INTERNACIONALNA AKADEMIJA NAUKA I UMJETNOSTI U BOSNI I HERCEGOVINI
RAZRED ZA MEDICINSKE NAUKE

INTERNATIONAL ACADEMY OF SCIENCE AND ARTS IN BOSNIA AND HERZEGOVINA
DEPARTMENT OF MEDICAL SCIENCES

UDRUŽENJE ZA KLINIČKU NEUROFIZIOLOGIJU U FEDERACIJI BOSNE I HERCEGOVINE

SOCIETY FOR CLINICAL NEUROPHYSIOLOGY IN THE FEDERATION BOSNIA AND HERZEGOVINA

# DRUGI AKADEMSKI BH NEUROLOŠKI FORUM

SIMPOZIJUM SA MEĐUNARODNIM SUDJELOVANJEM

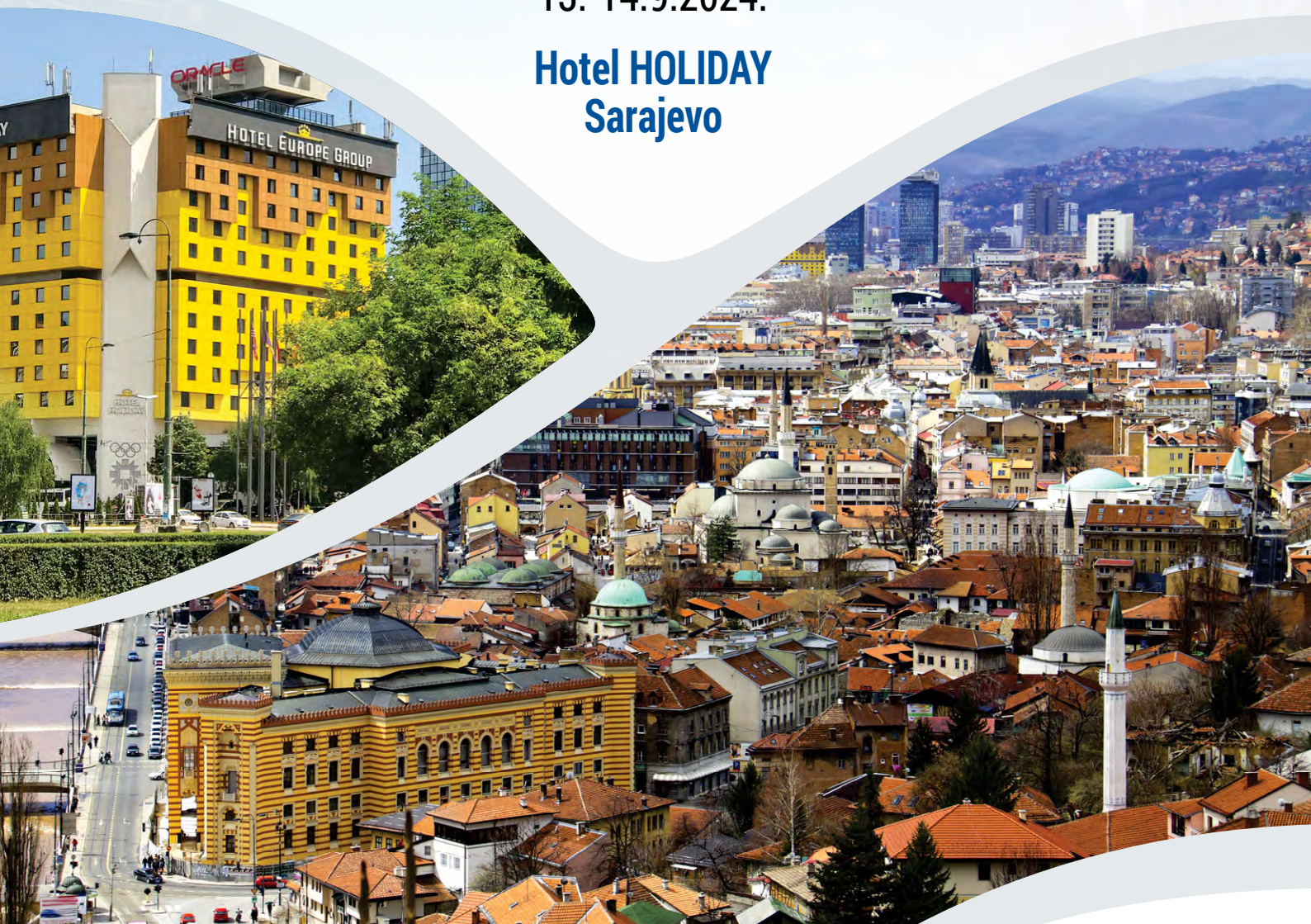
# THE SECOND ACADEMIC B&H NEUROLOGY FORUM

SYMPOSIUM WITH INTERNATIONAL PARTICIPATION

## ZBORNIK SAŽETAKA / ABSTRACT BOOK

13.-14.9.2024.

**Hotel HOLIDAY**
**Sarajevo**



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# PROGRAM

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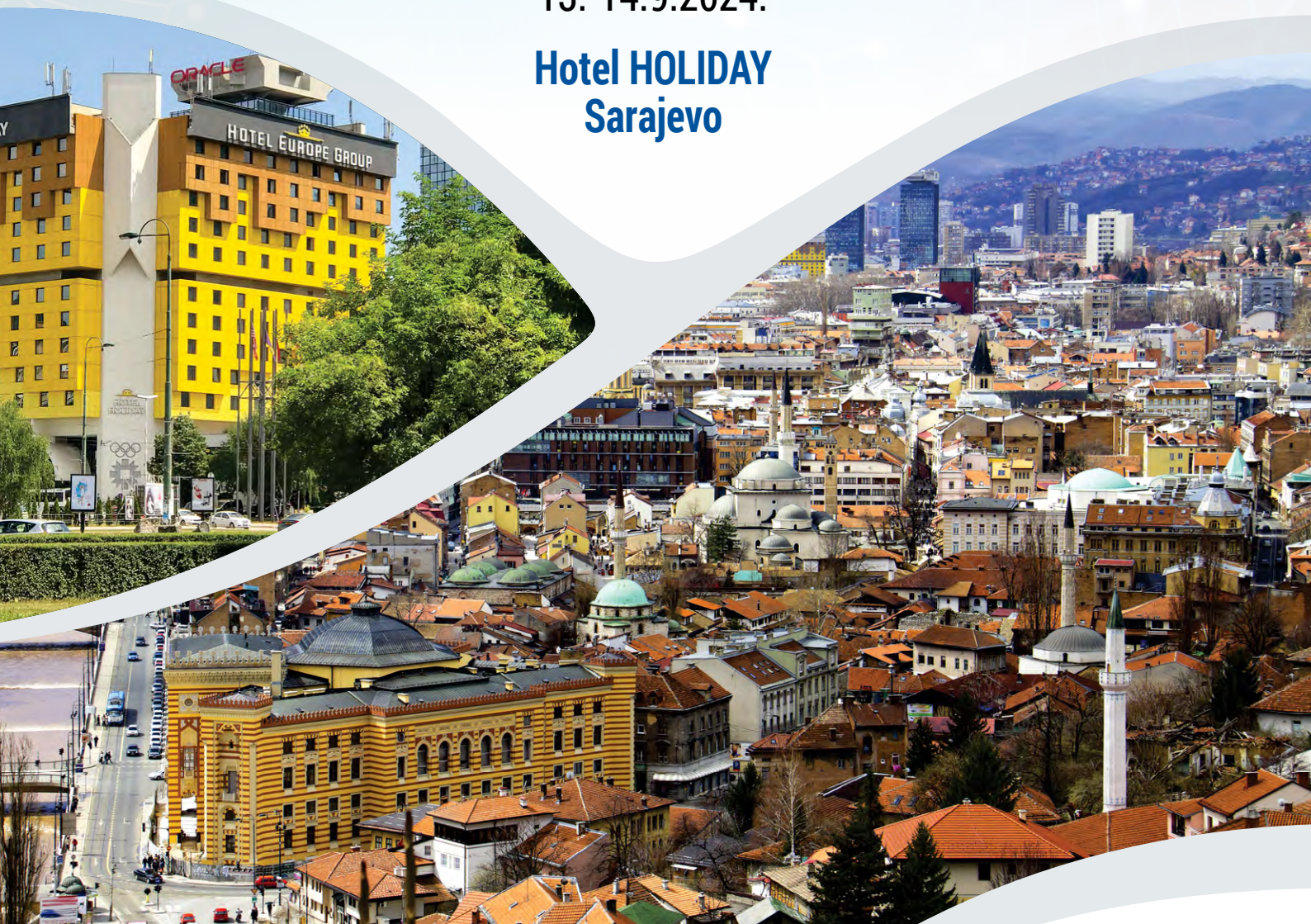
## Hotel HOLIDAY Sarajevo



**Lista predavača** (List of lecturers):

Azra ALAJBEGOVIĆ (Sarajevo/Bosna i Hercegovina)
Amel AMIDŽIĆ (Sarajevo/Bosna i Hercegovina)
Slobodan APOSTOLSKI (Beograd/Srbija)
Dragan BABIĆ (Mostar/Bosna i Hercegovina)
Silva BUTKVIĆ SOLDO (Osijek/Hrvatska)
Silva BANOVIĆ (Tuzla/Bosna i Hercegovina)
Silvio BAŠIĆ (Zagreb/Hrvatska)
Vanja BAŠIĆ KES (Zagreb/Hrvatska)
Jasminka ĐELIOVIĆ VRANIĆ (Sarajevo/Bosna i Hercegovina)
Vlasta ĐURANOVIĆ (Zagreb/Hrvatska)
Mevludin HASANOVIĆ (Tuzla/Bosna i Hercegovina)
Miro JAKOVLJEVIĆ (Zagreb/Hrvatska)
Stjepan JURIĆ (Osijek/Hrvatska)
Petar KES (Zagreb/Hrvatska)
Frederik LUNDQVIST (Malme, Sweden)
Milena MILEUSNIĆ (Vienna, Austria)
Mirsad MUFTIĆ (Sarajevo/Bosna i Hercegovina)
Igor PETROVIĆ (Beograd/Srbija)
Nataša PEJANOVIĆ ŠKOBIĆ (Mostar/Bosna i Hercegovina)
Zvezdan PIRTOŠEK (Ljubljana/Slovenija)
Ranko RAIČEVIĆ (Beograd/Srbija)
Osman SINANOVIĆ (Tuzla/Sarajevo/Bosna i Hercegovina)
Marina SVETEL (Beograd/Srbija)
Selma ŠABANAGIĆ HAJRIĆ (Sarajevo/Bosna i Hercegovina)
Merita TIRIĆ ČAMPARA (Sarajevo/Bosna i Hercegovina)
Zlatko TRKANJEC (Zagreb/Hrvatska)
Nilda TURGUT (Tekirdag/Turkiye)

## **Petak, 13.9.2024.** (Friday, September 13, 2024)

**8:30-9:1** **Registracija**
(Registration)

**9:15-9:45** **Otvaranje simpozija**
(Opening)

**Sesija 1. Kultura empatije kao temelj dobre kliničke prakse**
(Session 1. A culture of empathy as the foundation of good clinical practice)

**Moderatori: Miro JAKOVLJEVIĆ (Zagreb) i Osman SINANOVIĆ (Tuzla/Sarajevo)**
(Moderators: Academician Miro JAKOVLJEVIĆ (Zagreb) and Osman SINANOVIĆ (Tuzla/Sarajevo)

**10:00-10:20** **Miro JAKOVLJEVIĆ (Zagreb)**
**Kultura empatije i personalizirana medicina: Kako povećati učinkovitost neurofarmakoterapije?**
(Culture of empathy and personalized medicine: How to increase the effectiveness of neuropharmacotherapy?)

**10:20-10:40** **Osman SINANOVIĆ (Tuzla, Sarajevo)**
**Što je to dobra klinička praksa u neurologiji i neuropsihijatriji?**

**10:40-11:00** **Vanja BAŠIĆ KES (Zagreb)**
**Neurobiološke osnove empatije**
(Neurobiological basis of empathy)

**11:20-:11:40** **Dragan BABIĆ (Mostar)**
**Komplementarna medicina i važnost kulture empatije**
(Complementary medicine and the importance of a culture of empathy)

**11:40-12:00** **Mevludin HASANOVIĆ (Tuzla)**
**Kultura empatije i duhovnost u liječenju neuroloških bolesnika**
(Culture of empathy and spirituality in the treatment of neurological patients)

**11:40-12:00** **Diskusija**
(Discussion)

**11:40-12:00** **Kafe pauza**
(Coffee break)

**Sesija 2. Meeting with experts**
(Sesion 2. Susreti sa ekspertima)

**Moderatori: Osman SINANOVIĆ (Tuzla/Sarajevo), Slobodan APOSTOLSKI (Beograd) i Silvio BAŠIĆ (Zagreb)**
(Moderators: Osman SINANOVIĆ (Tuzla/Sarajevo), Slobodan APOSTOLSKI (Beograd) i Silvio BAŠIĆ (Zagreb)

**12:00-12:20** **Slobodan APOSTOLSKI (Beograd)**
**Različitosti poremećaja neuromišićne transmisije**
(Diversity od neuromuscular disorders)

**12:20-12:40** **Ranko RAIČEVIĆ (Beograd)**
**Farmakoekonomski aspekti moždanog udara**
(Pharmacoeconomic aspects of stroke)

**12:40-13:00** **Silvio BAŠIĆ (Zagreb)**
**Autoimuni encefalitisi**
(Autoimmune encephalitis)

**13:00-13:20** **Stjepan JURIĆ (Osijek)**
**Poremećaji spavanja u neurologiji**
(Sleep disorders in neurology)

**13:20-13:50** **Bosnalijek: Sponzorski simpozijum**
(Bosnalijek: Sponsor symposium)
**Osman SINANOVIĆ (Tuzla/Sarajevo)**
**Liječenje neuropatske boli**
(Treatment of neuropathic pain)

**13:50-14:10** **Dr. Werner Pharma: Sponzorski simpozijum**
(Dr. Werner Pharma: Sponsor sympozium)
**Slobodan APOSTOLSKI (Beograd)**
**Uloga Peanila u liječenju neuropatske boli**
(The role of Peanil in the treatment of neuropathic pain)

**14:10-15:30** **Ručak**
(Lunch)

**Sesija 3. Glavobolje**
(Session 3. Headaches)

**Moderatori: Jasminka ĐELILOVIĆ VRANIĆ (Sarajevo) i Silva BUTKOVIĆ SOLDO (Osijek)**
(Moderators: Jasminka ĐELILOVIĆ VRANIĆ (Sarajevo) and Silva BUTKOVIĆ SOLDO (Osijek)

**15:30-15:50** **Vlasta ĐURANOVIĆ (Zagreb)**
**Glavobolje u dječijoj i adolescentskoj dobi**
(Headaches in childhood and adolescence)

**15:50-16:10** **Merita TIRIĆ ČAMPARA (Sarajevo)**
**Terapijske opcije kod migrene odraslih**
(Therapeutic options for migraine in adults)

**16:10-16:30** **Silva BUTKOVIĆ SOLDO (Osijek)**
**Može li biofeedback pomoći osobama sa glavoboljama?**
(Can biofeedback help people with migraines?)

**16:30-16:50** **Jasminka ĐELILOVIĆ VRANIĆ (Sarajevo)**
**Glavobolja i multipla skleroza**
(Headache and multiple sclerosis)

**Sesija 4. Neuroimunologija**
(Session 4. Neuroimmunology)

**Moderatori: Azra ALAJBEGOVIĆ (Sarajevo), Nataša PEJANOVIĆ ŠKOBIĆ (Mostar) i Vanja BAŠIĆ KES (Zagreb)**
(Moderators: Azra ALAJBEGOVIĆ (Sarajevo), Nataša PEJANOVIĆ ŠKOBIĆ (Mostar) and Vanja BAŠIĆ KES (Zagreb)

**9:00-9:20** **Nilda TURGUT (Tekirdag)**
**Treating progressive multiple sclerosis**
(Liječenje progresivne multiple sklerze)

**9:20-9:40** **Nataša PEJANOVIĆ ŠKOBIĆ (Mostar)**
**Razlike i sličnosti MS, NMOSD i MOGAD**
(Differences and similarities of MS, NMOSD and MOGAD)

**9:40-10:00** **Vanja BAŠIĆ KES (Zagreb)**
**Multipla skleroza i trudnoća**
(Multiple sclerosis and pregnancy)

**10:00-10:20** **Petar KES (Zagreb)**
**Terapijska afereza u liječenju neuroloških bolesnika**
(Therapeutic apheresis in the treatment of neurological patients)

**10:20-10:40** **Azra ALAJBEGOVIĆ (Sarajevo)**
**Komplementarna i alternativna terapija multiple skleroze**
(Complementary and alternative therapy of multiple sclerosis)

**10:40-11:10** **Ottobock: Sponzorski simpozijum**
(Ottobock: Sponsor symposium)
**Frederik LUNQVIST (Malme)**
(Inventor of the Expuse Mollii Suit/Izumitelj Expulse Mollii odijela)
**Millena MILEUSNIĆ (Vienna/Beč)**
Kliničke koristi od neinvazivnog uređaja za neuromodulaciju kod pacijenata sa fibromialgijom i poremećajima kretnja zbog spazma (CP, MS, MU)
(Clinical benefits of non-invasive neuromodulation device in patients suffering from fibromyalgia and spastic movement disorders (CP, MS, stroke)

**11:10-11:30** **Kafe pauza**
(Coffee break)

**Sesija 5. Ekstrapiramidni i neurodegenerativni poremećaji**
(Session 5. Extrapyramidal and neurodegnerative disorders)

**Moderatori: Zlatko TRKANJEC (Zagreb), Marina SVETEL (Beograd) i Mirsad MUFTIĆ (Sarajevo)**
(Moderators: Zlatko TRKANJEC (Zagreb), Marina SVETEL (Beograd) and Mirsad MUFTIĆ (Sarajevo)

**11:30-11:50** **Zvezdan PIRTOŠEK (Ljubljana)**
**Distonije**
(Dystonias)

**11:50-12:10** **Marina SVETEL (Beograd)**
**Invazivna terapija Parkinsonove bolesti**
(Invasive therapy of Parkinson's disease)

**12:10-12:30** **Zlatko TRKANJEC (Zagreb)**
**Terapija rane faze Parkinsonove bolesti**
(Therapy of the early phase of Parkinson's disease)

**12:30-12:50** **Igor PETROVIĆ (Beograd)**
**Uticaj nemotornih simptoma na terapijske prioritete u Parkinsonovoj bolesti**
The influence of non-motor symptoms on therapeutic priorities in Parkinson's disease

**12:50-13:10** **Selma ŠABANAGIĆ HAJRIĆ (Sarajevo)**
**Frontotemporalna demencija**
(Frontotemporal dementia)

**13:10-13:25** **Synthesis Pharma: Sponzorski simpozij**
(Sinthesis Pharma: Sponsor symposium)
**Amel AMIDŽIĆ (Sarajevo)**
**Značaj primjene Neurozan-a kod kognitivnog poremećaja (Prikaz slučaja)**
The importance of using Neurozan in cognitive disorders (Case Report)

**13:25-13:45** **Silva BANOVIĆ (Tuzla)**
**Augmentativna i alternativna komunikacija za osobe sa neurološkim oboljenjima**
(Augmentative and alternative communication for persons with neurological diseases)

**13:45-14:05** **Mirsad MUFTĆ (Sarajevo)**
**Moderni koncepti neurorehabilitacije**
(Modern concepts of neurorehabilitation)

**14:05:-14:25** **Osman SINANOVIĆ (Tuzla/Sarajevo)**
**Nove mogućnosti liječenja amiotrofičke lateralne skleroze**
(New treatment options for amyotrophic lateral sclerosis)

**14:25-14:30** **Zatvaranje simpozijuma**
(Closing of the symposium)



Simpozijum će biti bodovan prema Pravilniku Liječničke-ljekarske Komore Kantona Sarajevo.

# KULTURA EMPATIJE I PERSONALIZIRANA MEDICINA: KAKO POVEĆATI UČINKOVITOST NEUROFARMAKOTERAPIJE?

Miro JAKOVLJEVIĆ

Medicinski fakultet Sveučilišta u Zagrebu, Zagreb, Republika Hrvatska
Medicinski fakultet Sveučilišta u Mostaru, Mostar, Bosna i Hercegovina

"Najviši oblik znanja je empatija, jer zahtijeva od nas da suspendiramo svoj ego i živimo u tuđem svijetu" - Platon

**Sažetak**

O ulozi empatije u kliničkoj praksi postoje različita mišljenja. Liječnici koji prakticiraju empatičan prijateljski pristup učinkovitiji su od onih koji prakticiraju emocionalno distancirani pristup bolesniku. Sve veći broj zdravstvenih radnika smatra da je kultura empatije kamen temeljac dobre kliničke prakse u personaliziranoj medicini ili medicini usmjerenoj na osobu u neurologiji. Personalizirana medicina razmatra kliničke i osobne karakteristike pacijenta kako bi predvidjela osjetljivost na bolest, pomogla u dijagnozi i primijenila individualizirano liječenje, precizna medicina traži objektivne pokazatelje, biomarkere, endofenotipove ili biopotpise, dok medicina usmjerena na osobu potiče pacijenta da bude proaktivan kao partner u liječenju. Empatija je važna komponenta emocionalne i socijalne inteligencije i omogućuje nam bolje razumijevanje života i svijeta u kojem živimo te kreativno povezivanje s drugim ljudima. Obično govorimo o emocionalnom ("Osjećam tvoju bol"), kognitivnom (Razumijem tvoj problem/situaciju), bihevioralnom ("Ovdje sam s tobom i uz tebe") i moralnom ("dobro je činiti dobro" ) aspektu empatije. Kultura (lat. colere: njegovati, rasti, uzgajati, kultivirati) predstavlja materijalne i duhovne tvorevine i uključuje moral, vrijednosti i norme koje slijedimo i koje određuju naš način bivanja u svijetu i kakve osobe postajemo i jesmo. Uključuje integrirane obrasce naučenih uvjerenja, misli, vrijednosti, stavova, motiva, stilova komunikacije te odnosa i običaja. Kultura kliničke empatije vrlo je poseban način komunikacije s pacijentima i njihovim obiteljima te, naravno, s našim kolegama. Odnosi se na bolje razumijevanje mentalnog stanja pacijenata, potreba, uvjerenja, vrijednosti, emocija, situacija, narativa pacijenata i perspektiva. Empatijsko razumijevanje i komunikacija igraju važnu ulogu u učinkovitijem i uspješnijem odnosu između liječnika i pacijenta. Empatija pospješuje povjerenje, poštovanje i iskrenu otvorenost te može izravno terapijski djelovati izazivanje placebo reakcije kod pacijenata. Nedostatak empatične komunikacije u kliničkoj praksi može rezultirati češćom nocebo reakcijom kod pacijenata i njihovom nesuradljivošću. Kultura empatije poboljšava dijagnostičku točnost, iskustvo pacijenata, zadovoljstvo i suradnju, povećava njihovu osobnu moć i smanjuje psihološki distres i medicinske komplikacije. Uključuje različite strategije poboljšanja dobrobiti koje su povezane s povećanjem placebo učinka i smanjenjem nocebo učinka i odgovora. Klinička empatija poboljšava pozitivno iskustvo pacijenta, osobnu moć i samokontrolu, suradnju i zadovoljstvo, zdravstvene ishode ali također i duševno blagostanje dobrobit liječnika.

Komplementarno poboljšanju ishoda liječenja kod pacijenata, kultura kliničke empatije je povezana s većim mentalnim i općim blagostanjem zdravstvenih djelatnika i povećanjem zadovoljstva životom što može biti u svezi sa smanjenim „sagorijevanjem“ na poslu (burn-out), osobnim distresom, anksioznošću i depresijom. Povećana empatija je praćena višim supervizorskim ocjenama kliničke kompetencije i vještina, smanjenim brojem parnica zbog nesavjesnog liječenja i povećanim zadovoljstvom poslom. Promicanje empatijskog vodstva u našem zdravstvenom sustavu ključno je za bolju zdravstvenu skrb pacijenata, bolje radno okruženje i zdravlje liječnika.

**Ključne riječi**: Kultura empatije – Klinička empatija – Neurofarmakoterapija – Terapijski savez za liječenje – Zadovoljstvo liječenjem – Povećanje placeba – Smanjenje nocebo učinaka

## CULTURE OF EMPATHY AND PERSONALIZED MEDICINE: HOW TO INCREASE EFFICIENCY OF NEUROPHARMACOTHERAPY?

Miro JAKOVLJEVIĆ

School of Medicine, University of Zagreb, Zagreb, Republic of Croatia
School of Medicine, University of Mostar, Mostar, Bosnia i Herzegovina

> “The highest form of knowledge is empathy, for it requires us to suspend our egos and live in another’s world” - Plato

**Abstract**

There are different opinions regarding the role of empathy in clinical practice. Physicians who practice an empathetic friendly approach are more effective than those practicing detached concern. Increasing number of the health care workers think that the culture of empathy is a cornerstone of the good clinical practice in personalized or person-centered medicine in neurology. Personalized medicine considers clinical and personality characteristics of a patient in order to predict susceptibility to disease, aid in diagnosis and apply tailor-made individualized neuropharmacology treatment, precision medicine searches objective measures, biomarkers, endophenotypes or biosignatures for choice of neuropharmacology therapy while person-centered medicine promotes a patient to be proactiveas partner in treatment. Empathy is an important component of emotional and social intelligence and it enables us to better understand life and the world we live in, to connect creatively with other people. We usually talk about emotional ("I feel your pain"), cognitive (I understand your problem/situation) and behavioral ("I'm here with you and by your side") and moral ("it's good to do the good") dimensions of empathy. Culture (lat. colere: nurture, grow, raise, cultivate) represents material and spiritual creations and includes morals, values and norms that we follow and that determine our way of being in the world and what kind of person we become and are. It involves integrated patterns of learnt beliefs, thoughts, values, attitudes, motives, communication styles and relationship and customs. Culture of clinical

empathy is a very special way of being with patients and their families and, of course with our colleagues. In refers to better understanding of patients' mental state, needs, beliefs, values, emotions, situations, patients' narratives and perspectives. Empathic understanding and communicating plays an important role in the more effective and successful physician-patient relationship. Empathy facilitates trust, respect and disclosure and can be directly therapeutic by increasing placebo response in patients. Lack of empathic communication in clinical practice may result in more frequent patients' nocebo response and uncooperativeness. Culture of empathy improves diagnostic accuracy, patient experience, satisfaction and cooperation, increases their personal mastery and decreases psychological distress and medical complications. It involves different well-being enhancing strategies that are associated with increasing placebo, and decreasing nocebo effects and responses. Clinical empathy improves patient experience, personal mastery, cooperation and satisfaction, health outcomes and also health practitioner well-being.

Complementary to improving treatment outcome in patients, culture of clinical empathy is interestingly associated with health practitioners' mental and overall well-being, increased life satisfaction associated with decreased burnout, personal distress, anxiety and depression. Increased empathy is followed by the higher supervisor ratings of clinical competence and skills, decreased malpractice litigation, and increased job satisfaction. Promoting empathic leadership in our healthcare system is essential for better health care for patients, a better working environment and physicians' health.

**Key words**: Culture of empathy – Clinical empathy – Neuropharmacotherapy – Therapeutic alliance – Treatment response and satisfaction – Increasing placebo – Decreasing nocebo effects

# ŠTA JE TO DOBRA KLINIČKA PRAKSA U NEUROLOGIJI?

Osman SINANOVIĆ

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## Sažetak

Dobra klinička praksa predstavlja skup međunarodno priznatih etičkih i naučnih zahtjeva i sistem obezbjeđenja kvaliteta koji se koriste u planiranju, sprovođenju, bilježenju i izvještavanju o kliničkim ispitivanjima koja se sprovode na ljudima. Usklađenost ispitivanja s dobrom kliničkom praksom osigurava da će prava, sigurnost i dobrobit bolesnika biti zaštićeni u skladu sa visok nivo znanja i mogućnosti i svjesnosti o limitima, i svojim i ustanove/sredine u kojoj radite. principima proisteklim iz Helsinške deklaracije, te da su rezultati dobiveni takvim kliničkim ispitivanjem vjerodostojni. Dobra klinička praksa, ne odnosi se naravno samo na poštivanje ovih principa kod kliničkih istraživanja, i ne samo poštivanje principa "primum non nocere"; podrazumijeva i

Klinička empatija igra važnu ulogu u odnosu ljekar-pacijent omogućavajući ljekarima da bolje razumiju iskustva i perspektive svojih pacijenata. Empatija, ili sposobnost ljekara da razumije pacijentovu jedinstvenu situaciju i emocije, da prenese svoje razumijevanje natrag pacijentu kako bi utvrdio tačnost, i da djeluje na altruistički način u skladu s pacijentovim vrijednostima, uvjerenjima i prioritetima, kritična je komponenta naše brige o neurološkom bolesniku. Zanimljivo je da ne postoji konsenzus o definiciji i konstruktu empatije, iako je potreba za konsenzusom prepoznata još od 1948. godine.

U oblasti biomedicine, klinička empatija se opisuje na pretežno kognitivni i bihevijoralni način. Neki istraživači i kliničari empatiju opisuju kao afektivni atribut, koji prvenstveno uključuje emociju zabrinutosti pojedinca (emotivno razumijevanje), dok drugi opisuju empatiju kao kognitivni atribut, prvenstveno koji uključuje razumijevanje zabrinutosti drugih. Klinička empatija igra važnu ulogu u odnosu ljekar-pacijent omogućavajući ljekarima da bolje razumiju iskustva i perspektive svojih pacijenata. Veća empatija liječnika povezana je s boljom kontrolom glikemije, većim zadovoljstvom i osnaživanjem pacijenata, te većom usklađenošću s liječenjem.

Nužno je u sveukupnom tretmanu svih neuroloških poremećaja imati empatijski pristup, ali prije svega poštovati osnove dobre kliničke prakse, koja podrazumijeva osim znanja, bez koga naravno ne možeš previse biti od koristi, znati znanje primijeniti; raditi ciljane pretrage; biti brzo koliko treba i koliko se u datim okolnostima može; imati znanje o terapijskim postupcima; moći ih primijeniti; "biti sa bolesnikom", sve vrijeme dijagnosticiranja, liječenja i oporavka; i kada "ide i kada ne ide". Pacijenti o kojima se brinu empatični liječnici imaju veću verovatnoću da će biti zadovoljni svojom njegom, da vjeruju svojim lijčnicima, da se pridržavaju planova liječenja i da imaju bolje ishode. Pored toga, razvijanje i negovanje empatije ljekara ima korisne efekte ne samo za jačanje dobrog odnosa ljekar-pacijent, nego i za jačanje dobrobiti pacijenata i liječnika. Ne samo da su pacijenti manje

pod stresom, depresivni i “agresivni”, kada zdravstveni radnici ispoljavaju adekevatnu empatiju prema njima, već empatija također smanjuje izgaranje liječnika, smanjuje stopu nesavjesnih postupaka i grešaka u liječenju i poboljšava cjelokupno zdravlje ljekara i drugih zdravstvenih djelatnika, uključenih u brigu o bolesniku.

**Ključne riječi:** Dobra klinička praksa – Klinička empatija – Neurologija

## WHAT IS GOOD CLINICAL PRACTICE IN NEUROLOGY?

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## Abstract

Good clinical practice is a set of internationally recognized ethical and scientific requirements and a quality assurance system used in the planning, conduct, recording and reporting of human clinical trials. Compliance of the trial with good clinical practice ensures that the rights, safety and well-being of the patient will be protected in accordance with the principles derived from the Declaration of Helsinki, and that the results obtained from such a clinical trial are credible. Good clinical practice, of course, does not only refer to the observance of these principles in clinical research, and not only to the observance of the "primum non nocere" principle; it also implies a high level of knowledge and possibilities and awareness of the limits, both of your own and of the institution/environment in which you work.

Clinical empathy plays an important role in the doctor-patient relationship, enabling doctors to better understand their patients' experiences and perspectives. Empathy, or the physician's ability to understand the patient's unique situation and emotions, to convey that understanding back to the patient to determine accuracy, and to act altruistically in accordance with the patient's values, beliefs, and priorities, is a critical component of our care for the neurological patient. It is interesting that there is no consensus on the definition and construct of empathy, although the need for consensus has been recognized since 1948. In the field of biomedicine, clinical empathy is described in a predominantly cognitive and behavioral way. Some researchers and clinicians describe empathy as an affective attribute, primarily involving the emotion of an individual's concerns (emotional understanding), while others describe empathy as a cognitive attribute, primarily involving understanding the concerns of others.

Clinical empathy plays an important role in the doctor-patient relationship by enabling doctors to better understand their patients' experiences and perspectives. Greater physician empathy is associated with better glycemic control, greater patient satisfaction and empowerment, and greater compliance with treatment.

In the overall treatment of all neurological disorders, it is necessary to have an empathetic approach, but first of all to respect the basics of good clinical practice, which

implies, in addition to knowledge, without which of course you cannot be of much use, knowing how to apply knowledge; perform targeted searches; to be as fast as necessary and as possible under the given circumstances; have knowledge of therapeutic procedures; be able to apply them; "being with the patient", all the time of diagnosis, treatment and recovery; and when it "works and when it doesn't".

Patients cared for by empathic physicians are more likely to be satisfied with their care, trust their physicians, adhere to treatment plans, and have better outcomes. In addition, the development and cultivation of physician empathy has beneficial effects not only for strengthening the good doctor-patient relationship, but also for enhancing the well-being of patients and physicians. Not only are patients less stressed, depressed, and "aggressive" when health care professionals show adequate empathy toward them, but empathy also reduces physician burnout, reduces malpractice and medication error rates, and improves the overall health of physicians and other health care professionals involved. in the care of the patient.

**Key words:** Good clinical practice – Clinical empathy – Neurology

# NOVE MOGUĆNOSTI LIJEČENJA AMIOTROFIČKE LATERALNE SKLEROZE

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## Apstrakt

Bolest sa oštećenjem i centralnog motornog neurona (CMN) i perifernog motorno neurona (PMN), bolest motornog neurona (BMN) ili amiotrofična lateralna skleroza (ALS), spada u neuromišićne i neurodegenerativne bolesti (propadanje ili "amiotrofije" motornih neurona). Srednja dob početka bolesti je 55 godina, a prosječno preživljavanje je 2-5 godina. Početni simptomi ALS-a mogu biti suptilni, ali se bolest neumoljivo širi. Ova progresija nije uvijek konstantna; neki pacijenti imaju sedmice ili mjesece sa malim ili ni malo gubitka funkcije. Incidencija ALS-a u Sjedinjenim Državama je 1,5 do 2,2 na 100 000, ali značajno varira ovisno o dobi, spolu i rasi. Muškarci imaju veću incidenciju ALS-a (1,7-2,6 na 100 000) od žena (1,1-1,5 na 100 000). Više od 90% slučajeva ALS-a je sporadična, a u 5-10% hereditarna bolest. Do danas je više od 50 gena identifikovano u etiologiji ALS-a. Oko 60% hereditarnih i 10% sporadičnih ALS slučajeva je povezano sa četiri najčešća gena: SOD1, TARDBP, FUS/TLS i C9ORF72. Vjeruje se da etiologija BMN-a uključuje složene interakcije okolišnih, životnih i genetskih faktora, ali do sada je ustanovljeno tek nekoliko uvjerljivih faktora rizika. Ova multifaktorska priroda etiologije bolesti delimično objašnjava zašto, uprkos intenzivnim istraživačkim naporima, efikasni tretmani ostaju još uvijek nedostižni, a ALS i dalje predstavlja neispunjenu medicinsku potrebu.

ALS je prilično heterogena bolest. Preživljavanje kod ALS-a ovisi od nekoliko faktora, uključujući kliničku prezentaciju (fenotip), brzinu progresije bolesti, rano prisustvo respiratorne insuficijencije i nutritivni status pacijenata. Identifikacija specifičnih fenotipova ima važne implikacije za pacijente, posebno u pogledu prognoze i preživljavanja, ali i za njihovo uključivanje u klinička ispitivanja. U tipičnim slučajevima piramidalni znaci (CMN) su vrlo jasni na nogama (slabost, spastičnost mišića, hiperrefleksija, Babinski može biti pozitivan, ali često izostaje), a na rukama su simptomi zahvaćenosti perifernih motornih neurona (PMN) (slabost, hipotrofija mišića, fascikulacije), hiperefleksija zbog istovremenog oštećenja centralnog motornog neurona/CMN).

Sve smjernice naglašavaju važnost multidisciplinarnog pristupa i tretmana za pacijente s ALS-om, a multidisciplinarna njega pacijentima pruža razne pogodnosti. Pokazano je, nadalje, da pacijenti koji primaju njegu u specijalizovanim klinikama za ALS, imaju duže preživljavanje i bolji kvalitet života.

Klinička ispitivanja proučavala su mnoge eksperimentalne lijekove za usporavanje progresije ALS-a na životinjskim modelima s obećavajućim rezultatima, međutim, malo ih je prevedeno na djelotvornost kod ljudi s tom bolešću. Donedavno, jedino je riluzol, lijek koji skromno modificira bolest bio odobren od strane američka FDA. Do augusta 2024. godine, FDA je odobrila sedam lijekova za usporavanje progresije bolesti i za liječenje ALS-a i njegovih simptoma: Rilutek (riluzol, oralna tableta) (1995); Tiglutik “zgusnuti” riluzol, oralna suspenzija) (2018); Exservan (oralni film riluzol) (2019); Nuedexta (dekstrometorfan HBr i

kinidin sulfat, kapsule) (2011); Radicava (edaravone) (2017/i.v., oralna formulacija/2022); Relyviro (AMX0035) (prašak za oralnu suspenziju ili kroz cijev za hranjenje) (2022); Qalsody (tofersen) (kroz lumbalnu punkciju) (2023). Riluzol je prvi lijek odobren za ALS (FDA 1995, EMA 2004) i može usporiti progresiju bolesti. Djeluje smanjenjem oslobađanja glutamata, neurotransmitera koji može uzrokovati neurodegeneraciju. Edaravone (FDA odobrila 2017, EMA 2019) je antioksidans koji pomaže u smanjenju oksidativnog stresa, što može usporiti progresiju ALS-a kod nekih pacijenata. Tofersen je specifičan za ALS povezanu s mutacijom SOD1 gena, odobren od FDAi EMA 2003. Djeluje kao antisense oligonukleotid koji smanjuje proizvodnju toksičnih proteina povezanih s ovom mutacijom. Kurativni tretman za ALS, dakle ne postoji, ali se čini da spomenute terapije umjereno usporavaju progresiju bolesti/produžuju preživljavanje ili odgađaju smrt. Nadalje, dok lijekovi koji modificiraju bolest imaju ograničenu korist, simptomatski tretmani imaju veliki utjecaj na preživljavanje i kvalitet života.

**Ključne riječi:** Amiotrofička lateralna skelroza – Tretman – Riluzole – Edevarone – Tofersen

## NEW TREATMENT OPTIONS FOR AMYOTROPHIC LATERAL SCLEROSIS

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**Abstract**

Disease with damage to both central motor neuron (CMN) and peripheral motor neuron (PMN), motor neuron disease (BMN) or amyotrophic lateral sclerosis (ALS), belongs to neuromuscular and neurodegenerative diseases (degeneration or "amyotrophy" of motor neurons). The median age of disease onset is 55 years, and the average survival is 2-5 years. The initial symptoms of ALS may be subtle, but the disease spreads inexorably. This progression is not always constant; some patients have weeks or months with little or no loss of function. The incidence of ALS in the United States is 1.5 to 2.2 per 100 000, but varies significantly by age, sex, and race. Men have a higher incidence of ALS (1.7-2.6 per 100 000) than women (1.1-1.5 per 100 000). More than 90% of ALS cases are sporadic, and in 5-10% it is a hereditary disease. To date, more than 50 genes have been identified in the etiology of ALS. About 60% of hereditary and 10% of sporadic ALS cases are associated with the four most common genes: SOD1, TARDBP, FUS/TLS and C9ORF72. The etiology of BMN is believed to involve complex interactions of environmental, lifestyle, and genetic factors, but so far only a few convincing risk factors have been established. This multifactorial nature of disease etiology partly explains why, despite intensive research efforts, effective treatments remain elusive and ALS continues to represent an unmet medical need.

ALS is a rather heterogeneous disease. Survival in ALS depends on several factors, including clinical presentation (phenotype), rate of disease progression, early presence of respiratory failure, and nutritional status of patients. The identification of specific phenotypes has important implications for patients, especially in terms of prognosis and survival, but also for their inclusion in clinical trials. In typical cases, pyramidal signs (CMN) are very clear on the legs (weakness, muscle spasticity, hyperreflexia, Babinski can be positive but often absent), and on the hands there are symptoms of peripheral motor neuron involvement (PMN)(weakness, muscle hypotrophy, fasciculations), hyperreflexia due to simultaneous central motor neuron/CMN damage).

All guidelines emphasize the importance of a multidisciplinary approach and treatment for patients with ALS, and multidisciplinary care provides a variety of benefits to patients. Furthermore, it has been shown that patients who receive care in specialized clinics for ALS have longer survival and a better quality of life.

Clinical trials have studied many experimental drugs to slow the progression of ALS in animal models with promising results, however, few have been translated into effectiveness in humans with the disease. Until recently, only riluzole, a modest disease-modifying drug, was approved by the US FDA. By August 2024, the FDA has approved seven drugs to slow disease progression and treat ALS and its symptoms:

Clinical trials have studied many experimental drugs to slow the progression of ALS in animal models with promising results, however, few have been translated into effectiveness in humans with the disease. Until recently, only riluzole, a modest disease-modifying drug, was approved by the US FDA. As of August 2024, the FDA has approved seven drugs to slow disease progression and treat ALS and its symptoms: Rilutek (riluzole, oral tablet) (1995); Tiglutik "thickened" riluzole, oral suspension) (2018); Exservan (oral film riluzole) (2019); Nuedexta (dextromethorphan HBr and quinidine sulfate, capsules) (2011); Radicava (edaravone) (2017/i.v., oral formulation/2022); Relyviro (AMX0035) (powder for oral suspension or through feeding tube) (2022); Qalsody (tofersen) (through lumbar puncture) (2023). Riluzole is the first drug approved for ALS (FDA 1995, EMA 2004) and can slow the progression of the disease. It works by reducing the release of glutamate, a neurotransmitter that can cause neurodegeneration. Edaravone (FDA approved 2017, EMA 2019) is an antioxidant that helps reduce oxidative stress, which may slow the progression of ALS in some patients. Tofersen is specific for ALS associated with SOD1 gene mutation, approved by the FDA and EMA in 2003. It acts as an antisense oligonucleotide that reduces the production of toxic proteins associated with this mutation. There is therefore no curative treatment for ALS, but the mentioned therapies seem to moderately slow the progression of the disease/prolong survival or delay death. Furthermore, while disease-modifying drugs have limited benefit, symptomatic treatments have a major impact on survival and quality of life.

**Key words:** Amyotrophic lateral sclerosis – Treatment – Riluzole – Edaravone – Tofersen

# MULTIPLA SKLEROZA I TRUDNOĆA

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**Sažetak**

Do kraja dvadesetog stoljeća većina neurologa savjetovala je pacijenticama s multiplom sklerozom (MS) da izbjegavaju trudnoću jer bi se klinička slika mogla pogoršati. Promjene u stajalištu neurologa nastupile su 1998. godine kada je objavljena studija PRIMS (Pregnancy in Multiple Sclerosis study), prva velika prospektivna studija koja je uključivala 254 trudnice s relapsno remitirajućom multiplom sklerozom radi razumijevanja utjecaja trudnoće na godišnju stopu relapsa i rizika od progresije osnovne bolesti. Rezultati studije pokazali su pad godišnje stope relapsa za vrijeme trudnoće, s najnižom stopom relapsa u trećem trimestru, u usporedbi s godinom prije trudnoće. Također, stopa relapsa bila je znatno viša u razdoblju od tri mjeseca nakon porođaja iako je samo 28% ispitanica imalo relaps u postpartalnom periodu. Godišnja stopa relapsa od trećeg do dvanaestoga postpartalnog mjeseca nije se razlikovala od stope relapsa u godini prije trudnoće. Pogoršanje invalidnosti nije nastupilo brže u razdoblju nakon porođaja u odnosu prema godini prije.

Trudnoća, dojenje, liječenje neplodnosti, oralni kontraceptivi i za sada ograničene terapijske mogućnosti u oboljelih trudnica utječu na tijek multiple skleroze. Dokazano je da je za vrijeme trudnoće snižena, a u ranome postpartalnom razdoblju povišena godišnja stopa relapsa. Nadalje, istraživanja su pokazala da je dojenje u bolesnica s multiplom sklerozom sigurno; trenutačno nema jasnog stajališta o sigurnosnom profilu oralnih kontraceptiva. S druge strane, smatra se da pri liječenju neplodnosti treba izbjegavati agoniste hormona koji oslobađa gonadotropin (GnRH). Ne preporučuje se uzimanje većine lijekova koji modificiraju tijek bolesti multiple skleroze za vrijeme trudnoće i dojenja, osim glatiramer acetata, odnosno interferona za vrijeme dojenja. Stoga ih je potrebno, ovisno o brzini njihove eliminacije iz organizma, ukinuti tijekom određenog razdoblja prije začeća. Relapsi bolesti u trudnica i dojilja mogu se liječiti pulsnim dozama kortikosteroida, s time da se u trudnica preporučuje njihovo izbjegavanje u prvom tromjesečju, dok se u dojilja preporučuje odgoditi dojenje za četiri sata nakon primljene terapije. U novije vrijeme istražuju se metode prevencije postpartalnih relapsa kao što su primjena intravenskih imunoglobulina, kortikosteroida i hormonske terapije, međutim, za konačni zaključak potrebno je provesti daljnja istraživanja.

**Ključne riječi:** Multipla skleroza – Trudnoća – Dojenje – Imunomodulatorni lijekovi

# MULTIPLE SCLEROSIS AND PREGNANCY

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## Abstract

Until the end of the twentieth century, most neurologists advised patients with multiple sclerosis (MS) to avoid pregnancy because the clinical picture could worsen. Changes in the opinion of neurologists occurred in 1998 when the PRIMS study (Pregnancy in Multiple Sclerosis study) was published, the first large prospective study that included 254 pregnant women with relapsing-remitting multiple sclerosis to understand the impact of pregnancy on the annual rate of relapse and the risk of progression of the underlying disease . The results of the study showed a decrease in the annual relapse rate during pregnancy, with the lowest relapse rate in the third trimester, compared to the year before pregnancy. Also, the rate of relapse was significantly higher in the period of three months after childbirth, although only 28% of the subjects had a relapse in the postpartum period. The annual relapse rate from the third to the twelfth postpartum month did not differ from the relapse rate in the year before pregnancy. Deterioration of disability did not occur faster in the period after childbirth compared to the year before

The course of multiple sclerosis is affected by pregnancy, breastfeeding, fertility treatment and oral contraceptives, as well as by the still limited therapeutic options for pregnant women with multiple sclerosis. It has been shown that the annualized relapse rate is reduced during pregnancy, but increased during the early postpartum period. Studies have also shown that breastfeeding in patients with multiple sclerosis is safe. Currently, there are no clear guidelines regarding usage of oral contraceptives. On the other hand, gonadotrophinreleasing hormone (GnRH) agonists should be avoided when treating infertility. Most disease-modifying drugs used in the treatment of multiple sclerosis are not recommended during pregnancy and breastfeeding, excluding glatiramer acetate and interferon, which is safe to use during breastfeeding. Such drugs should be discontinued some time before pregnancy, depending on the rate of their elimination from the body. Relapses during pregnancy and breastfeeding can be treated with pulse steroid therapy; however, such therapy should be avoided during the first trimester of pregnancy. In patients who are breastfeeding, it is recommended to postpone it for at least 4 hours after receiving treatment. Recently, methods for preventing postpartum relapses are being investigated, such as intravenous immunoglobulin, corticosteroid and hormone therapy; however, further research is needed in order to make any final conclusions.

**Key words:** Multiple sclerosis – Pregnancy – Breastfeeding – Immunomodulatory drugs

# KOMPLEMENTARNA MEDICINA I VAŽNOST KULTURE EMPATIJE

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**Sažetak**

Posljednjih desetljeća "službena medicina i psihijatrija" sve više dobivaju svoje mjesto u liječenju osoba s duševnim smetnjama. Zbog sve većeg interesa javnosti za komplementarne metode liječenja kao i brojnih dokaza o njihovoj terapijskoj učinkovitosti uz potporu svjetske zdravstvene organizacije, nerijetko naši pacijenti traže neki prirodni lijek ili neki drugi oblik komplementarne medicine. Naš zadatak je uz službene metode liječenja poznavati i propisati metode komplementarne medicine koje priznaje i savjetuje Svjetska zdravstvena organizacija te tako pomoći našim pacijentima. Svojim poštovanjem, razumijevanjem i podrškom našim pacijentima povećavamo naš empatijski odnos, što svakako doprinosi učinkovitosti liječenja.

Empatija je sposobnost osjećanja i razumijevanja proživljenih iskustava drugih i nevidljiva sila koja povezuje ljude, a koja je iznimno važna za individualno i kolektivno mentalno zdravlje, za suradnju, terapijsku komunikaciju i uspjeh terapije. Empatija se pokazala značajnom psihološkom funkcijom zdravih ljudi, jer im pomaže u očuvanju zdravlja i više uživanju u životu. Osobe s višom razinom empatije manje su sklone na osobe s psihičkim problemima gledati kao na agresivne i neprijateljski nastrojene. Deficit empatije često se javlja kod osoba kojima je dijagnosticiran poremećaj osobnosti kao i psihotični poremećaj. Klinička empatija je ključ u interakciji i kamen temeljac u oblikovanju terapijskog i etičkog odnosa liječnik-pacijent te pomaže u izgradnji poštovanja pacijenta neophodnog za bolji zdravstveni uspjeh. Cilj ovog rada je razjasniti vezu između komplementarne medicine i kulture empatije.

**Ključne riječi:** Komplementarna medicina – Važnost – Kultura empatije

# COMPLEMENTARY MEDICINE AND THE IMPORTANCE OF A CULTURE OF EMPATHY

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**Abstract**

In recent decades, "official medicine and psychiatry" has increasingly gained its place in the treatment of people with mental disorders due to the growing interest of the public in

complementary treatment methods as well as numerous evidences of their therapeutic effectiveness with the support of the World Health Organization. Quite often, patients ask us for some natural remedy or some other form of complementary medicine. Our task is to know and prescribe the methods of complementary medicine recognized and advised by the World Health Organization in addition to the official methods of treatment and thus help our patients. Through our respect, understanding and support of our patients, we increase our empathetic relationship, which certainly contributes to the effectiveness of treatment.

Empathy is the ability to feel and understand lived experiences of someone else and an invisible force that connects people, which is extremely important for individual and collective mental health, for cooperation, therapeutic communication and the success of therapy. Empathy has shown to be a significant psychological function of healthy people, as it helps them preserve their health and enjoy life more. People with a higher level of empathy are less inclined to view people with psychological problems as aggressive and hostile. Deficit of empathy often occurs in people who have been diagnosed with a personality disorder as well as a psychotic disorder. Clinical empathy is the key in the interaction and the cornerstone in shaping the therapeutic and ethical doctor-patient relationship and helps to build the patient's respect necessary for better health success.The aim of this paper is to clarify the connection between complementary medicine and the culture of empathy.

**Keywords:** Complementary medicine – Importance – Clinical empathy

# KULTURA EMPATIJE I DUHOVNOST U LIJEČENJU NEUROLOŠKIH BOLESNIKA

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## Sažetak

Danas svjedočimo svakodnevnom napretku nauke i tehnologije u pristupu liječenja bolesti, a s druge strane sve većem nezadovoljstvu zdravstvenih radnika, pacijenata i članova njihovih porodica te brojnim stanjima na koja kurativna medicina nema očekivani uticaj. Biopsihosocijalni model liječenja baziran na kliničkom modelu orjentisanom na pacijenta, zahtijeva integrativni/holistički pogled na nerazdvojne dimenzije ljudske individue, stoga je nužno da zdravstveni radnici prošire percepciju i zdravstveno zbrinjavanje sa isključivo fizioloških somatskih dimenzija svojih pacijenata i na psihološke, društvene, emotivne i duhovne dijelove bolsnika. Ovakav pristup omogućava mogućnost ostvarenja potpunijeg ozdravljenja bolesnika, bolji kvalitet njihovog života i rasterećenje članova porodice čiji je član u procesu liječenja.

Savremeno doba, poboljšava globalno kvalitrt života što doprinosi produženjem prosječnog životnog vijeka. Biološko starenje značajno povećava pojave neuroloških i neurodegenerativnih stanja poput moždanog udara, Alzheimerove bolesti i Parkinsonove bolesti. Evidentno je da su neurološki poremećaji među vodećim uzrocima invalidnosti starijih osoba, što za Bosnu Hercegovinu uslijed porasta broja starijeg stanovništva, nakon rata 1992-1995, nakon COVID-19 pandemije te retraumatizacije aktuelnim ratovima u Urajini a sada i Palestini, predstavlja značajan javnozdravstveni problem. Sve je veća nesamostalnost zbog češćih neuroloških oboljenja, što zahtijeva pojačanu potrebu za liječenjem neuroloških bolesnika, njihovom rehabilitacijom i drugim uslugama podrške za neurološke poremećaje.

Neurološke bolesti sa svojim specifičnostima nepredvidljivog toka bolesti, značajnih disfunkcija, emocionalnih promjena uz promjene ponašanja, zahtijevaju od zdravstvenih radnika kulturu empatije kroz primjenu biosocijalnog modela u sagledavanju potreba bolesnika. Neurološko liječenje traje od početka neurološke bolesti do kraja života bolesnika. Efikasniji efekti liječenja se postiže empatijskom sposobnođću zdravstvenih radnika da slušaju strahove, snove i bolne ekspresije neuroloških bolesnika i da tako stvaraju terapijski odnos i prilike za potpunijim izlječenjem. Potrebno je pacijenta osposobiti da, uprkos patnji i bolu, pronađe utjehu, pripadnost, svrhu i osjećaj spašenosti. Ovaj model, ukorijenjen u duhovnosti koristeći empatiju, nadu, priznanje subjektivnost bolesniku, koji iako je društveno neproduktivan uz povećana ograničenja svakodnevnih aktivnosti, obezbjeđuje puno mogućnosti u perspektivi iscjeljenja.

**Ključne riječi**: Kultura – Empatija – Biopsihosocijalni model – Holistički - Duhovnost – Neurološki bolesnik

# CULTURE OF EMPATHY AND SPIRITUALITY IN THE TREATMENT OF NEUROLOGICAL PATIENTS

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## Abstract

Today, we are witnessing daily progress in science and technology in the treatment of diseases. On the other hand, there is increasing dissatisfaction among health workers, patients, their family members, and numerous conditions for which curative medicine does not have the expected effect. The biopsychosocial model of treatment, based on the patient-oriented clinical method, requires an integrative/holistic view of the inseparable dimensions of the human individual. Therefore, it is necessary for health professionals to expand their perception and approach to health care from focusing exclusively on the physiological somatic dimensions of their patients to also include the psychological, social, emotional, and spiritual aspects of the sick person. This approach enables a more complete recovery of the patient, improves the quality of their life, and provides relief to the family members involved in the treatment process. Modern advancements have improved the global quality of life, contributing to an increased average life expectancy. However, biological aging significantly increases the occurrence of neurological and neurodegenerative conditions such as stroke, Alzheimer's disease, and Parkinson's disease. Neurological disorders are among the leading causes of disability in the elderly, which presents a significant public health problem in Bosnia and Herzegovina due to the increasing elderly population following the 1992-1995 war, the COVID-19 pandemic, and recent re-traumatizationfrom the current wars in Ukraine and Palestine. There is a growing lack of independence among the elderly due to the more frequent occurrence of neurological diseases, which increases the demand for neurological treatment, rehabilitation, and other support services.

Neurological diseases, with their unpredictable course, significant dysfunctions, and emotional and behavioral changes, require healthcare workers to cultivate a culture of empathy through the application of the biopsychosocial model when assessing the needs of patients. Neurological treatment extends from the onset of the disease to the end of the patient's life. More effective treatment outcomes are achieved through the empathetic ability of healthcare workers to listen to the fears, dreams, and painful expressions of neurological patients, thereby creating a therapeutic relationship and opportunities for more complete healing. It is necessary to help patients find comfort, belonging, purpose, and a sense of salvation despite their suffering and pain. This model, rooted in spirituality and employing empathy, hope, and recognition of the patient's subjectivity, provides many possibilities for healing, even for those who, despite increased limitations in daily activities, may be considered socially unproductive.

**Key words:** Culture – Empathy - Biopsychosocial model – Holistic – Spirituality – Neurological patient

# RAZLIČITOSTI POREMEĆAJA NEUROMIŠIĆNE TRANSMISIJE

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## Sažetak

Poremećaji neuromišićne transmisije (PNMT) obuhvataju nekoliko heterogenih kliničkih sindroma i bolesti. Blok neuromišićne transmisije može biti presinaptički (poremećaj oslobadjanja acetilholina), sinaptički (disfunkcija holinesteraze) i najčešće postsinaptički (disfunkcija mišićnih receptora). PNMT se klasifikuje u nasledne, kongenitalne miasteničke sindrome (KMSs) i u stečene dobro definisane neurološke bolesti. KMSs su heterogena grupa genetskih PNMT sa ranim početkom uzrokovana mutacijama proteina uključenih u organizaciju, održavanje, funkciju ili modifikaciju motorne ploče. Mutacije najmanje 32 gena su odgovorne za autozomno dominantne i autozomno recesivne forme KMSs. Ove su mutacije se odnose na 8 presinaptičkih, 4 sinaptička, 15 postsinaptičkih i 5 glikolizirajućih proteina. Ovi proteini funkcionišu kao jonski kanali, enzimi ili kao strukturni, signalni, senzorni ili transportni proteini. KMSs se klinički karakterišu abnormalnom zamorljivošću, prolaznom ili trajnom slabošću ekstraokularnih, mimičkih, bulbarnih, trunkalnih, respiratornih, ili slabošću mišića ekstremiteta.

Stečeni PNMT su uzrokovani infekcijom, intoksikacijom, ali su najčešće posredovani imunskom patogenezom kod antigen specifičnih autoimunskih bolestia a ređe kod antitelima posredovanih paraneoplastičkih bolesti. Infekcija sa sporama anaerobne bakterije Clostridium botulinum kod dece a mnogo ređe kod odraslih dovodi do produkcije botulinskog toksina. Intoksikacija sa botulinskim toksinom iz kontaminirane hrane uzrokuje klasični oblik botulizma odraslih.

Botulinski toksin uzrokuje presinaptički blok NMT sprečavajući egzocitozu acetilholina iz presinaptičkih nervih završetaka. Klinička slika je predstavljena akutnom, simetričnom descendentnom mlitavom paralizom i autonomnim poremećajima. Bulbarni znaci su često prisutnu na početku bolesti.

Najčešći stečen PNMT je autoimunska miastenija gravis (MG). MG je tipičan postsinaptički PNMT uzrokovan antitelima protiv konstituenata postsinaptičke membrane motorne ploče. Manifestuje se abnormalnom zamorljivošću i slabošću skeletnih mišića koja se pogoršava zamaranjem, a smanjuje sa odmorom. Različite subpopulacije bolesnika sa MG stvaraju autoantitela sa posebnom ciljnom specifičnošću i specifičnom patogenezom poremećaja funkcije i gubitka postsinaptičkih acetilholinskih receptora (AChRs) i bloka neuromišićne transmisije (seropozitivna MG). Najčešći oblik seropozitovne MG sa anti-AchR antitelima obuhvata 85% svih bolesnika sa MG. Ciljni antigen ovih autoantitela je ekstracelularni deo alfa subjedinice (alfa67-alfa76), takozvani glavni imunogeni region (MIR) nikotinskog AChR. Kod 40-70% bolesnika sa MG bez anti-AchR antitela postsinaptički blok neuromišićne transmisije je uzrokovan IgG4 antitelima na mišićno specifičnu tirozinkinazi (MuSK) koja blokiraju grupisanje AChR na postsinaptičkoj membrani. U manjeg broja seronegativnih MG bolesnika IgG1 i IgG2 antitelana "*low-density lipoprotein receptor-*

*related protein 4*" (Lrp4) blokiraju agrinski signal za grupisanje AChR. Najmanji broj seronegativnih bolesnika ima niskoafinitetna antitela na AChR koja se mogu detektovati vezivanjem za rapsinom grupisane AChR. Sve ove podgrupe autoimunske MG imaju specifičan fenotip i različiti odgovor na inhibitore holinesteraze i imunosupresivne lekove kao i različitu patologiju timusa. Podgrupa seropozitivne MG sa anti-AChRantitelima je udružena sa timomom (paraneoplastična MG) I sa antitelima na titinirijanodinski receptor.

Lambert-Eaton mijastenički sindrom (LEMS) je presinaptički PNMT, autoimunska kanalopatija uzrokovana antitelima na voltažno zavisne kalcijumske kanale (VGCCs). Udruženost sa sitno ćelijskim karcinomom bronha je prisutna u 60% bolesnika (Paraneoplastični LEMS), dok kod 40% nema udruženosti sa malignom bolešću (Neparaneoplastični LEMS.). Antitela na P/Q tip voltažno zavisnih kacijumskih kanala su odgovorna za smanjenje influksa kalcijum u nervne završetke sa posledičnim presinaptičkim blokom neuromišićne transmisije. Kod pacijenata sa paraneoplastičkim LEMS, VGCCs tumorskih ćelija su ciljni angtigen koji indukuje ukršteni imunski odgovor protiv nervnih završetaka. U diferencijaciji paraneoplastičnog od neparaneoplastičnog LEMS pomaže detekcijaanti-SOX1 antitela prisutnih samo kod paraneoplastičnog. Klinička slika LEMS je predstavljena mišićnim zamorom i slabošću proksimalnih mišića ekstremiteta, mišićnim bolovima, arefleksijom, gubitkom telesne težine, suvoćom usta, impotencijom i konstipacijom. PNMT može prolazno biti uzrokovan lekovima a izvesni lekovi mogu deklanširati subkliničku autoimunsku MG.

**Ključne reči:** Neuromišićna transmisija – Različitosti poremećaja

## THE DIVERSITY OF NEUROMUSCULAR TRANSMISSION DISORDERS

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### Abstract

Neuromuscular transmission disorders (NMTD) include several heterogeneous clinical sindromes and diseases. The block of neuromuscular transmission can be presynaptic (altered release of acetylcholine), synaptic (cholinesterase dysfunction) and most frequently postsynaptic (muscle receptor dysfunction). NMTD can be classified in hereditary, congenital myasthenic syndromes (CMSs) and in acquired well defined neurological diseases. CMSs are a heterogeneous group of early-onset genetic NMTD due to mutations in proteins involved in the organisation, maintenance, function, or modification of the motor endplate. Mutations in at least 32 genes are made responsible for autosomal dominant or autosomal recessive CMSs. These mutations concern 8 presynaptic,4 synaptic, 15 post-synaptic, and 5 glycolisation proteins. These proteins function as ion-chnnels, enzymes, or structural , signaling, sensor or transporter proteins. CMSs are clinically characterized by abnormal fatigability, or transient or permanent weakness of extra-ocular, facial, bulbar, truncal, respiratory, or limb muscles.

An acquired NMTD are caused by infection, by intoxication and most frequently by autoimmune pathogeneses in antigen specific autoimmune disease and less frequenty in antibody mediated paraneoplastic diseases.Infection with anaerobic, spore-forming bacterium Clostridium botulinum in children and less frequently in adults results in botulinus toxin production. Intoxication with botulinus toxin produced in contaminated food causes the classical typ of botulism in adults.

Botulinus toxin causes the presynaptic NMTD blocking the exocytosis of acetylcholine at the presynaptic level. The clinical presentation of the desease is characterised by acute, simmetric, descending, flaccid paralysis of motor and autonomic nerves. Bulbar signs are often the initial clinical features of the disease.

The most frequent acquired NMTD is autoimmune myasthenia gravis (MG). MG is typical postsinaptic NMTD caused by antibody mediated pathology of the postsynaptic membrane of the motor end plate. MG is manifested by abnormal fatigue ability and weakness of skeletal muscles that worsens with continued effort and improves with rest. Different subsets of MG patients develop autoantibodies with distinct target specific itiesand pathogenic mechanisms which cause loss and dysfunction of postsynaptic acetylcholine receptors (AChRs) and failure of neuromuscular transmission (seropositive MG).

The most frequent seropositive MG with anti- AChR antibodies comprises 85% of all MG patients. The target of these antibodies is primarily a portion of the extracellular domain of the alpha subunit (a67-a76), the so-called main immunogenic region (MIR) of the nicotinic AChR. In 40-70% of MG patients without anti-AChR antibodies the postsynaptic block of neuromuscular transmission is caused by IgG4 antibodies to muscle specific tyrosine kinase (MuSK) which block the clustering of AChR at the postsynaptic membrane. In the minority of seronegative MG patients IgG1 and IgG2 antibodies to low-density lipoprotein receptor-related protein 4 (Lrp4) block agrin signaling and clustering of AChR. Small number of seronegative patients have low-affinity IgG1 antibodies to AChR which can be detected by binding to rapsin-clustered AChR. These subgroups of autoimmune MG have specific phenotypes and different response to cholinesterase inhibitors and immunosuppression as well as different thymus pathology. Subgroup of seropositive MG with anti-AChR antibodies is associated with thymoma (paraneoplastic MG) and antibodies to titin and ryanodine receptor.

Lambert-Eaton myasthenic syndrome (LEMS) is presynaptic NMTD, autoimmune channelopathy caused by antibodies against voltage gated calcium chnnels (VGCCs). The association with small-lung carcinoma is present in 60% of LEMS patients (Paraneoplastic LEMS), whereas in other 40% there is no association with malignancy (Nonparaneoplastic LEMS.). The autoantibodies to P/Q type voltage-gated calcium channels (VGCCs) are responsible for the physiological abnormality in LEMS, in which there is decrease of influx of calcium in nerve terminals with consequent block of presinaptic transmission. In paraneoplastic LEMS patients VGCCs of tumor cells are target antigens inducing immune response with cross reaction towards nerve terminals. The association with anti-SOX1 antibodies in patients with LEMS is specific for paraneoplastic LEMS. Symptoms mainly include late onset muscle fatigue and proximal extremity muscle weakness, muscle pain, areflexia, weight loss, dry mouth, male impotence, and constipation. NMTD cen be

transiently induced by medication and some drugs may provoke the onset of subclinical autoimmune MG.

**Key words:** Neuromuscular transmission - Diversity of disorders

# FARMAKOEKONOMSKI ASPEKTI MOŽDANOG UDARA

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## SAŽETAK

Moždani udar predstavlja hitno, životno opasno, neurološko stanje koje zahtijeva hitnu pomoć. U proteklih nekoliko decenija u oblasti neurologije, posebno moždanog udara, svjedoci smo potpunog oporavka nervnog sistema nakon teških kliničkih manifestacija, uglavnom ishemijskih, ali i hemoragijskih moždanih udara. Međutim, moždani udar je drugi uzrok smrti u Republici Srbiji (RS) i glavni uzrok invaliditeta kod odraslih. Globalno, u protekle tri decenije, ukupan broj godina proživljenih sa invaliditetom (Disability-adjusted Life Years, DALYs) zbog moždanog udara značajno se povećao (sa 91,5 miliona u 1990. na 125 miliona u 2019, povećanje od 33,5 miliona). Postoje različiti trendovi u zemljama sa visokim prihodima i onima sa niskim do srednjim prihodima, kojima pripada i RS. Veliki porast globalnog tereta moždanog udara nije samo zbog rasta populacije i starenja, već i zbog značajnog povećanja izloženosti važnim faktorima rizika, kao što su visoki indeks tjelesne mase, zagađenje okoliša, visoki nivoi glukoze u krvi, visoki krvni tlak, konzumiranje alkohola, fizička neaktivnost, disfunkcija bubrega i visoke temperature. Iako je došlo do opšteg smanjenja standardizovane incidencije, prevalencije, mortaliteta i stopa DALY, zemlje sa niskim do srednjim dohotkom nose najveći procenat opterećenja moždanim udarom. Veliki broj moždanih udara mogao bi se uspešno sprečiti, što predstavlja značajan potencijal za smanjenje tereta moždanog udara, uključujući značajno smanjenje dugoročnih posljedica. S obzirom na visoku stopu morbiditeta i mortaliteta, moždani udar predstavlja značajan medicinski i socioekonomski problem. Cilj ovog rada bio je definiranje djelovanja zdravstvenog sistema za postizanje najboljih ishoda liječenja pacijenata sa moždanim udarom u RS. Da bi se postigli najbolji mogući zdravstveni ishodi, važno je uspostaviti prioritete i principe za njegu moždanog udara, uključujući dijagnostičke i terapijske protokole koji se protežu od primarne prevencije do dugotrajne rehabilitacije, s fokusom na klinički put kao temeljnu komponentu pristupa liječnika. Kao rezultat toga, Udruženje neurologa Srbije (ANS) odobrilo je izradu „dokumenta o konsenzusu za prevenciju, liječenje i rehabilitaciju

можданог удара у RS" 8. Ovaj dokument nudi sveobuhvatnu preporuku za liječenje можданог удара у RS i služi kao praktični vodič za kliničare i zdravstvene radnike, uzimajući u obzir rizike, komplikacije pacijenata i pristupe dijagnozi i liječenju zasnovane na dokazima (EB). projekti zdravstvene politike i zdravstvene ekonomije, „ZEM Solutions", sa ciljem detaljnijeg sagledavanja problema.

**Ključne reči:** Можданi удар - Farmakoekonomika

## PHARMACOECONOMIC ASPECTS OF STROKE

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## ABSTRACT

A stroke represents an urgent, life-threatening, neurological medical condition that requires immediate attention. Over the past few decades in the field of neurology, especially stroke, we have witnessed the complete recovery of the nervous system after severe clinical manifestations, mainly ischemic but also haemorrhagic strokes. However, stroke is the second cause of death in the Republic of Serbia (RS) and the main cause of disability in adults. Globally, over the past three decades, the total number of years lived with disability (Disability-adjusted Life Years, DALYs) due to stroke has significantly increased (from 91.5 million in 1990 to 125 million in 2019, an increase of 33.5 million) . There are different trends in countries with high income and those with low to middle income, to which RS belongs. The large increase in the global burden of stroke is not only due to population growth and aging but also due to a significant increase in exposure to important risk factors, such as high body mass index, environmental pollution, high blood glucose levels, high blood pressure, alcohol consumption, physical inactivity, kidney dysfunction, and high temperatures. Although there has been a general reduction in standardized incidence, prevalence, mortality, and DALY rates, low to middle-income countries carry the highest percentage of the stroke burden 'A large number of strokes could be successfully prevented, representing a significant potential for reducing the burden of stroke, including a significant

reduction in long-term consequences. Given the high morbidity and mortality rates, stroke represents a significant medical and socioeconomic problem. The aim of this paper was to define the healthcare system's actions for achieving the best treatment outcomes for stroke patients in RS. To achieve the best possible health outcomes, it is important to establish priorities and principles for stroke care, including diagnostic and therapeutic protocols spanning from primary prevention to long-term rehabilitation, with a focus on the clinical path as a fundamental component of a doctor's approach. As a result, the Association of Neurologists of Serbia (ANS) approved the development of the "consensus document for the prevention, treatment, and rehabilitation of stroke in RS" 8. This document offers a comprehensive recommendation for stroke care in RS and serves as a practical guide for clinicians and healthcare professionals, taking into account patients' risks, complications, and evidence-based (EB) approaches to diagnosis and treatment 8. In 2021, a study was initiated by the ANS and the regional, international consulting agency for health policy and health economics projects, "ZEM Solutions", with the aim of providing a detailed understanding of the problem.

**Key words:** Stroke - Pharmacoeconomics

# AUTOIMUNE EPILEPSIJE

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## Sažetak

Autoimune epilepsije prvi put su kao zaseban klinički entitet opisane u literature 2002. godine, a u službenu ILAE klasifikaciju epilepsija uvrštene su 2017. godine. Unatoč rastućem broju publikaciju unazad dva desetljeća, još uvijek su nedovoljno prepoznat klinički entitet, čime brojni pacijenti ostanu zakinutu za adekvatnu i pravovremenu terapiju, budući je terapijski pristup u ovom slučaju bitno različit od ostalih epilepsija. Dijagnostičke procedure, uključujući MR, EEG, laboratorijsku analizu likvora i seruma te testiranje na protutijela, često su ograničene vrijednosti buduću su nalazi u trećine do polovice bolesnika negativni, odnosno uredni. Stoga se sumnja na autoimune epilepsije često temelji na kliničkoj slici, a kasniji pozitivni nalazi protutijela ili odgovor na terapiju potvrđuju dijagnozu. Negativni ili neprispjeli nalazi dijagnostičke obrade ne odgađaju početak specifičnog liječenja, koje se također temelji na uobičajenim postulatima liječenja autoimunih bolesti te osobnom iskustvu I razmišljanju liječnika, budući još uvijek ne postoje jasne i klinički dokazane terapijske smjernice s visokom razinom dokaza. Kao prva linija liječenja najčešće se primjenjuju visoke doze kortikosteroida, intravenski imunogloblini i rjeđe plazmafereza. Kao druga linija u obzir dolaze rituksimab, ciklofosfamid, azatioprin, bortezomib ili tocilizumab. Budući autoimuna epilepsija može biti povezana s malignom bolešću, u svakog bolesnika preporuča se skrining na uobičajene maligne bolesti, te specifične ovisno o spolu i detektiranim protutijelima.

**Ključne riječi:** Autoimune epilepsije – Dijagnoza – Tretman

# AUTOIMMUNE EPILEPSY

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## Abstract

Autoimmune epilepsy has been described in literature as a separate clinical entity for the first time in 2002, and recognised as a distinct entity in the latest 2017 ILAE epilepsy classification. Despite growing published evidence in last two decades, Autoimmune epilepsy is still an under recognized condition with unknown true incidence. Proper diagnosing is crucial because of different therapeutic approach from other epilepsies. Currently, diagnosis is often based on clinical presentation, since diagnostic procedures including MRI, EEG, serum and cerebrospinal fluid analysis often could be of limited value. New-onset refractory status epilepticus (NORSE), multifocal frequent seizures at onset or new-onset refractory seizures along with subacute progressive cognitive decline and behavioural or psychiatric dysfunction, faciobrachial dystonic seizure and personal or family history of autoimmune disease, rise suspicion to Autoimmune epilepsy. When autoimmune epilepsy is suspected, empirical immunotherapyshould be considered. At this moment there are no evidence-based immunotherapy guidelines exist, however high-dose steroids, IVIg, and plasma exchange are common first-line options, based on personal experience and published observational evidence. Second-line agents such as rituximab, cyclophosphamide, azathioprine, bortezomib or tocilizumab are used in refractory cases or as a maintenance therapy to prevent relapses. Autoimmune epilepsy can be associated with a cancer as a paraneoplastic syndrome, hence, cancer screening is recommended.

**Keywords:** Autoimmune epilepsy – Diagnsis – Treatment

# POREMEĆAJI SPAVANJA U NEUROLOGIJI

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## Sažetak

Spavanje je značajan dio života svakog pojedinca a kvalitetno spavanje je temelj za opće zdravlje i kvalitetan život. Zdrav odrasli čovjek trebao bi spavati prosječno 8h, odnosno trećinu života(prosječno tijekom života provedemo 26 godina spavajući!).

Neurolozi na žalost često zanemaruju činjenicu da postoji dvosmjerna veza između spavanja i neuroloških poremećaja. Većina neuroloških bolesti popraćene su karakterističnim poremećajima spavanja a s druge strane poremećaji spavanja mogu negativno utjecati na različite neurološke bolesti, naročito na moždani udar, multiplu sklerozu (MS), epilepsiju, neuromuskularne poremećaje i glavobolje. Npr, poremećaji ritma budnosti i spavanja (sleep–wake and circadian disorders, SWCD) čimbenici su rizika za neke neurološke poremećaje: dugo trajanje spavanja i poremećaj disanja tijekom spavanja (SRBD) za moždani udar; nesanica i SWCD za Alzheimerovu bolest (AD); REM parasomnije (REM sleep behavior disorder, RBD) za Parkinsonovu bolest (PD). Drugo, SWCD su vrlo česti kod neuroloških poremećaja: umor je prisutan u značajnog broja bolesnika s moždanim udarom, MS i PD-om; prekomjerna dnevna pospanost (EDS) u bolesnika s PD, AD, moždanim udarom, migrenom, epilepsijom i neuromuskularnim poremećajima; nesanica je često prisutna u bolesnika s PD, AD, moždanim udarom, MS, epilepsijom i migrenom; SRBD (Sleep-Related Breathing Disorders) česti su u pacijenata s moždanim udarom ali i u pacijenata s PD, MS, epilepsijom, glavoboljom i neuromuskularnim poremećajima; sindrom nemirnih nogu (Restless legs syndrome, RLS)i periodički pokreti udova u spavanju (periodic limb movements of sleep, PML) česti su u bolesnika s PB, MS i glavoboljom; RBD je čest u bolesnika s PD. Nadalje, poremećeno spavanje može biti prekursor nekih neuroloških bolesti kao što su Alzheimerova bolest, Parkinsonova bolest i demencija s Lewyjevim tjelešcima, stoga ih je neophodno rano prepoznati.

Poremećaji spavanja ne utječu samo na kvalitetu spavanja i kvalitetu života, nego mogu imati duboke posljedice na funkcioniranje mozga stoga je za svakog neurologa važno razumjeti ovu kompleksnu vezu kako bi unaprijedili metode dijagnostike i terapije te poboljšali živote svojih pacijenata.

**Ključne riječi:** Spavanje – Poremećaji spavanja – Neurologija

# SLEEP DISORDERS IN NEUROLOGY

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## Abstract

Sleep is a critical component of human physiology, essential for maintaining overall health and well-being. A healthy adult typically requires approximately 8 hours of sleep per night, which amounts to about one-third of their lifespan, or roughly 26 years spent sleeping on average. The interplay between sleep and neurological disorders is bidirectional, yet it is often underrecognized in clinical practice. Neurological diseases frequently manifest with many sleep disturbances, and conversely, sleep disorders can exacerbate various neurological conditions, including stroke, multiple sclerosis (MS), epilepsy, neuromuscular disorders, and headaches.

For example, sleep-wake and circadian rhythm disorders (SWCD) have been identified as risk factors for several neurological conditions: prolonged sleep duration and sleep-related breathing disorders (SRBD) increase the risk of stroke; insomnia and SWCD are associated with an elevated risk of Alzheimer's disease (AD); REM sleep behavior disorder (RBD) is a significant risk factor for Parkinson's disease (PD). Furthermore, SWCD are highly prevalent among patients with neurological disorders: fatigue is commonly observed in patients with stroke, MS, and PD; excessive daytime sleepiness (EDS) is frequently reported in individuals with PD, AD, stroke, migraine, epilepsy, and neuromuscular disorders; insomnia is prevalent among patients with PD, AD, stroke, MS, epilepsy, and migraine; SRBD are commonly observed in stroke patients as well as in those with PD, MS, epilepsy, headaches, and neuromuscular disorders; restless legs syndrome (RLS) and periodic limb movements during sleep (PML) are frequently seen in patients with PD, MS, and headaches; RBD is notably common in patients with PD.

Moreover, sleep disturbances can precede the onset of certain neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Lewy body dementia, underscoring the importance of early detection. The impact of sleep disorders extends beyond sleep quality, with significant implications for cognitive and neurological function. Therefore, it is imperative for neurologists to fully understand the complex interrelationship between sleep and neurological disorders to enhance diagnostic methods, optimize therapeutic strategies, and ultimately improve patient outcomes.

**Key words:** Sleeping – Sleeping disorders – Neurology

# GLAVOBOLJE U DJECE I ADOLESCENATA

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**Sažetak**

Glavobolja je najčešći simptom zbog kojeg djeca dolaze na pregled neuropedijatru. Incidencija glavobolja raste s dobi djeteta, pa do 18. godine više od 90% adolescenata ima barem jedan napadaj glavobolje godišnje. Prevalencija glavobolja u dječjoj dobi je oko 54%, a prevalenciija migrene oko 9%. Glavobolje se klasificiraju kao primarne (uzrok je intrinzičan i nalazi se unutar središnjeg živčanog sustava) ili sekundarne (glavobolja je samo simptom neke druge podliježeće bolesti), te kao bolne kranijske neuropatije. Najčešće primarne glavobolje u djece su tenzijska glavobolja i migrena. Trigeminalne autonomne glavobolje se javljaju rijetko i to kod djece starije od 10 godina.

*Tenzijske glavobolje* (TG) su najčešće glavobolje u djece. Obilježava ih trajna, blaga, tupa i nepulzirajuća bol poput pritiska ili stezanja obruča. Bol nastaje postupno, traje od nekoliko minuta do nekoliko sati ili dana, nije praćena mučninom i povraćanjem, ne pojačava se pri tjelesnom naporu, a vrlo rijetko je prisutna foto ili fonofobija. Najčešće su srednjeg do umjerenog intenziteta i obostrane lokalizacije. U epizodnim oblicima glavobolja traje manje od 15 dana u mjesecu, a u kroničnim, glavobolja traje više od 15 dana u mjesecu. *Etiologija* tenzijske glavobolje je najčešće školski stres, prekobrojne izvanškolske aktivnosti i zlostavljanje u školi, što potvrđuje činjenica da glavobolja prestaje ljeti. Smatra se da je TG posljedica djelovanja perifernih mehanizama (miofascijalnenocicepcije) I centralnih mehanizama (senzitizacije i neadekvatne endogene kontrole boli). *Terapija* tenzijske glavobolje je eliminacija nekih izvanškolskih aktivnosti, relaksacija, TENS – transkutana elektrostimulacija), analgetici paracetamol i ibuprofen, te prema potrebi psihoterapija.

*Migrenske glavobolje* su karakteriziane ponavljajućim napadajima umjerene do jake pulsirajuće boli koja traje 1-72 sata. Bol je lokalizirana na polovici lica i pojačava se s naporom. Praćene su mučninom, povraćanjem, fotofobijom i/ili fonofobijom. Nakon povraćanja slijedi olakšanje, nakon čega djeca zaspu. Migrenske glavobolje u djece traju kraće negoli u odraslih i češće su obostrane lokalizacije (bifrontalno ili bitemporalno). Oko 10% djece s migrenom ima auru koja uključuje vizualne, osjetne, motoričke, retinalne simptome, smetnje govora ili simptome moždanog debla. Kronična migrena je najčešća kronična glavobolja djece i adolescenata, a karakterizirana je glavoboljom koja se javlja kroz 15 ili više dana tijekom mjeseca. U djetinjstvu učestalost migrene je podjednaka u oba spola a nakon ulaska u pubertet češća je u djevojčica. *Liječenje migrene* je nefarmakološko i farmakološko. Nefarmakološko liječenje čine: promjena stila života, regulacija spavanja, dijeta, umjerena tjelovježba, akupunktura i biofeedback. *Akutna farmakološka terapija* je: paracetamol (15 -20 mg/kg), Ibuprofen (10 mg/kg). Najviše pomaže rehidracija, mirovanje I ležanje u mraku i tišini. Preventivna terapija se provodi ukoliko se napadaji migrene javljaju

češće od 3-4x mjesečno, koji su tako intenzivni da onemogućavaju dijete u njegovim dnevnim aktivnostima i uzrokuju učestalo izostajanje iz škole i isključivanje iz svakodnevnog života.

*Sekundarne glavobolje* su organske glavobolje, koje obilježavaju simptomi povećanog tlaka u glavi i progresivna neurološka disfunkcija. Uvijek imaju podležeći uzrok. Razvijaju se u uskom vremenskom odnosu s podležećim stanjem i prestaju izlječenjem toga stanja. Najčešće su benigne etiologije, npr. posljedica febrilne virusne bolesti gornjega dišnog sustava, gripe i sl., no mogu biti posljedica traume glave ili potencijalnog životno ugrožavajućih stanja, kao što su infekcije središnjega živčanog sustava ili spaciokompresivne lezije mozga (tumori, intrakranijsko krvarenje, teška hipertenzija i/ili hipoksija, ishemija...). U većine bolesnika dijagnoza se postavlja detaljno uzetom anamnezom, pažjivim kliničkim i neurološkim pregledom i ciljanom dodatnom obradom. Iznenadna intenzivna glavobolja s povraćanjem upućuje na intrakranijsko krvarenje, a pozitivan meningitički sindrom upućuje na meningoencefalitis ili subarahnoidalno krvarenje. Uzroci akutne recidivirajuće glavobolje mogu biti migrena ili hipertenzija, a uzroci kronične glavobolje - poremećaj vida, rjeđe hipertenzija. Vrlo su ozbiljne kronične progresivne glavobolje koje se javljaju najčešće ujutro ili bude dijete noću, pogoršavaju se tijekom tjelesne aktivnosti, praćene su znakovima povećanja intrakranijskog tlaka i neurološkim odstupanjem. U tom slučaju, svakako treba isključiti tumorsku bolest.

U dijagnostičkoj obradi glavobolja u djece, od koristi je i dnevnik glavobolja te fizikalni i neurološki pregled. Treba ispitati oštrinu vida te učiniti pregled očne pozadine i otorinolaringološki pregled. Kod sumnje na epilepsiju učiniti i EEG. Životno ugrožavajuća stanja u djeteta s glavoboljom, koja zahtijevaju hitnu i slikovnu obradu su: brzi razvoj ekstremno bolne glavobolje ("poput udara groma") s kočenjem šije i bolovima u vratu; pozicijska glavobolja koja se pogoršava pri ustajanju, budi dijete iz sna, kronična progresivna glavobolja, glavobolja udružena s jutarnjim povraćanjem, promjenama ponašanja, ataksijom ili nespretnošću, glavobolja u djece s malignim bolestima, koagulopatijama ili cijanotičnim srčanim greškama, produženi poremećaj svijesti >60 min., edem papile vidnog živca (PNO) i meningitis, te fokalni neurološki znaci ili fokalni napadaji.

**Ključne riječi:** Glavobolja – Djeca i adolescenti – Uzroci – Dijagnostika - Terapija

## HEADACHES IN CHILDREN AND ADOLESCENTS

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### Abstract

Headache is the most common symptom for which children visit a neuropediatrician. The incidence of headaches increases with the age of the child, so by the age of 18, more than 90% of adolescents have at least one headache attack per year. The prevalence of headaches in children is about 54%, and the prevalence of migraines is about 9%. Headaches are classified as primary (the cause is intrinsic and located within the central nervous system) or secondary (the headache is only a symptom of another underlying disease), and as painful cranial neuropathies. The most common primary headaches in children are tension headache and migraine. Trigeminal autonomic headaches rarely occur in children older than 10 years.

*Tension headaches (TG)* are the most common headaches in children. They are characterized by persistent, mild, dull and non-pulsating pain like pressure or ring tightening. The pain occurs gradually, lasts from a few minutes to a few hours or days, is not accompanied by nausea and vomiting, does not increase with physical effort, and photo or phonophobia is very rarely present. Most often, they are of medium to moderate intensity and bilateral localization. In episodic forms, the headache lasts less than 15 days a month, and in chronic forms, the headache lasts more than 15 days a month. The etiology of tension headache is usually school stress, excessive extracurricular activities and bullying at school, which is confirmed by the fact that the headache stops in the summer. It is believed that TG is a consequence of peripheral mechanisms (myofascial nociception) and central mechanisms (sensitization and inadequate endogenous pain control). Therapy for tension headache is the elimination of some extracurricular activities, relaxation, TENS - transcutaneous electrostimulation), analgesics paracetamol and ibuprofen, and, if necessary, psychotherapy.

*Migraine headaches* are characterized by recurrent attacks of moderate to severe throbbing pain lasting 1-72 hours. The pain is localized on half of the face and increases with exertion. They are accompanied by nausea, vomiting, photophobia and/or phonophobia. Vomiting is followed by relief, after which the children fall asleep. Migraine headaches in children last shorter than in adults and are more often bilateral (bifrontal or bitemporal). About 10% of children with migraine have an aura that includes visual, sensory, motor, retinal symptoms, speech disturbances, or brainstem symptoms. Chronic migraine is the most common chronic headache in children and adolescents, and is characterized by a headache that occurs for 15 or more days during the month. In childhood, the frequency of migraine is equal in both sexes, and after entering puberty, it is more common in girls. Migraine treatment is non-pharmacological and pharmacological. Non-pharmacological treatment consists of: lifestyle changes, sleep regulation, diet, moderate exercise, acupuncture and biofeedback. Acute pharmacological therapy is: paracetamol (15-20 mg/kg), Ibuprofen (10 mg/kg). Rehydration, rest and lying down in the dark and quiet help the most. Preventive therapy is carried out if migraine attacks occur more often than 3-4 times a month, which are so intense that they disable the child in his daily activities and cause frequent absences from school and exclusion from everyday life.

*Secondary headaches* are organic headaches, characterized by symptoms of increased pressure in the head and progressive neurological dysfunction. They always have an underlying cause. They develop in a close temporal relationship with the underlying condition and end with the cure of that condition. The most common are benign etiologies, e.g. the result of a febrile viral disease of the upper respiratory system, flu, etc., but they can be the

result of head trauma or potentially life-threatening conditions, such as infections of the central nervous system or spatiocompressive lesions of the brain (tumors, intracranial hemorrhage, severe hypertension and/or hypoxia, ischemia...). In most patients, the diagnosis is established by taking a detailed history, careful clinical and neurological examination and targeted additional treatment. Sudden intense headache with vomiting suggests intracranial hemorrhage, and a positive meningitic syndrome suggests meningoencephalitis or subarachnoid hemorrhage. The causes of acute recurring headache can be migraine or hypertension, and the causes of chronic headache - vision disorder, less often hypertension. They are very serious chronic progressive headaches that occur most often in the morning or when the child wakes up at night, worsen during physical activity, are accompanied by signs of increased intracranial pressure and neurological abnormalities. In this case, tumor disease should definitely be ruled out.

In the *diagnostic processing of headaches in children*, a headache diary and a physical and neurological examination are also useful. Visual acuity should be tested, and an examination of the fundus of the eye and an otorhinolaryngological examination should be performed. If epilepsy is suspected, do an EEG. Life-threatening conditions in a child with a headache, which require immediate and imaging treatment, are: rapid development of an extremely painful headache ("like a lightning strike") with neck stiffness and neck pain; positional headache that worsens when standing up, wakes the child from sleep, chronic progressive headache, headache associated with morning vomiting, behavioral changes, ataxia or clumsiness, headache in children with malignant diseases, coagulopathies or cyanotic heart defects, prolonged disturbance of consciousness >60 min. , optic nerve papilla edema (PNO) and meningitis, and focal neurological signs or focal seizures.

**Key words:** Headache – Children and adolescents – Causes – Diagnostics – Therapy

# LIJEČENJE PROGRESIVNE MULTIPLE SKLEROZE

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## SAŽETAK

Multipla skleroza je hronično inflamatorno stanje centralnog nervnog sistema koje karakteriše demijelinizacija i popratna aksonalna i neuronska degeneracija. Otprilike 85% pacijenata sa multiplom sklerozom ima relapsno-remitentni tok bolesti. Većina ovih pacijenata napreduje u progresivni tok bolesti nakon 15 do 20 godina od početka bolesti (sekundarna progresivna multipla skleroza). Preostalih 10% do 15% pacijenata ima sporo i postepeno neurološko pogoršanje od samog početka (primarna progresivna multipla skleroza).

Sve trenutno odobrene terapije koje modificiraju bolest indicirane su za aktivnu sekundarnu progresivnu multiplu sklerozu. Terapijska mogućnost protuupalnih lijekova za liječenje progresivne multiple skleroze je povećana kod mlađih osoba i kraćeg trajanja bolesti. Liječenje progresivne bolesti ovisi o osnovnim mehanizmima koji uzrokuju oštećenje centralnog nervnog sistema. Imunitet skriven iza netaknute krvno-moždane barijere, nedostatak energije i disfunkcija membranskih kanala mogu biti ključni procesi u progresivnoj bolesti. Ometanje ovih mehanizama može pružiti neuroprotekciju i spriječiti napredovanje invaliditeta, dok potencijalno obnavlja aktivnost i provod duž oštećenih aksona popravkom mijelina.

Progresivna multipla skleroza je najveći terapijski izazov s kojim se danas suočava zajednica oboljelih od multiple skleroze. Nepotpuno razumijevanje patogeneze progresivne multiple skleroze otežava identifikaciju potencijalnih ciljnih puteva i novih lijekova. Nadalje, budući da se čini da višestruki mehanizmi pokreću i održavaju oštećenje kod progresivne multiple skleroze, mogu biti potrebne kombinatorne terapije kako bi se zaustavili različiti mehanizmi koji uzrokuju oštećenje i vratila funkcija svim sistemima.

**Ključne riječi:** Progresivna multipla skleroza - Terapija

# TREATING PROGRESSIVE MULTIPLE SCLEROSIS

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## ABSTRACT

Multiple sclerosis is a chronic inflammatory condition of the central nervous system that is characterized by demyelination and concomitant axonal and neuronal degeneration. Approximately 85% of patients with multiple sclerosis present with a relapsing-remitting course of the disease. The majority of these patients advance to a progressive disease course after 15 to 20 years after disease onset (secondary progressive multiple sclerosis). The remaining 10% to 15% of patients have a slow and gradual neurologic deterioration from the onset (primary progressive multiple sclerosis).

All currently approved disease-modifying therapies are indicated for active secondary progressive multiple sclerosis. The therapeutic opportunity of anti-inflammatory drugs for the treatment of progressive multiple sclerosis is enhanced in those who are younger and have a shorter disease duration. Treatments for progressive disease depend on underlying mechanisms causing central nervous system damage. Immunity sheltered behind an intact blood–brain barrier, energy failure, and membrane channel dysfunction may be key processes in progressive disease. Interfering with these mechanisms may provide neuroprotection and prevent disability progression, while potentially restoring activity and conduction along damaged axons by repairing myelin.

Progressive multiple sclerosis is the greatest therapeutic challenge facing the multiple sclerosis community today. Incomplete understanding of pathogenesis of progressive multiple sclerosis make identification of potential target pathways and new treatment agents difficult. Furthermore, because multiple mechanisms appear to trigger and sustain damage in progressive multiple sclerosis, combinatorial therapies may be required to put a stop to the various mechanisms causing damage and restore function to all systems.

**Key words:** Progressive multiple sclerosis - Therapy

# RAZLIKE I SLIČNOSTI MULTIPLE SKLEROZE, NMOSD i MOGAD

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## Sažetak

Bolesti vezane uz antitijela na mijelinski oligodendrocitni glikoprotein (MOGAD), akvaporin 4–pozitivni poremećaji iz spektra optičkog neuromijelitisa (AQP4-NMOSD) i multipla skleroza (MS) različiti su upalni demijelinizirajući poremećaji SŽS-a koji dijele kliničke značajke koje se preklapaju. NMOSD i MOGAD su rijetke bolesti, koje su puno manje rasprostranjene od MS-a. Simptomi i kliničke slike ovih poremećaja mogu se preklapati, što može otežati kliničku kategorizaciju pacijenata radi testiranja na antitijela. Unatoč nekim manifestacijama koje se preklapaju, postoje velike razlike među ovim entitetima bolesti, posebice u pogledu težine napadaja i kliničkog tijeka. Točna dijagnoza ključna je za pravilno liječenje i praćenje aktivnosti bolesti.

Dok su AQP4-NMOSD i MOGAD karakterizirani teškim napadima koji obično rezultiraju velikom akutnom onesposobljenošću (npr. paraplegija, encefalopatija, sljepoća) i često su popraćeni velikim MRI T2 lezijama u mozgu (>3 cm u najvećem promjeru) ili kralježničkoj moždini (≥3 susjedna segmenta tijela kralješka), napadi MS-a obično su blaže kliničke težine i popraćeni manjim lezijama na magnetskoj rezonanci mozga/kralježničke moždine, iako se kod nekih pacijenata javljaju tumefektivne MS lezije koje mogu biti slične onim lezijama kod NMOSD ili MOGAD pacijenata. Čak i samo jedan recidiv NMOSD može uzrokovati tešku trajnu onesposobljenost. MOGAD se tipično javlja s manjim oštećenjem vida i motorike nego AQP4-NMOSD. Unatoč minimalnom motoričkom oštećenju u MOGAD-u, javljaju se često se sfinkterijelne i erektilne disfunkcije i kognitivni poremećaj. U MS i AQP4-NMOSD sfinkterijelna i erektilna disfunkcija obično su povezane i sukladne težini motoričkog deficita. Dugoročno, međutim, tijek ovih poremećaja općenito ne odražava težinu početnih napada: pacijenti s MOGAD-om često imaju bolji ishod od onih s AQP4-IgG-NMOSD unatoč sličnoj težini početnih kliničkih simptoma, dok je sekundarna progresivna onesposobljenost u biti isključiva za pacijente s MS-om unatoč blažim napadima bolesti u samom početku, osobito kod neliječenih pacijenata ili kod onih kod kojih je liječenje kasno započeto. Točni razlozi ovih kliničkih razlika nisu jasni.

Najvažnija poruka koju treba zapamtiti kada razmišljamo o diferencijalnoj dijagnozi ove tri bolesti je da se liječenja razlikuju i mogu biti štetna ako nemamo točnu dijagnozu. Moramo biti svjesni da mnogi imunomodulatorni lijekovi koji se propisuju kod pacijenata sa MS-om ne djeluju, ili čak mogu povećati rizik kod pacijenata sa AQP4-NMOSD ili MOGAD.

**Ključne riječi:** Multipla skleroza (MS) – NMOSD – MOGAD

# DIFFERENCES AND SIMILARITIES OF MULTIPLE SCLEROSIS, NMOSD AND MOGAD

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## Abstract

Myelin oligodendrocyte glycoprotein associated disorders (MOGAD), aquaporin 4–positive neuromyelitis optica spectrum disorder (AQP4-NMOSD), and multiple sclerosis (MS) are distinct inflammatory demyelinating disorders of the CNS that share overlapping clinical features.NMOSD and MOGAD are rare diseases, that are much less prevalent than MS. The symptoms and presentations of these disorders may overlap, which can make it difficult to categorise patients clinically in order to test for antibodies. Despite some overlapping manifestations, there are major differences among these disease entities, especially concerning attack severity and clinical course. Accurate diagnosis is crucial for correct treatment and disease activity monitoring. While AQP4-NMOSD and MOGAD are characterized by severe attacks that typically result in major acute disability (e.g., paraplegia, encephalopathy, blindness) and are frequently accompanied by large MRI T2 lesions in the brain (>3 cm in maximum diameter) or the spinal cord (≥3 contiguous vertebral body segments), MS attacks are typically of milder clinical severity and accompanied by smaller lesions on brain/spinal cord MRI, although tumefactive MS lesions occur in some patients and can resemble to those lesions in NMOSD or MOGAD patients. NMOSD even single relapse can cause severe permanent disability. MOGAD typically presents with less visual and motor disability than AQP4-NMOSD.Despite minimal motor impairment in MOGAD, sphincter, erectile and cognitive disability occurs. In MS and AQP4-NMOSD sphincter and erectile dysfunction associates with motor problems. In the long term, however, the course of these disorders does not generally reflect the severity of the initial attacks: patients with MOGAD frequently have better outcomes than those with AQP4-IgG-NMOSD despite similarly severe attacks, while secondary progressive disability is essentially exclusive to MS despite milder disease attacks in this condition.The exact reasons for these clinical differences are unclear.

The most important message to remember when we think about differential diagnosis of these three diseases is that treatments differ and can be harmful if we don't have the correct diagnosis, for example many DMTs prescribed for MS patients, don't work or even can make thing worse for patientswith AQP4-NMOSD or MOGAD.

**Key words:** Multiple sclerosis (MS) – NMOSD – MOGAD

# TERAPIJSKA AFEREZA U LIJEČENJU NEUROIMUNOLOŠKIH BOLESTI

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## Sažetak

Uloga terapijske afereze (TA) u neurološkim bolestima promijenila se u posljednjih 40 godina. Poznato je da autoantitijela i imuni kompleksi igraju ključnu ulogu u mnogim vrstama neuroloških autoimunih bolesti. Prepoznato je da je uklanjanje ovih (autoantitijela i imunoloških kompleksa) i nekih drugih patogenih tvari (posrednika upale, sastavnica komplementa i citokina) iz plazme bolesnika učinkovit način liječenja. U različitim neurološkim poremećajima, randomizirane kontrolirane studije pokazale su učinkovitost TA (npr. kod akutne upalne demijelinizirajuće polineuropatije /AIDP; Guillain-Barreov sindrom/, kronične upalne demijelinizirajuće poliradikuloneuropatije /CIDP/, miastenije gravis /MG/ i paraproteinemijskih polineuropatija / PP/). Za ove poremećaje, TA je prihvaćena kao prva linija terapije, bilo kao primarni samostalni terapijski postupak ili u kombinaciji s drugim načinima liječenja. Iako se naširoko koristi, manje je jasna potencijalna korist TA u liječenju akutnog diseminiranog encefalomijelitisa (ADEM), kroničnog žarišnog encefalitisa (Rasmussenov encefalitis), Lambert-Eatonovog miastenijskog sindroma (LEMS), multiple skleroze (MS) i optičnog neuromijelitisa (NMO; Devicov) bolest). Za ove poremećaje, TA je prihvaćena kao terapija druge linije, bilo kao samostalan terapijski postupak ili u kombinaciji s drugim načinima liječenja.

**Ključne riječi:** Neuroimunološke bolesti – Terapijska afereza

# THERAPEUTIC APHERESIS IN THE TREATMENT OF NEUROIMMUNOLOGICAL DISEASES

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## Abstarct

The role of therapeutic apheresis (TA) in neurologic diseases has changed over the past 40 years. It is known that autoantibodies and immune complexes play a crucial role in many kinds of neurological autoimmune diseases. It has been recognized that removing these (autoantibodies and immune complexes) and some other pathogenic substances (inflammatory mediators, complement components, and cytokines) from a patient's plasma is an efficient means of treatment. In various neurological disorders, randomised controlled studies have demonstrated the efficacy of TA (eg, in acute inflammatorydemyelinating polyneuropathy

/AIDP; Guillain-Barre´ Syndrome/, chronic inflammatory demyelinating polyradiculoneuropathy /CIDP/, myasthenia gravis /MG/, and paraproteinemic polyneuropathies /PP/). For these disorders, TA is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Although widely used, the potential benefit of TA in the treatment of acute disseminated encephalomyelitis (ADEM), chronic focal encephalitis (Rasmussen's encephalitis), Lambert-Eaton myasthenic syndrome (LEMS), multiple sclerosis (MS), and neuromyelitis optica (NMO; Devic's disease) is less clear. For these disorders, TA is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.

**Key words:** Neuroimmunological diseases – Therapeutic apheresis

# KOMPLEMENTARNA I ALTERNATIVNA TERAPIJA MULTIPLE SKLEROZE

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**Sažetak**

Komplementarne metode liječenja su u sprezi s konvencionalnim liječenjem**.** Alternativna terapija je terapija druge mogućnosti i isključuje konvencionalno liječenje. Optimalan pristup liječenju je tzv. Integrativan pristup koji podrazumijeva istodobnu primjenu metoda konvencionalne i nekonvencionalne medicine. Konvencionalna medicina svoje prakse temelji na najboljim dostupnim znanstvenim dokazima (EBM - evidence based medicine). Alternativna medicina uglavnom temelji svoju praksu na postupcima koji se zasnivaju na dokazima koji ne moraju nužno ispunjavati najviše i najstrože kriterije učinkovitosti i sigurnosti.

Neke prakse alternativne medicine, uključuje i upotrebu nekih dodataka prehrani. Djelotvorne tehnike kanabinoidi: oralni (za spazam i bol), sintetski THC ( za spazam i bol, ali slabije od oralnih kanabinoida) te oromukozni sprej Sativex (nedjelotvoran za simptome spasticiteta, boli i povećane urinarne frekvencije – slabije od oralnih kanabinoida) i kanabis koji se puši (nedjelotvoran)

Nedjelotvorne tehnike: upotreba pčelinjeg otrova, gingko biloba (slabije djelotvorna kod umora i smanjene kognitivne funkcije) lofepramin s fenilalaninom i B12 vitaminom nedjelotvoran za onesposobljenost, simptome depresiju i umor), dijeta s niskim udjelom masnoća te nadomjestkom omega-3 masnih kiselina (nedjelotvorna), magnetoterapija (slabije djelotvorna za umor) i relfeksologija (slabije djeluje). Biološki temeljene terapije: program Padma 28, linoleinska kiselina, kreatin monohidrat, acetil-L-karnitin, inozin, treonin, glukozamin sulfat, naltrekson u maloj dozi, kreatin monohidrat, transdermalna primjena histamina i kofeina, hiperbarična oksigenacija, manipulativne terapije i tjelesne terapije: hipoterapija, joga, kiropraktika, masaža, akupunktura, elektroakupunktura i progresivna relaksacija mišića, energomedicina: naturopatija i neuralna terapija, terapija usmjerena na interakciju um-tijelo: biofeedback, muzikoterapija, trening usredotočene svjesnosti, hipnoza. tradicionalna kineska medicina, zamjena dentalnih amalgama i tai chi još su neki od primjera terapija KAM za koje ne postoje snažni dokazi o djelotvornosti. KAM kao jedini lijek: 90 %, koriste ovu terapiju kao dodatnu prehrana i dijetni režimi, povećani unos nezasićenih masnih kiselina (omega-3) i antioksidansapitanju prehrane se odnosi na dodatak polinezasićenih masnih kiselina (PUFA) prehrani, izbjegavanje alergena (gluten i mlijeko), vitamine i mikronutrijente kao što je selen, ekstrakte biljke Gingko biloba te konzim Q10. Primjena KAM tehnika liječenja svakako ima svoje mjesto kao dodatna terapija uz onu propisanu od nadležnog neurologa, a ponajprije iz okvira imunomodulacijske i imunosupresorske terapije.

Model sveobuhvatnog MS liječenja treba uključivati integraciju stručnjaka medicinski srodnih područja koji bi svaki sa svoje strane mogao pružiti preporuke kako bi se praćenje

bolesti i njeno liječenje bolesniku olakšalo. Stoga se i preporuča oformiti skupinu stručnjaka odnosno tim koji bi se prigodom jednog dolaska bolesnika mogli osvrnuti na sve zdravstvene poteškoće s kojima se ona ili on susreću. Ovakav pristup bolesnicima doprinosi njihovom osjećaju sigurnosti. Preporuka je da voditelj ovakvog tima bude neurolog, budući da njegovo znanje omogućava postavljanje dijagnoze, uočava daljnje simptome te određuje postupke liječenja te stoga najlakše koordinira ostale članove tima.

**Ključne riječi:** Multipla skleroza – Komplementarna terapija – Alternativna terapija

## COMPLEMENTARY AND ALTERNATIVE THERAPY OF MULTIPLE SCLEROSIS

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**Abstract**

Complementary methods of treatment are in conjunction with conventional treatment, while the alternative therapy is a therapy of other possibilities and excludes conventional treatment. The optimal approach to treatment is the so-called integrative approach, or the simultaneous application of methods of conventional and unconventional medicine. Conventional medicine bases its practice on the best available scientific evidence (EBM - evidence based medicine). Alternative medicine generally bases its practice on evidence-based procedures that do not necessarily meet the highest and strictest criteria of efficacy and safety.

Some alternative medicine practices include the use of some dietary supplements. Effective techniques involve cannabinoids - oral (for spasm and pain), synthetic THC (for spasm and pain, but weaker than oral cannabinoids) and oromucosal spray Sativex (ineffective for symptoms of spasticity, pain and increased urinary frequency – weaker than oral cannabinoids) and cannabis smoking (ineffective). Ineffective techniques involve: use of bee venom, Ginkgo biloba (less effective for fatigue and reduced cognitive function), lofepramine with phenylalanine and vitamin B12 (ineffective for disability, symptoms of depression and fatigue), low-fat diet and omega-3 fatty acid replacement (ineffective), magnetotherapy (less effective for fatigue) and relfexology (less effective). Biologically based therapies: Padma 28 program, linoleic acid, creatine monohydrate, acetyl-L-carnitine, inosine, threonine, glucosamine sulfate, low-dose naltrexone, creatine monohydrate, transdermal application of histamine and caffeine, hyperbaric oxygenation, manipulative therapies and physical therapies: hippotherapy, yoga, chiropractic, massage, acupuncture, electroacupuncture and progressive muscle relaxation, energy medicine: naturopathy and neural therapy, mind-body interaction therapy: biofeedback, music therapy, focused awareness training, hypnosis. Traditional Chinese medicine, dental amalgam replacement and tai chi are some other examples of CAM therapies for which there is no strong evidence of effectiveness. If KAM is used as the only medicine: 90% use this therapy as additional

nutrition and dietary regimes, increased intake of unsaturated fatty acids (omega-3) and antioxidants. The nutritional question refers to the addition of polyunsaturated fatty acids (PUFA) to the diet, avoiding allergens (gluten and milk), vitamins and micronutrients such as selenium, extracts of the Gingko biloba plant and coenzyme Q10. The application of KAM treatment techniques certainly has its place as an additional therapy to that prescribed by the competent neurologist, primarily within the framework of immunomodulation and immunosuppression therapy.

A model of comprehensive MS treatment should include the integration of experts in related fields of medicine, each of whom could provide recommendations to facilitate the monitoring of the disease and make its treatment for the patient easier. Therefore, it is recommended to form a group of experts, that is, a team who, on the occasion of one visit of the patient, could look at all the health problems that he/she is facing. This approach to patients contributes to their feeling of safety and security. It is recommended that the leader of such a team be a neurologist, since its knowledge enables the diagnosis, notices further symptoms and determines the treatment procedures and, therefore, easier coordinates the other members of the team.

**Key words:** Multiple sclerosis – Complementary therapy – Alternative therapy

# DISTONIJA

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**Sažetak**

Distonija je treći najčešći poremećaj kretanja nakon esencijalnog tremora i Parkinsonove bolesti, karakteriziran dugotrajnim ili povremenim mišićnim kontrakcijama koje rezultiraju abnormalnim položajima i ponavljajućim pokretima. U ovoj prezentaciji raspravljat ću o najnovijim dostignućima u dijagnozi, klasifikaciji i liječenju distonije, uključujući genetske, idiopatske i stečene oblike. Distonija predstavlja dijagnostički izazov zbog širokog fenotipskog spektra i nepostojanja pouzdanih biomarkera za idiopatske oblike. Može se manifestirati u izoliranim oblicima ili u kombinaciji s drugim poremećajima kretanja, poput tremora, mioklonusa ili parkinsonizma. Patofiziologija distonije pripisuje se disfunkcijama u motoričkim mrežama koje uključuju bazalne ganglije, mali mozak, talamus i korteks, a često su pod utjecajem genetskih i okolišnih čimbenika.

Nedavna promjena u sustavu klasifikacije distonije naglašava kliničke značajke (dob početka, distribucija tijela, temporalni obrazac) i etiologiju (genetska, stečena ili idiopatska). Molekularne genetičke studije identificirale su ključne gene, kao što su TOR1A, THAP1 i GNAL, povezane s nasljednim oblicima distonije, dok kombinirane distonije uključuju druge poremećaje kretanja, osobito parkinsonizam. Uvedene su nove smjernice za nomenklaturu kako bi se poboljšala jasnoća u kategorizaciji genetske distonije.

Liječenje distonije uključuje injekcije botulinum toksina kao temelj terapije, osobito za žarišne oblike kao što je cervikalna distonija. Oralni lijekovi, uključujući antikolinergike, baklofen i benzodiazepine, dodatne su opcije, dok je duboka moždana stimulacija (DBS) učinkovita kirurška terapija za refraktorne slučajeve, posebno kod genetskih distonija kao što je DYT-TOR1A. Nedavna istraživanja također su istraživala tretmane usmjerene na patogenezu, uključujući gensku terapiju, za specifične oblike distonije kao što je distonija koja reagira na dopu.

Prezentacija također naglašava važnost točne dijagnoze kako bi se izbjegle pogrešne klasifikacije, osobito u razlikovanju distonije od drugih mimika kao što su Parkinsonova bolest, esencijalni tremor i funkcionalna distonija. Nove terapije, kao što su neinvazivna stimulacija mozga i genske terapije, nude nadu za ciljanije i učinkovitije tretmane. Unatoč značajnom napretku u razumijevanju patofiziologije i liječenja distonije, izazovi ostaju, osobito u liječenju složenih, kombiniranih i refraktornih oblika.

**Ključne riječi:** Distonija - Klasifikacija - Terapija

# DYSTONIA

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## Abstract

Dystonia is the third most common movement disorder after essential tremor and Parkinson's disease, characterized by sustained or intermittent muscle contractions resulting in abnormal postures and repetitive movements. In this presentation I will discuss the latest advancements in the diagnosis, classification, and management of dystonia, encompassing genetic, idiopathic, and acquired forms. Dystonia presents a diagnostic challenge due to its wide phenotypic spectrum and the absence of reliable biomarkers for idiopathic forms. It can manifest in isolated forms or in combination with other movement disorders, such as tremor, myoclonus, or parkinsonism. The pathophysiology of dystonia is attributed to dysfunctions in motor networks involving the basal ganglia, cerebellum, thalamus, and cortex, often influenced by genetic and environmental factors.

A recent shift in the classification system of dystonia emphasizes clinical features (age of onset, body distribution, temporal pattern) and etiology (genetic, acquired, or idiopathic). Molecular genetic studies have identified key genes, such as TOR1A, THAP1, and GNAL, linked to hereditary forms of dystonia, while combined dystonias involve other movement disorders, notably parkinsonism. New nomenclature guidelines have been introduced to improve clarity in genetic dystonia categorization.

The management of dystonia involves botulinum toxin injections as a cornerstone therapy, particularly for focal forms such as cervical dystonia. Oral medications, including anticholinergics, baclofen, and benzodiazepines, are adjunctive options, while deep brain stimulation (DBS) is an effective surgical therapy for refractory cases, especially in genetic dystonias such as DYT-TOR1A. Recent research has also explored pathogenesis-directed treatments, including gene therapy, for specific forms of dystonia like dopa-responsive dystonia.

The presentation also highlights the importance of accurate diagnosis to avoid misclassifications, particularly in distinguishing dystonia from other mimics such as Parkinson's disease, essential tremor, and functional dystonia. Emerging therapies, such as non-invasive brain stimulation and gene therapies, offer hope for more targeted and effective treatments. Despite significant progress in understanding dystonia’s pathophysiology and treatment, challenges remain, particularly in the management of complex, combined, and refractory forms.

**Keywords:** Dystonia – Classification – Treatment

# INVAZIVNA TERAPIJA PARKINSONOVE BOLESTI

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## Sažetak

Terapija Parkinsonove bolesti (PB) pomaže pacijentu uadekvatnomsamozbrinjavanju, pokušava da zaštiti njegovunezavisnost, održavanje radne sposobnostii socijalnu kompetentnost. Ona targetuje motorne, psihijatrijske, autonomne poremećaje i kognitivni status.Modaliteti invazivne terapije PB podrazumevaju duboku moždanu stimulaciju, lezione intervencije i primenu pumpi kaonaina za dopremanje leka.

U lezione procedure spadaju radifrekventna ablacija jedara (talamusa, subtalamičkoj jedra i globus palidusa) kao i ablacija jedara uz metode radiohirurgije i fokusiranog ultrazvuka. U nelezione procedure spada primena duodenalne ili apomorfinske pumpe, kao i duboka moždana stimulacija (DMS).

DMS je najčešće korišćeni hirurški pristup u kontroli motornih simptoma PB, uključujući bradikineziju, rigor i tremor, ali i u smanjenju trajanja „off" epizoda, kao i potrebnih doza dopaminomimetika dopamina, ublažavajući na taj način lekovima izazvane diskinezije.Trajanjestabilnogodgovoraposle DMS se možeodržavatinajmanje 10 godina.DMS poboljšava one simptome koji reaguju na levodopu, efikasna je u kontroli „on-off" fluktuacija i diskinezija. Efekti su vrlo varijabilni kada su u pitanju posturalni poremećaji, poremećaji hoda, govora i gutanja, kao i dejstvo na nemotorne simptome PB, poput kognitivnog statusa, spavanja, mokrenja i dr. Zbog toga kandidati za operaciju nisu osobe koje su osobe koje su dementne, imaju razvijenu autonomnu disfunkciju, atipični parkinsonizam, nestabilnu psihijatrijsku bolest, frizing hoda i poremećaj balansa. Preporučuje se kao terapija za obolele sa ranom ili uznapredovalom bolešću ukoliko su se kod pacijenta pojavila komplikacije dugotrajnog lečenja.

Intrajejunalna infuzija levodope je registrovana za lečenje uznapredovalih stadijuma bolesti sa značajnim motornim fluktuacijama, koje često koincidiraju sa diskinezijama. Ovu proceduru kojom se obezbeđuje stabilna koncentracija levodope dopremljene preko perkutane gastrostome treba preporučiti osobama sa uznapredovalom bolešću koja nije adekvatno kontrolisana medikamentima.

Subkutana kontinuirana infuzija dopaminskog agoniste apomorfina nalazi svoje mesto u osoba sa onesposobljavajućim interdoznim diskinezijama ili off periodima koji zapremaju više od 30% dana. Preperativno apomorfin može biti korišćen u slučaju velikih abdominalnih hirurških intervencija, kada bolesnici ne mogu uzimati peroralnu terapiju. Osim toga ovaj oblik lečenja treba da bude preporučen uvek pre funkcionalne neurohirurgije i kod obolelih koji su hendikepirani posle palidotomije ili hirurške intervencije. I ovu proceduru treba preporučiti osobama sa uznapredovalom bolešću koja nije adekvatno kontrolisana medikamentima

U poređenju sa DMS, i apomorfinska infuzija i intrajejunalna levodopa obezbeđuju slično i uporedivo motorno poboljšanje ali ne utiču na diskinezije. Jednostrana radiofrekventna palidotomija može biti razmatrana kod osoba sa uznapredovalom PB i fluktuacijama terapijskog dgovora ukoliko DMS ili primena pumpi iz nekog razloga nisu moguće. Talamotomija radiofrekventnom termokoaulacijom može se razmotriti jednostrano za kontrolu parkinsonog tremora, ali se ne preporučuje. Ablacija bilo kog jedra radiohirurgijom se ne preporučuje, kao i primena fokusirano ultrazvuka osim u istraživačke svrhe.

**Ključne riječi:** Parkinsonova bolest – Lezione/nelezione procedure

## INVASIVE THERAPY OF PARKINSON'S DISEASE

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**Abstract**

The therapy of Parkinson's disease (PD) improves the patient in adequate self-care, tries to protect his independence, maintenance of working ability and social competence. It targets motor, psychiatric, autonomic disorders and cognitive status. Modalities of invasive PD therapy include deep brain stimulation, lesional interventions and the use of pumps as a means of drug delivery.

Lesional procedures include radiofrequency nuclear ablation (of the thalamus, subthalamic nucleus and globus pallidus) as well as nuclear ablation with radiosurgery and focused ultrasound methods. Non-lesional procedures include duodenal or apomorphine pump, as well as deep brain stimulation (DBS).

DBS is the most used surgical approach in the control of motor symptoms of PD, including bradykinesia, rigor and tremor, but also in reducing the duration of "off" episodes, as well as the required doses of dopaminomimetics, thereby alleviating drug-induced dyskinesias. The duration of a stable response after DBS can be maintained for at least 10 years. DBS improves those symptoms that respond to levodopa, is effective in controlling "on-off" fluctuations and dyskinesias. The effects are very variable when it comes to postural disorders, disorders of walking, speech and swallowing, as well as the effect on non-motor symptoms of PD, such as cognitive status, sleep, urination, etc. Therefore, candidates for surgery are not persons who are demented, have developed autonomic dysfunction, atypical parkinsonism, unstable psychiatric illness, freezing of gait and balance disorder. It is recommended as a therapy for patients with early or advanced PD if the patient has complications from long-term treatment.

Intrajejunal infusion of levodopa is registered for the treatment of advanced stages of the disease with significant motor fluctuations, which often coincide with dyskinesias. This

procedure, which provides a stable concentration of levodopa delivered via a percutaneous gastrostomy, should be recommended for people with advanced diseases that is not adequately controlled by medication.

Subcutaneous continuous infusion of the dopamine agonist apomorphine finds its place in individuals with disabling inter-dose dyskinesias or off periods that occupy more than 30% of the day. Preoperatively, apomorphine can be used in the case of major abdominal surgical interventions, when patients cannot take oral therapy. In addition, this form of treatment should always be recommended before functional neurosurgery and in patients who are handicapped after pallidotomy or surgical intervention. This procedure should also be recommended for people with an advanced disease that is not adequately controlled by medication

Compared with DBS, both apomorphic infusion and intrajejunal levodopa provide similar and comparable motor improvement. Unilateral radiofrequency pallidotomy may be considered in individuals with advanced PD and fluctuations in therapeutic speech if DBS or pumps are not possible for some reason. Radiofrequency thermocoagulation thalamotomy can be considered unilaterally to control Parkinsonian tremor but is not recommended. Ablation of any basal ganglia structures by radiosurgery is not recommended, as is the use of focused ultrasound except for research purposes.

**Key words:** Parkinson's disease – Lesional/nonlesional procedures

# TERAPIJA RANE FAZE PARKINSONOVE BOLESTI

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**Sažetak**

Parkinsonova bolest (PB) je druga najčešća neurodegenerativna bolest starije životne dobi. Zahvaća oko 1% populacije stare > 60 godina, a učestalost raste sa starenjem. U većine bolesnika bolest počinje postupno i podmuklo. Dijagnoza se postavlja kliničkim pregledom, a za dijagnozu je potrebna prisutnost usporenosti pokreta (bradikineza) s još jednim od simptoma: tremor frekvencije 4- do 8-Hz poput "valjanja pilula, povećanim tonusom mišića (rigor) i često poremećajem posturalnih refleksa zaduženih za održavanje stava tijela.Uzrok bolesti je gubitak pigmentiranih dopaminergičkih neurona u supstanciji nigri. Gubitak neurona u supstanciji nigri uzrokuje smanjenje neurotransmitera dopamina. Glavni metabolički poremećaj u PB je smanjena aktivnost dopaminergičnog nigrostriatalnog sustava, a cilj terapije je osigurati kontinuiranu stimulaciju dopaminergičkih receptora u striatumu. Farmakološka terapija PB uključuje: nadomještanje dopamina primjenom prekursora dopamina – levodopa jer dopamin ne krvno-moždanu barijeru; blokiranje razgradnje dopamina; dopaminergički agonisti; amantadin; antikolinergici.

Levodopa koja je metabolički prekursor dopamina, prolazi krvno moždanu barijeru i ulazi u bazalne ganglije gdje se dekarboksilira i pretvara u dopamin. Bradikinezija i rigor su simptomi kod kojih najviše pomaže, premda se i tremor često značajno smanjuje. Istodobna primjena inhibitora periferne dekarboksilaze, karbidope i benzerazida smanjuje potrebnu dozu sprječavanjem katabolizma levodope i omogućuje učinkovitija doprema levodope u mozak, a tako se smanjuju i periferne nuspojave.

Primjenom dopaminergičkih agonista postiže se direktna stimulacija postsinaptičkih dopaminergičkih receptora je, za razliku od levodope, ne zahtijevaju metaboličku pretvorbu u dopaminergičkim neuronima. Osim toga imaju duže poluvrijeme života od levodope čime se postiže kotinuiranija stimulacija receptora. Danas se primjenjuju ne-ergotski dopaminergički agonisti: peroralni pramipeksol i ropinirol, te trandermalni rotigotin. Ove lijekove je u početku terapije potrebno postupno titrirati.

Amantadin je nekompetitivni antagonist NMDA receptora, djelomični antagonist nikotinskih receptora i djelomični agonist dopamina. Koristan je u terapiji ranog, blagog parkinsonizma u pojedinih bolesnika, kao i u pojačavanju učinaka levodope u kasnijem tijeku bolesti, te u terapiji diskineza u kasnijim fazama bolesti. Međutim, amantadin često gubi svoju učinkovitost nakon nekog vremena.

Monoamino oksidaza B (MAO-B) i katehol-O-metil transferaza (COMT) su enzimi koji razgrađuju dopamin i ostale kateholamine i monoamine. Inhibicijom navedenih enzima povećava se koncentracija raspoloživog dopamina i na taj način se ublažavaju simptomi bolesti. Selegilin i noviji rasagilin inhibiraju enzim MAO-B. U početku PB mogu se

primijeniti sami, a u kasnijim fazama PB mogu se primijeniti uz levodopu. Entakapon i noviji opikapon inhibitori su enzima COMT, a primjenjuju se zajedno s levodopom i povećavaju raspoloživost levodope. Od antikolinergičkih lijekova najčešće se primjenjuje biperiden kao monoterapija u liječenju ranih stadija PB, a kasnije kao dopuna levodopi. Međutim, zbog čestih nuspojava u zadnje vrijeme se biperiden sve rjeđe propisuje.

U liječenju rane faze PB na raspolaganju su svi navedeni lijekovi. Liječenje se počinje jednim lijekom, a odluku o tome kojim lijekom započeti liječenje mora biti personalizirana i donosi se na temelju individualnih karakteristika svakog pojedinog bolesnika: radni status i zanimanje bolesnika, vrsta i ozbiljnost simptoma, dob, kognitivna funkcija, komorbiditeti, osobne sklonosti itd. Najčešće se terapija započinje primjenom levodope jer je levodopa najučinkovitiji lijek u terapiji PB: Liječenje počinje s jednom tabletom najčešće tri puta dnevno, a doza se može postupno povećavati dok se ne postigne maksimalan učinak. Međutim, neki mlađi bolesnici možda će preferirati pogodnost doziranja jednom dnevno s MAO-B inhibitorima ili dugodjelujućim dopaminergičkim agonistima.

**Ključne riječi:** Parkinsonova bolest – Farmakološka terapija

## THERAPY OF THE EARLY PHASE OF PARKINSON'S DISEASE

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**Abstract**

Parkinson's disease (PD) is the second most common neurodegenerative disease of old age. It affects about 1% of the population aged > 60 years, and the frequency increases with age. In most patients, the disease begins gradually and insidiously. The diagnosis is made by clinical examination, and the diagnosis requires the presence of slowness of movement (bradykinesis) with another symptom: tremors with a frequency of 4- to 8-Hz like "rolling pills", increased muscle tone (rigor) and often a disorder of postural reflexes responsible for posture maintaining. The cause of the disease is the loss of dopaminergic pigmented neurons in the substantia nigra.Loss of neurons in the substantia nigra causes a decrease of neurotransmitter dopamine.

The main metabolic disorder in PD is reduced activity of the dopaminergic nigrostriatal system, and the goal of therapy is to ensure continuous stimulation of dopaminergic receptors in the striatum. Pharmacotherapy of PD includes:replacement of dopamine using dopamine precursor - levodopa, because dopamine does not cross the blood-brain barrier; blocking the breakdown of dopamine; dopaminergic agonists; amantadine; anticholinergics.

Levodopa, which is a metabolic precursor of dopamine, crosses the blood-brain barrier and enters the basal ganglia, where it is decarboxylated and converted into dopamine. Bradykinesia and rigor are the symptoms that best respond to levodopa, although the tremor is often significantly reduced. Simultaneous administration of peripheral decarboxylase inhibitors, carbidopa and benserazide reduces the required dose by preventing levodopa catabolism and enables more effective delivery of levodopa to the brain, thus reducing peripheral side effects. The use of dopaminergic agonists achieves direct stimulation of postsynaptic dopaminergic receptors and, unlike levodopa, does not require metabolic conversion in dopaminergic neurons. In addition, they have a longer half-life than levodopa, which results in more continuous receptor stimulation. Today, non-ergot dopaminergic agonists are used: oral pramipexole and ropinirole, and transdermal rotigotine. These drugs should be gradually titrated in the beginning of therapy.

Amantadine is a non-competitive NMDA receptor antagonist, partial nicotinic receptor antagonist and partial dopamine agonist. It is useful in the treatment of early, mild parkinsonism in some patients, as well as in enhancing the effects of levodopa in the later course of the disease, and in the treatment of dyskinesia in later stages of the disease. However, amantadine often loses its effectiveness after some time.

Monoamine oxidase B (MAO-B) and catechol-O-methyl transferase (COMT) are enzymes that break down dopamine and other catecholamines and monoamines. By inhibiting these enzymes, the concentration of available dopamine increases and disease symptoms are alleviated. Selegiline and the newer rasagiline inhibit the MAO-B enzyme. In early stage of PDthey can be used alone, and in the later PD stages they are usually used in addition to levodopa. Entacapone and newer opicapone are inhibitors of the COMT enzyme, and they are used together with levodopa increasing the availability of levodopa. Biperiden is anticholinergic drugs, most often used as monotherapy in the treatment of early stages of PD, and later as a supplement to levodopa. However, due to frequent side effects, biperiden has been prescribed less frequently.

In the treatment of the early stage of PD, all these drugs are available. Treatment is started with one drug, and the decision about which drug to start treatment with must be personalized and made based on the individual characteristics of each patient. We must consider work status and occupation of the patient, type and severity of symptoms, age, cognitive function, comorbidities, personal preferences, etc. Most often, therapy is started with levodopa, because levodopa is the most effective drug in PD therapy: Treatment usually starts with one tablet three times a day, and the dose can be gradually increased until the maximum effect is achieved. However, some younger patients may prefer the convenience of once-daily dosing with MAO-B inhibitors or long-acting dopaminergic agonists.

**Key words:** Parkinson's disease – Pharmacological therapy

## UTICAJ NEMOTORNIH SIMPTOMA NA TERAPIJSKE PRIORITETE U PARKINSONOVOJ BOLESTI

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**Sažetak**

Parkinsonovabolest (PB) je progresivna neurodegenerativna bolest kod koje patološki process zahvata veći broj transmiterskih sistema i neuronskih mreža zaduženih za kontrolu motorike, afekta i kognitivnih funkcija. Nemotorni simptomi su prepoznati kao sastavni deo kliničkog ispoljavanja PB, a skoriji nalazi ukazuju na njihov presudan uticaj ne samo na kvalitet života, već i na obrazac i brzinu progresije neurodegenrativnog procesa. Osim ovoga, pojedini nemotorni simptomi nastaju kao posledica među odnosa patološkog procesa I specifične antiparkinsone terapije. Konačno značaj nemotornih simptoma je evoluirao u concept nemotornih podtipova PB sa značajnim terapijskim implikacijama. Sve navedeno, nameće izmenu tradicionalnog stava u preporukama i vodičima za lečenje PB koje se dominatno zasnivaju na motornim simptomima i motornim komplikacijama terapije. U radu će biti razmatran značaj nemotornih simptoma na izbor medikamentozne i invazivne terapije u različitim stadijumima PB.

**Ključne riječi:** Parkinsinova bolest – Nemotorni simptomi

## THE INFLUENCE OF NON-MOTOR SYMPTOMS ON THERAPEUTIC PRIORITIES IN PARKINSON'S DISEASE

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**Abstract**

Parkinson's disease (PD) is a progressive neurodegenerative disease in which the pathological process involves several transmitter systems and neural networks responsible for controlling motor, affective and cognitive functions. Non-motor symptoms are recognized as an integral part of the clinical manifestation of PD, and recent findings indicate their decisive influence not only on the quality of life, but also on the pattern and speed of the progression of the neurodegenerative process. In addition to this, some non-motor symptoms arise as a result of the interplay between the pathological process and specific antiparkinsonian therapy. Finally, the importance of non-motor symptoms has evolved into the concept of non-motor

subtypes of PD with significant therapeutic implications. Combining all of the above imposes a change in the traditional recommendations and guides for the treatment of PD, which are predominantly based on motor symptoms and motor complications of therapy. The paper will discuss the importance of non-motor symptoms on the choice of medical and invasive therapy in different stages of PD.

**Key words:** Parkinson disease – Non-motor symptoms

# FRONTOTEMPORALNA DEMENCIJA

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**Sažetak**

Frontotemporalna demencija (FTD) je skupina klinički i neuropatološki heterogenih neurodegenerativnih poremećaja koje karakterišu značajne promjene u ponašanju i ličnosti i/ili afazije a koji su udruženi sa degeneracijom frontalnih i/ili parijetalnih režnjeva mozga. FTD je jedna od najčešćih uzroka ranih demencija sa prosječnom dobi početka bolesti u šestoj deceniji života. Predstavlja 4. najčešći uzrok progresivnih demencija (nakon Alzheimer demencije, Vaskularne i Lewy body demencije), odprilike 20% svih slučajeva progresivnih demencija.

Razlikuju se tri glavne kliničke prezentacije FTD: bihejvioralna varijanta (bvFTD) i dvije forme primarne progresivne afazije (PPA), nefluentna i semantička varijanta. Patologija je heterogena i karakterišu je anormalne inkluzije tau, TAR DNA-binding protein 43 (TDP-43), FET and drugih proteina. FTD je autosomno-dominanto nasljedna bolest , što je učočeno kod 10 % do 25 % FTD pacijenata. Najčešće genske mutacije uključuju : microtubule-povezani protein tau (*MAPT*), granulin precursor (*GRN*) gen, i hexanucleotide expansion kod hromosome 9 okvir 72 (*C9orf72*). Iako većina pacijenata (bvFTD) nemaju izražene motorne simptome u ranom toku bolesti, tri klinička sindroma uzrokovana FTD patologijom se manifestiraju sa motornom simptomima: Bolest motornog neurona, Kortikobazalni sindrom i progresivna supranuklearna paraliza.

Dijagnoza je primarno klinička, zasnovana na karakterističnim kliničkim simptomima uz odsustvo signifikantnog oštećenja funkcija pamćenja i vizuelnoprostorne orijentacije. Neuroimaging je neophodan zbog isključenja strukturalne patologije kao i evaluacije atrofičnih promjena čije prisustvo može doprinjeti postavljanju dijagnoze. Neurofunkcionalni imaging može ukazati na hipometabolizam u specifičnim regijama mozga, a neuropsihološko testiranje je korisno u diferencijaciji prema drugim neurodegenrativnim sindromima i psihijatrijskim poremećajima. Konačna dijagnoza FTD se potvrđuje biopsijom ili postmortalnom histopatološkom analizom ili potvrdom postojanja poznate genske mutacije.

Tretman se sastoji od farmakoloških (simptomatskih) i nefarmakoloških intervencija. Novija saznanja u oblasti genetike, patofiziologije, neuropatologije i neuroimunologije FTD je stvorilo mogućnosti za istražavanja specifičnih bolest-modificirajućih terapija.

Iako rijetka bolest, frontotemporalna demencije je u fokusu interesovanja istraživača zahvaljujući najnovijim saznanjima o patološkim mehanizmima nastanka bolesti i boljem razumjevanje razlika u odnosu na pacijente koji imaju Alzheimer demenciju.

**Ključne riječi**: Frontotemporalna demencija

# FRONTOTEMPORAL DEMENTIA

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## Abstract

Frontotemporal dementia (FTD) consists of a group of clinically and neuropathologically heterogeneous neurodegenerative disorders characterized by prominent changes in social behavior and personality or aphasia accompanied by degeneration of the frontal and/or temporal lobes. It is one of the most common causes of early-onset dementiawith an average age of symptom onset in the sixth decade and the 4th the most common progressive dementia(after Alzheimer diesease (AD), Vascular and Lewy body dementia), aproximatelly 20% cases of progressive dementia.

FTD includes three clinical presentations: behavioral variant FTD (bvFTD) and two forms of primary progressive aphasia (PPA), the nonfluent and semantic variants. The pathology is heterogeneous. It is categorized by abnormal protein inclusions due to tau, the TAR DNA-binding protein 43 (TDP-43), FET and other proteins. FTD is highly heritable with an autosomal-dominant inheritance pattern observed in approximately 10 to 25 percent of patients with FTD. The most common disease-causing genetic mutations include those in microtubule-associated protein tau (*MAPT*), the granulin precursor (*GRN*) gene, and a hexanucleotide expansion in chromosome 9 open reading frame 72 (*C9orf72*).Although most patients (bvFTD) do not manifest prominent motor features early in the disease course, three clinical syndromes caused by FTD patology manifest with motor symptoms in addition to cognitive and behavioral symptoms. Those are Motor neuron disease, Corticobasal syndrome and Progressive supranuclear palsy.

The diagnosis is made primarily by clinical assessment with prominent clinical characteristics and the absence of significant memory or visual spatial deficits. Neuroimaging scans are required to exclude structural pathology where lobar atrophy findingsmight be supportive and also functional neuroimaging. Neuropsychological testing ishelpful in differentiation from other neurodegenerative syndromes and psychiatric disorders. Definite FTD pathology, is confirmed by either biopsy or postmortem histopathologic evidence of FTD or evidence of a known pathogenic mutation.

Treatment includes farmacological (symptomatic) and non pharmacological treatments. Recent advancements in the understanding of the genetics, pathophysiology, neuropathology, and neuroimmunology of the FTD expanded possibilities for development of disease-modifying and symptom-targetedtreatments.

Although still considered a rare diseas, eFTD is gaining awareness in clinicians and researchers thanks to the recent developments and knowledge of pathological mechanisms and better definition of those patients who do not have an AD pathology.

**Key words**: Frontotemporal dementia

# AUGMENTATIVNA I ALTERNATIVNA KOMUNIKACIJA ZA OSOBE SA NEUROLOŠKIM OBOLJENJIMA

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**Sažetak**

Augmentativna i alternativna komunikacija(AAC) je područje kliničke prakse koje se bavi potrebama pojedinaca sa značajnim i složenim smetnjama komunikacije, koje karakteriziraju teškoće i poremećaji u produkciji i/ili razumjevanju govornog jezika. Kao osnovni cilj AAC je pomoći osobama s komunikacijskim teškoćama povećati sudjelovanje u željenim aktivnostima i stvoriti prilike za socijalnu interakciju. AAC promatramo iz ugla dopune postojećeg govora, ali i zamjene govora kada je govor u potpunosti odsutan ili nije funkcionalan. AAC može biti privremeno, ali i trajno sredstvo komuniciranja u ovisnosti od stanja u kojem se klijent kojem se AAC preporučuje nalazi.

AAC sustavi podrazumijevaju upotrebu ručnih znakova, gesti, ali i crteža, simbola, slika i komunikacijskih ploča, kao i uređaja za generiranje govora. Logopedi diljem svijeta zagovaraju dinamičku evaluaciju kojom se postiže interaktivna i sistematično detaljna procjena vještina, a sa ciljem izbora AAC sustava koji će najbolje odgovarati svakom pojedincu.

Osobe koje će imati koristi od AAC možemo podijeliti u dvije skupine; osobe sa urođenim onesposobljenjima koje usvajaju jezik koristeći AAC sredstva; te osobe sa stečenim onesposobljenjima u kojih komunikacijske teškoće variraju i mogu se mijenjati kroz vrijeme ovisno o očuvanosti jezika i kognicije u vrijeme povrede ili pojave bolesti i napredovanja iste. Među neurološka oboljenja koja će kao posljedicu ostaviti blaže ili izraženije komunikacijske teškoće, a prilikom kojih klijenti mogu imati benefite od upotrebe AAC, ubrajamo motoričke govorne poremećaje (apraksiju, dizartriju), te kognitivno-komunikacijske poremećaje (afaziju, traumatske povrede mozga, te progresivna neurološka stanja poput demencije, amiotrofičnu lateralnu sklerozu ili primarno progresivnu afaziju).

Napredak tehnologije donio je brojne benefite i na području AAC, te tako danas postoji mogućnost da i osobe s s težim oštećenjima postignu veću neovisnost i pristup komunikaciji. Adekvatno i pravovremeno upućivanje na logopedsku procjenu, te preporuka za korištenje odgovarajućeg AAC sustava, kao i prihvatanje od strane osoba s neurološkim oboljenima i članova njihovih obitelji su značajno u porastu globalno promatrajući ovo područje, međutim Bosna i Hercegovina nažalost i dalje poprilično zaostaje, te se nameće važnost urgencije sa ciljem pružanja potpunije i kvalitetnije zdravstvene usluge.

**Ključne riječi:** Augmentativna konunikacija – Alternativna komunikacija – Neurološka oboljenja

# AUGMENTATIVE AND ALTERNATIVE COMMUNICATION FOR PEOPLE WITH NEUROLOGICAL DISEASES

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## Abstract

Augmentative and alternative communication (AAC) is an area of clinical practice that addresses the needs of individuals with significant and complex communication disabilities, characterized by difficulties and disorders in the production and/or understanding of spoken language. The main goal of AAC is to help people with communication difficulties increase participation in desired activities and create opportunities for social interaction. AAC can be looked from the point of view of supplementing existing speech, but also replacing speech when speech is completely absent or not functional. AAC can be a temporary or permanent way of communication, depending on the situation in which the client to whom AAC is recommended is in.

AAC systems include the use of hand signs, gestures, but also drawings, symbols, pictures and communication boards, as well as devices for generating speech. Speech therapists around the world advocate dynamic evaluation, which achieves an interactive and systematically detailed assessment of skills, with the goal of choosing the AAC system that will best suit each individual.

People who will benefit from AAC can be divided into two groups; persons with congenital disabilities who acquire language using AAC; and persons with acquired disabilities in which communication difficulties vary and can change over time depending on the preservation of language and cognition at the time of the injury or the onset of the disease and its progression. Among neurological diseases that will result in mild or more pronounced communication difficulties, and in which clients can benefit from the use of AAC, we include motor speech disorders (apraxia, dysarthria), and cognitive-communication disorders (aphasia, traumatic brain injuries, and progressive neurological conditions such as dementia, amyotrophic lateral sclerosis or primary progressive aphasia).

Advances in technology have brought numerous benefits in the field of AAC, so today there is a possibility that even people with severe impairments can achieve greater independence and access to communication. Adequate and timely referral to a speech therapy assessment, as well as a recommendation for the use of an appropriate AAC system, as well as acceptance by people with neurological diseases and their family members are on the rise globally, but Bosnia and Herzegovina unfortunately still lags behind, and there is evidence of urgency with the aim of providing a more complete and high-quality health service.

**Key words:** Augmentative communication – Alternative communication – Neurological diseases

# MODERNI KONCEPTI NEUROREHABILITACIJE

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**Sažetak**

Neurološka rehabilitacija (NR) je specijalizirani dio fizikalne medicine i rehabilitacije i usmjerena je ka pacijentima sa bolestima ili ozljedama centralnog nervnog sistema (CNS) i perifernog nervnog sistema (PNS). Osnovi cilj neurološke rehabilitacije da se putem različitih terapijskih pristupa poboljša funkcionalna sposobnost, kvalitet života i neovisnost pacijenata. Najčešća stanja koja se tretiraju u okviru NR su: cerebrovaskularni inzulti; kraniocerebralne ozljede; spinalne ozljede; operativni zahvat na mozgu i kičmenoj moždini; ozljede perifernih živaca; cerebralna paraliza (CP); multipla skleroza (MS); Parkinsonova bolest; polineuropatije; kompresivni sindromi perifernih živaca; mišićna distrofija.

Ključne komponente za NR su procjena pacijenata koja se vrši kroz analizu motornih, senzoričkih, emocionalnih i kognitivnih funkcija pacijenta. Nakon procjene pacijenta i objektivizacije stanja koja se vrši različitim dijagnostičkim procedurama pristupa se individualiziranom planu NR u okviru kojeg se razvija personalni plan rehabilitacije temeljen na specifičnim potrebama i ciljevima.

Za neurološku rehabilitaciju se koriste metode fizikalne terapije, fizioterapiju, okupaciona terapija, psihološka potpora pacijenata i edukacija pacijenata. Najznačajniji fizikalni modaliteti u NR su: magnetoterapija, elektroterapija, elektrostimulacija, laseroterapija, ultrazvučna terapija, temoterapija, limfna drenaža, T-care terapija, Dry needling, Mirror terapija. U okviru fizioterapije koriste se vježbe za poboljšanje koordinacije; vježbe fleksibilnosti, snage, ravnoteže, te specifične tehnike za ponovno učenje pokreta. U okviru fizioterapijskih intervencija najznačajnije tehnike su: Bobath koncept i PNF koncept. Bobath koncept - individualizirani terapijski pristup koji se temelji na ponovnom učenju normalnog pokreta i držanja tijela. Postoji Bobath koncept za neurorizičnu djecu, te Bobath koncept za odrasle (nakon CVI; Parkinsonova bolest; MS).Proprioceptivna neuromuskularna fascilitacija (PNF) ima za cilj poboljšanje funkcije pokreta, odnosno aktivnosti. Fizioterapeut uči pacijenta vježbama koje dovode do aktivacije mišića na specifičan način kako bi se aktivirao ispravan pokret i dobila bolja pokretljivost i ojačala muskulatura.

Okupaciona i radna terapija (OT) – programi OT treba da razviju funkcionalnu sposobnost, vještine svakodnevnog življenja,rekreativna znanja, edukativna znanja (čitanje, pisanje, trening percepcije), kreativna znanja (muziko umjetost), te manuelna znanja.

Psihološka podrška – provodi se u smislu psihološke i emocionalne podrške za pacijente i članove obitelji. U okviru ove podrške koriste se i terapijski programi za smanjenje psihičkih problema vezanih za određena neurološka oboljenja (depresija, anksioznost).

Robotska neurorehabilitacija predstavlja najnoviji vid terapijskog prisutupa u okviru NR i koristi robotske i senzorne uređaje koji pomažu i pojačavaju učinak terapije. Robotski asistirani sistemi utiču na reorganizaciju nervnog sistema i neuroplastičnost. Opseg primjena

robotske neurorehabilitacije su: robotski asistirane vježbe hoda; robotski asistirane vježbe za ruke; robotski asistirane vježbe za ravnotežu; govorne vježbe; vježbe gutanja i analiza hoda.

**Ključne riječi:** Neurorehabilitacija – Moderni koncepti

## MODERN CONCEPTS OF NEUROREHABILITATION

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**Abstract**

Neurological rehabilitation (NR) is a specialized part of physical medicine and rehabilitation and is aimed at patients with diseases or injuries of the central nervous system (CNS) and peripheral nervous system (PNS). The basic goal of neurological rehabilitation is to improve functional ability, quality of life and independence of patients through various therapeutic approaches. The most common conditions treated within NR are: cerebrovascular insults; craniocerebral injuries; spinal injuries; surgery on the brain and spinal cord; peripheral nerve injuries; cerebral palsy (CP); multiple sclerosis (MS); Parkinson's disease; polyneuropathies; compressive syndromes of peripheral nerves; muscular dystrophy. Key components for NR are patient assessment, which is done through analysis of the patient's motor, sensory, emotional, and cognitive functions. After the assessment of the patient and the objectification of the condition, which is carried out by various diagnostic procedures, an individualized NR plan is accessed, within which a personal rehabilitation plan based on specific needs and goals is developed.

Physical therapy methods, physiotherapy, occupational therapy, psychological patient support and patient education are used for neurological rehabilitation. The most important physical modalities in NR are: magnetotherapy, electrotherapy, electrostimulation, laser therapy, ultrasound therapy, thermotherapy, lymphatic drainage, T-care therapy, dry needling, mirror therapy. Physiotherapy uses exercises to improve coordination; exercises for flexibility, strength, balance, and specific techniques for relearning movements. In the framework of physiotherapy interventions, the most important techniques are: Bobath concept and PNF concept.

Bobath concept - an individualized therapeutic approach based on relearning normal movement and body posture. There is a Bobath concept for neuro-risk children, and a Bobath concept for adults (after CVI; Parkinson's disease; MS).

Proprioceptive neuromuscular fascilitation (PNF) aims to improve movement function, that is, activity. The physiotherapist teaches the patient exercises that lead to muscle activation in a specific way in order to activate the correct movement and gain better mobility and strengthen the musculature.

Occupational and work therapy (OT) - OT programs should develop functional ability, daily living skills, recreational skills, educational skills (reading, writing, perception training), creative skills (musical art), and manual skills.

Psychological support – is implemented in terms of psychological and emotional support for patients and family members. As part of this support, therapeutic programs are also used to reduce psychological problems related to certain neurological diseases (depression, anxiety).

Robotic neurorehabilitation represents the latest type of therapeutic approach within NR and uses robotic and sensory devices that help and enhance the effect of therapy. Robotic assisted systems influence the reorganization of the nervous system and neuroplasticity. The range of applications of robotic neurorehabilitation are: robot-assisted walking exercises; robotically assisted hand exercises; robotically assisted balance exercises; speech exercises; swallowing exercises and gait analysis.

**Key words:** Neurorehabilitation – Modern concepts

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