TREATMENT OF ALZHEIMER'S DISEASE WITH A COMBINATION OF LASER, MAGNETIC FIELD AND CHROMO LIGHT (COLOUR) THERAPIES:

A DOUBLE-BLIND CONTROLLED TRIAL BASED ON A REVIEW AND OVERVIEW OF THE ETIOLOGICAL PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Hayk S. Arakelyan

Clinical Research Dept., UNESCO Chair in Life Sciences, Yerevan, Armenia

Alzheimer's disease presents a major problem as far as successful treatment is concerned, which is exacerbated by the ageing of the world's population, and the increasing number of elderly in the 'at risk' age groups. Low reactive-level laser therapy (LLLT) has been reported as having beneficial effects on the blood vascular and neurological systems, including the regeneration of degenerated axons. The present study with 154 AD patients examined LLLT used as a monotherapy (intravenous HeNe laser irradiation) as well as magnetic field therapy (MFT), light chromotherapy (LCT) and conventional AD pharmacotherapy all as monotherapies, compared with a placebo control group. A further group received a combination of LLLT, MFT and LCT (the LMLCT group). Patients were assessed using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) before treatment and at the end of the 18-month treatment regimen. LLLT and MFT significantly slowed down AD-related deterioration compared with controls ($p < 0.05$), but the LMLCT group was even more significantly effective ($p < 0.001$). Of all the monotherapies, LLLT was the most effective compared with the others, but the differences were not statistically significant. This may have been a factor of the low statistical power of the study due to small group numbers. Pharmacotherapy was the second most efficacious approach, but is associated with severe side effects particularly in elderly patients, and is often contraindicated. The results of the study suggest that combined LLLT, MFT and LCT is a safe, effective, easy-to-deliver, well-tolerated and side effect free therapeutic approach for slowing down the deterioration associated with AD.

Key words: Alzheimer's disease, laser therapy, light chromotherapy, magnetic field therapy, cholinergic system, beta-amyloid cascade

Introduction

Alzheimer's disease (AD), like cardiological and oncological diseases, is a great problem worldwide and there is a pressing need for more effective therapy, particularly in regard to the 'graying' of the world's population in developed countries. At present there are more than 25 million patients with AD. In the United States and Europe 4-5% of people older than 65 years of age have severe AD and 15 % have mild dementia due to AD. Of those older than 80 years of age, approximately 20% have severe dementia caused by AD. The onset of the disease generally occurs in late life, most commonly in the 60s, 70s and 80s and beyond, but in rare instances, the disorder appears in the 40s and 50s (known as early-onset dementia). The incidence of AD increases with age and it is

estimated at 0.5% per year in the 65 to 69 age group, 1 % in the 70 to 74 age group, 2% in the 75 to 79 age group, 3% in the 80 to 84 age group, and 8% per year from the age of 85 onward. Progression is gradual but steadily downwards, with an average duration from onset of symptoms to death of 8 to 10 years. A plateau may occur, but progression generally resumes after 1 to several years. The risk factors for the development of AD include being female, having a first degree relative with the disorder, and having a history of head injury. Patients with the dementia of Alzheimer's type occupy more than 50% of nursing home beds.

AD is associated with gradual progressive memory loss and brain cortex dysfunction. At present the pharmacological treatment of AD is not effective and is limited by side effects and the presence of concomitant diseases in the elderly. New therapy options are desperately needed. Data are appearing which show that laser therapy, magnetic field therapy, light and chromo- (colour) therapy may offer a new, promising approach to the treatment of AD. Until now, these methods have been used with greater or lesser

Addressee for Correspondence:

Hayk S Arakelyan MD PhD,
Dean of Pain and Clinical Research Dept.,
UNESCO Chair in Life Sciences,
14, Apt 40, Bashinjagyan St.,
Yerevan, Armenia.
Tel (3749) 40 94 97; FAX (3741) 350687
e-mail: saspeir@netsys.am

Manuscript received: December 2004
Accepted for publication: February 2005

degrees of success in monotherapy for AD. It is therefore a reasonable assumption that their use in combination therapy for AD may enhance the efficacy due to additive or synergistic effects. The present study was therefore designed to assess and compare the efficacy of laser therapy, magnetic field therapy and chromotherapy in combined- *versus* monotherapy for AD using a double-blinded placebo controlled trial.

Subjects and Methods

145 patients (54 men, 91 women, mean age 73.1) with AD participated in a randomized blind placebo controlled clinical trial. Selection for the clinical trial was performed using the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association) that emphasize the presence of memory impairment and the associated presence of at least one other symptom of cognitive decline (aphasia, apraxia, agnosia, or abnormal executive functioning) and require a continuing and gradual decline in functioning, impairment in social or occupational functioning and the exclusion of other causes of dementia. The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) was taken as the main neuropsychometric test for comparison of the results of different therapeutic options. All candidates were assessed before the trial with the ADAS-cog test and patients with approximately the same severity of AD were selected to achieve the maximal possible heterogeneity in clinical trial groups.

Selected patients were randomized to 6 groups: the first group (25 patients, 8 men, 17 women) received LLLT (intravenous (IV) HeNe laser (633 nm, 4 mW, every day for 5-9 minute, each course consisting of 15 procedures, 6 courses delivered during 18 months of the clinical trial), the second group (25 patients, 10 men, 15 women) was treated by means of magnetic field therapy - MFT (impulse magnetic field capacity 40-60 mTesla, transcutaneous non invasive hemomagnetotherapy by placing magnetic induc-

tor on the projection of the main blood vessels for 10-12 minutes, each course consisting of 15 procedures every day, 6 courses delivered during 18 months of clinical trial; a course once every three months). The third group (17 patients, 7 men, 10 women) received visual light and visual color stimulating chromotherapy - LCT (lemon color visual chromotherapy every day alternated with yellow and green colors, each course consisting of 15 procedures for 15-20 minutes, 6 courses delivered over the 18 months of the clinical trial), the fourth group (25 patients, 9 men, 16 women) were treated with combined intravenous LLLT, MFT and LCT (the LMLCT group) performed simultaneously according to the regimes of each monotherapy (6 courses delivered over 18 months, 15 procedures per course). The fifth group had standard pharmacotherapy for AD (cholinesterase inhibitors: physostigmine, tacrine, donepezil, vitamin E, ergot mesylates, selegiline, estrogens in women, etc) for 18 months. The sixth group (15 patients, 6 men, 9 women) took a placebo medication for 18 months. At the end of the clinical trial all patients were tested by means of ADAS-cog and the data were compared with the results of ADAS-cog testing before the clinical trial performing. The ADAS-cog testers were blinded regarding information on which group the patients were placed in.

Results

The results of ADAS-cog testing before and after clinical testing of different therapeutic options are shown in Table 1. LMLCT was the most effective treatment of AD and was significantly more effective than placebo ($p < 0.001$) and LCT ($p < 0.05$). This treatment more than any other tested therapy option slowed down AD deterioration. Although statistically LMLCT did not surpass in effectiveness LLLT, MFT and pharmacotherapy, actually it was more effective and probably in the case of more numerous trial groups the difference may become statistically significant. LLLT, MFT and standard pharmacotherapy were also statistically more

Table 1: Comparison of ADAS-cog testing results of patients with AD before and after randomized placebo controlled clinical trial of LLLT, MFT, LCT, LMLCT and standard pharmacotherapy for AD.

Groups	n	Age (mean)	ADAS-1 (mean)	ADAS-1 %age (mean)	ADAS-2 (mean)	ADAS-2 %age (mean)	Difference (mean)	Difference of placebo (mean)
LLLT	25	73.9	33.8	48.3	40.7	58.1	9.8	9.8*
MFT	25	74.2	36.7	52.4	45.6	65.2	12.8	6.8*
LCT	17	71.8	37.5	53.5	48.0	68.7	15.2	4.4
LMLCT	25	73.5	36.2	51.7	39.8	56.8	5.1	14.5**
Pharmacotherapy	38	72.7	34.9	49.8	44.0	60.3	10.5	9.1*
Placebo	15	72.8	37.9	54.1	51.6	73.7	19.6	--

LLLT: low reactive-level laser therapy (intravenous delivery); MFT: magnetic field therapy; LCT: light and visual colour stimulating chromotherapy; LMLCT: combined LLLT, MFT and LCT. * - $p < 0.05$ (regarding placebo); ** - $p < 0.001$ (regarding placebo)

effective than placebo ($p < 0.05$), but statistically no more effective than LCT ($p > 0.05$). LCT was not significantly more effective than the placebo ($p > 0.05$). LLLT, MFT and standard pharmacotherapy had no significantly advantageous efficacy compared with each other ($p > 0.05$), but standard pharmacotherapy resulted in many side effects and was 5-12 times more expensive than the other tested therapy options.

Discussion

Before discussing the results of our research and the mechanisms of action of IV LLLT, MFT and LCT, it is reasonable to review briefly all the latest data and concepts regarding AD pathogenesis so that points of intervention with combination therapy can be identified. In AD, pathogenetic changes take place in the affected organism such as hypo- and dysfunction of the cholinergic system of the organism; dysfunction of the glutamatergic and serotonergic systems and formation of the pathological beta-amyloid cascade and all its consequences. It is necessary to stress that all pathogenic chains are interconnected, as can be seen from Figure 1b. The pathological changes will now be examined one by one.

Cholinergic system:

In AD there is a profound degradation of this system particularly based on a set of important receptors and inhibitors as follows.

Muscarinic acetylcholine receptors (MCRs): It has been shown that, besides their basic receptor functions, MCRs take part processing the B amyloid precursor protein. This fact makes it reasonable to look for new agonists for these receptors or physical factors that modulate these receptors' activity. The neuroprotective action mechanism of MCR agonists is as follows. It is known that the effects MCRs are mediated by the G protein and at the same time the MCR M1, M3 and M5 subtypes stimulate phosphoinositol hydrolysis via phospholipase "C" activation, whereas M2 and M4 subtypes take place in adenylatcyclase inhibition. The G protein binds receptors in neuronal membrane which regulate the splitting of pre B amyloid protein (APP). So, the activation of the M1 population leads through the activation of phospholipase "C" to hydrolysis of phosphoinositide and production of diacylglycerol. The latter activates protein kinase "C", which in its turn provides APP phosphorylation. As a result, the trophic, eliminating form of the amyloid peptide is formed and the production and accumulation of beta-amyloid decreases (Figure 1).

Hypofunction of MCRs or the MCR/G protein functional interaction breakdown can thus cause protein kinase "C" deactivation, APP phosphorylation inhibition and excessive production and accumulation of pathological amyloid peptide. The use of MCR pharmacological drugs is extremely limited because of their numerous undesirable side effects. These effects are determined predominantly by stimulation of the M2 and M3 peripheral receptor. For

neuroprotective purposes the most useful are the M1 agonist factors, because they predominate in the central nervous system (CNS).

Nicotinic acetylcholinergic receptors (N-Rs): These receptors are directly connected with ionic channels and play a very important role in brain cognitive functions. The receptors are divided to two groups: 1) alpha (six subgroups - $\alpha 2$ - $\alpha 7$); 2) beta ($\beta 2$ - $\beta 4$). Neuronal N-Rs, as a rule, consists of two alpha subunits and three beta subunits (pentameric complex). The only exception is the alpha 7 subtype which takes part in intraneuronal Ca^{++} homeostasis and plays a considerable role in learning processes and memory. Autoradiographic and positron emission tomography data show that in AD the number of N-R binding sites dramatically decreases. The amount of N-Rs is quite different in different parts of the brain, and the brain cortex contains 70 % of the receptors. From the diagnostic point of view it is important that there is a decrease in the number of N-Rs in the early stages of AD. In the AD pathologic chain an especially important role is played by the alpha7 and alpha4b2 subtypes because it has been revealed that stimulation of alpha7 N-Rs considerably increases cognitive function and alpha7 and alpha4b2 activation protects the neurons against the toxic effects of beta-amyloid and glutamate action. Estrogens also decrease the beta-amyloid toxic action via the stimulation of N-Rs.

Acetylcholinesterase inhibitors (AIs): AIs have a classic cholinomimetic action, but also stimulate cognitive function, compensate for choline deficits and influence the course of amyloidosis. This is determined by the fact that cholinesterase inhibition additionally stimulates those muscarinic receptors that take part in amyloid precursor protein processing. Besides, cholinesterase influences transformation of the beta-amyloid toxic form. Cholinesterase also modulates amyloid accumulation in brain tissue. So, besides a direct cholinomimetic effect, AIs also have neuroprotective effects, and further AI roles will be discussed during the explanation of the beta-amyloid cascade.

Factors influencing acetylcholine synthesis and release

Acetylcholine synthesis and release are important factors of any organism's cholinergic balance. Some substances (lecithin, phosphatidylcholine, exogenous choline, etc.) which can cause an increase in the amount of acetylcholine precursor in the organism demonstrate cholinomimetic and cognitive stimulating effects. Acetylcholine release may be stimulated by means of several mechanisms such as potassium M channel selective inhibition in the presynaptic endings of cholinergic neurons, Ca^{++} channel blockade and inhibition of H3-histaminergic neurofibrils.

Beta Amyloid Cascade:

This cascade is very important in AD and it has been seriously studied during the last decade. Accordingly to the present outlook the main cause of neurodegenerative changes in AD is production of a pathologic form of amyloid peptide (AP) from its precursor protein (APP). In normal

Figure 1a

Fig 1: Pathophysiological stages leading to development of Alzheimer's disease (AD), and the possible intervention points of combined low reactive-level laser therapy and magnetic field therapy. (a): Possible pathways in which combined LLLT and MFT could help ameliorate the pathogenic changes associated with AD. Both modalities have almost the same ultimate neuroprotective effects, but the pathways by which the modalities reach them are different. It is this duality of action which makes the combination of LLLT and MFT of great interest in the treatment of AD. (b): A schematic showing the pathogenic mechanisms and cascades in the various areas which lead to the neurological deterioration associated with AD. For an explanation of the abbreviations, please refer to the text. combined LLLT/MFT enters the process via a reduction of acetylcholinesterase leading to neuroprotection via mitochondrial protection, and upregulation of powerful antioxidants such as sodium dismutase (SOD). For a full discussion, please refer to the text.

Figure 1b

conditions AP is produced with the participation of alpha-protease in its soluble form (SAPPa) which has trophic functions. With ageing or APP gene modulation changes occur in this protein splitting mechanism and as a consequence SAPPa synthesis decreases and at the same time pathological amyloid APb production increases. This process is controlled by b and g proteinases. APb may be produced in several forms that have different number of amino acid remnants (APb-40, APb-42, APb-43). APb further aggregation causes formation of insoluble fibrils or so called compact forms formation, that take part in formation of the so called senile plaques in the brain. APb-42 and APb-43 have toxic effect on neurons both in soluble and aggregated forms, meanwhile APb-40 is toxic only in the aggregated form.

The main beta amyloid neurodegenerative mechanisms include impairment of calcium homeostasis; increased oxidative stress; potentiation of the toxic effects of stimulating transmitters (glutamate, aspartate); and initiation of processes that take part in apoptosis.

Factors that inhibit APb production

The most effective way of inhibiting APb production is to decrease the formation of APb from APP. As has been mentioned above, APP processing is controlled by muscarinic cholinoreceptors, protein kinases, while APP expression is controlled by some endogenous factors including cytokines, neurotrophic factors (BFGF, EGF), estrogens, stress situations (focal ischemia, trauma), etc.

APb formation is recognized as being accomplished in two stages. In the first stage, intracellular proteolysis by b-secretases leads to the formation of APb aminoterminal remnants and intracellular splitting by g secretases in the direction of APb's "C"-terminal remnant. At present there is little information regarding b and g secretases; only in 1999 was it revealed that b secretase takes part in APb processing and at present there is an intensive search for b secretase inhibitors. Regarding g secretase even fewer data are available. In the second stage, glutamate receptors participate in APb metabolism as well, in particular, the stimulation of 1-alpha-metabotropic glutamate receptors increases SAPPa production which should naturally inhibit APb production and have a positive effect on the course of AD.

Substances and factors that affect APb aggregation, disaggregation and binding

APb transformation from the soluble to the aggregated form is the main condition for manifestation of the APb toxic neurodegenerative effect. Any substances or factors which could stop or slow down this transformation will thus have auspicious and positive effects on the course of AD. Lately it has been revealed that acetylcholinesterase considerably modulates APb aggregation, accelerating transformation of APb soluble forms to fibrillar complexes during which process the formation of an acetylcholinesterase-APb complex

occurs. The latter has extremely high neurotoxic potential and the APb40-acetylcholinesterase complex is especially toxic. So, all factors capable of inhibiting acetylcholinesterase have neuroprotective properties.

The neurotoxic actions of APb include increasing and potentiating the toxic effect of stimulating neurotransmitters (glutamate, aspartate); exhaustion of cell energy resources and mechanisms; initiation of membrane lipid peroxidative oxidation and generation of free radical metabolites; impairment of calcium metabolism; and induction of apoptosis mechanisms.

The role of glutamergic system in the pathogenesis of AD.

Endogenous glutamate and aspartate have been reported to have a toxic effect on neurons (excitotoxicity). The participation of the glutamergic system in development of AD is proved by the following. A considerable decrease in the number of glutamate receptors (GluR) occurs in hippocampus in patients with AD. It is also known that NMDA subtype glutamate receptors play an important role in cognitive process and memory. Next, excitotoxicity (ET) must be considered, which is the result of GluR stimulation in the CNS by the so-called endogenous stimulating amino acids (ESA) aspartate and glutamate.

ET may be found in the in acute, classic or chronic form. The first is divided to 3 substages: In the first substage, primary depolarization of neuronal membrane by AMPA-GluR that leads to intensive influx of Na^+ and Cl^- into neurons. As a result, osmotic hyperhydration and swelling of cells occur. In the second substage, NMDA-GluR hyperactivity leads to the presence of much higher levels of Ca^{2+} ions in neurons that activate particular intracellular enzyme systems (protease, nuclease, lipase) which in turn initiate cytodeneration and cell lysis. In the third substage, cellular exocytosis leads to the excretion of large amounts of glutamate and activation of glutamate receptors with the usual adverse consequences.

The ET metabolic, slow developing form, is quite different from the acute form. It occurs in the case of a normal concentration glutamate and the main cause of its development is a decrease in the energetic status of the cell. The main trigger factor is mitochondrial ATP production dysfunction. As a result, the activity of ATP-dependent enzymes decreases, (such as the very important Na^+/K^+ -ATPase, which among other things is responsible for membrane potential preservation through its control of the sodium-potassium pump), slow depolarization of the cell membrane occurs, Ca^{++} enters the cell in extremely large quantities, which severely affects cellular homeostasis and stimulates the initiation of the intracellular degeneration process, leading to apoptotic-mediated cell death. In addition, it has been recently reported that APb potentiates the glutamate neurotoxic effect.

The role of metabotropic glutamate receptors (mGluR)

These receptors, unlike the NMDA and AMPA receptors, are not directly associated with ionic channels and participate in intracellular Ca^{++} metabolism via the G-protein and secondary messengers. There are 3 types of m glutamate receptors. The first type are mGluR 1 and mGluR5 that stimulate phosphoinositol hydrolysis and as a result, Ca^{++} mobilization from intracellular stores. Stimulation of these receptors increases the neuronal response to stimuli. The second type (mGluR2 and mGluR3) and the third type (mGluR 4-6-8) inhibit adenylatcyclase and decrease the amount of available AMP, leading to a decrease in cell response.

The Role of Calcium

It is known that APb performs its toxic effect by means of Ca^{++} associated mechanisms. Ca^{++} and glutamate ageing concepts have very many of common elements and the most important one is the cytotoxic degenerative effect caused by increased intracellular Ca^{++} concentration very much beyond the normal ranges. In the case of AD, mutation of presenilin 1 (PS1) has been shown to occur determined by abnormalities of Ca^{++} -mediated homeostasis. With ageing, a concomitant increase can be seen in cell death as determined by Ca^{++} binding proteins, and in particular this has been strongly associated with decreases in the amount of calbindin in cholinergic neurons.

The role of the antioxidant system in AD

Oxidative stress and the subsequent accumulation of free radical metabolites in brain cells play an important role in AD pathogenesis. In AD, free radical metabolites (FRM) are generally produced in the CNS as a result of APb action on the cells. During this interaction some oxygen-containing radical metabolites are produced (nitroxide and peroxide radicals, and so on). Intracellular Ca^{++} plays a key role in this process through the stimulation of metabolic reactions in the mitochondria. As a result, the O_2 radical is split, and the calmodulin complex stimulates NO-synthase and increases NO production. Interaction of these radicals causes production of extremely active peroxynitrite ions (NO_3) capable of degrading intracellular proteins and nucleic acids. Fe ions have an important catalytic role in the formation of hydroxyl radicals from hydrogen peroxide. Neurons have a defensive system for detoxification of oxygen radicals - glutathione peroxidase and catalase. These enzymes are induced by means of nuclear transcription of the NF-kB factor. Androgens and estrogens have a powerful antioxidative effect as well, and androgens are furthermore capable of increasing the secretion of soluble sAPPa and decreasing production of APb.

Melatonin (N-acetylserotonin) has positive effect on AD because melatonin has a protective effect against the consequences of oxidative stress in brain; it has a protective effect on mitochondria; it regulates APP processing and inhibits formation of amyloid fibril production; melatonin

protects neurons against glutamate ET and against neurotoxic effects; and melatonin has been shown to have an antiapoptotic effect.

Thus, melatonin has complex neuroprotective effects, including a specific anti-amyloid effect, so this could be classed as a nonspecific antiageing action. Taking all of the following into consideration, and the additional fact that, with ageing, significantly decreased melatonin synthesis is strong evidence of the probably considerable role of the melatonin deficit in the pathogenesis of AD.

The role of inflammation mediators in AD development

In AD brain tissue, degeneration is accompanied by a CNS inflammatory reaction with participation of cytokines IL-1 and IL-6, activation of complement cascade, production of anaphylatoxins, formation of membrane-active complex, and so on. Until the present it is not clear if inflammation is a cause of AD or if it is a consequence of the presence of increased beta-amyloid levels and the accumulation of fibrils. Cytokines IL-1 and IL-6 are neurotoxic and may potentiate beta-myloid neurodegenerative action. The inflammatory cascade finally causes oxidative stress with all its adverse consequences.

In addition to the above, the cyclooxygenase 2 enzyme (COX-2) plays a conspicuous role in AD pathogenesis. In AD the amount of the enzyme decreases, and, furthermore, COX-2 is mainly localized in the neocortical synapses and the hippocampus. Any of the factors mentioned which are capable of influencing any inflammatory chain component may have positive effect on the course of AD. All above explained facts, data and information is integrated in Figure 1, showing the pathogenesis of AD and pathways by which intravenous (IV) low reactive-level laser therapy (LLLT) and magnetic field therapy (MFT) can intervene in this pathogenesis, using the patient's own natural healing powers rather than exogenous pharmaceuticals.

Treatment methodologies

Our clinical data showed clearly that IV LLLT and MFT as monotherapies were significantly more effective than the placebo ($p > 0.05$) in slowing down the deterioration associated with AD. LLLT on its own was the most effective of all the modalities, although the difference was not significant. In other words, as monotherapies MFT and particularly LLLT were able to decrease the rapidity of the deterioration AD patients, were effective therapeutic options and may therefore be a good choice for AD treatment. Although conventional pharmacotherapy was the second most effective modality after LLLT, it is especially important to bear in mind that pharmacotherapy causes a great number of undesirable side effects particularly in elderly AD patients, and because of this is in fact contraindicated for many AD patients. On the other hand, IV LLLT and MFT have minimal or no contraindications, are well tolerated, are extremely

Table 2: Summary of the main effects associated with LLLT, very often involving restoration of homeostasis in an unbalanced organism.

Main LLLT Effects	
Release of antioxidants	Increased blood oxygen levels
Stimulation of cellular immunity	Stimulation of hormonal immunity
Modulation of immunogenesis	Modulation of blood insulin
Regulation of the number of beta lymphocytes	Modulation of pancreatic Langerhans' beta cell behavior
Modulation of blood rheology	Decreased blood cholesterol levels
Decreased sympathetic hypertension	Increased parasympathetic control
Increased tissue trophic factors	Regulation of blood pressure
Decreased glomerular and canalicular proteinuria	Increased diuresis via increasing of glomerular filtration
Mitigation of hyperthermia	Modulation of free radical production
Regulation of pulmonary ventilation	Powerful pain attenuation
Sleep regulation	Increased levels of activity
Enhanced feeling of well-being	Powerful anti-inflammatory effect
Antiedemic effect	Activation of lymphatic system
Activation of microcirculation	Decreased oxidation of lipid peroxides
Stimulation of regeneration	Stimulation of ATP production
Stimulation of protein synthesis (DNA, RNA)	Regulation of intra- and extracellular Na^+ - K^+ co-transport
Increased Ca^{++} signaling	Upregulation of osteogenesis
Increased amount of estrogens	Increased beta-endorphins

cost-effective and offer great convenience of use in clinical practice.

Light chromotherapy: Light chromotherapy (LCT) did not demonstrate any statistical efficacy *versus* the placebo, although the clinical impression was that it might be an effective treatment as well. The small size of the groups should be taken into consideration, however: 17 patients in the LCT group and 15 in the placebo. The statistical power of these groups is therefore very low, and it could be that larger populations would reveal a better statistical result for LCT. In any event, the latest scientific data show that visible light and color have a powerful physiological effect.

When light strikes the retina, the transmission via the optic nerve is split into two impulses: the first goes to the brain's occipital zone where visual image is synthesized, the second goes to the hypothalamus which regulates the organism's functions, in particular the activity of the neurological and endocrine system'. So, the light has two important functions: first, it carries visual information (optical- 25%); and second, it delivers a biological function (visual field energy function, 75%). Taken together with this, the color of visible light, being a particular waveband on the electromagnetic spectrum, is a powerful information regulator of the physiology of an organism.

It has been proposed that metabolism and cell communication are controlled by ultra-weak photon emission. Scientific data exist that chromotherapy may increase the efficacy of laser therapy, and so, in addition to its trial as monotherapy, in the present study we added LCT to the combined therapy group, the LMLCT group, together with LLLT and MFT. The color of the LCT was selected, taking into account that yellow increases psycho-emotional activity and attention, stimulates the left hemisphere of the brain and has a positive effect on learning, education, professional functioning, mood, in addition to mitigating depression. Yellow is the key color for the nervous system. Green provides equilibrium of the physical and psychological components of the human being, increases hypophysis activity and muscular tone. Green has a sedative effect, increases the ability to concentrate attention, improves self-control, and facilitates logical thinking. The color lemon, being a mixture of yellow and green, is a brain and sexual stimulator. The chromotherapy phenomenon needs to be more deeply studied in patients with AD.

IV LLLT: As to IV LLLT, laser therapy, in general, has been shown to be extremely effective and can influence all systems and organs of the organism. Table 2 summarizes the main effects of LLLT as shown in the literature over the past four decades, following the late Endre Mester's first reports at the

Table 3: Summary of the main effects associated with magnetic field therapy (MFT).

Main effects associated with MFT	
Increased tissue trophic factors	Analgesic effect
Energetic mobilization of cells	Antiswelling effect
Non specific adaptogenic effect	Hypotensive, spasmolytic effect
Stimulation of regeneration	Anti-inflammatory effect
Microcirculation increasing	Blood rheology amendment
General sympatholytic effect	Immunomodulation
Antioxidant effect	Endorphin production increasing
Influence on organism natural ferromagnetics (catalase)	Improvement of nervous system functional state
Increased number of astrocytes	Biomembrane stabilization
Modulation of organism' cholinergic system	

end of the 60's on the successful application of LLLT for the healing of torpid crural ulcers. LLLT allows both a shortened treatment time and the a lower number and dose of pharmacological during pharmacotherapy.

The primary acceptors (triggers) of LT are extremely wavelength-specific. For instance, the acceptor for the helium-neon laser or any system delivering 633 nm is any porphyrin-containing catalase enzyme, which actually has a peak absorbance at 628 nm, and results in an antioxidant effect.. The same is true regarding the enzyme superoxide dismutase (SOD) and the result is the antioxidant effect occurring simultaneously with a decrease in the oxidation of lipid peroxide. The mechanism of action of near infrared LLLT mainly depends upon structural changes of the water molecule, which is accompanied by many different photochemical and photophysical. The initiation of the photochemical processes, particularly associated with visible wavelengths, is associated with changes in the level of excitation, and hence the orbit, of the electrons in the atoms of the photoacceptor. Photophysical reactions, mostly associated with infrared wavelengths, are determined mainly by excitation of the molecules of the cellular membranes through molecular vibrational and rotational changes resulting in gentle warming and heat dispersion, depending on the photon density of the incident beam.

The physical depth of penetration of laser energy depends on the wavelength of the incident beam. Biological tissues are considered optically transparent to near infrared light (700 nm – around 1,000 nm), whereafter the rising absorption in the water molecule limits penetration. The percentage absorption of laser light by tissues is as follows: Skin and muscles: 20-30%; Bones: 50%; Parenchymal organs: 100%. Light at 633 nm, the wavelength of the HeNe laser, has a penetration depth of 15 mm, but in actual clinical practice, useful photon densities exist only till about 2-3 mm.

The most important photoreceptors of the organism are the following: 1. Hemoglobin; 2. Cyclic nucleotides; 3. Fe; 4. Cu-containing enzymes; 5. Enzymes associated with Krebs cycle; 6. Certain biological pigments, and so on. Hemoglobin and water are the very good acceptors for infrared laser light. When irradiated with laser energy, water changes its pH, electrical conductivity, and oxygen solubility. Laser transforms molecular O₂ into short life very active (especially regarding the membranes) singlet oxygen. LT mechanisms in AD can be seen in Figure 1a. LLLT efficacy especially increases when it is combined with magnetic field therapy (MFT).

Magnetic field therapy: Magnetotherapy is used in the treatment of AD in different forms and with different regimens. MFT has multiple effects on the organism as well. For instance, a static magnetic field rotated around the molecular magnetic dipolar axis increases the intrinsic energy of the molecules. A magnetic field, by maintaining the ionized molecules of the tissues in an ionized state, increases the efficacy of the laser and other curable factors. Under the influence of magnetic field the ionized molecules in the vessels and blood cells are pressed to the vessel endothelium and a turbulent flow is initiated which increases their oxygen saturation. Thus, MFT not only complements LLLT effects in AD therapy, but also considerably increases LT efficacy in general. Table 3 summarizes the main effects associated with MFT.

Both LLLT and MFT cause changes in the water molecule behavior and modulate tissue hydration of the organism. Water is thus not only a photoacceptor, but is able to perform a secondary messenger function maintaining within itself and conveying electromagnetic information of any kind.

In conclusion, as we can see from Figure 1a, since the electromagnetic fields of both LLLT and MFT affect different organs and systems of the organism, the combination of

LLLT and MFT consecutively applied offers great potential, and is based on the following: precepts:

1. From the evolutionary point of view the light and magnetic fields are the most biotropic external collectors for the organism.
2. The application of LLLT and MFT in a complementary manner give physicians an opportunity to shorten treatment times, while at the same time decreasing the intensity of one or another factor.
3. Their combined use significantly increases the membrane stabilizing effect.
4. The effect of both modalities on the neuromediators is nearly the same, although the pathways are different.
5. Both LLLT and MFT have a positive effect on the organism antioxidant system.

Thus, IV LLLT and MFT in combination may offer a very reasonable option in the treatment of AD. The effect may be further enhanced with the addition of lemon, yellow and green LCT. The use of these three modalities in combination gives a synergistic effect much greater than the sum of the efficacy of the individual components, and considerably increases treatment efficacy, but without increasing the risk of side effects. The combined use of these therapeutic options is therefore a effective, safe, inexpensive and convenient option in AD treatment.