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Drugi hrvatski kongres kliničke farmakologije i terapije
s međunarodnim sudjelovanjem
Klinička farmakologija: racionalna terapija za današnje izazove

Second Croatian Congress of Clinical Pharmacology and Therapeutics
with International Participation
Clinical Pharmacology: Rational Therapy for Today's Challenges

pharmaca

GLASILO HRVATSKOG DRUŠTVA ZA
KLINIČKU FARMAKOLOGIJU I TERAPIJU

HRVATSKI ČASOPIS ZA FARMAKOTERAPIJU

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Final Programme and Abstracts

from the

Second Croatian Congress Of Clinical Pharmacology And Therapeutics With International Participation

Theme: *Clinical Pharmacology: Rational Therapy for Today's Challenges*

18-20 September, Opatija, Croatia

Guest Editors:

Dinko Vitezić

Viktorija Erdeljić Turk

SADRŽAJ / *CONTENTS*

EDITORIAL

With this new supplement, our journal once again shows its active role in congresses, something I am especially pleased about. As always, we are publishing abstracts of lectures, posters, and workshops, with the hope that they will best present the Second Croatian Congress of Clinical Pharmacology and Therapeutics with international participation, to be held in Opatija from September 18 to 20, 2025. The Congress is organized by the Croatian Society for Clinical Pharmacology and Therapeutics of the Croatian Medical Association, under the patronage of the Ministry of Health of the Republic of Croatia, with the strong support of the University of Rijeka School of Medicine and the University Hospital Centre Rijeka.

Opatija is not only a wonderful place for rest and leisure but also a well-established venue for high-quality and well-attended congresses. Beyond its beautiful promenades and blue sea, it has long supported science and expertise, making it a natural choice for our meeting once again.

Because clinical pharmacology is always oriented towards the future, this year's Congress will focus on perspectives in new therapies, along with their benefits, limitations, and challenges. The main theme is "Clinical Pharmacology: Rational Therapy for Today's Challenges." The program includes plenary lectures, symposia, sessions, and workshops designed for both experienced professionals and young pharmacologists. Topics range from regulatory issues, rational pharmacotherapy, drug use in special patient groups, and drug hypersensitivity, to focused discussions on oncology, cardiovascular drugs, antimicrobials, and immunotherapy. The multitude of topics ensures that every participant will find an area of interest.

We are also proud to highlight our collaboration with the British Pharmacological Society and the editors of the British Journal of Clinical Pharmacology. These partnerships confirm that the Croatian Society for Clinical Pharmacology and Therapeutics is fully aligned with international institutions in its ideas, commitment, research, education of young professionals, and wide range of activities.

Every congress is a valuable opportunity to meet colleagues, share opinions, discuss, learn, and enjoy time together. I therefore wish this Congress every success in its scientific program, as well as many opportunities for collegial exchange and collaboration.

Prim. Ksenija Makar-Aušperger, MD, PhD

Editor-in-Chief

UVODNIK

Još jedan suplement u našem časopisu znači da smo aktivni i na polju kongresa i to mi je neobično drago. Kao i uvijek donosimo sažetke predavanja, postera i radionica, nadajući se da će oni na najbolji mogući način predstaviti Drugi hrvatski kongres kliničke farmakologije i terapije s međunarodnim sudjelovanjem koji se održava u Opatiji od 18. do 20. rujna 2025. godine. Kongres organizira Hrvatsko društvo za kliničku farmakologiju i terapiju Hrvatskog liječničkog zbora pod pokroviteljstvom Ministarstva zdravstva Republike Hrvatske i uz veliku pomoć Medicinskog fakulteta Sveučilišta u Rijeci te Kliničkog bolničkog centra Rijeka.

Opatija je nezaobilazno mjesto, kako za dobar odmor, tako i za kvalitetne i posjećene kongrese. Opatija je svakako puno više od prekrasnih šetnica i plavog mora, ona podržava stručnost i znanost pa ne čudi da je i ovaj puta izabrana za mjesto našeg kongresa.

A kako je klinička farmakologija uvijek okrenuta prema budućnosti, tako i Kongres donosi perspektive novih terapija sa svim prednostima, manama i izazovima. Stoga je i glavna tema: „Klinička farmakologija: racionalna terapija za današnje izazove“. Brojna su predviđena plenarna predavanja, simpoziji, sekcije i radionice, za iskusne, ali i mlade i buduće kliničke farmakologe. Regulativni problemi na području lijekova, racionalna farmakoterapija, primjena lijekova u posebnih skupine bolesnika, preosjetljivost na lijekove samo su neka od tema kojima će se Kongres posebno baviti, a naglasak na onkološikim, kardiovaskularnim, antimikrobnim lijekovima i imunoterapiji je apsolutno razumljiv i prihvatljiv. Brojnost tema sigurno će pomoći svakome da pronađe onaj dio koji ga najviše zanima!

Treba istaći suradnju s Britanskim farmakološkim društvom (British Pharmacology Society) kao i s urednicima Britanskog časopisa za kliničku farmakologiju (British Journal of Clinical Pharmacology) što sve ukazuje da se Hrvatsko društvo za kliničku farmakologiju i terapiju uklapa u međunarodne institucije po svojim idejama, predanosti, istraživanju, edukaciji mladih, brojnim aktivnostima i radu.

Svaki kongres je odlična prilika za susrete, upoznavanje kolega, dijeljenje mišljenja, raspravljanje, učenje, ali i druženje. Stoga Kongresu želim svakako uspješan rad, ali i mnogo prilika upravo za druženje.

Prim. dr. sc. Ksenija Makar-Aušperger

Glavna urednica časopsa Pharmaca

FOREWORD

It is my great pleasure to present this supplement of Pharmaca Journal, which brings together the abstracts from the Second Croatian Congress of Clinical Pharmacology and Therapeutics with International Participation, held in Opatija, Croatia, from September 18–20, 2025.

The Croatian Society for Clinical Pharmacology and Therapeutics (HDKFiT) organized this Congress under the central theme: “Clinical pharmacology: rational therapy for today’s challenges.” This theme reflects the dynamic development of our discipline in contemporary setting. Today, clinical pharmacology is characterized by rapidly advancing research, new therapeutic approaches, and the ongoing challenge of aligning medical innovations with the financial resources of healthcare systems and frameworks for covering the costs of novel therapies. These issues affect health systems worldwide and highlight the importance of gatherings such as this Congress, where knowledge and experience can be shared across the field.

The scientific program was carefully structured to address the key questions of clinical pharmacology and therapeutics. In addition to plenary lectures, symposia, and interactive sessions, the Congress opened with pre-congress activities for young clinical pharmacologists, providing opportunities for education, networking, and mentorship. A special workshop on different designs of clinical trials further enriched the program, offering practical insights into one of the most important methodological foundations of our field. We are particularly proud of our collaboration with the British Pharmacological Society (BPS), highlighted by a joint symposium on rare diseases, as well as with the editors of the British Journal of Clinical Pharmacology (BJCP), which further strengthened the international dimension of the event. The multidisciplinary exchange, bringing perspectives from academia, clinical practice, and industry, enriched discussions and broadened our understanding of rational pharmacotherapy in today’s healthcare environment.

This Congress was made possible through the generous support of our sponsors, whose recognition of the importance of clinical pharmacology we greatly value. All sponsors are acknowledged in the Congress materials and are listed at the end of this issue. We also extend our gratitude to the Ministry of Health of the Republic of Croatia, under whose auspices the Congress is held, as well as to our partners, Faculty of Medicine, University of Rijeka, and the University Hospital Centre Rijeka, for their strong support and collaboration.

Opatija, with its unique charm on the Adriatic coast, provided an inspiring setting for this meeting. Beyond its scientific program, the Congress offered an opportunity to strengthen professional connections and friendships, while enjoying the cultural heritage and natural beauty of the Kvarner region.

We believe that the abstracts collected in this issue reflect the breadth and quality of contributions presented at the Congress. They represent not only progress in clinical pharmacology but also the spirit of collaboration and commitment to improving patient care that defines our field.

On behalf of the Croatian Society for Clinical Pharmacology and Therapeutics, I extend my sincere thanks to all authors, participants, and partners who contributed to the success of this Congress. We look forward to future opportunities to advance clinical pharmacology together and to continue building bridges between science, practice, and health policy.

Professor Dinko Vitezić, MD, PhD

President, Croatian Society for Clinical Pharmacology and Therapeutics Croatian Medical Association

PREDGOVOR

Dragi kolege,

Veliko mi je zadovoljstvo predstaviti ovaj suplement časopisa Pharmaca, u kojem su okupljeni sažetci Drugog hrvatskog kongresa kliničke farmakologije i terapije s međunarodnim sudjelovanjem, održanog u Opatiji, Hrvatska

Hrvatsko društvo za kliničku farmakologiju i terapiju (HDKFiT) organiziralo je ovaj Kongres s glavnom temom: „Klinička farmakologija: racionalna terapija za današnje izazove“. Ova tema odražava dinamičan razvoj naše discipline u suvremenom okružju. Klinička farmakologija danas je obilježena brzim razvojem istraživanja, novim terapijskim pristupima te izazovima usklađivanja medicinskih dostignuća s resursima zdravstvenih sustava i okvirima koji su mogući za pokrivanje troškova novih terapija. Ta pitanja utječu na zdravstvene sustave diljem svijeta i naglašavaju važnost skupova poput ovog našeg Kongresa, gdje možemo razmjenjivati znanja i iskustva u ovom području.

Znanstveni program pažljivo je oblikovan kako bi obradio ključna pitanja kliničke farmakologije i terapije. Uz plenarna predavanja, simpozije i interaktivne sekcije, Kongres je započeo s predkongresnim aktivnostima namijenjenima mladim kliničkim farmakolozima, koji su pružili priliku za edukaciju, umrežavanje i mentorstvo. Posebna radionica o različitim dizajnima kliničkih ispitivanja dodatno je obogatila program, nudeći praktičan uvid u jednu od najvažnijih metodoloških osnova naše discipline. Posebno smo ponosni na suradnju s Britanskim farmakološkim društvom (BPS), naglašenu zajedničkim simpozijem o rijetkim bolestima kao i sa suradnjom s urednicima Britanskog časopisa za kliničku farmakologiju (BJCP), čime je dodatno ojačana međunarodna dimenzija događaja. Multidisciplinarna razmjena, uključujući motrište iz akademske zajednice, kliničke prakse i industrije, obogatila je raspravu i proširila naše razumijevanje racionalne farmakoterapije u današnjem zdravstvenom okruženju.

Ovaj Kongres omogućila je velikodušna potpora naših sponzora, čije prepoznavanje važnosti kliničke farmakologije iznimno cijenimo. Svi sponzori navedeni su u kongresnim materijalima te na kraju ovog izdanja. Također izražavamo zahvalnost Ministarstvu zdravstva Republike Hrvatske, pod čijim se pokroviteljstvom Kongres održava, kao i našim suradnim ustanovama, Medicinskom fakultetu Sveučilišta u Rijeci i Kliničkom bolničkom centru Rijeka na snažnoj potpori.

Opatija, sa svojim jedinstvenim šarmom na jadranskoj obali, pruža inspirativno okruženje za ovaj skup. Osim bogatog znanstvenog sadržaja, Kongres je prilika za jačanje profesionalnih veza i prijateljstava, uz doživljaj kulturne baštine i prirodnih ljepota Kvarnerskog područja.

Vjerujemo da sažeci okupljeni u ovom izdanju odražavaju širinu i kvalitetu priloga predstavljenih na Kongresu. Oni ne predstavljaju samo napredak u kliničkoj farmakologiji, već i duh suradnje te predanosti unaprjeđenju skrbi za pacijente koji definira naše područje.

U ime Hrvatskog društva za kliničku farmakologiju i terapiju, srdačno zahvaljujem svim autorima, sudionicima i partnerima koji su pridonijeli uspjehu ovog Kongresa. Veselimo se budućim prilikama za zajednički napredak kliničke farmakologije te nastavku izgradnje mostova između znanosti, prakse i zdravstvene politike.

Prof. dr.sc.Dinko Vitezić, dr.med.

Predsjednik, Hrvatsko društvo za kliničku farmakologiju i terapiju
Hrvatski liječnički zbor

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CONGRESS ORGANISED BY

Croatian Society of Clinical Pharmacology and Therapeutics, Croatian Medical Association

UNDER THE AUSPICES

Ministry of Health of the Republic of Croatia

Faculty of Medicine of the University of Rijeka

University Hospital Centre Rijeka

PROGRAM / PROGRAME

ČETVRTAK / THURSDAY (18.09.2025.)

08.45 – 11.00

Pre-Congress Symposium: *Young Clinical Pharmacologists – Opportunities and Challenges*

09.00 – 09.45 Presentations and Discussion

Andrej Belančić: *Academic-scientific and professional opportunities for young clinical pharmacologists: career path and opportunities along the way*

Ivana Stević: *Opportunities in the pharmaceutical world – from clinical trials through regulation and market access to clinical research*

Petar Mas: *PRAC experience of a young clinical pharmacologist*

Dominik Strikić: *Clinical aspect of the newest young specialist in clinical pharmacology in Croatia*

Robert Likić: *Options for young clinical pharmacologists from a mentor's perspective – "Yesterday, Today and Tomorrow"*

Best selected abstract by a young clinical pharmacologist or student with work in clinical pharmacology

09.45 – 10.35

Round Table: *Shaping the Future of Clinical Pharmacology: Global Perspectives and Career Pathways*

Moderator: Robert Likić

Topics to be covered: *Education and Training Opportunities, Residency / Specialization Pathways, Career Options and Market Demand, Research Opportunities and Access, Differences in National Roles, Organization and Responsibilities, International Mobility and Collaboration*

Panelists: Andrej Belančić, Juraj Ban Jović, Slobodan Janković, Farideh Javid, Sandra Knežević, Noora Kula, Kaisa Litonius, Ines Potočnjak, Igor Rubinić, Tabassome Simon, Dominik Strikić, Dinko Vitezić

Closing Remarks and invitation to the Workshop on Clinical Trials.

11.00-13.00 **Workshop**: Tabassome Simon (Paris, France): *Different designs of clinical trials*

Cilj ove radionice je pregledati trenutno korištene dizajne (uključujući umbrella i basket) za klinička ispitivanja, opisivanjem njihovih obilježja, prednosti i nedostataka, uz korištenje praktičnih primjera.

The aim of this workshop is to review currently used designs (including umbrella and basket) for clinical trials, by describing their characteristics, their advantages and disadvantages, using practical examples.

14.00-14.30 OTVARANJE KONGRESA / *CONGRESS OPENING CEREMONY*

14.30-15.00 PLENARNO IZLAGANJE / *PLENARY LECTURE*

Tabassome Simon (Pariz/Paris, Francuska, France): *Developing Clinical Pharmacology in a University Hospital: My Journey as a Clinical Pharmacologist*

Predsjedavajući / Chair: Suzana Mimica

15.00-16.30 Izazovi u Kliničkoj Farmakologiji I / *Challenges in Clinical Pharmacology I*

Predsjedavajući / *Chairs*: Iveta Merćep and Suzana Mimica

15.00-15.20 **I**veta Merćep: Klinička ispitivanja u Hrvatskoj – uloga i izazovi SEP-a u njihovu odobravanju / *Clinical Trials in Croatia – Role and Challenges of the Central Ethics Committee in the Approval Process*

15.20-15.40 Suzana Mimica: Depreskripcija i polipragmazija / *Deprescribing and Polypharmacy*

15.40-16.00 Matea Radačić Aumiler: Izazovi primjene lijekova u trudnoći / *Dilemmas in Drug Use During Pregnancy*

16.00-16.20 Maja Ilijanić Samošćanec: Točnost medicinskih savjeta danih dojiljama / *Accuracy of Medical Advice Given to Breastfeeding Women*

16.30 – 17.00 Pauza za kavu / *Coffee Break*

17.30 – 18.30 Kakva je dostupnost lijekova u Hrvatskoj? / *What is the Current State of Drug Availability in Croatia?*

Predsjedavajući / *Chairs*: Tea Strbad i Tonći Buble

17.30-17.50 Tonći Buble: Dostupnost lijekova u RH – drugačiji pogled / *Drug Availability in Croatia – A Different Perspective*

17.50-18.10 Jelena Matuzović: Dostupnost novim lijekovima na teret

obveznog zdravstvenog osiguranja / *Availability of New Medicines Reimbursed by the National Health Insurance*

18.10-18.30 Tea Strbad: Praćenje ishoda i dostupnost lijekova / *Monitoring Treatment Outcomes and Drug Availability*

Okrugli stol / *Panel Discussion*: Dostupnost lijekova / *Access to Medicines*

Moderator: *Dinko Vitezić*

Panelisti / *Panelists*: Tonći Buble, Jelena Matuzović, Tea Strbad, Iveta Merćep, Suzana Mimica

Zaključci panel rasprave / *Conclusions of the Panel Dicussion*

18.30 Prijem dobrodošlice i druženje/ Welcome & Networking reception

PETAK / *FRIDAY* (19.09.2025.)

08.15-10.00 Antibiotici s mjerom: izazovi I mogućnosti

***Predsjedavajući / Chairs**: Vera Vlahović- Palčevski i Iva Mikulić*

08.15-8.30 Iva Mikulić: Alergija na penicilin: vrijeme za preispitivanje, ponovnu procjenu i uklanjanje netočnih dijagnoza / *Penicillin Allergy – Time for Reassessment and Removal of Inaccurate Diagnoses*

08.30-8.45 Zvonimir Čagalj: Izazovi u primjeni antibiotika u primarnoj zdravstvenoj zaštiti / *Challenges in Antibiotic Use in Primary Healthcare*

08.45-9.00 Igor Rubinić: Višestruko otporne bakterije: ima li lijeka? / *Multidrug-Resistant Bacteria – Is There a Cure?*

09.00-9.15 Slobodan Janković (Kragujevac, Srbija): Prediktori ciljnih vrijednosti PK/PD indeksa ceftazidima i toksične razine lijeka u plazmi odraslih hospitaliziranih pacijenata / *Predictors of Target PK/PD Indices and Toxic Plasma Levels of Ceftazidime in Hospitalized Adult Patients*

09.15-9.30 Vera Vlahović-Palčevski: Antimikrobna terapija danas: gdje smo i kamo idemo? / *Antimicrobial Therapy Today – Where Are We and Where Are We Headed?*

09.30-10.00 **Rasprava / *Discussion***

10.00-10.30 Pauza za kavu / *Coffee Break*

10.30-12.30 ***Rare Diseases & Orphan Medicines***
Joint Symposium: *BJCP/BPS and Croatian Society of Clinical Pharmacology and Therapeutics*

Predsjedavajući / *Chairs: Serge Cremers and Dinko Vitezić***

10.30-10.50 Dinko Vitezić: *Regulatory Aspects of Orphan Medicines Approval in the EU – Challenges in Ensuring Patient Access*

10.50-11.10 Robert Likić: *AI and Machine Learning in Rare Diseases and Orphan Medicines: Identifying Therapeutic Targets through In Silico Approaches*

11.10-11.30 Oscar Della Pasqua (London, UK): *Dose rationale and clinical*

trial design optimization in early development of orphan medicines

11.30-12.30 Andrej Belančić: *Real-World Insights and Economic Implications of Orphan Medicines – Examples from Spinal Muscular Atrophy*

12.30-13.00 **PLENARNO IZLAGANJE / *PLENARY LECTURE***
Serge Cremers (New York, USA): *Lab-based Clinical Pharmacology in Support of Patient Care*

Predsjedavajući / *Chair:* Robert Likić

14.00 – 16.00 Farmakoterapija u hemato-onkologiji – gdje smo danas? / *Pharmacotherapy in Hemato-Oncology – Where Do We Stand Today?*

Predsjedavajući/Chairs: *Viktorija Erdeljić Turk, Elitza Petkova Markova-Car*

14.00-14.20 Viktorija Erdeljić Turk: Kombinirana terapija u onkologiji: novi standard / *Combination Drug Therapies in Oncology: the new standard*

14.20-14.40 Inga Mandac Smoljanović: Transfuzijska ovisnost i ukupno preživljenje – nova saznanja i dileme / *Transfusion Dependence and Overall Survival – New Insights and Emerging Dilemmas*

14.40-15.00 Dražen Huić: Radioligandna terapija – novo poglavlje u personaliziranom onkološkom liječenju /
Radioligand Therapy – A New Chapter in Personalized Cancer Treatment

15.00-15.20 Luka Vončina:
Epizode skrbi – prema održivoj zdravstvenoj skrbi utemeljenoj na vrijednostima /
Episodes of Care – Toward Sustainable, Value-Based Healthcare

15.20-15.40 Elitza Petkova Markova-Car:
Precizna medicina u onkologiji – doprinos farmakogenomike i kronoterapije u liječenju karcinoma debelog crijeva /
Precision Medicine in Oncology – *The Role of Pharmacogenomics and Chronotherapy in Colorectal Cancer Treatment*

15.40-16.00 **Rasprava / *Discussion***

16.00-16.30 Pauza za kavu / *Coffee break*

16.30-18.20 **Šećerna bolest i debljina – kako racionalno koristiti lijekove? / *Diabetes and Obesity – How to Use Medicines Rationally?***

Predsjedavajući / *Chairs:* Jurica Nazlić, Aleksandar Knežević:

16.30-16.50 Jurica Nazlić: Uporaba lijekova u šećernoj bolesti tip II – nova saznanja / *Drug Use in Type 2 Diabetes – New Findings in Treatment*

16.50-17.10 Aleksandar Knežević: Kardiovaskularni učinci peroralnih antidijabetika / *Cardiovascular Effects of Oral Antidiabetic Drugs*

17.10-17.30 Sanja Klobučar: Debljina u fokusu – novi horizonti farmakoterapije / *Obesity in Focus – New Horizons in Pharmacotherapy*

17.30-17.50 Josipa Josipović: Novi dokazi u liječenju kronične bubrežne bolesti / New Evidence in the Treatment of Chronic Kidney Disease

17.50-18.20 **Rasprava / *Discussion***

18.20-19.15 **Okrugli stol / Round Table: Klinička farmakologija i klinička farmacija – koje su mogućnosti i prednosti suradnje/ Clinical Pharmacology**

Moderator: Viktorija Erdeljić Turk

Panelisti/Panelists: Emilija Katarina Lozo, Iva Mikulić, Matea Radačić Aumiler, Marko Skelin, Ana Soldo, David Šarčević, Dinko Vitezić

20:10 Kongresna večera / *Congress Dinner*

SUBOTA / *SATURDAY* (20.09.2025.)

08:30–09:30 Upoznajte urednike časopisa BJCP i Pharmaca /
Meet the Editors of the BJCP and Pharmaca Journal

Predsjedavajući / Chairs: Prof. Serge Cremers, Editor-in-Chief of BJCP; Asst. Prof.; Viktorija Erdeljić Turk, Editorial Secretary of the journal Pharmaca

Prof. Serge Cremers: *Introduction and Welcome Duration: 5 minutes Content: Brief introduction to the session, overview of the editorial teams, and topics to be covered.*

Prof. Serge Cremers: *Presentation on Journal Metrics, Focus, and Future Directions Duration: 10 minutes Content: Overview of BJCP journal metrics, areas of focus, opportunities for collaboration, and future strategic goals for the journal, including steps to enhance impact and readership.*

Prof. Robert Likić: *Themed Issues and Spotlight Commentaries Duration: 5 minutes Content: Insight into the development and focus of themed issues, the role of spotlight commentaries in enhancing topic-specific impact, and their relevance to the journal's audience.*

Prof. Oscar Della Pasqua: *The Importance of Peer Review: Quality, Timeliness, and Motivation Duration: 5 minutes Content: Discussion on the importance of rigorous peer review in maintaining high standards, considerations for timely reviews, and motivating reviewers to contribute meaningfully to scientific quality.*

Prof. Ana Alfirević: *Research Ethics and Research Integrity Duration: 5 minutes Content: Publishing ethical research, challenges and barriers in scientific publishing and BJCP's approach to research integrity and trustworthiness.*

Dr. Andrej Belančić: *Opportunities for Young Researchers in BJCP Duration: 5 minutes Content: Emphasis on the journal's support for young researchers, including publication pathways, mentorship, and roles within the Associate Senior Editor program to promote emerging talent.*

Asst. Prof. Viktorija Erdeljić Turk: *Pharmaca: Focus, Future Directions, and Possibilities for Collaboration*

Content: *Overview of Pharmaca journal metrics, areas of focus, opportunities for collaboration, and future strategic goals for the journal, including steps to enhance impact and readership.*

Panel Discussion and Audience Q&A, All Editors

Duration: 15 minutes

TOTAL TIME: 60 minutes

09:30–10:30 Izazovi u kliničkoj farmakologiji II / *Challenges in Clinical Pharmacology II*

Predsjedavajući / *Chairs*: Arnes Rešić, Ivana Mudnić

09.30-9.45 Arnes Rešić: Pedijatrijska klinička farmakologija – primjena beta-blokatora u terapiji infantilnih hemangioma / *Pediatric Clinical Pharmacology: Use of Beta-Blockers in the Treatment of Infantile Hemangiomas*

9.45-10.00 Hana Kalinić: Postoje li međuetničke razlike u farmakokinetici lijekova? / *Are There Interethnic Differences in Drug Pharmacokinetics?*

10.00-10.15 Ivana Mudnić: Primjena peptida u liječenju boli u palijativnoj skrbi – iskustva i izazovi / *Use of Peptides in Pain Management in Palliative Care: Current Experiences, Challenges, and Opportunities*

10.15-10.30 Sanita Maleškić Kapo (Sarajevo, BiH): Ciljana modulacija proinflamatornih puteva lokalno primijenjenim NSAIL u eksperimentalnom artritisu / *Targeted Modulation of Proinflammatory Pathways by Topically Applied NSAIDs in Experimental Collagen-Induced Arthritis*

11.00–12.15 Klinička farmakologija u regulativi lijekova / Clinical Pharmacology in Drug Regulation

Predsjedavajući / *Chairs*: Viola Macolić Šarinić, Danica Juričić Nahal

11.00-11.20 Viola Macolić Šarinić: Regulatorne mjere minimizacije rizika i primjena u praksi – san ili stvarnost? / *Risk Minimization Regulatory Measures and Their Application in Clinical Practice – Just a Dream or Reality?*

11.20-11.40 Danica Juričić Nahal: Zašto je odobrenje anti-amiloidnih protutijela za Alzheimerovu bolest izuzetno teško? / *Navigating a Complex Environment: Why Is the Approval of Anti-Amyloid Antibodies for Alzheimer's Disease So Challenging?*

11.40-12.00 Petar Mas: Uloga stvarnih dokaza i zdravstvenih registara u praćenju sigurnosti lijekova za rijetke i teške bolesti / *The Role of Real-World Evidence and Health Registries in Monitoring the Safety of Medicines for Rare and Severe Diseases*

12.00-12.20 Maja Vajagić: Razvoj Registra ishoda liječenja HZJZ-a: lijekovi izvan Liste HZZO-a / *Development of the Croatian Institute of Public Health (CIPH) Treatment Outcome Registry: Medicines Outside the Croatian Health Insurance*

Fund (HZZO) Reimbursement List

12.20–14.00 Klinička farmakologija i obiteljska medicina / *Clinical Pharmacology and Family Medicine*

Predsjedavajući / *Chairs*: Ivana Čegec, Ana Havidić

12.20-12.50 Ivana Čegec / Ana Havidić: Suradnja kliničkog farmakologa i liječnika obiteljske medicine – optimizacija terapije u primarnoj zdravstvenoj zaštiti / *Collaboration Between Clinical Pharmacologists and Family Physicians: Optimizing Therapy in Primary Care*

12.50-13.00 Nives Radošević Kvadranti / Nataša Skočibušić: Od protokola do ordinacije – suradnja kliničke farmakologije i obiteljske medicine / *How Do Clinical Pharmacology and Family Medicine Collaborate?*

13.10 - 14.00 Okrugli stol: Koje su mogućnosti boljeg povezivanja kliničke farmakologije i obiteljske medicine / *Oportunities to Strengthen the Cooperation between Clinical Pharmacology and Family Medicine*

Moderator: Suzana Mimica

Panelisti / Panelists: Ivana Čegec, Ana Havidić, Nives Radošević Kvadranti, Vjekoslava Amerl Šakić

14.00-14.15 Zatvaranje kongresa / *Congress Closing and Farewell*

SAŽETCI / ABSTRACTS

Note: The organizers are not responsible for the contents of submitted abstracts

PRE-CONGRESS SYMPOSIUM

YOUNG CLINICAL PHARMACOLOGIST – OPPORTUNITIES AND CHALLENGES

ACADEMIC-SCIENTIFIC AND PROFESSIONAL OPPORTUNITIES FOR YOUNG CLINICAL PHARMACOLOGISTS: CAREER PATH AND OPPORTUNITIES ALONG THE WAY

Andrej Belančić [1,2]

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[2] Department of Basic and Clinical Pharmacology with Toxicology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

KEYWORDS: Academia; Career Development; Clinical Pharmacology; Networking; Scientific Publishing

Young clinical pharmacologists today face a dynamic and expanding landscape of academic, scientific, and professional opportunities. Early engagement in teaching activities at Faculties of Medicine plays a pivotal role in consolidating core pharmacological knowledge, improving communication skills, and fostering academic growth.

In the scientific arena, involvement in peer-review and editorial processes offers unparalleled benefits: broadening scientific insight, learning the principles of evidence-based medicine, staying informed on the latest therapeutic developments, and building critical appraisal skills. Personal experience as an assistant senior editor, peer reviewer, and themed-issue editor across various journals exemplifies how editorial involvement serves as both a learning platform and a professional milestone. Additionally, umbrella societies such as the European Association for Clinical Pharmacology and Therapeutics (EACPT) provide structured pathways for growth through initiatives like the Early Career Clinical Pharmacologists Working Group, offering mentorship, collaboration, and international visibility.

Collectively, these academic and professional avenues not only enhance clinical and research competencies but also enable young pharmacologists to widen their networks, gain interdisciplinary insights, and shape their future roles within the field. Embracing these opportunities is essential for developing the next generation of leaders in clinical pharmacology.

OPPORTUNITIES IN THE PHARMACEUTICAL WORLD – FROM CLINICAL TRIALS THROUGH REGULATION AND MARKET ACCESS TO CLINICAL RESEARCH

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KEYWORDS: Pharmaceutical Industry; Innovation; Lifelong Learning; Professionals

The pharmaceutical industry is one of the most highly regulated industries worldwide, governed by a complex framework of legislative acts, regulatory guidelines, recommendations, instructions, etc. Within such a system, professionals working in it are required not only to possess strong qualifications but also to commit to continuous professional development and lifelong learning.

Careers in the pharmaceutical world are broad and varied, offering a diverse spectrum of career opportunities, from early-stage research and development of new drug entities to preclinical investigations and clinical trials that establish the safety and efficacy of new drugs.

After marketing authorization is obtained, additional challenges appear. For a new drug (or technology) to reach patients, creating and implementing effective pricing and market access strategies is crucial. They are not limited to economic and health technology assessments but also include negotiations with third parties, such as payers and health authorities, with the goal of balancing innovation, affordability, accessibility, and sustainability of a new health technology, such as a drug.

During the entire lifecycle of a drug, different regulatory and pharmacovigilance activities are conducted in accordance with the legal requirements of different markets in order to maintain patient safety during both the pre- and post-marketing phases.

Work in the pharmaceutical sector is no longer limited to traditional settings but is expanding into new areas, creating exciting opportunities for professionals with a biomedical background (e.g. development of personalized therapies and the utilization of digital health technologies, etc).

The pharmaceutical world operates as an ecosystem where science, regulation, and market demands have a common goal: improving patient outcomes through sustainable solutions, while providing a variety of opportunities for skilled professionals with multidisciplinary expertise and the ability to adapt to scientific, regulatory, and market changes.

PRAC EXPERIENCE OF A YOUNG CLINICAL PHARMACOLOGIST

Petar Mas[1]

[1] Agency for Medicinal Products and Medical Devices of Croatia (HALMED)

KEYWORDS: Drug Regulatory Agency; Pharmacovigilance; Regulatory Decision-Making; Clinical Pharmacology

Drug regulatory agencies in the European Economic Area are responsible for ensuring that only safe, effective, and high-quality medicines are available on the market. To achieve this, they rely on experts from diverse biomedical and pharmaceutical disciplines. Clinical pharmacologists, through their training, gain a unique combination of knowledge about medicines and practical insight into their use in everyday clinical practice. This expertise is particularly valuable in regulatory decision-making, where benefit–risk considerations must be aligned with real-world medical practice. This presentation will share the perspective of a young clinical pharmacology specialist working in pharmacovigilance and serving as a member of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which is responsible for the assessment and monitoring of the safety of human medicines and risk management. Reflections on the contribution of clinical pharmacology to regulatory science, as well as personal experiences from PRAC work, will be discussed.

CLINICAL ASPECTS OF THE NEWEST YOUNG SPECIALIST IN CLINICAL PHARMACOLOGY IN CROATIA

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KEYWORDS: Young Clinical Pharmacologists, Clinical Pharmacology; Evidence-Based Medicine

Clinical pharmacology in Croatia is a rapidly developing discipline that combines basic pharmacological knowledge with direct patient care, therapeutic optimisation and public health priorities. Young clinical pharmacologists are in a unique position at the interface of research, education and clinical practise, facing both challenges and opportunities in the national healthcare system. Their role includes individualised therapy through pharmacogenetics, safe and rational prescribing in polypharmacy and multimorbidity, and contributing to the development of national guidelines. The increasing burden of chronic diseases as well as economic constraints and the legal framework designed by the Croatian Health Insurance Fund (HZZO) emphasise the importance of cost-effectiveness analyses and the generation of real-world data. Young clinical pharmacologists are also active in hospital drug committees, pharmacovigilance and antimicrobial stewardship programmes, thus having a direct impact on patient safety and quality of care. Despite this progress, obstacles remain, including limited staffing, modest integration into multidisciplinary teams and the need for greater visibility at European level. However, international collaborations, participation in clinical trials under the EU Clinical Trials Regulation and advances in precision medicine provide a solid platform for growth. Looking to the future, young clinical pharmacologists in Croatia need to find a balance between scientific innovation and pragmatic solutions to improve the rational use of medicines, optimise resource allocation and improve patient outcomes. Their perspectives emphasise the commitment to promoting clinical pharmacology as a central pillar of evidence-based medicine in Croatia.

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OPTIONS FOR YOUNG CLINICAL PHARMACOLOGISTS FROM A MENTOR'S PERSPECTIVE – "YESTERDAY, TODAY AND TOMORROW"

Robert Likić [1,2]

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[2] School of Medicine, University of Zagreb, Zagreb, Croatia

KEYWORDS: Young Clinical Pharmacologists; Academia; Clinical Practice; Career Pathways; Mentorship

Clinical pharmacology has undergone remarkable transformation over the past decades, shaped by evolving therapeutic landscapes, advances in translational science, and growing demands from healthcare systems worldwide. For young clinical pharmacologists, the pathways to professional growth are diverse yet often challenging, requiring navigation between academia, clinical practice, regulatory affairs, and industry. From the perspective of a mentor, it is essential to highlight both the opportunities and the obstacles encountered along this journey. This lecture will reflect on the "yesterday" of the discipline, marked by the foundational role of rational therapeutics and early clinical trials; the "today," where molecular medicine, pharmacogenomics, and health technology assessment are expanding the scope of clinical pharmacology; and the "tomorrow," where artificial intelligence, personalized medicine, and global collaboration are poised to redefine the field. By drawing on personal mentoring experience and lessons learned from guiding young colleagues, the talk will emphasize how resilience, curiosity, and interdisciplinary engagement can empower the next generation of clinical pharmacologists. Ultimately, the goal is to inspire young professionals to recognize the breadth of their potential contributions and to embrace the evolving identity of clinical pharmacology as a discipline at the intersection of science, medicine, and society.vouchers for the development of new antibiotics. Despite these important improvements, there are some concerning elements in the Commission proposal. If adopted, their negative impact will overcome the positive measures just described. In particular this is the reduction of the duration of the regulatory data protection (or orphan market exclusivity) and making the recuperation of the lost years dependent on factors that are outside the control of pharmaceutical industry. EFPIA has provided extensive arguments against these proposals and has tabled alternative solutions. Europe needs to get this revision right as it will regulate the way we authorize, develop and produce medicines in Europe for the next 20 to 30 years. And this matters for patients, for the sustainability of our health systems and for our economies.

PLENARY LECTURE

DEVELOPING CLINICAL PHARMACOLOGY IN A UNIVERSITY HOSPITAL: MY JOURNEY AS A CLINICAL PHARMACOLOGIST

Tabassome Simon [1,2]

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KEYWORDS: Clinical Pharmacology; University Hospital; Drug Development; Clinical Research; Career Progression; Lecturer

The journey to becoming a clinical pharmacologist in a university hospital unfolds through several distinct stages, each building on the last. It begins in medical school, where foundational knowledge is established. This is followed by an introduction to pharmacology at the university level, sparking an interest in drug development and therapeutics.

Next, mine started as a physician within a pharmacology department, initially focusing on early-phase clinical trials. For example, during this stage, I worked on evaluating the relationship between phenotype, genotype and drug response in phase I and phase II studies, which provided essential insights into the complexities of clinical research. The progression continued with the design and coordination of phase III clinical trials and observational studies. For instance, I contributed to large-scale studies assessing drug efficacy and efficacy in patient with myocardial infarction but also others comparing the sex and gender differences in cardiovascular risk factors, drug response and outcomes. Completing The PhD thesis, an endeavor that allows to refine one's research skills and deepen one's expertise, was a pivotal moment in my career, opening new doors in academic and clinical research. With growing experience, advancement to lecturer positions became possible. This role allowed for mentoring new students and sharing knowledge gained from practical research. My appointment as a lecturer enabled me to guide future clinical pharmacologists, fostering the next generation of leaders in the field. The path lead to becoming a full professor of medicine and pharmacology—a position that recognizes notable achievements such as significant publications, leadership roles in research consortia, or awards.

Throughout this progression, each stage has been marked by meaningful experiences and achievements, all of which shape a career. By highlighting a few concrete examples, this story aims to inspire younger people who are considering following a similar path.

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CHALLENGES IN CLINICAL PHARMACOLOGY I

DEPRESCRIBING AND POLYPHARMACY

Suzana Mimica [1,2]

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KEY WORDS: Polypharmacy, Drug Interactions, Rational Therapy; Potentially Inappropriate Medication; Beers Criteria

Polypharmacy is associated with increased risk of drug–drug interactions, adverse drug reactions (ADRs), hospitalizations, and higher healthcare costs. The optimal approach to a patient with polypharmacy is complex and should be individualised. Clinical pharmacologists play a significant role in the management of polypharmacy, based on their expertise in pharmacotherapy and medicine in general, they are able to perform adequate medication reviews and implement personalized deprescribing. Some authors suggest a comprehensive approach termed “polypharmacy stewardship.”

Closely related to polypharmacy in older adults is the “prescribing cascade,” when a medication is prescribed to treat the side effect of another drug, often leading to a chain reaction of further polypharmacy and inappropriate medication use. A list of 65 significant potentially inappropriate prescribing cascades has been published recently.

Deprescribing can be defined as a systematic process of identifying and discontinuing drugs when potential or actual harms outweigh benefits. It may involve complete withdrawal of a drug or dose reduction.

Potentially inappropriate medications (PIMs) are defined as drugs for which the risks of adverse effects outweigh the potential clinical benefits, particularly when safer or more effective alternatives exist. Examples of the important tools for identifying PIMs are the Beers Criteria, STOPP/START or EU(7)-PIM lists. Deprescribing interventions guided by explicit PIMs criteria have been shown to effectively reduce polypharmacy, the use of PIMs, and the incidence of ADRs in older adults. Meta-analyses of randomized controlled trials demonstrate that these interventions lower the proportion of older adults exposed to PIMs and ADRs and improve medication adherence.

DILEMMAS IN DRUG USE DURING PREGNANCY

Matea Radačić Aumiler [1,2,3]

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KEY WORDS: Pregnancy, Breastfeeding, Rational Therapy; Counselling

Many pregnant women and their physicians face the decision of whether to use medications during pregnancy, and this often presents significant challenges and numerous uncertainties. Many pregnant women require treatment, and discontinuation of therapy may represent a greater risk than the use of the medication itself. However, many drugs increase the risk of congenital malformations, preterm birth, or pregnancy loss. Data show that 7 out of 10 pregnant women take at least one medication during pregnancy. Safety data are often insufficient, as pregnant women are excluded from clinical trials.

Despite the increased availability of information on teratogenic risks, the use of medications in pregnancy causes uncertainty and fear both among women and among physicians. According to recent studies assessing risk perception, women tended to overestimate the magnitude of teratogenic risk. Although it is very difficult to assess the actual risk of medication use during pregnancy, unrealistic risk perception by pregnant women can lead to poor adherence, discontinuation of treatment, and even termination of an otherwise desired pregnancy. Counselling on the use of medications during pregnancy enables a more balanced decision about therapy. The way information is presented is very important. The perception and explanation of the benefits of treatment can have the greatest impact on acceptance of risk. Physicians are confronted with numerous dilemmas, such as which medications can be used, which should be avoided or not prescribed, which conditions must be treated, how to manage uncertainty, where to seek answers, which databases and registries to consult, what to expect, how to assess risk, and whom to consult.

In overcoming these uncertainties and challenges, the role of the clinical pharmacologist is crucial. One of the activities of clinical pharmacology is an outpatient clinic for counselling on the use of medications during pregnancy and breastfeeding, as well as the preparation of clinical pharmacology expert opinions with specific answers to posed questions, which are of exceptional value to both pregnant women and their physicians.

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ACCURACY OF MEDICAL ADVICE GIVEN TO BREASTFEEDING MOTHERS

Maja Ilijanić Samošćanec [1]

[1] Karlovac General Hospital, Karlovac, Hrvatska.

KEYWORDS: Breastfeeding, Peer Counseling; Health Care Professionals; Facebook

Background: Organization Parents in Action's (RODA) provides breastfeeding support through peer counselling. As a clinical pharmacologist and breastfeeding counsellor within RODA, I observed concerns raised by mothers in RODA's Facebook group regarding the safety of medications during breastfeeding, often after consulting a healthcare professional.

Methods: This retrospective study analysed posts from RODA's Facebook group published between 2022 and 2024 that mentioned advice given by healthcare professionals regarding medication use during breastfeeding. The appropriateness of this advice was assessed using the e-lactancia database. Advice was categorized as “accurate”, “inaccurate”, “unclear/conflicting”, or “unrelated to medication”.

Results: Healthcare professionals’ advice was cited in 55 posts, representing 75 references to 59 distinct pharmaceutical agents, radiological procedures, contrast media, and vaccines. The most frequently discussed items were antibiotics (n = 22), antipyretics/analgesics (n = 8), diagnostic imaging/contrast agents (n = 5), and each appearing proton-pump inhibitors, antihistamines, and local anaesthetics. Among the advice provided, 58.2 % was inaccurate (e.g. classifying amoxicillin–clavulanate or bisoprolol as incompatible with breastfeeding), 21.8 % were unclear or conflicting (e.g. uncertainty about desloratadine or azithromycin, divergent opinions on ibuprofen, azithromycin, or MRI), 18.2 % were accurate (e.g. confirming compatibility of verapamil or thiamazole), and 1.8 % were unrelated.All 21 recommendations to cease breastfeeding were inappropriate and involved commonly used agents such as amoxicillin, cefaclor, lidocaine, and contrast imaging procedures. One notable exception concerned chloropyramine, a temporary interruption of breastfeeding was justified, yet the recommended duration was incorrect.

Conclusion: The results highlight inaccuracies in medical advice, particularly regarding unnecessary weaning. These findings emphasize the need for improved training and access to evidence-based resources for healthcare professionals to better support breastfeeding women.

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WHAT IS THE CURRENT STATE OF DRUG AVAILABILITY IN CROATIA?

DRUG AVAILABILITY IN CROATIA – A DIFFERENT PERSPECTIVE

Tonći Buble[1]

[1] Advisor at the Ministry of Health, Zagreb, Croatia

KEYWORDS: Drug Availability; Marketing Authorisation Holders; Public Funding

Access to medicines in Croatia primarily depends on the activities of marketing authorisation holders (MAH), the measures of the Pricing & Reimbursement (P&R) system, and sources of public funding for medicines. Medicines fall under a highly regulated part of the Croatian healthcare system, where the maximum allowed price (MAP) is set by the Agency for Medicinal Products and Medical Devices, while the inclusion of medicines on the reimbursement list and their public funding is handled by the Croatian Health Insurance Fund (CHIF).

In the public sphere, through the media and artificial intelligence (AI), information has been published about delays in the availability of new therapies in Croatia. The source of this information is a publicly available EFPIA study, which did not include all data on existing access channels, making the reported figures on the number of medicines insufficient. Likewise, the reported timelines of availability relative to central EU marketing authorisation fail to take into account the fact that access is directly dependent on the actions of the MAH. In over 50% of the medicines analysed, authorisation holders had not even initiated the reimbursement procedure in Croatia.

Access to medicines in Croatia should be considered not only through the prescribed P&R system procedures but also in relation to alternative access routes for medicines that are not on CHIF's lists or are on the list but do not cover the approved medical indications. In Croatia, an alternative route is enabled by Article 21 of the Mandatory Health Insurance Act (MHIA) which has significantly increased medicine availability.

Regarding public funding of medicines via CHIF, there are multiple channels: through prescriptions issued by family physicians (the so-called pharmacy channel), from hospital budgets, from special hospital programmes (blood products, transplants, etc.), as well as through special channels for expensive hospital medicines (PSL) and genetic testing.

CHIF's budget allocation for prescription medicines has been continuously increasing,

due to the inclusion of new medicines on the reimbursement lists, the growing number of prescriptions, as well as the reclassification of certain hospital medicines to the pharmacy channel to improve patient access (for example, biologics for long-term use in multiple sclerosis, rheumatologic diseases, etc.)

The budget for PSL medicines has also been steadily growing, given the inclusion of an increasing number of innovative medicines on the list, the expansion of indications for medicines already included, and a significant rise in the number of patients receiving them. The CHIF Drug Committee (based on scientific-medical documentation, pharmacoeconomic analysis, and the status of the medicine in other EU countries) sets medical criteria and financial conditions that MAH

must accept for their product to be listed by CHIF. This has increased transparency, improved and accelerated the inclusion process for new medicines, while also allowing rationalisation of existing expenditures in the largest financial categories of medicines, particularly in the PSL channel (immunotherapy, oncology, etc.). In 2024 alone, about 30 new medicines were added to CHIF's lists, of which 13 were included in the PSL channel, along with the approval of 15 new indications for medicines already on PSL.

The alternative route, under Article 21 of MHIA, enables access to numerous costly innovative medicines even before their inclusion on CHIF's reimbursement lists, based on proposals from hospital drug committees. A significant source of funding for this additional access has been hospital budget restructuring.

Regarding shortages of medicines already in widespread use, availability is ensured through the collection of information on product shortages and Agency for Medicinal Products and Medical Devices' urgent interventions, as well as through prevention measures, primarily the broad range of generic and therapeutic equivalents on CHIF's lists. This ensures multiple therapeutic options within the same indication and high security of medicine supply in Croatia, even in the context of global medicine shortages. Additionally, for medicines where pricing could have been a potential cause of shortages, prices have been raised (for example, antibiotics and immunoglobulins).

In conclusion, Croatia has a highly developed P&R system and multiple public funding channels for medicines. Medicine availability significantly depends on the actions of MAH, there are alternative access and financing routes for innovative medicines, and there are established systems for preventing shortages of medicines in use.

AVAILABILITY OF NEW MEDICINES REIMBURSED BY THE NATIONAL HEALTH INSURANCE

Jelena Matuzović [1]

[1] Croatian Health Insurance Fund, Zagreb, Croatia

KEYWORDS: High Costs Medicines; Patient Access to Medicines; Basic List; Health Insurance Fund

Under the compulsory health insurance, insured persons in Croatia are entitled to receive medicines listed on the Basic and Supplementary Lists of Medicines, in accordance with the criteria defined therein. Medicines on the Basic List are fully covered by the Croatian Health Insurance Fund (HZZO), while for medicines on the Supplementary List, patients participate in the cost. The process of including medicines on these lists, as well as determining their prices, is regulated by specific by laws. Updated lists are publicly available on the HZZO website. Currently, the lists comprise 4885 medicines, with more than 80% included on the Basic List, meaning they are entirely accessible to patients without co-payment. To ensure wider availability of high-cost medicines, the Fund for Expensive Drugs was established in 2005, financed from earmarked HZZO resources, thereby relieving hospitals from the financial burden. The List of Expensive Drugs (PSL) contains medicines for rare and severe diseases, as well as innovative targeted therapies intended for a small number of patients but associated with exceptionally high costs. Since its establishment, the PSL has expanded significantly, with the inclusion of new drugs and indications. At present, it comprises 217 packages with 106 different active substances (INN). The increased availability of these medicines has considerably improved patients' quality of life and extended treatment outcomes. However, this expansion has also resulted in a continuous rise in expenditure. Consequently, HZZO closely monitors consumption, particularly of high-cost medicines, adjusts treatment costs by indication, and applies additional models to keep expenditures within predictable financial limits. Despite these challenges, the Croatian healthcare system consistently invests efforts in improving access to medicines. Through the introduction of new therapies, optimization of medicine lists, and strengthening of transparency, patients are provided with faster and fairer access to modern treatments, ensuring that advanced therapies reach those who need them most.

MONITORING TREATMENT OUTCOMES AND DRUG AVAILABILITY

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KEYWORDS: Accessibility, Treatment Outcomes; Health Outcomes

Summary

The Croatian Health Insurance Fund (hereinafter: CHIF) within the framework of compulsory health insurance invests limited financial resources rationally in quality and efficient health services and programs, including medicines. It is important for a patient to receive the medicine they need to treat their illness. Therefore, it is necessary to ensure timely and acceptable treatment with quality, safe and effective medicine, with expected and possible minimal obstacles. Three words describe the concept through obstacles that need to be removed: availability (a medicine with a valid marketing authorization is placed on the list of reimbursed medicines), accessibility (the medicine is on the market, there are no supply disruptions, it is available throughout the country, from the recommendation to the use of the medicine in treatment there is no waiting), affordability (the medicine is financially affordable for both: the patient and the health insurance). CHIF, within its powers, facilitates the availability of medicines through various measures. Among the first in the EU, the Republic of Croatia introduced electronic prescriptions more than 15 years ago, as well as prescriptions on recurring electronic prescriptions and the prescribed medicines are dispensed in pharmacies, also recently, such prescribing has also been allowed for some expensive drugs. New expensive drugs are added on reimbursement list of medicines and in order not to burden hospital budgets for more than 20 years, additional funds for these drugs are provided from a special financial position of the CHIF. Health outcomes of treatment represent changes in the patient's health that occur as a result of health care and include clinical measures of treatment success such as mortality and survival, complications during treatment, and improvement in quality of life. Monitoring the effect of the administered medicine and paying for effective treatment is necessary because financial resources are not unlimited. For the last 15 years, CHIF has been monitoring the effects of the administered medicine from the List of Particularly Expensive Medicines, namely the short-term outcome of the disease after each reevaluation of the effect of the administered medicine (cure, disease progression, transition to a second line of treatment, death). The availability of data depends on the data set provided by the hospital. Documentation for medical expertise and outcome monitoring is submitted electronically and analyzed through an integrated information system. This obligation is now legally binding from 2024. The

existing data, which are collected and analyzed, will represent the basis for systematic monitoring of outcomes according to various criteria, and then the basis for proposing changes. In order to meet the challenges of medicines financing, payment contracting models will increasingly be based on payment for effective treatment. We hope for a bright future with early diagnosis, accessible medicines and excellent treatment outcomes.

Sažetak

Hrvatski zavod za zdravstveno osiguranje (dalje u tekstu: HZZO) ima obvezu brinuti se za osigurane osobe i u okviru obveznog zdravstvenog osiguranja osigurati prava svim oboljelima od mnogobrojnih i različitih bolesti. Funkcioniranje zdravstvenog sustava potrebno je organizirati na način da kvalitetna zdravstvena zaštita bude dostupna svima. To se može postići na način da se dostupna i ograničena financijska sredstva ulažu racionalno u kvalitetne i efikasne zdravstvene usluge i programe, uključujući i lijekove.

Dostupnost lijekova

Pojam „dostupnosti“ je široko u primjeni, a za njegovo bolje razumijevanje u odnosu na lijekove u engleskom govornom području koriste se tri različite riječi, a koje opisuju koje su to moguće prepreke koje se moraju svladati kako bi se omogućila potpuna dostupnost nekom lijeku. Dostupnost ne znači dostupnost lijeku sad i odmah ili odmah svim lijekovima, nego se pod tim pojmom podrazumijevaju različite mjere kojima se bolesnicima omogućava pravovremeno i pod prihvatljivim uvjetima doći do, za liječenje njihove bolesti, kvalitetnog, sigurnog i djelotvornog lijeka, uz očekivane i moguće minimalne prepreke, a što sve upućuje na opća načela racionalne farmakoterapije.

- **Availability ili dostupnost u smislu otklanjanja pravnog odnosno regulatornog ograničenja**

podrazumijeva s jedne strane da su završena klinička ispitivanja i da je od strane regulatornih tijela lijek odobren za primjenu u određenoj indikaciji te da je za lijek utvrđen način izdavanja, a s druge strane da je proveden i završen postupak stavljanja lijeka na listu lijekova HZZO-a te da su utvrđeni uvjeti za primjenu lijeka na teret zdravstvenog osiguranja. Ne može se govoriti o ograničenju dostupnosti nekom lijeku ako nije omogućena primjena lijeka na teret zdravstvenog osiguranja za lijek koji nije odobren za primjenu ili za indikaciju za koju lijek nema važeće odobrenje za stavljanje lijeka u promet.

- **Accessibility ili dostupnost u smislu otklanjanja nekih drugih ograničenja**

podrazumijeva fizičku dostupnost, koja znači da je lijek stavljen u promet i prisutan na tržištu, da se može nabaviti te da nema prekida u opskrbi i da bolesnik može relativno lako doći do mjesta gdje može biti opskrbljen lijekom, zatim vremensku dostupnost, koja znači da od odobrenja lijeka do stavljanja lijeka na važeće liste lijekova nema većeg

odmaka od onog utvrđenog pravnim propisima te da od postavljanja indikacije za primjenom lijeka nema čekanja do ostvarivanja prava na lijek i na kraju geografsku dostupnost, koja podrazumijeva da je svim osiguranim osobama, neovisno gdje žive (u gradu, selu, na otocima) omogućena jednaka dostupnost lijeku te da se primjena lijeka ne ograničava samo na određene zdravstvene ustanove. Nedostupnost u ovim okvirima najčešće nastaje zbog privremenih poremećaja u opskrbi lijekom (defektura) ili zbog trajnog prekida opkrbe.

- **Affordability ili dostupnost u smislu otklanjanja financijskih ograničenja**

podrazumijeva osiguranje dostatnih financijskih sredstava od strane zdravstvenog osiguranja, mogućnost svih bolnica da primijene lijekove unatoč njihovoj cijeni ili npr. „priuštivost" lijeku od strane bolesnika ako je utvrđena obveza doplate odnosno sudjelovanja u cijeni lijeka ili ako bolesnik mora sam snositi trošak lijeka u cijelosti ako se lijek ne nalazi na listi lijekova HZZO-a. Kad se govori o nedostupnosti nekom lijeku, najčešće se misli na ovu financijsku nedostupnost.

Za bolesnika dostupnost znači da nema nikakvih zapreka da dobije lijek koji mu je potreban za liječenje njegove bolesti. Bolesnik ne bi trebao voditi brigu o tome da se riješe zapreke kako bi dobio potreban lijek (pravne, vremenske, prostorne, fizičke ili financijske prirode). HZZO u okviru osiguranih financijskih sredstava nastoji osigurati stručno preporučenu, dostupnu i kvalitetnu zdravstvenu zaštitu, uključujući i lijekove.

HZZO različitim mjerama i poduzetima aktivnostima olakšava ostvarivanje prava i dostupnost lijekovima, a u tome značajna pomoć proizlazi iz informatičke podrške. Uspostavljen je informatički zdravstveni sustav kroz koji se izmjenjuju i pohranjuju podaci o indiciranim odnosno propisanim te primijenjenim ili izdanim lijekovima. Uspostavljena je baza za ekonomsku i medicinsku analizu potrošnje zdravstvenih usluga i lijekova. HZZO je među prvima u EU uveo propisivanje lijekova na elektronski recept prije više od 15 godina i omogućeno je izdavanje lijekova na temelju propisanog lijeka na ponavljajući recept.

Radi osiguranja bolje dostupnosti lijekovima koji su skupi i koji bi opterećivali bolnički proračun te time smanjivali financijsku dostupnost lijeku, HZZO od 2005. godine (> 20 godina) osigurava posebno izdvojena financijska sredstva koja su namijenjena za primijenjene lijekove na Popisu posebno skupih lijekova. Kako bi se „teret" brže dostupnosti i moguće neučinkovitosti primijenjenih lijekova preraspodijelio između HZZO-a i Nositelja odobrenja za stavljanje lijeka u promet, za posebno skupe lijekove sklapaju se ugovori, a kojima se međusobno utvrđuju prava i obveze u svezi financiranja lijeka (HZZO u tome ima iskustvo dulje od 18 godina).

Praćenje ishoda

Zdravstveni ishodi liječenja predstavljaju promjene u zdravlju bolesnika koje nastaju kao

posljedica zdravstvene skrbi, a uključuju kliničke mjere uspjeha liječenja poput smrtnosti i preživljenja, komplikacija tijekom liječenja te kvalitete života.

Praćenje učinka pojedinog lijeka i plaćanje učinkovitog liječenja nužno je jer financijska sredstva nisu neograničena, a troškovi lijekova očekivano rastu iz svima dobro poznatih razloga: populacija stari, sve je veći broj kroničnih bolesnika, bolja je dijagnostika bolesti, postoje novi lijekovi za liječenje bolesti koje se do sada nisu liječile lijekovima, inovativni lijekovi su skupi, terapije se kombiniraju, a za nove lijekove u liječenju rijetkih bolesti, zbog ubrzanog procesa odobravanja (zbog nezadovoljenih potreba liječenja), podaci o učinkovitosti lijeka u kliničkoj praksi su malobrojni i nedostatni.

Kako bi HZZO bio siguran da se financijska sredstva primjenjuju u skladu s kriterijima za primjenu lijeka, a koji su utvrđeni kod stavljanja lijeka na listu lijekova i koji su javno objavljeni uz svaki lijek na Osnovnoj listi lijekova te predstavljaju uvjete za početak ili nastavak liječenja, te obvezu za prekid terapije ako ista nije učinkovita, više od 15 godina HZZO kontrolira primjenu lijekova provođenjem medicinskih vještačenja te prati kratkoročne ishode pojedinog lijeka kod svakog zahtjeva za nastavkom liječenja, a ta je obveza sada od 2024. godine i pravno obvezujuća.

Zdravstveni podaci su „zlato" 21. stoljeća. Međutim, iz „mora" podataka važno je moći izvući strukturirane informacije. Podacima se može i mora mjeriti trošak, ali isto tako se mora i procjenjivati uspjeh terapije. Rezultati se moraju uspoređivati i zajedno sa stručnim znanjima mogu se donositi razumske odluke za nekim promjenama, a sve s ciljem da se rezultati liječenja poboljšaju.

Praćenjem ishoda mogu se očekivati koristi za zdravstveni sustav u smislu bolje organizacije i smanjenja troškova za pružanje zdravstvenih usluga. U definiranju samog postupanja kod praćenja ishoda u početku je važno donijeti odluku o opsegu podataka i načinu dostavljanja dokumentacije. Tijekom vremena, vrlo se lako može dogoditi da se uoče neki nedostaci u samom postupku prikupljanja i/ili analizi podataka, a koji se kontinuirano mora dorađivati i poboljšavati, kako bi dobiveni rezultati analiza bili upotrebljivi za donošenje odluka o nekim promjenama vezano za ostvarivanje prava na lijekove ili financiranje lijekova. Ne bi imalo smisla prikupljati i analizirati podatke, ako uočena odstupanja u ishodima u odnosu na očekivane ishode, koji su prezentirani za pojedini lijek u postupku stavljanja lijeka na listu lijekova i postupku određivanje cijene lijeka koju će plaćati HZZO, HZZO ne bi mogao koristiti za donošenje odluka o promjenama (povećanje dostupnosti, snižavanje cijena, ograničavanje kriterija itd.).

U Europskoj uniji, između zemalja članica pa i unutar samih zemalja, postoje značajne razlike u ishodima liječenja.

Ishode bi trebali mjeriti na isti i usporediv način, koji će omogućiti otkrivanje najboljih praksi.

Prate li se ishodi u RH?

Bolnica se ugovorom s HZZO-om obvezala da će provoditi racionalnu farmakoterapiju te da će se doktori specijalisti prilikom preporučivanja lijekova pridržavati indikacija i kriterija za primjenu lijeka na teret sredstava HZZO-a, navedenih uz lijek u listama lijekova HZZO-a. Bolničko povjerenstvo za lijekove odobrava, na preporuku bolničkog specijaliste, uz ponekad prethodno pribavljenu suglasnost Multidisciplinarnog tima (MTD) ili Referentnog centra za pojedinu bolest, primjenu lijeka i liječenje tim lijekom bolesnik ostvaruje preko bolnice.

HZZO prati ishode učinka primijenjenog lijeka s Popisa posebno skupih lijekova i to kratkoročni ishod nakon svake reevaluacije učinka primijenjenog PSL lijeka. Predviđeno je praćenje konačnog ishoda (izlječenje, progresija bolesti, prelazak na drugu liniju liječenja, smrt), ali dostupnost podataka ovisi o setu podataka koje dostavi bolnica. Dokumentacija se dostavlja elektroničkim putem, vještači i analizira putem integriranog informacijskog sustava, koji se stalno dorađuje i nadograđuje. Postoje posebni obrasci sa zahtjevom za početak i nastavak liječenja, ali i poseban obrazac predviđen za praćenje ishoda u slučaju kad je liječenje prekinuto i/ili završeno. Za praćenje ishoda važno je povezivanje svih dostupnih baza podataka.

Iako se zna da bi za cjelovitu sliku ishoda liječenja trebalo imati više podataka, kako o tome kad je bolest dijagnosticirana, kad je započelo liječenje i slično, postoje li komorbiditeti, s čime je bolesnik prethodno liječen i drugo, kad se govori o praćenju ishoda danas se pod time podrazumijeva praćenje učinka primijenjenog lijeka.

Broj bolesnika kod kojih je primijenjen neki PSL lijek i za koje HZZO proveo medicinsko vještačenje u smislu kontrole primjene lijeka i evidentiranja učinka primijenjenog lijeka, vidljivo je da je u zadnjih 10-ak godina taj broj porastao gotovo dvostruko (uz napomenu da je broj vještačenja veći jer se vještači svaki nastavak primjene lijeka): 2014. godine s nekim od PSL lijeka liječeno je oko 7.500 bolesnika, a 2024. godine taj broj se povećao na više od 14.500 bolesnika.

Primjeri ... dostupnost → praćenje ishoda → olakšana i brža dostupnost

Zbog toga jer zdravstvene potrebe rastu brže i financijske potrebe su veće od dostupnih i osiguranih financijska sredstava, a koja nisu neograničena, HZZO možda ponekad nekim „nepopularnim“ promjenama, ali mjerama koje su stručno opravdane, nastoji pronaći dodatna financijska sredstva redefiniranjem određenih prava unutar pojedinih grupa bolesnika odnosno unutar prava na liječenje pojedinih bolesti. U medijima se nastoji okriviti „administraciju” zbog „nedjelovanja” i „zanemarivanja potreba bolesnika” jer se neki novi lijek nije odmah stavio na listu, ne vodeći pri tome računa da se postupci stavljanja lijekova i pomagala na Listu HZZO-a provode sukladno propisanim procedurama te da sve iziskuje vrijeme i da se unaprijed moraju planirati i financijska sredstva.

- **lijekovi za liječenje dijabetesa su dostupni, komplikacija bolesti je puno, ishodi se ne mjere (?)**

U RH osigurane osobe koje boluju od dijabetesa imaju dostupne lijekove i pomagala, osigurane na teret sredstava zdravstvenog osiguranja, za liječenje i kontrolu svoje bolesti na razini bogatih zemalja EU. Međutim, unatoč tome što postoje dobri uvjeti za liječenje i kontrolu bolesti, u RH rezultati liječenja dijabetesa nisu dobri. Zato si možemo postaviti pitanje: Kako je moguće da optimalna dostupnost lijekova nije dovela do dobrih ishoda? Zbog navedenog je nužno da onaj tko je lijek platio, a to je HZZO, prati ishode liječenja.

- **generički lijekovi su dostupni, ne prate se ishodi**

Prije 10-ak godina jedan je statina, lijek atorvastatin, bio „šampion" po broju pakiranja i zaštićenih imena lijekova na listi lijekova HZZO-a, sa 70 različitih pakiranja. Zbog cjenovne politike određivanja cijena lijekova i smanjenja cijena kod ulaska svakog sljedećeg generičkog lijeka na listu lijekova HZZO-a, cijena originatora tog lijeka je kroz 15 godina došla na razinu od 14% u odnosu na početnu cijenu lijeka kod stavljanja na listu lijekova. U odnosu na vrijeme prije 10 godina, danas je 20 pakiranja atorvastatina na listi lijekova manje i njegova cijena je dodatno snižena. Danas je na listi lijekova prvo mjesto po broju pakiranja preuzeo lijek rivaroksaban, od kojih veliki dio njih nije do sada niti stavljen u promet. Pitanja koja se nameću su sljedeće: Jesu li se lijekovi povukli s tržišta i izbrisali s liste lijekova HZZO-a zbog niske cijene lijeka i znači li to smanjenje dostupnosti tom lijeku ili je dostupnost ostala nepromijenjena (neobično je da su se izbrisali generički lijekovi, a na listi lijekova je ostao originator)? S druge strane, znači li veliki broj pakiranja na listama lijekova ujedno i osiguranje njihove dostupnosti na tržištu?

- **dolazak novije generacije lijekova i njihova dostupnost ne ovisi samo o HZZO-u**

Promatrajući primjer dolaska atipičnih antipsihotika na liste lijekova HZZO-a može se vidjeti kako dostupnost lijeka osiguranim osobama ne ovisi samo o postupcima koje provodi HZZO jer se dio vremena „utroši" čekajući da se završe klinička ispitivanja i lijek odobri za primjenu. Od početka studija za risperidon do prvog odobrenja za primjenu lijeka u RH prošlo 17 godina, a za olanzapin je od patentiranja lijeka do prvog

odobrenja prošlo 25 godina. U vrijeme kad je risperidon dobio svoje odobrenje za stavljanje u promet (1993. godine) na našoj listi lijekova nalazili su se od antipsihotika samo flufenazin, haloperidol i klozapin. Risperidon je dobio važeće odobrenje za promet u RH 1997. godine i do vremena kad je lijek postao dostupan na teret zdravstvenog osiguranja odnosno do stavljanja na važeću listu lijekova 2000. godine prošle su 2g i 9mj. Iste je godine (2000), nakon 3g i 4mj od dobivanja odobrenja za promet u RH, lijek stavljen na listu obveznog zdravstvenog osiguranja. U početku se za propisivanje na recept ovih

lijekova trebalo ishoditi posebno odobrenje Zavoda, kasnije je to administrativno opterećenje maknuto i lijekovi su postali široko dostupni.

- **postupno smanjivanje administrativnih barijera radi povećanja dostupnosti lijekovima**

HZZO prati potrošnju lijekova i ishode liječenja i s tim u vezi poduzima aktivnosti. Jedan od primjera koji se može spomenuti je hormona rasta. U početku kad je lijek stavljen na listu lijekova, financiranje lijeka je teretilo bolničke proračune i HZZO je odobravao primjenu lijeka. Kasnije je lijek stavljen na Popis posebno skupih lijekova. Utvrđeni su jasni kriteriji za njegovu primjenu. Početak i nastavak liječenja je odobravalo Bolničko povjerenstvo za lijekove, a HZZO je kontrolirao odobrenja. S obzirom da je potrošnja bila ograničena na određenu skupinu bolesnika uz jasne kriterije za primjenu, HZZO je dozvolio da se lijek propisuje na recept HZZO-a, uz odobrenje Bolničkog povjerenstva za lijekove i za početak i nastavak liječenja. Danas se lijek može početi propisivati na recept uz odobrenje Bolničkog povjerenstva, a za svako nastavno propisivanje lijeka dovoljna je preporuka bolničkog specijaliste kod kojeg se dijete redovito kontrolira.

Slična situacija prebacivanja lijeka iz primjene u bolnici na teret bolničkog proračuna, preko financiranja na teret PSL-a i na kraju omogućavanjem propisivanja na recept, dogodila se kod lijekova za liječenje multiple skleroze te tzv. bioloških lijekova koji se primjenjuju u liječenju reumatoloških bolesti, bolesti upalnih bolesti crijeva i psorijaze.

Kod lijekova za liječenje hemofilije omogućena je primjene lijekova u tzv. kućnom liječenju. U početku su se lijekovi podizali u bolnici, a danas se došlo do toga da se lijekovi mogu podizati u najbližoj ljekarni prema mjestu stanovanja i izboru pacijenta, uz odobrenje Bolničkog povjerenstva za lijekove i Zavoda.

Dostupnost lijekova u RH u odnosu na EU

Uspoređujući podatke o dostupnosti lijekova u različitim zemljama EU kroz „The Patient W.A.I.T. (Waiting to Access Innovative Therapies) Indicator" (izvor: https://www.efpia.eu/media/oeganukm/efpia-patients-wait-indicator-2024-final-110425.pdf), a kojim su analizirani podaci o 173 centralizirano odobrena nova lijeka u razdoblju između 2020. i 2023. godine, došlo se do sljedećeg: uzimajući u obzir prosjek kroz 27 država članica EU, u 2024. godini bolesnicima je bilo dostupno manje od polovice (80/173 = 46%) centralizirano odobrenih inovativnih lijekova, a u RH se u prometu našlo malo više od ¼ odobrenih lijekova (46/173 = 26,5%).

Prema podacima koji pokazuju koliko je dostupnih lijekova u nekoj zemlji u cijelosti osigurano na teret javnog zdravstvenog osiguranja, onda je vidljivo da se podaci kreću u vrlo širokom rasponu dostupnosti na teret zdravstvenog osiguranja: prosječno se u EU radi samo o 29% od ukupno odobrenih lijekova, što je pad u odnosu na 2019. godinu kada je taj udio iznosio 42% od onih lijekova koji su stavljeni u promet. Postotak

dostupnosti lijeka koji je u prometu u nekoj zemlji, a u cijelosti je dostupan na teret zdravstvenog osiguranja iznosi 63% u EU, u Češkoj samo 17%, a u RH 85%.

Dodatno se može uočiti i to da se povećava udio lijekova koji jesu dostupni, ali isključivo uz neke dodatne restrikcije za primjenu na teret sredstava zdravstvenog osiguranja, a koje zemlje EU uvode uz pojedine lijekove. Taj se udio lijekova s restrikcijom u ostvarivanju dostupnosti u zadnjih 5 godina gotovo utrostručio.

Analizom podataka o vremenskoj dostupnosti lijekovima unutar EU, a koja promatra vrijeme od odobrenja lijeka (marketing authorisation) do datuma kada je lijek u nekoj zemlji postao dostupan bolesnicima kroz listu lijekova, vidljivo je da se prosječno vrijeme dostupnosti lijeka produljilo za više od mjesec dana u odnosu na godinu dana ranije te da sada iznosi 578 dana. I dalje su među zemljama ostale značajne razlike u vremenskoj dostupnosti: lijekovi su najbrže dostupni u Njemačkoj (128 dana), a pacijenti u Portugalu čekaju najdulje (840 dana). Pacijenti u Hrvatskoj čekaju da lijek postane dostupan prosječno 549 dana (manje od EU prosjeka).

Gledajući pojedine grupe lijekova, prosječno vrijeme dostupnosti najviše se produžilo za lijekove koji se primjenjuju za liječenje rijetkih bolesti i lijekove koji su namijenjeni za kombinirano liječenje. Vrijeme dostupnosti za lijekove koji se primjenjuju u liječenju rijetkih bolesti produženo je u RH na 690 dana, ali je ta vremenska nedostupnost odnosno „čekanje" na lijek za tu grupu lijekova, podjednaka i u Francuskoj (666 dana) i u Češkoj (696 dana). Zanimljivo je vidjeti kako se Njemačka ne uklapa u uočenu shemu produljenog vremena dostupnosti za orphan lijekove: prosječna dostupnost svih lijekova je u toj zemlji 128 dana, a orphan lijekovi postaju dostupni za samo 97 dana.

Dostupnost „orphan" lijekova za liječenje rijetkih bolesti na teret zdravstvenog osiguranja razlikuje se značajno među zemljama EU: najmanja je dostupnost u Poljskoj i ona iznosi 8%, a prosjek EU je 62%. RH se našla među 5 zemalja u kojima su na teret zdravstvenog osiguranja orphan lijekovi s liste lijekova dostupni u cijelosti (100%), zajedno s Njemačkom, Belgijom, Nizozemskom i Luxemburgom. Zanimljivo je uočiti kako među tri zemlje u kojima se prosječno jednako „čeka" na dostupnost orphan lijekova, u konačnici u cijelosti na teret zdravstvenog osiguranja ti lijekovi osiguravaju za samo 11% bolesnika u Češkoj, 49% u Francuskoj i 100% u Hrvatskoj.

Uporne, otporne i značajne varijacije u dostupnosti novim lijekovima postoje u svim zemljama i postoje mnogobrojni različiti razlozi koji dovode do odgode dostupnosti i to nije karakteristično samo za RH.

Izvještaj (The CRA Report on root causes of unavailability and delays; https://www.efpia.eu/media/h4fps4xq/cra-efpia-root-causes-of-unavailability-and-delay-final-2025-report-summary-29-apr-2025-stc.pdf) je prikazao moguće razloge varijacija faktora koji utječu na dostupnost i njihove česte kombinacije. Ističu se spori regulatorni procesi kod odobravanja, kašnjenje nositelja odobrenja u zahtjevima za daljnjim

postupcima procjene, kašnjenje u odlukama zdravstvenih osiguranja itd. Dodatno se treba spomenuti i kašnjenje ili smanjenje dostupnosti nekom lijeku, unatoč pozitivnoj odluci da se lijek financira iz zdravstvenog osiguranja. Tu se kao primjer navode nedostatni dijagnostički kapaciteti, nedostatak specijaliziranog osoblja za primjenu nekog lijeka itd.

Stavljanje lijekova na listu lijekova HZZO-a provodi se sukladno odredbama važećeg pravilnika i razdoblje od podnošenja zahtjeva do stavljanja na listu prema Direktivi EU ne bi smjelo biti duže od 90 dana. Kad bi se svaki zahtjev rješavao u najkraćem mogućem roku trajanje postupka bi iznosilo oko 3 mjeseca maksimalno (to se vrijeme odnosi na razdoblje od predaje zahtjeva, pripreme Dnevnog reda za sjednicu, analize zahtjeva, određivanja cijene, donošenja mišljenja na sjednici Povjerenstva za lijekove, donošenja konačne odluke Upravnog vijeća Zavoda i primjene liste lijekova). U stvarnosti je to ipak malo drukčije, posebno za nove inovativne lijekove i ovisi o lijeku za koji se traži stavljanje na listu i to o indikaciji za koju se predlaže, cijeni i ukupno predvidivom trošku za HZZO.

Primjeri ... dostupnost → praćenje troškova → praćenje ishoda → promjene → olakšana i brža dostupnost

- **Lijekovi za liječenje kroničnog C hepatitisa → jednostavna mjerljivost ishoda**

Jedan od „reprezentativnih" primjera na koji način je HZZO mijenjao odnosno povećavao dostupnost lijekovima i pratio ishode su lijekovi za liječenje kroničnog hepatitisa C (HCV). Unazad 20 godina, od postojanja Popisa PSL-a, na njemu su se nalazili lijekovi za liječenje HCV-a, u početku pegilirani interferoni i ribavirin, a 8 godina kasnije i lijekovi iz grupe inhibitora proteaze. Prije nešto više od 10 godina na razini EU održan je i sastanak na „visokoj razini", a kako bi se donijela neka strategija liječenja hepatitisa C u smislu osiguranja novih skupih terapija, budući se na tržištu pojavio lijek Sovaldi s iznimno visokom cijenom, a s obzirom i na broj pacijenata koji bi lijek trebali dobiti, s visokim potencijalom troška koji bi za države bio financijski nemoguć. Čekajući dolazak novih lijekova, HZZO je zajedno sa strukom polako pripremao strategiju stavljanja lijekova na liste, utvrđeni su jasni kriteriji za primjenu lijekova. 2015. godine na liste su stavljeni prvi novi peroralni lijekovi za liječenje HCV-a. Liječenje je odobravano od strane struke i Zavoda prema prioritetima. Uspostavljeno je praćenje ishoda, što za ovu vrstu lijekova i samu bolest nije bilo teško budući da je ishod jasan – nestanak viremije i izlječenje bolesti. Kroz godine se cijena lijekova smanjivala, lijekovima se prema registraciji skraćivalo vrijeme primjene, tako da je HZZO mogao u okviru jednakih financijskih sredstava u konačnici osigurati lijekove za sve bolesnike (2017. godine moglo se liječiti 75% bolesnika, a već 2020. godine su svi bolesnici mogli biti liječeni). S Nositeljima odobrenja su se od 2015. godine sklapali financijski po modelu plaćanja učinkovitog liječenja. Budući da su praćeni ishodi ukazali na vrlo visoku učinkovitost lijekova te da su cijene lijekova

dodatno smanjene, lijekovima je promijenjen je status te je omogućeno da se isti propisuju na recept HZZO-a.

- **Genska terapija → potreba za dugogodišnjim praćenjem bolesnika sa svrhom procjene ishoda**

Osiguranje tzv. genske terapije na teret zdravstvenog osiguranja iziskuje iznimno velika financijska sredstva, a donošenje odluke otežava činjenica da se radi o novim lijekovima za koje nema kliničkih iskustava u stvarnom svijetu i da nema dovoljno raspoloživih podataka o dugoročnim ishodima ove terapije. Zbog navedenog je važno sklapanje financijskih ugovora s posebnim modelima plaćanja i s posebnom obavezom praćenja ishoda. Radi se o relativno malom broju bolesnika koji dobivaju te lijekove pa HZZO prati ishod za svakog pojedinog bolesnika. Rezultati ishoda su za sada u okvirima očekivanih, prema kliničkim studijama.

- **Posebno skupi lijekovi za liječenje onkoloških bolesnika → prate se i bilježe ishodi primjene lijeka**

Pitanje dostupnosti i u dijelu opsega lijekova koji se mogu primjenjivati na teret sredstava zdravstvenog osiguranja, ali u dijelu koji se odnosi na brzinu dostupnosti lijeka na tržištu RH, zbog broja novoodobrenih lijekova, novih lijekova za liječenje bolesti za koje do sada nije bilo lijeka, za primjenu u liječenju određenih mutacija itd., velika pozornost pacijenata, struke i medija uvijek je usmjerena na lijekove za liječenje onkoloških bolesnika.

HZZO u okviru raspoloživih financijskih sredstava kontinuirano na listu lijekova stavlja nove lijekove i proširuje indikacije za primjenu uz lijekove koji se već nalaze na listama.

Nove spoznaje i otkrića mehanizma nastanka određenih bolesti pomogla su u prepoznavanju ciljnih mjesta na koja se može djelovati i u tom smislu su registrirani novi lijekovi. Danas je pacijente moguće liječiti ciljano, „po mjeri" svakog bolesnika. Na taj način su smanjene i nuspojave i mogućnosti neučinkovitog liječenja.

Učinak primijenjenog skupog lijeka se procjenjuje u određenom vremenskom razdoblju nakon početka liječenja i utvrđuje se potreba za nastavkom primjene lijeka ako je lijek doveo do poboljšanja (ili remisije) ili se liječenje prekida ako lijek nije pokazao očekivani učinak i kod bolesnika je došlo do progresije bolesti.

Uspoređujući troškove za lijekove s Popisa posebno skupih lijekova u odnosu na indikacije u kojima se primjenjuju, vidljiv je trend potrošnje u zadnjih 10 godina: 2014. godine je za liječenje onkoloških i hemato-onkoloških bolesti HZZO izdvajao nešto više od 1/3 troškova PSL-a. Stavljanjem novih lijekova za nove dijagnoze i uvođenjem imunoterapije, struktura potrošnje se promijenila: više od 2/3 troškova za PSL lijekove (oko 70%) odnosi se na lijekove koji se primjenjuju za liječenje onkoloških i hemato-onkoloških bolesti, pri čemu se 26% troškova odnosi na lijekove koji se primjenjuju kao

imunoterapija.

Postoje mnogobrojni razlozi zbog kojih rastu troškovi za skupe lijekove i svi su ti razlozi očekivani i poznati:

- sve je veći broj novih registriranih lijekova od strane regulatornih agencija (skupih, inovativnih, pametnih),

- bolja je dijagnostika bolesti pa je za očekivati i veći broj otkrivenih bolesti,

- sve je veći broj bolesnika koji se liječe, a i bolesnici uz terapiju duže žive,

- sve je veći broj djece koja su (teško) bolesna,

- sve je veći broj rijetkih onkoloških bolesti koje se liječe iznimno skupim lijekovima,

- uvedeni su i provode se novi programi ranog otkrivanja bolesti, pri čemu se otkrivaju novi bolesnici,

- bolesnici često imaju više bolesti (komorbiditeti),

- uz standardnu terapiju dodaju se i novi lijekovi i/ili se liječenje odmah započinje s kombinacijom lijekova,

- novootkriveni bolesnici istovremeno ili u slijedu liječenja koriste u kratkom vremenu, zbog prirode bolesti, više lijekova,

- tijekom liječenja neke bolesti, produžuje se vrijeme do progresije bolesti, ali unatoč terapiji bolest zbog svoje prirode, bolest ipak napreduje pa se posljedično bolesnici liječe s više linija liječenja,

- genska terapija s jednokratnom primjenom i trenutnim troškom, a očekivanim učinkom kroz sljedeća desetljeća,

- i drugo ….

Skupljanje podataka u liječenju onkoloških bolesnika je neizmjerno važno jer analiza podataka može doprinijeti i boljim ishodima i manjim troškovima.

Podaci su mnogobrojni, ali ih treba „filtrirati”, strukturirati, analizirati i pametno iskoristiti. Za navedenu uspostavu prikupljanja „iskoristivih” podataka treba vremena, a potrebno je i vrijeme praćenja kako bi se pratili i dugoročni ishodi.

Jednostavno praćenje ishoda kod onkoloških bolesnika temelji se na praćenju incidencije i smrtnosti u općoj populaciji, neovisno o podtipu bolesti, početku liječenja, duljini primjene i vrsti primijenjenih lijekova i slično. Međutim, i navedeni podaci jasno ukazuju da je unatoč visokoj incidenciji određenih malignih bolesti (npr. prostate kod muškaraca i dojke kod žena) smrtnost smanjena, što može, između ostalog, ukazivati i na to da je uvođenje lijekova na liste lijekova i primjena ciljane terapije kod bolesnika kroz godine

unazad bila učinkovita.

U današnje vrijeme ishod liječenja u onkologiji ne smije biti stvar sreće. Liječenje onkoloških bolesnika danas se zasniva na jasnim stručnim smjernicama i protokolima. HZZO u listi utvrđuje i posebne uvjete koji moraju biti zadovoljeni kod bolesnika za početak i nastavak liječenja. Navedeni kriteriji nisu uvedeni kako bi se ograničila dostupnost lijeku, nego zato da se lijek može dati kod bolesnika kod kojeg se očekuju dobri ishodi uz primijenjeni lijek. Danas se terapija ne indicira samo na temelju dijagnoze i preporuke jednog specijaliste, već se odluka o liječenju donosi multidisciplinarno. Važan je individualizirani pristup svakom bolesniku i donošenje plana i cilja liječenja za svakog bolesnika posebno. Tako se može očekivati dobar ishod.

Praćenje ishoda, bilo ovog kratkoročnog koje HZZO provodi kontrolom preporuka za početkom i nastavkom primjene lijeka, bilo planirano dugoročnog praćenja ishoda primjene lijeka, dovesti će zasigurno do promjena u donošenju odluka.

Zaključak

- Sigurno ćemo biti izloženi izazovima inovacija i morati ćemo se više angažirati u praćenju novih tehnologija. Kontinuirana edukacija i multidisciplinarna suradnja biti će važna za donošenje odluka.
- Da bi se odgovorilo na izazove financiranja lijekova, modeli ugovaranja plaćanja lijekova sve će se više temeljiti na plaćanju učinkovitog liječenja.
- Podaci koji postoje, koji će se prikupljati i analizirati, biti će temelj za sustavno praćenje ishoda po raznim kriterijima, a onda i baza za predlaganje promjena.
- Svaki pojedinac mora biti odgovoran za brigu oko svog zdravlja i dobru kontrolu bolesti.
- Interes za zdravlje i što bolju kontrolu bolesti kod svakog pojedinca mora biti u fokusu svih u zdravstvenom sustavu.
- Individualni pristup u pružanju zdravstvene zaštite svakom bolesniku važan je za kvalitetno liječenje i kontrolu bolesti.
- HZZO ima obvezu osigurati najvišu moguću kvalitetu usluge, lijekova i pomagala u okviru osiguranih sredstava.
- Sprečavanje komplikacija, praćenje ishoda liječenja i kontrole bolesti važni su za planiranje troškova.
- Komunikacija između svih dionika u zdravstvenom sustavu ima važnu ulogu u dobroj informiranosti bolesnika.
- Komunikacija s medijima, udrugama i pojedincima mora doprinijeti širenju

točnih i pravovremenih informacija.

Nadamo se svijetloj budućnosti uz ranu dijagnostiku, dostupne lijekove i odlične ishode liječenja.

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ANTIBIOTICS WITH CAUTION: CHALLENGES AND OPPORTUNITIES/

PENICILLIN ALLERGY: TIME TO RETHINK, REASSESS, AND DE- LABEL

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KEYWORDS: Beta-Lactam Antibiotics; Penicillin Allergy; Allergy De-Labeling; Antimicrobial Stewardship; Patient Safety

Introduction: Beta-lactam antibiotics are among the most commonly prescribed and most effective antimicrobial agents. However, up to 25% of hospitalized patients report a penicillin allergy, despite evidence showing that over 90% of these labels are incorrect. Inaccurate allergy documentation leads to the use of broad-spectrum and second-line antibiotics, which are often less effective, more toxic, and contribute to antimicrobial resistance. It also increases the risk of adverse events, treatment failure, Clostridium difficile infection, and longer hospital stays.

Methods: This presentation explores the clinical and public health consequences of incorrect beta-lactam allergy labels and outlines a structured approach to allergy evaluation, including risk stratification, skin testing, and oral challenge. Special focus is given to the role of de-labeling in improving patient safety and its integration into antimicrobial stewardship programs (ASPs).

Results: Clinical pharmacologists are uniquely positioned to lead de-labeling initiatives through interdisciplinary collaboration, protocol development, and interpretation of test results. Despite the clear benefits, implementation remains limited due to barriers such as lack of training, testing resources, and institutional frameworks.

Addressing these challenges through education and team-based care models is essential for embedding de-labeling as a core stewardship strategy.

Conclusion: By removing inaccurate allergy labels, clinicians can ensure safer and more effective use of antibiotics. De-labeling is not just a diagnostic correction—it is a critical patient safety and public health intervention.

CHALLENGES IN ANTIBIOTIC USE IN PRIMARY HEALTHCARE

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KEYWORDS: Antimicrobial Resistance; Primary Health; Patient Adherence

Introduction: Inappropriate antibiotic use in primary health care significantly contributes to the development of antimicrobial resistance (AMR), a growing global public health threat. Since the majority of antibiotics are prescribed in primary care settings, general practitioners play a crucial role in ensuring responsible use. However, they often face diagnostic uncertainty, time constraints, and patient expectations, all of which can lead to unnecessary or suboptimal prescribing. Understanding the key factors influencing antibiotic use in this setting is crucial for improving prescribing practices.

Methods: This presentation is based on a review of current literature addressing antibiotic resistance rates and prescribing patterns in primary health care. Additionally, insights will be provided from the clinical experience of a clinical pharmacologist, reflecting on everyday medical practice and highlighting common challenges and decision-making processes encountered by physicians.

Results: Literature data indicate that a substantial proportion of antibiotic prescriptions in primary health care do not align with established guidelines. Clinical experience supports these findings, revealing frequent situations of diagnostic uncertainty, perceived patient pressure, and limited access to rapid diagnostic tools. These factors often lead to precautionary prescribing, despite awareness of the risks associated with antimicrobial resistance.

Conclusion: Rational antibiotic use in primary health care is a complex issue shaped by both systemic limitations and practical realities. Addressing these challenges requires improved diagnostic support, effective patient communication, and stronger adherence to clinical guidelines. Most importantly, continuous education and training of physicians is essential to strengthen antibiotic stewardship and reduce inappropriate antibiotic use.

MULTIDRUG-RESISTANT BACTERIA: IS THERE A CURE?

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KEYWORDS: Multidrug-Resistant Organisms; Healthcare Costs; Antimicrobial Resistance; Faecal microbiota transplantation

Introduction: Antimicrobial resistance (AMR) is one of the most urgent global health threats, with multidrug-resistant organisms (MDROs) limiting therapeutic options and leading to increased morbidity, mortality, and healthcare costs. The need for new treatment strategies is critical as traditional antibiotics lose efficacy at an alarming rate.

Methods: A structured literature review was done with looking for ongoing developments in the management of infections caused by MDROs. Emphasis was placed on both newly approved antibiotics and alternative approaches currently under clinical or experimental investigation.

Results: Recent years have seen the introduction of novel antimicrobials active against MDROs. However, their long-term effectiveness is challenged by the continuous emergence of resistance. Alternative approaches are also advancing. Faecal microbiota transplantation (FMT) shows promise in reducing intestinal colonization with resistant bacteria. Bacteriophage therapy, with its pathogen-specific activity, is being revisited as a potential therapeutic option. Other innovative strategies under investigation include antimicrobial peptides, immunotherapeutics, and microbiome-based interventions. Collectively, these approaches illustrate a shift from exclusively pathogen-directed treatments to strategies that also strengthen host defences and restore microbial balance.

Conclusion: While there is no single definitive cure for multiresistant bacteria, progress is being made through the parallel development of novel antibiotics and innovative alternatives. The future of combating AMR will likely depend on combining these emerging therapies with robust antimicrobial stewardship to ensure sustainable use and preserve effectiveness

PREDICTORS OF CEFTAZIDIME PK/PD INDEX TARGET VALUES AND TOXIC PLASMA LEVELS IN ADULT HOSPITALIZED PATIENTS

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KEYWORDS: Ceftazidime; Therapeutic Drug Monitoring (TDM); Systemic Bacterial Infections; Toxic Plasma Concentrations; Renal Function; Sex Differences; Age-Related Variability

Introduction: How effective antibiotics are in the treatment of systemic bacterial infections depends not only on the sensitivity of microorganisms, but also on achieving an adequate concentration of antibiotics in tissues. The aim of this study was to investigate predictors of achieving target values of pharmacokinetic/pharmacodynamic (PK/PD) index relevant for ceftazidime, as well as factors associated with toxic plasma concentrations of the same drug.

Methods: The study was designed as a cross-sectional observational study in hospitalized patients treated for systemic bacterial infection with ceftazidime. It was conducted at the University Clinical Center Kragujevac (UKCK), Serbia, during the year 2024, within the framework of routine therapeutic drug monitoring.

Results: The study included a total of 59 adult hospitalized patients receiving ceftazidime, who had their ceftazidime concentration measured at least twice during the dosing interval. In total 44 patients achieved the target value of PK/PD index fT above MIC, and 22 patients experienced toxic plasma concentrations of ceftazidime. While males had less chances to achieve target fT above MIC (ORadusted = 0.07 [0.009 - 0.464]), older patients with elevated creatinine serum levels and higher daily dose of ceftazidime were more prone to have toxic plasma concentrations of ceftazidime.

Conclusions: In order to achieve optimum effectiveness and safety of ceftazidime, itd dose should be carefully adjusted according to sex, age and kidney function.

ANTIMICROBIAL THERAPY TODAY. WHERE ARE WE AND WHERE ARE WE HEADING?

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KEYWORDS: Multidrug-Resistant Organisms; Morbidity; Prescribing; Novel Agents; Antimicrobial Stewardship

Antimicrobial therapy remains one of the most transformative advances in modern medicine, yet its future is challenged by the accelerating emergence of antimicrobial resistance, limited drug development, and shifting patterns of infectious disease.

Multidrug-resistant organisms have become a major cause of morbidity, mortality, and healthcare cost worldwide. At the same time, the antimicrobial development pipeline is insufficient, with fewer novel agents reaching the market compared to previous decades. This gap is compounded by economic disincentives for pharmaceutical innovation. Traditional market models do not provide adequate returns for antibiotic developers due to short treatment durations, stewardship-driven restrictions, and rapid resistance emergence, resulting in low profitability and industry withdrawal from antibiotic research and development. New financial models, such as market entry rewards, subscription models, and public benefit corporations, are urgently needed to create sustainable incentives for innovation and commercialization. In addition to economic concerns, regulatory, and implementation barriers persist, necessitating multidisciplinary collaboration and policy reform.

Safeguarding the future of antimicrobial therapy globally and locally requires a multifaceted approach—balancing innovation, stewardship, global collaboration, and public health policy.

In Croatia, inappropriate antimicrobial prescriptions account for more than 50% of prescribing, contributing to resistance and adverse outcomes which indicates the necessity for the implementation of antimicrobial stewardship programs.

Only through coordinated action can we preserve the utility of existing agents while fostering new solutions for the future.

RARE DISEASES & ORPHAN MEDICINES

REGULATORY ASPECTS OF ORPHAN MEDICINES APPROVAL IN EU: WHICH ARE CHALLENGES FOR THE PATIENTS AVAILABILITY

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KEYWORDS: Health Technology Assesment; Orphan Drugs; Budgetary Impact; Value-Based Pricing; Cost-Effectiveness

In the European Union (EU), an estimated 6-8% of the population, approximately 27 to 36 million people, are affected by rare diseases, defined as conditions impacting fewer than 5 in 10,000 individuals. The European Medicines Agency (EMA) and its Committee for Orphan Medicinal Products (COMP) oversee the evaluation of orphan designation applications. Between 2000 and 2024, COMP reviewed 4,586 applications, issued 3,026 positive opinions, granted 3,012 European Commission (EC) designations, and authorised 261 orphan medicines, with 58 extensions of indication.

While regulatory approval is a critical milestone, actual patient access depends on national reimbursement decisions made by Health Technology Assessment (HTA) agencies and payers, heavily influenced by the financial capacity of health systems. HTA assessments typically focus on relative effectiveness, comparing new orphan drugs to existing therapeutic alternatives. However, orphan medicines are often priced several times higher than non-orphan drugs, creating sustainability challenges.To address this, value assessment frameworks must integrate disease-specific parameters, i.e. incidence, prevalence, aetiology, pathogenesis, and clinical severity, and include pharmacoeconomic analysis reflecting both manufacturer costs and patient outcomes. Adjusted cost-effectiveness thresholds, particularly incremental cost-effectiveness ratios (ICERs), can support value-based pricing strategies that balance innovation incentives with affordability. As the budgetary impact of orphan drugs continues to grow, transparent and evidence-based methodologies for pricing and reimbursement are essential to ensure equitable and timely patient access across the EU. Strengthening alignment between regulatory approval and HTA processes will be pivotal in translating orphan drug designations into real-world health benefits.

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AI AND MACHINE LEARNING IN RARE DISEASES AND ORPHAN MEDICINES: IDENTIFYING THERAPEUTIC TARGETS THROUGH IN SILICO APPROACHES

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KEYWORDS: Rare Diseases; Artificial Intelligence; Potential Therapeutic Targets; Orphan Diseases; Machine Learning

Rare diseases affect millions of patients worldwide, yet therapeutic options remain limited because of scarce data and underpowered studies. Artificial intelligence and machine learning offer new possibilities by integrating molecular, clinical and literature-derived data into models that can identify potential therapeutic targets and repurposable medicines. In this lecture, practical in silico approaches will be presented, combining transcriptomic and genomic datasets with drug databases to build disease networks and prioritize promising targets. Illustrative examples will demonstrate how methods such as transfer learning, network analysis and explainable machine learning can extract value from small and fragmented datasets, generating clinically relevant hypotheses. Case vignettes will show how these predictions can support drug repurposing, guide preclinical validation and inform early dialogue with regulatory and health technology assessment bodies. The presentation will emphasize how transparent and reproducible AI tools can create new opportunities in the development of orphan medicines, while highlighting the importance of collaboration between clinicians and data scientists.

DRUG UTILISATION USING HEALTH RECORDS

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KEYWORDS: Drug Utilisation; Routine Health Data; Rare Disease

High quality data are essential to drive clinical practice, research and regulation in both common and rare disease. From a therapeutics perspective we can also think about drugs that might not be commonly used as these may not be for rare disease but fall into the same challenges as understanding drug use for rare disease. We will talk about the possible sources of data on drugs and disease in the real world, how rare disease and specific groups can be targeted and what approaches can be used, and what we can do to improve data quality to understand drug use in general.

REAL-WORLD INSIGHTS AND ECONOMIC IMPLICATIONS OF ORPHAN MEDICINES: EXAMPLES FROM THE SPINAL MUSCULAR ATROPHY FIELD

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KEYWORDS: Real Worlds Evidence; Spinal Muscular Atrophy; Orphan Medicines; High-Cost Therapy; Drug Evaluation

Orphan medicines are often associated with disproportionately high costs due to complex development pathways and limited market volumes, which restrict return on investment. Although these therapies can deliver substantial clinical benefits for patients with rare diseases, they are frequently deemed not cost-effective under conventional health economic thresholds. This raises critical questions about the appropriateness of using standard willingness-to-pay (WTP) benchmarks when evaluating treatments for rare conditions.

The growing public health burden of rare diseases has driven a paradigm shift in regulatory and reimbursement landscapes, especially in the increasing incorporation of real-world evidence (RWE) to support the clinical and economic value of orphan medicines. Despite this progress, significant challenges remain in balancing innovation, affordability, and equitable access. Addressing these issues requires intensified collaboration among regulators, payers, industry stakeholders, patient advocacy organizations, and international bodies.

This lecture will examine these themes through the lens of spinal muscular atrophy (SMA), a rare but devastating neuromuscular disorder. It will synthesize findings from systematic reviews, real-world analyses, and economic modelling studies to assess the cost-effectiveness and budgetary impact of disease-modifying therapies for SMA. The aim is to provide a comprehensive and pragmatic perspective on resource allocation, value assessment, and sustainable access strategies for orphan medicines, informed by the evolving SMA treatment landscape.

PLENARY LECTURE

LAB-BASED CLINICAL PHARMACOLOGY IN SUPPORT OF PATIENT CARE

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KEYWORDS: Clinical Pharmacology; Research; Laboratory Data

Clinical pharmacologists (CPs) come in all shapes and sizes. There are of course the patient-facing MD clinical pharmacologists, whose tasks include prescribing, medication consults, participation in drugs and therapeutics committees (DTCs), and oversight of experimental medicine and early drug development studies, the more research-oriented PhD clinical pharmacologists, often engaged in modelling and simulation and in epidemiological research, and the PharmD clinical pharmacologists whose tasks also include consults and participation in DTCs. Regardless of their titles and training, most clinical pharmacologists are involved in translational and clinical research and depending on the country or region where they practice, there is considerable overlap in areas covered by these different types of clinical pharmacologists.

All clinical pharmacologists use data, whether it is for research, for drug development, or for the treatment of an individual patient. Data can be deceitful though, and for appropriate interpretation of data, especially in challenging cases, it is essential to know the pivotal specific aspects of the methodologies that were used to generate those very data. This might apply to drug prescription and clinical data, to imaging data, or to data generated in clinical chemistry, microbiology, molecular diagnostics, haematological, pharmacokinetic and/or toxicological laboratories.

Clinical laboratories around the world are directed by different professionals. Clinical and chemical pathologists, laboratory physicians, clinical (bio-)chemists, and in some countries, hospital pharmacists, may all be the medical director of these different laboratories, with training and board certification requirements varying substantially between nations and states. Interestingly, with the exception of some countries, clinical pharmacologists are not so much involved as clinical laboratory directors. Instead, together with their other patient-facing colleagues such as internists, MD and PharmD clinical pharmacologists often are the end-users of the data generated in clinical laboratories with only a modest knowledge of the actual assays used to generate this data, which might be sufficient for the treatment of the majority of patients, but might not be good enough

when specific assay-related interpretive challenges arise when treating a patient.

This lecture will provide several examples where a straight-forward use of the laboratory data would have led to suboptimal treatment, and optimal treatment of the patient strongly depended on a correct interpretation of the assay results, which was only possible because the medical director of the clinical laboratory also happened to be a clinical pharmacologist who was able to address these issues. These examples, focused on Therapeutic Drug Monitoring, will hopefully lead to improved training of clinical pharmacologists in laboratory medicine and are at the same time intended to advocate for an increased number of clinical and chemical pathologists, and clinical (bio-)chemists to be specifically trained and active in clinical pharmacology.

PHARMACOTHERAPY IN HEMATO-ONCOLOGY – WHERE DO WE STAND TO-DAY?

COMBINATION DRUG THERAPIES IN ONCOLOGY: THE NEW STANDARD

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KEYWORDS: oncology, combination therapy, treatment standards, immunottherapy

Combination therapy in oncology has advanced substantially, driven by the integration of immune checkpoint inhibitors (ICIs), targeted agents, antibody-drug conjugates (ADCs), and cytotoxic chemotherapy. The rationale for these combinations is to exploit synergistic mechanisms, overcome resistance, and improve clinical outcomes. Notably, the combination of enfortumab vedotin (an ADC) with pembrolizumab (an ICI) has demonstrated superior efficacy in first-line treatment of advanced urothelial carcinoma, nearly doubling progression-free and overall survival compared to platinum-based chemotherapy, with a manageable safety profile dominated by skin toxicity, neuropathy, and hyperglycemia. ICI–tyrosine kinase inhibitor (TKI) combinations are now standard in advanced renal cell carcinoma and endometrial cancer, offering improved response rates and survival but with increased risk of hypertension, hepatotoxicity, and immune-related adverse events. In melanoma and renal cell carcinoma, dual ICI regimens (nivolumab plus ipilimumab) provide durable survival benefits, though at the cost of higher rates of severe immune-mediated toxicity. ICI plus chemotherapy regimens are established as first-line therapy in non-small cell lung cancer, urothelial carcinoma, and triple-negative breast cancer, with improved survival and response rates compared to chemotherapy alone. Combinations of ICIs with targeted therapies (e.g., PARP inhibitors, angiogenesis inhibitors) and ADCs are under active investigation across multiple tumor types, with early data supporting enhanced antitumor activity and manageable safety profiles. Meta-analyses confirm that while combination regimens increase specific toxicities, overall adverse event rates are comparable to monotherapy, underscoring the importance of patient selection and monitoring.

Collectively, these strategies represent a paradigm shift in oncology, establishing new standards of care and expanding therapeutic options for patients with advanced malignancies.

TRANSFUSION DEPENDENCE AND OVERALL SURVIVAL - NEW INSIGHTS AND EMERGING DILEMMAS

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KEYWORDS: Myelodysplastic syndromes; Red Blood Cell Transfusion; Luspatercept

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid neoplasms characterized by ineffective hematopoiesis, leading to peripheral blood cytopenias and an increased risk of progression to acute myeloid leukemia (AML). MDS represents one of the most common causes of anemia in older adults, and the majority of patients become dependent on red blood cell (RBC) transfusions during the course of the disease.

Anemia and transfusion dependence aggravate comorbidities and correlate with shorter survival and reduced quality of life. Since the treatment of MDS depends on the dynamic clinical course of the disease itself, long-term outcomes are often difficult to predict. The current approach to the management of lower-risk MDS aims not only to improve cytopenias but also to prolong survival, with particular attention to maintaining quality of life. Most patients with lower-risk MDS present with anemia, which until only a few years ago was most commonly treated with RBC transfusions or erythropoietin, targeting the early phase of erythropoiesis.
A new hope and significant advancement in treatment has been brought by luspatercept, which acts in the late phase of impaired or ineffective erythropoiesis, demonstrating efficacy not only in MDS but also in other hematologic entities.

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RADIOLIGANDS THERAPY (RLT) – NEW CHAPTER IN PERSONALISED ONCOLOGICAL TREATMEN

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KEYWORDS: Therapeutic; Diagnostic; Radioligands

Theranostics or theragnostics, is a technique more often used in personalised medicine. In nuclear medicine one radioactive drug is used to identify and a second radioactive drug is used to treat cancerous tumours (most often thyroid cancer, prostate cancer, neuroendocrine tumours). Simply to say, theranostics combines radionuclide imaging and radiation therapy which targets specific biological pathways.

The term "theranostic" is a combination of two words, therapeutic and diagnostic, thus referring to a combination of diagnosis and treatment that also allows for continuing medical assessment of a patient.

Theranostics originated in the field of nuclear medicine; iodine isotope 131 for the diagnostic study and treatment of thyroid cancer was one of its earliest applications. Nuclear medicine encompasses various substances (for example prostate specific membranous antigen (PSMA), somatostatin receptors, some blood cell antigens), either alone or in combination, that can be used for diagnostic imaging and targeted therapy. By using these mechanisms, theranostics enables the localization of pathological tissues with imaging and the targeted destruction of these tissues using high doses of radiation (beta and alfa rays).

The introduction of radioligands therapy presents a great challenge for medical health systems, regarding to diagnosis, patients' referral to multidisciplinary teams, RTL facilities in nuclear medicine departments,

therapy costs and radioactive waste management. Now many European countries are seeking best solutions for their patients.

EPISODES OF CARE BASED REIMBURSEMENT OF MEDICINES

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KEYWORDS: Reimbursement; Value for Money; Medicines

Traditional reimbursement based on agreeing prices for indications and prescribing restrictions that define lines of treatment has been a cornerstone of decision making on public financing of novel medicines for decades. It was well suited to address key payors priorities: ensuring rational treatment and value for money.

However, scientific advances have been increasingly making the concept outdated and consequently of little use. Clinical medicine is fast progressing towards personalized treatment, for instance by examining genetic mutations which then influence choice and sequencing of therapies. A single medicine can, based on this and other criteria, hold multiple lines of treatment in a single indication. On top of this, a large number of medicines has increasingly been authorized for multiple indications.

In all these indication and line of treatment combinations, medicines can have considerably varying results in terms of relative therapeutic benefit compared to established competitors. Therefore, deciding on a true general value of a novel medicine is becoming increasingly difficult as it can vary considerably from case to case. To continue, ensuring rational treatment has become much more complex and should now in many cases be evaluated on a patient-by-patient basis.

Reimbursement through managed entry agreements, whether outcome-based or financial, that assess medicines within episodes of care offers a stronger way to address these complexities and support payor priorities than traditional approaches.

PRECISION ONCOLOGY: THE CONTRIBUTION OF PHARMACOGENOMICS AND CHRONOTHERAPY IN COLORECTAL CANCER CARE

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KEYWORDS: Colorectal Cancer; DPYD; Chronotherapy; Circadian Rhythm.

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality globally. Although fluoropyrimidines (5-fluorouracil and capecitabine) and irinotecan represent the backbone of systemic treatment, their clinical use is frequently complicated by inter-individual variability in drug metabolism and toxicity. Two complementary precision medicine strategies, pharmacogenomics and chronotherapy, have shown significant promise in enhancing both the safety and efficacy of CRC treatment. Genetic polymorphisms in the DPYD gene (e.g., c.1905+1G>A, c.1679T>G, c.2846A>T, c.1236G>A) are associated with reduced dihydropyrimidine dehydrogenase (DPD) activity and a significantly increased risk of severe fluoropyrimidine-related toxicity. Pre-treatment DPYD genotyping, recommended by international guidelines (CPIC, DPWG, EMA), enables genotype-guided dose adjustments or alternative treatment strategies, thereby reducing toxicity-related hospitalizations and mortality. In line with these recommendations, and aiming to improve patient care at the University Hospital Centre Rijeka we have implemented routine screening for DPD deficiency prior to fluoropyrimidine therapy. In addition to established DPYD variants, our panel includes c.496A>G and 6*c.2194G>A based on emerging evidence supporting their clinical relevance. Chronotherapy, the time-dependent administration of chemotherapy in alignment with circadian biology, further enhances treatment tolerability and efficacy. Clinical studies, such as EORTC 05011, have demonstrated improved outcomes with circadian-timed delivery of 5-FU, oxaliplatin, and irinotecan, especially when schedules are adapted to sex-specific chronobiological patterns. The integration of pharmacogenomic testing and chronotherapy represents a robust, individualized treatment framework for CRC, reducing the risk of adverse effects while maintaining, or even improving, therapeutic effectiveness. This dual approach paves the way toward a more precise and patient-centred oncology

DIABETES AND OBESITY – HOW TO USE MEDICINES RATIONALLY?

USE OF MEDICATIONS IN THE TREATMENT OF TYPE 2 DIABETES - NEW INSIGHT

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KEYWORDS: Glycaemic Control; Individualised Treatment Strategies; Patient-Centred Approach

Diabetes mellitus has emerged as a rapidly escalating global health crisis demanding comprehensive and coordinated strategies to improve prevention, early detection and effective treatment. Pharmacotherapy is fundamental in the comprehensive management of type 2 diabetes mellitus (T2DM). The American Diabetes Association (ADA) 2025 guidelines emphasize individualized treatment strategies to optimize glycemic control and minimize complications. Healthy behaviors, diabetes self-management education and support, avoidance of therapeutic inertia, and social determinants of health should be included in the management of T2DM. There is increased emphasis on personalized treatment plans, incorporating patient preferences and comorbidities. New evidence supports broader use of SGLT2 inhibitors and GLP-1 receptor agonists or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists for cardiovascular and renal protection, expanding indications beyond glycemic control. In patients with concomitant metabolic dysfunction–associated steatotic liver disease (MASLD) and overweight or obesity incretin based drugs are prefered for glycemic management and as an adjunctive to healthy interventions for weight loss. Tailoring therapy requires consideration of comorbidities, hypoglycaemia risk, weight effects, convenience, and cost. In patients with contraindications or intolerance to certain drugs, alternative options are sought. Additionally, the guidelines highlight the importance of early combination therapy in high-risk patients. Advances in diagnostic tools and monitoring strategies are emphasized, alongside recommendations for more aggressive targets in specific populations. These updates aim to optimize clinical outcomes by integrating recent evidence and promoting a more individualized, patient-centred approach to T2DM management.

CARDIOVASCULAR EFFECTS OF ORAL ANTIDIABETIC DRUGS

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KEYWORDS: Oral Antidiabetic Drugs; Cardiovascular Outcomes Trials; Major Adverse Cardiovascular Events

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM), highlighting the need for therapies that deliver benefits beyond glycemic control. Cardiovascular outcomes trials (CVOTs) have provided critical insights into the cardiovascular efficacy and safety of glucose-lowering medications, reshaping treatment recommendations and clinical practice.

Evidence from CVOT has shown that sodium–glucose co-transporter-2 (SGLT2) inhibitors consistently reduce hospitalizations for heart failure, with some also lowering major adverse cardiovascular events (MACE) and cardiovascular mortality, while glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce MACE and now demonstrate efficacy with both injectable and oral formulations (semaglutide).

Pioglitazone has been associated with a reduction in recurrent vascular events in patients with prior cerebrovascular incidents and insulin resistance, although its use remains limited.

Oral medications with cardiovascular safety but not incremental efficacy include dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas such as glimepiride. Trials have confirmed cardiovascular neutrality of DPP-4 inhibitors, although saxagliptin raised concerns about heart failure risk.

Older agents such as metformin continue to serve as first-line therapy despite more limited cardiovascular evidence.

Current clinical guidelines recommend prioritizing SGLT2 inhibitors and GLP-1 RAs in patients with T2DM and established CVD, heart failure, or chronic kidney disease, regardless of HbA1c. Cardiovascular outcomes data have thus redefined diabetes management, highlighting the need for optimized therapy combinations, broader accessibility, and evidence-based application across diverse patient populations.

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NEW AND STRONG EVIDENCE IN TREATMENT OF PATIENTS WITH CHRONIC KIDNEY DISEASE AND DIABETES TYPE 2

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KEYWORDS: Chronic Kidney Disease; Diabetes Type Two; Semaglutide.

Chronic kidney disease (CKD), an independent cardiovascular (CV) risk is an important cause of death and DALYs. When associated with diabetes type 2 (T2D) this risk further increases. All relevant international guidelines emphasize a holistic approach that integrates lifestyle modifications with pharmacological interventions tailored to individual patient needs. In last several years we are facing a revolution of glucose-lowering therapies with drugs with clear benefits far beyond glucose control having significant impact on cardio-kidney health. Treatment algorithms for selecting appropriate drugs are based on eGFR levels and patient comorbidities. A notable study, the FLOW trial, showed semaglutide benefits in patients with T2D and CKD revealing a 24% reduction in the composite outcome of CKD progression, CV events, and kidney death with semaglutide use. Additionally, semaglutide slowed the decline in kidney function (eGFR), and reduced the risk of MACE (18%) and all-cause mortality (20%) with excellent safety profile. The SELECT trial demonstrated the long-term kidney outcomes associated with semaglutide in patients with obesity and CV disease. Semaglutide 2.4 mg reduced MACE for 20%, and the risk of the main kidney composite endpoint by 22% compared with placebo. The results of the SELECT trial are particularly important keeping in mind increasing prevalence of obesity. For individuals with T2D and CV disease, the 2025 ADA standards prioritize SGLT2 inhibitors or GLP-1 RA with proven cardio-kidney benefits. Semaglutite is evidence-based

proven drugs. Regular reassessment of all risk factors is crucial for optimizing treatment strategies and preventing disease progression.

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MEET THE EDITORS OF THE BJCP AND PHARMACA JOURNAL

INSIDE THE BRITISH JOURNAL OF CLINICAL PHARMACOLOGY: EDITORIAL INSIGHTS, FUTURE DIRECTIONS, AND OPPORTUNITIES FOR RESEARCHERS

Andrej Belančić[1], Robert Likić[1], Ana Alfirević[1], Oscar Della Pasqua[1], Serge Cremers[1,*] on behalf of the British Journal of Clinical Pharmacology

[1]British Journal of Clinical Pharmacology (BJCP)

KEYWORDS: Clinical Pharmacology; Collaboration; Editorial Process; Peer Review; Scientific Publishing

The British Journal of Clinical Pharmacology (BJCP) is a leading international journal in the field of clinical pharmacology and therapeutics. Positioned in the first quartile (Q1) of pharmacology journals, BJCP publishes high-quality research spanning drug discovery and development, clinical trials, pharmacokinetics, pharmacogenetics, pharmacovigilance, and therapeutics. With a global readership and strong international editorial board, the journal is committed to advancing innovation, integrity, and accessibility in clinical pharmacology.

This session, convened at the 2nd Croatian Congress on Clinical Pharmacology, brings together BJCP editors to share perspectives on the journal's priorities, future direction, and opportunities for researchers. Prof. Serge Cremers will introduce the session and outline BJCP's scope, strategic focus, and long-term goals to expand scientific reach and collaboration. Prof. Robert Likić will discuss the impact of themed issues and spotlight commentaries, which provide a platform to highlight emerging areas and foster focused discourse. Prof. Oscar Della Pasqua will emphasize the central role of peer review in safeguarding scientific quality, addressing challenges of timeliness and strategies for reviewer engagement. Prof. Ana Alfirević will reflect on ethical imperatives, the barriers to publishing novel findings, and the future of scientific dissemination in an evolving landscape. Dr. Andrej Belančić will conclude by presenting opportunities for young researchers within BJCP, including pathways to publication, mentorship, and roles that nurture early-career involvement in the editorial process.

By offering insights directly from its editorial team, this session will provide congress participants with a unique opportunity to understand the inner workings of BJCP, gain practical advice for publishing, and explore new possibilities for collaboration in advancing the field of clinical pharmacology.

PHARMACA: FOCUS, FUTURE DIRECTIONS, AND POSSIBILITIES FOR COLLABORATION

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KEYWORDS: Evidence-Based Medicine, Independent Journals; Bulletins; Education, Clinical Pharmacology

Scientific pharmacology journals and independent professional journals serve complementary roles in advancing rational drug therapy. Scientific journals generate the foundational evidence base through publication of clinical trials, observational studies, and systematic reviews, but the complexity, volume, and variable quality of these studies often make translation into clinical practice difficult.

Independent journals and bulletins, including Pharmaca, Prescrire, Australian Prescriber, Therapeutics Letter, and Arzneimittelbrief, address this gap by critically appraising, synthesizing, and contextualizing evidence. They provide unbiased evaluations, therapeutic guidance, and expert commentary that distil complex data into practical recommendations. Their value has been recognized in the medical literature and endorsed by organizations such as WHO and IUPHAR. Importantly, these journals are members of the International Society of Drug Bulletins, a global network of journals and bulletins committed to promoting high-quality, independent information on medicines. In Croatia, Pharmaca has played a central role since its foundation in 1963 as one of the earliest pharmacotherapy journals in the region. From its beginning, it has maintained editorial and financial independence, ensuring objectivity in drug evaluation and local adaptation of pharmacotherapy recommendations. After ceasing publication in 2011, Pharmaca was relaunched in 2020, supported by the creation of the e-Pharmaca educational portal, and it continues to provide clinicians with reliable, independent, and evidence-based information. Looking ahead, closer cooperation between scientific journals and independent pharmacology journals such as Pharmaca will be essential for optimizing evidence translation, supporting rational prescribing, and improving patient outcomes. Such collaboration can be realized through interdisciplinary partnerships and joint forums, co-development of guidelines and consensus statements, as well as academic detailing and educational outreach.

CHALLENGES IN CLINICAL PHARMACOLOGY II

USE OF BETA-BLOCKERS IN THE TREATMENT OF INFANTILE HEMANGIOMAS

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KEYWORDS: beta-blockers; infantile hemangiomas

Introduction: Infantile hemangiomas (IH) are the most common benign vascular tumors in children, with an incidence of 4–5% in the infant population and are more frequently observed in girls (female-to-male ratio of 2.5–4:1). These lesions are characterized by a proliferative phase of rapid growth, followed by spontaneous regression and involution. Although most IHs do not require treatment, 10–20% of cases do—especially those located on vital structures or associated with ulceration, functional impairment, or significant cosmetic disfigurement.

Aim: To describe the available therapeutic modalities with an emphasis on the use of beta-blockers in the treatment of infantile hemangiomas.

Methods: We present the treatment of patients with IH at the Children's Hospital Zagreb. Management included pharmacotherapy, surgical intervention, or a combination of both, with oral propranolol as the first-line treatment. Propranolol, a non-selective beta-blocker, acts through multiple mechanisms—including vasoconstriction, inhibition of angiogenesis, and induction of apoptosis in endothelial cells—effectively halting growth and promoting hemangioma regression. Therapy is introduced gradually, with careful monitoring for side effects such as gastrointestinal and respiratory symptoms, bradycardia, hypotension, and hypoglycemia. Treatment typically lasts at least six months, until the end of the proliferative phase. Despite its favorable safety profile, continuous monitoring is essential, particularly in early infancy. For smaller superficial hemangiomas that are non-ulcerated and do not involve mucosal surfaces, topical 0.5% timolol may be an effective treatment option. During the involution phase, laser therapy is recommended to reduce residual changes such as telangiectasias and to improve the cosmetic appearance of lesions.

Conclusion: Propranolol is the drug of choice for the treatment of complicated infantile hemangiomas. Guideline-based management is essential for standardizing care, supporting evidence-based decision-making, and achieving optimal outcomes with minimal risk to the child.

DO PHARMACOKINETICS OF MEDICATIONS VARY BY ETHNICITY?

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KEYWORDS: pharmacokinetics; pharmacogenetics; personalised treatment.

The examination of the prevalence of inter-ethnic variations in medication pharmacokinetics is the main emphasis of the presentation. This difference occurs and is clinically important, according to 31 study results. Thirty percent of events are genetically determined, whereas the remaining seventy percent are non-genetic (influenced by nutrition, lifestyle, and environment).

Significant differences exist between ethnic groups in key pharmacogenetic enzymes that impact medication metabolism and dose, namely CYP2D6, CYP2C19, CYP3A5 and TPMT.

CYP2D6 is in charge of metabolising around 1/4 of all medications. With notable variations in allele frequency it exhibits notable inter-ethnic diversity. There are 15 distinct gene alleles known to exist for the CYP2C19 enzyme, and the frequency of the phenotype varies significantly across ethnic groups. Significant variation has also been reported in the CYP3A5 enzyme.

TPMT genetic polymorphisms vary widely among ethnic groups, with poor metabolisers Caucasians having the TPMT3A allele and Chinese, Japanese, and African-Americans having the TPMT3C allele. The value of measuring TPMT enzyme levels has been recognised, notably in the prescription of the medicine azathioprine.

Polymorphisms in VKORC1 and CYP2C9 alter warfarin administration, with Asians often requiring lower doses.

Knowledge of potential changes in medication pharmacokinetics is required to prescribe effective and safe medicine to the patient in the appropriate dose while avoiding its adverse impact. This problem is not just clinically significant, regulatory authorities are also aware of it. ICH E5 has classified medications as ethnically sensitive or non-sensitive, and the FDA has mandated Diversity Action Plans in clinical trials since 2024, with a suggestion that 30-40% of subjects be from minority ethnic groups. The objective is to conduct clinical trials with outcomes that are as global as feasible.

We currently live in a globalised environment, so personalised treatment will become essential rather than optional.

PEPTIDES AS THERAPEUTIC AGENTS IN PALLIATIVE CARE PAIN MANAGEMENT: HISTORY, CHALLENGES AND OPPORTUNITIES

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KEYWORDS: peptides; palliative care pain management; ziconotide.

Peptides have been important in pharmacotherapy since 1922, beginning with the extraction of insulin for the treatment of Type I diabetes. Over the years, peptides have played essential roles in human physiology, acting as hormones, neurotransmitters, growth factors, and immune modulators, with nearly 100 peptide-based drugs now approved. The peptide therapeutics market continues to expand.

In the field of pain management, particularly in palliative care, peptide-based therapies are increasingly recognized for their potential. FDA/EMA-approved ziconotide, an intrathecal peptide analgesic, provides a potent alternative to opioids but is associated with significant psychiatric and neurological side effects. Future innovations in its delivery and administration could enhance its therapeutic profile.

Endogenous opioid peptides, such as enkephalins, endorphins, and nociceptin, bind to opioid receptors and exhibit analgesic properties with a lower risk of dependence compared to synthetic opioids. However, their clinical application remains limited due to rapid enzymatic degradation and poor membrane permeability.

In addition, non-opioid peptides, including substance P, bradykinin, calcitonin gene-related peptide, cholecystokinin, neuropeptide FF, neurotensin, endothelin-1, melanostatin, ghrelin, glucagon-like peptide-1, and neuropeptide Y, are emerging as novel targets for pain modulation. As the opioid crisis shifts research priorities, these peptides hold promise, particularly in the management of chronic cancer pain.

Despite promising preclinical data, the clinical translation of neuropeptide-based therapies remains challenging, though advances in multifunctional peptides and CNS drug delivery systems offer hope for their future use as analgesics.

TARGETED MODULATION OF PRO-INFLAMMATORY PATHWAYS BY TOPICAL NSAIDS IN EXPERIMENTAL COLLAGEN-INDUCED ARTHRITIS

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KEYWORDS: IL-17, STAT3, PGE2, NSAID, Arthritis

Introduction: The present study aimed to assess and compare the anti-inflammatory effects of topically administered diclofenac, ketoprofen, and piroxicam on key inflammatory mediators—interleukin-17 (IL-17), prostaglandin E2 (PGE2), and signal transducer and activator of transcription 3 (STAT3)—in a rat model of collagen-induced arthritis (CIA).

Methods: Thirty male Wistar rats were randomly allocated into five groups: three treatment groups receiving topical diclofenac, ketoprofen, or piroxicam; a positive control group administered a placebo patch; and a negative control group without collagen induction. CIA was induced via bovine type II collagen emulsified with incomplete Freund's adjuvant. Arthritis severity was evaluated using macroscopic scoring. Nonsteroidal anti-inflammatory drug (NSAID) patches were applied to the right hind paw for 6 hours daily over five consecutive days. Levels of inflammatory mediators were measured using enzyme-linked immunosorbent assay (ELISA). Data were analysed using ANOVA, Kruskal–Wallis, and mixed-effects models to assess temporal and group differences.

Results: Topical NSAID application resulted in a statistically significant

reduction in IL-17, PGE2, and STAT3 levels compared to the positive control group ($p<0.05$), with ketoprofen demonstrating the most substantial effect. These results suggest that topical NSAIDs can exert targeted anti-inflammatory effects, potentially influencing the pathogenesis of rheumatoid arthritis through modulation of cytokine-mediated pathways.

Conclusion: This study supports the therapeutic potential of topically applied diclofenac, ketoprofen, and piroxicam in attenuating inflammatory responses associated with rheumatoid arthritis. The findings underscore the promise of topical NSAIDs as a localized, potentially safer alternative to systemic treatment, meriting further exploration in chronic application settings.

CLINICAL PHARMACOLOGY IN DRUG REGULATION

RISK MINIMISATION MEASURES IN CLINICAL PRACTICE – REGULATORY DREAM OR REALITY CHECK?

FROM EU REGULATORY ACTION TO CLINICAL REALITY: INSIGHTS FOR CLINICAL PHARMACOLOGY PRACTICE IN CROATIA

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KEYWRODS: Risk Minimization Measures; Pharmacovigilance; Patient Safety. Pharmacovigilance Legislation

Background: Risk minimisation measures (RMMs) are essential regulatory tools to ensure the safe use of medicinal products in the European Union (EU). The EU pharmacovigilance legislation requires systematic evaluation of RMMs so that they can be adapted or improved when insufficient. Under its remit, the European Medicines Agency (EMA) has conducted several EU multinational studies to evaluate the effectiveness of RMMs and their implementation in clinical practice. These studies provide valuable insights into the translation of regulatory measures into real-world outcomes and support maintaining a positive benefit–risk balance.

Methods: We analysed outcomes from EMA-coordinated research projects evaluating regulatory RMMs across diverse therapeutic areas and medicinal product in the EU. Studies used healthcare databases, surveys, or mixed-methods approaches to measure changes in prescribing behaviour, patient outcomes, awareness, or guideline integration. Results were grouped by demonstrated clinical impact versus limited/no measurable impact. Country coverage was reviewed to assess generalisability to other EU Member States, with reflection on relevance for Croatia.

Results:

Demonstrated clinical impact:

- Codeine in children: Prescribing in children <12 years markedly decreased in the targeted countries France, Spain, UK, Germany, and Norway, aligning with regulatory restrictions. Near elimination of prescribing for pain was achieved, though the impact on cough/cold indications was more limited.
- Diclofenac cardiovascular risk: Significant reductions in prescribing were

observed across Denmark, the Netherlands, England, and Scotland, particularly in high-risk patients, although contraindicated prescribing persisted.

Limited or no clinical impact:

- Valproate pregnancy prevention program (PPP): Despite general awareness of teratogenic risks, patient and healthcare professional awareness of pregnancy prevention program (PPP) measures was low. Declines in use were modest and inconsistent across countries (Italy, Spain, UK, Netherlands), with persistently low rates of contraception coverage and continued pregnancies during exposure.

- Oral retinoids: Minimal change in utilisation patterns post-2018 PPP revision in Denmark, Netherlands, Spain, and Italy where the study was conducts. Pregnancies continued to occur, and information on contraception/pregnancy testing was poorly captured.

- Fluoroquinolones: Regulatory referral (2018) showed no consistent impact on prescribing trends in six (Belgium, France, Germany, The Netherlands, Spain, UK) EU countries, with temporal changes unrelated to EMA intervention.

- Methotrexate (weekly dosing safety): A 2022 survey in five (France, Greece, Germany, Poland, and Sweden) EU countries revealed low awareness, knowledge, and adherence to RMMs among prescribers, pharmacists, and patients. RMMs were not effective by predefined criteria.

Implementation in clinical practice guidelines (CPGs): Analysis of 136 CPGs from six (Denmark, Greece, Latvia, The Netherlands, Portugal and Slovenia) EU countries showed RMM inclusion in only 25% of relevant guidelines. Key barriers were limited awareness among clinicians, perceived low utility, and lack of interaction between regulators and guideline developers.

Discussion:
Studies demonstrate that regulatory RMMs can be effective (e.g., codeine, diclofenac) but often fail to achieve intended outcomes (e.g., valproate PPP, retinoids, methotrexate). Effectiveness varies by therapeutic area, regulatory dissemination, national healthcare context, and stakeholder awareness. Extrapolation across EU countries is feasible given the shared regulatory framework, but local factors (prescribing culture, reimbursement, healthcare system structure) influence uptake. For Croatia, conducting similar studies would provide essential insights into national implementation gaps, strengthen collaboration between regulators, clinicians, and guideline developers, and ensure that RMMs translate into safer clinical practice.

Conclusions:
The evaluation of RMMs reveals variable success across therapeutic areas in the EU. While some interventions demonstrate strong clinical impact, others highlight persistent

gaps in awareness, implementation, and integration into clinical decision-making. Future efforts should prioritise stronger communication strategies, linkage with clinical guidelines, and continuous monitoring of RMMs at national level, including in Croatia, to optimise safe use of medicines.

NAVIGATING A COMPLEX ENVIRONMENT: WHY IS THE APPROVAL OF ANTI-AMYLOID ANTIBODIES FOR ALZHEIMER'S DISEASE SO CHALLENGING?

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KEYWRODS: Anti Amyloid Antibodies; Alzheimer's Disease; Ethical Challenges; European Union

This presentation will explore various regulatory decisions related to the approval of anti-amyloid antibodies through several key questions: What factors are taken into account in the equation for approving a new drug? Why did lecanemab receive a positive opinion from the European Medicines Agency (EMA), while donanemab did not? What happened with aducanumab? How do regulatory decisions in the EU differ from those in the United States? How do regulators assess the risks of therapy, and how do they determine when a risk is unacceptable?

We will address these questions by analysing and interpreting clinical studies, while considering practical and ethical challenges—such as the availability of MRI and PET scanners and APOE genotyping—as well as the expectations of patients and the medical community. By connecting these elements, the presentation will provide a comprehensive insight into the complex process of drug approval for Alzheimer's disease within the European Union.

THE ROLE OF REAL-WORLD EVIDENCE AND HEALTH REGISTRIES IN MONITORING THE SAFETY OF ORPHAN DRUGS

Petar Mas [1]

[1] Agency for Medicinal Products and Medical Devices of Croatia (HALMED)

KEYWRODS: Orphan Druga; Post Authorisation Requirements; Clinical Trials; Real World Evidence; Health Registries

The clinical development of orphan drugs is often constrained by major methodological and practical challenges. Patient populations are typically very small, limiting the statistical power of clinical trials and the generalizability of their findings. As a result, many orphan drugs authorized in the EEA carry post-authorisation obligations to further evaluate their safety and effectiveness, either through clinical trial extensions or other types of studies. However, conducting such trials can be costly, logistically demanding, and in some cases even not feasible. In this context, real-world evidence and health registries are increasingly used as complementary or alternative approaches to fulfil post-authorisation requirements. This presentation will review orphan drugs approved in recent years in the EEA, focusing on their post-marketing safety obligations, and will evaluate the impact of real-world evidence studies compared with traditional clinical trials.

DEVELOPMENT OF THE CROATIAN INSTITUTE OF PUBLIC HEALTH (CIPH) TREATMENT OUTCOMES REGISTRY: DRUGS OUTSIDE THE CHIF LIST

Maja Vajagić

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KEYWORDS: Particularly Expensive Drugs; Healthcare Spending; Monitoring Treatment Outcomes, Healthcare System

Introduction: Health systems are faced with significant technological developments and increased spending, which directly affects their sustainability. Part of the defined costs in the health system are the so-called particularly expensive drugs, for which significant funds are allocated from the mandatory health insurance fund, and which are rising every year. The Croatian Health Insurance Fund (CHIF), since 2006 has a list of particularly expensive drugs and allocated funds to cover the costs of these drugs, in accordance with the defined indications. However, the use and consumption of this group of drugs outside the indications, as well as expensive drugs that are not on CHIF lists, are financed by hospitals from their own funds, and there is currently no available data on the use and financial consumption of this group of drugs.

Objectives: To present the development of a system for integrated monitoring of the use, consumption, financial burden on hospitals and treatment outcomes with drugs from this group. Description of the variables for reports, the reporting process as initially defined, and proposals for the availability of information to hospitals as a basis for expert discussion and proposals for improvement. Also, to show the initial information collected from all publicly owned hospitals in 2024 on the use of particularly expensive drugs at the expense of hospital funds: outside the defined indication and which are not on the CHIF list of drugs that are defined as expensive (annual consumption per patient is higher than the amount of gross domestic product (GDP) per capita of the Republic of Croatia for the previous year (for 2023: EUR 19,686)).

Methods: Presentation of the process and documentation for the development of the register of treatment outcomes, description of the reporting process and proposal for the availability of the report. The initial data on the use of particularly expensive drugs were collected by an electronic survey during the third quarter of 2024.

Results: Initial documentation for the development of an integrated data collection system for this group of drugs and a list of variables for the report and a proposal for the system development and data collection process were prepared. Initial data on the use of drugs were submitted by 46 hospitals (77%) out of 61 publicly owned hospitals. 18

hospitals used drugs from the described group (4 Clinical Hospital Centers, 3 Clinical Hospitals, 2 Clinics and 9 general hospitals). Of the 123 drugs on the CHIF list drugs, 50 were used without defined indication. Of the drugs not covered by CHIF, in total 74 drug were used. According to the analysis of drug use by trade name and by hospitals, the differences between hospitals were significant. For drugs from the CHIF list, from 1 to 35 drugs per hospital, and for drugs not covered by CHIF, from 1 to 29 drugs per hospital.

Conclusion: The use of particularly expensive drugs varies between hospitals, and the development of a monitoring system will improve the use of these drugs, improve treatment outcomes, and have effect on the sustainability of the health system. Further research into the use of these drugs and adherence to guidelines is needed.

CLINICAL PHARMACOLOGY AND FAMILY MEDICINE

COLLABORATION BETWEEN CLINICAL PHARMACOLOGIST AND FAMILY MEDICINE PHYSICIAN: OPTIMIZATION OF THERAPY IN PRIMARY HEALTH CARE

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KEYWORDS: Collaboration; Rational Pharmacotherapy; Optimisation; Treatment Safety; Clinical Pharmacology; Primary Health Care

Collaboration between clinical pharmacologists and general practitioners plays a vital role in optimizing pharmacotherapy, particularly within primary healthcare. Through pharmacotherapy consultations, day hospital care, and multidisciplinary services, clinical pharmacologists provide expert support in managing complex cases of drug hypersensitivity, polypharmacy, adverse drug reactions, and potential drug interactions, thereby improving treatment safety and effectiveness.

This presentation highlights clinical cases that demonstrate the practical application of pharmacological expertise. In a patient with documented antibiotic hypersensitivity, comprehensive drug testing enabled the safe use of cephalosporins and macrolides, while aminopenicillins were contraindicated. Complex polypharmacy cases, particularly in elderly patients with multiple comorbidities, require an individualized approach, including pharmacogenetic analysis of drug-metabolizing enzymes. Such assessments allow for dose adjustments, reduction of adverse effects, and rationalization of therapy.

Particular attention is given to patients with chronic diseases (cardiovascular disease, diabetes mellitus, chronic kidney disease), where clinical pharmacologists assist in optimizing antihypertensive, antithrombotic, and lipid-lowering therapy. The presentation also addresses the differentiation between true drug allergies and adverse effects, preventing the unnecessary exclusion of therapeutic options.

In conclusion, multidisciplinary collaboration enables rational and safe pharmacotherapy, improving patients' quality of life. The role of general practitioners remains essential, yet with the support of clinical pharmacologists, a more personalized and effective treatment approach is achieved.

THE ROLE OF CLINICAL PHARMACOLOGISTS IN OPTIMIZING PHARMACOTHERAPY AND COLLABORATION WITH FAMILY PHYSICIANS

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KEYWORDS: Clinical Pharmacology; Therapeutic Challenges; Patient-Specific Needs; Family Medicine

Introduction: In an era of rapid development of innovative therapies, clinical pharmacologists are essential in optimizing pharmacotherapy. Collaboration with family physicians is vital to address complex medication challenges and meet patient-specific needs in primary care.

Methods: A narrative review of literature and outpatient case studies was conducted, focusing on key areas of collaboration: evaluating drug hypersensitivity, managing polypharmacy, addressing drug interactions and adverse reactions. Data from clinical pharmacology consultations were analyzed to illustrate common referral reasons and intervention outcomes.

Results: Close coordination between clinical pharmacologists and family physicians enhances prescribing accuracy, reduces adverse effects and drug interactions, and supports deprescribing through individualized treatment plans and patient education.

Conclusion: Effective communication between clinical pharmacologists and family physicians is fundamental to the optimization of pharmacotherapy. Combining pharmacological expertise with family physicians' patient knowledge reduces medication-related risks and enhances healthcare quality

COLLABORATION BETWEEN CLINICAL PHARMACOLOGISTS AND FAMILY PHYSICIANS: OPTIMIZING THERAPY IN PRIMARY CARE

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KEYWORDS: Primary Care; Clinical Pharmacology; Family Physicians; Collaboration; Quality of Care; Personalised Medicine

Introduction: Family medicine physicians are the patient's first point of contact with the healthcare system and are often the most trusted individuals when making therapeutic decisions, including the decision to participate in clinical trials.

Discussion: Collaboration between primary care and clinical pharmacology is essential for optimization of therapy in terms of drug selection, dose adjustment, monitoring of adverse drug reactions, whereby family doctor can consult and refer the patient to a clinical pharmacologist and cooperate in complex therapeutic cases that require an individualized approach (patients with comorbidities and polytherapy, pregnant women, nursing mothers, elderly people). With the cooperation of pharmacologists and family physicians, better control of patients with chronic diseases can be achieved, also the need for hospitalization and the frequency of adverse drug events can be reduced.

The primary care physician could play a key role in the identification, motivation and continued care of patients in clinical trials. One of the main reasons why family physicians rarely inform patients about available studies is the lack of effective communication channels between primary and secondary health care. In collaboration with a clinical pharmacologist, it is possible to develop models that enable safe patient involvement, expert counselling on therapy, and timely recognition and management of adverse drug reactions.

Conclusion: The partnership between clinical pharmacology and primary care has been proven to improve the quality of care, enable early recognition of side effects, more economical drug selection and more successful clinical trials. Such cooperation is the basis of safe and personalised medical care.

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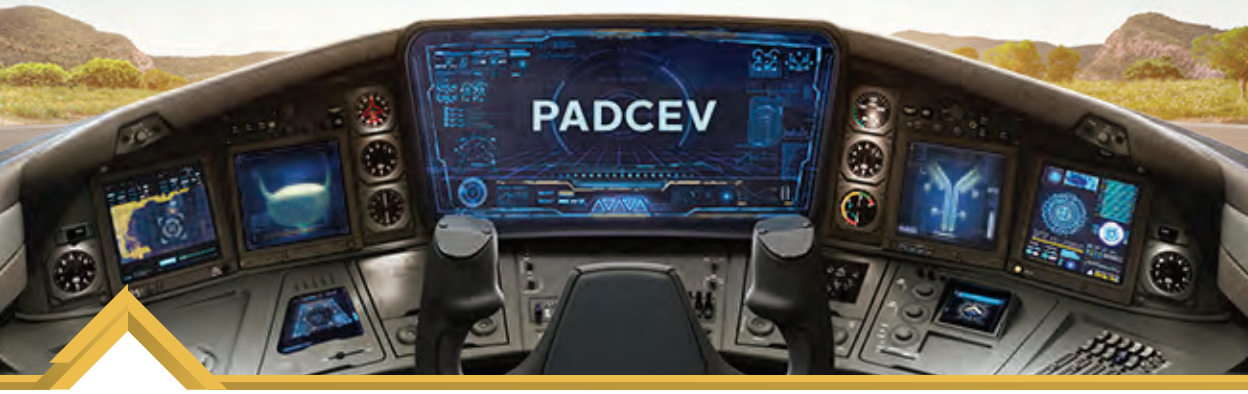

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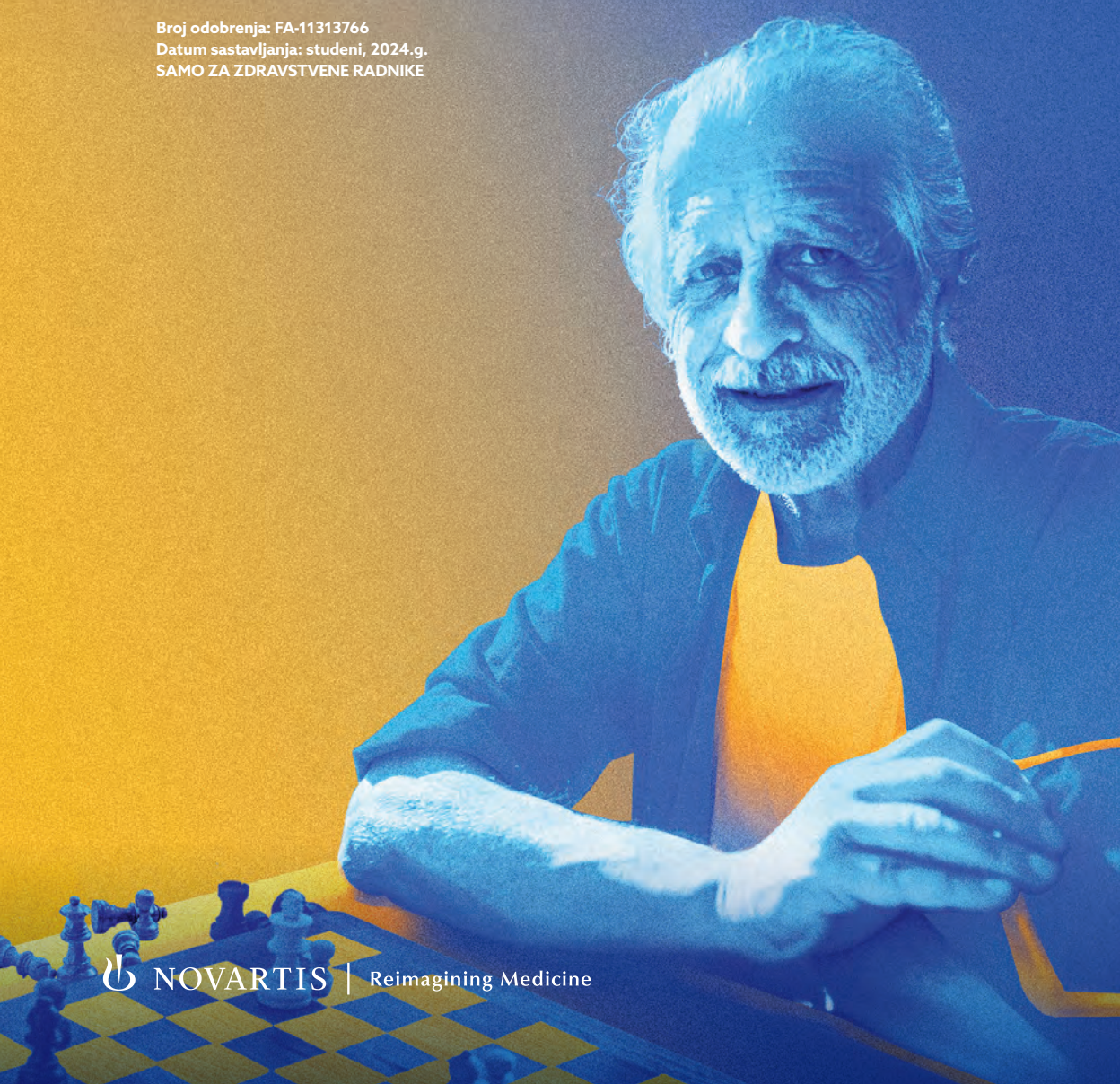

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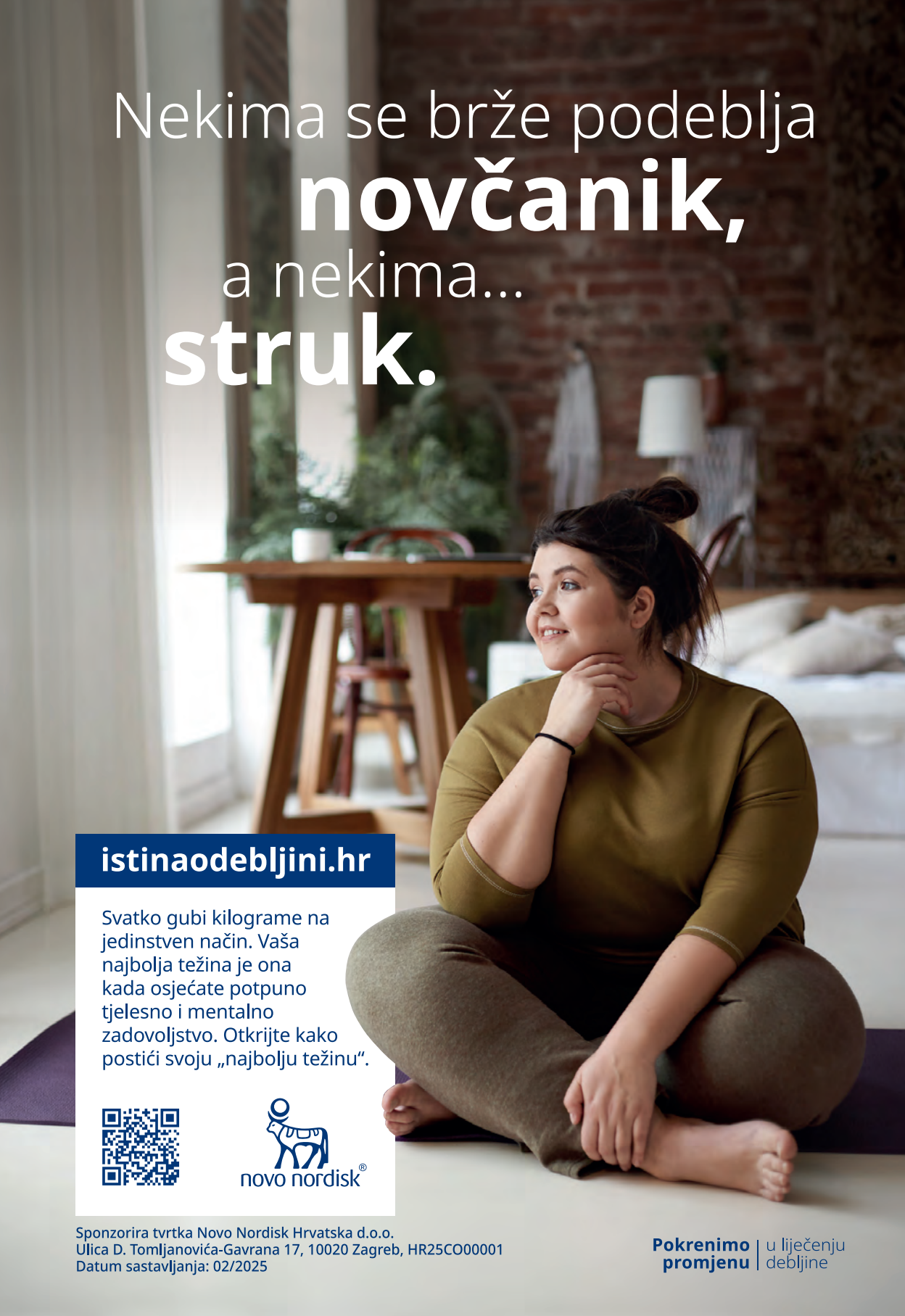

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