Srpsko lekarsko društvo
Serbian Medical Society

Sekcija za kliničku farmakologiju „dr Srđan Đani Marković"
Section of Clinical Pharmacology „dr Srđan Đani Marković"

Organizuju nacionalni kongres
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XVI NEDELJA BOLNIČKE KLINIČKE FARMAKOLOGIJE

XVI WEEK OF THE HOSPITAL CLINICAL PHARMACOLOGY

28. - 29. decembar 2024.
December 28th - 29th, 2024

ZBORNIK SAŽETAKA
BOOK OF ABSTRACTS
Beograd, 28. - 29. decembar 2024.

Izdavač
Sekcija za kliničku farmakologiju Srpskog lekarskog društva „dr Srđan Đani Marković", Džordža Vašingtona 19, Beograd, 2024

Za izdavača
Prof. dr Boris Milijašević

Glavni i odgovorni urednik
Prim. dr Dragana A. Kastratović - Maca

Urednici:
Prof. dr Boris Milijašević
Dr Srđan Z. Marković - Đani

Grafičko-tehničko uređenje
Prof. dr Boris Milijašević

Štampa
Sekcija za kliničku farmakologiju Srpskog lekarskog društva „dr Srđan Đani Marković", Džordža Vašlngtona 19, Beograd, 2024

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PROGRAM
PROGRAMME

XVI NEDELJA BOLNIČKE KLINIČKE FARMAKOLOGIJE
XVI WEEK OF THE HOSPITAL CLINICAL PHARMACOLOGYS

SUBOTA, 28. decembar 2024. / SATURDAY, 28th December 2024

10:00-10:30 **Šesnaest godina rada Sekcije za kliničku farmakologiju „dr Srđan Đani Marković" Srpskog lekarskog društva**
Sixteen years of activity of the Section for Clinical Pharmacology „dr Srdjan Djani Marković" of the Serbian Medical Society
Dragana Maca A. Kastratović, Srdjan Djani Z. Marković, Slobodan M. Janković, Boris Ž. Milijašević, Radmila M. Veličković-Radovanović, Momir M. Mikov, Mira H. Vuković, Viktorija M. Dragojević-Simić, Branka M. Terzić, Biljana P. Radojević, Zoran M. Todorović, Aleksandar L. Rašković, Ivana Miličević, Snežana Panić, Olga J. Horvat, Dejana T. Ružić-Zečević, Ivana P. Timotijević-Marković

10:30-11:00 **Terapija malignih bolesti T-ćelijama sa himernim receptorom za tumorski antigen (CAR T-ćelije)**
Therapy of malignant diseases with T-cells having chimeric receptor for tumor antigen (CAR T-cells)
Slobodan M. Janković

11:00-11:30 **Savremena terapija srčane insuficijencije**
Modern treatment of heart failure
Boris Ž. Milijašević, Kristina B. Savić, Radmila N. Popović, Zdenko S. Tomić, Nemanja B. Todorović

11:30-12:00 **Kognitivna stimulacija i emocionalna trankilizacija depresivnosti aktivacijom retikularnog sistema**
Cognitive stimulation and emotional tranquilisation of depression by activation of the reticular system
Ivana P. Timotijević, Mirjana M. Todorović, Katarina B. Crnić

12:00-12:30 **Antikoagulantna terapija u hronićnoj bubrežnoj bolesti**
Anticoagulation in chronic kidney disease
Radmila M. Veličković-Radovanović

12:30-13:00 **Tardivne diskinezije kod pacijenata na terapiji antipsihoticima**
Tardive dyskinesia in patients on antipsychotic therapy
Žana B. Stanković

13:00-13:30 **Značaj palimitoiletanolamida u terapiji bolnih stanja**
The importance of palimitoylethanolamide in the treatment of painful conditions
Dane A. Krtinić, Gorana G. Nedin-Ranković, Dragana S. Stokanović, Dragana S. Milijašević, Hristina M. Jovanović, Hristina S. Trajković, Jovana M. Cvetković, Marija R. Jevtić, Vuk Z. Pejčić, Milan V. Čevrljaković

13:30-14:00 **Menadžment primene transfuzije krvi pacijentu u vanrednim uslovima**
Patient blood management in Natural Hazards and Emergency Situations
Ljubinka I. Nikolić, Dragana A. Kastratović

14:00-14:30 **Klinička ispitivanja prve faze: učesnici, organizacija, legislativa**
First phase clinical trials: participants, organization, legal regulations
Viktorija M. Dragojević-Simić

14:30-15:00 **Principi I tehnike ukidanja benzodiazepina u tretmanu zavisnika**
Principles and techniques of benzodiazepines discontinuation in the treatment of addicts
Katarina B. Crnić, Mirjana M. Todorović, Ivana P. Timotijević-Marković

15:00-15:30 **Stabilni multidisciplinarni timovi u zdravstvu**
Stable multidisciplinary teams in healthcare
Dragana A. Kastratović, Srdjan Z. Marković, Miloš D. Mojović, Slobodan M. Janković, Mira H. Vuković

15:30-16:00 **Kombinovana superkritična CO_2 ekstrakcija i lipozomalna enkapsulacija bioaktivnih komponenti pokožica grožđa Vranac u cilju njihove topikalne primene**
Combined supercritical CO_2 extraction and liposomal encapsulation of bioactive compounds from vranac grape skins for topical applications
Spomenka Ž. Babić Banković, Miloš D. Mojović, Đura J. Nakarada, Srđan Z. Marković, Dragana A. Kastratović

NEDELJA, 29. decembar 2024. / SUNDAY, 29th December 2024

10:00-10:30 **Humana i veterinarska medicina iz perspektive Jedne medicine do Jednog zdravlja**
Human and Veterinary Medicine from a One Medicine to One Health Perspective
Olga J Horvat, Zorana R. Kovačević

10:30-11:00 **Funkcionalnost nusproizvoda prehrambene industrije kao novih farmaceutskih ekscipijenasa u lekovima dobijenim tehnologijom 3D štampe**
Functionality of food industry by-products as new pharmaceutical excipients in drugs obtained by 3D printing technology
Mladena N. Lalić-Popović, Nemanja B. Todorović, Jelena M. Čanji-Panić, Senka Z. Popović, Aleksandra D. Ćoškov, Marija R. Dangubić, Boris Ž. Milijašević

11:00-11:30 **Regulatori cirkadijalnog ritma i tretman depresije**
Circadian rhythm regulators and treatment of depression
Mirjana M. Todorović, Katarina B. Crnić, Ivana P. Timotijević-Marković

11:30-12:00 **Akutna trovanja lekovima u pedijatrijskom uzrastu**
Pediatric Drug Poisoning in Vojvodina, Serbia: A Retrospective Clinical and Toxicological Assessment
Jovan M. Baljak, Aleksandra S. Stojadinović, Miljana M. Poparić, David Z. Strilić, Aleksandar L. Rašković

12:00-12:30 **Topikalni kortikosteroidi**
Topical corticosteroids
Dragana S. Stokanović, Valentina N. Nikolić, Gorana G. Nedin Ranković, Dane A. Krtinić, Hristina M. Jovanović, Hristina S. Trajković

12:30-13:00 **Razvoj farmaceutske formulacije ternarne čvrste disperzije ketoprofena**
Development of pharmaceutical formulation of ternary solid dispersion of ketoprofen
Nemanja B. Todorović, Ana N. Stjepanović, Ivana B. Marinković, Aleksandra D. Ćoškov, Jelena M. Čanji-Panić, Boris Ž. Milijašević, Mladena N. Lalić-Popović

13:00-13:30 **Savremeni pristup u lečenju uznapredovalog melanoma - ciljana i imunoterapija**
Current treatment of advanced melanoma: immunotherapy and targeted therapy
Aleksandra, M. Kovačević

13:30-14:00 **Bezbednosni profil novih oralnih antikoagulanasa u kombinaciji sa politerapijom: izazovi u kliničkoj praksi**
Safety profile of Novel Oral Anticoagulants in combination with polytherapy: chalenges in clinical practice
Gorana G. Nedin-Ranković, Dane A. Krtinić, Dragana S. Stokanović, Hristina M. Jovanović, Hristina S. Trajković

14:00-14:30 **Diskusija i zaključci**
Discussion and Conclusions
Dragana A. Maca Kastratović, Slobodan M. Janković, Aleksandar L. Rašković, Boris Ž. Milijašević, Viktorija M. Dragojević Simić, Radmila M. Veličković Radovanović

POSTERI
POSTER SESSION

Poster 1 **Formulacione karakteristike farmaceutskih oblika doziranja sa modifikovanim oslobađanjem u Republici Srbiji**
Formulation characteristics of modified-release pharmaceutical dosage forms in the Republic of Serbia
Aleksandra D. Ćoškov, Nemanja B. Todorović, Boris Ž. Milijašević, Mladena N. Lalić Popović

Poster 2 **Upotreba opioidnih analgetika u Srbiji**
Opioid analgesics use in Serbia
Sara V. Vasović, Dušan V. Prodanović, Lucija V. Vasović, Aleksandra V. Hinić, Nebojša P. Stilinović, Velibor M. Vasović, Ana D. Tomas-Petrović

Poster 3 **Biotin u dijagnostici: prepoznavanje interferencije i metode njene prevencije**
Biotin in Diagnostics: Recognizing Interference and Methods for Its Prevention
David Z. Strilić, Bojan G. Stanimirov, Maja P. Đanić

Poster 4 **Zastupljenost jedinjenja sa fluorom na deklaracijama predmeta opšte upotrebe u Republici Srbiji**
Identification of Fluorine-Containing Compounds on Labels of General Use Items in the Republic of Serbia
Nemanja B. Todorović, Mladena N. Lalić-Popović

Poster 5 **Metafedron (3-metilmetkatinon): farmakološki, klinički i toksikološki profil**
Metaphedrone (3-Methylmethcathinone): Pharmacological, Clinical, and Toxicological Profile
Igor M. Kelečević, Ljubica D. Gugleta, Ana-Marija T. Vejnović, Vesna M. Mijatović-Jovin

Poster 6 **Potrošnja lekova i troškovi lečenja u terapiji glaukoma u Republici Srbiji**
Drug consumption and costs of the glaucoma therapy in the Republic of Serbia
Aleksandra D. Ćoškov, Dijana R. Savanović, Nemanja B. Todorović, Mladena N. Lalić-Popović, Nataša Z. Tomić, Boris Ž. Milijašević

Poster 7 **Toksični efekti hinolona: dokazi iz pretkliničkih i kliničkih istraživanjm**
Toxic effects of quinolone: evidence from preclinical and clinical studies
Sara V. Vasović, Dušan V. Prodanović, Lucija V. Vasović, Nebojša P. Stilinović, Velibor M. Vasović, Ana D. Tomas-Petrović

Poster 8 **Upotreba *off-label* lekova u lečenju novorođenčadi: Iskustva sa Odeljenja za neonatalnu intenzivnu negu i terapiju**
Use of *off-label* drugs in the treatment of neonates: Experience from the Neonatal intensive care and therapy department
Nemanja B. Martić, Jovana D. Jančić, Milica M. Paut Kusturica, Nikola B. Martić, Aleksandar L. Rašković, Gordana M. Vilotijević-Dautović, Tanja D. Radovanović, Marija V. Đermanović, Slobodan D. Spasojević

Poster 9 **Značaj fiksnih kombinacija u terapiji hipertenzije**
The importance of fixed-dose combinations in therapy of hypertension
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Sekcija za kliničku farmakologiju „dr Srđan Đani Marković”
Srpsko lekarsko društvo

ZBORNIK SAŽETAKA

BOOK OF ABSTRACTS

HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

Šesnaest godina rada Sekcije za kliničku farmakologiju „dr Srđan Đani Marković" Srpskog lekarskog društva

Dragana Maca A. Kastratović[1a], Srdjan Z. Marković[1a], Slobodan M. Janković[1b], Boris Ž. Milijašević[1c], Radmila M. Veličković-Radovanović[1d], Momir M. Mikov[1c], Mira H. Vuković[1e], Branka M. Terzić[1a], Viktorija M. Dragojević-Simić[1a], Biljana P. Radojević[1a], Aleksandar L. Rašković[1c], Ivana Miličević[1f], Snežana Panić[1g], Olga J. Horvat[1c], Dejana T. Ružić-Zečević[1b], Ivana P. Timotijević-Marković[1a], Dane A. Krtinić[1d]

[1] Sekcija za Kliničku farmakologiju „dr Srđan Đani Marković" Srpskog lekarskog društva: [a]Beograd, [b]Kragujevac, [c]Novi Sad, [d]Niš, [e]Valjevo, [f]Užice, [g]Kruševac

Sekcija za kliničku farmakologiju Srpskog lekarskog društva (SKFSLD) osnovana je 19. februara 2009., sa ciljem da implementira i unapredi bolničku primenu znanja kliničke farmakologije u sve medicinske oblasti. Na predlog Predsedništva i Naučnog odbora SKFSLD uz jednoglasnu podršku Predsedništva SLD ustanovljena je godišnja nagrada za primenjenu bolničku farmakologiju „dr Srđan Đani Marković". Nagrada je jednoglasnom odlukom Predsedništva i Naučnog odbora SKFSLD dodeljena za 2020. dr Srdjanu Djaniju Markoviću - našem Sekretaru, istraživaču lekaru, ECRIN correspodentu i monitoru, idejnom ocu i članu Uređivačkog odbora stručno - naučnog časopisa Hospital Pharmacology – International Multidisciplinary Journal. Za 2021. godinu godisnja nagrada za primenjenu bolničku farmakologiju „dr Srđan Đani Marković" je jednoglasnom odlukom Predsedništva i Naučnog odbora SKFSLD dodeljena prof prim dr Slobodanu Jankoviću – našem Predsedniku naučnog odbora SKFSLD, članu Uređivačkog stručno - naučnog časopisa Hospital Pharmacology – International Multidisciplinary Journal, osnivač i rukovodilac bolničke kliničke farmakologije kliničkog centra Kragujevac, rukovodiocu i istraživaču u više od 100 međunarodnih i nacionalnih naučnih projekata, autoru više od 600 naučnih radova i visokog ranga citiranosti, mentoru velikog broja doktorskih disertacija. Za 2022 godinu nagrada za primenjenu bolničku farmakologiju „dr Srđan Đani Marković" je jednoglasnom odlukom Predsedništva i Naučnog odbora SKFSLD dodeljena prof dr Borisu Milijaševiću – našem sekretaru Sekcije, izvršnom uredniku stručno-naučnog časopisa Hospital Pharmacology – International Multidisciplinary Journal, rukovodiocu i istraživaču u projektima farmakoekonomije i farmakogenetike, kolegi koji postojano doprinosi razvoju bolničke kliničke farmakologije kroz izuzetan pedagoški rad sa studentima. Za 2023 nagrada za primenjenu bolničku farmakologiju „dr Srdjan Djani Marković" jednoglasnom odlukom Predsedništva i Naučnog odbora naše sekcije dodeljena je Prim dr Miri Vuković, članu Uredjivačkog odbora naučnog časopisa Hospital Pharmacology – International Multidisciplinary Journal, koja je svojim radom u Zdravstvenom centru Valjevo kao lekar, naučnik i menadžer ostvarila zapažene rezultate.

Tokom ovih 16 godina članovi SKF „Dr Srdjan Đani Marković" radili su veoma vredno kroz:

1. Kontinuiranu medicinsku edukaciju. Kursevi su akreditvani kao Prva kategorija kod Zdravstvenog saveta Srbije, sto je slušaocima donelo maksimalan broj poena u Lekarskoj komori Srbije za licencu za rad. Kursevi su namenjeni lekarima, farmaceutima, ekolozima, biohemičarima, tehničarima.
2. Simpozijume Nedelja Bolnićke kliničke farmakologije I-XVI. Tema Simpozijuma je Integracija nauke i prakse, učesnici izlažu svoje radove kroz usmene prezentacije, postere, okrugle stolove, komercijalna predavanja, 2020-22 on line. Svake godine učestvuje oko 100 lekara svih medicinskih specijalnosti, farmaceuta, biohemičara. Gosti predavači bile su kolege iz Francuske, USA, Nemačke, Grčke, Bugarske, Austrije.
3. Predavanja po pozivu u saradnji sa Akademijom medicinskih nauka, održali su: Prof Dr David T. W. Wong (USA), Primarius Dragana Maca Kastratović, Prof Dr Edoardo Spina (Italy), Prof Dr Jacques Demotes Mainard (France), Prof Pharm Christine Kubiak (France), Emil Miltchev Gatchev (Bulgaria), Vangelis G. Manolopoulos (Greece), Markus Zeitlinger (Austria), itd. Tokom 2022 nije bilo predavanja po

pozivu iz inostranstva. Predavači po pozivu iz Republike Srbije su redovni učesnici Simpozijuma NBKF.
4. Naučno-stručni časopis pokrenuli smo 2014. na predlog Dr Srdjana Djanija Markovića, kao online, open access, free full text Hospital Pharmacology International Multidisciplinary Journal, dostupan na http://www.hophonline.org.
5. Uspesi. Tokom ovih 16 godina svi lekari SKFSLD postizali su značajne uspehe na radnim mestima, kroz doktorske disertacije, akademske/profesionalne pozicije. Profesori Momir Mikov, Radmila Veličković-Radivojević, Ivana Timotijević-Marković, Mihajlo Jakovljević primljeni su u AMNSLD. Profesor Primarijus Slobodan Jankovic postao je clan Akademije medicinskih nauka BIH. Nagradu za izuzetna ostvarenja u bolničkoj farmakologiji dobili su Dr Srdjan Djani Marković za 2020, Prof Prim dr Slobodan Janković za 2021. godinu, Prof dr Boris Milijašević za 2022., Prim dr Mira Vuković za 2023.
6. The Pharmacology International, časopis IUPHAR-a, više puta je objavljivao tekstove o radu SKFSLD.
7. Ostvarenje razvoja kliničke farmakologije i dalje će ići kroz KME, podršku mlađim lekarima da uče kliničku farmakologiju i primene znanja u bolnicama. Podstičemo kolege da svoje stručno-naučne rezultate publikuju u stručno-naučnom časopisu Hospital Pharmacology – International Multidisciplinary Journal. Starije kolege razvijaće i nadalje nacionalnu i međunarodnu saradnju u oblasti primenjene nauke, sa naglaskom na uključivanje mlađih kolega u multidisciplinarne timove.

Sixteen years of activity of the Section for Clinical Pharmacology „dr Srdjan Djani Marković" of the Serbian Medical Society

Dragana Maca A. Kastratović[1a], Srdjan Z. Marković[1a], Slobodan M. Janković[1b], Boris Ž. Milijašević[1c], Radmila M. Veličković-Radovanović[1d], Momir M. Mikov[1c], Mira H. Vuković[1e], Branka M. Terzić[1a], Viktorija M. Dragojević-Simić[1a], Biljana P. Radojević[1a], Zoran M. Todorović[1a], Aleksandar L. Rašković[1c], Ivana Miličević[1f], Snežana Panić[1g], Olga J. Horvat[1c], Dejana T. Ružić-Zečević[1b], Ivana P. Timotijević-Marković[1a]

[1] Section for Clinical Pharmacology „dr Srđan Đani Marković" of the Serbian Medical Society: [a]Belgrade, [b]Kragujevac, [c]Novi Sad, [d]Niš, [e]Valjevo, [f]Užice, [g]Kruševac

The Section for Clinical Pharmacology „Dr Srdjan Djani Marković" of the Serbian Medical Association was established on February 19, 2009, with the aim of implementing and improving the hospital application of knowledge of clinical pharmacology in all medical fields.

At the suggestion of the Presidency and the Scientific Committee of the CCPSMS, with the unanimous support of the Presidency of the SMS, the annual award for applied hospital pharmacology „dr Srdjan Djani Marković" was established. The award was given by a unanimous decision of the Presidency and the Scientific Committee of SCPSMS for 2020 to Dr Srdjan Djani Markovic - our Secretary, researcher, doctor, ECRIN correspondent and monitor, the father of the launch and a member of the Editorial Board of the scientific journal Hospital Pharmacology - International Multidisciplinary Journal (www.hophonline.org). For the year 2021, the annual award „Dr Srdjan Djani Marković" was awarded by a unanimous decision of the Presidency and the Scientific Board of the SKFSLD to Prof. Dr. Slobodan Janković - our President of the Scientific Board, a member of the editorial professional and scientific journal Hospital Pharmacology - International Multidisciplinary Journal, founder and head of Cenre for hospital clinical pharmacology of the University Clinical Center Kragujevac, principal investigator and researcher in more than 100 international and national scientific projects, author of more than 600 scientific papers with high citation rank, mentor of a large number of doctoral dissertations. For the year 2022, the award for Applied Hospital Pharmacology „Dr. Srđan Đani Marković" was awarded by a unanimous decision of the Presidency and the Scientific Board of SKFSLD to Prof. Borisu Milijašević MD, executive editor of the scientific journal Hospital Pharmacology - International Multidisciplinary Journal, manager and researcher in pharmacoeconomics and pharmacogenetics projects, a colleague who constantly contributes to the development of hospital clinical pharmacology through exceptional pedagogical work with students. For the year 2023, the award for Applied Hospital Pharmacology „Dr. Srđan Đani Marković" was awarded by a unanimous decision of the Presidency and the Scientific Board of SKFSLD to Prim Miri Vuković MD, editorial board member of the scientific journal Hospital Pharmacology - International Multidisciplinary Journal, manager and researcher in the Health Center Valjevo.

During these 16 years, the members of SCPSMA have worked very hard through:

1. Continuous medical education. The courses were accredited as the first category with the Health Council of Serbia, which brought the students the maximum number of points in the Medical Chamber of Serbia for a work license. The courses are intended for doctors, pharmacists, biochemists, technicians.
2. Symposiums Week of Hospital Clinical Pharmacology I-XVI. The topic of the Symposium is the inte gration of Science and Practice, participants present their works through oral presentations, posters, round tables, commercial lectures, 2020 on line. About 100 doctors of all medical specialties, pharmacists and biochemists participate every year. Guest lecturers were colleagues from France, USA, Germany, Greece, Bulgaria, Austria.
3. Lectures by invitation in cooperation with the Academy of Medical Sciences, were held by: Prof. Dr. David TW Wong (USA), Primarius Dragana Maca Kastratović, Prof. Dr. Edoardo Spina (Italy), Prof. Dr.

Jacques Demotes Mainard (France), Prof. Pharm Christine Kubiak (France), Emil Miltchev Gatchev (Bulgaria), Vangelis G. Manolopoulos (Greece), Markus Zeitlinger (Austria), etc. During 2022, there were no lectures by invitation from abroad. Lecturers invited from the Republic of Serbia are participants in the Symposium.

4. Based on the idea of Dr Srdjan Djani Markovic the scientific-professional journal SCPSMS was launched in 2014, as an online, open access, free full text Hospital Pharmacology International Multidisciplinary Journal, available at http://www.hophonline.org.

5. Successes. During these 16 years, all SCPSMA physicians have achieved significant success in the workplace, through doctoral dissertations, academic / professional positions. Professors Momir Mikov, Radmila Veličković Radivojević, Ivana Timotijević Marković, Mihajlo Jakovljević were admitted to the AMNSLD. Professor Primarius Slobodan Jankovic became a member of the Academy of Medical Sciences of BiH. The award for outstanding achievements in hospital pharmacology was awarded to Dr Srdjan Djani Marković for 2020, Prof. Prim. Dr Slobodan Janković for 2021, Prof Dr Boris Milijašević for 2022, Prim Dr Mira Vuković for 2023.

6. The Pharmacology International, a journal of IUPHAR, has repeatedly published articles on the work of SCP „Dr Srdjan Djani Marković" Serbian Medical Society.

7. The realization of the development of clinical pharmacology will continue to go through KME, supporting junior doctors to learn clinical pharmacology and applying knowledge in hospitals. We encourage colleagues to publish their professional-scientific results in the professional-scientific journal Hospital Pharmacology - International Multidisciplinary Journal. Senior colleagues will continue to develop national and international cooperation in the field of applied science, with an emphasis on the inclusion of younger colleagues in multidisciplinary teams.

Terapija malignih bolesti T-ćelijama sa himernim receptorom za tumorski antigen (CAR T-ćelije)

Slobodan M. Janković

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Terapija malignih oboljenja T-ćelijama sa himernim receptorom za tumorski antigen (CAR T-ćelijska terapija) se sastoji od preuzimanja T-limfocita iz organizma bolesnika, unošenja u njih gena za himerni receptor za tumorski antigen, umnožavanja tako modifikovanih limfocita i njihove intravenske infuzije posle limfodeplecije zračenjem ili hemioterapijom. Tako izmenjeni T-limfociti se sada vezuju za maligne ćelije preko himernog receptora, aktiviraju se i ubijaju malignu ćelije. T-limfocit biva aktiviran nezavisno od glavnog kompleksa histokompatibilnosti (MHC) ili humanog leukocitnog antigena (HLA). Od T-limfocita najčešće se u CAR T-preparatima nalaze CD4+, CD8+ i memorijske T-ćelije.

Za sada postoji 5 generacija himernog receptora, koje se razlikuju primarno prema intraćelijskom delu. Prva generacija nije imala kostimulatorni molekul, dok druga generacija ima i kostimulatorni molekul i CD3zeta koreceptor. Treća generacija pored CD3zeta koreceptora ima dva kostimulatorna molekula. Četvrta generacija ima CD3zeta koreceptor, jedan kostimulatorni molekul i nuklearni faktor aktivirane T-ćelije. Najzad, peta generacija ima i deo receptora za interleukin 2.

Tisagenlecleucel, akicabtagen ciloleucel, breksukabtagen autoleucel i lisokabtagen maraleucel su autologne CAR T-ćelijske terapije usmerene na CD19 koji su pokazale odličnu efikasnost kod pacijenata sa malignitetima poreklom od B-limfocita (akutna limfoblasta leukemija i limfomi). Ciltacabtagene autoleucel i Idecabtagene vicleucel su odobreni za lečenje multiplog mijeloma rezistentnog na ciljanu i imunoterapiju.

Therapy of malignant diseases with T-cells having chimeric receptor for tumor antigen (CAR T-cells)

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Therapy of malignant diseases with T-cells with a chimeric tumor antigen receptor (CAR T-cell therapy) consists of taking T-lymphocytes from the patient's body, introducing into them the gene for a chimeric tumor antigen receptor, multiplying the lymphocytes thus modified and their intravenous infusion after lymphodepletion by radiation or chemotherapy. The modified T-lymphocytes now bind to the malignant cells via a chimeric receptor, activate and kill the malignant cells. The T-lymphocyte is activated independently of the major histocompatibility complex (MHC) or human leukocyte antigen (HLA). Of the T-lymphocytes, CD4+, CD8+ and memory T-cells are most often found in CAR T-preparations.

For now, there are 5 generations of chimeric receptors, which differ primarily according to the intracellular part. The first generation did not have a costimulatory molecule, while the second generation has both a costimulatory molecule and a CD3zeta coreceptor. The third generation has two costimulatory molecules in addition to the CD3zeta coreceptor. The fourth generation has the CD3zeta coreceptor, one costimulatory molecule and the nuclear factor of activated T-cell. Finally, the fifth generation has a part of the receptor for interleukin 2.

Tisagenlecleucel, acicabtagen ciloleucel, brexucabtagen autoleucel and lisocabtagen maraleucel are autologous CD19-directed CAR T-cell therapies that have shown excellent efficacy in patients with B-lymphocyte-derived malignancies (acute lymphoblastic leukemia and lymphomas). Ciltacabtagene autoleucel and Idecabtagene vicleucel are approved for the treatment of multiple myeloma resistant to targeted and immunotherapy.

Savremena terapija srčane insuficijencije

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Uvod: Pored dostupnosti utvrđenih tretmana, srčana insuficijencija je i dalje povezana sa lošom prognozom i njegova terapija je suboptimalna, što naglašava potrebu za novim opcijama za lečenje i prevenciju. U skorije vreme identifikovani su patofiziološki mehanizmi koji predstavljaju novo potencijalno target mesto za lekove, kao što su valsartan-sakubitril, SGLT-2 inhibitori, ivabradin, vericiguat i omecamtiv mecarbil

Cilj: Cilj našeg rada bio je da analiziramo dostupnost, troškove lečenja, kao i potrošnju novijih lekova u terapiji srčane insuficijencije.

Materijal i metode: Istraživanje je sprovedeno sistematskom analizom literature uvidom u online baze podataka Google Scholar, PubMed i SCIndeks korišćenjem ključnih reči poput „savremena terapija srčane insuficijencije", „ARNi", „SGLT2 inhibitori", „ivabradin", „vericiguat", „omecamtiv mecarbil" i dr. Informacije o dostupnosti, cenama i potrošnji lekova dobijene su pretragom zvaničnog sajta Republičkog fonda za zdravstveno osiguranje (RFZO), kao i zvanično sajta Agencije za lekove i medicinska sredstva (ALIMS) Republike Srbije.

Rezultati: Glavni rezultati prikazuju godinu registracije, troškove lečenja po pacijentu na dnevnom, nedeljnom, mesečnom i godišnjem nivou, kao i potrošnju valsartan-sakubitrila, dapagliflozina, empagliflozina, ivabradina i vericiguata.

Zaključak: Od novije terapije srčane insuficijencije u Republici Srbiji dostupni su valsartan-sakubitril, dapagliflozin, empagliflozin, ivabradin i vericiguat. Oni predstavljaju skuplju alternativu u odnosu na standardnu terapiju, naročito valsartan-sakubitril, čija je cena po pacijentu 50 puta veća u odnosu na enalapril (179.612,85 RSD vs 3.591,60 RSD na godišnjem nivou), ali njihova potrošnja se svakako povećava iz godine u godinu.

Ključne reči: srčana insuficijencija; ARNi, SGLT-2 inhibitori, ivabradin, vericiguat, omecamtiv mecarbil

Modern treatment of heart failure

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Introduction: Heart failure is a serious health issue, characterized by poor prognosis and suboptimal therapy, highlighting the urgent need for new treatment and prevention options. Recent advances in understanding the pathophysiological mechanisms of the disease have opened the door to new therapeutic approaches, including medications such as valsartan-sacubitril, SGLT-2 inhibitors, ivabradine, vericiguat, and omecamtiv mecarbil.

Goal: The aim of our study was to analyze the availability, treatment costs, and consumption of newer drugs in the therapy of heart failure.

Material and methods: The research was conducted through a systematic literature review using online databases such as Google Scholar, PubMed, and SCIndeks. Keywords used for the search included „modern therapy for heart failure", „ARNi", „SGLT-2 inhibitors", „ivabradine", „vericiguat" and „omecamtiv mecarbil". Data on availability, prices, and consumption of medications were obtained from the official websites of the Republic Fund for Health Insurance (RFZO) and the Agency for Medicines and Medical Devices (ALIMS) of the Republic of Serbia.

Results: The analysis of results presents the year of registration, treatment costs per patient on a daily, weekly, monthly, and yearly basis, as well as the consumption of medications such as valsartan-sacubitril, dapagliflozin, empagliflozin, ivabradine and vericiguat.

Conclusion: In the Republic of Serbia, the available newer therapies for heart failure include valsartan-sacubitril, dapagliflozin, empagliflozin, ivabradine, and vericiguat, while omecamtiv mecarbil is not approved anywhere in the world. These drugs represent a more expensive alternative compared to standard therapy, particularly valsartan-sacubitril, which costs 50 times more per patient than enalapril (179,612.85 RSD vs 3,591.60 RSD annually), but their consumption is certainly increasing year by year.

Key words: heart failure, ARNi, SGLT-2 inhibitors, ivabradine, vericiguat, omecamtiv mecarbil

Kognitivna stimulacija i emocionalna trankilizacija depresivnosti aktivacijom retikularnog sistema

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Značajna struktura koja reprodukuje bazične, fundamentalne manifestacije normalnog i patološkog humanog habitusa jeste Retikularni aktivirajući sistem (RAS), deo mozga koji igra ključnu ulogu u regulaciji budnosti, pažnje, svesti i spavanja. Nalazi se u moždanom stablu, tačnije u produženoj moždini i srednjem mozgu. RAS je mreža nervnih ćelija i vlakana koja prenose senzorne informacije do kore velikog mozga, pomažući osobi da se fokusira na važne podražaje dok filtrira nevažne.
RAS je ključan za svakodnevno funkcionisanje, jer omogućava mozgu da filtrira ogromnu količinu informacija i obradi samo one koje su relevantne.
I linija: NA (noradrenalin) i 5-HT (Serotonina) sa efektom –
CEREBRALNI CORTEX (kognitivne funkcije)
PREFRONTALNI, FRONTALNI (Pažnja, Memorija, Učenje)
Kognitiuvna relaksacija
II linija: NA, 5HT, DA, Ach-
LIMBIČKI SISTEM (emocije raspoloženje) HIPOCAMPUS (Emocije, Pažnja, Pamčenje) AMIGDALA (Emocije, Pamćenje) HIPOTHALAMUS (Endokrini sistem, Sistem nagrade Bihebioralni sis) MOZAK I SRCE
Emocionalna trankilizacija
Očekivani terapijski efekti se najčešće vezuju za mehanizme delovanja lekova, strukture CNS u kojima se u najvećoj meri odvijaju agonistička i antagonistička dejstva na receptore, ključne strukture prefrontalne kore CNS, hipokampusa i amigdaloidnih jedara. **Svakako ne treba zanemariti ulog RAS, jer psihofarmaci sa dejstvom na tom nivou značajno deluju kod afektivnih i kognitivnih simptoma u širokom spektru mentalnih poremećaja**.

Cognitive stimulation and emotional tranquilisation of depression by activation of the reticular system

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An important structure that reproduces the basic, fundamental manifestations of normal and pathological human habitus is the Reticular Activating System (RAS), a part of the brain that plays a key role in the regulation of wakefulness, attention, consciousness and sleep. It is located in the brain stem, more precisely in the medulla oblongata and midbrain. The RAS is a network of nerve cells and fibers that carry sensory information to the cerebral cortex, helping a person focus on important stimuli while filtering out unimportant ones. The RAS is crucial for everyday functioning, as it allows the brain to filter the vast amount of information and process only those that are relevant.

I line: NA (noradrenaline) and 5-HT (Serotonin) with effect -
CEREBRAL CORTEX (cognitive functions)
PREFRONTAL, FRONTAL (Attention, Memory, Learning)
Cognitive relaxation

II line: NA, 5HT, DA, Ach- LIMBIC SYSTEM (Emotions Mood) HIPPOCAMPUS (Emotions, Attention, Memory) AMYGDALA (Emotions, Memory) HYPOTHALAMUS (Endocrine System, Reward System Behavioral System) BRAIN AND HEART.
Emotional tranquilization

The expected therapeutic effects are most often related to the mechanisms of drug action, the structures of the CNS in which the agonistic and antagonistic effects on receptors take place to the greatest extent, the key structures of the prefrontal cortex of the CNS, the hippocampus and the amygdaloid nuclei. **We should certainly not ignore the role of RAS, because psychopharmaceuticals with effects at that level have a significant effect on affective and cognitive symptoms in a wide range of mental disorders**.

Antikoagulantna terapija u hronićnoj bubrežnoj bolesti

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Hronična bubrežna bolest (HBB) je veliki globalni problem javnog zdravlja, često komplikovana kardiovaskularnim morbiditetom i povećavanim rizikom od tromboembolijskih događaja i krvarenja. Pacijenti sa HBB 4-5. stepena su često isključeni iz kontrolisanih randomizovanih studija zbog čega ne postoje validni dokazi i preporuke o efikasnosti i bezbednosti oralne antikoagulantne terapije(OAK). Ne postoji jedinstven konsenzus o preporukama za OAK, posebno u HBB 4-5. stepena. Dokazi iz randomizovanih kontrolisanih ispitivanja podržavaju efikasnu i bezbednu upotreba varfarina i direktnih oralnih antikoagulansa (DOAC) kod blage i umerene HBB. Naprotiv, podaci su nevalidni i kontroverzni za HBB 4-5. stepena. DOAC se preporučuju u HBB stepen 1 do 3. Kod pacijenata sa HBB stepen 4. izbor je varfarin u odnosu na DOAC, uzimajući u obzir farmakokinetiku lekova i karakteristike pacijenta. Varfarin je prva linija terapije u terminalnoj fazi bubrežne bolesti, mada je odluka o upotrebi ili neupotrebi antikoagulanasa strogo individualna. Primena heparina je bezbedna kod bubrežnih bolesnika koji ne zahtevaju dijalizno lečenje, ali ostaje izazov kod pacijenata na hemodijalizi.

Postoji potreba za kardiorenalnim konsenzusom u primeni antikoagulantne terapije u HBB. Adekvatan izbor oralnog antikoagulansa i pažljiv monitoring su izuzetno korisne mere za optimalnu terapiju.

Ključne reči: hronična bubrežna bolest, direktni oralni antikoagulansi, varfarin, heparin

Anticoagulation in chronic kidney disease

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Chronic kidney disease (CKD) is a major global public health problem, being closely connected to cardiovascular disease. CKD involves an elevated thromboembolic risk and requires anticoagulation, but the high rates of hemorrhage render it quite challenging. There are no consensus recommendations regarding oral anticoagulation in CKD. Due to the currently limited data, clinicians need practical clues for monitoring and optimizing the treatment. Evidence from randomized controlled trials supports the efficient and safe use of warfarin and direct oral anticoagulants (DOACs) in mild and moderate CKD. On the contrary, the data are poor and controversial for advanced stages. DOACs are preferred in CKD stages 1 to 3. In patients with stage 4 CKD, the choice of warfarin vs DOACs will take into consideration the pharmacokinetics of the drugs and patient characteristics. Warfarin remains the first-line treatment in end-stage renal disease, although in this case the decision to use or not to use anticoagulation is strictly individualized. Anticoagulation with heparins is safe in nondialysis-dependent CKD, but remains a challenge in the hemodialysis patients.

Although there is a need for cardiorenal consensus regarding anticoagulation in CKD, adequate selection of the anticoagulant type and careful monitoring are some extremely useful indications for overcoming management challenges.

Key words: chronic kidney disease, direct oral anticoagulants, heparin, warfarin

Tardivne diskinezije kod pacijenata na terapiji antipsihoticima

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Tardivne diskinezije (TD) su „kasno" ili „odloženo" „abnormalno kretanje". Najčšća manifestacija TD je bukolinguomastikatorni sindrom (lice i jezik).

Ređi tardivni poremećaji kretanja su tardivna distonija (uvijanje i savijanje), tardivna horea (izgleda kao igra), tardivni turetizam (izgleda kao Tourette-ov sindrom), tardivni tremor ili mioklonus, kao i akatizija (uznemirenost), bol (oralna i genitalna regija), respiratorne negularnosti.

Nevoljni pokreti otežavaju govor i uzimanje hrane. Oni su povezani sa stresom, lošom terapijskom adherencom i smanjenjem kvaliteta života.

Incidenca TD je ~5% godišnje tokom hroničnog lečenja, obično >3 meseca, često godinama. Kod starijih pacijenata i žena je prisutan veći rizik od pojave TD. Drugi faktori rizika su dužina lečenja, doze lekova, povreda mozga, diabetes mellitus, poremećaji raspoloženja.

Uzroci pojave TD su najčešće lekovi koji se koriste u lečenju shizofrenije i drugih psihijatrijskih poremećaja-tipični antipsihotici (TA) (fenotijazini, butirofenoni, benzamidi), kao i atipični antipsihotici (AA) (risperidon, olanzapin).

Kod primene AA je incidenca TD i ekstrapiramidnih neželjenih efekata manja u odnosu na TA zbog njihovog nižeg afiniteta za dopaminske D2 receptore u dorzalnom striatumu i prateće blokade serotoninskih 5-HT2A/2C receptora.

Antidepresivi (triciklični i serotonergični antidepresivi), kao i litijum i drugi lekovi (flunarizin, antiemetici, antibiotici), takođe mogu izazvati pojavu TD. TD je povezana sa polimorfizmima dopamin D3 receptora Ser9Gli kao i genima receptora serotonina 2A i 2C.

Najbolja strategija redukcije TD je prevencija, koja podrazumeva primenu antipsihotika za specifine indikacije, najmanje moguće efektivne doze u najkraćem mogućem vremenskom periodu, kao i izbegavanje upotrebe antiholinergičke medikacije.

Kada su TD umerene ili dovode do značajnog kliničkog pogoršanja, preporučuju se prema smernicama, VMAT2 (Vezikularni monoaminski transporter 2) inhibitor valbenazin ili deutetrabbenazin.

Tardive dyskinesia in patients on antipsychotic therapy

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Tardive Dyskinesia (TD) are „late" or „delayed" „abnormal movement". The most common manifestation of TD is buccolinguomasticatory syndrome (face and tongue). Less common tardive movement disorders are tardive dystonia (twisting and bending), tardive chorea (looks like dancing), tardive tourettism (looks like Tourette syndrome), tardive tremor or myoclonus. Other tardive syndromes are akathisia (restlessness), pain (oral or genital regions), respiratory irregularity.

Involuntary movements make it difficult to speak and take food. There are associated with stress, poor therapeutic adherence and a decrease in quality of life.

Incidence of TD is ~5% per year during chronic treatment. Treatment duration is usually >3 months, often years. Elderly patients and women are at higher risk of developing TD. Other risk factors are treatment duration, dose, brain injury, diabetes mellitus, mood disorder.

The causes of the appearance of TD are the most often drugs which are used in the treatment of schizophrenia and other psychiatric disorders-typical antipsychotics (TA) (phenothiazines, butyrophenones, benzamides), as well as atypical antipsychotics (AA) (risperidone, olanzapine).

With the use of atypical AA, the incidence of TD and extrapyramidal adverse effects is lower in relation to TA due to their lower affinity for dopamine D2 receptors in the dorsal striatum and concomitant blockade of serotonin 5-HT2A/2C receptors.

Antidepressants (tricyclic and serotonergic antidepressants) as well as lithium and other drugs (flunarizine, antiemetics, antibiotics) also can cause TD. TD has been associated with polymorphisms dopamine D3 receptor Ser9Gly as well as the serotonin 2A and 2C receptor genes.

The best strategy for reducing TD is prevention, which involves the use of antipsychotics for specific indications, the lowest possible effective dose for the shortest possible period of time, and the avoidance of the use of anticholinergic medication.

When TD are moderate or lead to considerable clinical deterioration, VMAT2 (Vesicular Monoamine Transporter 2) inhibitor valbenazine or deutetrabenazine are recommended according to the guidelines.

Značaj palimitoiletanolamida u terapiji bolnih stanja

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Palmitoiletanolamid (PEA) je endogeni amid palmitinske kiseline sličan endokanabinoidnom anandamidu (endogeni kanabinoidni neurotransmiter) i poseduje sposobnost da inhibira oslobađanje medijatora zapaljenja iz aktiviranih mastocita i da smanji infiltraciju i aktivaciju na mestu povrede nerava. Efikasnost PEA pri postojanju simptoma hroničnog i neuropatskog bola potvrđena je u više od 30 kliničkih istraživanja sa preko 6000 pacijenata. Koncept da lipidni N-aciletanolamini kao PEA deluju autokoidnim mehanizmom prvi put je predložila Rita Levi-Montalcini, dobitnik Nobelove nagrade, dokazavši da se PEA sintetiše kao posledica povrede ili upale kako bi se organizam izborio sa ovim patološkim stanjem. PEA ispoljava svoje efekte tako što smanjuje migraciju i degranulaciju mastocita, privlačenje neutrofila i prekomernu aktivaciju astrocita i glijalnih ćelija, te se mastociti i glijalne ćelije transformišu iz aktiviranih imunih ćelija u ćelije u mirovanju. PEA smanjuje ekspresiju proinflamatornih enzima kao što su COX-2 i proinflamatornih citokina: IL-1, prostaglandin E2 i TNF-α. Takođe, ispoljava afinitet prema vaniloidnom receptoru TRPV1, koji se smatra molekulskim vratima bola i nuklearnom receptoru PPAR-α, čija aktivacija dovodi do inhibicije proinflamatornog signalnog puta posredstvom nuklearnog faktora NF-κβ. PEA se oslobađa paralelno sa anandamidom iz uobičajenog prekursora fosfolipida i ispoljava afinitet prema kanabinoidnim receptorima GPR55 i GPR119 i konkuriše endogenom opioidu anandamidu za degradaciju od strane enzima hidrolaze amida masne kiseline (MAAH), povećavajući na taj način nivo anandamida, pa se ponekad naziva i kanabinomimetikom. Dokazana je efikasnost ovog molekula od dijabetesne polineuropatije, preko fizijatrijskih i reumatoloskih indikacija, pa sve do terapije polineuropatije malignog porekla.

The importance of palimitoylethanolamide in the treatment of painful conditions

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Palmitoylethanolamide (PEA) is an endogenous palmitic acid amide similar to the endocannabinoid anandamide (an endogenous cannabinoid neurotransmitter) and possesses the ability to inhibit the release of inflammatory mediators from activated mast cells and to reduce infiltration and activation at the site of nerve injury. The effectiveness of PEA in the presence of symptoms of chronic and neuropathic pain has been confirmed in more than 30 clinical studies with over 6000 patients. The concept that lipid N-acylethanolamines as PEA act by an autocoidal mechanism was first proposed by Rita Levi-Montalcini, winner of the Nobel Prize, proving that PEA is synthesized as a result of injury or inflammation in order for the body to cope with this pathological condition. PEA exerts its effects by reducing mast cell migration and degranulation, neutrophil attraction, and excessive activation of astrocytes and glial cells, and mast cells and glial cells transform from activated immune cells to resting cells. PEA reduces the expression of pro-inflammatory enzymes such as COX-2 and pro-inflammatory cytokines: IL-1, prostaglandin E2 and TNF-α. It also exhibits an affinity for the vanilloid receptor TRPV1, which is considered the molecular gate of pain, and the nuclear receptor PPAR-α, the activation of which leads to the inhibition of the pro-inflammatory signaling pathway through the nuclear factor NF-κβ. PEA is released in parallel with anandamide from a common phospholipid precursor and exhibits affinity for the cannabinoid receptors GPR55 and GPR119 and competes with the endogenous opioid anandamide for degradation by the enzyme fatty acid amide hydrolase (MAAH), thereby increasing anandamide levels, and is sometimes referred to as a cannabinomimetic. The effectiveness of this molecule has been proven from diabetic polyneuropathy, through physiatry and rheumatological indications, up to the treatment of polyneuropathy of malignant origin.

Menadžment primene transfuzije krvi pacijentu u vanrednim uslovima

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Menadžment primene transfuzije krvi pacijentu (PBM) je multidisciplinarni multimodalni pristup usredsređen na pacijenta dizajniran da svede na minimum upotrebu alogenih komponenti krvi kako bi se poboljšao klinički ishod lečenja pacijenata.

PBM se sastoji od 3 glavna stuba/postulata sa kliničkim ciljevima: 1) Prvi stub: povećanje mase crvenih krvnih zrnaca uključujući kliničku farmakološku korekciju kao što su agensi za stimulaciju eritropoeze - gvožđe i drugi lekovi i optimizacija vremena za hirurišku intervenciju u odnosu na postizanje potrebne vrednosti hemoglobina; 2) Drugi stub: minimizirati gubitak krvi adekvatnim izborom hirurških i anesteziooloških tehnika, tretmanom traneksamičnom kiselinom (TxA) i autolognim spasavanjem krvi i upotrebom krvnih zamena, odnosno perfluorougljenika kao transportera kiseonika, 3) Treći stub: povećanje tolerancije pacijenata na anemiju kroz maksimalno poboljšanje plućne i srčane funkcije, optimizaciju ventilacije, oksigenaciju i restriktivnu primenu komponenti krvi. Klinička farmakologija primenjena u bolničko-bolničkoj farmakologiji je pomoćna grana medicine koja poboljšava ishode lečenja i ponekad može anterogradno da ukaže na promenu u dijagnozi bolesti.

Vanredne situacije koje mogu uticati na uspešnu transfuziju uključuju elementarne vremenske nepogode, seizmičke događaje, vanredne masovne zdravstvene situacije čime je znatno smanjen broj dobrovoljnih davalaca krvi što sve zajedno dovodi do raspolaganja nedovoljnim brojem jedinica krvi. PBM u vanrednim situacijama podrazumeva brzo delovanje usled otežane nabavke labilnih komponenta krvi i oslanja se na stabilne produkte od krvi (krvne derivate) i farmakološku intervenciju (TXA, perfluorougljenici). U organizacionoj šemi ne treba ispustiti deo vezan za transport krvi na teško pristupačnim terenima, uključujući i savremenu tehnologiju korišćenja dronova za transport krvi.

Dobro uigrani transfuziološki timovi u redovnim uslovima rada treba da ovladaju dobrom organizacijom netvorka davalaca i zdravstvenih radnika kako bi snabdevanje krvlju zadovoljilo potrebe u vanrednim uslovima.

Patient blood management in Natural Hazards and Emergency Situationst

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Patient blood management (PBM) is a multidisciplinary multimodal patient-centered approach designed to minimize the use of allogeneic blood components in order to improve the clinical outcome of patient treatment.

PBM consists of 3 main pillars with clinical goals:1) First pillar: increasing red cell mass including clinical pharmacological correction such as erythropoiesis stimulating agents - iron and another drugs, and optimizing the time for surgical intervention in relation to achieving the required hemoglobin value; 2) Second pillar: minimize blood loss through an adequate selection of surgical and anesthetic techniques, treatment with tranexamic acid (TXA) and autologous blood salvage, and the use of blood substitutes, i.e. perfluorocarbons as oxygen transporters, 3) Third pillar: increasing the patient's tolerance to anemia through maximum improvement of pulmonary and cardiac function, optimizing ventilation, oxygenation and restrictive application of blood components. Clinical pharmacology applied in hospitalshospital pharmacology is a supportive branch of medicine that improves the outcomes of treatment and can sometimes anterograde indicate a change in the diagnosis of the disease.
Emergency situations that can affect a successful transfusion include natural disasters, seismic events, mass health emergencies, which significantly reduce the number of voluntary blood donors, which together lead to the availability of insufficient numbers of blood units.

PBM in emergency situations implies rapid action without possible procurement of labile blood components and relies on stable blood products (blood derivatives) and pharmacological intervention (TXA, perfluorocarbons). In the organizational scheme, the part related to blood transport in hard-to-reach areas should not be omitted, including the modern technology of using drones for blood transport.

Well-coordinated transfusion teams in regular working conditions should master the good organization of the network of donors and health workers in order to ensure that the blood supply meets the needs in natural hazards and in emergency conditions.

Klinička ispitivanja prve faze: učesnici, organizacija, legislativa

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Razvoj leka je logičan niz procedura u kojima se saznanjanja iz manjih, ranih studija koriste radi podrške i planiranja kasnijih, koje su određenije i odlučujuće. Početna ispitivanja omogućavaju ranu evaluaciju bezbednosti i podnošljivosti i informacije o farmakokinetičkim karakteristikama ispitivanog medicinskog proizvoda (IMP). Vremenski povezane faze (I–IV) nisu uvek odgovarajuća osnova za podelu kliničkih studija, jer se jedan tip ispitivanja može pojaviti u nekoliko faza. Tako se farmakološka ispitivanja u ljudi obično sprovode u fazi I kliničkog ispitivanja, ali neka od njih se sprovode i u nekoj od preostalih faza. Uključuju se učesnici koji su zdravi dobrovoljci, ali to iz etičkih razloga mogu biti i pacijenti odgovarajućih kategorija. Nakon ispitivanja u kojima se IMP daje prvi put ljudima (first-in-human trials, FIH), naredni/e delovi/studije su rana kliničko-farmakološka ispitivanja (RKFI). Pored toga što za njihovu realizaciju važe svi principi dobre kliničke prakse (DKP), kao i kod kasnijih faza ispitivanja, postoje i posebni evropski vodiči o strategijama da se identifikuju i ublaže rizici kod ispitivanja FIH i RKFI. Iz istog razloga, postoji i poseban aneks smernica za sprovođenje DKP inspekcijskog nadzora u jedinicama za realizaciju prve faze kliničkih ispitivanja IMP. Potrebno je da ne samo osoblje, prostorije i oprema zadovoljavaju visoke standarde, već i dokumentacija i procedure koje se sprovode u cilju smanjenja rizika i postizanja kvaliteta koji se traži.

First phase clinical trials: participants, organization, legal regulations

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Drug development is a logical sequence of procedures which imply that findings from smaller, early studies are used to support and plan later, more specific and decisive ones. Initial studies allow early evaluation of safety and tolerability, as well as information on the pharmacokinetic characteristics of the investigational medicinal product (IMP). Time-related phases (I-IV) are not always an appropriate basis for dividing clinical studies, as one type of trial may occur in several phases. Thus, pharmacological trials in humans are usually conducted in Phase I clinical trials, but some of them are also conducted in one of the remaining trials, if needed. Participants who are healthy volunteers are included, but for ethical reasons they can also be patients of appropriate categories. After first-in-human trials (FIH), the next parts/studies are early clinical pharmacology (ECP) trials. In addition to the fact that all the principles of Good Clinical Practice (GCP) are applied to their implementation, as well as in the later phases of the trial, there are also specific European guidelines on strategies to identify and mitigate risks in FIH and ECP trials. For the same reason, there is also a special annex of guidelines for the implementation of the GCP inspection supervision in the units for the implementation of the first phase of IMP clinical trials. It is necessary that not only personnel, premises and equipment meet high and special standards, but also the documentation and procedures implemented since reducing risks and required quality should be achieved.

Principi i tehnike ukidanja benzodiazepina u tretmanu zavisnika

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Benzodiazepini su najčešće korišćeni psihofarmaci u našoj sredini i njihovo delovanje je anksiolitičko i hipnotičko. Deluju preko GABA receptorskog sistema, široko rasprostranjenog u CNS. Najčešće se propisuju za lečenje anksioznosti, nesanice i za relaksaciju muskulature. Poznati su po svojoj brzini delovanja i efikasnosti, ali i po brzom stvarnju tolerancije i rizika za zavisnost. Neki podaci govore zavisnosti već posle 2-4 nedelje upotrebe, ali češće je posle dugotrajne, višemesečne upotrebe. Veći rizik za zavisnost predstavljaju kratkodelujući anksiolitici. Posledice su neregulisani osnovni simptomi, težnja ka povećanju doza, kognitivna oštećenja, u populaciji starijih sklonost konfuznim stanjima, padovima i povredama. U populaciji zavisnika od drugih psihoaktivnih supostanci je zloupotreba benzodiazepina prisutna u visokom procentu i remeti njihov tretman. Problem ukidanja benzodiazepina je značajan, zbog pojave apstinencijalnog sindroma u visokom procentu. Cilj je smanjiti apstinencijalne simptome i izbeći povratak početnih simptoma. Preporučuju se različite tehnike, koje se često kombinuju, uz flehibilan plan. Posebno se vodi računa o individualnoj osetljivosti tokom procesa ukidanja. Najčešće se primenjuje tkz. Cut and Hold tehnika, pri čemu se smanjuje određeni procenat aktuelne doze i čeka se dok se apstinencijani simptomi smire. Najčešće se inicijalna doza smanjuje za 5% od aktuelne doze, u kasnijim fazama i manje. Ukoliko pacijenti to teško podnose, uvodi se Cross-tittration sa diazepamom, gde se uporedo uvodi dugodelujući diazepam do postizanja stabilnosti. Druga tehnuika je tkz- mikroredukcija, gde se na 1-3 dana smanjuju male doze. Ovaj metod podrazumeva saradnju sa farmaceutom zbog neophodnosti pravljenja lekova u rastvoru. Trajanje procesa ukidanja je često dugo, 3-6 meseci prosečno, a neophodno je pacijentu pružiti podršku kroz network terapiju i KBT tehnike, vodjenje dnevnika. Ozbiljni apstinencijalnii simptoma ili suicidalna ideacije su razlog prekida procesa.

Principles and techniques of benzodiazepines discontinuation in the treatment of addicts

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Benzodiazepines are the most commonly used psychopharmaceuticals in our environment and their action is anxiolytic and hypnotic. They act through the GABA receptor system, widely distributed in the CNS. They are most often prescribed for the treatment of anxiety, insomnia and muscle relaxation. They are known for their speed of action and efficiency, but also for the rapid creation of tolerance and the risk of addiction. Some data indicate addiction after 2-4 weeks of use, but it is more common after long-term, several-month use. Short-acting anxiolytics pose a greater risk of addiction. The consequences are unregulated basic symptoms, a tendency to increase doses, cognitive impairment, and in the elderly population, a tendency to confusion, falls and injuries. In the population of addicts of other psychoactive substances, the abuse of benzodiazepines is present in a high percentage and disrupts their treatment. The problem of discontinuation of benzodiazepines is significant, due to the occurrence of abstinence syndrome in a high percentage. The goal is to reduce withdrawal symptoms and avoid the return of initial symptoms. Various techniques are recommended, often combined, with a flexible plan. Particular attention is paid to individual sensitivity during the withdrawal process. The so-called Cut and Hold technique is most often applied, whereby a certain percentage of the current dose is reduced and the withdrawal symptoms subside. Most often, the initial dose is reduced by 5% of the current dose, in later stages even less. If patients cannot tolerate it, cross-titration with diazepam is introduced, where long-acting diazepam is simultaneously introduced until stability is achieved. Another technique is the so-called microreduction, where small doses are reduced for 1-3 days. This method implies cooperation with a pharmacist due to the necessity of making medicines in solution. The duration of the withdrawal process is often long, 3-6 months on average, and it is necessary to provide the patient with support through network therapy and CBT techniques, keeping a diary. Serious withdrawal symptoms or suicidal ideation are the reason for stopping the process.

Stabilni multidisciplinarni timovi u zdravstvu

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Komponovanje dobrih timova je osnova menadžmenta uopšte. Multidisciplinarni medicinski tim je ekipa medicinskog i naučnog osoblja koji su članovi različitih profesija i organizacija (lekari , fiziko-hemičari, socijalni radnici, inženjeri, medicinske sestre, a u skorije vreme i pravnici), koji zajedno rade na donošenju odluka u vezi sa tretmanom pacijenata i pravilnom upotrebom savremene opreme. Svaki od članova tima unosi svoje znanje i veštine u cilju postizanja što boljeg rezultata lečenja. Odluke se na taj način donose sa više dokaza iz naučne / stručne literature nego da ih je donela samo jedna osoba. Za uspešno upravljanje kadrovima u timu koji je u stanju da se nosi sa svim izazovima i preprekama koje nosi savremeno doba življenja sa akcentom na zaokrete u zdravstvenim nedaćama, neophodna je odgovarajuća edukacija i profesionalne veštine glavnog menadžera. Timski rad ima svoje prednosti i nedostatke koje dobar vođa mora hendlovati. Multidisciplinarni zdravstveni timovi često imaju problem kvantifikacije uloženog rada za postizanje zadovoljavajućih terapijskih rezultata. Formiranje multidisciplinarnih timova u zdravstvu je obavezan vid rada u uspešnoj zdravstvenoj ustanovi. Pored uobičajene medicinske edukacije, poželjno je uvesti edukaciju za rad na svim pozicijama u zdravstvenom timu. Najvažniji cilj multidisciplinarnih timova je dobrobit pacijenta, što zahteva visoke etičke i profesionalne kvalitete osoblja. Iako izgleda jednostavno i odavno poznato uplivom uticaja iz nemedicinskih delatnosti medicinski timovi su dobili iskušanje više, ali kao takvi lakše mogu da amortizuju uticaje i izaberu bolje rešenje za pacijenta.

The importance of collecting adverse effects of new drugs

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Building good teams is the foundation of management in general. A multidisciplinary medical team is a team of medical and scientific personnel who are members of different professions and organizations (doctors, physico-chemists, social workers, engineers, nurses, and more recently lawyers, ect), who work together to make decisions regarding the treatment of patients and proper use of modern equipment. Each of the team members contributes their knowledge and skills in order to achieve the best possible treatment result. In this way, decisions are made with more evidence from scientific / professional literature than if they were made by just one person. For the successful management of personnel in a team that is able to cope with all the challenges and obstacles brought by the modern era of living with an emphasis on turns in health problems, appropriate education and professional skills of the main manager are necessary. Teamwork has its advantages and disadvantages that a good leader must handle. Multidisciplinary healthcare teams often have the problem of quantifying the work invested to achieve satisfactory therapeutic results. The formation of modern multidisciplinary teams in healthcare is a mandatory type of work in a successful healthcare institution. In addition to the usual medical education, it is desirable to introduce education for work in all positions in the health team. The most important goal of multidisciplinary teams is the well-being of the patient, which requires high ethical and professional qualities of the staff. Although it seems simple and has been known for a long time due to the impact of influences from non-medical activities, medical teams have been tempted more, but as such they can more easily amortize the influences and choose a better solution for the patient.

Комбинована суперкритична CO_2 екстракција и липозомална енкапсулација биоактивних компоненти покожица грожђа Вранац у циљу њихове топикалне примене

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Винска индустрија производи велике количине отпада, посебно комину грожђа која се састоји од покожица, семенки и петељки. Иако овај нуспроизвод представља еколошки изазов, истовремено је богат извор биоактивних једињења, попут полифенола као што су кверцетин и ресвератрол. У овом раду испитане су покожице грожђа сорте Вранац, познате по високом садржају полифенола, као извор биоактивних компоненти за козметичку примену, с посебним фокусом на утицај липозомалне енкапсулације на њихову антиоксидативну активност.

Биоактивне компоненте су екстраховане из покожица методом суперкритичне CO_2 екстракције и инкапсулиране у DPPC липозоме, које су погодне за топикалну примену. Хемијска анализа екстракта, извршена методом Orbitrap масене спектрометрије, потврдила је висок садржај ресвератрола. Антиоксидативна активност, мерена EPR спектроскопијом, показала је умерену активност против DPPH радикала и снажну активност према хидроксилним и супероксидним радикалима. Липозоми су окарактерисани методом динамичког расејања светлости (DLS) и мерењем зета потенцијала, док је EPR анализа указала на умерену флуидност липозомалних мембрана.

Резултати су показали да инкапсулирани екстракт задржава своја антиоксидативна својства, чинећи га стабилним и ефикасним за топикалну примену. Овај приступ не само да доприноси решавању проблема управљања отпадом, већ пружа и одрживу основу за развој високовредних козметичких производа.

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Combined supercritical CO_2 extraction and liposomal encapsulation of bioactive compounds from vranac grape skins for topical applications

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The wine industry produces significant amounts of waste, particularly grape pomace, which consists of skins, seeds, and stems. While this byproduct poses environmental challenges, it is also a rich source of bioactive compounds, such as polyphenols, including quercetin and resveratrol. This study investigates the potential of Vranac grape skins, known for their high polyphenol content, as a source of bioactive components for cosmetic applications, with a specific focus on the effect of liposomal encapsulation on their antioxidant activity.

Bioactive compounds were extracted from grape skins using supercritical CO_2 extraction and encapsulated into DPPC liposomes, suitable for topical applications. Chemical analysis of the extract, performed using Orbitrap mass spectrometry, confirmed a high resveratrol content. Antioxidant activity, measured by EPR spectroscopy, showed moderate activity against DPPH radicals and strong activity toward hydroxyl and superoxide radicals. Liposomes were characterized using Dynamic Light Scattering (DLS) and zeta potential measurements, while EPR analysis indicated moderate liposomal membrane fluidity.

The results demonstrated that the encapsulated extract retained its antioxidant properties, making it a stable and effective agent for topical use. This approach not only addresses waste management challenges but also provides a sustainable foundation for developing high-value cosmetic products.

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Humana i veterinarska medicina iz perspektive Jedne medicine do Jednog zdravlja

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Bliska povezanost ljudi i životinja kroz istoriju imala je ključan uticaj na razvoj medicine, a drevne prakse poput domestikacije stoke i ritualnih žrtvovanja u Egiptu značajno su doprinele nastanku ranih medicinskih znanja. Ipak, humani i veterinarski pristupi medicini razdvojili su se u 19. veku, delimično zbog usmerenja veterinarske medicine na stoku i konje, pre nego što je medicina kućnih ljubimaca dobila na značaju 1970-ih. Uprkos razdvajanjima, obe oblasti dele osnovna znanja o anatomiji, uzrocima bolesti i strategijama lečenja. Hronične bolesti, poput raka i kardiovaskularnih oboljenja, pogađaju i ljude i životinje, dok bakterijski patogeni, poput MRSA i E. coli, predstavljaju zajedničke izazove. Preklapanje u korišćenju antibiotika, uključujući kritično važne poput fluorohinolona i kolistina, naglašava zajedničke brige o antimikrobnoj rezistenciji (AMR). Zoonotski patogeni, koji čine 60% ljudskih zaraznih bolesti, ističu potrebu za pristupom „Jedno zdravlje“ u borbi protiv AMR-a i zoonoza. Poboljšanje saradnje između humane i veterinarske medicine može započeti od studenata. Interdisciplinarni projekti u medicinskim i veterinarskim kurikulumima mogu podstaći timski rad i zajedničko razumevanje. Na Univerzitetu u Novom Sadu procenjeni su znanje, stavovi i praksa studenata medicine, stomatologije i veterine o upotrebi antibiotika, pri čemu je uočena potreba za poboljšanjem u svim grupama. Jačanje edukacije u okviru pristupa „Jedno zdravlje“ ključno je za očuvanje zdravlja ljudi, životinja i životne sredine.

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Human and Veterinary Medicine from a One Medicine to One Health Perspective

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The longstanding relationship between humans and animals has shaped medicine, with ancient practices like cattle domestication and ritual sacrifice in Egypt contributing to early medical knowledge. However, human and veterinary medicine diverged in the 19th century, partly due to veterinary medicine's focus on livestock and horses before the rise of companion animal care in the 1970s. Despite this, both fields share foundational knowledge in anatomy, disease origins, and treatment strategies. Chronic diseases like cancer and heart disease affect both humans and animals, while bacterial pathogens such as MRSA and E. coli pose shared challenges. Overlapping antibiotic classes, including critically important ones like fluoroquinolones and colistin, highlight mutual concerns about antimicrobial resistance (AMR). Zoonotic pathogens, which account for 60% of human infectious diseases, underscore the need for a One Health approach to combat AMR and zoonoses. Improving collaboration between human and veterinary medicine can begin with students. Interdisciplinary projects in medical and veterinary curricula can foster teamwork and shared understanding. At the University of Novi Sad, medical, dental, and veterinary students' knowledge, attitudes, and practices regarding antibiotic use were evaluated, revealing a need for improvement across all groups. Strengthening One Health education is crucial to safeguarding health for humans, animals, and the environment.

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Funkcionalnost nusproizvoda prehrambene industrije kao novih farmaceutskih ekscipijenasa u lekovima dobijenim tehnologijom 3D štampe

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Tehnologija 3D štampe je sve aktuelnija u različitim industrijama. Iako je odlikuju brojne prednosti, veću primenu ove tehnologije u farmaceutskoj industriji ograničava nedostatak odgovarajućih farmaceustkih ekscipijenasa. Koncentrat proteina soje i pogača uljane tikve golice su nusproizvodi prehrambene industrije koje odlikuje visoka bezbednost i potencijal za primenu u farmaceutskoj industriji.

Kao model supstanca odabran je ketoprofen (niska rastvorljivost, visoka permeabilnost, BSK klasa 2). Hidroksipropilceluloza je upotrebljena kao osnovni polimer, a ispitivanja su urađena i sa dodatkom koncentrata proteina soje ili pogače uljane tikve golice u udelima od 10%. Manitol je upotrebljen kao plastifikator. Natrijum-skrobglikolat je dodat u udelima od 2% i 10% kako bi se ispitali njegovi efekti u 3D štampanim tabletama. Tablete su izrađene tehnikom deponovanja istopljenog filamenta, od filamenata dobijenih metodom ekstruzije topljenjem. FTIR i DSC analiza je sprovedena u cilju karakterizacije čvrstog stanja. Disoluciona ispitivanja su urađena u medijumima dve pH vrednosti (1,2 i 6,8).

Metodom ekstruzije topljenjem se dobijaju filament homogenog sadržaja, dimenzija i glatke strukture, a dodatak ispitanih nusproizvoda prehrambene industrije ne menja značajno njihova svojstva. Ketoprofen je ispoljio efekte plastifikatora. Tablete ketoprofena u dozi od 25 mg su uspešto štampane, ujednačenih dimenzija, mase i sadržaja. Visoki udeli natrijum-skrobglikolata su otežavali 3D štambu i nisu doprineli ubrzanju rastvaranja. Tablete karakteriše produženi profil oslobađanja ketoprofena, koji se ubrzava pod dejstvom dodatka koncentrata proteina soje.

Natrijum-skrobglikolat kao konvencionalni dezintegrator ne ispoljava iste efekte u 3D štampanim tabletama i otežava njihovu izradu. Do ubrzanja oslobađanja ketoprofena iz 3D štampanih tableta sa hidroksipropilcelulozom kao osnovnim polimerom može doći uz dodatak koncentrata proteina soje.

Ključne reči: FDM, HME, ketoprofen, koncentrat proteina soje, pogača uljane tikve golice

Functionality of food industry by-products as new pharmaceutical excipients in drugs obtained by 3D printing technology

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3D printing technology is increasingly actual in various industries. Although it is characterized by numerous advantages, the greater application of this technology in the pharmaceutical industry is limited by the lack of suitable pharmaceutical excipients. Soy protein concentrate and pumpkin seed oil cake are by-products of the food industry that are characterized by high safety and potential for use in the pharmaceutical industry.

Ketoprofen (low solubility, high permeability, BCS class 2) was chosen as a model substance. Hydroxypropylcellulose was used as the basic polymer, and the tests were also done with the addition of soy protein concentrate or pumpkin seed oil cake in proportions of 10%. Mannitol was used as a plasticizer. Sodium starch glycolate was added at 2% and 10% to investigate its effects in 3D printed tablets. The tablets are made using the fused deposition modeling technique, from filaments obtained by the hot-melt extrusion method. FTIR and DSC analysis was carried out in order to characterize the solid state. Dissolution tests were performed in media of two pH values (1.2 and 6.8).

Using the hot-melt extrusion method, filaments of homogeneous content, dimensions and smooth structure are obtained, and the addition of the examined by-products of the food industry does not significantly change their properties. Ketoprofen had plasticizer effects. Ketoprofen tablets in a dose of 25 mg were successfully printed, with uniform dimensions, mass and content. High proportions of sodium starch glycolate made 3D printing difficult and did not contribute to the acceleration of dissolution. The tablets are characterized by a prolonged release profile of ketoprofen, which is accelerated by the addition of soy protein concentrate.

Sodium starch glycolate as a conventional disintegrator does not exhibit the same effects in 3D printed tablets and makes them more difficult to manufacture. Acceleration of the release of ketoprofen from 3D printed tablets with hydroxypropyl cellulose as a base polymer can occur with the addition of soy protein concentrate.

Key words: FDM, HME, ketoprofen, soy protein concentrate, pumpkin seed oil cake

Regulatori cirkadijalnog ritma i tretman depresije

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Depresija je mentalni poremećaj sa visokom prevalencijom u celom svetu, ugrožava radno sposobnu populaciju i dovodi do ozbiljnih posledica. Epidemiološke studije ukazuju na stalni rast broja obolelih svake godine, uz porast propisivanja antidepresiva i troškova lečenja. Iako se u tretmanu depresije koriste brojni antidepresivi, traga se za novim farmakološkim pristupima, jer je poznato je da najviše korišćeni antidepresivi, SSRI , pokazuju visok procenat delimičnog odgovora i izostanka potpune remisije. Svi vitalni procesi u organizmu odvijaju prema 24-časovnom- cirkadijalnom ritmu, pri čemu je jedan od najvažnijih ciklus spavanje-budnost. Kao najznačajniji regulator ovog ritma se opisuje HPA osovina, koja je jedan od značajnih faktora u neurofiziologiji depresije, a poremećaj spavanja je pak jedan od najčešćih simptoma depresije. Stoga se razvijaju supstance koje su kao neuroregulatori uključene u regulaciju cirkadijalnog ritma. Jedna od njih je agomelatin, koji deluje kao agonist melatonergičkih receptora MT1 i MT2 i antagonist 5HT2C receptora. Aktivacija melatonergičkih receptora u hipotalamusu dovodi do resinhronizacije cirkadijalnog ritma, produžava spavanje, smanjuje buđenje tokom noći i reguliše raspoloženje. Antagonistčko delovanje na 5HT2C receptore povećava oslobadjanje noradrenalina i dopamina u frontalnom korteksu. Naglašava se brže delovanje, povoljan bezbednosni profil, izostanak seksualne disfunkcije, uz adekvatnu efikasnost. Drugi važni neuromodulator cirkadijalnog ritma je orexin, neuripeptid koji se luči u hipotalamusu. Brojne studije ukazuju na njegovu ulogu u regulaciji spavanja, reward sistema, odgovora na stres, a blokada orexin receptora izaziva snažan antidepresivni efekat. Već su razvijeni novi hipnotici na bazi antagonizma orexin receptora, a u toku su kliničke studije III faze, koje proveravaju antidepresivni efekat ovih supstanci. Svakako, regulatori cirkadijalnog ritma predstvljaju obećavajuće nove pristupe tretmanu depresije.

Circadian rhythm regulators and treatment of depression

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Depression is a mental disorder with a high prevalence throughout the world, endangering the working population and leading to serious consequences. Epidemiological studies indicate a constant increase in the number of patients every year, along with an increase in the prescription of antidepressants and the cost of treatment. Although many antidepressants are used in the treatment of depression, new pharmacological approaches are being sought, because it is known that the most used antidepressants, SSRIs, show a high percentage of partial response and lack of complete remission. All vital processes in the body take place according to the 24-hour circadian rhythm, one of the most important of which is the sleep-wake cycle. The HPA axis is described as the most important regulator of this rhythm, which is one of the important factors in the neurophysiology of depression, and sleep disturbance is one of the most common symptoms of depression. Therefore, substances are developed that are involved in the regulation of the circadian rhythm as neuroregulators. One of them is agomelatine, which acts as an agonist of melatonergic receptors MT1 and MT2 and an antagonist of 5HT2C receptors. Activation of melatonergic receptors in the hypothalamus leads to resynchronization of the circadian rhythm, prolongs sleep, reduces awakening during the night and regulates mood. Antagonistic action on 5HT2C receptors increases the release of noradrenaline and dopamine in the frontal cortex. Faster action, favorable safety profile, absence of sexual dysfunction, with adequate efficiency are emphasized. Another important neuromodulator of the circadian rhythm is orexin, a neuripeptide secreted in the hypothalamus. Numerous studies point to its role in the regulation of sleep, the reward system, and the response to stress, and the blockade of the orexin receptor causes a strong antidepressant effect. New hypnotics based on orexin receptor antagonism have already been developed, and phase III clinical studies are underway to test the antidepressant effect of these substances. Certainly, circadian rhythm regulators represent promising new approaches to the treatment of depression.

Akutna trovanja lekovima u pedijatrijskom uzrastu

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Akutno trovanje lekovima predstavlja značajan problem javnog zdravlja među pedijatrijskom populacijom. Cilj ovog istraživanja je bio da se procene kliničke karakteristike trovanja lekovima kod dece na području Vojvodine od 2018. do 2023. godine. Retrospektivnom opservacionom studijom obuhvaćena su 82 pacijenta sa potvrđenim trovanjem lekovima, a prikupljeni su podaci o demografskim karakteristikama, kliničkim manifestacijama, lekovima koji su izazvali trovanje i primenjenim terapijskim intervencijama. Ozbiljnost trovanja je procenjena primenom skora za procenu stepena težine trovanja (PSS), a toksikološka analiza je obavljena metodom gasne hromatografije-masene spektrometrije (GC-MS). Rezultati su pokazali da su trovanja najzastupljenija kod adolescenata (72%), pri čemu je 78% slučajeva posledica namernog trovanja, dok su slučajna trovanja češća kod mlađe dece. Benzodiazepini, antipsihotici i analgetici su bili najčešći uzročnici trovanja. Većina pacijenata (78%) je ispoljila blage kliničke simptome (PSS=1), dok je 9% dece doživelo teško trovanje (PSS=3), povezano sa komplikacijama kao što su aspiraciona pneumonija i akutna bubrežna insuficijencija.

Rešavanje problema trovanja lekovima kod dece u Vojvodini zahteva povećan fokus na preventivnoj strategiji, uključujući edukaciju roditelja i odgovarajuću psihosocijalnu podršku mladima.

Pediatric Drug Poisoning in Vojvodina, Serbia: A Retrospective Clinical and Toxicological Assessment

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Acute drug poisoning represents a significant public health issue among the pediatric population. The aim of this study was to evaluate the clinical characteristics of drug poisoning in children in the Vojvodina region from 2018 to 2023. In a retrospective observational study, 82 patients with confirmed drug poisoning were included, and data was collected regarding demographic characteristics, clinical manifestations, types of drugs involved, and the therapeutic interventions administered. The severity of poisonings was evaluated using the Poisoning Severity Score (PSS), and toxicological analysis were performed using the gas chromatography-mass spectrometry (GC-MS) method. The results indicated that poisonings were most prevalent in adolescent girls (72%), with 78% of cases resulting from intentional poisoning, while accidental poisonings were more common in younger children. Benzodiazepines, antipsychotics, and analgesics were the primary drugs involved in these poisoning incidents. The majority of patients (78%) exhibited mild clinical symptoms (PSS=1), whereas 9% of children experienced severe poisoning (PSS=3), related to complications such as aspiration pneumonia and acute renal failure.

Solving the problem of drug poisoning in children in Vojvodina requires an increased focus on preventive strategies, including parental education and appropriate psychosocial support for the youth.

Topikalni kortikosteroidi

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Topikalni kortikosteroidi imaju široku upotrebu u dermatologiji, ali i oftalmologiji i drugim granama medicine, zbog svog antiinflamatornog, antiproliferativnog i imunosupresivnog dejstva.

Idealni lek treba da ima odgovarajuće farmakokinetske (visoka liposolubilnost koja omogućava difuziju leka, inaktivacija leka nakon apsorpcije) i farmakodinamske osobine (izražena lokalna efikasnost i minimalni sistemski i lokalni neželjeni efekti). Topikalni kortikosteroidi se međusobno razlikuju po svojoj potentnosti, što korelira sa njihovom vazokonstriktornom aktivnošću. Na izbor leka u dermatologiji, utiče: dužina trajanja terapije, mesto primene, veličina promene i debljina epidermisa na mestu primene, kao i efikasnost kortikosteroida u terapiji. Farmaceutski oblik ima veliku ulogu u povećanju komplijanse pacijenata, ali i u poboljšanju efikasnosti, povećavajući penetraciju leka. Osim toga, mesto primene određuje farmaceutski oblik leka.

Najčešći lokalni neželjeni efekti kortikosteroida na koži su: atrofične promene, petehije i ekhimoze, stroidne akne, rosacea, pogoršanje i/ili maskiranje infekcije, alergijski kontaktni dermatitis, hipertrihoza, hiperpigmentacije i tolerancija. Na oku, mogući neželjeni efekti su: katarakta, glaukom, sklonost ka infekcijama i usporeno zarastanje rana. Sistemski neželjeni efekti su retki, ali se mogu javiti kod dugotrajne upotrebe jakih kortikosteroida na veće površine.

Lokalna primena steroida je bezbednija u odnosu na sistemsku primenu, ali, ipak, njihova primena treba biti racionalna kako bi se smanjila učestalost neželjenih efekata.

Topical corticosteroids

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Topical corticosteroids are widely used in dermatology, but also in ophthalmology and other fields of medicine, due to its anti-inflammatory, antiproliferative and immunosuppressive effects.

The ideal drug should have certain pharmacokinetic (high lipophilicity enabling drug diffusion, drug inactivation after absorption) and pharmacodynamic properties (high local efficacy and minimal systemic and local adverse effects). Topical corticosteroids differ in their potency, which correlates to their vasoconstrictor activity. The choice of drug in dermatology, depends on treatment duration, localization, surface size and epidermis thickness at the site of administration, as well as the efficacy of corticosteroids in the treatment. Drug formulation has a significant role in increasing patients' compliance, as well as in increasing efficacy, by enabling better drug penetration. Besides, the site of drug administration determines the formulation used.

The most common corticosteroids local adverse effects on skin are atrophic changes, petechiae and ecchymosis, steroid acne, rosacea, progression and/or infection masking, allergic contact dermatitis, hypertrichosis, hyperpigmentation, and tolerance. Possible ocular adverse effects are cataract, glaucoma, decreased resistance to infections and delayed wound healing. Systemic adverse effects are rare but may occur after long term use of potent corticosteroids on wide surfaces.

Local use of corticosteroids is safer than systemic use, but, nevertheless, their use should be rational to decrease the frequency of adverse effects.

Razvoj farmaceutske formulacije ternarne čvrste disperzije ketoprofena

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Ketoprofen je prestavnik aktivnih farmaceutskih sastojaka čiju biološku raspoloživost ograničava niska rastvorljivost. Čvrste disperzije su efikasan i industrijski primenljiv način za prevazilaženje ovog problema. U zavisnosti od hemijske prirode hidrofilnog matriksa poštoje različite generacije čvrstih disperzija, a treća komponenta se dodaje u cilju dodatnog povećanja efikasnosti i stabilnosti dobijenih formulacija.

Čvrste disperzije su formilsane kao prva (kristalni manitol), druga (semikristalni polimer polietilenglikol 4000) i treća generacija uz dodatak poloksamera 188 ili poloksamera 407 kao treće komponente. Rastvorljivost je ispitane u vodi na 37˚C i izračunata Gibsova slobodna energija. Na ovaj način su odabrane dve formulacije koje su ušle u dalja ispitivanja i za koje je optimizovan proces ekstruzije topljenjem (temperatura, brzina motora i broj ekstruzija). Procesni parametri formulacije sa najboljim rezultatima rastvorljivosti i brzine rastvaranja su odabrani za dobijanje finalnih formulacija, od kojih su formulisane tablete i kapsule sa konvencionalnim farmaceutskim ekscipijensima. Sprovedena je farmaceutsko-tehnološka karakterizacija dobijenih čvrstih farmaceutskih oblika.

Poloksamer 407 u većoj meri doprinosi povećanju rastvorljivosti u odnosu na poloksamer 188. Promena Gibsove slobodne energije je više izraženo pri biorelevantnoj temperaturi u odnosnu na sobnu temperaturu. Reekstruzija na višim temperaturama je pokazala najveći uticaj na povećanje rastvorljivosti i brzine rastvaranja. Dobijene čvrste disperzije su procesibilne i moguće je formulisati tablete i kapsule zadovoljavajućih rezultata testova variranja mase, ujednačenosti sadržaja, raspadljivosti, brzine rastvaranja, frijabilnosti (tablete) i otpornosti na lomljenej (tablete).

Ključne reči: manitol, PEG 4000, HME, poloksamer 188, poloksamer 407

Development of pharmaceutical formulation of ternary solid dispersion of ketoprofen

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Ketoprofen is a representative of active pharmaceutical ingredients whose bioavailability is limited by low solubility. Solid dispersions are an efficient and industrially applicable way to overcome this problem. Depending on the chemical nature of the hydrophilic matrix, there are different generations of solid dispersions, and the third component is added in order to further increase the efficiency and stability of the obtained formulations.

Solid dispersions are formulated as first (crystalline mannitol), second (semicrystalline polymer polyethylene glycol 4000) and third generation with the addition of poloxamer 188 or poloxamer 407 as a third component. The solubility was tested in water at 37 ˚C and the Gibbs free energy was calculated. In this way, two formulations were selected that entered further tests and for which the hot-melt extrusion process was optimized (temperature, motor speed and number of extrusions). The process parameters of the formulation with the best solubility and dissolution rate results were selected to obtain the final formulations, from which tablets and capsules were formulated with conventional pharmaceutical excipients. The pharmaceutical-technological characterization of the obtained solid pharmaceutical forms was carried out.

Poloxamer 407 contributes to a greater extent to the increase in solubility compared to poloxamer 188. The change in Gibbs free energy is more pronounced at biorelevant temperature than at room temperature. Reextrusion at higher temperatures showed the greatest effect on increasing solubility and dissolution rate. The resulting solid dispersions are processable and it is possible to formulate tablets and capsules with satisfactory test results of mass variation, content uniformity, disintegration, dissolution rate, friability (tablets) and resistance to crushing (tablets).

Key words: mannitol, PEG 4000, HME, poloxamer 188, poloxamer 407

Savremeni pristup u lečenju uznapredovalog melanoma - ciljana i imunoterapija

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Melanom je tumor sa visokim malignim potencijalom, čini oko 4% svih slučajeva raka kože a uzrok smrti je kod 75% obolelih od metastatske bolesti. Na globalnom nivou je incidenca obolevanja od ove bolesti u porastu, dok stopa mortaliteta u protekloj deceniji opada, zahvaljujući merama ranog otkrivanja kao i značajnom napretku u lečenju uznapredovalog oblika ove bolesti razvojem imuno- i ciljane terapije. Uvođenjem u sistemsku terapiju inhibitora imunskih kontrolnih tačaka (CTLA-4, PD-1 i PDL-1 inhibitori) i ciljane terapije (BRAF i MEK inhibitori), kao i lokalnom imunoterapijom onkolitičkim virusom (TVEC), značajno je poboljšan kvalitet života obolelih, a povećani su dužina preživljavanja i preživljavanje bez pojave recidiva.

Sredstva koja se izdvajaju za navedene modalitete lečenja dodatno opterećuju budžete nacionalnih zdravstvenih sistema, dostižući granicu visine troškova po QALY (godine života korigovane prema kvalitetu) koju određuju donosioci odluka. Dalji razvoj novih modaliteta lečenja i procena njihovog socioekonomskog uticaja, ukazuje na neophodnost razvoja boljih prognostičkih i prediktivnih metoda da bi se primenila najbolja personalizovana terapija, odnosno identifikovali pacijenti koji će imati najveću korist od adjuvantnog lečenja.

Current treatment of advanced melanoma: immunotherapy and targeted therapy

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Melanoma is the most aggressive form of skin cancer with a high capacity for metastasis. It accounts for 4% of all skin cancer cases, but 75% of all skin cancer-related deaths are from melanoma. The incidence of this disease has increased worldwide, but mortality has declined mainly due to prevention and early detection measures. The survival rates, recurrence-free survival, and quality of life for patients with metastatic disease have significantly improved since the introduction of systemic therapies, including immune checkpoint inhibitors (CTLA-4, PD-1, and PDL-1 inhibitors), BRAF and MEK inhibitors, and a local oncolytic virus therapy, TVEC.

The costs of adjuvant treatments place a significant burden on healthcare budgets. Costs per QALY (Quality-adjusted life year) exceed the national benchmarks, indicating the necessity of determining their socioeconomic impact. Further development of new treatment modalities indicates the necessity to improve prognostic and predictive tools for tailored treatment plans for patients who will benefit from adjuvant treatment.

Bezbednosni profil novih oralnih antikoagulanasa u kombinaciji sa politerapijom: izazovi u kliničkoj praksi

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Uvođenje novih oralnih antikoagulanasa (NOAK) u kliničku praksu značajno je unapredilo prevenciju i lečenje tromboembolijskih stanja, zahvaljujući predvidivom farmakološkom profilu, smanjenoj potrebi za monitoringom i nižem riziku od interakcija u poredjenju s antagonistima vitamina K. Medjutim, NOAK se često primenjuju kod pacijenata sa pridodatim komorbiditetima, koji uzimaju veći broj lekova istovremeno što povećava rizik od interakcija, koje mogu ugroziti bezbednost i efikasnost terapije. Farmakokinetske interakcije su najčešće posledica uticaja na CYP3A4 i transportni proteing P-gp, pa tako antiepileptici poput karbamazepina i fenitoina mogu značajno smanjiti efikasnost NOAK indukcijom CYP3A4 i P-gp. Rifampicin kao snažan induktor CYP3A4 može umanjiti koncentraciju NOAK. S druge strane, antimikotici poput ketokonazola i itrakonazola, zatim makrolidni antibiotici kao što su eritromicin i klaritromicin usled inhibicije CYPa povećavaju rizik od hemoragijskih komplikacija u slučaju istovremene primene sa NOAK. Antidepresivi iz grupe SSRI i SNRI, kao što su sertralin, fluoksetin, duloksetin u kombinaciji sa NOAK mogu povećati rizik od krvarenja usled farmakodinamske interakcije. Nesteroidni antiinflamatorni lekovi, poput ibuprofena kada se primene sa NOAK povećavaju rizik ok gastrointestinalnog krvarenja. Iako NOAK predstavljaju značajan iskorak u antikoagulantoj terapiji, njihova primena u složenim kliničkim scenarijima zahteva multidisciplinaran pristup, uključujući pažljivo razmatranje potencijalnih interakcija i prilagodjavanje terapijskih strategija kako bi se obezbedila maksimalna bezbednost i efikasnost.

Safety profile of Novel Oral Anticoagulants in combination with polytherapy: chalenges in clinical practice

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The introduction of new oral anticoagulants (NOAC) into clinical practice has significantly improved the prevention and treatment of thromboembolic conditions, thanks to a predictable pharmacological profile, a reduced need for monitoring and a lower risk of interactions compared to vitamin K antagonists. However, NOACs are often used in patients with additional comorbidities, who take many drugs at the same time, which increases the risk of interactions that may compromise safety and effectiveness of therapy. Pharmacokinetic interactions are most often the result of effects on CYP3A4 and the transport protein P-gp, so antiepileptics such as carbamazepine and phenytoin can significantly reduce the effectiveness of NOACs by inducing CYP3A4 and P-gp. Rifampicin, as a strong inducer of CYP3A4, can decrease the concentration of NOAC. On the other hand, antimycotics such as ketoconazole and itraconazole, then macrolide antibiotics such as erythromycin and clarithromycin due to CYP inhibition increase the risk of hemorrhagic complications in the case of simultaneous administration with NOACs. Antidepressants from the group of SSRIs and SNRIs, such as sertraline, fluoxetine, duloxetine in combination with NOAC can increase the risk of bleeding due to pharmacodynamic interaction. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, when administered with NOACs increase the risk of gastrointestinal bleeding. Although NOACs represent a significant step forward in anticoagulant therapy, their application in complex clinical scenarios requires a multidisciplinary approach, including careful consideration of potential interactions and adaptation of therapeutic strategies to ensure maximum safety and efficacy.

Formulacione karakteristike farmaceutskih oblika doziranja sa modifikovanim oslobađanjem u Republici Srbiji

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Formulacije sa modifikovanim oslobađanjem uključuju posebne proizvodne tehnike ili supstance za promenu brzine oslobađanja ili lokacije aktivnog sastojka, sa ciljem poboljšanja komplijanse, smanjenja doze leka, neželjenih efekata i povećanja terapeutske efikasnosti. Istraživanje se bazira na farmaceutskim oblicima sa modifikovanim oslobađanjem dostupnim u Republici Srbiji, oslanjajući se na podatke dobijene iz Agencije za lekove i medicinska sredstva (ALIMS) i baze podataka Mediately. Navedeno je ukupno 27 lekova sa modifikovanim oslobađanjem, a najčešći lekovi bili su oni koji sadrže tamsulosin, a zatim formulacije diklofenaka i gliklazida. Tvrde kapsule čine 44% ukupnog broja, a zatim tablete sa procentom od 41% kao i film tablete koje čine 15% formulacija sa modifikovanim oslobađanjem. Takođe, dat je prikaz ekscipijenata i karakteristika formulacije ovih proizvoda. U tabletama sa modifikovanim oslobađanjem uobičajene pomoćne materije koje se koriste su mikrokristalna celuloza, laktoza, sredstva za raspadanje poput krospovidona i lubrikans kao što je magnezijum-stearat. Film tablete su uglavnom zasnovane na matriks sistemima sa hidrofilnim ili hidrofobnim polimerima, a tvrde kapsule se sastoje od želatina koji je glavna komponenta, kopolimera metakrilne kiseline i etil akrilata i mikrokristalne celuloze. Rezultati ukazuju na to da je tamsulosin najzastupljenija aktivna farmaceutska supstanca u tehnologiji tableta sa modifikovanim oslobađanjem u Republici Srbiji, dok su pored toga dostupni i mnogi drugi lekovi u formi tableta, film tableta i kapsula sa modifikovanim oslobađanjem.

Formulation characteristics of modified-release pharmaceutical dosage forms in the Republic of Serbia

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Modified-release formulations involve special manufacturing techniques or substances to alter the release rate or location of the active ingredient, with the goal of improving compliance, reducing drug dosage and side effects, and enhancing therapeutic efficiency. The study deals with the modified-release pharmaceutical dosage forms available in the Republic of Serbia, relying on data derived from the Agency for Medicines and Medical Devices (ALIMS) and the Mediately database. A total of 27 modified-release drug products were listed, and tamsulosin-containing medicines were the most frequent products, followed by diclofenac and gliclazide formulations. Hard capsules consitute 44% of the total, and then tablets with a percentage of 41%. as well as film tablets which constitute 15% of these modified-release formulations. The study gives an account of the excipients and the formulation characteristics of these products. Modified-release tablets are the ones which usually utilize microcrystalline cellulose, lactose, disintegrants like crosspovidone, and lubricants as magnesium stearate. The film tablets are generally based on matrix systems with hydrophilic or hydrophobic polymers, and the hard capsules are composed of gelatin which is the main component, methacrylic acid-ethyl acrylate copolymer and microcrystalline cellulose. The results point out to tamsulosin as the most extensive substance in modified-release tablet technologies in the Republic of Serbia, with a wide range of tablets, film tablets, and capsule forms available.

Upotreba opioidnih analgetika u Srbiji

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Uvod: Opioidni analgetici imaju ključnu ulogu u lečenju bola. Podaci o trednovima upotrebe opioidnih analgetika u Srbiji su ograničeni.

Cilj ovog istraživanja bio je da se analiziraju trendovi u upotrebi opioidnih analgetika u Srbiji.

Metodologija: Analiza je obuhvatila podatke Agencije za lekove i medicinska sredstva Srbije za period od 2014. do 2019. godine. Upotreba je izražena kao definisane dnevne doze na 1000 stanovnika na dan (DDD/1000 stanovnika/dan) i broj pakovanja lekova, korišćenjem ATC/DDD metodologije verzija 2020.

Rezultati: Ukupna potrošnja opioidnih analgetika u Srbiji pokazuje blagi pad, sa 6,79 DDD/1000 stanovnika/dan u 2014. na 6,06 DDD/1000 stanovnika/dan u 2019. godini. Ovo smanjenje je rezultat pada u upotrebi slabih opioida, posebno kombinacije kodeina, paracetamola, kofeina i propifenazona, koja je činila preko 85% ukupne potrošnje tokom većeg dela posmatranog perioda. Nasuprot tome, upotreba jakih opioida, kao što su morfin i fentanil, beleži porast. Potrošnja fentanila je porasla za 17,64% (sa 0,096 na 0,113 DDD/1000 stanovnika/dan), dok je morfin zabeležio rast od 31,57% (sa 0,057 na 0,075 DDD/1000 stanovnika/dan). Transdermalni fentanil postaje dominantan oblik za jake opioide, sa 0,133 DDD/1000 stanovnika/dan u 2019.

Zaključak: Iako slabiji opioidi i dalje dominiraju u ukupnoj potrošnji, trend rasta u primeni jakih opioida ukazuje na potencijalni pomak u terapiji bola.

Ključne reči: opioidni analgetici, DDD, tramadol, fentanil

Opioid analgesics use in Serbia

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Introduction: Opioid analgesics play a crucial role in managing pain, Data on trends in opioid use in Serbia is limited.

Aim: This study aimed to analyze trends in opioid analgesic use in Serbia.

Methodology: The analysis was based on data from the Medicines and Medical Devices Agency of Serbia for the period 2014–2019. Utilization was expressed as defined daily doses per 1000 inhabitants per day (DDD/1000 inhabitants/day) and the number of drug packages, following the ATC/DDD methodology version 2020.

Results: The total consumption of opioid analgesics showed a slight decrease, from 6.79 DDD/1000 inhabitants/day in 2014 to 6.06 DDD/1000 inhabitants/day in 2019. This decline was primarily driven by reduced use of weak opioids, particularly the combination of codeine, paracetamol, caffeine, and propiphenazone, which accounted for over 85% of total consumption in most years. In contrast, strong opioids, such as morphine and fentanyl, exhibited an increasing trend. Fentanyl usage increased by 17.64% (from 0.096 to 0.113 DDD/1000 inhabitants/day), while morphine consumption increased by 31.57% (from 0.057 to 0.075 DDD/1000 inhabitants/day). Transdermal fentanyl became the dominant formulation for strong opioids, reaching 0.133 DDD/1000 inhabitants/day in 2019.

Conclusion: Although weak opioids still dominate total consumption, the growing use of strong opioids indicates progress in pain management practices.

Key words: opioid analgesics, DDD, tramadol, fentanyl

Biotin u dijagnostici: prepoznavanje interferencije i metode njene prevencije

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Sve češća upotreba biotina kao suplementa i terapijskog sredstva dovela je do problema interferencije u laboratorijskim testovima, posebno u imunološkim analizama koje koriste biotin-streptavidin tehnologiju. Ova interferencija može izazvati netačne rezultate, dovesti do pogrešnih kliničkih tumačenja i neadekvatnog lečenja pacijenata. Povećane koncentracije biotina u uzorku se vezuju za streptavidin, ometajući vezivanje antitela za analizirane uzorke, što dovodi do lažno povišenih rezultata u kompetitivnim odnosno lažno smanjenih rezultata u nekompetitivnim testovima. Najosetljiviji su testovi za analizu funkcije štitaste žlezde (TSH, FT3, FT4), merenja paratiroidnog hormona (PTH), testosterona, humanog horionskog gonadotropina (hCG) i srčanih markera poput troponina. Uvođenje testa za detekciju biotina u dijagnostički proces omogućava identifikaciju visokih koncentracija biotina, pružajući kliničarima pouzdan indikator potencijalne interferencije i smanjujući potrebu za dodatnim metodama potvrde. Kao preventivnu meru, pacijentima koji uzimaju biotin preporučuje se prekid suplementacije najmanje 48 sati pre testiranja kako bi se izbegla interferencija. Laboratorije mogu primeniti serijsko razblaživanje ili protokole za uklanjanje biotina iz uzoraka pre analize. Razvoj biotinski otpornih imunoeseja ključan je za smanjenje uticaja interferencije u budućnosti. Podizanje svesti među zdravstvenim radnicima i pacijentima kroz edukativne strategije, kao što su predavanja, brošure i upozorenja, od suštinskog je značaja za sprečavanje netačnih laboratorijskih rezultata uzrokovanih biotinom.

Biotin in Diagnostics: Recognizing Interference and Methods for Its Prevention

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The increasing use of biotin as a supplement and therapeutic agent has led to significant challenges in laboratory diagnostics, particularly in immunoassays utilizing biotin-streptavidin technology. Biotin interference can produce inaccurate results, leading to misinterpretations and inappropriate clinical management. Elevated biotin concentrations bind to streptavidin, disrupting the interaction between antibodies and target analytes. This results in falsely elevated values in competitive immunoassays and falsely decreased values in non-competitive assays. Tests most affected include thyroid function assays (TSH, FT3, FT4), parathyroid hormone (PTH), testosterone, human chorionic gonadotropin (hCG), and cardiac markers such as troponin. Incorporating biotin detection tests into diagnostic workflows enables identification of high biotin levels, providing clinicians with a reliable indicator of potential interference and reducing the need for additional confirmation methods. As a preventive measure, patients taking biotin are advised to discontinue supplementation at least 48 hours before sample collection. Laboratories can implement serial dilution techniques or biotin removal protocols to minimize interference. Developing biotin-resistant immunoassays remains critical for mitigating this issue in the future. Raising awareness among healthcare providers and patients through educational initiatives, such as lectures, brochures, and alerts, is essential for reducing the risk of biotin-induced errors in laboratory test results.

Zastupljenost jedinjenja sa fluorom na deklaracijama predmeta opšte upotrebe u Republici Srbijie

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Per- i polifluoroalkil supstance (PFAS) uključujući i perfluorooktansku kiselinu (PFOA) privlače pažnju opšte i naučne javnosti zbog potencijala za bioakumulaciju i ispoljavanje ozbiljnih toksičnih efekata. Posebna zabrinutost postoji u slučajevima njihovog prisustva kod proizvoda koji se svakodnevno primenjuju. PFAS ostvaruju efekte u različitim tehnološkim procesima, a iako se njihova upotreba smanjuje ili čak potpuno zabranjuje oni i dalje mogu biti prisutni u različitim kategorijama proizvoda opšte upotrebe. Cilj rada bio je utvrditi prisustvo jedinjenja sa fluorom na deklaracijama proizvoda dekorativnih kozmetičkih preparata dostupnih na tržištu Republike Srbije. Analizirane su dve zvanične veb stranice velikih apotekarkih lanaca koje su dostupne za naručivanje proizvoda od strane kupaca. Upotrebom filtera selektovani su proizvodi koji se označavaju kao vodootporni i utvrđen je njihov kvalitativan sastav na osnovu deklaracije. Od ukupno 1213 proiyvoda iz grupa maskara, olovka za oči, ajlajner, senka za oči i olovka za obrve, 91 proizvod je označen kao vodootporen. Ni jedan proizvod nema deklarisane PFAS. Međutim, 13 proizvoda sadrži sintetski fluorflogopit (sintetska mica), a 25 micu (pet proizvoda sadrži oba sastojka). Iako mica ne sadrži fluor, a sintetski fluorflogopit ne pripada grupi PFAS, iz etimoloških razloga može postojati zabuna kod odabira proizvoda i zabrinutost od strane proizvođača. Sintetski fluorflogopit se koristi kao sredstvo za dopunjavanje ili modifikator viskoznosti i prema sadašnjoj praksi i u primenjivanim koncentracijama se smatra potpuno bezbednim sastojkom kozmetičkih proizvoda. Potrebno je da zdravstveni radnici budu edukovani i spremni da daju adekvatan i naučno zasnovan savet korisnicima svojih usluga.

Ključne reči: PFAS, PFOA, sintetski fluorflogopit, sintetska mica

Zahvalnica: Istraživanje sprovedeno uz podršku Fonda za nauku Republike Srbije, #7010, Integration of Biological Responses and PBTK Modeling in Chemical Toxicity Assessment: A Case Study of Perfluorooctanoic Acid (PFOA) – ToxIN.

Identification of Fluorine-Containing Compounds on Labels of General Use Items in the Republic of Serbia

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Per- and polyfluoroalkyl substances (PFAS), including perfluorooctanoic acid (PFOA), attract the attention of the general and scientific public due to their potential for bioaccumulation and the manifestation of serious toxic effects. Particular concern exists in cases of their presence in products that are applied daily. PFAS have effects in various technological processes, and although their use is being reduced or even completely banned, they can still be present in various categories of products of general use. The aim of the work was to determine the presence of compounds with fluorine on product declarations of decorative cosmetic preparations available on the market of the Republic of Serbia. Two official websites of large pharmacy chains available for ordering products by customers were analyzed. Using the filter, the products that are marked as waterproof were selected and their qualitative composition was determined based on the declaration. Out of a total of 1213 products from the mascara, eye pencil, eyeliner, eye shadow and eyebrow pencil groups, 91 products are marked as waterproof. No product has declared PFAS. However, 13 products contain synthetic fluorphlogopite (synthetic mica) and 25 contain mica (five products contain both ingredients). Although mica does not contain fluorine, and synthetic fluorphlogopite does not belong to the PFAS group, for etymological reasons there may be confusion in product selection and concern by manufacturers. Synthetic fluorphlogopite is used as a filler or viscosity modifier and according to current practice and in the applied concentrations is considered a completely safe ingredient in cosmetic products. It is necessary for health professionals to be educated and ready to give adequate and scientifically based advice to the users of their services.

Keywords: PFAS, PFOA, synthetic fluorphlogopite, synthetic mica

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Metafedron (3-metilmetkatinon): farmakološki, klinički i toksikološki profile

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Uvod: Sintetski katinoni su grupa novih psihoaktivnih supstanci, a koriste se kao alternativa klasičnim rekreativnim drogama. Nakon što su starije generacije ovih jedinjenja postale zakonom zabranjene, nove formulacije su se pojavile na tržištu droga. Jedna od njih je metafedron (3-metilmetkatinon, 3-MMC), psihostimulativna supstanca koja je strukturni izomer 4-metilmetkatinona. Metafedron je, za kratko vreme, postao popularan u velikom broju zemalja.

Cilj: Prikupljanje, analiza i pregled literature koja se odnosi na metafedron, kako bi se prikazale informacije o farmakološkom, kliničkom i toksikološkom profilu ovog jedinjenja. Procena značaja i uloge metafedrona u obrascima zloupotrebe novih psihoaktivnih supstanci među korisnicima rekreativnih droga.

Metodologija: Upotrebom pretraživača poput Google Scholar-a i PubMed-a, pretražena je i analizirana literatura od interesa. Pretraga nije bila ograničena na određeni vremenski period. Svi podaci, koji su se odnosili na supstancu od interesa, su analizirani i predstavljeni u istraživanju.

Glavni rezultati i diskusija: Sve nove psihoaktivne supstance se zloupotrebljavaju zbog njihovih željenih efekata, a to su: stimulativno dejstvo, halucinatorna aktivnost, disocijativne osobine i/ili euforija. Korisnici 3-metilmetkatinona obično izaberu ovu supstancu za rekreativne svrhe i/ili seksualnu stimulaciju. Metafedron ima potencijal da izazove psihološku zavisnost kod osoba koje ga zloupotrebljavaju. Utvrđeno je, u relevantnim studijama, da je starost većine korisnika između 17 i 50 godina. Stariji korisnici obično primenjuju metafedron intravenski, dok oni mlađi ovu drogu unose ušmrkivanjem ili oralnim putem. U Srbiji, metafedron je zakonom kontrolisana supstanca. Po farmakodinamskim osobinama, metafedron je sličan klasičnim rekreativnim drogama. Farmakokinetskim profilom bi mogao da se objasni način upotrebe, prvenstveno ponavljano korišćenje tokom jedne seanse. Najčešći simptomi i znaci intoksikacije ovom drogom su simpatomimetske prirode, poput tahikardije, bolova u grudima, hipertenzije, preznojavanja i agitacije. Najveći broj intoksikacija i smrtnih ishoda desio se u slučajevima gde su korisnici zloupotrebili nekoliko psihoaktivnih supstanci. Nije pronađena korelacija između izmerenih koncentracija ove supstance u krvi i ishoda intoksikacije. Mehanizmi toksičnosti metafedrona nisu u potpunosti razjašnjeni.

Zaključak: Postoji rastući trend zloupotrebe metafedrona među korisnicima rekreativnih droga. Buduće studije bi trebalo da istražuju farmakološke i toksikološke efekte metafedrona na životinje i ljude.

Metaphedrone (3-Methylmethcathinone): Pharmacological, Clinical and Toxicological Profile

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Introduction: Synthetic cathinones are a group of novel psychoactive substances used as an alternative to classical recreational drugs. As a result of legal prohibitions on older generations of these compounds, new formulations appeared on the drug market. One of them is metaphedrone (3-methylmethcathinone, 3-MMC), a structural isomer of 4-methylmethcathinone and a psychostimulant drug. Metaphedrone became popular in a large number of countries in a short period of time.

The aim: The collection, analysis, and review of relevant research on the subject of metaphedrone in order to present information about the pharmacological, clinical, and toxicological profile of this compound. An assessment of the significance and role of metaphedrone in consumption patterns of novel psychoactive substances among recreational drug users.

Methodology: By using search engines like Google Scholar and PubMed, the relevant literature on metaphedrone was looked for and analyzed. The search was not limited to a specific period of time. All information regarding the compound of interest was analyzed and presented.

Key results and discussion: All novel psychoactive substances are abused due to their pronounced stimulatory, hallucinogenic, dissociative, and euphoric and/or relaxing characteristics. Users of 3-methylmethcathinone usually opt for this substance for recreational purposes and/or sexual stimulation. Metaphedrone has the potential to cause a psychological dependence to the users. It was determined in relevant studies that most users are from 17 to 50 years of age. Older users usually administer metaphedrone intravenously, while younger ones usually choose snorting and oral ingestion of the drug. In Serbia, metaphedrone is a legally controlled substance. The pharmacodynamic properties make metaphedrone similar to classical recreational drugs. The method of administration, mainly repeated administration in a single session, could be explained using the pharmacokinetic profile of the drug. The most reported symptoms of intoxication were those of a sympathomimetic nature, such as tachycardia, chest pain, hypertension, diaphoresis, and agitation. Most intoxications and fatal outcomes occurred to users who combined several psychoactive substances. The correlation between measured blood concentrations of the drug and outcomes of intoxication was not found. The mechanisms of metaphedrone's toxicity are not fully understood.

Conclusions: There is an increasing trend of abuse of metaphedrone among recreational drugs users. Future studies should focus on pharmacological and toxicological effects of metaphedrone on animals and humans.

Potrošnja lekova i troškovi lečenja u terapiji glaukoma u Republici Srbiji

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Uvod: U terapiji glaukoma osnovni cilj jeste očuvanje vidne funkcije i kvaliteta života pacijenta. Povišen IOP je jedan od najznačajnijih faktora rizika za razvoj glaukoma na koji se može uticati adekvatnom medikamentoznom terapijom. Terapija lekovima predstavlja glavni vid lečenja glaukoma, jer je efikasna, sigurna, praktična i jeftina.

Cilj: Cilj rada bio je analiza potrošnje lekova kao i troškova lečenja glaukoma na mesečnom i godišnjem nivou u Republici Srbiji u periodu od 2015. do 2020. godine.

Materijal i metode: Istraživanje je zasnovano na retrospektivnoj analizi podataka za period od 2015. do 2020. godine koji su prikupljeni sa zvaničnih sajtova Agencije za lekove i medicinska sredstva Srbije i Instituta za javno zdravlje Srbije „Dr. Milan Jovanović Batut" za ispitivanje potrošnje i troškova lekova u Republici Srbiji.

Rezultati: Prikazani su podaci o potrošnji lokalne antiglaukomske terapije, kao i cena mesečne i godišnje terapije po pacijentu u periodu od 2015. do 2020. godine. Najkorišćeniji lekovi bili su iz grupa analoga prostangladina (latanoprost) i beta-blokatora (timolol), dok su od fiksnih kombinacija najčešće propisive timolol-dorzolamid i timolol-latanoprost.

Zaključak: Detaljnom analizom podataka, uočena je najveća potrošnja latanoprosta, zatim timolola i fiksne kombinacije timolol-dorzolamida. Najpristupačniji lek bio je timolol, dok su cene svih lekova generalno opadale u periodu od 2015. do 2020. godine. Najveći pad potrošnje zabeležen je kod pilokarpina u toku petogodišnjeg perioda.

Ključne reči: glaukom, antiglaukomski lekovi, potrošnja, intraokularni pritisak

Drug consumption and costs of the glaucoma therapy in the Republic of Serbia

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Introduction: In glaucoma therapy, the main goal is to preserve the patient's visual function and quality of life. Elevated IOP is one of the most significant risk factors for the development of glaucoma, which can be influenced by adequate drug therapy. Drug therapy is the main form of glaucoma treatment because it is effective, safe, practical and cheap.

Objective: The objective of the research was to analyze the consumption of drugs as well as the costs of glaucoma treatment on a monthly and annual basis in the Republic of Serbia in the period from 2015 to 2020.

Material and methods: The research is based on a retrospective analysis of data for the period from 2015 to 2020, which were collected from the official websites of the Agency for Medicines and Medical Devices of Serbia and the Institute for Public Health of Serbia „Dr. Milan Jovanović Batut" for examining the consumption and costs of medicines in the Republic of Serbia.

Results: Data on the consumption of local antiglaucoma therapy, as well as the price of monthly and annual therapy per patient in the period from 2015 to 2020, are presented. The most used drugs were from the groups of prostaglandin analogs (latanoprost) and beta-blockers (timolol), while the most commonly prescribed fixed combinations were timolol-dorzolamide and timolol-latanoprost.

Conclusion: A detailed analysis of the data revealed the highest consumption of latanoprost, followed by timolol and the fixed combination of timolol-dorzolamide. The most affordable drug was timolol, while the prices of all drugs generally decreased in the period from 2015 to 2020. The largest decrease in consumption was recorded for pilocarpine during the five-year period.

Keywords: glaucoma, antiglaucoma drugs, consumption, intraocular pressure

Toksični efekti hinolona: dokazi iz pretkliničkih i kliničkih istraživanja

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Uvod: Fluorohinoloni predstavljaju jednu od najpropisivanijih grupa antibiotika u svetu. Uprkos njihovoj efikasnosti, fluorohinoloni su povezani sa značajnim toksičnim efektima, uključujući tendinopatije, aortopatije i neurotoksičnost, što dovodi do ozbiljnih kliničkih posledica.

Cilj: Cilj ovog istraživanja bio je integrisati dokaze iz pretkliničkih i kliničkih ispitivanja kako bi se sagledala priroda i mehanizam toksičnih efekata fluorohinolona, s posebnim fokusom na tendinopatije i oštećenja aorte.

Metodologija: Pretraga naučnih radova sprovedena je na osnovu ključnih reči poput „quinolone", „adverse effects" i „tendon injury" koristeći baze podataka poput Google Scholar. Analizirani su radovi dostupni na engleskom jeziku, objavljeni pre marta 2023. godine, s fokusom na rezultate iz kontrolisanih istraživanja i retrospektivnih analiza.

Rezultati: Pretklinička istraživanja ukazuju da fluorohinoloni, poput ciprofloksacina, povećavaju ekspresiju matriksnih metaloproteinaza (MMP) i smanjuju sintezu inhibitora ovih enzima (TIMP), što dovodi do slabljenja ekstracelularnog matriksa tetiva i zida aorte. Kod miševa sa Marfanovim sindromom, ciprofloksacin je povećao incidencu rupture aorte na 79%, uz značajnu fragmentaciju elastičnih vlakana i smanjenu ekspresiju enzima LOX. U istraživanjima na pacijentima, incidenca tendinopatija uzrokovanih fluorohinolonima iznosila je između 0,5% i 2%, dok je kod osoba starijih od 60 godina rizik povećan za čak 8,3 puta. Klinička ispitivanja su takođe potvrdila da istovremena primena fluorohinolona i glukokortikoida nosi devet puta veći rizik od razvoja tendinopatija.

Zaključak: Rezultati ukazuju na jaku povezanost između primene fluorohinolona i razvoja toksičnih efekata, posebno kod pacijenata sa predispozicijama poput kardiovaskularnih bolesti i starije populacije. Zbog ozbiljnih posledica, preporučuje se oprez u propisivanju ovih lekova, posebno u rizičnim grupama, uz razmatranje alternativnih terapija.

Ključne reči: hinoloni, ciprofloksacin, tendinopatije, oštećenja aorte

Toxic effects of quinolone: evidence from preclinical and clinical studies

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Introduction: Fluoroquinolones are among the most frequently prescribed antibiotics worldwide. Despite their efficacy, fluoroquinolones are associated with significant toxic effects, including tendinopathies, aortopathies, and neurotoxicity, resulting in serious clinical consequences.

Objective: This research aimed to synthesize evidence from preclinical and clinical investigations to understand the nature and mechanisms of fluoroquinolone-induced toxic effects, focusing on tendinopathies and aortic damage.

Methodology: A literature review was conducted using keywords such as „quinolone", „adverse effects" and „tendon injury" in databases like Google Scholar. The analysis included full-text studies published in English before March 2023, focusing on data from controlled studies and retrospective analyses.

Results: Preclinical studies reveal that fluoroquinolones, such as ciprofloxacin, increase the expression of matrix metalloproteinases (MMPs) while reducing the synthesis of tissue inhibitors of metalloproteinases (TIMPs), leading to the weakening of the extracellular matrix in tendons and aortic walls. In mice with Marfan syndrome, ciprofloxacin increased the incidence of aortic rupture to 79%, with significant fragmentation of elastic fibers and reduced expression of the LOX enzyme. In patient studies, the incidence of fluoroquinolone-induced tendinopathies ranged from 0.5% to 2%. Among individuals aged over 60, the risk was 8.3 times higher. Clinical trials also showed that co-administration of fluoroquinolones and glucocorticoids carries a ninefold increased risk of developing tendinopathies.

Conclusion: The findings highlight a strong association between fluoroquinolone use and toxic effects, particularly in patients with predispositions such as cardiovascular conditions and the elderly. Given the severe consequences, caution is advised in prescribing these drugs, especially in high-risk groups, and alternative therapies should be considered.

Keywords: quinolones; ciprofloxacin; tendinopathy; damage to the aorta.

Upotreba *off-label* lekova u lečenju novorođenčadi: Iskustva sa Odeljenja za neonatalnu intenzivnu negu i terapiju

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Off-label primena lekova podrazumeva primenu za indikacije koje nisu opisane u sažetku karakteristika o leku, u dozi koja je veća ili manja od dozvoljene, kod dece van definisanog opsega godina, van utvrđenog puta primene za određeni lek i u indikacijama kada je prema dozvoli primena kontraindikovana.

Cilj istraživanja je ispitivanje stepena primene *off-label* lekova kod novorođenčadi na Odeljenju za neonatalnu intenzivnu negu i terapiju Instituta za zdravstvenu zaštitu dece i omladine Vojvodine u Novom Sadu.

Retrospektivno su prikupljani podaci pacijenata hospitalizovanih u periodu od januara do decembra 2023. godine, uključujući pol, gestacijsku starost, porođajnu telesnu masu, porođajnu težinu, dijagnozu, uzrast, dužinu hospitalizacije i terapiju.

Najveći broj pacijenata čine ročna novorođenčad (gestacijska starost ≥37 gestacijskih nedelja). Kod svih pacijenata su se primenjivali antiinfektivni lekovi za sistemsku primenu i lekovi za oboljenja alimentarnog trakta i metabolizma i kardiovaskularnog sistema. Najčešće primenjeni lekovi su bili gentamicin, vitamin D3, probiotik, kofein, fentanil, dopamin, poraktant-α i flukonazol, a najviše različitih vrsta lekova dobili su pacijenti između 24. i 27. gestacijske nedelje.

Kod prevremeno rođene novorođenčadi prema sažetku karakteristike leka postoji mali broj odobrenih lekova. Kod terminski rođene novorođenčadi veći broj lekova je odobren za primenu u poređenju sa prevremeno rođenom, ali se terapijski režimi najčešće razlikuju u odnosu na preporučene. Potrebne su dodatne studije kako bi se dobio jasniji uvid u vrstu lekova koji se primenjuju u novorođenačkoj populaciji i time dale smernice za bezbedniju primenu.

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Use of *off-label* drugs in the treatment of neonates: Experience from the Neonatal intensive care and therapy departmens

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Off-label drug use refers to the administration of medications for indications not described in the summary of product characteristics, at doses higher or lower than the approved dose, in children outside the defined age range, through routes of administration not specified for a particular drug, and for indications where the use is contraindicated according to the approved indications.

The aim of this study is to examine the extent of *off-label* drug use in neonates at the Neonatal Intensive Care and Therapy Department of the Institute for Health Protection of Children and Youth of Vojvodina in Novi Sad.

Retrospective data were collected from patients hospitalized between January and December 2023, including gender, gestational age, birth weight, birth weight, diagnosis, age, length of hospitalization, and therapy.

The majority of patients were full-term neonates (gestational age ≥37 weeks). All patients were treated with anti-infective medications for systemic use, as well as drugs for gastrointestinal, metabolic, and cardiovascular disorders. The most commonly used drugs were gentamicin, vitamin D3, probiotics, caffeine, fentanyl, dopamine, poractant-α, and fluconazole. The highest number of different medications was administered to patients between the 24th and 27th gestational week.

In preterm neonates, there is a small number of approved medications according to the summary of product characteristics. In full-term neonates, a greater number of drugs are approved for use compared to preterm neonates; however, therapeutic regimens often differ from the recommended ones. Further studies are needed to gain a clearer understanding of the types of medications used in the neonatal population, which will provide guidelines for safer drug administration.

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Značaj fiksnih kombinacija u terapiji hipertenzije

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Uvod: Kardiovaskularne bolesti su vodeći uzroci umiranja u svetu i kod nas. Jedan od glavnih faktora rizika za nastanak kardiovaskularnih bolesti je arterijska hipertenzija. Lekovi prvog izbora u lečenju arterijske hipertenzije su: diuretici, beta adrenergički blokatori, blokatori kalcijumskih kanala, inhibitori angiotenzin konvertujućeg enzima i blokatori angiotenzin II receptora. Fiksna kombinacija antihipertenzivnih lekova pojednostavljuje lečenje i poboljšava saradnju bolesnika.

Cilj: Cilj rada bio je da se analizira potrošnja fiksnih kombinacija lekova za lečenje arterijske hipertenzije u Republici Srbiji za period 2008.-2015. godine i da se dobijeni rezultati uporede sa onim u Finskoj i Norveškoj tokom posmatranog perioda.

Materijal i metode: Potrošnja lekova izražena je po broju definisanih dnevnih doza na 1000 stanovnika na dan prema anatomsko-terapijsko-hemijskoj klasifikaciji. Podaci o potrošnji lekova preuzeti su sa zvaničnih internet stranica od Agencije za lekove i medicinska sredstva Srbije, Finske agencije za lekove (Fimea) i Norveškog instituta za javno zdravlje za period 2008.– 2015. godina.

Rezultati: Najveća potrošnja lekova u sve tri zemlje odnosi se na lekove za lečenje kardiovaskularnih bolesti (grupe C). U okviru ove grupe lekova u sve tri zemlje najveća je potrošnja ACE inhibitora. U Srbiji se najviše koriste fiksne kombinacije ACE inhibitora sa diureticima.

Zaključak: Potrošnja lekova koji se svrstavaju u lekove prvog izbora u lečenju hipertenzije u Srbiji je neujednačena. Ovakva neujednačena potoršnja se ne uočava ni u Norveškoj ni u Finskoj.

Ključne reči: arterijska hipertenzija, potrošnja fiksnih kombinacija lekova, farmakoepidemiologija

The importance of fixed-dose combinations in therapy of hypertension

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Introduction: Cardiovascular diseases are the leading cause of death world wide as well as in our country. Hypertension is one of the major risk factors of cardiovascular complications. The treatment choice of hypertension is made with: diuretics, beta adrenergic blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and inhibitors of angiotensin II receptor. Fixed combinations of antihypertensive drugs simplify treatment and enhance patient is compliance.

Objective: The aim of this study was to analyze consumption of fixed combinations of drugs for the treatment of hypertension in the Republic of Serbia in the period 2008-2015 and to compare it with the results in Finland and Norway for the same period.

Material and methods: Consumption of finished drugs is expressed by the number of defined daily doses per 1,000 inhabitants per day according to the anatomical therapeutic chemical classification. Data on consumption of medicinal products are taken from the official website of the Agency for medicines and medical devices of Serbia, the Finnish medicines agency (Fima) and the Norwegian institute of Public Health for the period 2008-2015.

Results: The highest consumption of drugs in all three countries relates to medicines for the treatment of cardiovascular diseases (group C). Within this group of drugs in all three countries most spending ACE inhibitors. In Serbia, the most used fixed combinations of ACE inhibitors with diuretics.

Conclusion: Consumption of drugs that are classified as drugs of first choice in the treatment of hypertension in Serbia is uneven. Such uneven consumption is not observed either in Norway or in Finland.

Keywords: hypertension, consumption fixed combinations of drugs, pharmacoepidemiology