the other hand, parameters for functional outcome is very different for the two studies and ADAS-Noncog score in both trials is negative. However, depending on the encouraging cognitive outcomes, this drug received FDA approval in 1993 (2, 8, 16, 17).

Investigators have been trying to find clues about which patients respond better to tacrine treatment as not all patients respond the same. It is postulated in one sudy that women carrying the ε2-3 allelles of the apolipoprotein E gene benefit more than those carrying the ε4 allelle, but one other study has denied any relationship of benefit with the mentioned allelles or gender (25). There is one study claiming that estrogen replacement treatment before and after tacrine treatment increases response, possibly due to the neurotropic property of estrogen. Nevertheless, none of these postulated clues have been agreed on so that they can be used in clinical practice (2, 25).

Tacrine has more adverse effects when compared to other drugs of the group. In the studies, the adverse effect rate of tacrine has been found to be 51% and that of placebo 34%. According to physicians' grading, the patients have mostly (95%) been exposed to adverse effects of mild to moderate degree (16). The most common adverse effects are asymptomatic increase in serum transferases (more than 50%), nausea and vomiting (35%), diarrhoea (18%) and

anorexia (12%) (24). The most important adverse effect is the hepatotoxicity which is manifested by asymptomatic, late and dose-independent increase in serum transferases. One study has shown that serum transferase levels in patients using tacrine are greater than the upper limit in over 50% of the patients, more than three times the upper limit in 25% and more than ten times the upper limit in 6% of the patients using tacrine, 6 weeks after initiation of treatment. Toxicity is reversed 5 - 6 weeks after discontinuation of the drug and reinitiation of the therapy does not generally cause hepatotoxicity again. The unpredictability and varying severity of the hepatoxicity makes it necessary to follow the serum transferase levels with weekly blood tests. Cholinergic adverse effects, gastrointestinal in particular, have also been found to occur more often compared to placebo. All these adverse effects make up the main cause of drop-outs from the treatment, which in some studies reach 40-60%. The drop-out rate is highest in the 160 mg/d dose, in which the drug is detected to be most effective. Another reason for the patients' discontinuation is the four-times-daily dosing of the drug, related to its short half-life (2-3 hours) in the blood (2, 8, 16, 17).

Tacrine has interactions with teophyllin and cimetidine through the cytochrome P450 enzyme. Another fact is that it may lead to gastrointestinal bleeding when used with nonsteroidal anti-inflammatory drugs, as it causes an increase in gastric acid secretion (17).

Conclusion: Tacrine is a drug with demostrated general effect on dementia, less effect in some patients, and a high adverse effect profile.

Donepezil (Aricept™)

This drug, which was approved for treatment of AD by FDA in November 1996, is a reversible acetylcholinesterase inhibitor of piperidine class. Compared to tacrine, it is selective for the central nervous system and has no effect on cardiac muscle, intestinal smooth muscle and other peripheral tissues. The long 70-hour plasma half-life of the drug enables once-daily dosage (26). Although the excretion of the drug is possible through mechanisms involving renal pathways and cytochrome P450 enzyme, there occurs no problem in patients with hepatic or renal failure, and there is no need for dose adjustment (2). It is available in Turkey as 5 mg tablets.

The first study on the efficacy of donepezil in AD was performed in 1996. In this trial, the 1, 3 and 5 mg/d doses of donepezil were compared to placebo and a dose-dependent response was obtained with the p values being <0,036 and <0,002 for 3 and 5 mg/d of donepezil, respectively. The drug's efficacy was shown to be superior to placebo in global assessment as well (p=0,039) and efficacy in higher doses has therefore been investigated (27). In a 24-week randomized, double-blind and multicenter trial designed for this purpose, the efficacy of 5 and 10 mg/d of donepezil was compared with placebo (28). At the end of the study the differences in

Table III.: Comparison of pharmacologic and dosage properties of FDA-approved cholinesterase inhibitors.

	Tacrine	Donepezil	Rivastigmine	Galantamine
Marketed since	1993	1997	2000	2001
Chemical class	Acridine	Piperidine	Carbamate	Phenanthrene alkaloid
Plasma half-life (hours)	2-4	~70	~1.5	~6
Bioavailability (%)	17-37	100	40	100
t_{max} (hours)	0.5-3	3-4	0.8-0.12	~1-2
Elimination pathway	Liver	Liver	Kidneys	50% Kidneys, 50% Liver
Brain selectivity	None	Present	Present (Brain region selectivity)	Present
Cholinesterase selectivity	AChE & BuChE	AChE	AChE & BuChE	AChE
Daily dose	4	1	2	2
Taken with meals	No	No	Yes	Yes
CYP 450 metabolism	Yes	Yes	Minimal	Yes
Plasma protein binding (%)	55	96	40	18
Drug interactions	Present	Present*	None known	Present**

t_{max}, time for maximal plasma concentration; **AChE**, acetylcholinesterase; **BuChE**, butyrylcholinesterase; **CYP 450**, cytochrome 450.
* of unknown clinical importance.
** During concomitant use with CYP 2D6 and CYP 3A4 inhibitors, significantly increased cholinergic adverse effects, mainly nausea and vomiting, occur.

Table IV.: Comparison of clinical effects of FDA-approved cholinesterase inhibitors.

	Tacrine	Donepezil	Rivastigmine	Galantamine
Indication	Symptomatic treatment of mild to moderate dementia of Alzheimer's type.			
Contraindication(s)	Hepatic disease, known hypersensitivity	Hypersensitivity to the drug or piperidine derivatives	None known	None known
Points of attention	Liver enzyme monitoring	Cardiac conduction disorder, asthma, seizures, known GI disease and patients on NSAIDs	None	None
Adverse effects	Hepatotoxicity, nausea & vomiting, syncope	Nausea & vomiting, diarrhoea, fatigue, insomnia, anorexia	Nausea & vomiting, fatigue, myalgia, urinary incontinence	Cholinergic GI symptoms in early stage

GI, gastrointestinal; NSAID, Nonsteroidal anti-inflammatory drug.

ADAS-Cog scores were significant in both groups when compared to placebo (p<0,0001). The rate of observed cases with a four-point improvement in ADAS-Cog is 53,3% in those receiving 10 mg/d of donepezil and 26,9% in those receiving placebo. The superiority of 5 and 10 mg/d of donepezil over placebo was also shown in CIBIC comparison (p<0,047 and p<0,0001) and in CDR comparison (p<0,0008 for both of the groups) (28). The difference in the life quality evaluations, however, was not found to be significant (28).

Donepezil is a drug with few adverse effects, especially if the treatment is initiated with the 5 mg/d dose and continued with the 10 mg/d dose 2 weeks after initiation. In a 12-week study designed to investigate the adverse effects of donepezil, the rates related to donepezil of 1, 3 and 5 mg/d doses and placebo were found to be 64%, 68%, 67% and 65%, respectively (27). The majority of these adverse effects is cholinergic, particularly gastrointestinal. Studies have demonstrated that the rate of diarrhoea and vomiting in patients receiving 10 mg/d is significantly higher than in those receiving 5 mg/d dose and placebo; the results of one study were related to rapid dose titration. Adverse effects related to donepezil are usually of mild severity and short duration (16). The drug does not have significant effects on the patient's vital signs, hematologic or biochemical parameters, and it has no hepatotoxicity (2).

Conclusion: Donepezil is a drug related with some degree of improvement in clinical condition of the AD patient and is preferrable due to its once-daily dosage, lack of hepatotoxicity and mild adverse effects.

Rivastigmine (Exelon™)

Approved by the FDA in May 1999, this drug of carbamate class is a noncompetitive acetylcholinesterase inhibitor with brain selectivity. It is used twice or three times a day. The initial dose is 4 mg/d, titrated up to 12 mg/d. Rivastigmine does not bind plasma proteins. The mechanism of action is binding acetylcholinesterase by mimicing acetylcholine and inhibiting the enzyme this way for a long time (16). As a result, the effect of the drug continues for a few hours after the drug is cleaned from the plasma. During enzyme activity, the drug molecule is cleaved into a product named NAP 226-90 and this molecule is rapidly excreted via the kidneys, therefore not involving the cytochrome P450 metabolism (16).

One of the largest clinical trials involving the AD drugs has been designed for rivastigmine. In the second one of 3rd phase clinical trials involving 3300 individuals diagnosed with mild to moderate dementia of AD, called ADENA, response to treatment with low-dose (1-4 mg/d), high-dose (6-12 mg/d) rivastigmine and placebo was measured in 699 patients (29). Of these, 78% completed the trial; among the high-dose groups this rate remained at 65% due to adverse effects. Patients receiving high-dose rivastigmine preserved their ADAS-Cog scores, while those receiving placebo experienced a detoriation of 3,78 points (p<0,001). In the same study, $^1/_4$ of the observed cases reached the goal of 4-point ADAS-Cog scale improvement. This ratio was 29% in a similar study the following year involving 725 patients (19% for placebo) (30). Considering the CIBIC scores in the 1998 study, significantly low detoriation was observed in both low- and high-dose groups (p<0,001 and

p<0,005, respectively). In the other study, the rates of CIBIC score improvement at the end of 26 weeks were determined as 37%, 30%, 20% for the high-dose, low-dose and placebo groups, respectively (2, 16).

The adverse effects related to rivastigmine are mild and transient, usually occurring during upward dose titration, being dose-dependent and resolving without treatment. They are gastrointestinal in general, nausea (48%) and vomiting (27%) occupying the first two ranks. Other adverse effects include fatigue, exhaustion, dizziness and sleepliness; the use of the drug has not been related to death, changes in laboratory parameters, electrocardiographic findings or vital signs (16). One interesting finding is the decrease in mean body weight of the people using rivastigmine while those on placebo have increased mean of body weight. The drop-out rates in the studies were found as 23% for the high-dose group, 7% for the low-dose and placebo groups (2).

Galantamine (Reminyl™)

This phenanthrene alkaloid obtained from *Nercissus pseudonercissus* is a competitive and reversible inhibitor of the acetylcholinesterase, moreover it allosterically inhibits the nicotinic receptors, eventually increasing the presynaptic reponse to acetylcholine (2, 8). This drug, which has been used in some countries for the treatment of myasthenia gravis for about forty years, was approved by the FDA in February 2001 for the treatment of AD, and is not present in the Turkish market yet. Its half-life in plasma is 5-6 hours and it is eliminated by way of cytochrome P450 mechanism (8).

The efficacy of galantamine has been demonstrated with two recent studies (31, 32). In the former of the studies mentioned, evaluation of ADL of the patients receiving 16 and 24 mg/d of galantamine was shown to have significant difference over placebo (Difference for 16 mg/d is –0,5 and that for 24 mg/d is –4,0. p<0,001 for both groups). The rate of patients with improved CIBIC scores was 68% in the group using 24 mg/d of galantamine, 64% in the group using 16 mg/d of galantamine and 47% in the group of patients on placebo. In the second study, at the end of 6 weeks of double-blind trial, mean changes in ADAS-Cog scores were detected as 1,7 points, 1,6 points and –2,2 points for 24 mg/d, 32 mg/d and placebo groups, respectively (p<0,001, p=0,02 and p<0,001, respectively). CIBIC stability at the end of 6 months is 70%, 68% and 55% for the groups mentioned above, respectively (p<0,005 for both groups compared to placebo). After the 6-month double-blind trial, the study was extended by giving all the patients galantamine at 24 mg/d. The patients who had previously had received galantamine at 24 mg/d continued the trial in a stable manner while those who had received 32 mg/d of galantamine experienced detoriation, having similar ADAS-Cog scores to those who had placebo in the first part of the trial (8).

The adverse effects of galantamine are gastrointestinal and of mild to moderate severity in general. The most common adverse effects are nausea, vomiting, diarrhoea, dizziness, anorexia and weight loss (2, 8). The drop-out rates in the first 6-month period of the trial was found to be 23%, 32% and 8% for the 24 mg/d, 32 mg/d and placebo groups, respectively. Forty-two percent of the drop-outs occured during upward dose titration. In the extension phase, only 16% of the patients discontinued treatment. No blood chemistry, hematology, urinanalysis, electrocardiography or vital sign changes were detected in the patients receiving the drug (8).

Conclusion: Use of galantamine in AD patients leads to significant improvement in cognitive and behavioral functions at 24 mg/d, and is safe.

NEW APPROACHES TO THE AD TREATMENT

Approaches to the AD treatment may be summarized as (a) inhibition of abnormal Aβ production, (b) prevention of the inflammatory process in the AD pathogenesis and (c) supporting the neuronal plasticity and regeneration.

The use of antioxidants has been postulated regarding the neuroprotective properties. The use of vitamin E and the monoamine oxidase inhibitor selegilin has been demonstrated to delay institutionalization, and the reduction of the activities of daily living in a 2-year, double-blind and placebo-controlled study, but the use in

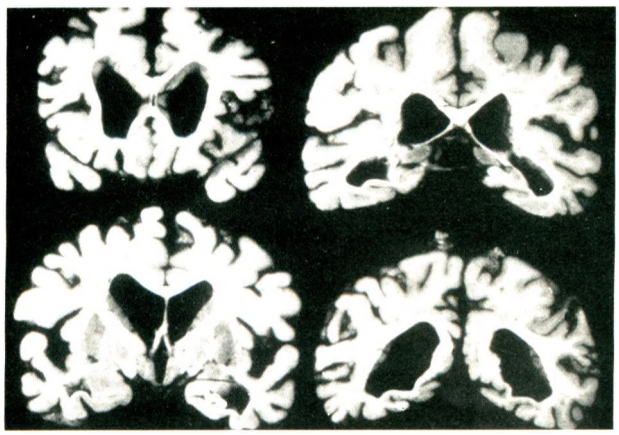

Fig. 1 : The cortical atrophy in these coronal sections of the brain in Alzheimer's disease is reflected by widened sulci and dilated ventricles (Okazaki H, Scheithauer B. Atlas of Neuropathology. Singapore: Gower Medical Publishing, 1988: 220).

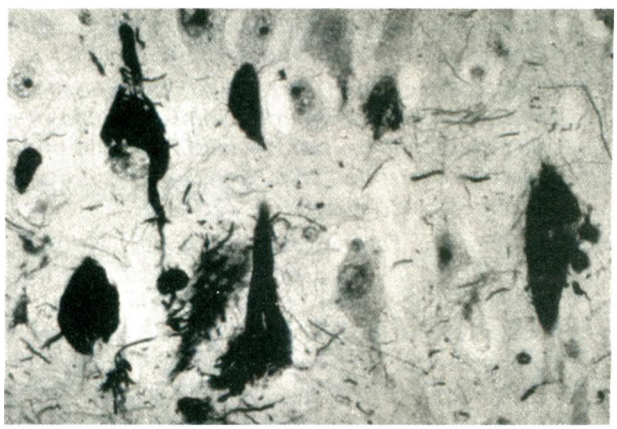

Fig. 2 : In this microscopic view, neurofibrillary tangles, which contain the tau protein as double helical filaments, are demonstrated with one of the silver impregnation techniques (Bielschowsky's method). Normal cytoskeletal elements are not seen. (Okazaki H, Scheithauer B. Atlas of Neuropathology. Gower Medical Publishing, 1988, Singapore. Page 220).

Courtesy of Professor Aydın Sav, M.D., of Marmara Universiy Institute of Neurological Sciences, İstanbul, Turkey.

clinical practice has not been advised because of the adverse effects of selegilin, some of which maybe serious. Indomethacin, a nonsteroidal anti-inflammatory drug, is also being studied. In a 6-month, randomized, double-blind clinical trial, it has been shown to cause a significant improvement in cognitive skills, compared to placebo. Idebenone, an anti-oxidant, and propentophylline, which increases the central endogenous neurogenerative factor, levocarnitine, which again increases choline acetyl transferase activity, are under investigation. Studies on estrogen, prednisone and ginkgo biloba extract (EGb 761) have given discouraging results (2, 8).

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