Pristup liječenju Alzheimerove bolesti

/ Treatment Approach to Alzheimer's Disease

Aida Križaj Grden[1], Ninoslav Mimica[1,2]

[1]Klinika za psihijatriju Vrapče, Referentni centar Ministarstva zdravstva Republike Hrvatske za Alzheimerovu bolest i psihijatriju starije životne dobi, Zagreb, [2] Sveučilište u Zagrebu, Medicinski fakultet, Zagreb, Hrvatska

/ [1]*University Psychiatric Hospital Vrapče, Referral Centre for Alzheimer's disease and Old Age Psychiatry of the Ministry of Health, Zagreb,* [2]*University of Zagreb, School of Medicine, Zagreb, Croatia*

Alzheimerova bolest (AB) je neurodegenerativna bolest mozga i najčešći oblik demencije. Radi se o sindromu sa progresivnim gubitkom kognitivnih funkcija popraćenom ponašajnim i psihičkim simptomima. Nakupljeni β-amiloid i neurofibrilarni snopići implicirani su u nastanku funkcionalnih i neurodegenerativnih promjena koje završavaju smrću stanice. Etiološko liječenje zasad ne postoji. Aktualne mogućnosti farmakološkog liječenja sastoje se od dviju skupina lijekova: inhibitori kolinesteraze (donepezil, galantamin, rivastigmin) i antagonisti NDMA receptora, koji su se pokazali učinkoviti u poboljšanju kognitivnih funkcija, pojedini i s utjecajem na biheviоralne simptome. Ni jedan od ovih lijekova ne mijenja tijek i ishod bolesti. Istražuju se nove supstancije koje ciljaju na metabolizam amiloida i tau proteina. Od neuromodulacijskih metoda najviše se istražuju rTMS i tDCS, koji su pokazali pozitivne učinke na kognitivne funkcije. Kognitivna stimulacija također ima pozitivne rezultate pa se sve više istražuju učinci neuromodulatorskih metoda liječenja kombiniranih s kognitivnim vježbama, što je u praksi moguće putem sustava NeuroAD™

/ Alzheimer's disease (AD) is a neurodegenerative brain disorder and the most common type of dementia. AD is a syndrome leading to progressive loss of cognitive functions, often followed by behavioural and psychological symptoms. Amyloid plaques and neurofibrillary tangles are implicated in functional and neurodegenerative changes leading to neuronal death. A curative treatment does not exist. Pharmacological treatments include cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and NDMA receptor antagonists, which have been shown to improve cognitive functions and some of them may also have positive effects on behavioural symptoms. None of these drugs effect the course and outcome of the disease. New drugs that can interfere with β-amyloid and tau protein metabolism are being researched. Neuromodulator methods of treatment such as TMS and tDCS are being researched and have shown positive effects on cognitive functions. Cognitive stimulation has also shown positive effects so it is not surprising that more research is being aimed at studying the combined effects of neuromodulator treatment and cognitive stimulation, which is in practice possible using the NeuroAD™ system.

ADRESA ZA DOPISIVANJE / *CORRESPONDENCE*:
Aida Križaj Grden, dr. med.
Klinika za psihijatriju Vrapče
Bolnička cesta 32
10090 Zagreb, Hrvatska
E-pošta: aidakrizaj@hotmail.com

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UVOD

Alzheimerova bolest (AB) neurodegenerativna je bolest mozga i najčešći oblik demencije koja predstavlja 60-70% svih slučajeva demencije. Oko 50 milijuna ljudi diljem svijeta boluje od ove bolesti, a projekcije su da će se ove brojke utrostručiti do 2050. godine (1,2), stoga AB postaje jedan od javnozdravstvenih prioriteta (2). Radi se o sindromu s progresivnim gubitkom kognitivnih funkcija; s deterioracijom pamćenja, spacijalne i temporalne orijentacije, jezičnih funkcija, sposobnosti učenje i komuniciranja (3) uz promjene u ponašanju i čestim popratnim psihičkim simptomima poput depresije, anksioznosti i deluzija. Prevalencija psihičkih simptoma povećava se s trajanjem bolesti (4) i u konačnici te osobe postaju potpune ovisne o okolini.

Etiopatofiziologija AB nije poznata; najraširenija je hipoteza amiloidne kaskade; βAmiloid se nakuplja stvarajući ekstracelularne amiloidne plakove. Amiloidni plakovi pak dovode do hiperfosforilacija tau proteina, koji su integralni dio neurofibrilarnih snopića, upalnih promjena, ekscitotoksičnost i neuronalne smrti (5). Druge hipoteze na prvo mjesto u patofiziologiji AB smještavaju neurofibrilarne snopiće koji dovode do destabilizacije aksona, gubitka sinaptičkih veza uz konačnu strukturnu degeneraciju neurona (6). U patofiziologiji AB sve se više pažnje pridaje vaskularnim učincima (7) .

METODE LIJEČENJA

Farmakološko liječenje

Patofiziološke promjene mozga u AB dovode do poremećaja neurotransmiterskih sustava osobito kolinergičkog sustava, koji ima bitnu ulogu u raznim kognitivnim procesima (8).

Iz ovih spoznaja proizišla su četiri lijeka koji djeluju kao inhibitori kolinesteraze (takrin, donepezil, rivastigmin, galantamin), a njihovo

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative brain disorder and the most common form of dementia contributing to 60-70% of all cases. It is estimated that 50 million people around the world suffer from AD, and this number is thought to triple by the year 2050 (1,2), making AD a public health priority (2). AD is a syndrome leading to progressive loss of cognitive functions, with a deterioration of memory, spatial and temporal orientation, language functions, and the ability to learn and communicate (3). This is often followed by behavioural and psychological symptoms such as depression, anxiety, and delusions. The prevalence of psychiatric symptoms increases with disease duration (4). The disease ultimately leads to complete caregiver dependence.

The etiopathophysiology of AD is not understood; the amyloid cascade hypothesis is the most widespread hypothesis. β amyloid accumulation leads to the formation of extracellular amyloid plaques. Plaques lead to hyperphosphorylation of tau protein, which forms intraneural neurofibrillary tangles, neuro-inflammatory processes, excitotoxicity, and neuronal death (5). In other hypotheses, neurofibrillary tangles are central in the pathophysiology of AD leading to axonal destabilization, synaptic loss, and finally structural degeneration of neurons (6). Vascular components in the pathophysiology of AD are also being paid more attention (7).

METHODS OF TREATMENT

Pharmacological treatment

Pathophysiological brain changes in AD lead to neurotransmitter abnormalities, especially in the cholinergic system, which has an important role in cognitive processes (8).

This knowledge has led to the development of four different cholinesterase inhibitors

djelovanje je simptomsko i ne mijenja prirodan tijek i ishod bolesti. Takrin, kao lijek s nepraktičnim režimom davanja (4 puta/dan) i najnepovoljnijim profilom nuspojava, gotovo se više i ne koristi u kliničkoj praksi.

Inhibitori kolinesteraze

Donepezil

Rezultati Cochrane studije koja je uključivala 8257 pacijenata s blagom, umjerenom i teškom AB pokazali su statistički značajne učinke donepezila na kognitivne funkcije, ljestvice za procjenu dnevnih aktivnosti i na ljestvici kliničke procjene globalnih promjena (*Clinician -Rated Global Impression of Change Scale*), ali bez utjecaja na bihevioralne simptome. Obje doze (5 i 10 mg) su se pokazale učinkovite uz nešto više nuspojava kod primjene većih doza, ponajprije gastrointestinalnih (9).

Rivastigmine

Rezultati studije Cochrane pokazali su učinkovitost rivastigmina kod blage do umjerene AB prigodom primjene visokih doza (6 – 12 mg/dan), sa statistički značajnim poboljšanjem kognitivnih funkcija bez značajnijih učinka na bihevioralne simptome. Nuspojave kod primjene viših doza bile su učestalije, ponajprije gastrointestinalne, ali su se javljale i glavobolje i sinkope. Ispitan je rivastigmin u obliku transdermalnog flastera; manji flaster, manje doze bio je jednako učinkovit kao veći flaster i peroralni oblik lijeka ekvivalentne dnevne doze, uz manje nuspojava (10).

Galantamine

Učinci galantamina su također analizirani studijom Cochrane koja je uključivala 6805 osoba; rezultati su pokazali statistički značajno poboljšanje kognitivnih funkcija kod blagog do umjerenog stupnja demencije, ali bez korelacije s dozom. Nuspojave su slične kao i kod drugih inhibitora kolinesteraze (11).

(tacrine, donepezil, rivastigmine, galantamine), whose effects are not disease-altering but only symptomatic. The use of tacrine has all but been abandoned in practise due to its profile of adverse effects and impractical dosing schedule (4 times daily).

Cholinesterase inhibitors

Donepezil

The results of a Cochrane study, which included 8257 people with mild, moderate, and severe AD showed statistically significant improvement in cognitive functions, activities of daily living, and clinician-rated global impression of change scale, with no significant effects on behavioural symptoms. Both doses (5 mg and 10 mg) were effective, with more adverse effects reported for the higher dose, mainly gastrointestinal (9).

Rivastigmine

According to the results of a Cochrane study, rivastigmine has led to statistically significant improvement in cognitive functions in patients with mild to moderate AD when administered in high doses (6–12 mg). It had no significant effect on behavioural symptoms. Adverse effects were quite common with high doses, mostly gastrointestinal symptoms, although headaches and syncopes were also reported. The rivastigmine transdermal patch was also tested; a smaller patch with a lower dosage was as effective as both the bigger patch (higher dosage) and the peroral form of the medicine, which was given in the equivalent daily dose but had less adverse effects (10).

Galantamine

The effects of galantamine were also analysed in a Cochrane study which included 6805 subjects, and the results showed a statistically significant improvement in cognitive functions in mild to moderate AD, with no dose-effect correlation. The side effects were similar to those of other cholinesterase inhibitors (11).

Antagonisti NMDA receptora

Memantin

Memantin djeluje kao nekompetativni antagonist N-metil-d-aspartat (NMDA) glutaminskih receptora. Glutamat je glavni ekscitatorni neurotransmitor mozga koji djeluje putem NMDA receptora s ključnom ulogom u funkcijama sinaptičke plastičnosti. Aktivacija sinaptičkih NMDA receptora kritična je za preživljavanje neurona (12), ali pretjerana glutaminergička stimulacija dovodi do ekscitotoksičnosti uz posljedičan gubitak sinaptičke funkcije i neuronalne smrti (13). Ovi procesi smatraju se etiološki povezanima s nastankom neurodegenerativnih promjena u AB (14).

Do vezanja memantina za receptore dolazi zbog povišene koncentracije glutamata u sinaptičkoj pukotini, kao što je slučaj u AB. Memantin djeluje nekompetitivnim vezanjem na ekstracelularne NMDA receptore za koje ima slab afinitet pa ubrzo nakon vezanja uslijedi disocijacija veze, posljedično tomu onemogućena je dugotrajna blokada i njeni negativni učinci na učenje i pamćenje (15).

Prema rezultatima studije Cochrane iz 2006. godine zaključeno je da šestomjesečna primjena memantina kod osoba s umjereno teškim i teškim stupnjem demencije ima blagotvorni učinak na kognitivne funkcije, ponašajne simptome i u ljestvicama procjene dnevnih aktivnosti. Kod pacijenata s blagom do umjerenom AB pozitivne promjene u kognitivnim funkcijama bile su jedva detektibilne, bez ikakvih poboljšanja ponašajnih simptoma i u ljestvicama procjene dnevnih aktivnosti. U pacijenata s vaskularnom demencijom nisu detektirana poboljšanja. Zaključeno je da pacijenti na terapiji memantinom rjeđe razvijaju agitaciju (16).

Meta-analitička studija iz 2017. godine uspoređivala je terapijski učinak i sigurnost primjene monoterapije donepezilom s kombiniranom terapijom donepezilom i memantinom u osoba s umjerenom i teškom AB. Analizirane su kogni-

NMDA receptor antagonists

Memantine

Memantine is a non-competitive N-methyl-d-aspartate (NMDA) glutamine receptor antagonist. Glutamate is the brain's main excitatory neurotransmitter, it binds to NMDA receptors and plays a crucial role in functions of synaptic plasticity. The activation of synaptic NMDA receptors is critical for the survival of neurons (12), but excessive glutaminergic stimulation leads to excitotoxicity which causes loss of synaptic function and neuronal death (13). These processes are believed to be a part of the pathogenesis leading to neurodegenerative changes in AD (14).

Memantine binds to receptors when high concentrations of glutamate are present in the synaptic fissure, as is the case in AD (15). Memantine binds to extracellular NMDA receptors non-competitively, and its low affinity for these receptors allows rapid dissociation and prevents prolonged receptor blockade, which has a negative impact on learning and memory (15).

According to the results of another Cochrane study from 2006, six months of treatment with memantine in subjects with moderate to severe AD had beneficial effects on cognitive functions, behavioural symptoms, and in activities of daily living (ADL). In mild to moderate AD the positive effects on cognitive functions were barely detectable, with no effect on behavioural symptoms and ADL. No detectable improvements were registered in subjects with vascular dementia. Patients receiving memantine were less likely to develop agitation (16).

A 2017 meta-analytic study compared the efficacy and safety between monotherapy of donepezil and combined therapy with donepezil and memantine in subjects with moderate and severe AD. The study analysed cognitive functions, behavioural and psychological symptoms, and global functions. The results showed the combination therapy to be superior in all domains, without significant adverse effects (16).

tivne funkcije, ponašajni i psihički simptomi te mjere globalnih funkcija. Rezultati su pokazali bolji učinak kombinirane terapije u svim analiziranim domenama, bez razvoja značajnih nuspojava (17).

Meta-analitička studija iz 2018. godine uspoređivala je učinkovitost i sigurnost pojedinih inhibitora kolinesteraze i memantina. Prema spomenutoj studiji najbolji učinak na poboljšanje kognitivnih funkcija kod blage do umjerene AB postignut je (pojedinačno) donepezilom u dozi od 10 mg i galantaminom u dozi 24 mg ili 32 mg/dan. Kod umjerene do teške demencije najučinkovitija je kombinacija 20 mg memantina sa 10 mg donepezila. Memantin je imao najbolji profil tolerancije. Nisu uočeni učinci na bihevioralne simptome (18).

Supstancije s djelovanjem na β-amiloid i tau protein

Jedan od glavnih ciljeva u istraživanjima AB je bolje razumijevanje patologije bolesti i pronalaženje terapije koja će utjecati na tijek i ishod bolesti. Među supstancijama koje se istražuju su one koje djeluju na β-amiloid (smanjena proizvodnja, smanjena agregacija ili povećan klirens pomoću imunoterapije), te razne molekule koje djeluju na patološke procese vezane za tau protein, uključujući one koje inhibiraju tau fosforilaciju (litij i valproat). Istražuje se učinkovitost i sigurnost aktivne i pasivne tau imunizacije (19,20).

Neuromodulacijske metode liječenja

Transkranijska magnetska stimulacija (TMS)

Transkranijskna magnetska stimulacija (TMS) je sigurna, neinvazivna, stimulacija mozga s neuromodulacijskim i terapijskim učinkom koji je duži od samog trajanja stimulacije. Ovisno o primijenjenim frekvencijama i intenzitetima stimulacije TMS utječe na neuronalnu ekscita-

A 2018 meta-analytic study compared the safety and effectiveness of cholinesterase inhibitors and memantine. According to this study, the most effective approach to improving cognitive functions in mild to moderate AD was (individually) donepezil 10 mg and galantamine 24 mg or 32 mg daily. For moderate to severe AD the most effective therapy was a combination of memantine 20 mg and donepezil 10 mg. Memantine had the best acceptability profile. No effects on behavioural symptoms were registered (18).

β-amyloid and tau protein targeting therapy

Trying to better understand the underlying pathology of AD and find disease-altering treatments has always been the main goal in research. Some of the substances being studied act upon β-amyloid (lowered production, lowered aggregation, or increased clearance with the use of immunotherapy), while others interfere with tau protein pathology, including inhibition of tau phosphorylation (lithium and valproate). The efficacy and safety of active and passive tau immunization is also being researched (19,20).

Neuromodulatory treatment

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a safe, non-invasive stimulation of the brain with neuromodulator effects and therapeutic responses that outlast the stimulation period. Depending on the frequency and intensity of TMS stimulation, excitatory neuronal effects are achieved not only in the stimulated areas but also in other interconnected brain regions (21). High frequencies have excitatory effects whereas low frequencies have inhibitory effects (22). TMS is approved for the treatment of depression, but its therapeutic effects are being

bilnost ne samo stimulirane moždane regije već i drugih međusobno povezanih moždanih regija (21). Visoke frekvencije imaju ekscitacijski, a niske frekvencije inhibicijski učinak (22). TMS je odobren za liječenje depresije, ali se istražuju mogućnosti korištenja u liječenju mnogih neuroloških i psihijatrijskih bolesti. Kod demencija TMS se koristi u istraživačke svrhe direktnim ispitivanjima kortikalne ekscitabilnosti kako bi se bolje razumjela patofiziologija bolesti te kao alat u dijagnosticiranju i diferencijaciji između starenja zdravog mozga, blagog kognitivnog poremećaja (engl. *Mild Cognitive Impairment* / MCI) i AB te u diferencijaciji različitih vrsta demencija (23). U ovom osvrtu bavimo se terapijskim mogućnostima TMS-a.

Studije su pokazale da korištenje visokih frekvencija repetitivne transkranijske magnetske stimulacije (rTMS) u stimulaciji dorzolateralnog prefrontalnog korteksa (DLPFK) kod osoba s AB i MCI dovodi do značajnih pozitivnih promjena u kognitivnim funkcijama ispitanih nizom neuropsihologijskih testova (24,25).

U jednoj studiji uspoređivali su se učinci stimulacije DLPFK visokim i niskim frekvencijama rTMS-a na kortikalnu ekscitabilnost i kognitivne funkcije. Značajno poboljšanje registrirano je kod tretiranih visokim frekvencijama rTMS-a, s razlikama u učinkovitosti među pojedinim podskupinama; naime kod pacijenata s blagom/umjerenom AB registrirana su poboljšanja, dok kod onih s uznapredovalom AB nije uočeno značajno poboljšanje (24).

Tri studije istih autora (Cotell i sur.) istraživale su utjecaj rTMS na imenovanje i jezične funkcije kod pacijenata oboljelih od AB. Korištene su visoke frekvencije rTMS-a nad DLPFC. U prvoj studiji uočeni su značajni učinci na imenovanje pokreta, ali ne na imenovanju objekta (26). U drugoj studiji dobiveni su isti rezultati, ali samo kod pacijenata s blažim stupnjem AB, dok su i kod onih s umjerenim i teškim stupnjem uočena poboljšanja u imenovanju pokreta i objekta (27). U trećoj, drugačije koncipiranoj studiji, researched in many other neurological and psychiatric disorders. In the research of dementia, TMS is being used as a neuroscientific tool for studying cortical excitability in order to better understand the pathophysiology of AD, as a diagnostic tool for differentiating between normal aging, mild cognitive impairment (MCI), and AD, and differentiating between different types of dementia (23). Here we discuss the therapeutic effects of TMS.

Studies show that stimulation of the dorsolateral prefrontal cortex (DLPFC) with high frequency repetitive transcranial magnetic stimulation (rTMS) in subjects with AD and MCI leads to significant positive changes in cognitive functions measured by a battery of neuropsychological tests (24,25).

One study compared the effects of high versus low frequency rTMS, applied over the DLPFC, on cortical excitability and cognitive functions. Significant improvements were seen in those stimulated with high frequency rTMS. Differences in efficacy were registered between individual subgroups; significant improvements were seen in subjects with mild/moderate AD, whereas in those with severe AD there were no significant improvements (24).

Three studies by the same group of authors (Cotell *et al.*) studied the effects of rTMS on naming and language functions in patients with AD using high frequency rTMS applied to the DLPFC. In the first study, significant improvements in action naming were seen, but were absent in object naming (26). The second study had the same results as the first for subjects with mild AD, while those with moderate and severe AD showed an improvement in both action and object naming (27). The third study, conceptually different from the previous two, showed no improvement in naming but rather in auditory sentence comprehension, with effects still present at 8 weeks after treatment (28).

A number of studies examined the effects of high frequency rTMS applied in combination

zultati nisu pokazali poboljšanja u imenovanju, već u auditornom razumijevanju rečenica. Ove promjene bile su prisutne i 8 tjedana nakon završetka tretmana (28).

Niz studija ispitivalo je učinkovitost visokih frekvencija rTMS-a u kombinaciji s kognitivnim vježbama koristeći sustav NeuroAD™ (29-31). U ovim studijama stimuliralo se šest moždanih regija; lijevi i desni DLPFK (prosuđivanje, egzekutivne funkcije, dugotrajno pamćenje), Brokin i Wernickeov centar (jezične funkcije), te lijevi i desni parijetalni somatosenzorni asocijativni korteks (spacijalna orijentacija, praksija). Moždane regije su individualno lokalizirane pomoću MR mozga, sa ciljano pripremljenim kognitivnim zadatcima koji odgovaraju pojedinoj regiji. U svim studijama neuropsihologijskim testovima (ljestvicama) potvrđeno je značajno poboljšanje ispitanih kognitivnih funkcija (32-37).

Jedna skupina autora istražila je učinak rTMS-a kao adjuvantne terapije u liječenju bihevioralnih i psihičkih simptoma kod pacijenata s AB. Rezultati su pokazali značajno poboljšanje kognitivnih funkcija, bihevioralnih i psihičkih simptoma u skupini kod koje je uz male doze antipsihotika primijenjen rTMS (38).

Transkranijska stimulacija istosmjernom strujom (tDCS)

U transkranijskoj stimulaciji istosmjernom strujom (tDCS) aplicira se električna struja jakosti 1 – 2 mA kroz dvije ili više elektroda smještenih na tjemenu s modulirajućim učinkom na neuronalnu aktivnost ciljane moždane regije. Anodalni tDCS povećava kortikalnu ekscitabilnost mozga dok ju katodalni tDCS smanjuje (39). Smatra se da tDCS ima modulacijski učinak na kognitivne funkcije u mnogim neuropsihijatrijskim bolestima (40).

U nekoliko studija malih uzoraka ispitivan je učinak tDCS na kognitivne funkcije pacijenta s AB. U jednoj od njih bilateralno je stimulirana temporoparijetalna regija mozga a rezultat je bio poboljšanje memorije prepoznavanja (41).

with cognitive training using the NeuroAD™ system (29-31). In these studies, six brain regions were stimulated: left and right DLPFC (reasoning, executive functions, long-term memory), Brocca and Wernick's area (language function), and the right and left parietal somatosensory associative cortex (spatial orientation, praxis). The brain regions were individually mapped using brain MR and the cognitive training tasks were prepared to match the stimulated brain regions. The results of these studies showed significant improvement of cognitive functions, measured using a battery of neuropsychological tests (32-37).

One group of authors studied the effects of high frequency rTMS as adjunctive treatment for behavioural and psychological symptoms in patients with AD. The results showed a significant improvement of cognitive functions and behavioural and psychological symptoms in those patients who received rTMS along with small doses of antipsychotics (38).

Transcranial direct current stimulation (tDCS)

In transcranial direct current stimulation (tDCS) an electric current of 1–2 mA is passed through two or more electrodes placed on the scalp, modulating neuronal activity of the stimulated brain region. Anodal tDCS increases cortical excitability whereas cathodal tDCS decreases it (39). It is believed that tDCS has a modulatory effect on cognitive functions in many neuropsychiatric disorders (40).

There are few studies of small sample sizes that have examined the effects of tDCS on cognitive functions in patients with AD. One such study used tDCS to bilaterally stimulate the temporoparietal brain region, with improvements in recognition memory (41).

The results of two other studies by the same group of researchers showed an improvement

Rezultati drugih dviju studija iste skupine istraživača navode poboljšanje memorije vizualnog prepoznavanja na zadatcima *Visual Recognition Memory* (VRM). Rezultati su održani tijekom 4 tjedna (42,43). U jednoj od najnovijih studija rezultati ukazuju na poboljšanje kognitivnih funkcija mjereno ljestvicom MMSE nakon višekratne primjene tDCS (44). Cotelli i sur. su ispitivali primjenu anodalnog tDCS nad DLPFK zajedno s individualiziranim kompjuteriziranim vježbama pamćenja ili motoričkim vježbama. Pacijenti su randomizirani tako da je jedna skupina primala tDCS + vježbe pamćenja, druga tDCS + motoričke vježbe, a treća placebo tDCS + vježbe pamćenja. Rezultati su pokazali poboljšanje pamćenja (asocijacije ime - lice) kod obje skupine koje su primali vježbe pamćenja (45).

U randomiziranoj placebo kontroliranoj studiji, u kojoj je primijenjen tDCS temporalno, autori Bystad i sur. nisu našli bitne razlike u neuropsihologijskim mjerama između aktivne i placebo skupine (46).

Kognitivna stimulacija

Rezultati recentne meta-analitičke studije, koja je uključivala 14 randomiziranih, placebo kontroliranih studija (731 osoba, 412 primalo kognitivnu stimulaciju) pokazali su da kognitivna stimulacija dovodi do poboljšanja kognitivnih funkcija mjereno ljestvicama ADAS-Cog i MMSE. Uočena su značajna poboljšanja u mjerama kvalitete života (QoL-AD), ali bez značajnijih promjena na ljestvici aktivnosti dnevnog života (ADL); bez utjecaja na raspoloženje i bihevioralne simptome (47). Cochrane meta-analitička studija iz 2012. godine imala je slične rezultate (48).

ZAKLJUČCI

Demencija je teška neurodegenerativna bolest koja zbog starenja populacije i sve veće pojavnosti postaje prioritetni javnozdravstveni problem. Etiopatofiziologija do danas nije jasna. Etiološko liječenje ne postoji. Antidementivi, koji uključu-

in visual recognition memory (VRM), and these results were retained for 4 weeks (42,43).

The results of a recent study showed improvements in cognitive functions measured by MMSE after multiple applications of tDCS (44). Cotelli and colleagues studied the application of anodal tDCS on the DLPFC combined with individualized computerized memory training or motor training. The patients were randomized into three groups: one group received tDCS + memory training, the second group received tDCS + motor training and the third placebo tDCS + memory training. The results showed improvement in memory (face-name association) in both groups receiving memory training (45).

In a randomized placebo-controlled study in which tDCS was applied temporally, Bystad *et al.* did not find significant differences in neuropsychological tests between the active and placebo groups (46).

Cognitive stimulation

The results of a recent meta-analytical study, which included 14 randomized controlled studies (731 subjects, 412 received cognitive stimulation), showed that cognitive stimulation leads to improved cognitive functioning as measured by ADAS-Cog and MMSE. Significant improvements were seen in Quality of Life assessment (QoL-AD) but without differences in the Activities of Daily Living (ADL) scale and with no benefits on mood and behavioural symptoms (47). A Cochrane meta-analytic study from 2012 showed similar results (48).

CONCLUSION

Dementia is a severe neurodegenerative disease. It has become a public health priority due to population ageing and increase in prevalence. The etiopathophysiology is still unknown. No etiological form of treatment exists. Antidementia drugs include cholinesterase inhibitors

ju inhibitore kolinesteraze i antagoniste NMDA receptora imaju simptomatski učinak, ali ne mijenjaju prirodan tijek i ishod bolesti. Trenutno se ispituju supstancije koje na razne načine djeluju na β-amiloid i tau proteine. Od neuromodulacijskih metode liječenja rTMS i tDCS su pokazali učinkovitost u poboljšanju kognitivnih funkcija, ali su, kao i kod drugih metoda liječenja, učinci vremenski ograničeni. U području neuromodulacijskog liječenja potrebna su daljnja standardizirana istraživanja na većim uzorcima. Premalo je randomiziranih placebo kontroliranih studija. Studije nisu standardizirane, velike su varijacije u metodologiji, kriterijima uključivanja, načinu praćenja i vremenu trajanja samih studija. Kognitivna stimulacija se pokazala učinkovitom u poboljšanju kognitivnih funkcija, ali bez bitnog utjecaja na druge simptome vezane uz AB (npr. raspoloženje, bihevioralni učinci).

and NMDA receptor antagonists which have only a symptomatic effect and do not change the course and outcome of the disease. Substances that effect β-amiloid and tau protein are being researched. Neuromodulator forms of treatment such as TMS and tDCS have been shown to improve cognitive functions, but as with all other forms of treatment are of limited duration. In the area of neuromodulation therapy there is a need for further standardized research studies with bigger sample sizes. There are not enough randomized placebo-controlled studies. Studies are not standardized; there is too much variation in methodology, inclusion criteria, follow-up methods, and study duration. Cognitive stimulation training also has positive effects on cognition but without much effect on other symptoms associated with AD (e.g. behavioural and mood changes).

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