



FACULTY OF PHARMACY
IN HRADEC KRÁLOVÉ
Charles University



**INTERNATIONAL MEETING
AND EUROPEAN TRAINING SCHOOL**

**“EUROPEAN PERSPECTIVES IN RATIONAL
AND INDIVIDUALIZED DRUG THERAPY
IN OLDER PATIENTS AND AGEISM
- PRIORITIES FOR NEXT DECADES”**

ABSTRACT BOOK

Organizers:

Fialová D. (Main Coordinator) (1,2), Lukačšínová-Ballóková A. (Co-organizer) (1), Ayalon L. (EU COST Action Chair) (1), Tesch- Römer C. (EU COST Action Vice-Chair) (1)

Main organizing subjects:

EU COST Action 1402 „Ageism- a Multinational, Interdisciplinary Perspective“ (1)
and University Educational Centre in Clinical Pharmacy, Faculty of Pharmacy,
Charles University in Prague, Czech Republic (2)

Date and place:

April 25- 27th, 2016

Hall of the Czech Medical Association of J.E.Purkyně, Prague, Czech Republic



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Edited by: Fialová Daniela, PharmD, PhD, BCCP, Head of the University Educational Centre in Clinical Pharmacy, Faculty of Pharmacy in Hradec Králové, Charles University in Prague, Czech Republic.

Guest Editors: Lukačšínová-Ballóková A., MS, Prof. Ayalon L. PhD. and Prof. Tesch-Römer C., PhD.

Main Organizers: 1/ The EU COST Action IS 1402 „Ageism- a Multinational, Interdisciplinary Perspective and 2/ The University Educational Centre in Clinical Pharmacy (UCCP), Faculty of Pharmacy in Hradec Králové, Charles University in Prague, Czech Republic.

Cooperating subjects: Department of Geriatrics and Gerontology, 1st Faculty of Medicine, Charles University in Prague, Czech Republic and Section of Clinical Pharmacy, Czech Pharmaceutical Society, Czech Medical Association J.E.Purkyně Cooperation offered to XXth Working Days of Clinical Pharmacy 2016

Supporting Team: Pezillo Andrea (Secretary), Grešáková Silvia, Miklasová Monika, MS, Vyšínová Tereza, Havlíková Šárka, Quittová Petra, Pohořalá Veronika, Fidranský Filip, Sirka Pavol, Klofáčová Aneta, Paulíková Kateřina, Krivošová Michaela, Hrdličková Petra (pregradual students)

CONTENT

Scientific program	page 1-3
Main organizers	page 3
Cooperating Institutions	page 3
Local participants	page 4
Honorary Guests	page 4
EU participants supported by the EU COST Action	page 5-6
Invited speakers	page 7

Abstracts of invited lectures and workshops

Ageing of the population, polypharmacy, potentially inappropriate prescribing and quality indicators.....	page 8
Efficacy and safety of medications in the old age, clinical guidelines and FORTA recommendations.....	page 10
EU COST Action 1402- “Inappropriate prescribing in older patients in Eastern Europe – a recent initiative”	page 12
Inappropriate prescribing in older adults in Serbia- use of risk management tools in pharmaceutical health care	page 13
Hospital care and older patients – inappropriate prescribing, drug related problems and experience with clinical pharmacy services	page 16
Risk management and clinical case-solving in older inpatients.....	page 20
Noncompliance in older adults - aspects of ageism, research tools and practical recommendations	page 22
Rational prescribing in older patients in nursing home care and home care in Europe- appropriate medication use, interprofessional approach	page 24
Minimizing drug use in the elderly – prevention of ageing and age-related diseases by changing eating habits.	page 28

Curriculum vitae- invited speakers

Prof. Petra Thürmann MD, PhD	page 29
Prof. Martin Wehling, MD, PhD	page 30
Dr. Daniela Fialová, PharmD, PhD, BCCP	page 31
Dr. Valentina Marinkovič, PharmD, PhD	page 33
Dr. Annemie Somers, PharmD, PhD.....	page 34
Prof. Jiří Vlček, RNDr., PhD.	page 36
Dr. Marcel Leppée, MD, PhD	page 38
Prof. Graziano Onder, MD, PhD.....	page 38
Prof. Eva Topinková, MD, PhD	page 40
Assoc. Prof. Soner Dogan, MD, PhD.....	page 42

SCIENTIFIC PROGRAM

**EU COST Action IS1402:
Ageism - a multi-national, interdisciplinary perspective**

INTERNATIONAL MEETING and EUROPEAN TRAINING SCHOOL

**“EUROPEAN PERSPECTIVES
IN RATIONAL AND INDIVIDUALIZED
DRUG THERAPY IN OLDER PATIENTS AND
AGEISM- PRIORITIES FOR NEXT DECADES”**

Organized by the EU COST Action 1402 (2015- 2018) “Ageism from a Multi-national, Inter-
disciplinary Perspective”

and

University Educational Centre in Clinical Pharmacy, Faculty of Pharmacy,
Charles University in Prague, Czech Republic

Date: 25- 27th April, 2016

**Place: Hall of the Czech Medical Association of J.E.Purkyně,
Prague, Czech Republic**

Address: Sokolská 31, 120 00 Prague 2, Czech Republic

Program-Day 1

- 9.00- 9.20 **Invitations by the EU COST Action Chairs and Local Organizers**
9.20- 10.00 **“Ageing of the population, polypharmacy, potentially inappropriate medications and quality indicators”**
Prof. Thürmann Petra MD, PhD
University of Witten/Herdecke, Wuppertal, Germany
- 10.00- 10.45 **“Clinical guidelines, ageism and inappropriate medication prescribing in older patients-FORTA recommendations”**
Prof. Wehling Martin MD, PhD
University of Heidelberg, Mannheim, Germany
- 10.45- 11.00 **Discussion**
11.00- 11.15 Coffee break
11.15- 11.45 **EU COST Action 1402- “Inappropriate prescribing in older patients in Eastern Europe – recent initiative”**
Fialová Daniela, PharmD, PhD, BCCP (Main Coordinator)
Faculty of Pharmacy and 1st Faculty of Medicine, Charles University in Prague, Czech Republic, University Educational Centre in Clinical Pharmacy, Charles University in Prague, Czech Republic
- 11.45- 12.15 **Inappropriate prescribing in older patients in Serbia- use of risk management tools in pharmaceutical health care**
Marinković Valentina, PharmD, PhD and Prof. Tasič Ljiljana, PharmD, PhD
University of Belgrade, Faculty of Pharmacy, Belgrade, Serbia
- 12.15- 13.00 **Panel Discussion with Invited Speakers and Honorary Guests**
“Rational Geriatric Pharmacotherapy- recent goals and future perspectives”
- 13.00- 14.30 Lunch break
14.30- 16.00 **Workshop 1: “Tools for the assessment of potentially inappropriate prescribing in older patients and quality indicators”**
Prof. Thürmann Petra MD, PhD
Universität Witten/Herdecke, Wuppertal, Germany
- 16.00- 16.15 Coffee break
16.15- 17.45 **Workshop 2: “Efficacy and safety of medications in the old age, clinical guidelines and recommendations”**
Prof. Martin Wehling, MD, PhD
University of Heidelberg, Mannheim, Germany

Program-Day 2

- 9.00- 9.15 **Welcome of invited speakers**
9.15- 10.00 **“Hospital care and older patients- inappropriate prescribing, ageism and practical experience with clinical pharmacy services”**
Somers Annemie, PharmD, PhD.
Ghent University Hospital, Belgium
- 10.00- 10.45 **“Risk management and clinical case-solving in older patients”**
Prof. Vlček Jiří, RNDr, PhD
Faculty of Pharmacy, Charles University in Prague, Czech Republic
- 10.45- 11.00 **Discussion**
11.00- 11.15 **Coffee break**
11.15- 11.45 **“Noncompliance in older patients- aspects of ageism, research tools and practical recommendations”**
Leppee Marcel, MD, PhD
Andrija Stampar Institute of Public Health, Zagreb, Croatia
- 11.45- 12.00 Discussion
12.00- 13.30 Lunch break
13.30- 15.00 **Workshop 1: “Hospital care- inappropriate prescribing in older patients, services of clinical pharmacists”**
Somers Annemie, PharmD, PhD.
University of Ghent and Ghent University Hospital, Belgium
- 15.00- 15.15 Coffee break
15.15- 16.45 **Workshop 2: “Risk management and clinical case-solving in older patients”**
Prof. Vlček Jiří, RNDr, PhD.
Faculty of Pharmacy, Charles University in Prague, Czech Republic

University Educational Centre in Clinical Pharmacy, Charles University in Prague,
Czech Republic
20.00 **Training School Dinner**
(Social event closed for the EU COST Action Trainees and Trainers)

Program- Day 3

9.00- 9.15 **Welcome of invited speakers**
9.15- 10.00 **“Rational prescribing in older patients in nursing home care and home care in Europe- appropriate medication use, interprofessional approach”**
Prof. Onder Graziano MD, PhD
Universita Cattolica del Sacro Cuore, Italy
10.00- 10.45 **“Geriatric frailty and medication use- clinical recommendations”**
Prof. Topinková Eva MD, PhD
1st Faculty of Medicine, Charles University in Prague, Czech Republic
10.45- 11.00 **Discussion**
11.00- 11.15 Coffee break
11.15- 11.45 **“Medication misuse in older patients- nutritional aspects and drug-food interactions”**
Associate Prof. Dogan Soner, MD, PhD
Yeditepe University School of Medicine, Istanbul, Turkey
11.45- 12.00 **Discussion**
12.00- 13.30 Lunch break
13.30- 15.00 **Workshop 1: “Rational geriatric prescribing in nursing home care and home care in Europe- appropriate medication use and interprofessional approach”**
Prof. Onder Graziano MD, PhD
Universita Cattolica del Sacro Cuore, Italy
15.00- 15.15 Coffee break
15.15- 16.00 **Workshop 2: “Practical assessment of geriatric frailty- clinical recommendations”**
Prof. Topinková Eva MD, PhD
1st Faculty of Medicine, Charles University, Prague, Czech Republic

MAIN ORGANIZERS

Fialová Daniela, PharmD, PhD., BCCP

COST ACTION WG1 CHAIR, Head of the University Educational Centre in Clinical Pharmacy,
Faculty of Pharmacy, Academic worker and Researcher, Department of Social and Clinical Pharmacy,
Faculty of Pharmacy and Department of Geriatrics and Gerontology,
1st Faculty of Medicine, Charles University in Prague, Czech Republic

Ballóková Anna, MS

State Institute for Drug Control in Prague and Department of Geriatrics and Gerontology, 1st Faculty
of Medicine, Charles University in Prague, Czech Republic

Prof. Liat Ayalon, PhD.

EU COST ACTION 1402 CHAIR, Bar Ilan University, Israel

Prof. Clemens Tesch-Römer, PhD.

EU COST ACTION 1402 VICE-CHAIR, President of the International Association of Geriatrics
and Gerontology (IAGG), Germany

Nava Kling, Ariel Toperoff

EU COST ACTION 1402 grant holders, Israel

COOPERATING INSTITUTIONS

Faculty of Pharmacy (FoP), Charles University in Prague, Czech Republic- supported by the Dean of the FoP,
Assoc. Prof. Tomáš Šimůnek, PharmD, PhD.
University Educational Centre in Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague,
Czech Republic
Department of Geriatrics and Gerontology, 1st Faculty of Medicine, Charles University in Prague, Czech
Republic
Section of Clinical Pharmacy, Czech Pharmaceutical Association, Czech Medical Association J. E. Purkyně.
Cooperation offered to XXth Working Days in Clinical Pharmacy 2016.

LOCAL PARTICIPANTS

Radek Petráš, MS	Ostrava, Czech Republic
Drahomíra Záhorková, MS	Strakonice, Czech Republic
Anna Vachková, PharmD	Ostrava, Czech Republic
Hana Hofhanzlová, MS	Jihlava, Czech Republic
Martina Sedláčková, MS	Slavonice, Czech Republic
Lenka Valášková, MS	Cerhovice-Drozdvov, Czech Republic
Gabriela Vaculová, PharmD	Olomouc, Czech Republic
Jaroslav Duda, MS	Březina-Blansko, Czech Republic
Karolína Sochorová, MS	Brno, Czech Republic
Kristina Pechandova, PharmD, PhD	Strakonice, Czech Republic
Kateřina Skopalová	Kroměříž, Czech Republic
Zuzana Mečiarová, MD	Pardubice, Czech Republic
Ivana Plechatá, PhD	Hrusice-Senohraby, Czech Republic
Lenka Pavlacká	Otrokovice, Czech Republic
Astrid Matějková, MD	Pardubice, Czech Republic
Pavol Sirka	FoP Hradec Králové, Czech Republic
Helena Šťastná-Koblihová	Říčany, Czech Republic
Petra Quittová	FoP Hradec Králové, Czech Republic
Dagmar Malotová, MD	Samotičky, Czech Republic
Hrdličková Petra	FoP Hradec Králové, Czech Republic
Monika Kopečná	Osek nad Bečvou, Czech Republic
Veronika Příhodová, MS	Vřesina, Czech Republic
Lukáš Dlouhý, MS	Prague, Czech Republic
Ivana Tašková, PharmD	Prague, Czech Republic
Vendula Dvořáčková, MS	Prague-Petrovice, Czech Republic
Zdenka Danzigová, MD	Prague, Czech Republic
Dagmar Kusáková, MD	Prague, Czech Republic
Pavel Havelka, MS	Brno, Czech Republic
Monika Miklasová	FoP Hradec Králové, Czech Republic
Silvia Grešáková	FoP Hradec Králové, Czech Republic
Filip Fidranský	FoP Hradec Králové, Czech Republic
Aneta Klofáčková	FoP Hradec Králové, Czech Republic
Kateřina Paulíková	FoP Hradec Králové, Czech Republic
Šárka Havlíková	FoP Hradec Králové, Czech Republic
Petra Vyvozilová	FoP Hradec Králové, Czech Republic
Tereza Vyšínová	FoP Hradec Králové, Czech Republic
Michaela Krivošová	FoP Hradec Králové, Czech Republic
Veronika Pohořalá	FoP Hradec Králové, Czech Republic
Daniel Tkáč, PharmD	Brno, Czech Republic

HONORARY GUESTS

Assoc. Prof. Šimůnek Tomáš, PharmD, PhD.	Dean of the Faculty of Pharmacy, Charles University in Prague, Czech Republic
Malý Josef, PharmD, PhD	Scientific Secretary of the Czech Pharmaceutical Society, Czech Medical Association J.E.Purkyně, Czech Republic
Kateřina Horská, PharmD	Veterinary and Pharmaceutical University Brno, Czech Republic, University Educational Centre in Clinical Pharmacy
Heislerová Marcela, PharmD, PhD	Institute for Postgraduate Studies in Health Care, Czech Republic Head of the Department of Pharmacy

TRAINING SCHOOL PARTICIPANTS

Participants supported by the EU COST Action 1402



ASTA MASTAVIČIŪTĖ
(Assoc. Prof.), Vilnius University,
Vilnius, Lithuania



AGNĖ JAKAVONYTĖ-AKSTINIENĖ,
Lithuanian University of Health
Sciences, Kaunas, Lithuania



NICOLETA LEFTER,
Clinical Hospital "Dr. C.I.
Parhon", Iasi, Romania



IOANA ALEXANDRA SANDU,
Clinical Hospital "Dr. C.I. Parhon",
Iasi, Romania



ADRIANA GABRIELA PANCU,
Clinical Hospital "Dr. C.I. Parhon",
Iasi, Romania



INGRID KUMMER,
Gradska ljekarna, Zagreb, Croatia



MARGITA DRŽAIĆ,
Gradska ljekarna, Zagreb, Croatia



CLAUDIA TEIXEIRA GOMEZ,
Alameda da Universidade, Lisboa,
Portugal



ANDREA BOR,
University of Szeged, Szeged,
Hungary



MÁRTA CSATORDAI,
University of Szeged, Szeged,
Hungary



DAISY VOLMER
(Assoc. Prof.), University of Tartu,
Tartu, Estonia



MARIKA SAAR,
University of Tartu, Tartu, Estonia



ANNE-GRETE MÄRTSON,
Tartu University Hospital,
Tartu, Estonia



GULNIHAL OZCAN,
Turkish Medicines and Medical
Devices Agency, Ankara, Turkey



GUNAY YETIK ANACAK
(Assoc. Prof.), Ege University,
Izmir, Turkey



TATJANA STOJKOVIĆ,
University of Belgrade,
Belgrade, Serbia



JOVANA BRKIĆ,
University of Belgrade, Belgrade,
Serbia



KUZELOVA MAGDALENA
(Prof.), Comenius University, Bratislava,
Slovak Republic



ELENA ONDRIAŠOVÁ,
Comenius University Bratislava,
Slovak Republic



TATIANA FOLTÁNOVÁ,
Comenius University Bratislava,
Slovak Republic



STANISLAVA JANKYOVÁ,
Comenius University Bratislava,
Slovak Republic



MAARIT DIMITROW,
Finland

VLASTA KÁKOŠOVÁ,
Hospital pharmacy Bratislava,
Slovak Republic

KAREL HLOCH,
Faculty of Pharmacy in Hradec
Králové, Charles University,
Czech Republic

JAN VOSÁTKA,
Faculty of Pharmacy in Hradec
Králové, Charles University,
Czech Republic

JOSÉ LUIS TRIGO
Pharmacy Office, Regional
Ministry of Health and Social
Policies
Mérida, Spain

INVITED SPEAKERS (honorary guests)



Prof. Petra Thürmann, MD, PhD

Professor of Clinical Pharmacology, Chair of Clinical Pharmacology
University of Witten/Herdecke, Germany



Prof. Martin Wehling, MD, PhD

Managing Director, Institute of Experimental and Clinical Pharmacology and Toxicology, Director
Clinical Pharmacology Mannheim, Medical Faculty Mannheim, University of Heidelberg,
Mannheim, Germany



Dr. Daniela Fialová, PharmD, PhD, BCCP

Head of the University Educational Centre in Clinical Pharmacy, Faculty of Pharmacy, Charles
University in Prague, Czech Republic, Researcher and Academic worker, Department of Geriatrics
and Gerontology, 1st Faculty of Medicine and Department of Social and Clinical Pharmacy, Faculty
of Pharmacy, Charles University in Prague, Czech Republic



Dr. Marinkovic Valentina, PharmD, PhD

Associate Professor, University of Belgrade, Faculty of Pharmacy, Belgrade, Serbia



Dr. Annemie Somers, PharmD, PhD

Head of the pharmaceutical care department, Ghent University Hospital, Belgium
Visiting professor pharmaceutical care, Ghent University, Belgium



Prof. Jiří Vlček, RNDr, PhD

Professor of clinical pharmacy and pharmaceutical care, Department of Social & Clinical Pharmacy,
Faculty of Pharmacy in Hradec Králové, Charles University in Prague



Dr. Marcel Leppé, MD, PhD

Researcher, Andrija Stampar Institute of Public Health, Zagreb, Croatia



Prof. Graziano Onder, MD, PhD

Professor of Geriatrics and Gerontology, Centro Medicina dell'Invecchiamento, Università
Cattolica del Sacro Cuore, Rome, Italy



Prof. Eva Topinková, MD, PhD

Professor and Head of the Department of Geriatrics and Gerontology, 1st Faculty of Medicine and
General Teaching Hospital in Prague, Czech Republic



Assoc. Prof. Soner Dogan, MD, PhD

Associate Professor at Yeditepe University School of Medicine in Istanbul, Turkey

Ageing of the population, polypharmacy, potentially inappropriate prescribing and quality indicators

*Prof. Petra A. Thürmann, MD, PhD
University of Witten/Herdecke, Germany*

Currently in the European Union older persons (aged 65 or over) have a 18.5 % share of the total population, with the highest proportions in Italy (21.4 %) and Germany (20.8 %) and the lowest in Ireland (12.6 %). This share of senior citizens will increase to an estimated 29 % in 2080. Consequences of aging are decreased physical (and cognitive) functions and multimorbidity. The latter is usually defined as the co-occurrence of two or more chronic medical conditions in one person and characterized by complex interactions between co-existing diseases. Multimorbidity results also in concurrent pharmacological treatments, where a daily medication load of 5 or more drugs is commonly defined as polypharmacy. It should be noted that guideline-adherent treatment of 2 or 3 frequent chronic conditions (e.g. hypertension, diabetes and COPD) automatically results in more than 5 drugs per day. Apart from polypharmacy and the inherent risk for drug-drug interactions even pharmacokinetics and pharmacodynamics of single drugs are different in older persons when compared to younger adults. Probably the most relevant and best described change is the decline of renal function with advancing age and thus accumulation of renally cleared drugs. It is well understood that even minor side effects like drowsiness can have catastrophic results in elderly patients, where anticholinergic and sedative side effects of drugs are of particular concern. Polypharmacy is paradoxically associated also with underuse of necessary drugs, thus potentially inappropriate prescribing encompasses overprescribing, misprescribing and underprescribing. Depending on data source and methodology, prevalence of polypharmacy in older adults above 65 years ranges between 25 % and 60 % in European countries, Australia and the USA. Moreover, the risk for non-adherence increases with the number of drugs and interventions to assure appropriate drug intake have not been very successful.

The above described aspects of age and polypharmacy explain the fact, that older persons have a higher risk for adverse drug reactions, resulting in a decreased quality of life, substantial morbidity, hospitalizations and mortality. As examples: older adults have a higher risk for NSAID-associated gastrointestinal bleeding, proton pump-inhibitor-associated *C. difficile* diarrhea and a 2.5-fold higher risk for hospitalization due to hypoglycemia induced by antidiabetic drugs than younger patients.

In 1991 Mark Beers and colleagues published the first list of potentially inappropriate medications (PIM) for nursing home residents. PIM drugs were defined as having a negative benefit/risk ratio in older patients and their use should - whenever possible

- be avoided and safer alternatives should be preferred. This concept was broadened some years later for community-dwelling seniors. In the years following the so-called Beers list was updated and comparable lists were developed in other countries, since drug markets and prescribing habits differ widely between the USA and European countries and also among the EU countries. The process of development followed a so-called delphi consensus process, where several experts in 2 (or 3) rounds decide upon the risk-benefit-ratio of drugs for older adults on a pre-selected list of medications. The delphi expert consensus method has been developed by the RAND corporation in the USA for many projects outside the health care sector, e.g. forecasting of hostile bombing raids and assessing the potential consequences of new technologies. This technique has been adapted by health service providers and other groups to generate a consensus about the appropriateness of medical services. Although the reliability, face, content and construct validity of delphi processes in health care could be demonstrated, there is still a lot of debate on the selection of experts, the background information they receive to prepare for the survey and the type of feedback during the process, just to name a few issues. This does explain why some drugs are on PIM lists in one, but not in other countries.

PIM drugs are explicit criteria, i.e. without consideration of individual patient characteristics. Several shortcomings have to be addressed: most drugs are not well studied in older patients and evidence for a benefit/risk ratio is scarce, drug interactions are not identified, indications/contraindications not considered, dosing errors and underprescribing are not reflected by those lists. Implicit criteria require information such as comorbidities to assess indication/contraindications. Instruments to evaluate appropriateness of prescribing are (selection): the START/STOPP criteria, the Medication Appropriateness Index (MAI), the fORTA criteria and a newly developed tool. Each of these instruments has its advantages and disadvantages: an explicit list can be applied easily to a medication list to detect a potential inappropriate medication, the application of the MAI means a comprehensive assessment of patient and his/her medication whereas the new tool by Fried and colleagues also encompasses items such as adherence problems and patient's perspective. The more explicit criteria are, the more easily they can be applied to databases and evaluate e.g. in claims databases the association between the criteria and adverse outcomes.

There is an ongoing debate which of the criteria is more sensitive to detect (and perhaps in the second

step prevent) adverse outcomes. A number of studies have shown no association between PIM use and adverse outcomes, others did not. Several methodological issues have to be considered and some important issues are named here: the quality of the database, the methods to calculate the strength of the association (e.g. propensity score matching), the population under study (community-dwelling older patients or those living in nursing homes), the adverse outcome (hospitalization, fall, fracture, office visits etc.).

To establish a quality indicator (QI) the essential rules therefore have to be considered. A QI is measurable element of prescribing for which there is evidence or consensus that it can be used to assess quality, and hence change in the quality, of treatment provided. The main elements are:

- content and face validity
- construct validity
- link to adverse outcomes
- concurrent validity

Considering the application of the Delphi consensus procedure content and face validity are assumed to be acceptable. The construct validity is more critical as studies to assess the risk of PIM use revealed contradictory results (see above). Belfrage et al have shown that neither polypharmacy nor START/STOPP criteria alone are valid indicators for the quality of medication. Wallerstedt and co-workers applying PIM (PRISCUS and French Laroche list) and START criteria found an acceptable specificity and positive predictive value of these criteria to identify patients with problematic prescribing, were interestingly the German PRISCUS list had a high specificity. However, sensitivity of all PIM lists was not sufficient to accept PIMs alone as a quality indicator of pharmacotherapy. A previous analysis had also shown that inappropriate prescribing (also drug-drug interactions) are more prevalent in PIM-users than in patients not receiving PIMs. It can be concluded that PIM lists are able to identify patients with a very high risk for problematic polypharmacy, but a substantial number of patients will be missed by this approach. Thus PIMs may be taken as a part of an indicator set to identify patients at risk for adverse events in clinical practice and claims databases as well.

As a last issue which has not been proven remains: does any intervention aimed at reducing inappropriate medications/prescribing result in a reduction of adverse outcomes? The most recent Cochrane Reviews show inconclusive data, however, a number of trial protocols to reduce inappropriate medication/prescribing **and** adverse outcomes in older adults have been published.

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Efficacy and safety of medications in the old age, clinical guidelines and FORTA recommendations

Prof. Martin Wehling, MD, PhD

*Managing Director, Institute of Experimental and Clinical Pharmacology and Toxicology
Director Clinical Pharmacology Mannheim, Medical Faculty Mannheim,
University of Heidelberg, Mannheim, Germany*

Drug therapy is the most relevant therapeutic intervention in medicine; elderly patients tend to suffer from multiple diseases (multimorbidity) and thus are likely to receive multiple drug treatments (polypharmacy). It has been demonstrated that patients aged 65 and older take five or more drugs in 44% (male) and 57% (female) of cases and 10 or more drugs in 12% of cases.

Taking 10 and more drugs is unpredictable and expensive and seems to cause more harm than good, given that up to 100,000 deaths in the United States annually are attributed to medications. Guidelines are considered as main drivers of therapeutic decisions under the conditions of evidence-based medicine (EBM); they are also the leading rationale for the prescription of drugs in elderly patients with multi-morbidity often resulting in >10 drugs. Simple mathematics describes additive prescribing as key drivers for unsafe medication use in the elderly: at age 80, 3 relevant diagnoses trigger the application of 3 guidelines each of which recommends 3 drugs in average. The guideline depository of the German Association of the Scientific Medical Societies (AWMF), was reviewed searching for guidelines for the elderly.

Out of 926 guidelines in total, only 2 are explicitly addressing geriatric patients in the title, one on nutrition, one on urinary incontinence. Chapters on elderly patients in other guidelines, if present, were found to be short and vague. As evidence for drug treatment in the elderly is generally lacking (underrepresentation in clinical trials), applying EBM-guidelines to elders without supportive data, results in experimental drug exposure often causing more harm than benefit. Though more clinical trial data are ultimately required, they will not solve the problem of disease-driven phenotypic variability which rises exponentially with age; this problem cannot be addressed by guidelines (or millions of them would be required), but by individualization of treatment under close clinical surveillance.

One of the first formal attempts to improve drug safety despite this lack of study data in the aged population was the establishment of criteria for drugs to be avoided by Beers in 1997, which was updated in 2003. Applying the Healthcare Effectiveness Data and Information Set 2006 measure to nearly 1 million U.S. veterans, potentially inappropriate prescribing (PIPE) occurred in 19.2% of older men and 23.3% of older women.

Table 1 Proposed drug classification fit for the aged FORTA

FORTA-Classification	Description	Examples
Class A drugs	indispensable drug, clear-cut benefit for efficacy/safety ratio proven even in elderly patients for a given indication, morbidity and/or mortality data unanimous	ACE-inhibitors/calcium-antagonists for hypertension, HMG-CoA-reductase inhibitors (statins) for cardiovascular protection, anticoagulants for atrial fibrillation, ACE-inhibitors/diuretics in heart failure treatment
Class B drugs	drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns; drugs could be omitted in case of side effects or under pressure of too many class A drugs	diuretics, betablockers in arterial hypertension, bisphosphonates for osteoporosis
Class C drugs	drugs with questionable efficacy/safety profiles in elderly which should be omitted under any pressure of too many drugs or side effects	spironolactone in arterial hypertension, ezetimibe for cholesterol lowering, amiodarone in atrial fibrillation
Class D drugs	Avoid in the elderly, delete first	benzodiazepines, promethazine, pentazocine

The evidence for the effectiveness of the Beers list is not compelling; a recent study showed no correlation with adverse effects if a patient received PIPE. For example, it does not allow for amiodarone treatment, although this may be necessary in some patients with atrial fibrillation and thus needs to be specified in the exceptions.

The other shortcoming of the Beers approach is that an important aspect remains uncovered, namely, that there should also be a positive labelling of drugs that indispensable in elderly people as data on morbidity, mortality, and safety are available or emerging for this particular treatment group. Although insufficient in major therapeutic areas at present, there is increasing clinical evidence for beneficial action of, for example, antihypertensive drugs (e.g., Systolic Hypertension in Europe Trial, Hypertension in the Very Elderly Trial) and lipid-lowering agents (e.g., Prospective Study of Pravastatin in the Elderly at Risk Trial) in elderly people.

The FORTA (“Fit fOR The Aged”) classification is the first implicit listing approach which involves both positive **and** negative labeling of commonly used medications for chronic illnesses (FORTA list). According to FORTA, medications belong to: Class A= (**Absolutely**): indispensable drug, clear-cut benefit; Class B= (**Beneficial**): proven efficacy but with safety concerns; Class C= (**Careful**): questionable efficacy/safety profiles, to be avoided or omitted when many other drugs are prescribed, review alternatives; or Class D= (**Don’t**): avoid in the elderly, omit first, review alternatives). (Table 1). The FORTA list has been developed as a clinical tool in a two-stage Delphi procedure involving 20 prominent experts in the field from Germany and Austria and is being tested in clinical trials. High consensus values for the evaluated drug labels were observed for the final FORTA list. Interventional studies indicate that implementation of FORTA improves medication quality and clinical outcomes (reduced fall risk, improved Barthel index). The proposed classification would be an extension of the Beers approach into the positive listing of valua-

ble drugs. This seems necessary, because overtreatment and undertreatment are both typical problems of the aged population. Undertreatment, for example, relates to the poor control of arterial hypertension or anticoagulation in elderly people and may leave more than half of the patients un- or undertreated.

The main advantage of this proposal over the Beers approach is thought to be the protection or even promotion of drugs that are known to be efficacious and safe in elderly patients that is based on evidence. The FORTA classification for antihypertensive drugs as an example is given in table 2.

The typical use of the FORTA scheme would address general practitioners who receive multiple medication advice from different medical specialities for their patients. They would then synthesize the recommendations into a rank order of drugs that they could—with some rational judgment on top of the scheme—use to cut the list short. If important drugs are lacking, they could even add important drugs. The utility of the classification could be limited to outpatients in general practices as the most prevalent patient group, and alternate classifications may be derived for other groups based on frailty, mobility, and other determinants.

Table 2 Classification of antihypertensive drugs according to their fitness for the aged FORTA

- diuretics	B
- betablockers	B
- renin-angiotensin-system blockers:	
- ACE-inhibitors	A
- angiotensin receptor antagonist	A
- long acting dihydropyridine	
calcium channel blockers	A
- calcium channel blockers,	
verapamil type	D
- spironolactone	C
- alphablockers	C
- clonidine	D
- minoxidil	D

3/ EU COST Action 1402- "Inappropriate prescribing in older patients in Eastern Europe – a recent initiative"

Fialová Daniela, PharmD, PhD, BCCP

Head of the University Educational Centre in Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, Czech Republic, Researcher and Academic Worker, Department of Geriatrics and Gerontology, 1st Faculty of Medicine and Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, Czech Republic

The significant trend in prolongation of life-expectancy has been observed in many countries, as well as exponential growth in the proportion of older adults in the world population. It is estimated that the number of persons aged 60 years and older will substantially increase from 600 million in 2002 to almost 2 billion by the year 2050, and the proportion of seniors in the world population will more than double – from 10% to 21%. In developing countries, the proportion of seniors in the whole population will nearly quadruple in the next 50 years. Within this old age group, the proportion of the "oldest old" (individuals 80 years and older) will be rising the most rapidly and e.g. in the Czech Republic it will increase 2-3 times from 18 % to 48 % between the years 2000 and 2065.

It is well documented that older people consume the highest proportion of costs for medications; approximately 30% of overall costs, and this high consumption relates also to multi-morbidity, polypharmacy, irrational prescribing and common misuse of medications. According to results of the European project ADHOC (AgeD in Home Care, 5th Framework Programme of the European Commission, 2001-2005, analyses in 8 EU countries: Italy, Czech Republic, Denmark, Finland, Iceland, Netherlands, Norway, UK), 51% of seniors in home care used 6 or more medications, and excessive polypharmacy (9+ medications) was observed in 22.2% (in the Czech Republic in 30% of seniors). Psychotherapy (at least 1 psychotropic medication) was prescribed to 43.4 % of older adults, with the highest prevalence in Northern European countries (e.g. more than 40% in Norway and over 60% in Iceland and Finland). The absence of medication review in the past 6 months was documented in 17.9 % of older home care patients and 19.8% of them used potentially inappropriate medications, even when safer and equally effective and accessible alternatives have been available on the pharmaceutical market. Adverse drug reactions and drug interactions occur 4-7 times more frequently in the geriatric population when compared to middle-aged individuals. The prevalence of adverse drug reactions is documented to be 20-30% in the 70-79 year age group compared to 3-6% in the 20-29 year old group. Frequent drug-related complications result in a higher percentage of acute care admissions (in 6.6 - 41.3 % of older patients), higher number of physicians' visits and consequently in a significantly greater proportion of total expenditure for drug treatment. Total drug-related costs are estimated to be 3-4 times

higher than the direct medication costs, and the rational use of drugs in the elderly is of major economic and social concern in many countries worldwide.

Particularly the oldest old seniors suffer from more disorders, use more medications and are more frail and dependent than younger individuals. Rational geriatric prescribing depends on a comprehensive knowledge of the pharmacological properties of prescribed drugs, clinical skills and knowledge of efficacy and safety of different medications in individual patients. It represents a challenge, because guidelines are mostly disease-specific and often cannot be generalized to complex frail older adults who are using polypharmacy and suffering from multiple, highly individual health problems. Rational use of medicine requires a multidisciplinary approach and the sharing of knowledge and skills to select the best strategy and yield optimal results. With the aging of the population and increasing burden on healthcare professionals, the role of geriatric clinical pharmacists in rational pharmacotherapy will significantly increase, and their involvement in multidisciplinary cooperation will be critically important in different settings of care.

Higher prevalence of multiple chronic disorders, symptoms and geriatric syndromes (sometimes as a consequence of inappropriate multiple drug therapy) as well as frailty, functional impairment, poor compliance and adverse drug events are common in the higher age population. Studies from the Central and Eastern European (CEE) countries document that these problems cause substantially higher burden on healthcare systems than in the Western European countries. In some CEE countries the demographic statistics predict an increase in the proportion of older adults of up to 30% and more by 2050, e.g. in Slovenia 33.7%, Bulgaria 31.1%, the Czech Republic and Poland 30.6 % which will even highlight the importance of solution of problems related to inappropriate prescribing and polypharmacy in older patients in this EU region.

For this reason, the EU COST Action 1402 WG1 during the period 2015-2018 focuses particularly on description of problems with inappropriate prescribing and potentially inappropriate medication use in Central and Eastern Europe. This action started in 2015 and already 8 EU countries joined this initiative- the Czech Republic, Poland, Slovak Republic, Lithuania, Serbia, Hungary, Romania, Croatia and Estonia. Researchers from these EEC countries work on analyses, specific comparisons

and recommendations in appropriate geriatric prescribing and medication use in this European region. One of the main goals of the EU COST Action is to prevent expected rise in problems of inappropriate prescribing and ageism in the healthcare systems in the future decades.

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4/ Inappropriate prescribing in older adults in Serbia- use of risk management tools in pharmaceutical health care

*Valentina Marinković, PharmD, PhD and prof. Ljiljana Tasić, PharmD, PhD
University of Belgrade, Faculty of Pharmacy, Belgrade, Serbia*

Introduction

Inappropriate prescribing to elderly patients has become an issue of global concern in health care due to the complexity of medication use in this population caused by various factors e.g. polypharmacy, adherence issues, the existence of comorbidities and age-related pharmacokinetic and pharmacodynamic changes. The failures, such as potentially inappropriate prescribing (PIP) and potential prescribing omissions (PPO) are considered to be significant contributors to the poor outcomes in elderly people, including increased morbidity and mortality rates, as well as higher health expenditures, as they are particularly vulnerable.

Nowadays, various tools have been available for detecting and measuring PIP and PPO, whereas the most commonly used are the Beers' criteria. However, this technique has significant limitations, since it does not take into account PPO and drug-drug interactions, thereby underestimating the complete magnitude of inappropriate prescribing. Another method- STOPP (Screening Tool for Older Persons' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria has become increasingly employed as well, providing various advantages over Beers' list, by enabling much more comprehensive review of both over-prescribing

(PIP) and under-prescribing (PPO) issues in elderly patients. The STOPP criteria is a physiological system based screening tool, which comprises 65 clinically significant indicators for detection of drug-drug and drug-disease interactions, while the accompanying START criteria consists of 22 indicators specialized for prescribing omissions. However, the fact that the most of these failures in prescribing stage of medication delivery are highly preventable, stresses out the necessity of prospective risk mitigation, by assessing systemic weaknesses and implementing remedial measures before the harm is incurred. Accordingly, the research focus in this area has been gradually shifted from the basic studies on incidence and types of prescribing errors in the elderly patients, by using before mentioned methods, to the advanced, systemic risk analyses, in order to find out what could lead to the errors occurrence. The most commonly used risk management tools for this type of assessment are Root Cause Analysis (RCA) and Failure Modes, Effects and Criticality Analysis (FMECA), which have already started being applied to the prescribing process.

Objectives

This study aims to review the published literature on the incidence, types and causes of inappropriate prescribing to the elderly patients, determined in various health care settings in Serbia, as well as to provide a comparative analysis of the risk management tools, used as a novel approach for a systemic assessment in this area.

Results and discussion

Several studies on the inappropriate prescribing issues, conducted in Serbia, have been identified. The analysis undertaken by Projovic et al. examined risk factors that could have been attributed to the prescribing failures incurred in the primary health care setting. Two retrospective, case-control studies were carried out simultaneously, whereas the case groups consisted of patients older than 65 years with at least one PIP identified by STOPP criteria (study one) or at least one PPO listed by START criteria (study 2). Control groups for both studies consisted of sex and age-matched patients from the same health care facilities, without any detected prescribing-related problem. All data were obtained by reviewing patients' primary care records, as well as by distributing questionnaires among patients and their general practitioners (GPs). A total of 138 PIP and 161 PPO were identified in 122 and 108 patients, respectively, by using 26 STOPP (41.3%) and 17 START criteria indicators (77.3%). The commonest PIP issues included use of long-acting benzodiazepines for more than 1 month (22.5 %), duplication of therapy (18.8 %), and use of theophylline as monotherapy for chronic obstructive pulmonary disease (10.1 %). On

the other hand, the major PPO identified included the lack of antiplatelet therapy in diabetic patients with associated cardiovascular risk factors (27.3 %), the omission of statins in the same population of patients (19.9 %) and the omission of aspirin or clopidogrel with a history of atherosclerotic coronary, cerebral, or peripheral vascular disease in patients with normal heart rhythm (15.5 %). The unhealthy behavior (sedentary lifestyle, improper nutrition, active smoking and heavy alcohol consumption), as well as polypharmacy and frequent contact of GPs with pharmaceutical sales representatives were singled out as the major risk factors attributed to the PIP and PPO in question. Furthermore, the before-and-after study conducted by Ilic et al. aimed to examine the impact of staff education on appropriateness of prescribing to the elderly residents of nursing homes. Prescribing practice was recorded and analyzed from the medical files prior to and 6 months after providing physicians and nursing home residents with the educational intervention. The number of inappropriately prescribed drugs identified was 349 by using the Beers' criteria, and 70 according to the STOPP criteria, while their rates decreased significantly when measured 6 months after the intervention, with the final number of 37 and 20 PIP by employing afore mentioned techniques, respectively. Relative to the START criteria, 143 drugs were identified as omitted before the intervention, while this number decreased to 67 omissions when analyzed 6 months after the educational intervention, which has thereby proved as fully suitable for prescribing improvement in elderly patients. Finally, the study conducted by Vezmar Kovacevic et al. aimed to determine the incidence of PIP and PPO in the community pharmacy setting, according to the STOPP/START tool. A prospective cross-sectional study was conducted during the 3-month period, with 509 patients as participants, who provided the pharmacists with their complete medical and biochemical records during the scheduled meetings. According to the STOPP criteria, 164 PIP were identified in 139 patients, by using 17 indicators (26.15%), whereas the commonest were long-term use of long-acting benzodiazepines (20.7%), use of nonsteroidal antiinflammatory drugs (NSAID) in patients with moderate-severe hypertension (20.1%), use of theophylline as monotherapy for chronic obstructive pulmonary disease (COPD, 15.9%), use of aspirin without appropriate indication (15.2%) and duplication of therapy (10.4%). The results obtained are comparable to the other studies. Furthermore, the employed START technique detected a total of 439 PPO in 257 patients, by using 15 indicators (68.18%). The omissions mostly derived from the cardiovascular and endocrine system (88.6%), with the lack of antiplatelet therapy and statins in patients with history of coronary, cerebral or peripheral vascular disease or in patients with diabetes mellitus with co-existing major cardiovascular risk factors, as the commonest ones. Applying STOPP/START

Table 1 Review of the failure modes and corrective actions identified by using FMECA for the prescribing process

Identified failure modes regarding prescribing phase	Proposed corrective actions regarding prescribing phase	Reference
-Typing error -Dosage determination error -Prescription of a solution impossible to produce	-Electronic prescribing and access to software with step by step guide	[5]
-Prescription protocol writing or validation error -Choice of the wrong protocol -Prescription error (i.e. dose, patient, route)	-Electronic prescribing by introducing CPOE	[6]
-Manual prescription (instead of CPOE) -Prescription with errors -Prescribing on wrong patient	-Education and training of physicians on CPOE -Improving clinical decision support -Improving software's database	[7]
-Dosage errors -Prescription omitted	-CPOE implementation -Double check by nurses -Clinical pharmacist	[8]

criteria has deemed to be suitable means of the improvement of prescribing appropriateness for elderly patients by community pharmacists, as the most accessible health care professionals.

Nowadays, the research focus in the field of patient safety and medication errors has been shifted to carrying out systemic risk analyses of the health care processes, in order to identify what could have led to the errors occurrence, as opposed to raising the basic question of their incidence and types. The most commonly applied technique for this type of assessment is FMECA, defined as "a proactive tool used to identify potential vulnerabilities in complex, high-risk processes and to generate remedial actions to counteract them before they result in adverse events". It includes identifying potential failure modes, gauging their causes and effects, and quantifying related risks with the aim of enabling further implementation of corrective actions that could be taken to prevent the incidents from happening or, at least, to lower the rate at which they occur. The application of this technique has already started to the prescribing process, majorly focusing on prescribing high-alert medications e.g. chemotherapy, as a part of a wider process of their use (with regard to dispensing and/or administration phases as well), and also mostly in the hospital care setting. The failure modes identified and corrective actions proposed regarding prescribing phase by using FMECA are summarized in table 1. The commonest systemic weaknesses included dose miscalculation or typing failure due to the manual prescription writing, while the major remedial measures considered introducing electronic prescribing via Computerized Physician Order Entry (CPOE) system.

Furthermore, RCA represents another type of systemic risk analysis with the aim to detect critical underlying causes of the error, as well as the measures to prevent it from happening again. However, in opposite to FMECA, this method is employed only

after the incident occurrence. The major causes for potential failures in the prescribing process detected by RCA included drug/CPOE knowledge deficit, lapses, work overload, frequent interruptions and a lack of standardized procedures.

Conclusion

Raising awareness of the issue of inappropriate prescribing to the elderly patients has resulted in the growing body of research over the last decade. Various studies on the incidence, types and causes of over- and under-prescribing failures have been conducted, emphasizing the magnitude of their impact on the patient outcomes. Additionally, since the majority of these patient safety incidents are highly preventable, what should be done in the foreseeable future is to increase the number of prospective systemic risk analysis in order to implement corrective actions before the harm is incurred. This is especially significant for the developing countries, such as Serbia, where the lack of this type of research is even more emphasized. However, it has to be noted that despite gaining greater and greater popularity with risk management specialists, the modern approach of risk amelioration, giving more weight to the systemic contribution to errors genesis than to blaming an individual for them, has not outweighed the traditional patient safety concept, which seems to be deeply rooted in the majority of health care environments. Therefore, the Institute of Medicine has declared the prospective transition from an individual-based concept of personal guilt for making an error to a system-based approach to it to be "the biggest challenge to moving toward a safer health system".

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5/ Hospital care and older patients – inappropriate prescribing, drug related problems and experience with clinical pharmacy services

Annemie Somers, PharmD, PhD

Head of the Pharmaceutical Care Department, Ghent University Hospital, Belgium

Visiting professor of Pharmaceutical care, Ghent University, Belgium

Abstract

This lecture addresses the issue of detection and prevention of drug related problems (DRPs) in older hospitalized patients, and focuses on the role of clinical pharmacists towards this problem.

The incidence and types of DRPs and adverse drug reactions (ADRs) in older hospitalized patients will be addressed and their clinical relevance for older persons will be discussed. Since DRPs frequently lead to hospital admission, it is important to recognize, treat and document them in order to prevent recurrence.

An overview of screening tools for detection of DRPs will be given, including explicit and implicit tools. Explicit tools consist of the lists of potentially inappropriate medicines in older people while implicit criteria consist of a structured approach for detecting potentially inappropriate prescribing. The concept of medication review in older persons with polypharmacy will be highlighted, in particular different aspects of drug use (e.g. dosing, ADRs, interactions, duration of therapy, underuse,...). Furthermore, drug prescribing in older people should also take into consideration specific aspects such as older people's cognitive and functional status, ability to deal with drugs, adherence and life expectancy, aiming at an individualized pharmaceutical care plan for the older patient.

Strategies to prevent DRPs rely on ensuring a safe drug process which includes seamless pharmaceutical care, detection and documentation of potential and existing drug related problems, and documentation

of changes in the drug regimen. Physician assisted electronic prescribing, as well as clinical pharmacy can be helpful to ensure appropriate prescribing. In this context, medication reconciliation, tools for medication review, clinical pharmacist recommendations, pharmaceutical discharge letters, electronic prescribing and information transfer will be also addressed.

Drug - related problems in older patients

The following definition for drug related problems (DRPs) is often used: 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes'. Another approach for DRPs is the division into three categories i.e. 'overuse', 'misuse' or 'underuse' of medicines. The scope of drug related problems occurring in older patients however varies between studies. Adverse drug reactions (ADRs) are most often included. Besides ADRs, also drug therapy failures due to inadequate dose or non-compliance are sometimes considered, as well as inappropriate drug choice, untreated indications and drug use without indication. Drug therapy potentially leading to drug related problems is often called 'inappropriate prescribing' and is particularly hazardous for older patients. In different studies it has been shown that older patients indeed suffer more often from drug related problems than middle-aged patients.

Various factors can explain the high incidence of drug related problems in older persons. Firstly, older people often suffer from different diseases,

and consequently are treated with many drugs, with a higher risk of adverse reactions and drug-drug interactions. Secondly, changes in pharmacokinetic and pharmacodynamic properties make older persons more prone to the occurrence of drug related problems. Thirdly, older patients are often treated by multiple healthcare professionals, in particular different prescribing physicians. Therefore, it can be difficult to keep an overview of the different medications prescribed in terms of indications, duration of therapy, monitoring of adverse reactions and follow-up of the effectiveness of the drugs for the different medical problems. Fourthly, decreased capability to handle drugs (e.g. taking tablets out of blisters, or inhalation techniques) can lead to decreased compliance and inappropriate drug therapy. Older persons are usually prescribed the same drugs as younger people, but these drugs can work differently in older people, and are also more frequently combined¹.

Clinical impact of drug - related problems in older patients

Older people are more prone to the occurrence of adverse drug reactions. These can lead to hospital admission, or can occur during hospitalization because of worsening condition, multiple diseases or drug-drug interaction. The reported percentages of ADRs in hospitalized patients vary between 2.4% and 10.9%. However, older patients usually take a higher number of drugs in comparison to younger patients, which is a well-known risk factor for developing adverse drug reactions. At the same time, it is a well-known problem that voluntary ADR reporting systems is characterized with important under-reporting. Therefore, when studying the incidence of ADRs, efforts should be made to combine spontaneous ADR reporting by different caregivers (physicians and nurses), with information taken directly from the patient, e.g. by interview during the ward visit.

The clinical impact of drug related problems in older persons is illustrated by the high incidence of drug related hospital admissions. When searching the literature, a wide range of drug related hospital admissions (DRHAs) is reported, varying between 4 to 30%. The majority of these problems concerns ADRs, with avoidability ranging between 50% to 97%.

The following problems seem to contribute often to hospitalization in older patients:

- bleeding due to the use of anticoagulants and non-steroidal anti-inflammatory drugs
- dehydration and electrolyte disturbances due to diuretics
- falls due to the intake of central nervous system drugs (hypnotics, antipsychotics, antidepressants)
- osteoporosis and fractures due to the prolonged use of corticosteroids

- hypoglycaemia due to oral antidiabetic drugs and insulin
- hyperglycaemia related to the intake of corticosteroids
- heart failure and renal failure due to non-steroidal anti-inflammatory drugs
- constipation due to the use of narcotic analgesics
- bradycardia and orthostatic hypotension related to the intake of beta blocking agents.

Although older patients are often hospitalized at acute geriatric wards with professional care including evidence based drug therapy, the risk of drug related problems during hospitalization is still present. The prolongation of the pharmacotherapy initiated before hospital admission, in combination with the acute treatment during admission makes the drug scheme often complex, not only due to numerous drugs but also with regard to the need for careful evaluation of which medicines should be continued, changed, temporarily or definitely stopped, and which drugs should be started with follow-up of effects and side-effects.

Prevention of DRPs in older patients

In order to define preventive strategies for drug related problems in older people, we must look at the factors explaining a high frequency of DRPs in older patients. The factor concerning different prescribing physicians underlines the need for careful evaluation of drug therapy within medication review processes. Hospital admission of older patients therefore could be the ideal moment to take a close look at the drug regimen in order to avoid misuse, overuse and underuse.

Various methods have been described to promote appropriate drug prescribing in older persons. These aim at avoiding potentially dangerous drugs, assessing the appropriateness of drug therapy in a systematic way, multidisciplinary geriatric evaluation teams, and clinical pharmacist recommendations. Another approach which could be helpful for more appropriate prescribing throughout the hospital (also for younger patients) is computerized physician order entry, more specifically with tools for assisted prescribing and with alerts when possible drug - related problems are detected. Moreover, moments of transition between care settings (e.g. unplanned hospital admission or discharge from hospital to the community) can lead to unintended discrepancies of the drug list, and to drug related problems after discharge.

Medication assessment tools

As mentioned before, certain drugs are considered to be inappropriate for older patients, when the potential risks outweigh the potential benefits. These drugs are called potentially inappropriate medications (PIMs). Various lists of PIMs have been developed and used in studies investigating the appropriateness of prescribing in older patients. Some

lists contain drugs to avoid in general, and some lists combine drugs with clinical data (e.g. certain drugs are considered inappropriate when a patient is suffering from a certain disease). These kind of medication assessment tools are called explicit criteria of inappropriate prescribing, i.e. consensus-based standards focusing on drugs and diseases.

Although lists of drugs to avoid and criteria for assessment of over-, mis- and underprescribing are valuable, they cannot replace individual clinical judgment for the purpose of medication review in older patients. Opposite to the explicit criteria of inappropriate prescribing, some medication assessment tools do not focus on specific drugs or diseases but on general criteria such as appropriate dosing, searching for drug-drug interactions, increasing compliance,... Using such an approach is called an implicit evaluation focusing on the patient and allowing differences between patients, and means in fact performing a medication review, by using a systematic approach. One of the methods that has undergone extensive reliability and validity testing is the Medication Appropriateness Index (MAI). The MAI has been used in various studies, as a measure for assessment of appropriateness of prescribing in older patients, and has been adapted towards a shorter and more practical tool in order to detect more DRPs in older hospitalized patients.

Clinical pharmacy

Over the last decades, the pharmacy profession has transitioned from a traditional drug-oriented perspective towards a patient-centered approach, which can be found in the concept of pharmaceutical care^[43]. Pharmaceutical care is delivered by clinical pharmacists with the aim to improve outcomes and safety of drug therapy. Basically, the pharmaceutical care process consists of four steps, which are cyclic for an individual patient. These steps are pharmaceutical anamnesis, medication review, design of a pharmaceutical care plan, and follow up of this plan. Although clinical pharmacists perform the pharmaceutical care process to manage the patient's drug therapy in every day clinical practice, the physician takes the ultimate responsibility for the care of the patient. Therefore, the clinical pharmacists work in close collaboration with physicians, nurses and other caregivers. Concerning older patients, optimization of drug therapy by clinical pharmacists is frequently investigated by assessment of the appropriateness of prescribing by using tools as previously described. Furthermore, the impact of clinical pharmacy can be measured by using process indicators, but it is clear that studying the impact on clinical and economic endpoints is recommended.

The organisation model for clinical pharmacy at Ghent University Hospital has been extensively discussed. When we overlook the milestones which accompanied the development of clinical pharmacy in our hospital, one of the important aspects concerns the implementation of electronic prescribing,

offering access to the electronic patient file and permitting pharmacists to document their recommendations.

Medication reconciliation

The aim of medication reconciliation is to prevent unintended discrepancies in drug lists at transfer moments, i.e. mainly at admission and discharge. As pharmacists, we play a key-role in the design of a safe drug process including pharmaceutical anamnesis, registration and communication of drug lists and changes. When pharmacists or pharmacy technicians perform medication reconciliation for unplanned admissions, they should focus on older patients with polypharmacy. In our hospital, we developed a standardized medication reconciliation form, and a specific electronic recording system for ambulatory drug therapy. Furthermore, a number of tools were developed e.g. a printable drug scheme for the patient, automatic generic substitution to formulary drugs, drug allergy registration and alerts, a 'home medication bag' (to bring all medication to the hospital in case of planned surgery or to provide medication at discharge) and pharmaceutical discharge letters.

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6/ Risk management and clinical case-solving in older inpatients

Prof. Jiří Vlček, PharmD, PhD

Professor of clinical pharmacy and pharmaceutical care, Department of Social & Clinical Pharmacy, Faculty of Pharmacy, Charles University, Hradec Králové

The risk management in pharmacotherapy is important part of work of clinical pharmacists in clinical pharmaceutical care and and pharmacists in pharmaceutical care. Risk management is focusing on risk minimization activity. The risk rate of pharmacotherapy in elderly is more frequent, comparing with a middle-aged population, for different reasons:

- 1/ age changes of pharmacodynamic and pharmacokinetic parameters in different elderly population (sometimes poor evidence because the majority of clinical trials avoids polymorbid elderly patients)
- 2/ sensitivity to harm concerning quick changes of internal environment (blood pressure, glycaemia, and hydration)
- 3/ higher probability of harm regarding contraindication due to higher incidence of comorbidities and due to higher sensitivity to adverse drug reaction – the reasons: ad 1 and 2/
- Ad 4/ higher probability of harm of drug/drug interaction due to frequent polypharmacotherapy and due to higher sensitivity to adverse drug reaction – the reasons: ad 1 and 2
- Ad 5/ higher chance of wrong diagnosis – adverse drug reaction of particular drugs can be masked by expected illness – frequently occurred in elderly – dementia, Parkinson’s disease, constipation, dizziness, falls etc.

The admission to the hospital is joined with other risks for elderly as well:

- 6/ frequently not exact medication and personal history with shortage of information about reason for prescribing of particular drug; how frequent are used medicines with signature: “according to the needs”, missing information about used OTC medicines and food

supplements and/or their duration and dosage scheme (elderly people use OTC medicines more frequently); no interest of hospital physicians about medication adherence

- 7/ lower adaptability of elderly for another surroundings – hospital surrounding is unknown, change of setting can stimulate depression, can cause falls, and sleep disturbances that are managed by different sedatives, which are again more risky for elderly.
- 8/ partial immobility of older inpatients-elderly suffer from the lack of physical activity and this can increase the risk of pneumonia (co-factor is a lower immunity the as well), b/ development of rigidity, c/ falls etc. An immobility can change insulin resistance and level of blood pressure as well.
- 9/ for easy nursing care for people who suffer with restlessness (from dementia, delirium etc.) sedatives are prescribed frequently (“chemical immobilization”). These medicines can cause harm to elderly patients.
- 10/ elderly people are visiting hospital for acute problems of chronic disease, which require emergency care - quick changes of internal environment can cause harm as well (quick changes of blood pressure, glycaemia, hydration).
- 11/ changes in pharmacotherapy – generic prescription according to the hospital positive list of medicines can be risky for elderly – advantage is that inpatients are monitored more frequently.
- 12/ better access to lab data in hospital (out-patients with poor mobility cancel frequent monitoring, ambulatory physicians save money spending for the test) and as a result it is easier to reach

optimal value of surrogates (blood pressure, and glycaemia). It can increase a risk similar to the risk described in point 10/.

- 13/ physicians and clinical pharmacists cannot be experts for geriatrics in particular hospitals
- 14/ prescribing of medicines during discharge – do we prescribe same brands as we recognized in medicine history by admission procedure? (risk of duplicity in ambulatory care); are we sure in patient's understanding on how to use and how to administer particular drugs?
- 15/ Blood pressure, glycaemia and INR for measurement of warfarin effect can be changed after discharging – change of diet, physical activity etc. Adaptation of therapy to outpatient regimen is necessary.

Advantages of hospital care

- 1/ care is taken all 24 hours
- 2/ access to lab data is easy – immobility of patient is not a barrier
- 3/ possibility to train application technique

As we see there is a lot of risks of pharmacotherapy and therefore role of clinical pharmacist is to minimize the risk. Generally we can say, that the risk minimization (risk management) is one of the most important activity in pharmaceutical care. It is a process by which we try to identify, to prevent and/or to minimize risk of pharmacotherapy: adverse drug reaction, contraindication, drug/drug interactions, medication errors and medication non-adherence. This process can be solved by algorithm SAFE. There is a need to expect some theoretical knowledge and individual steps of management from health care workers.

Algorithm SAFE includes four steps: two theoretical ones: 1/ **Signal of risk**; 2/ **Analysis of risk** and two events for minimization of risk: 3/ **Founding and monitoring of individual risk** and 4/ **Elimination of risk**. First step is focusing on creating a signal of risk. The signal of risk is based on a/ pharmacological knowledge of individual medicines, b/ drug formulation knowledge; c/ lab data out of physiological values, d/ drug-drug interaction potential of medicines; e/ explicit criteria for risky medicine by elderly; f/ knowledge regarding contraindication and g/ missing or not well managed safety culture on particular department. Second step is focusing on the analysis of potential risk – it needs to refresh knowledge regarding risk factors of potential adverse drug reaction (including drug/drug interaction) and risk factors of complications of ADR (complication of ADR – example – the risk of a fracture in osteoporosis. In the step three - “founding of monitoring of individual risk” can help you to judge individual risk. “Is very important part, you need to find methods how to monitor a/risk itself, b/ risk factors from the step 2; and 3/ how to analyze risk benefit for the particular patient“. Elimination of risk is the last step. You use knowledge and information from all three before-mentioned steps. There are different options:

a/ risk is only theoretical and is of lower clinical sig-

nificance; risk benefit proportion is low

b/ risk is theoretical, but of high clinical significance; risk/benefit ratio is high or low

c/ risk already caused some changes in the patient body but clinical significance is low, risk benefit is low

d/ risk which already caused some changes in the body and clinical significance is high – risk of harm to patient ; risk benefit can be high or low

By the way, risk/benefit ratio can increase for the individual patient – risk is getting higher for them because there are presence of some risk factors for risk and/or for consequences of ADR and opposite in case that this drug is important for particular patient and we have no other chance to substitute it.

Therefore we can use different strategies for prevention and management of ADR:

a/ monitoring of risk itself

b/ reducing risk factors of risk and risk complication of ADR

c/ preventable treatment of risk

d/ substitution of original medicine with another drug formulation/active substances (from the same pharmacological or therapeutic group without particular risk)

A management of ADR is another option and we need to combine it with preventive methods. For the management we can use:

a/ compensation of ADR with another treatment (obstipation, glycaemia, dehydration)

b/ substitution of original medicine with another drug formulation/active substances (from the same pharmacological or therapeutic group without particular risk)

When one has troubles to use SAFE algorithm for risk minimization – we can offer him (her) simpler algorithm - **algorithm of 3 pillars** of risk minimization. It is similar as SAFE - it solves the particular ADRs but don't take in risk minimization into account individual treatment and therefore requires higher activity of caring physicians.

1st pillar pushes pharmacist to include all theoretical knowledge about this ADR (type of ADR according WHO, risk factors of ADR, complications of ADR and their risk factors). **2nd pillar** make theoretical summary how and when it is possible to monitor ADR (lab data, symptoms, physical measurement, monitoring of behavior of patients, physicians strategy etc.) and **3rd pillar** tries to recommend methods and strategies how to minimize risk or to treat risk (a changes in drug administration; a prevention of medication non-adherence, a monitoring (what and when?); a medication review (dosage, substitution of active substances with another ones; add new drugs to treat or to prevent ADR etc.), a life style changes including selection of food and amount of fluid and sometimes a self-medication.

The algorithm SAFE is more complex than the algorithm of three pillars and we will use both of them for discussion of pharmacotherapy of two selected cases of older inpatients during the afternoon workshops.

7/ Noncompliance in older adults - aspects of ageism, research tools and practical recommendations

*Marcel Leppee, MD, PhD
Andrija Stampar Institute of Public Health, Zagreb, Croatia*

Medication noncompliance is a very complicated problem, particularly for people with chronic diseases and multimorbidity. Our society relies on drugs to prevent illness and treat diseases. Numerous studies have shown that drugs reduce illness and disability, and improve clinical outcomes. Despite such findings, many people do not realize the full potential benefits of their prescribed medications.

The impact of poor compliance grows as the burden of chronic disease grows worldwide.

Compliance to long-term therapy for chronic illnesses in developed countries averages 50% (World Health Organisation). It is undeniable that many patients experience difficulty in following treatment recommendations. Noncommunicable diseases and mental disorders, human immunodeficiency virus/acquired immunodeficiency syndrome and tuberculosis, together represented 54% of the burden of all diseases worldwide and will exceed 65% worldwide in 2020 (World Health Organisation). The poor are disproportionately affected. Poor compliance to long-term therapies severely compromises the effectiveness of treatment making this a critical issue in population health, both from the perspective of quality of life and of health economics. Interventions aimed at improving compliance would provide a significant positive return on investment through primary prevention (of risk factors) and secondary prevention of adverse health outcomes. Compliance is an important modifier of health system effectiveness. Health outcomes cannot be accurately assessed if they are measured predominantly by resource utilization indicators and efficacy of interventions. The population health outcomes predicted by treatment efficacy data cannot be achieved unless compliance rates are used to inform planning and project evaluation. Without a system that addresses the determinants of compliance, advances in biomedical technology will fail to realize their potential to reduce the burden of chronic illness. Access to medications is necessary but insufficient in itself for the successful treatment of disease. Health systems must evolve to meet new challenges

In developed countries, the epidemiological shift in disease burden from acute to chronic diseases over the past 50 years has rendered acute care models of health service delivery inadequate to address the health needs of the population. In developing countries, this shift is occurring at a much faster rate.

Measurement of compliance provides useful information that outcome-monitoring alone cannot provide, but it remains only an estimate of a patient's actual behaviour. Several of the measure-

ment strategies are costly or depend on information technology (e.g. pharmacy databases) that is unavailable in many countries. Choosing the "best" measurement strategy to obtain an approximation of compliance behaviour must take all these considerations into account. The goals of the provider or researcher, the accuracy requirements associated with the regimen, the available resources, the response burden on the patient and how the results will be used should also be taken into account. Finally, no single measurement strategy has been deemed optimal. A multi-method approach that combines feasible self-reporting and reasonable objective measures is the current state of the art in measurement of compliance behaviour.

Although compliance is probably not affected by old age itself, it is affected by several factors that are common among older people, such as physical or mental impairments, the use of more drugs, and an increased risk of drug-drug interactions and side effects. Taking several drugs makes remembering when to take each drug harder and increases the risk of adverse drug reactions, particularly when over-the-counter drugs are also being taken. Doctors may be able to simplify the drug regimen—by using one drug that serves two purposes or by reducing the number of times a drug must be taken—to improve compliance and to reduce the risk of interactions.

Medication noncompliance, can include:

- Taking less or more of a medication than prescribed
- Taking outdated medications
- Taking a medication prescribed for someone else
- Storing medications improperly
- Failing to initially fill a prescription
- Failing to refill a prescription as directed
- Omitting a dose
- Prematurely discontinuing medication
- Taking a dose at the wrong time
- Taking a dose with prohibited foods, liquids, and other medications
- Taking damaged medications
- Improperly using medication administration devices (e.g., inhalers)

Compliance, adherence and persistence are all terms commonly used in the literature to describe medication-taking behaviors. Adherence has become the preferred term, defined by the World Health Organization as "the extent to which a person's behavior [in] taking medication...corresponds with agreed recommendations from a health care provider". The term compliance has come into disfavor because it suggests that a person is passive-

ly following a doctor's orders, rather than actively collaborating in the treatment process. Adherence, on the other hand, requires the person's agreement to the recommendations for therapy. Persistence is defined as the ability of a person to continue taking medications for the intended course of therapy. In the case of chronic diseases, the appropriate course of therapy may be months, years, or even the person's lifetime. A person is classified as non-persistent if he or she never fills a prescription or stops taking a prescription prematurely. Discussing the intended course of therapy when medications are first started has been shown to be an important factor in keeping people persistent with a medication regimen.

Compliance is a multidimensional phenomenon determined by the interplay of five sets of factors, termed "dimensions" by the World Health Organization: social/economic factors, provider-patient/health care system factors, condition-related factors, therapy-related factors and patient-related factors.

The best known and most widely usable scale for research adherence is MAQ (Medication Adherence Questionnaire) by Morisky, which has several advantages: identifies barriers to nonadherence, is the shortest scale, easiest to score and very adaptable for various groups of medication. SEAMS (Self-Efficacy for Appropriate Medication Use Scale) is a 13-question scale, more complex than the previous one. BMQ (Brief Medication Questionnaire) consists of four main question headings (regimen, belief, recall and access screen) and multiple sub-questions. MARS (Medication Adherence Rating Scale) is a 10-question scale focused mainly on psychiatric populations. ARMS (Adherence to Refills and Medication Scale) is a valid and reliable medication adherence 14-question scale when used in a chronic disease population, with good performance characteristics even among low-literacy patients. The Hill-Bone Compliance Scale address barriers and self-efficacy and focuses on hypertensive patients. Some scale are modified depending on the disease or kinds of medication.

Consequences of medication noncompliance

Noncompliance with medication regimens may result in increased use of medical resources, such as physician visits, laboratory tests, unnecessary additional treatments, emergency department visits, and hospital or nursing home admissions. Noncompliance may also result in treatment failure.

In the context of disease, medication noncompliance can be termed an "epidemic." More than 10% of older adult hospital admissions may be due to noncompliance with medication regimens. In one study, one-third of older persons admitted to the hospital had a history of noncompliance. Nearly one-fourth of nursing home admissions may be due

to older persons' inability to self-administer medications. Problems with medication compliance were cited as a contributing factor in more than 20% of cases of preventable adverse drug events among older persons in the ambulatory setting. In addition, approximately 125,000 deaths occur annually in the US due to noncompliance with cardiovascular medications.

Of all age groups, older persons with chronic diseases and conditions benefit the most from taking medications, and risk the most from failing to take them properly. Among older adults the consequences of medication noncompliance may be more serious, less easily detected, and less easily resolved than in younger age groups.

Improving compliance with medication regimens can make a difference. A recently published study found that for a number of chronic medical conditions (diabetes, hypertension, hypercholesterolemia, and congestive heart failure) higher rates of medication compliance were associated with lower rates of hospitalization, and a reduction in total medical costs.

Ageism and medication noncompliance in the elderly

To understand ageism, one must understand the process of stereotyping. A stereotype is a well-learned set of associations that link a set of characteristics with a group. Stereotypes differ from personal beliefs, which are propositions that are endorsed and accepted as true. While all individuals learn about cultural stereotypes through socialization, only a subset of people endorse the stereotype and believe it to be true.

People respond to each other almost automatically using stereotypes based on race, age, and gender. Perceptions and judgments about others are made instantaneously, without conscious thought or effort, which is why stereotypes remain insidious. Stereotypes typically exaggerate certain characteristics of some members of a group and attribute the negative characteristic to aging. They do not recognize that individual characteristics vary greatly and also change over time.

Ageism appears in many forms. A few examples illustrate how the behavior of an older person is described in an ageist manner, where the same behavior by a younger person is explained without stereotypes. When older people forget using medicines, they are viewed as senile. When a younger person fails to remember using medications, we usually say he or she has a faulty memory.

Age by itself is not a determining factor in medication noncompliance. Only, in older age more factors contributing to noncompliance accumulate with higher age and older patients are at higher risk of noncompliance. Therefore they need better care and support in their medication compliance.

8/ Rational prescribing in older patients in nursing home care and home care in Europe- appropriate medication use, interprofessional approach

Prof. Graziano Onder, MD, PhD

Centro Medicina dell'Invecchiamento, Università Cattolica del Sacro Cuore, Rome, Italy

The aging process is characterized by a high level of complexity, which makes the care of older adults and in particular the use of medications a challenging task. Typically, older adults and particularly those in home care or in nursing home, show the co-occurrence of multiple chronic diseases (comorbidity) and conditions – like urinary incontinence, delirium or falls – that cannot be ascribed to a specific organ system pathology and have multiple causes (the so called geriatric syndromes). This high degree of complexity is further complicated by the presence of cognitive and functional impairment, which is common in this population. Social problems, like lack of informal support or poor income, are also widely represented in this age group. Pharmacological treatment of this complex patient represents a challenge for prescribing physician and it may cause several iatrogenic hazards.

Comorbidity - the presence of comorbidity, defined as the concomitant presence of multiple coexisting diseases in the same individual, is a major issue in geriatrics and will increase its importance in the next future. The prevalence of comorbidity increases with age, mostly due to the higher frequency of individual chronic conditions in advanced age. In the United States, 35.3% of persons aged between 65 and 79 years present multiple clinical conditions, and this prevalence is twofold higher among those aged 80 years or older. For example, after age 65, 48% of community-dwelling persons in the United States report arthritis, 36% hypertension, 27% heart disease, 10% diabetes, and 6% a history of stroke. When the prevalence of arthritis, coronary artery disease, COPD, diabetes, cerebrovascular disease was analysed in the NHANES sample, it was observed that the majority of participants experiencing each disease had at least 1 other coincident disease. The percentage of participants experiencing each disease alone varied from 15.2% to 47.2%. Similarly, in a Swedish sample, chronic diseases were more likely to occur with comorbid conditions than alone. Hypertension, chronic artery disease and depression were the most frequent diseases occurring and heart failure was the condition most often associated with other comorbidities.

The high level of comorbidity observed in older adults has clearly a relevance to the occurrence of iatrogenic illness and several studies have suggested that number of coexisting diseases is associated with an increased risk of Adverse Drugs Reactions (ADR). Indeed, this findings may be related to several factors. First explanation includes the occurrence of drug-disease interaction. This phenomenon happens when drugs that are helpful in one disease

have the potential to exacerbate an underlying disease or medical disorder. For example, some beta-blockers taken for heart disease or high blood pressure can worsen asthma and mask hypoglycemia in diabetic patients or metoclopramide for gastric dysmotility may increase dopamine receptor blockade and worsen motor symptoms in a patient with Parkinson's disease.

Second explanation includes the occurrence of specific conditions that may alter drug metabolism. Typical examples of this phenomenon are kidney and liver diseases which lead to a reduced drug clearance and therefore to a higher risk of ADR. Another common condition that may impair drug metabolism and lead to iatrogenic illness is heart failure (HF). Indeed, pathophysiological changes in pharmacokinetics are common in patients with HF, including diminished renal and hepatic blood flow, reduced splanchnic blood flow and liver metabolic capacity and hepatic venous congestion. In addition, HF is associated with a reduction in the volume of distribution. As a result of these changes plasma concentrations of drugs are usually higher in patients with HF than in healthy subjects. Furthermore, HF plays an important role in the down-regulation of hepatic CYP involved in drug metabolism through several mechanisms which include hepatocellular damage, hypoxia and elevated levels of pro-inflammatory cytokines.

Finally, specific health conditions may lead to an increased rate of ADR by a non-metabolic mechanism. For example, several studies have suggested the presence of an association between depression and iatrogenic illness. Indeed, depressed patients can amplify somatic symptoms, causing a higher report rate of ADR and psychological symptoms of emotional distress can lead to an increased attention directed towards one's body, with a consequent decrease in the threshold of any noxious somatic sensation. For example, Lustman et al. have found that among diabetic patients, depression was significantly correlated with an increased subjective report of symptoms commonly associated with poor glycemic control (i.e., polydipsia, polyuria, etc.), independent from glycemic HbA1 levels. An alternative explanation to the link between depression and ADR is related to the fact that psychological distress can determine the activation of neurally-regulated biological processes, which can result in a reduction of the body's ability to combat pathological processes and can thus favorite the onset of negative outcomes, including ADRs.

Geriatric syndromes - Also presence of geriatric syndromes may influence the effect of

pharmacological treatment and increase the risk of ADR. The term geriatric syndromes, refers to one symptom or a complex of symptoms with high prevalence in frail elderly patients, resulting from multiple diseases and multiple risk factors. Geriatric syndromes can have a devastating effect on quality of life of elderly patients. Specific syndromes such as falls and polypharmacy have some direct implications for how intensely providers may actually manage chronic diseases. Other geriatric syndromes, such as depression, orthostatic hypotension, urinary incontinence, and chronic pain are more common among elderly patients with chronic diseases and may be of great importance to the patient. Presence of these syndromes may influence potential benefits of pharmacological treatments and increase the risk of iatrogenic illness. For example, Gage et al showed an increased risk of intracranial hemorrhage in patients with atrial fibrillation at high risk of falls (based on physician's documentation in patient's medical record: "frequent falls, history of falls, multiples falls, or tendency for falls") compared to other patients. Similarly, orthostatic hypotension a relevant cause of fall-related injuries, which substantially limit patients' quality of life and increase mortality, is directly related to antihypertensive medications, indicating the need of a less intensive treatment of hypertension in subjects suffering from this condition.

Cognitive impairment - Cognitive impairment is a common condition among older adults and it is associated with other diseases commonly observed in older people, including hypertension, cardiovascular disease, diabetes, and osteoporosis. Memory loss, decline in intellectual function, and impaired judgment and language, commonly seen in patients with cognitive impairment, have obvious effects on decision-making capacity, alter benefits and burdens, impact on treatment adherence and may cause communication difficulties including decreased ability to report adverse effects. For example Brauner and coll have shown that, in presence of dementia, use of medications commonly indicated to treat osteoporosis can put the patient at great risk for developing serious iatrogenic illness.

Limited life expectancy - Limited life expectancy is a parameter not easy to estimate and many variables may influence it. An estimation of life expectancy is important to understand if a patients can benefit from a certain treatment. For example, in the case of diabetes, it is suspected that elderly patients should have at least 5 years of life expectancy in order to benefit from intensive lowering of glucose levels and such an approach may only lead to an increased risk of ADR and no clear health benefit.

Disability - Presence of functional deficits and disability may limit the ability of patients to take medicines accurately. Functional deficits were related to a reduced ability to manage pill containers and therefore to reduced compliance with

medication. In addition, impaired physical function is a major determinants of life expectancy and this may in turn reduce benefits from a pharmacological treatment.

GUIDELINES PITFALLS

Medical complexity of older adults may have a great role in the onset of ADR and should always be considered before prescribing a pharmacological treatment in the elderly in order the minimize the risk of drug related illness. Also drugs that have proven in clinical trials clear beneficial effects to treat a chronic conditions and whose use is indicated in clinical guidelines (CGL) should be used carefully in complex older adults (33) since they may interact with co-existing diseases or geriatric syndromes, may not be assumed correctly because of presence of cognitive deficits or disability or may be useless because the health expectancy of the patient is too short to determine a beneficial effect of the drug. In these situations the risk of iatrogenic illness is elevated and it may exceed the potential benefit observed from a given pharmacological treatment.

However, CGL used in everyday practice clinicians rarely address the common problems encountered in geriatric care. With a few notable exceptions they do not provide indications for treatment in subjects with limited life expectancy and focus on reducing mortality rather than on quality of life issues and in general patient centered care is not addressed. Cognitive impairment is rarely discussed as possible modifiers of treatment plan, even though 1 in 5 of those over 80 years old will develop a clinically detectable form of dementia. Geriatric syndromes in general deserve little attention in CGL, notwithstanding the fact that any physician of any specialty will see every day patients suffering from these conditions, and it has been clearly demonstrated that drug are frequently implicated in their pathogenesis.

In addition, CGL usually rely on results of large clinical trials which are usually conducted on young subjects, usually with only one disease and limited (if any) comorbidities, usually strictly related to the target disease. Patients recruited in trials take a limited number of drugs, almost all for conditions related to the specific disease studied, and for a short period of time (months or at most a few years). This makes difficult to extrapolate their results on older complex people, with many comorbid conditions, who use many different drugs, are cognitively impaired and disabled.

THE IMPORTANCE OF COMPREHENSIVE GERIATRIC ASSESSMENT AND MANAGEMENT IN DRUG PRESCRIBING AND IATROGENIC ILLNESS

Based on this background, it seems clear that a global assessment of patients characteristics, including comorbidities, geriatric syndromes, cognitive and

functional status and life expectancy, is necessary to have a full assessment of iatrogenic illness and to improve quality of prescribing. The traditional approach to patients diseases and needs does not provide information on the these problematic areas. In the past decades the comprehensive geriatric assessment (CGA) has been proposed as a methodology to provide a more global approach and assessment of older adults and their problems, allowing a more specific and sensible care plan for each single patient. CGA is considered the “technology” of Geriatrics and its application results in a better quality of care, as a result of the evaluation of various problematic areas. An extensive literature has documented that use of CGA in association with an integrated team of geriatric physicians, nurses, social workers and other professionals (the so called ‘geriatric team’) assessing and managing the health care problems identified by the CGA, and developing individualized care plans, has resulted in more detailed evaluation, improved care planning, and overall better quality of care.

CGA also allows a complete and global assessment and management of the health care problems, including evaluation of drugs with the goal of recognizing and preventing potential drug-related problems and improve quality of prescribing. As shown in table 1 several studies have assessed the effect of CGA and management on drug prescribing and drug related illness, showing a substantial improvement in quality of prescription.

Noticeably a large study assessing the effect of CGA associated with a geriatric team approach, as compared with usual care on 834 frail older adults admitted to Veterans Hospitals in the US showed a 35% reduction in the risk of a serious adverse drug reaction and a substantial reduction in unnecessary and inappropriate drug use and in the number of conditions with omitted drugs significantly associated with the intervention.

Results of these studies confirm that in complex older adults, a full and global evaluation of the problems and needs obtained by CGA may be extremely helpful in simplifying drug prescription and prioritizing pharmacological and health care needs, resulting in an improvement in quality of prescribing and in a reduction in the risk of drug related illness.

In conclusion, medical complexity of older adults may make drug prescribing a challenging task and may increase the risk of drug related illness. For this reason, a complete and global examination of patient characteristics is mandatory in the drug prescribing process. Recommendations of clinical guidelines do not always address the level of complexity observed in older adults and for this reason they should be applied with caution in this population. Indeed, in these type of patients, the prescribing process should be individualized and flexible. Changes in medications regimen over time are needed to adapt to the evolving health status, as medications with

proven efficacy at some point in middle or even late life, could become redundant and possibly dangerous in vulnerable elderly people.

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9/ Minimizing drug use in the elderly - prevention of ageing and age-related diseases by changing eating habits

*Assoc. Prof. Soner Dogan, MD, PhD
and Burak Demir, Ozan Sen*

Department of Medical Biology, Yeditepe University School of Medicine, Istanbul, Turkey

Ageing is a complex biological process and defined as the sum of all changes occurring in an organism over time that increases the risk for diseases and decreases the life-span by causing systemic dysfunction of almost all organs. At the cellular level ageing is a senescence process, resulting in decrease in cellular responds to stress factors and increased homeostatic imbalance. Many diseases such as cancer, Alzheimer's Disease, cardiovascular diseases, and diabetes are associated with ageing. It is widely accepted that ageing/longevity is a result of a combinational effect of genes (25%) and environmental factors (75%). Every year, billions of dollars are spent on delaying ageing and preventing or curing age-related diseases worldwide. Although many treatment methods and drugs have been used in order to delay ageing over the centuries there is still no any available drugs or methods to prevent or delay ageing. Today one of the most effective methods of delaying the progression of ageing and promoting healthy ageing is calorie restriction (CR) and appropriate natural diet components such as flavanol, dairy products, sulforaphane (SFN),

curcumin (CCM) and epigallocatechin gallate (EGCG) and resveratrol (RSV), which are shown to have positive effects on delaying age-related diseases and extending lifespan both in animal models and humans. Studies have shown that nutritional factors or CR may slow ageing or contribute to healthy ageing by modifying a variety of molecular mechanisms such as transcription factors, micro RNAs, histone modification, DNA methylation and different gene activations. In this talk, the beneficial effects of a variety of natural food components and calorie restriction on ageing/lifespan and age-related diseases such as Alzheimer's Disease, diabetes, cardiovascular diseases, osteoporosis and cancer will be discussed. Also, their possible molecular mechanisms will be briefly mentioned. Moreover, data from different studies will be summarized to show how unnecessary drug use in the elderly could be minimized by simple changes in lifestyle and eating habits. Acknowledgement: We thank Turkish Scientific Research Council (TUBITAK) for the grants 114S429, 114S894, 114S100 and the COST actions BM1402 and IS1402.

Curriculum Vitae
Prof. Petra Thürmann, MD, PhD

Chair of Clinical Pharmacology, University Witten/Herdecke
Director of the Philipp Klee-Institute for Clinical Pharmacology; HELIOS Universitätsklinikum Wuppertal
Heusner Str. 40; D-42283 Wuppertal, GERMANY

13.8.1960	born in Frankfurt am Main, Germany
1979 -1986	Studies of Medicine, Johann Wolfgang Goethe-University in Frankfurt/Main, Germany
Dec. 1986 - May 1997	Physician, assistant lecturer, later assistant Professor at the Institute of Clinical Pharmacology (Director: Prof. Dr. N. Rietbrock) at the Johann Wolfgang Goethe-University in Frankfurt/Main, Germany.
1987	Degree „Doctor of Medicine“ (Dr. med.)
1992	Consultant in „Clinical Pharmacology“
March 1997	Habilitation and venia legendi (Privat Dozent) in Clinical Pharmacology
June 1st 1997	Director of the Institute of Clinical Pharmacology at the HELIOS Universitätsklinikum Wuppertal
September 1st 1998	Professor and Chair of Clinical Pharmacology at the University of Witten/Herdecke, Germany
1999-2003	Medical Vice-Director of the HELIOS Universitätsklinikum Wuppertal
2004 – 2010	HELIOS Research Center, Berlin, CEO

Memberships in Scientific Societies

1992-2002	Council of the German Society for Clinical Pharmacology (GKPharm, now DGKliPha)
1999	President of the 9. Annual Meeting of the German Society for Clinical Pharmacology and Therapy e.V.
2002	Division of Clinical Pharmacology of the International Union of Experimental and Clinical Pharmacology (IUPHAR), 2004-2006 Treasurer, 2006-2014 Secretary; since 2014 Treasurer of IUPHAR

- Member of the International Society of Pharmacovigilance
- British Society of Pharmacology (BPS), Section Clinical Pharmacology
- American Society of Clinical Pharmacology and Therapeutics (ASCPT)
- German Coalition for Patient Safety

Memberships in Editorial Boards

2000	Editorial Board of the International Journal of Clinical Pharmacology and Therapeutics
2006	International Advisory Board of Basic & Clinical Pharmacology & Toxicology
2007	Editorial Board of the European Journal of Clinical Pharmacology
1996-2004	Memberships in other Medical, Scientific and Public Health Boards Commission D of the Federal Institute for Drugs and Medical Devices (BfArM)
2000-2003	Commission „Drugs in the Statutory Health Insurance“ (“Positivliste”) of the German Ministry of Health 2000 - 2003
2004	Extraordinary Member of the Drug Commission of the German Medical Association (since 2006 full member)
2005-2009	Expert group „Pharmacovigilance“ of the German Ministry of Health
2006	Scientific Advisory Board of the German Medical Association
2007	Scientific Advisory Board of the Federal Institute for Drugs and Medical Devices (BfArM)
2009-2011	Scientific Advisory Board of the Institute for Quality and Efficiency in Health Care (IQWiG)
2011	Advisory Council on the Assessment of Developments in the Health Care System of the German Ministry of Health
2013	Scientific Advisory Board of the Scientific Institute of the AOK (Allgemeine Ortskrankenkasse; Health Insurance Fund)

Scientific Focus/Core Expertise

Pharmacovigilance, safe prescribing
Geriatric Pharmacotherapy (PRISCUS-list), multi-disciplinary interventions in nursing homes and primary care; Patient information about drug therapy
Sex/Gender-related differences in drug therapy
Cardiovascular Drugs, Phase I Studies

Experience in clinical trials according to GCP-ICH and German Drug Law (AMG)

Study physician in total: approx. 60 clinical trials
Principal Investigator in total: approx. 25 clinical trials

Curriculum vitae Prof. Martin Wehling, MD, PhD

Born 12. 1. 1957 in Stade, Germany, married, two sons, 26 and 29 years old.
1974 school graduation Staatliches Internatsgymnasium Schloß Plön.
1974 state prize "Jugend musiziert" as pianist.
1975 begin of studies in chemistry and medicine at the University of Kiel.
1979 - 1980 scholarship by the Studienstiftung des Deutschen Volkes, research fellow with Professor A. Schwartz in the Department of Pharmacology and Cell Biophysics, Cincinnati, USA.
1981 board exam, full approbation as physician.
1981 promotion on "drug-induced phospholipoidosis" at the Institute of Pharmacology, University of Kiel, grade "summa cum laude".
1982 - 1983 residency at the Medical Policlinic, University of Zurich (head: Professor Siegenthaler).
1983 - 1984 military service.
1984 - 1995 resident, lecturer at the Medical Clinic, University of Munich.
1990 board exam as internist.
1992 board exam as cardiologist.
1992 habilitation.
1993 board exam as clinical pharmacologist.
1993 - 1995 Heisenberg-scholarship by the Deutsche Forschungsgemeinschaft.
1993 - 1994 sabbatical at the Baker Research Institute with Prof. John Funder, Melbourne, Australia.
From 1994 head of the division of clinical pharmacology and head of the Klinische Forschergruppe (clinical research group) "clinical pharmacology" by the Deutsche Forschungsgemeinschaft.
From 1995 ordinarius (full professor) for clinical pharmacology and director of the institute of clinical pharmacology, faculty of clinical medicine Mannheim, University of Heidelberg.
1997-2001 dean of studies at the faculty of clinical medicine at Mannheim, University of Heidelberg.
1998-2001 member of the executive committee, faculty of clinical medicine at Mannheim, University of Heidelberg.
2000 foundation of two centers of excellence: i) center for therapeutic research which provides structural help for the conduct of GCP-ICH-studies, and ii) the **center of gerontopharmacology which deals with the challenge of drug therapy in the elderly.**
2004 – 2006 director of discovery medicine/experimental medicine at AstraZeneca R&D, Mölndal.

Main tasks: translational medicine, linking pre-clinical and clinical activities across borders, development of efficacy and safety biomarker and valid proof-of-principle concepts, mainly in cardiovascular medicine, with some attention to gastrointestinal issues.

From January 1st, 2007, back as full professor for clinical pharmacology at the University of Heidelberg (end of sabbatical). Present position: managing director of the institute of experimental and clinical pharmacology and toxicology, Medical Faculty Mannheim, University of Heidelberg.

Scientific interests: Cardiovascular pharmacology: betablockers, steroids, ACE-inhibitors, antimineralocorticoids. Mechanisms of cardiovascular steroid action, nongenomic steroid action, integrative pharmacology, translational medicine: concepts, biomarkers, predictivity assessment, PoP-study designs,

early drug/device/ diagnostic tool development, gerontopharmacology, prioritization processes in polypharmacy (FORTA).

Clinical background: Invasive cardiologist, appr. 4000 cardiac catheters including interventions (PTCA, stenting), 11 years of clinical routine. 51 phase I-IV trials, mostly in the fields of hypertension, heart failure and endocrine disorders, mainly in collaboration with 15+ drug companies.

Publications: From 1980 to present approximately 300 PubMed citations, 4 books including "Drug Therapy for the Elderly (Springer 2013)"

Avocations: Piano playing

Curriculum vitae Dr. Daniela Fialová, PharmD, PhD, BCCP

Home address: Petřilova 3307/25
Prague 4, 143 00, Czech Republic
Email: daniela.fialova@faf.cuni.cz

Date of birth: 30.1.1975

Recent positions:

Head of the University Educational Centre in Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, Czech Republic

Researcher and Clinical Pharmacist, Clinical Consultant in Rational Geriatric Pharmacotherapy
Dept of Geriatrics and Gerontology, 1st Faculty of Medicine, Charles University in Prague, Czech Republic

Academic researcher, Department of Social and Clinical Pharmacy, Faculty of Pharmacy in Hradec Králové, Charles University, Czech Republic

Board member of the Section of Clinical Pharmacy, Czech Pharmaceutical Society, Czech Medical Association J.E. Purkyně, Czech Republic

Area of expertise:

clinical pharmacy in geriatrics, pharmacotherapy risk assessment and management in geriatric patients, geriatric pharmacoepidemiology, risk-management in the elderly

Education/Degrees/Work opportunities

- Master Degree in Pharmacy, Faculty of Pharmacy, Charles University in Prague (1998)
- Ward Certification Training in Clinical Pharmacy, Thomayer's Teaching Hospital, Prague (1998-2001)
- Ward Certification Degree in Clinical Pharmacy, Institute for Postgraduate Training in Health Care, Prague, Czech Republic (2001)
- Fellowship in Clinical Pharmacy in Geriatrics, Assistant Professor, Department of Geriatrics and Gerontology, 1st Faculty of Medicine and Dept of Social and Clinical Pharmacy, Faculty of Pharmacy, Czech Republic (2001-2006, 2003- 2006)
- FCE, ESOL Examinations, University of Cambridge, Level 1 Certificate (2003)
- Doctoral Degree in Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, Czech Republic (PharmD, PhD degree- 2006)
- Researcher, Department of Geriatrics and Gerontology, 1st Faculty of Medicine, Prague
- Chair of the Scientific Group "Aging and therapeutic value of medications in the old ages", Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, Czech Republic
- Chair of the University Educational Clinical Pharmacy Centre, Faculty of Pharmacy, Charles University in Prague, Czech Republic (2014- until now)

Experience – EU and international projects

EU ADHOC project ("AgeD in Home Care", 5th FP EC, 2001-2005)- researcher in rational geriatric pharmacotherapy, analyses of risk-benefit of medications in older patients in home care
EU SHELTER project ("Services and Health in the Elderly in Long Term Care, 7th FP EC, 2009-2014)- researcher in rational geriatric pharmacotherapy, analyses of risk-benefit of medications in older patients in long-term care
EU PREDICT project ("Participation of Older Adults in Clinical Trials, 7th FP, 2009-2011) – research works in the field of underrepresentation of older adults in clinical trials

EU CARPOOL project- invited researcher (“Combined Approach to Reduce POlypharmacy and improve quality of prescribing in OLder adults”, H2020, 2014 submitted)

EU REPAIR project- WP3 proposer (“Resolving problematic polypharmacy and suboptimal adherence in older adults”, H2020, 2014 submitted)

EU COST Action 1402 “Ageism- multi-national, interprofessional perspective”- Chair of WG1b “Healthy clinical strategies for healthy aging”- grant period 2015-2018

InterRAI corporation- research works for the interRAI corporation (2005-2007 member, 2007-2009

Associated Fellow, 2010 Full Fellow), clinical and research works on MED CAPs (“Medication Clinical Assessment Protocols”)

Other scientific experience

Chair of the Scientific Committee for 42nd ESCP Symposium on Clinical Pharmacy „Implementation of clinical pharmacy practice: research, education and management“, October 16-18th, 2013, Prague

Regular presentations in foreign scientific meetings, conferences, workshops (2-3 times a year)- conferences of IAGG (International Association of Geriatrics and Gerontology), EUGMS (European Union of Geriatric Medicine Society), ESCP (European Society of Clinical Pharmacy), EACPT (European Association of Clinical Pharmacology and Therapeutics)

Invited Speaker at international conferences, e.g. CIHI InterRAI conference Ottawa, Canada 2007, IAGG congress- Paris, France 2009, Bologna, Italy 2011, Seoul, South Korea 2013, Dublin, Ireland 2015, EU COST Action meeting Berlin, Germany 2015, ESCP conference in Lisbon, Portugal 2015, EACPT conference in Budapest, Hungary, 2009

Author of 1 monography “Specific Features of Geriatric Pharmacotherapy- changes in the therapeutic value of drugs in the elderly”, Karolinum, Prague 2007, co-author of 1 monography “Clinical pharmacy- 1st Edition”, Grada, Prague 2005

Member of the Board of Clinical Pharmacy Field, Faculty of Pharmacy, Charles University in Prague, Czech Republic

Member of the Board of Geriatrics and Gerontology Field, 1st Faculty of Medicine, Charles University in Prague, Czech Republic

Regular reviewer for several international journals, e.g. Drugs and Aging, Drugs Safety, Current Drug Metabolism.

National research projects

Principle investigator - grant GAUK (Grant Agency of the Charles University) No 95/2001 (2001-2003) „Interactions on isoforms CYP450- key for evaluation of the risk of pharmacotherapy in the old age“

Principle investigator- grant GAUK (Grant Agency of the Charles University) No 138/2004 (2004-2006)

“Risks of the drug regimes with high anticholinergic activity- impact on clinical status and consumption of healthcare services in seniors“

Co-investigator of the grant IGA No 10-029-4 (2009-2011) Internal Grant Agency of the Ministry of Health, Czech Republic „Increase in the quality of prescribing in seniors- validation of the instruments for the purposes of national drug policy in the Czech Republic“

National initiatives in rational pharmacotherapy

Initiator and the first authors of the „National consensus on potentially inappropriate medications in older patients in the Czech Republic („Czech national criteria of potentially inappropriate prescribing in older adults“)- publications: [Fialová D. et al.](#) Expert consensus of the Czech Republic 2012 on drugs and drug procedures potentially inappropriate in older adults (in Czech). Clinical pharmacology and pharmacy 2013; 27(1): 180-90 or [Fialová D. et al.](#) Rational pharmacotherapy in the old age: Expert consensus of the Czech Republic 2012 on drugs and drug procedures potentially inappropriate in the elderly (in Czech). Geriatrics and gerontology 2013; 2(1): 4-10

Founder and Chair of the University Educational Centre on Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, Czech Republic (2014- until now)

Research studies, clinical training and courses

2002 - Summer School “European Master in Gerontology- Health and Ageing in European Countries”, Valencia, Spain (1 week)

2003 - Course in Patient Centered Teaching for Clinical Pharmacists and Clinical Pharmacy Teachers, Malta (1 week)

2002 - Study stay in Clinical Pharmacy- College of Pharmacy, University of Iowa, Iowa, USA (2 weeks)

2003 - Study stay in geriatric clinical pharmacy- Lothian Primary Care NHS Trust- Pharmacy Service, Edinburgh, Scotland (1 month)

- 2004 - Research stay in geriatric pharmacoepidemiology (analyses), Università Cattolica Sacro Cuore, Roma, Italy (3 months)
- 2006 - Research stay in geriatric pharmacoepidemiology (study design, methodology), Department of Clinical Pharmacology and Pharmacoepidemiology, University of Bordeaux, France (1 month)

Teaching and publication activities:

- lecturer in geriatric pharmacotherapy- master courses of geriatrics (Czech, English) (2001-until now), applied geriatric pharmacology- postgraduate courses (2005- until now)
- lecturer for nurses and general practitioners in continuing educational courses (2004- until now)
- pregraduate and postgraduate education in clinical pharmacy (2003- until now)
- continuing education in clinical pharmacy and pharmacotherapy risk assessment and management- lecturer of the Czech Chamber of Pharmacist, Prague region (2004- until now)
- postgraduate courses in geriatric clinical pharmacy (2003- until now)
- presentations at international and national scientific meetings, moderator of international workshops, invited speaker at international conferences, professional publications in national and international journals (2003- until now)
- tutor and Head of the Department for Postgraduate Training in Clinical Pharmacy, Institute for Postgraduate Training in Healthcare, Prague, Czech Republic (2005-2007, 2007- until now)
- Head and main organizer of educational courses of the University Clinical Pharmacy Educational Centre, Faculty of Pharmacy, Charles University in Prague, Czech Republic (founded Sept 2014- until now)

Membership in Professional Societies and boards:

- Section of Clinical Pharmacy, Czech Pharmaceutical Society, Czech Medical Society J.E.Purkyně- Board Member (2001-), Scientific Secretary (2007- 2009), Head (2009-2011), Board Member (2012- until now)
- Vice-Chair of the Accreditation Committee of Clinical Pharmacy, Ministry of Health, Czech Republic (2006- 2013),
- Member of the Czech Society of Geriatrics and Gerontology (2005- until now)
- Member and Full Fellow of the InterRAI Corporation (2005- until now)
- Member and Professional lecturer of the European Society of Clinical Pharmacists (2004- until now)
- Member of the Editorial Board of the Czech Journal of Clin Pharmacology and Pharmacy (2006- until now)
- Member of the panel and grant reviewer of the Agency for Healthcare Research, Ministry of Health, Czech Republic, panel "Age-related diseases" (2015- until now)

Achievements/Awards

- Award of the Dean, Faculty of Pharmacy in Hradec Králové, Charles University, Czech Republic (1996, 1997, 1998)
- French Award in Pharmacy, French Embassy in Prague (2005)
- Scientific Award of the Czech Medical Society of J.E.Purkyně (2005)
- Scientific Award of Dr. Paul Janssen for Pharmacoconomics and Drug policy (2006)

Curriculum vitae Dr. Valentina Marinković, PharmD, PhD

Address: Visokog Stevana 10/6,
11000 Belgrade, Serbia
+ 381 60 322 17 05
vmrinkovic@pharmacy.bg.ac.rs

Academic work experience

2011 – Present ASSOCIATE PROFESSOR – University of Belgrade, Faculty of Pharmacy, Belgrade
2010 – 2011 ASSOCIATE PROFESSOR – University of Niš. Faculty of Technology, Leskovac
2005 – 2010 ASSISTANT PROFESSOR – University of Niš. Faculty of Technology, Leskovac

Corporate Work experience

2010 – 2015 QUALITY MANAGER WEST BALKANS – Alvogen pharma, Serbia
Managing one production site and various wholesales in WB countries
Corporate auditing to the suppliers and contractors according EU GMP, EU GDP and FDA

2003 – 2010 QUALITY AFFAIRS DIRECTOR – ACTAVIS – Zdravlje Leskovac, Serbia
2000 – 2003 QUALITY CONTROL DIRECTOR – Zdravlje Leskovac

1998 – 2000 QUALITY CONTROL ASSISTANT DIRECTOR – Zdravlje Leskovac
1993 – 1998 QUALIFIED PERSON FOR BATCH RELEASE – Zdravlje Leskovac
1987 – 1993 RESPONSIBLE PERSON FOR STABILITY STUDIES AND ANALYTICAL METHOD DEVELOPMENT – Zdravlje Leskovac

Awards

2009 Annual award of Serbian Quality Association for the best Quality Systems company
1998 Annual award of Belgrade Chamber for Master degree thesis
- Synergy of science and industry

Publications 3 handbooks

- Quality in pharmacy (2012)
- Integrated management systems in pharmaceutical supply chain (2013)
- Pharmaceutical law and ethics (2014)

28 scientific papers in international journals (sci listed)

More than 100 of expert and scientific papers presented in International and National Conferences

Membership

Serbian Quality Association – Vice President
Serbian Pharmacy Association – member
European QP association – member
International Pharmaceutical Federation – FIP – member
Center of Study of Bioethics, Cambridge working group - member

Specialization

2014 – Present Organizational Transactional Analysis –
Psychopolis Institute, Belgrade
1990 – 1993 Medicines examination and QC testing –
Faculty of Pharmacy, Belgrade, National QC laboratory, Belgrade

Education

2003 PhD DEGREE –
University of Belgrade, Faculty of Pharmacy, Belgrade
1995 – 1997 MSc DEGREE –
University of Belgrade, Faculty of Pharmacy, Belgrade
1982 – 1987 BSc DEGREE –
University of Belgrade, Faculty of Pharmacy, Belgrade

Curriculum vitae Dr. Annemie Somers PharmD, PhD

Born: 05/12/1971, Bruges, Belgium

Address: Ghent University Hospital
Pharmacy
De Pintelaan 185, 9000 Ghent, Belgium
annemie.somers@uzgent.be
Tel +32 9 3325373

Senior pharmacist, section of pharmaceutical care

Responsibilities:

- clinical pharmacy (ward pharmacy and back-office clinical pharmacy)
- seamless pharmaceutical care
- coordination of Pharmacy & Therapeutics Committee (formulary, guidelines, drug information)
- medication safety
- implementation and continuous improvement of electronic prescribing

PhD Dissertation:

Detection and prevention of drug related problems in older hospitalized patients: the challenge for the clinical pharmacist (promoter: prof. dr. M. Petrovic) (June 13, 2012)

Academic position:

Visiting professor pharmaceutical care at Ghent University Hospital
Courses in clinical pharmacy, organization of the hospital pharmacy, practical aspects of pharmaceutical care; master theses (1st master of pharmacy and hospital pharmacy)

Publications (First author)

- **Somers A**, Bauters T, Robays H et al. Evaluation of human albumin use in a university hospital in Belgium. *Pharm World Sci* 2002;24(3):111-116.
- **Somers A**, Petrovic M, Robays H et al. Reporting adverse drug reactions on a geriatric ward: a pilot project. *Eur J Clin Pharmacol* 2003;58(10):707-714
- **Somers A**, Robays H, Vander Stichele R, Van Maele G, Bogaert M, Petrovic M. Contribution of drug related problems to hospital admission in the elderly. *J Nutr Health Aging* 2010;14:475-82
- **Somers A**, Robays H, Audenaert K, Van Maele G, Bogaert M, Petrovic M. The use of hypnotic sedative drugs in a university hospital: has anything changed in 10 years? *Eur J Clin Pharmacol* 2011;67(7):723-9
- **Somers A**, Mallet L, van der Cammen T, Robays H, Petrovic M. Applicability of an adapted Medication Appropriateness Index (MAI) for detection of drug related problems in geriatric inpatients. *Am J Geriatr Pharmacother* 2012;10(2):101-9.
- **Somers A**, Robays H, De Paepe P, Van Maele G, Bogaert M, Petrovic M. Evaluation of clinical pharmacist's advices at the geriatric ward in a Belgian university hospital. *Clin Interv Aging* 2013;8:703-709.
- **Somers A**, Petrovic M. Major drug related problems leading to hospital admission in the elderly. *J Pharm Belg*. 2014 (2):34-8
- **Somers A**, Claus B, Vandewoude K, Petrovic M. Experience with the implementation of clinical pharmacy services and processes in a university hospital in Belgium. *Drugs Aging* 2016;33(3):189-97

Other publications

- Warie H, Petrovic M, **Somers A**, Mariman A, Robays H, Pevernagie D. The use of hypnotic sedative drugs in a university hospital setting. *Acta Clin Belg* 2003;58(4):225-32
- Colpaert K, Claus B, **Somers A**, Vandewoude K, Robays H, Decruyenaere J. Impact of computerized physician order entry on medication prescription errors in the intensive care unit: a controlled cross-sectional trial. *Crit Care* 2006;10(1):R21
- Verrue CL, Mehuys E, **Somers A**, Van Maele G, Remon JP, Petrovic M. Medication administration in nursing homes: pharmacists' contribution to error prevention. *J Am Med Dir Assoc* 2010;11(4):275-83
- Onder G, Petrovic M, Tangiisuran B, Meinardi MC, Markito-Notenboom WP, **Somers A**, Rajkumar C, Bernabei R, van der Cammen TJ. Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR risk score. *Arch Intern Med* 2010;170(13):1142-8
- Verrue C, Petrovic M, Mehuys E, Boussery K, **Somers A**, Spinewine A, Bauwens M, Gobert M, Elseviers MM, Vander Stichele R. Organization of the medication management process in Belgian nursing homes. *J Am Med Dir Assoc* 2011;12(4):308-11
- Onder G, van der Cammen TJ, Petrovic M, **Somers A**, Rajkumar C. Strategies to reduce the risk of iatrogenic illness in complex older adults. *Age Ageing* 2013;42(3):284-91
- Pepersack T, Gilles C, Petrovic M, Spinewine A, Baeyens H, Beyer I, Boland B, Dalleur O, De Lepeleire J, Even-Adin D, Van Nes MC, Samalea-Suarez A, **Somers A**. Working Group Clinical Pharmacology, Pharmacotherapy and Pharmaceutical Care; Belgian Society for Gerontology and Geriatrics. Prevalence of orthostatic hypotension and relationship with drug use amongst older patients. *Acta Clin Belg*. 2013 Mar-Apr;68(2):107-12
- Kruse V, **Somers A**, Van Bortel L, De Both A, Van Belle S, Rottey S. Sunitinib for metastatic renal cell cancer patients: observational study highlighting the risk of important drug-drug interactions. *J Clin Pharm Ther* 2014;39(3):259-65
- Pehudoff K, Azermai M, **Somers A**, Vander Stichele R, Petrovic M. Medication discrepancies in older patients admitted to non-geriatric wards: An exploratory study. *European Geriatric Medicine* 2015; 6(1):41-45
- Tommelein E, Petrovic M, **Somers A**, Mehuys E, van der Cammen T, Boussery K. Older patients' prescriptions screening in the community pharmacy: development of the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP3S) tool. *J Public Health* 2015
- Tommelein E, Mehuys E, Petrovic M, **Somers A**, Colin P, Boussery K. Potentially inappropriate prescribing in community-dwelling older people across Europe: a systematic literature review. *Eur J Clin Pharmacol* 2015;71(12):1415-27
- Petrovic M, **Somers A**, Onder G. Optimization of Geriatric Pharmacotherapy: Role of Multifaceted Cooperation in the Hospital Setting. *Drugs Aging* 2016;33(3):179-88

Curriculum vitae Prof. Jiří Vlček RNDr, PhD

Address Štefánikova 374, 50011 Hradec Králové
Mobil 739 488 202, 603 504 244
E-mail vlcek@faf.cuni.cz

Birth 6th January 1954

Work experience

Dates

Occupation or position held

1995- present

Head of the Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University (FaP CU), Czech Republic

Name of employer Faculty of Pharmacy, Charles University
Akademika Heyrovského 1203/5, 500 05 Hradec Králové
University Hospital in Hradec Králové
Sokolská 581, 500 02 Hradec Králové

Dates 1995- 2008, 2008- present

Occupation or position held

Name of employer Associate Professor (1995-2008), Professor (2008- present)
Department of Social and Clinical Pharmacy
Faculty of Pharmacy, Charles University
Akademika Heyrovského 1203/5, 500 05 Hradec Králové

Dates 2006 – present

Occupation or position held

Head of Jointed Drug Information Centre at the FaP CU and University Hospital in Hradec i Králové

Name of employer University Hospital in Hradec Králové, Sokolská 581, 500 02 Hradec Králové
Faculty of Pharmacy, Charles University
Akademika Heyrovského 1203/5, 500 05 Hradec Králové

Dates 2007 – 2012

Occupation or position held

Clinical pharmacist

Name of employer 4th Department of Internal Medicine
University Hospital in Hradec Králové
Sokolská 581, 500 02 Hradec Králové

Dates 1993 – 1995

Occupation or position held

Assistant professor

Name of employer Faculty of Pharmacy, Charles University
Akademika Heyrovského 1203/5, 500 05 Hradec Králové

Dates 1985 – 1993

Occupation or position held

Assistant professor at the Department of Pharmacology and Toxicology

Name of employer Faculty of Pharmacy, Charles University
Akademika Heyrovského 1203/5, 500 05 Hradec Králové

Membership in Professional Associations and other Professional Activities

Dates 1994 – present

Occupation or position held

Member of the Scientific Board of the Faculty of Pharmacy, Charles University

Dates 2001 – 2010

Occupation or position held

Member of the Scientific Board „Cardiology at Faculty of Medicine, Masaryk University in Brno

Dates 2004 – 2009

Occupation or position held

Member of the Scientific Board of the University of Defence

Dates 2014 – present

Occupation or position held

Chairman of the Advisory board for Clinical and Social pharmacy at FaP CU

Dates 2011- present

Occupation or position held

National representative to monitor the consumption of antibiotics in ECDC Stockholm

Dates 2010 – present

Occupation or position held

A member of the Accreditation Committee of Clinical Pharmacy and member of the board of examiners for the Ministry of Health Graduate Diploma in the field of Clinical Pharmacy

Dates 2010 – present

Occupation or position held

Member of the WHO working group for the creation Patient safety curriculum guide

Dates 2010 – present

Occupation or position held

Member of the Medicines Commission Hamza sanatorium

Dates 2006 – present

Occupation or position held

Member of the Advisory board for Cardiology at Faculty of Medicine, MU Brno

Dates 2005 – 2011

Occupation or position held

National representative of ESAC project (European surveillance of antimicrobial consumption)

Dates 2003 – 2006

Occupation or position held

Member of the expert group on safe medication practices at the European Parliament

Dates 1997 – 2006

Occupation or position held

Vice Dean for Development and Cooperation of the FaP CU with clinical practice

Teaching Activity

Lectures and examinations in Clinical Pharmacy, Pharmaceutical care

Lectures and seminars in the subject Clinical Pharmacy - risks of pharmacotherapy

Chairman of the examination committee for state examinations in the program of Pharmacy

Educational Activity

Research in the field of pharmacoepidemiology, consumption of drugs, drug compliance, behavior of health professionals and patients in the use of drugs, analysis of drug risk for adverse drug reactions and drug errors and risk management in pharmacotherapy, and pharmacoinformatics.

Supervisor of PhD graduates in the field:

1. Clinical Pharmacy: Mgr.H. Müllerová, (1997) Mgr. M. Jandová (1999), Mgr. P. Matoulková (2001), Mgr. P. Fialová (2003), Mgr. Z. Kučera (2004); Mgr. Miroslava Hejdová (2004), Mgr. Retnosari Andrajati (2005), Mgr. D. Fialová (2006), Mgr. Peter Červený (2008); Mgr. E. Tlustá (2009), Mgr. J. Pokladníková (2009), Mgr. Magda Vytřísalová (2010) Mgr. Šárka Blažková, Mgr. Josef Malý (2013), Mgr. Martin.Doseděl (2013), Mgr. Lucie Hromádková (2013); Dr. Abbubaker Abased (2015);
2. Social Pharmacy: Mgr. I. Minarčíková (2006); MUDr. Eva Kopečná (2014), PharmDr. Jiří Klimeš (2014); Mgr. Martin Srba (2014); Mgr. Jan Kostřiba (2014)

Education and Degrees

Year 2008	Qualification achieved	Prof.- Professor of Clinical and Social Pharmacy
Year 1998	Qualification achieved	Postgraduate specialization in Clinical Pharmacy level II
Year 1997	Qualification achieved	Postgraduate specialization in Clinical Pharmacy level I
Year 1995	Qualification achieved	Doc.- Associate Professor in Pharmacology and Toxicology
Year 1988	Qualification achieved	CSc.- Candidatus scientiarum
Year 1981	Qualification achieved	RNDr.- Rerum naturalium doctor

Research stays abroad

Year 2007

Location and length Visiting professor at Iowa University, Iowa, USA (7 days)

Dates 1995

Location and length Dept of Pharmacoepidemiology, University of Utrecht, Utrecht, Netherlands (14 days)

Dates 1994

Location and length Welsh School of Pharmacy - the stipend of British Council (14 days)
Year 1987
Location and length Division of Clinical Pharmacology, Teaching Hospital, Basel, Switzerland (12 months)

Curriculum vitae Dr. Marcel Leppé, MD, PhD

Marcel Leppé graduated from the School of Medicine, University of Zagreb. He has completed two postgraduate studies, i.e. Public Health in 1978 and Health Information Systems in 1986, and passed specialist exam in Social Medicine and Health Care Structure in 1982.

He was employed at The Croatian National Institute of Public Health since 1979. to 1984 and since 1984, he has been employed at the Department of Public Health and the Department of Pharmacoepidemiology, Andrija Stampar Institute of Public Health in Zagreb. He acquired PhD in 2008. He has been working in the public health, social medicine, gerontology, chronic disease and Healthy Ageing pharmacoepidemiology issues for years. His professional interest being focused on demographic and health statistics, gerontology, healthy and active ageing, drug consumption, adherence to drugs and interpretation of this phenomenon.

He is the member of the Croatian Medical Association and Croatian Society for Public Health. He published over 250 professional and scientific papers and abstracts.

Participation in some European projects:

COST Action IS1402 Ageism - a multi-national, interdisciplinary perspective

COST Action IS1211 Cancer and Work (CANWON)

Joint Programming Initiative "More Years, Better Lives"

MoPAct - Mobilising the Potential of Active Ageing in Europe

innovAge - Social Innovations Promoting Active and Healthy Ageing

JA CHRODIS - Joint Action Addressing Chronic Diseases and Healthy

Scientific work in public health and pharmacoepidemiology

Health databases (health statistics, cancer registry, diabetes registry)

Gerontology: Active and Healthy Ageing

Pharmacoeconomic analysis

Curriculum vitae Prof. Graziano Onder, MD, PhD

Address Via Suvereto 247
00139, Rome, Italy
Telephone 0039 06 30154341
Fax 0039 06 3051911
E-mail graziano.onder@rm.unicatt.it
Nationality Italian
Date of birth 15-11-1972

EXPERTISE

Geriatric medicine. Clinical aspects of aging, geriatric syndromes, chronic diseases.

Research activities in the following areas:

Pharmacoepidemiology in the elderly. Prevalence and risk factors for Adverse Drug Reactions in the elderly, inappropriate prescribing in the elderly, prevalence of use and effects of antihypertensive drugs, pharmacological treatment for prevention of disability.

Physical performance and disability in the elderly. Development of scales to measure physical performance in older adults, factors involvement in the development of disability, interventions to prevent decline in physical function and disability.

Sarcopenia. Consequences and determinants of sarcopenia and interventions that can impact on this condition.

Adults with Down Syndrome. Prevalence of diseases and comprehensive assessment in adults with Down syndrome.

Comprehensive Assessment. Development and validation of tools to perform comprehensive assessment in populations with special needs.

WORK EXPERIENCE

Dates (from – to) Aug-Sept 1993
Name and address of employer Pittsburgh Transplantation Institute, Pittsburgh
Occupation or position held Guest Researcher
Dates (from – to) Aug-Sept 1996
Name and address of employer Nuclear Medicine Dept., National Institute of Health, Bethesda, MD
Occupation or position held Guest Researcher
Dates (from – to) 2001- 2002
Name and address of employer J. Paul Sticht Center on Aging - Wake Forest University,
Winston Salem, NC, USA
Occupation or position held Research Associate
Dates (from – to) 2004-present
Name and address of employer UCSC, Rome, Italy
Occupation or position held Assistant Professor in Geriatric Medicine
Dates (from – to) 2004-present
Name and address of employer Course for Physical Therapists - University of Cassino, Italy
Occupation or position held Teacher of Geriatrics
Dates (from – to) 2007-2009
Name and address of employer Course for Physical Therapists – UCSC, Roma, Italy
Occupation or position held Teacher of Geriatrics
Dates (from – to) 2008-present
Name and address of employer Course for Occupational Therapists – Università Claudiana ,
Bolzano, Italy
Occupation or position held Teacher of Epidemiology
Dates (from – to) 2011-2013
Name and address of employer IRCCS San Raffaele, Rome, Italy
Occupation or position held Member of the Institutional Review Board
Dates (from – to) 2012-2013
Name and address of employer Italian Geriatrics Society (SIGG), Florence, Italy
Occupation or position held Member of the Scientific Committee
Dates (from – to) 2013-present
Name and address of employer Italian Medicines Agency (AIFA), Rome, Italy
Occupation or position held Member of Geriatric Working Group
Dates (from – to) 2014 – present
Name and address of employer Course for Occupational Therapists – Università Claudiana,
Bolzano, Italy
Occupation or position held Director

EDUCATION AND TRAINING

Dates (from – to) 1992 – 1997
Name and type of organization providing education and training UCSC, Rome, Italy
Title of qualification awarded MD
Dates (from – to) 1999 – 2002
Name and type of organization providing education and training UCSC, Rome, Italy
Title of qualification awarded Ph.D. in Preventive Geriatric Medicine
Dates (from – to) 2000-2001
Name and type of organization providing education and training J. Paul Sticht Center on Aging - Wake Forest University, Winston Salem,
NC, USA
Title of qualification awarded Research Fellow
Dates (from – to) June-July 2001
Name and type of organization providing education and training Bloomberg School of Public Health, Johns Hopkins University,
Baltimore, MD, USA
Title of qualification awarded Courses in Principles of Epidemiology and Statistical Reasoning
in Public Health I and II
Dates (from – to) 2002-2004
Name and type of organization providing education and training UCSC, Rome, Italy
Title of qualification awarded Geriatric Clinical Fellow
Dates (from – to) 2004-2007
Name and type of organization providing education and training Institut Universitarie Kurt Bosch, Sion, Switzerland

Title of qualification awarded Advanced Postgraduate Course of the European Academy
for Medicine of Aging

LANGUAGES

MOTHER TONGUE	Italian
OTHER LANGUAGES	English
• Reading skills	Excellent
• Writing skills	Excellent
• Verbal skills	Excellent

ADDITIONAL INFORMATION

He served as a reviewer for more than 20 journals including Journal of Gerontology Medical Sciences, The Lancet, Canadian Medical Association Journal, Archives of Internal Medicine, BMJ.

He is member of the editorial board of Current Drugs Safety, The Scientific World Journal, Journal of Gerontology & Geriatric Research, Journals of Gerontology Medical Sciences, Frontiers in Internal Medicine and Associate Editor of the European Journal of Internal Medicine

Most relevant research projects:

- PI of the project 'Development of CRiteria to assess Appropriate Medication use among Elderly complex patients: CRIME project' funded by the Italian Ministry of Health
- Investigator in the AgeD in the Home Care Project - AD-HOC, funded by the 5th Framework Programme (FP)
- Coordinator of the Services and health for elderly in long term care – SHELTER project funded by FP7
- WP leader of the Identifying best practices for care-dependent elderly by Benchmarking Costs and outcomes of Community Care - IBenC project
- WP leader in the Joint Action CHRODIS funded by the EU Health Programme 2014-2020
- WG leader in the COST on Ageism
- Investigator in the Sarcopenia and Physical Frailty in older people: multicomponent Treatment strategies SPRINT-T project funded by IMI

PUBLICATIONS

He has authored or co-authored 250 publications in peer reviewed journals.

H-index: 47

He is author of the chapter 'International Gerontology' in Hazzard's Geriatrics

Curriculum vitae Prof. Eva Topinková, MD, PhD

Department of Geriatrics, 1st Faculty of Medicine, Charles University (1. LF UK) in Prague and General University Hospital (since 2001),

Chair Department of Gerontology and Geriatrics, Institute of Postgraduate Medical Education in Prague-IPVZ (since 1997)

Education and Degrees:

Medical Faculty, Charles University, Prague, 1971-1977 (MD),

PhD Fellowship, Dpt. Biology FVL UK, Praha, 1977-1981 (PhD),

Board Certification and Medical Licence in Internal Medicine I. and II. degree 1981 and 1985

Board Certification and Medical Licence in Geriatric Medicine, 1991

Associate Professor, Internal Medicine 1996, Charles University, Prague

Full Professor, Social Medicine and Health Care Organization 2001, Charles University, Prague

Teaching and Educational Activities:

First Faculty of Medicine:

undergraduate training: geriatric medicine, health gerontology, health service organization in master medical studies, bachelor studies in nursing (geriatric nursing), ergo/physiotherapy and nutritionist (since 1992, continuing), postgraduate training courses for physicians in specialty training (geriatric medicine, internal medicine since 2011, continuing)

Institute for Postgraduate Studies in Health Care: postgraduate and continuing medical education programs in geriatric medicine (1982-) in CR and abroad (Spain, France, Italy),

Chair of Academic Board , postgradual doctoral studies “Gerontology”, Charles University Praha (2001-),
Chair of the Accreditation Committee “Geriatrics”, Ministry of Health CR (2005-2015),
Member and Chair, National Board Certification Committee for “Geriatrics”

Research Activities:

National Research Grants:

Principal Investigator grants IGA Ministry of Health CR No. 2084-3 “Geriatric Care and its Management.
”, IGA MZ CR No. 2418-2 “Evaluating Effectiveness of Geriatric Visiting Team”, No. 3541-3 “Economic and
Medico-social Aspects for Health Policy in Geriatric Care”,
co-investigator VZ UK CEZ J 13/98 1111 00001 “Brain Plasticity – theoretical and clinical aspects of
development, maturation and aging”,(2001-2003)
grant Ministry of Education CR „European Master Studies in Gerontology“ Charles Univ. Praha (2004), and
educational grant „Geriatric Medicine for Primary Care“, MIAH, USA, 2005-2007
IGA MZČR NS 10-029-4/2008 „Improving quality of prescription for seniors“ (2008-2011),
IGA MZ CR NT 13238-4/2012 „Narcolepsy – clinical course, pathophysiology, aging, commorbidities“ (2012-
2015), co-investigator
Research Program Charles University PRVOUK UK Praha, P 25/LF1/2 „Late Complications of Metabolic
Diseases“ (2012 – 2016) co-investigator

International research grants:

co-ordinator for CR in interRAI projects “Improvement of Quality of Care for the Elderly ”, “Validation of
RAI-Home Care Instrument”, “Palliative Care Instrument” , “Emergency Department Screener” (2013),
“What do we owe the elderly”, co-investigator, The Hastings Center, New York
International European research projects (co-investigator and national co-ordinator for Czech Republic)
5th Framework Programme Research and Technology Development (FP RTD) projects supported by
European Commission “The Elderly in Home Care in Europe, AD HOC”,(2000- 2003), “Cross-national
Determinants of Quality of life and Health Services for the Elderly” (CLESA), (2002-2004),
6th FP RTD “Nutrition and Aging” (NUTRI-SENEX) 2004-2006,
7th FP RTD “Increasing participation of older subjects in clinical trials” (PREDICT) 2008-2010, „A
randomized clinical trial to evaluate the effectiveness of a multi-modal intervention in older people with
type 2 diabetes on frailty and quality of life: THE MID-FRAIL STUDY“.HEALTH-F2-2012-2788003 (2012 –
2017), „Using Multidimensional Prognostic Indices (MPI) to improve the cost-effectiveness of interventions
in frail older persons with multimorbidity“ HEALTH- 2013 12 02 Executive Agency for Health and
Consumers European Commission, (2014-2017) , „Sarcopenia and Physical fRailty IN older people: multi-
component Treatment strategies- SPRINTT Project“. Inovative Medicine Initiative Joint Undertaking, Grant
115621-SPRINTT, (2014-2019)
Investigator in numerous clinical studies (phase II-IV) in the area of Alzheimer’s disease, dementia, mild
cognitive impairment, decubitus ulcer, incontinence,

Membership in Professional Associations and other Professional Activities:

Czech Medical Association Czech Society of Gerontology and Geriatrics - Board Member and Scientific
Secretary (2001-2015), vice-president (2015-), Czech Society of Internal Medicine – member (1982-),
National Coordinating Board for Disabled Persons 2003- 2004, International Association of Geriatrics and
Gerontology – European Region (IAGG-ER) Secretary General (2003-7), President, Clinical Section (2007-
2014, 2015- immediate past president), Board Member and national delegate in: Geriatric Medicine Section
UEMS, in European Union Geriatric Medicine Society (EUGMS) 2008-2012, in European network „Centers of
Excellence -GERONTONET“ in aging research, and in international research consortium „interRAI“
Chair and Vice-Chair of the Internal Grant Agency Ministry of Health CR (IGA MZ CR), Committee No.
12, 2005-7, board member 2008 ongoing), Grant Agency for Health Care Research Committee member “Age
related diseases” (2014 -)

Editorial and publication activities:

Chief Editor Czech Geriatrics Revue (2004-2010), Assoc. Editor European Geriatric Medicine (2012-)
Gerontology and Geriatrics (2012 -), member of Editorial Board Czech and Slovak Psychiatry, Postgraduate
Medicine (Czech), Aging (Italy),
Author and co-author of 18 monographies or textbooks and more than 350 articles in national/international
journals

Curriculum vitae
Assoc. Prof. Soner Dogan, MD, PhD

Dr. Soner Dogan is an Associate Professor at Yeditepe University School of Medicine in Istanbul. He has earned his Ph.D. degree at the University of Minnesota, USA. His Ph.D. thesis was on "The Effects of Sex Steroid Hormones on Intracellular Calcium Signaling Proteins in Smooth Muscle". Then, he continued his academic career as a postdoctoral research fellow at Hormel Institute Medical Research Center, USA where he studied to discover the molecular signaling link between obesity/calorie restriction and mammary tumor development using transgenic mice models and cell culture techniques. Specifically, the roles IGF-I, leptin, adiponectin and mTOR signaling molecules in breast cancer development were investigated. In addition, to improve his teaching skills Dr. Dogan taught introductory biological courses at Riverland College in Austin, MN for four years until 2012. Dr. Dogan has a faculty position as an Associate Professor at Yeditepe University Medical School in Istanbul where he has been trying to understand the roles of micro RNAs, inflammation and oxidative stress in mammary tumor prevention by calorie restriction. In recent years, his research focuses on the roles of different diet consumption style on aging and age related disease. Dr Dogan has also been teaching Medical Biology and Molecular Biology courses to Medical, Dental and Pharmacy students at Yeditepe University since 2012. Dr. Dogan is a regular reviewer for numerous international scientific journals and also panelist to evaluate grant applications for Turkish Scientific Grant Agency (TUBITAK).

Associate Professor
Yeditepe University
School of Medicine
Department of Medical Biology
Istanbul
Email: soner.dogan@yeditepe.edu.tr
Phone: 0 (216) 578-0000 (ext: 1570)
Ph.D: University of Minnesota

Title	Department/ Research Field	University	Year
Assoc. Prof.	Medical Biology	Yeditepe University	2015-
Asst. Prof.	Medical Biology	Yeditepe University	2012-2015
Visiting Scientist	Obesity and Breast Cancer Prevention	Hormel Institute Medical Research Center, University of Minnesota	2012-
Biology Faculty	Natural Science	Riverland College, Minnesota	2008-2012
Research Associate	Molecular Research on Obesity and Breast Cancer Prevention	Hormel Institute Medical Research Center, University of Minnesota	2009-2012
Postdoctoral Fellow	The effects of calorie restriction on mammary tumor development	Hormel Institute Medical Research Center, University of Minnesota	2004– 2009
Ph.D.	Medical Biology	University of Minnesota	2004
Undergraduate		Ankara University	1994

Research Interest:

My recent research area is focused on breast cancer and obesity. My lab is trying to understand the molecular mechanisms of how calorie restriction prevents or delay mammary tumor development. Specifically, we are focused on different signaling pathways such as adipokines like leptin, adiponectin and cytokines, also IGF-I, mTOR, oxidative stress, miRNA and epigenetic modifications using transgenic mammary tumor mice models, cell culture and recent molecular biology techniques.

Research Grants

- 2014-2017, TÜBİTAK 1001 Research Grant (Primary Investigator): Determining the Roles of Epigenetic Modifications of Adipokine Genes and microRNAs in the Preventive Effects of Calorie Restriction in Mammary Tumor Development in MMTV-TGF- β Mice.
- 2014-2016, TÜBİTAK 3001 Research Grant (Primary Investigator): Study of the effects of calorie restriction on oxidative stress and mammary tumor development in MMTV-TGF- β transgenic mice.

- 2015-2016, TÜBİTAK 1002 Research Grant (Primary Investigator): Determining the Roles of Pro-Inflammatory Cytokines in Prevention of Mammary Tumor Development by Calorie Restriction in MMTV-TGF- α mice.
- 2014-2016, TÜBİTAK 3001 (Co-Investigator): Spindle assembly checkpoint in chromosomal abnormalities: Evaluation of Slx5 in *Saccharomyces cerevisiae* as a chemotherapy target

Other Academic Activities

- 2013 – present TUBITAK 1001 research grant evaluation panelist
- 2012 – present Co-coordinator for 2nd year medical students (Yeditepe University)
- 2012 - present Yeditepe University Research Animals Ethic Committee Member

Book Chapters

White, T. A., Deshpande, D. A., Dogan, S., Panettieri, R. A., Walseth, T. F. and Kannan, M. S., Cyclic ADP-Ribose and NAADP Structures, Metabolism and Functions (Calcium Regulation in Smooth Muscle Through the CD38/Cyclic ADP-Ribose Pathway), Hon Cheung Lee (editor), pp. 427-450, Dordrecht:Kluwer, KLUWER ACADEMIC PUBLISHERS. ISBN 1-4020-7281-3, 2002

Awards

- 2011 Grant award from the Chancellor's office of the Minnesota State Colleges and Universities (MnSCU)
- 2011 Recipient of Professional Development Grant for Higher Education Faculty given by Education Minnesota Foundation.
- 2010 Perkins Grant, in the amount of \$10, 000 as a start of setting up cell culture unit in the biotechnology lab.
- 2007 Scholarship from AACR (American Association for Cancer research) to attend the "Pathobiology of Cancer" educational workshop, The Edward A. Smuckler Memorial Workshop. Snowmass Village Resort, CO. July 15-22, 2007
- 2007 Ksenia Shambarger Scholarship from Keystone Symposia at the Molecular Targets for Cancer meeting. Whistler Resorts, Whistler, BC, Canada, March 18-23, 2007.
- 2006 Received an AICR (American International Cancer Research) foundation scholarship to attend the conference in Washington DC, July 14-15, 2005.
- 2001-2004 Travel awards from University of Minnesota to present abstracts and/or give talks at scientific meetings

List of International Journals, Reviewer for:

- Nutrition and Cancer, International Journal
- Cancer Letters
- Endocrine-related Cancer;
- Journal of Translational Medicine ;
- GENE
- Human and Experimental Toxicology
- Malaysian Journal of Medical Sciences
- Tumor Biology

Professional Memberships

- Member of AACR (American Association for Cancer Research), 2006-present
- Member of Society for the Experimental Biology and Medicine 2003-2005
- Member of Departmental Graduate Study Committee, University of Minnesota, 2002
- Member of Society for the Study of Reproduction 1999-2005
- United State Soccer Federation, 1997- present

