



**UNIVERSITY OF MEDICINE AND
PHARMACY "GRIGORE T. POPA"
IAȘI, ROMÂNIA**

HABILITATION THESIS

COMPLEX APPROACH TO GERIATRIC PATIENTS

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REZUMAT

Numele meu este Ioana Dana Alexa și sunt profesor la disciplina de Medicină Internă, Nefrologie, Geriatrie a Universității de Medicină și Farmacie "Grigore T Popa", Iași. Experiența mea medicală însumează peste 32 de ani iar cea academică peste 28 de ani.

Sunt medic specialist în medicină internă din 1994 și medic primar în aceeași specialitate din 1998. Un an mai târziu am început a doua specialitate, Geriatrie și Gerontologie; am devenit medic specialist în 2002 și medic primar în 2008. Această experiență mi-a oferit șansa de a înființa Compartimentul de Geriatrie (2003), ulterior devenit Secția de Geriatrie (2012) la Spitalul Clinic "Dr. C. I. Parhon" Iasi, singura din Moldova.

În decembrie 1990 am intrat în învățământul superior prin concurs și în februarie 1991 am fost angajată ca asistent universitar la Disciplina de Medicină Internă a Facultății de Medicină, Universitatea de Medicină și Farmacie "Grigore T. Popa" Iasi. În cei 28 de ani de carieră didactică am parcurs toate treptele ierarhiei universitare: șef de lucrări (2000), conferențiar (2008) și profesor universitar (2015).

Prezenta lucrare oferă o privire de ansamblu asupra activității mele științifice, profesionale și academice în vederea obținerii abilitării de a coordona doctoranzi. Prezentarea este structurată în trei secțiuni, subdivizate la rândul lor în capitole, după cum urmează:

Secțiunea I reprezintă un rezumat al activității mele științifice de la începutul carierei didactice și până la obținerea titlului de profesor.

Capitolul unu reprezintă o scurtă prezentare a direcțiilor de dezvoltare pe care le-am parcurs în cariera mea academică și de dezvoltare științifică de la absolvire până în prezent.

Cel de-al **doilea capitol** este axat pe cercetarea științifică curentă în domeniul abordării multidisciplinare a pacientului vârstnic și pe contribuțiile mele în această direcție. În acest capitol sunt descrise particularitățile medicale, psihologice, sociale de care trebuie să se țină cont la primul contact cu persoana vârstnică pentru elaborarea unui plan terapeutic corect, adaptat la posibilitățile și dorințele pacientului, cu evitarea polipragmaziei și iatrogeniei. Capitolul prezintă cărțile și capitolele de carte, articolele și studiile clinice elaborate în acest domeniu în ultimii 10 ani, cu prezentarea pe larg a unui studiu realizat în 2014 pe un eșantion populațional din nord-estul României și care a evaluat impactul auto-medicației asupra contingentului vârstnic din aceasta regiune. Lucrarea este printre foarte puținele de acest gen în țara noastră.

Capitolul trei prezintă contribuțiile mele în domeniul studiului fragilității la populația vârstnică. Capitolul prezintă preocupările mele și ale echipei de medici geriatrici pe care o conduc în domeniul fragilității fizice - cu prezentarea unui studiu ce evaluează rolul agenților oxidativi în procesul de îmbătrânire, fragilitatea psihică și relația acesteia cu calitatea vieții vârstnicului precum și asupra metodelor de determinare și cuantificare a fragilității, sarcopeniei și stării de nutriție.

Capitolul patru trece în revistă preocupările mele în domeniul iatrogeniei în general și în mod deosebit asupra impactului iatrogeniei în geriatrie. Sunt prezentate pe larg modul în care persoana vârstnică reprezintă candidatul preferat al iatrogeniei precum și modul în care iatrogenia poate afecta direct bunele rezultate așteptate de la o schemă terapeutică prescrisă cu cele mai bune intenții. Sunt prezentate numeroasele contribuții aduse de-a lungul anilor în acest domeniu, reprezentate de cărți și capitole de carte, articole și studii. Sunt prezentate pe larg mai multe studii care prezintă cauzele necompliancei terapeutice în diverse categorii de pacienți vârstnici internați în spital, cu polipatologie și iatrogenie.

Capitolul cinci prezintă contribuțiile mele în domeniul studiului problemelor de etică ce apar la persoanele vârstnice și a organizării serviciilor de asistență socială necesare îngrijirii acestora. Sunt prezentate în detaliu două proiecte de cercetare realizate împreună cu echipa de psihologi de la Asociația "Psittera" condusă de prof. dr. Ovidiu Gavrilovici, Facultatea de

Psihologie a Universității "A. I. Cuza" Iași și care au avut drept scop identificarea abuzului psihologic la persoana vârstnică, metodele de soluționare a acesteia și căile de promovare a unei bătrâneți cu demnitate. Este prezentat pe larg un alt proiect realizat între departamentele de geriatrie din trei țări europene și care a avut drept scop identificarea auto-neglijării la vârstnic, cauzele și posibilitățile de rezolvare a acesteia. O mențiune specială se acordă studiilor noastre asupra consimțământului informat al persoanei vârstnice și particularitățile întâlnite, mai ales în cazul tulburărilor cognitive.

Capitolul șase prezintă rezultatele preocupărilor echipei de geriatrie în domeniul gerontotehnologiei, rezultate obținute împreună cu echipa de ingineri și biofizicieni - condusă de prof. dr. Hariton Costin de la Facultatea de Bioinginerie a Universității de Medicină și Farmacie "Grigore T. Popa" - și echipa de fizicieni - condusă de prof. dr. Gabriel Bozomitu, Facultatea de Electronică, Telecomunicații și Tehnologia Informației, Universitatea Tehnică "Gheorghe Asachi" Iasi. Sunt prezentate pe larg rezultatele obținute la 2 granturi naționale care au avut drept obiectiv realizarea de sisteme de monitorizare la domiciliu a parametrilor vitali la persoanele vârstnice și de asistență medicală la persoanele cu dizabilități.

Secțiunea II descrie proiectele viitoare pe care intenționez să le întreprind pe plan academic, profesional și de cercetare. Din punct de vedere didactic, sunt prezentate principalele direcții de dezvoltare în ceea ce privește colaborarea cu studenții, rezidenții și tinerii medici care își desăvârșesc pregătirea în cadrul Clinicii de Geriatrie. Din punct de vedere științific, prezint principalele direcții de cercetare pe care intenționez să le dezvolt în continuare în colaborare cu colegii mei de disciplină.

Secțiunea III enumeră cele mai relevante referințe bibliografice utilizate în elaborarea prezentei teze de abilitare.

SUMMARY

My name is Ioana Dana Alexa, MD, PhD, Professor in the Department of Internal Medicine, Nephrology and Geriatrics at the University of Medicine and Pharmacy "Grigore T Popa", Iași, with a medical experience in the field of internal medicine and geriatric health care of over 32 years and an academic experience of 28 years.

I became specialist in Internal Medicine in 1994 and senior specialist in 1998. One year later I chose as second specialty Geriatrics and Gerontology; I became specialist in 2002 and senior specialist in 2008. This experience gave me the possibility to organize and lead the new Compartment of Geriatrics (2003), then upgrade to Clinic of Geriatrics (2012) at the "Dr. C. I. Parhon" Hospital.

In February 1991 I gained by competition my first university position - assistant in Internal Medicine at the University of Medicine and Pharmacy "Grigore T. Popa" Iasi. Ever since I have won all the academic positions, the last being in 2015 as Professor.

This work represents my habilitation thesis to get an empowerment of leading PhD students. It is structured in three sections, subdivided into chapters, as follows:

Section I represents a summary of scientific activity from the beginning of my medical and teaching career until accreditation for the title of University Professor.

The first chapter represents a brief introduction that outlines the development of my career from graduation until now.

The second chapter reviews my most significant contributions in the domain of multidisciplinary approach for geriatric patients. This chapter goes into details about the medical, psychological, and social particularities of senior patients that should be considered when deciding about therapy. Conceiving a tailored treatment for each and every senior patient is a big challenge for the geriatric team because it should respond to all medical problems while avoiding polypharmacy and iatrogeny. My team and I have had a vast activity in this domain, and I present some of our most important studies and projects that we had done in the last ten years. I present in detail a study performed in 2014 on a large group of patients from the North-Eastern part of Romania that evaluated the impact of self-medication on the senior population. This paper still remains one of the very few in this field.

Chapter three reviews my most significant contributions in the domain of fragility and its impact over senior population. I present two studies performed by our geriatric team: one study looked into the role of oxidative stress in the process of ageing and the degree of physical frailty, and the other studied the best methods we should use in order to assess frailty, sarcopenia, and nutritional state in the senior population.

Chapter four presents my long-term preoccupations in the field of iatrogeny and the impact of iatrogeny in the senior population. I consider that elders represent the ideal candidates for iatrogeny due to their particularities, due to the presence of concomitant diseases and polypharmacy, the increased risk for non-compliance to medical recommendations. I present my vast experience in the domain as it represents my main interest for the last 20 years, emphasizing on our interest in non-compliance to medical recommendations. I discuss furthermore on the possibilities physicians have in order to identify and fight the causes for iatrogeny that are more frequently found in the senior population.

Chapter five reviews my contributions in the domain of ethical problems and social services provided for elderly patients. I present two projects performed together with the psychological team from "Psiterra" Association, and lead by Professor Ovidiu Gavrilovici from the Faculty of Psychology, University "A. I. Cuza" Iasi. These projects aimed to identify and solve the problem of psychological abuse in senior population and, based on this information, to generate simple rules in order to facilitate a dignified ageing for everyone. I present another ambitious project performed in this area of interest, that studied the problem of self-neglect in

three different European countries – the causes and the possibilities to solve them for the elderly patients admitted in our Geriatric Clinic. I also present my experience in the study of the role of obtaining the informed consent of the elders with and without cognitive disorders.

Chapter six presents the contributions of our geriatric team in the domain of Gerontechnology. We worked with two great teams, one formed mainly by engineers and biophysicists and lead by Professor Hariton Costin from the Faculty of Bioengineering, University of Medicine and Pharmacy “Grigore T. Popa” Iasi, and the second team lead by Professor Gabriel Bozomitu from Faculty of Electronics, Telecommunications and Information Technology, “Gheorghe Asachi” Technical University Iasi. We were together in two national grants that studied the possibilities at hand to use electronic systems in order to monitor vital parameters in senior persons at distance and to assist senior patients with disabilities.

Section II describes my future projects in the academic, professional and research field. From the didactic point of view, I present the development directions regarding the partnership with the students, residents or training physicians that is taking place in the Geriatric Clinic. In the research domain, I present the main scientific directions that I plan to expand together with my younger colleagues.

Section III includes the selected bibliographic references that I considered suitable, pertinent and useful in the elaboration of this material.

SECTION I. SCIENTIFIC, PROFESSIONAL AND ACADEMIC ACHIEVEMENTS

1. INTRODUCTION

I have a professional experience that covers 32 years of medical profession and 27 years of academic activity - beginning with February 1991, date on which I have won my first university position - assistant - through competition at the vast discipline of "Internal Medicine" at the "Grigore T. Popa" University, Iași. Ever since I have double responsibilities, in health care and in academic areas, as a Senior Specialist in Internal Medicine and later as Senior Specialist in Geriatrics and Gerontology, Chief of Geriatric Clinic in "Dr. C. I. Parhon" Hospital and as Professor at the Faculty of Medicine, Discipline of Internal Medicine, Nephrology and Geriatrics, second Medical Department of the "Grigore T. Popa" University of Medicine and Pharmacy of Iași.

I graduated from the University of Medicine and Pharmacy „Grigore T. Popa” Iași in 1986 with maximum grade, and then I trained for 3 years as an intern of the PublicHealthAdministrationHospitalIași, as were the rules at that time. It was very good medical experience as I worked in 6 different specialties, which prepared me for my next step - General Practitioner at Medical Dispensary of Ungheni, Iași District, Romania, where I worked for 2 years. That was a completely new but excellent experience because it gave me the possibility to get out of the hospital environment and work in a rural area - a different way to solve medical problems.

In 1991 I participated at the national residency examination and was admitted as medical resident in Internal Medicine. The same year I participated in the contest for the position of Assistant in the Internal Medicine Department, Faculty of Medicine, University of Medicine and Pharmacy „Grigore T. Popa” Iași, Romania. From this period on my professional life developed as a highly stimulating mixture between medical and academic training.

In 1994 I became specialist in Internal Medicine, and the same year I was admitted for doctoral studies in Professor Victor Tacu study group. Since 1997 I am PhD in Medicine, my thesis „Pregnancy-induced hypertension – new insights concerning pathophysiology and clinico-biological aspects” was presented publicly and I obtained my PhD Diploma - OM 5374/20.11.1997. The theme of my PhD thesis was a real challenge at the time, as very little research was conducted and was available in our libraries. It was also a medical concern for several specialties, including Internal Medicine, Obstetrics, and Nephrology. That gave me a huge opportunity to learn and understand the multidisciplinary approach of a patient, knowledge that I will expand and develop my entire medical carrier.

During my period of preparing my PhD thesis I benefit from a three months TEMPUS mobility grant followed by a 12 months fellowship offered by the Romanian Ministry of Education at the Institute of Urology & Nephrology, Division of Nephrology, Middlesex Hospital, London, UK, under the supervision of Professor Guy Neild, MD, FRCP. This 15 months' period was beneficial for my medical and academic training. I was involved in the medical work of the Nephrology Clinic and also in Professor Neild's activities in Renal Transplantation. During my fellowship I had academic activity as well, being invited to have Nephrology classes at Hammersmith Hospital Diploma Course Students in London.

I was also allowed to participate at the medical rounds in the Obstetrics Clinic, which gave me the opportunity to talk and consult pregnant women with different pregnancy

problems, including hypertension and even pre-eclampsia. This activity gave me the opportunity to start a research project based on my PhD theme, concerning the study of the plasma compounds in normal pregnancies compared to eclamptic pregnancies. In the fulfilment of this project I was helped by an excellent researcher, Peta Foxall who, at the time was greatly interested in the performances of ^1H - MRI spectroscopy in determining different compounds of serum and red blood cells.

Together we studied the possible role of nuclear magnetic resonance spectroscopy in the diagnosis of modifications of lipids and the oxidative stress in red blood cell during pre-eclampsia. The modifications we discovered were communicated at the Society of Gynaecological Investigation in 1997 and were the topic of several papers published in the following years that were greatly appreciated by the number of citations we recorded afterwards.

This project gave me the possibility to deepen my knowledge regarding oxidative stress and its negative effects in all the biological systems, which offered me a large area of other projects in the domain. The theme of my PhD thesis was the starting point for a book centred on hypertensive diseases in pregnancy.

I became Senior Specialist in Internal Medicine in 1998, and in 2001 I became Lecturer in Internal Medicine, continuing the symbiosis between medical and academic activity.

During my activity in the Internal Medicine Clinic I became more and more interested in the particularities of treating elderly people. This is why I started my second medical specialty in Geriatrics and Gerontology and in 2002 I became Specialist in Geriatry and Gerontology and in 2007 Senior Specialist in the same medical field.

From 2002 till present my medical career was based on both specialties, which gave a better understanding of therapeutic approach of geriatric population; my previous training helped me better understand and apply the multidisciplinary approach of these patients.

In 2004 Geriatrics becomes part of the university curricula for students and nurses at the University of Medicine and Pharmacy “Grigore T. Popa” Iași and I became Head of the Geriatric Department at the University of Medicine and Pharmacy “Grigore T. Popa” Iași.

In 2004 the Geriatric Compartment at the “Dr. C. I. Parhon” Hospital was created, the first such medical facility to treat emergencies of elderly patients in Moldova county, Romania (20 beds). I was Head of the Compartment till 2011, when we gained more beds and became Geriatric Clinic, the only one in Moldova County, Romania. I am Head of the Geriatric Clinic ever since.

My academic career developed at the same pace as my medical achievements. In the period 2001 - 2007 I was Lecturer in Internal Medicine in the Department of Internal Medicine, Nephrology and Geriatry at the Faculty of Medicine, University of Medicine and Pharmacy “Grigore T. Popa” Iași. In 2007 I became Assistant Professor and in 2015 I was confirmed as Professor in the same department, concluding all the steps for building a university career.

I have had the opportunity to experience each of the teaching positions one at a time, from Assistant Professor to Professor, and that led to the development of a powerful ability to interact with students and residents in practical classes, in lectures and during research activity. I have permanently strived to upgrade and improve the teaching methods. Interactive teaching has and will always be an essential part of my relationship with the students, and their appreciation of my methods has always been reflected in the annual performance feed-back given by the students (highest appreciation).

In over 27 years of teaching, I believe I have shown a constant interest in sharing my experience and knowledge with the residents and trainees. My career as a physician in Internal Medicine and Geriatrics was developed side by side with my experience as a teacher. This has helped me in forming a connection based on respect and mutual trust with students, residents and young researchers I have encountered throughout the years.

As a result of this connection, I have always been involved in student manifestations, both as a moderator and as coordinator for those interested in my field of research.

My teaching interest focuses as well on the post university segment, being lecturer at several courses of continuous medical education dealing with different specialties and interdisciplinary themes presented in various university centres from Romania and which were attended by a large number of residents and young specialists.

The interest in teaching the young generation materialized in the publication of numerous manuals and medical books. These volumes express my interest in several medical domains, such as: internal medicine, geriatrics and gerontology, iatrogenic problems, and they were highly appreciated by students and residents because the information was presented in a clear, attractive and concise manner.

In 2000 I published the book "Prezentari de cazuri - medicina interna" (Case Presentations in Internal Medicine), my first book entirely dedicated to students and residents in Internal Medicine and other medical specialties. At that moment it was the first to discuss the steps to go for a good case presentation, necessary for all students and residents in all exams in their medical and academic career. I believe it was written at the right time, because I had numerous positive feed-backs about this book over the years.

One of my most well received book is *Medicina Interna - notiuni de baza*" (Internal Medicine – basic notions), Ed. Junimea, 2004, ISBN 973-37-0952-2. It was especially written for medical nurses, to accommodate them with the basic notions of Internal Medicine. I received many positive feed-backs, including from my very own medical staff, for the very clear, synthetic way of presenting the main medical diseases and their therapeutical approach.

In the same period my interest in Geriatrics and Gerontology began to manifest, and my activities slowly began to concentrate on this field more than others. Even if Geriatry was not a new specialty in Romania, the level of information about the particularities of practicing medicine in senior population was quite low. This was the reason why in 2006 I started a medical course entitled "Emergencies in Geriatry", which was approved and supported by the Medical College Iasi, and was addressed to General Practitioners in Romania. I had had cycles of such courses in several counties of Romania: Iasi, Constanta, Bacău, Onesti, TârguNeamt, with very favourable feed-backs.

Ever since 2004, when Geriatry becomes part of the university curricula for students and nurses I published several books of Geriatry for students, nurses and residents:

In 2005 I published my first Textbook of Geriatry destined for nurses and medical students, and in 2006 I wrote a second edition, with more information in this rapidly developing domain. In 2012 appeared the French version of my course in Geriatry, addressed to students and residents alike.

Another important part of my teaching activity is the constant preoccupation in residency program. Since 2007 I have been the coordinator of the residency program in Geriatrics and Gerontology and thus, I have coordinated the activity of all our geriatric residents throughout their residency, taking good care of respecting the curricula, helping them with finding fellowships abroad in order to broadening their knowledge and recommending them for jobs anytime I could after finishing residency and becoming specialists. I must say that more than 70% of my specialists in Geriatrics and Gerontology work now all-around Europe, being esteemed doctors in Geriatric hospitals and private clinics.

I am also in charge with the coordination of the Internal Medicine curricula of all medical specialties, such as: Neurology, Oncology, Cardiology, Rheumatology, Infectious Diseases, etc. The challenge is to approach every specialty, theoretically and practically so that it would complete the knowledge they must have at the end of their residency. It is with great passion and interest that I am preparing their courses, as they should be slightly different one from the other, depending on the group of specialties I am addressing to. I am also supervising their

practical activities, so that, at the end of the Internal Medicine module, they can deal with every day medical problems by themselves.

I am constantly in touch with my former residents, discussing difficult cases or sharing experience, things that give me immense satisfactions and constant challenges that help me keep up-to-date with the latest progresses in my specialty and keep an open mind at all times.

One of my most important goals over the last 10 years is to broaden my research areas by building interdisciplinary teams with different other medical disciplines.

An important and long-lived such relationship is with the Orthopaedic Team. This mutual interest is based on our preoccupation for a better therapeutic approach of senior patients with multiple concomitant diseases and fractures or in need of major orthopaedic surgery. The pre- and post-operative period of care and the recovery, both physical and psychological, of the patient were the subject of many papers that were either published or communicated to national and international congresses over the years.

Another long-standing relationship is with the Physics Team, Professor Hariton Costin and Professor Gabriel Bozomitu; we had great projects together and I hope we shall continue our researches in the domain of Gerontotechnology.

Last, but not least, I would like to mention our team work with Psychology team, Professor Ovidiu Gavrilovici and Psiterra team; we developed great work in the abuse field toward the senior population.

My career has followed several main directions of concern and scientific activity, and my Habilitation Thesis briefly presents them.

2. MULTIDISCIPLINARY APPROACH FOR GERIATRIC PATIENTS

2.1. GERIATRICS AND THE PHYSIOLOGICAL AGING PROCESS

Population aging is a global phenomenon that affects all countries in recent decades all over the world. The overall decrement of birth rate and the constantly increasing number of elderly population are leading to a different balance between generations. This is a long-term phenomenon. In the last century the share of elderly in the total population structure has been growing, tendency that will remain and will be aggravated in the XXI century. If in 1950 the percent of elderly in the world was 8%, by 2050 this percentage will increase to 22% of the total population of the globe. In 2050, it is estimated that one of five people will be over 60 years of age. Moreover, people aged over 80 represent 13% of the population over 60 years old; in industrialized countries, the value of this indicator will increase by 2050 from 19% to 29% (1). This process is an important indicator of the social and medical progress, increment of quality of life and social protection, and reduced mortality with an increasing life expectancy (2).

During the last century the proportion of older people in general population increased constantly all over the world, including in Romania. This phenomenon raises the problem of adapting health care approach for this segment of population to their distinct ethical issues (3). World Health Organization considers as "older people" persons aged 65 years and over. They represented a little bit more than 10% of total Romanian population in 1990, i.e. nearly 1 in 10 persons was beyond the accepted limit between adults and older people. Estimation for 2008 was 15%, i.e. 1 in 7 persons, but according to 2011 National Census, a total of 16.1% people were beyond the age of 65 years and 1.3% of entire population was older than 85 years. That means over 1% increase during the last three years before census. It seems to be a very high rate, but one needs to take into account that over two million of younger generations emigrated from Romania to various countries, mostly in Europe, during the last decades. This resulted into a relative imbalance in the process of demographic ageing, especially in rural areas where older people became much more prevalent as compared to urban areas. Moreover, a demographic characteristic of Romania is a very high prevalence of rural population as compared to other European countries: almost 46%. An important aspect that contributed to growing prevalence of older persons in Romania was the increased life expectancy from around 70 years in 2000 to 74.51 years in 2011, with a difference between the two genders: 78 years for women and 71 years for men (4).

Geriatrics is the branch of medicine that focuses on health care of the elderly; it aims to promote health and to prevent and treat diseases and disabilities in senior patients. The geriatric team aims to treat the disease (most of the cases multiple concomitant diseases) and to decrease the effects of aging on the body. Years of training and experience, above and beyond basic medical training, go into recognizing the difference between what is normal aging and what is in fact pathological (5).

In the United States, geriatricians are primary care physicians who are board-certified in either family medicine or internal medicine and who have also acquired the additional training necessary to obtain the Certificate of Added Qualifications (CAQ) in geriatric medicine. In the United Kingdom, most geriatricians are hospital physicians, while some focus on community geriatrics. In contrast to the United States, geriatric medicine is a major specialty in the United Kingdom; geriatricians are the single most numerous internal medicine specialists (6).

Geriatrics differs from adult medicine in many respects. The body of an elderly person is substantially different physiologically from that of an adult. Old age is the period of manifestation of decline of the various organ systems in the body. The decline in physiological

reserve in organs makes the elderly develop diseases and be liable to complications from mild problems when comparing with adult population. Functional ability, independence and quality of life issues are of greater concern to geriatricians, perhaps, than to adult physicians (7).

A major difference between Geriatrics and adult medicine is that elderly persons sometimes cannot make decisions for themselves. The issues of power of attorney, privacy, legal responsibility, advanced directives and informed consent must always be considered in geriatric procedure. Elder abuse is also a major concern in this age group. In a sense, geriatricians often have to "treat" the caregivers and sometimes, the family, rather than just the elder. The caregivers are either family members or various professionals that provide medico-social services for older people. It is important to note that elderly women have more and more often as caregivers their own daughters that are old themselves and suffering from one or more chronic conditions (6, 7).

Ageing, although irreversible and affecting each and every human being, continues to be subject to a number of very little understood or even unknown factors and phenomena. Due to a constant growth in the global population and, specifically, in the older population, a more comprehensive understanding of ageing is a must in order to be able to implement measures for ensuring and maintaining a successfully active ageing proportionate with societal expectations. This is a key pre-requisite for a better functioning society, given that the maintenance of quality of life in the ageing population requires increasingly massive costs, most particularly in relation to those persons suffering from pathological ageing associated with numerous comorbidities and disabilities (8).

Furthermore, while medical scientific literature approaches quite substantially the phenomena of ageing, most of it, however, only addresses the subject from the molecular and genetic perspective that is specific to certain organs and system. Only very little of it addresses the risk factors that lead to premature ageing on a global level.

There is a lack of a comprehensive definition for ageing because the process can be looked at and characterized from various perspectives, such as socially, psychologically, morphologically, from the cellular/molecular perspective, etc. The closest definition that relates to the biological reality postulates ageing as a functional, progressive and generalized impairment, resulting in loss of adaptive capacity to stress, loss of mobility and an increase in morbidity risk (9).

Ageing is characterized by the failure to maintain homeostasis under conditions of biological stress and is associated with decreased viability and increased vulnerability of the organism. The changes occurring during ageing are universally met by all species; they are degenerative, progressive and intrinsic.

The paper:

Alexa ID. The challenge of managing the elderly patient. <i>Journal of Aging and Geriatric Medicine</i> , Editorial, 2017.
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underlines the need for individual-centred and a global, multidimensional approach while providing medico-social services for senior people; it is very important to use several screening tools for a holistic evaluation of several problems: vision, hearing, continence, cognition, mood, mobility, equilibrium and risk of falls, nutrition and physical disability. When investigating functional status of an older person there are several dimensions that have to be addressed: medical, cognitive, affective, environmental, economic, social support, oral health and spirituality (10). All interact and influence each other and each contributes to the functional status of an older subject.

The distinguishing marks associated with old age comprise both physical and mental characteristics. The marks of old age are so unlike the marks of middle age that it has been suggested that, as an individual transition into old age, he/she might well be thought of as different persons “time-sharing” the same identity.

These marks do not occur at the same chronological age for everyone. Also, they occur at different rates and order for different people. Because each person is unique, marks of old age vary between people, even those of the same chronological age.

A basic mark of old age that affects both body and mind is “slowness of behaviour.” This “slowing down principle” finds a correlation between advancing age and slowness of reaction and task performance, both physical and mental (10).

My personal experience in approaching the geriatric patient led to the establishment of the following markers used in their general organic and functional evaluation:

A. Physical marks of old age include the following:

- Multiple chronic diseases; in 2007-2009, the most frequently occurring conditions among older persons in the United States were uncontrolled hypertension (34%), diagnosed arthritis (50%), and heart disease (32%). Managing such situations without inducing iatrogenic effects proves to be a challenge.
- *Cardiovascular disorders* are the leading causes for hospitalization in very old patients: heart insufficiency, hypertension and acute myocardial infarction, not to forget orthostatic hypotension, usually iatrogenic-induced.
- *Digestive disorders* such as difficulty in swallowing, inability to eat enough and to absorb nutrition, constipation and bleeding; this will be associated frequently with malnutrition, diminution of immune system and inadequate response to stress, that will lead to disability and frailty.
- *Diminished eyesight* will make it more difficult to read in low lighting and in smaller print; we should also remember this detail while prescribing drugs.
- *Falls* - every year, about one-third of those 65 years + and over half of those 80 years + fall; falls are the leading cause of injury and death for old people, a loss of confidence and a fear of falling that will lead to a deterioration of functioning in daily life and to social isolation.
- *Hearing impairment* - by age 75 years +, 48% of men and 37% of women encounter impairments in hearing that will make talking to them difficult and tiring.
- *Pain* afflicts old people at least 25% of the time, increasing with age up to 80% for those in nursing homes; often, pain is unrecognized, misdiagnosed and untreated and, unfortunately, has a high impact on quality of life, and on physical, cognitive and social functioning. Pain induces distress, sadness, fear, depression and loss of control, but, due to comorbidities, drug interactions and increased sensitivity for side-effects of analgesic drugs, pharmacologic treatment of pain can be difficult and disappointing.
- *Urinary incontinence* is one of the giants of geriatric medicine, and the management of the underlying disorders is often neglected. It is both a marker of dependency, of poorer health and also leads to an increased likelihood of institutionalization.

B. Mental marks of old age include the following:

- *Sleep trouble* holds a chronic prevalence of over 50% in old age and results in lower sleep efficiency and daytime sleepiness; these chronic sleep disturbances induce poorer daytime functioning and different degrees of depression. Insomnia can be part of a sleep disorder but in the very old patients it can be more usually a symptom associated with another condition, or related to behavioural, environmental or pharmacological factors; identification of the causes of insomnia are therefore central to patient management as it

can have serious consequences including an increased risk of falls and cognitive impairment.

- *Depressed mood* is the most frequent cause of emotional suffering; it decreases the quality of life and increases functional decline and, when severe, is associated with a shortened life expectancy
- *Dementia*, including Alzheimer's disease is characterized by progressive cognitive and behavioural deficits associated with significant morbidity, disability and mortality; the devastation of dementia affects both the patient and the caregivers, and involve physical, socioeconomic, psychological, functional and quality of life aspects.

Based on how and to which extent aging affects the organism, it may result in a physiologically harmonious ageing within due correlation of the biological and the chronological age. During physiological ageing, the organism maintains its capacity for low risk of disease and disability, a functionally superior physical and mental capacity and even the continuation of a strong motivation to live. However, one must also consider the rather frequent pathological or non-physiological ageing, featuring:

- Premature ageing, i.e. early specific phenomena associated with ageing, resulting in a biological age corresponding to a more advanced chronological age than in normal real life;
- Accelerated ageing, when the rhythm of ageing suffers an increase in speed, most frequently after a significant physical or psychological stress.

Changes occur at organism level secondary to ageing, either in the context of primary ageing (i.e. a result of the interactions between genetic, intrinsic factors with extrinsic environmental and way of life factors) or in the context of secondary ageing, which is defined as an adaptive modification to the changes of primary ageing. The latter is principally dealt with at the psychological level and should not be interfered upon.

Therefore, ageing should be addressed by actions on either the intrinsic factors or the extrinsic ones. There are multiple genetic factors from mitochondrial ones, to factors that imply telomeres, to the production of free radicals, the compounds of advanced glycosylation etc.

With multiple coexisting chronic diseases, it becomes difficult, and often impossible, to assess the severity or manifestations of individual diseases and to ascribe health and functional status to specific disease process. Many distressing symptoms, such as pain, fatigue, dizziness, sleep problems, sensory impairment, may be the result of the accumulated effect of multiple external factors related to the elderly social condition. Approaching the elderly patient with multiple health problems should be the result of team work of different specialists who should work together in order to achieve the best goal with less iatrogenic effects (10).

2.2. THERAPEUTICAL APPROACH TO VERY OLD PATIENTS

In the industrialized countries, life expectancy and, thus, the old age population have increased consistently over the last decades. In the United States the proportion of people aged 65 or older increased from 4% in 1900 to about 12% in 2000. In 1900, only about 3 million of the nation's citizens were 65 or older (out of 76 million total American citizens). By 2000, the number of senior citizens had increased to about 35 million (of 280 million US citizens). Population experts estimate that more than 50 million Americans—about 17 percent of the population—will be 65 or older in 2020. By 2050, it is projected that at least 400,000 Americans will be 100 or older (11).

The increase of life expectancy has resulted in increased proportion of individuals reaching the eighth and ninth decade of life. Individuals 80 years + are consistently found to be

the fastest growing segment of the population. There is a disproportionate life advantage favouring woman over men that has created a progressive feminization of the older population. According to Erik Erikson's "Eight Stages of Life" theory, the human personality is developed in a series of eight stages that take place from the time of birth and continue on throughout an individual's complete life. He characterizes old age as a period of "Integrity vs. Despair", during which a person focuses on reflecting back on his life. Those who are unsuccessful during this phase will feel that their life has been wasted and will experience many regrets. The individual will be left with feelings of bitterness and despair. Those who feel proud of their accomplishments will feel a sense of integrity (12).

Successfully completing this phase means looking back with few regrets and a general feeling of satisfaction. These individuals will attain wisdom, even when confronting death. Coping is a very important skill needed in the aging process to move forward with life and not be 'stuck' in the past. The way a person adapts and copes, reflects his aging process on a psycho-social level.

Elderhood was proposed by Joan Erikson as the ninth stage of life and it refers to those individuals who live past the life expectancy of their birth cohorts. There are two different types of people described in this stage of life. The "young old" are the healthy individuals who can function on their own without assistance and can complete their daily tasks independently. The "old old" are those who depend on specific services due to declining health or diseases (13).

The first contact between a senior patient with the medical staff, be it a GP or a physician from various specialties to which the patient is sent for inter-clinical examinations, is totally different from the other age categories. Carrying out the anamnesis and clinical exam on senior patients can prove difficult in case of frail and/or very old people; sometimes, it is necessary to fill in the information after speaking with the family or the person that takes care of the patient (for institutionalized seniors) and even under these circumstances, the anamnesis might not provide the expected information. There are situations when the personal history and objective examination cannot be carried out simultaneously due to the advanced stage of tiredness or exhaustion of the patient (7).

There are many differences between approaching an adult and a senior patient; my experience in this domain helped me to configure them as follows:

The first contact with the senior patient shall be conducted while considering the following elements:

- subjective accuses are numerous and varied, which makes it difficult to establish the underlying disease
- the existence of some sensorial disturbances (sight, hearing) hinders communication
- the perspective of the elder towards elements natural in the aging process might conceal manifestations of the underlying condition:
 - constipation, as a revelatory element in the digestive tract neoplasm
 - joint pain, as an onset sign in the gout or the multiple myeloma
 - decrease of memorizing ability, as an onset sign in the vascular dementia or Alzheimer
- the symptoms of diseases might differ from the ones described by the younger patients
 - angina pains are less frequent, due to the reduced physical effort and can be replaced by "angina equivalents": dyspnea, tachycardia
- anamnesis is carried out by discussing with the patient, since he is the one who can relate the events he is embarrassed by; the presence of the family is necessary only if the elder shows cognitive disorders which impend the disease history.

The personal history of the patient can be conducted by the physician through questions that include general symptoms and complaints, but only if we discuss with a cooperative elder,

who can provide useful data for establishing the diagnosis. When the provided data is insufficient, inconclusive and incomplete, the physician shall get in touch with the family in order to fill in the information, especially in what concerns treatment administration at home.

The first contact with the elder is very important due to several characteristics of presentation of diseases in old age. Firstly, illnesses are paucisymptomatic and/or have a silent manifestation or may have atypical clinical presentation. It is quite frequent to find out that the acute condition of a specific organ will manifest elsewhere, at a site of minimal resistance.

Another important aspect that raises several ethical problems is the fact that there are still physicians that would consider certain symptoms and signs in older people to be "normal" and due only to advanced age. These characteristics will often be a source for discrimination based solely on chronological age, frequently an adequate medical service being denied since the manifestations are considered "normal" and not amenable to any intervention.

The interview of an old patient should be managed with care and patience; usually, if you ask the patient about everyday concerns and social circumstances you could find out information about one's psychology. It will help orient and guide the interview if you ask him to describe a typical day - it may reveal more than focusing only on the main complaint and it will give information about quality of life, liveliness of thought, and physical independence. This approach is very important especially during the first meeting because it is important to establish a good relationship with the patient: it will help you to communicate with him and the family members and to obtain adherence with treatment.

If the patient follows a medical treatment at home, the administered doses, schedule, tolerance and adherence to the treatment shall be checked; also, a list including the topical medications (for example, eye drops, ointments) and those issued without a medical prescription and which could interfere with the rest of the medication shall be drawn-up (for example, diuretic tea).

The physician shall test the ability of the elder to memorize the prescribed drugs, to read the administration instructions, unbox the packs and foils with medicines, recognize each of the drugs and know the purpose of administration. In case the patient cannot administrate the medication by himself, it is required to get hold of the person responsible of the elder: be it family member, caretaker, social worker, and shall check whether he knows the therapeutic instructions.

The physician shall know in detail the lifestyle of the senior patient:

- diet: whether he has a specific diet (low-sodium, low-fat, low-sugar)
- eating habits
- incomes allotted to food
- means of procurement and preparation (distance to the market, grocery store, access to kitchen, rate of kitchen use etc.)
- consumption of alcohol and/or coffee
- smoker status
- daily physical effort
- conditions of living (number of rooms, distance to the kitchen, restroom, level of ventilation, heating, lighting)
- marital status.

All this information will be of great help to build a tailored treatment, perfect adapted to the personality and habits of the patients, which would ensure the best therapeutical adherence and quality of life.

A precious help in collecting all of this information can be obtained when requiring the elder to speak about the way in which a regular day of his life goes; the physician will be able to ask questions in order to complete the history and the patient shall gain a sense of comfort in his presence.

Physical examination:

- the assessment of the nutrition status shall be carried out by assisted weighing and measuring of the patient (risk of fall) and calculation of the Body Mass Index; this data can be inaccurate, because aging determines height drop and the modification of the report between the muscle mass and the water mass
 - measuring the length of the arm provides data about the initial waist of the patient, which allows an accurate calculation of the BMI
 - measuring the pre-sternal cutaneous fold provides better data about the water level than doing it in the triceps.
- the osteoarticular system shall be carefully and gently evaluated (most of the elders suffer from rheumatic pain or osteoporosis), by writing down any elements that might interfere or conceal the development of some conditions that the patient either ignores or does not treat them as he should; for example, the simultaneous presence of pain irradiating from the spine and angina pain can lead to:
 - angina pain exaggeration - constant pain, which does not respond to the administration of nitroglycerine, occurs when resting and can be wrongly interpreted as an unstable angina or even acute myocardial infarction
 - angina pain takes the “second place” - silent ischemia is more frequent in elders than in other age categories
- evaluation of the cardiovascular system:
 - the apex of the heart might seem moved down and to the left in people suffering from kyphoscoliosis
 - auscultation usually reveals a pluri-orifice systolic murmur, due to atherosclerotic aortic stenosis in most of the cases, which might not be hemodynamically significant; however, if the murmur irradiates on the carotid arteries, one should require an echocardiography and vascular Doppler examination
 - decrease of heart rate under 60 beats/min is frequently encountered and well-tolerated, but must be investigated by means of EKG
 - blood pressure and pulse shall be measured in both arms; blood pressure shall be measured at least 3 times and an average of the obtained values shall be carried out
 - vascular system examination shall be carried out meticulously:
 - presence of bulky varices can be the cause of orthostatic hypotension and syncope
 - presence of the post-thrombotic syndrome indicates important modifications of the deep venous system and risk of pulmonary thromboembolism
 - presence of varicose ulcer requires careful long-term treatment, as well as an adequate education of the patient
 - the peripheral arteries shall be carefully examined and in patients with high vascular risk (big smokers) an oscillometry shall be carried out; the presence of peripheral arterial disease stresses out a pluri-arterial damage and triggers the investigation of ischemic heart disease (effort test, Holter EKG monitoring) and ischemic nephropathy (renal screen test, captopril test)
- evaluation of the neurological and psychiatric status should comprise the motor and cognitive functions
- evaluation of the functional and homeostatic status of the elder (frailty, sarcopenia, hepatic and renal functions, elements of pharmacokinetics and pharmacodynamics) should be performed with great care and skill, as these results might influence the decision of using certain drugs or drug combinations, medication doses, rhythms of administration etc.

All these data conclude that the first contact with a senior patient is a minutios, time-consuming, and complex process, which should be performed by several specialists in different domains, also called the multidimensional approach of the elderly patient.

A relatively new approach of care of older people in community is the use of technology in the form of smart homes and telecare systems. They are based also on communication with outside world in order to alert caregivers when the older person is no more able to cope by herself/himself. Even though this external support can provide information to the professionals, sometimes it might be intrusive and raise some ethical concerns. This is true especially when the systems are not preset to offer the required information but are based on the possibility of the caregiver to check the activity of the older person in the house (14).

The first contact with a senior patient will end with the generation of a prescription. This one of the most challenging medical act as senior patients are highly exposed to polimedication and iatrogeny.

One of the first studies published in 1997 about polimedication and elderly population reported that 35% of ambulatory patients presented adverse side-effects that required medical assistance; institutionalized old persons reported much higher values that went up to 66%. Negative side effects such as: falls, loss of appetite, fatigue or cognitive dysfunction most often were considered as inevitable changes due to old age and not iatrogenic consequences (15).

The paper:

Alexa ID. Prescribing for senior patients – a perpetual challenge. Romanian Journal of Gerontology and Geriatrics, vol 4, No 2, 2015.

underlines that there are many cases of polimedicine, polimedication and iatrogeny, with disastrous effects not only on treatment adherence but also on the patient's attitude toward his/her medical condition. One such patient, in most cases, would become depressed and give up therapy completely; shortly after, the relapse of the (most probably) cardiovascular symptoms would force him to go to the hospital, where he would become a victim of nosocomial infections and complications of prolonged bed rest.

The solution in these situations is the proper education of physicians to devise individual therapeutic plans for complex elderly patients with multiple chronic diseases. Individualized regimens, flexibility and understanding of the wishes of the elderly, providing a psychological and emotional comfort to motivate him to maintain constant health, are just a few elements that should be considered when starting treating such patients. In this context, palliative care becomes an essential link in structuring multidisciplinary geriatric treatment (16).

In Romania, geriatric palliative care addresses especially the patients hospitalized for oncologic pathologies, acute exacerbations of chronic progressive diseases such as chronic pulmonary disease, heart failure, chronic kidney disease, diabetes mellitus and its complications, worsening of dementia syndrome.

Although there are numerous studies that emphasize the importance of palliation, the physicians still don't recommend it often enough in the non-oncological elderly patients. Most senior persons with terminal chronic illnesses spend months or years in need of palliative care based on optimizing the physical, mental, spiritual and social condition. Without this kind of help, more and more of them cross the threshold to death on a hospital bed, alone, depressed and humiliated by their diseases rather than wait for this transition in peace, in a familiar environment, surrounded by loved ones and serene in the face of destiny (16).

The multidisciplinary approach is a complex evaluation, performed by several specialists and coordinated by the geriatrician's team, who will conduct the **comprehensive geriatric assessment (CGA)**.

CGA is the cornerstone of the practice of geriatric medicine. The 1987 National Institutes of Health (NIH) consensus conference defined CGA as “a multidisciplinary evaluation in which the multiple problems of older patients are uncovered, described, and explained, if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan developed to focus interventions on the person's problems”. This approach is useful in all settings in which we encounter senior patients, whether in the home, office, hospital, day facility, or institutional setting. CGA means several types of evaluation, such as evaluation of functional status, mental health, social environment etc (17).

Evaluation of **functional status** includes information on the patient's ability to perform basic and complex activities of daily living. Gait, balance, and risk of falls should also be assessed. The findings on functional assessment are often linked to the basic physical health assessment.

Functional assessment includes typically activities of daily living (ADL) performance, which is lost in a predictable sequence: skills for bathing and dressing are diminished before transferring, toileting, grooming, and eating. An atypical pattern of loss may have diagnostic significance (for instance, early loss of continence may reflect a more localized problem with the genito-urinary system). ADL deficits often indicate a need for in-home assistance in the community setting. The number and type of deficits suggest the amount of assistance needed. Problems with bathing alone may indicate a need for a home health aide 2 to 3 times per week, whereas dependence in more areas may require daily or 24-hour care.

Occupational therapists often evaluate instrumental activities of daily living (IADL) when completing patient assessments. Assessments may include 9 types of IADLs that are generally optional in nature and can be delegated to others:

- care of others (including selecting and supervising caregivers)
- care of pets
- child rearing
- use of communication devices
- community mobility
- financial management
- health management and maintenance
- meal preparation and cleanup
- safety procedures and emergency responses

Mental health evaluation should include the use of standardized cognitive screens (Mini Mental State Evaluation - MMSE) and more thorough testing when indicated. Because of the atypical presentation of depression in this age group, screening for depression should also be included.

The social assessment should identify support network strengths and weaknesses. Some

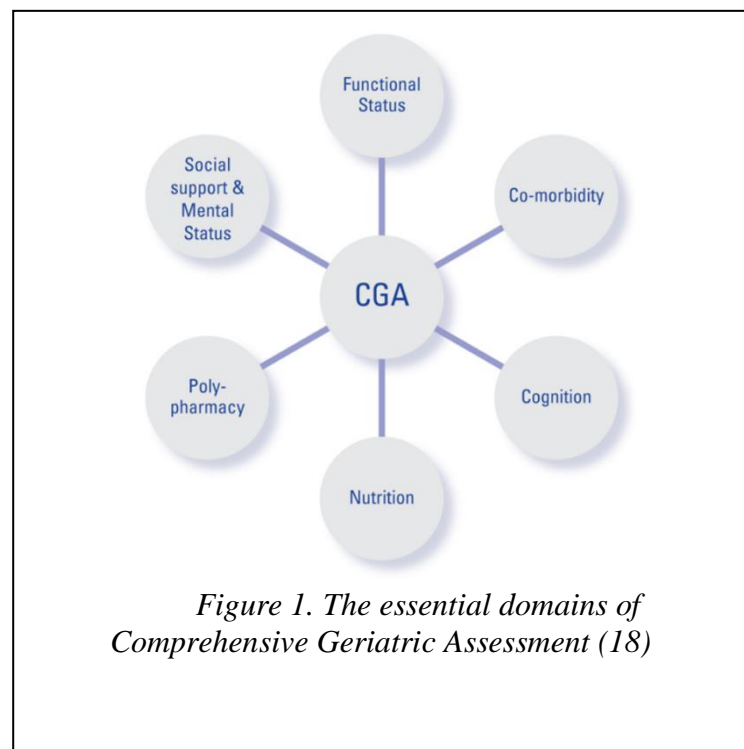


Figure 1. The essential domains of Comprehensive Geriatric Assessment (18)

determination of the patient's values and the presence or absence of formal advance directives should be determined. Caregiver burden should be evaluated. Financial resources to meet current and future needs should also be assessed.

Environmental issues should be evaluated through patient and/or family reports or direct observation of the living situation. Accurate information allows for recommendations that may maximize functional independence in the individual's environment and address basic safety issues. Senior patients need a careful monitorization and a refined therapeutical individualization because they are difficult to include in the standardized medical procedures due to comorbidities with functional deficits, which may need multiple drugs with possible medical interferences (19).

Therapeutical individualization must take care of the patient's and his family's needs, respecting the rules of informed consent; these patients should have a multidisciplinary approach without excessive hospitalization due to the complex psycho-social context of the patients himself.

The demographic trend of the aging of population with an increment of the old and very old persons suggest the imperious need of a geriatric education for all doctors, no matter the specialty, which should be acquired during student hood and afterwards. Geriatry, until recently still in the process of defining itself, begins to surface in the first line of medical assistance (in hospitals and out-patient system) as every specialist would have to treat elderly persons (3).

2.3. MAGEMENT OF PAIN IN THE SENIOR PATIENTS

2.3.1. Introduction

Based on best quality studies of general population samples, the estimated prevalence of chronic pain in the UK is 43%. This equates to just fewer than 28 million people (referencing population statistics from 2013). Chronic pain prevalence rises steadily with increasing age, affecting up to 62% of the population over the age of 75, suggesting that the burden of chronic pain may increase further still, in line with an ageing population, if the incidence remains unaltered (20).

These data represent a real challenge for the geriatric team, as it should be responsible with the proper management of chronic pain in senior patients. Correct treatment will ensure a good quality of life and will maintain a correct cognitive function and a good degree of independence. What is the best treatment of chronic pain in a patient with altered physiological functions and concomitant chronic diseases? Our team explored in the past years several alternatives of this theme published in next papers:

Alexa-Stratulat T, Luca A, Badescu M, Bohotin CR, Alexa ID. Chap. 2. Nutritional Modulators in Chemotherapy-Induced Neuropathic Pain. In: Nutritional Modulators of Pain in the Aging Population. Edited by R.R. Watson and S. Zibadi, Academic Press, an imprint of Elsevier, 2017, ISBN: 9780128051863.

Alexa AI, Alexa Stratulat T, Leon Constantin MM, Alexa ID, Tamba BI. Local Silver Nanoparticles Administration Promotes Inflammation and Hyperalgesia in Rats. Rev. Chim., 2017; 68(3): 490-495.

Alexa ID, Pancu AG, Moroşanu AI, Ghiciuc CM, Lupuşoru C, Prada GI, Cepoi V. The impact of self-medication with NSAIDS / analgesics in a North-Eastern region of Romania. Farmacia, 2014; 62(6): 1164-70. ISSN: 0014-8237.

These works explored different perspectives over the physiology of pain, with different therapeutical approaches. In order to better explain our results, we present in detail our study concerning the impact of self-medication with NSAIDS / analgesics in a North-Eastern region of Romania.

2.3.2. Material and method

The study was conducted between August 2013 -January 2014 on a population group from North-Eastern Romania (rural versus urban), with the help of several General Practitioners from different areas of Moldavia: Suceava, Vaslui, and Iași counties. Our study included 461 people aged between 20 and 90 years. The research was carried out using questionnaires concerning self-administered drug consumption on a period of six months prior to the interview. The questionnaires were anonymous and the data obtained were used exclusively for statistical processing. They were sent by post and we recorded an 87% response rate. The study had the approval of the Ethics Committee of the University of Medicine and Pharmacy “Grigore T. Popa” Iași. The collected data were analysed by the SPSS 18.0 software, using the paired T test for quantitative analyses and Chi-square test for differences in proportions.

2.3.3. Results

From the total of 461 subjects, 281 were from urban area - students from various universities from Iași and 180 were randomly selected from several rural areas: Putna and Dragomirna from Suceava county, Miclești from Vaslui county and Lețcani from Iași county. The analysis of the demographic data showed that more than 70% of the study population was under 30 years old (Figure2) and, regardless of the origin, most of our participants were females (75.48 %).

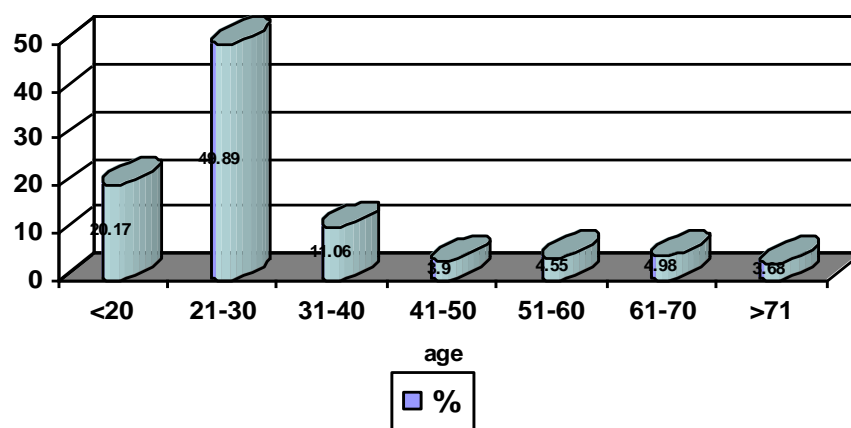


Figure 2. Study population distribution by age

The number of persons who used self-medication increased proportionally with the duration of time: 45.55% were recorded in the first month *versus* 80.55% in the total of 6 months of our study. Analyzing self-administered drug consumption in relation with residence area, we found that there was no significant difference between urban (92%) and rural (80,55%) areas, but the most commonly used drug was paracetamol (46,6%), followed by ibuprofen (30,4%) and metamizole (12,7%) (Figure 3).

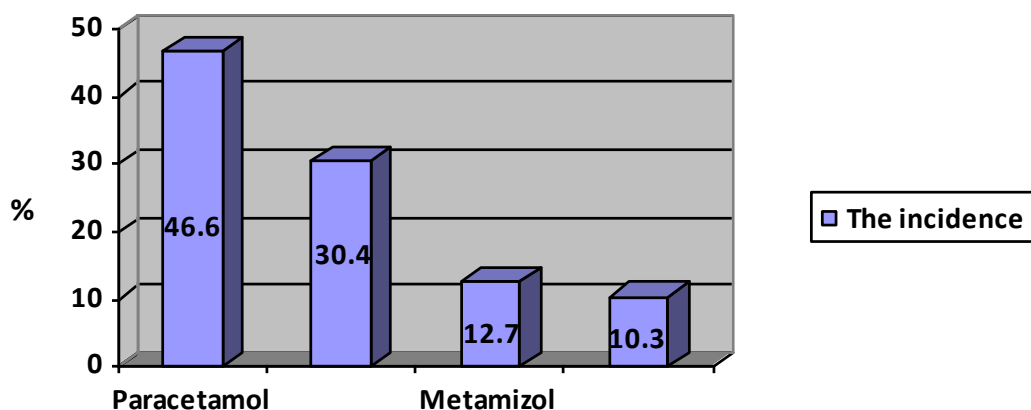


Figure 3. The incidence of the drugs used by the subjects

The most frequent symptoms that required self-medication were:

- rhinorrhea and cough, significantly increased in urban areas (67%) compared to rural areas (27,9%, $p = 0.002$)
- headache, in similar proportions in both areas (46.4% in rural vs 40% in urban areas)
- abdominal pain, in similar proportions in both areas (46.4% in rural vs 44% in urban area) (Table I).

Table I. Symptoms for which the drugs were used in rural area and urban area

Symptoms	Rural area		Urban area	
	Percent%	Statistical differences	Percent %	Statistical differences
Rhinorrhea cough	27.9%	$\chi^2=9.91$ df=1 p=0.002	67%	$\chi^2=8.36$ df=1 p=0.004
Headache	46.4%	$\chi^2=11.98$ df=1 p=0.001	40%	$\chi^2=90.5$ df=1 p=0.001
Abdominal pain	46.4%	$\chi^2=11.98$ df=1 p=0.001	44%	$\chi^2=111.4$ df=1 p=0.001

χ^2 - Chi square test

df - degrees of freedom

p - level of statistical significance, the mean difference is significant at the 0.05 level

2.3.4. Discussions

Our study explored the risk of self-medication in the North-Eastern region of Romania, and our population group had representatives from all groups of age, equally distributed according to gender and residence area. We focused mainly on young, educated people from urban area (mostly students from various universities) and senior people from agricultural rural zones.

Our data showed that there were no significant differences based on education, gender, residence area considering self-medication as all people implied in the study were exposed equally to advertisements and availability of drugs from pharmacies. Self-medication was equally found in rural and urban areas (80.55% vs 92%), our group having predominantly female gender (75.48%) and young population (70.06%).

We focused on three drugs related to self-medication: paracetamol, ibuprofen (one of the safest non-steroidal anti-inflammatory drugs) and metamizole, as they are currently part of the composition of a large number of drugs used to treat headaches, colds and transient pain. Our data showed that paracetamol was used in 46.6% cases, being preferred in headaches, different types of pains and general symptoms of cold indiscriminately. The second place was occupied by ibuprofen, 30.4%, very popular in the treatment of cold and headaches, followed by metamizole, 12.7%, and different associations of the three (10, 3%). Symptoms that required more frequently this medication were rhinorrhea and cough, significantly increased in urban areas (67%) *versus* rural areas (27%, $p = 0.002$), followed by headache and abdominal pain, equally found in both residence areas.

Based on these observations it becomes obvious that preventing risks of self-medication should become the main concern of health professionals, as they are responsible for information, therapeutic advice and education of population. Whenever health professionals are prescribing drugs, they should give proper instructions for the patient to understand and make his own decisions. Given information should be at patient's comprehension level so that it will be helpful for them to understand its management. Proper health education should be given to the patients. By regularly adopting an educational attitude we can have an effect on large sectors of the population, on people who, in turn, may directly influence their friends and family. This aspect is of particular importance with respect to the self-medication of children by their parents or relatives.

2.4. GERIATRIC EMERGENCIES - FALLS AND FRACTURES IN THE ELDERLY

2.4.1. Introduction

Gerontologists have recognized the very different conditions that people experience as they grow older within the years defined as old age. In developed countries, most people in their 60s and early 70s are still fit, active, and able to care for themselves. However, after 75, they will become increasingly frail, a condition marked by serious mental and physical debilitation. Therefore, gerontologists have recognized the diversity of old age by defining sub-groups: the young old (65 to 74), the old old (74 to 84), and the very old (85+) (6).

Approximately 30% of people over 65 fall each year, and for those over 75 the rates are higher. Between 20% and 30% of those who fall suffer injuries that reduce mobility and independence and increase the risk of premature death. Fall rates among institution residents are much higher than among community-dwellers.

While the proportion of falls resulting in fracture is low, the absolute number of senior people suffering fractures is high, placing heavy demands on health care systems. Approximately 10% of falls result in serious injury, of which 5% are fractures (21), the most commonly associated age-related fractures being wrist, spine, hip, humerus, and pelvis.

Hip fractures comprise approximately 25% of fractures resulting from falls in the community but the incidence is higher in residential settings, with rates of up to 81 per 1000 persons years. Approximately half of all fallers who fracture their hips are never functional walkers again and 20% will die within six months.

The most frequent risk factors for falls found in elderly population are (22):

- age
- history of falls

- gender: women fall more often than men and are far more likely to incur fractures when they fall
- living alone – it has been shown to be a risk factor for falls, although part of this effect appears to be related to certain types of housing older people may occupy
- medicines: benzodiazepine use in older people is associated with an increase of as much as 44% in the risk of hip fracture and night falls. There is a significant increased risk of falling with use of medications such as psychotropics, class 1-a anti-arrhythmic medications, digoxin, diuretics, and sedatives. The use of four or more medications is associated with a nine-fold increased risk of cognitive impairment and fear of falling.
- medical conditions: cardiovascular and circulatory diseases, chronic obstructive pulmonary disease, depression and arthritis are each associated with an increased risk of 32%. Other medical conditions are represented by: thyroid dysfunction, diabetes, arthritis, depression and incontinence.
- impaired mobility and gait
- sedentary behaviour - fallers tend to be less active and may inadvertently cause further atrophy of muscle around an unstable joint through disuse (23)
- psychological status - fear of falling - up to 70% of recent fallers and up to 40% of those not reporting recent falls acknowledge fear of falling. Up to 50% of people who are fearful of falling restrict or eliminate social and physical activities because of that fear. Strong relationships have been found between fear and poor postural performance, slower walking speed and muscle weakness, poor self-rated health and decreased quality of life.
- nutritional deficiencies - a low body mass index suggesting malnutrition is associated with increased risk. Vitamin D deficiency is particularly common in older people in residential care facilities and may lead to abnormal gait, muscle weakness, and osteoporosis
- impaired cognition - cognitive deficit is clearly associated with increased risk, even at a relatively modest level (short of florid dementia).

No screening tool has been used or validated Europe-wide to assess risk of falling among older people either in the community or in residential care facilities. Nonetheless, there are several tools that have been used in a number of trials and clinical settings, such as: the STRATIFY risk assessment tool (it has been validated for hospital inpatients only), the Falls Risk Assessment Tool - FRAT (easy to complete but not appropriate for use in hospital or residential care facilities), the Physiological Profile Assessment (PPA) (takes 45 minutes to complete, requires formal training, and is not practical for ordinary clinical screening) (24).

Fall prevention programs can be effective in reducing the number of people who fall and the rate of falls. Targeted strategies aimed at behavioural change and risk modification for those living in the community appear to be most promising. Multifactorial intervention programs that include risk factor assessment and screening have been shown to be effective. Patients with cognitive impairment in hospital after a fall have not benefited from multifactorial interventions, but cognitively impaired residents of care facilities have responded to tailored fall prevention. Coherent multidisciplinary programs can be developed at the national level. These should be implemented with national data collection mechanisms to evaluate interventions by outcome (e.g. fall/fracture rates) rather than process (people seen) or structure (clinics set up) (25).

Effective interventions used in a multifactorial program include:

- home-based professionally prescribed exercise, to promote dynamic balance, muscle strengthening and walking
- group programs based on dynamic balance and strength training as well as floor coping strategies

- home visits and home modifications for older people with a history of falling
- medication review, particularly for those on four or more medicines and withdrawal of psychotropic medications where feasible.

Due to physiological changes, falls and fractures can be more severe in the elderly or rare occurrences may be present. This is a strong reason to ensure a good collaboration between the Trauma surgeon and the geriatric team (24, 25), which was the source of several papers, two of which are presented below:

Alexa O, Cozma T, Puha B, **Alexa ID**: Bilateral hip dislocation in a 79 years patient. *Chirurgia*, 2012 Jan-Feb;107(1):122-5.

Alexa O, Gheorghievici TS, Popescu D, Veliceasa B, **Alexa ID**. Survival of nonagenarian patients with hip fractures: a cohort study. *Acta Ortop Bras*. 2017;25(4):132-6.

2.4.2. From case presentation to cohort studies

The paper "patient "presents the case of a 79 years old man that was involved in an agricultural accident in which a heavy load fell on both his feet while he was laying on the ground. The approximate weight of that load was assessed at over 100 kg and the impact was antero-posterior.

On admission, he complained of extreme intense bilateral pain at hip level and total functional impotency that affected both his hips. No signs of open fracture were noted. Clinical examination revealed internal rotation, adduction and moderate fixed flexion for both inferior limbs, with the left one showing less pronounced clinical signs, except important shortening. These malpositions were considered to be irreducible due to the resistance encountered when trying to reduce them by gentle movements.

The patient was assessed for possible associated injuries. A pelvic radiograph was performed in the Trauma department, revealing bilateral posterior hip dislocation with an associated left-side acetabular fracture and also a minimum displaced anterior left pelvic ring fracture. A geriatric consult was requested due to the advanced age of the patient and the need for a medical systematic evaluation. The geriatrics specialist's consult reported that he was in previous excellent health, with no associated pathologies. Anamnesis did not reveal any history of ligament abnormalities, tissue disorders or other general or local conditions that could have participated in the etiology of the injury.

Both hips were reduced within three hours of presentation by closed manipulation under spinal anaesthesia; the stability of the reduction was tested by means of passive flexing 30°-70° of the hip performed in order to check if the dislocation would reappear. A second radiograph was performed in order to assess the results of the treatment and to exclude any intra-articular fragments. The acetabular fracture did not receive any treatment due to its small size, the age of the patient, and the fact that its existence did not affect ulterior hip stability.

After reduction, the patient was monitored for a few days in our department and was afterwards discharged; he was advised to maintain bed rest for 45 days, followed by six weeks of non-weight bearing and kinetotherapy; the next check-up was scheduled after 3 months. Although this was not a case of late presentation, the fact that a closed reduction was performed together with the fact that the patient was elderly required increased vigilance and screening for complications of the hip reduction: avascular necrosis of the femoral head and arthrose; 6 month and one-year follow-up revealed no such complications.

Hip fractures represent a major public health problem because of their substantial impact on health and healthcare costs. It is estimated that approximately 6.5 million hip fractures will occur around the world in 2050. The majority of hip fractures (80%) occur in persons aged 65

years and older. The age of patients with hip fracture is known to be associated with a significant increase in postoperative complications, high immediate and long-term mortality, and poor functional prognosis. The maximum vulnerability is specific to the first 3-6 months, and death in the first 12 months must be perceived as an effect of trauma or surgical intervention. If post-fracture status involves limits on activity, this must be considered a component of long-term mortality because it favours the intensification of comorbidities.

Due to favourable reviews received for this case presentation, we decided to perform a cohort study involving the survival of nonagenarian patients with hip fracture. The results were published in *Acta Ortop Bras* in 2017 (Alexa O, Gheorghevici TS, Popescu D, Veliceasa B, Alexa ID. Survival of nonagenarian patients with hip fractures: a cohort study).

2.4.2.1. Material and method

This retrospective study assessed 137 nonagenarian patients admitted to our university hospital between 1 January 2007 and 31 December 2015 according to demographic data (gender, age, background) and medical information (intra- or extracapsular fracture type, surgical or non-surgical treatment, type of surgical intervention [internal fixation or arthroplasty], ASA score, status at hospital discharge). We only considered those comorbidities which were described as significant to the prognosis of patients with hip fracture according to Aharonoff et al.

We also collected data about the time between the occurrence of the fracture and the date of surgery, hospitalization period, and complications and deaths during hospitalization.

The data were obtained through the Hospital Manager Program, hospital charts, and surgical protocols.

The inclusion criteria were: single level I trauma centre, age > 90 years, patients with intracapsular and extracapsular fractures (ICD-10-AM codes S72.0 and S72.1), and unintentional fall (ICD-10-AM codes W00 to W19).

The exclusion criteria were: open fracture, subtrochanteric fracture, polytrauma, pathological fracture, and patients transferred to other hospitals (3 cases, at the patient's request).

Because the program does not provide information about the date the hip fracture occurred, the hospital admission date was considered as the date the fracture occurred, since hip fracture leads to total functional incapacity and patients are normally brought to the hospital by ambulance that same day.

After approval was obtained from the institutional review board (1/13.01.2016; no formal written approval was required, because of the retrospective design of the study), the names and social security numbers of the patients were sent to the National Population Register in order to obtain mortality and survival data.

All patients included in the study were treated by the medical staff at the Orthopaedic and Traumatology Clinic. Fractures were evaluated using X-rays of the pelvis or hip. The type of osteosynthesis was decided by the treating physician. A preoperative medical evaluation was conducted by the Geriatric team and the clinic's anaesthesiologist to establish operative risk and improve biological status. After surgery, all patients were included in a medical rehabilitation program under the supervision of a physical therapist.

The results obtained were overlapped with the patient database, and consequently the survival period post-fracture was obtained for the patients included in the study.

Statistical analysis was performed using IBM SPSS Version 20 software (SPSS Inc, Chicago, IL, USA). We assessed the data according to the continuous or non-parametric nature of the variable using the Fischer contingency test and the unpaired Student's t test. Continuous data were expressed as mean \pm standard error and median. In order to evaluate survival and possible influential factors, we utilized Kaplan-Meier analysis.

2.4.2.2. Results

Of the 138 nonagenarian patients presenting with hip fracture, 137 were eligible for inclusion and we recruited 134. Three patients were transferred to other hospitals at the request of the patient or family. One patient with bilateral hip fracture occurring two years after the first fracture on the opposite site was excluded from the study.

The group was homogeneous by sex, age, origin, and age of disease ($p > 0.05$). There were more females than males, with a ratio of 1.7:1.

There was an increasing trend in the prevalence of fractures in nonagenarian patients ($y = 6.83 + 0.85x$); the prognosis for 2019 is approximately 17% prevalence. (Figure 4).

Mean patient age was 92.53 years and median age was 92 years (range 90-103 years); 85 patients (63.5%) were women and 49 patients (36.5%) were men. Patient sex distribution according to ASA score was bimodal in women (23.5% ASA 2 and 36.5% ASA 3); while in males peak frequency occurred in ASA 3 (51%). The average ASA score was significantly higher in women, 3.53 vs 2.92. ($p = 0.004$). In our sample, the frequency distribution for prevalence of intertrochanteric fracture (64.2%) was significantly higher in women than men, 71.8% vs 51%. ($p = 0.026$).

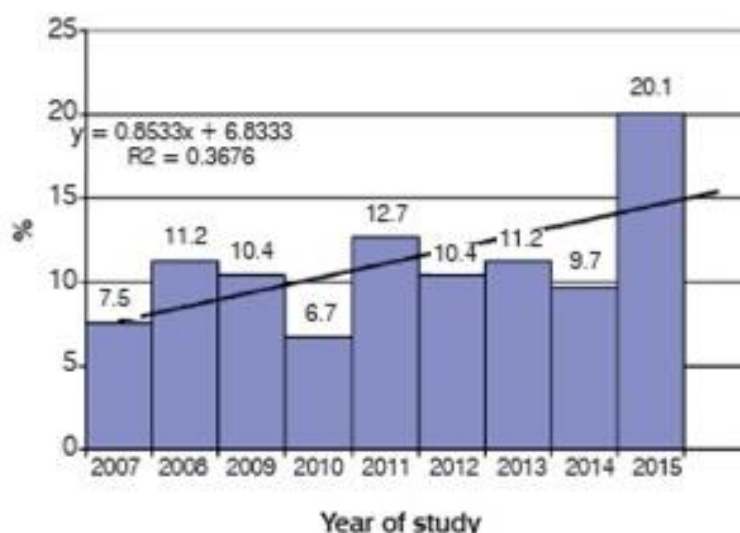


Figure 4. Prevalence of fractures in the nonagenarian patients

In 40 (29.9%) cases, a conservative non-surgical approach was chosen because of the high ASA score, the recommendation of the anesthesiologist, or in cases where the patient refused surgical treatment. Among the patients that were treated surgically, 62 (46.3%) were treated with internal fixation and 20 (23.9%) with arthroplasty.

Arthroplasty was performed in only 34.7% of men and 17.6% of women, while internal fixation was conducted in 44.9% of the men and 47% of the women ($p = 0.047$).

The preoperative interval varied from 0 to 15 days, with a mean of 4.34 ± 3.33 days; no significant differences were seen for sex ($p = 0.521$), diagnosis ($p = 0.487$), or type of surgery ($p = 0.518$) (Figure 5).

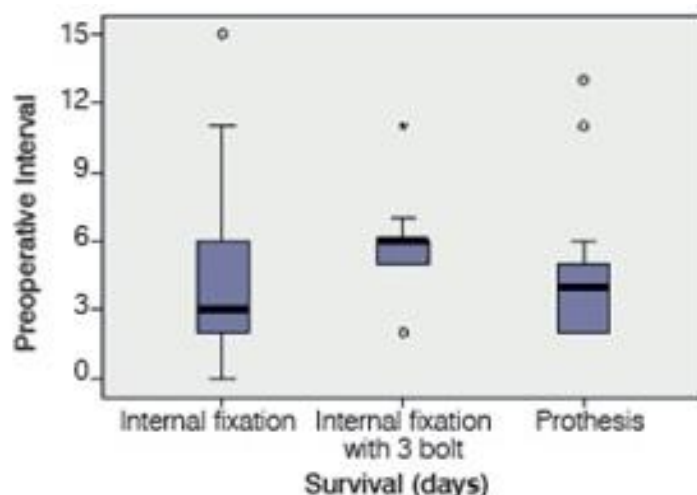


Figure 5. The variation of the preoperative interval

Hospitalization ranged from 1 to 56 days, with an average of about 13 days without significant differences according to sex ($p=0.102$) or diagnosis ($p=0.537$).

Depending on the type of surgery, patients with internal fixation were hospitalized between 2 and 56 days (15 days on average), and patients who received prosthetics were hospitalized between 5 and 27 days (14 days on average), especially women ($p=0.001$).

The probability of survival in nonagenarian male patients with femoral neck fracture drops to about 60% in the first year, and 30% of men and 65% of women survive this type of fracture (Figure 6).

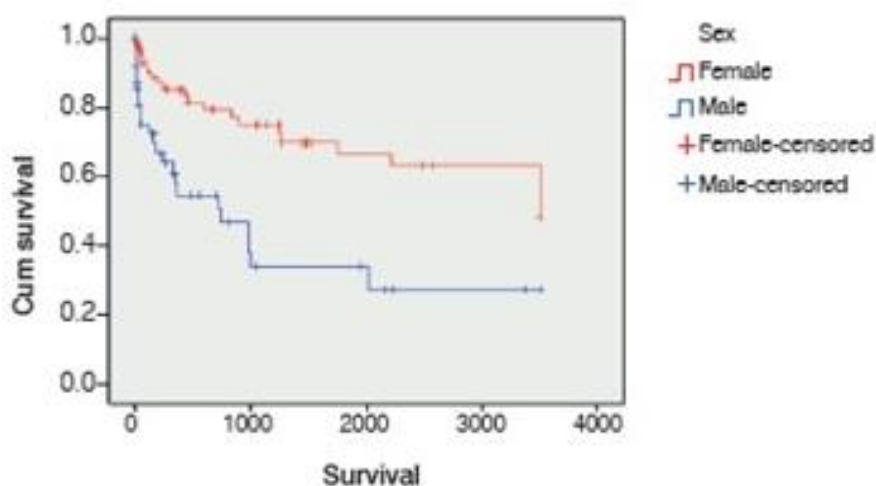


Figure 6. The probability of survival in the nonagenarian patients

The likelihood of survival of both genres, in the first 3 years for the patients with trochanteric fracture, is reduced to 50-60%, after that, is reduced to 20% in men and by 40% in women. Patients with functional treatment had the lowest probability of survival; about 60% of cases survived the first year, with the probability of survival at 2 years at approximately 30%.

Patients with internal fixation have a slightly higher probability of survival, but this drops below 40% 3 years after surgery. Patients with internal fixation using 3 screws survived almost

3 years; in patients who received arthroplasty the probability of survival decreases to about 50% in the first 2 years after surgery.

2.4.2.3. Discussions

Although this is not the first study of its kind, our investigation provides new information on postoperative survival time, the association between preoperative interval, type of treatment, and postoperative survival.

Hip fractures are a formidable pathology in senior patients which may be associated with significant morbidity and high mortality. Despite progress in surgical techniques and postoperative care, mortality remains high: 14-30% one year after surgery, according to recent data. Numerous studies have tried to identify the main factors responsible for high morbidity and mortality after a hip fracture. Most authors consider advanced age to be correlated with other factors, such as patient's gender, the presence of comorbidities, ASA score, time between fracture occurrence and surgical intervention, and type of fracture (26).

As the global population ages, an increase in the frequency of hip fractures is inevitable. Our data are in line with the rising tendency toward hip fracture in nonagenarians.

In our study we obtained lower mortality values at one year than in the literature: 14.3-31.0% in men and 5.9-59.0% in women ($p=0.001$). The higher mortality rate in men was consistent with other previous studies. In the study by Ooi LH (27) on 84 nonagenarian patients with hip fracture treated both surgically and non-surgically, the 2-year mortality was 49%, but the study suggested that surgery significantly increases the ability to move about independently. Our study did not focus on patient mobility and independence after fracture, although we believe this is an important outcome.

In our study, the 2-year overall mortality was lower (11.9%) and the group with the longest survival period also was the one that received surgical treatment with internal fixation (14%, $p=0.177$).

The likelihood of survival for both genders in the first 3 years for patients with trochanteric fracture is reduced to 50-60%, and after that period is reduced to 20% in men and 40% in women.

Preoperative timeframe is another parameter which influences prognostics for senior patients with hip fracture. Delaying the surgical intervention is necessary in the context of measures which seek to correct any possible imbalances and optimize the patient's biological status. In a 2011 study, it was found that mortality is influenced by the preoperative period, with a rate of about 3.5% for patients operated within the first 48 hours that doubles after this period. Most current guides (28) confirm that delaying surgical intervention leads to a rise in immediate mortality and mortality during hospitalization. In our group, the preoperative interval varied from 0 to 15 days with a mean of 4.34 ± 3.33 days, and no significant differences were seen for sex ($p=0.521$), diagnosis ($p=0.487$) or type of surgery ($p=0.518$). The correlation between survival time and preoperative interval was indirect and low intensity; a short preoperative interval is associated with increased survival period in only 10.9% of nonagenarian subjects, and the results cannot be extrapolated to the general population ($r= - 0.109$, $R^2=0.0119$, $p=0.297$).

Patient gender is another parameter that must be taken into consideration when evaluating mortality. Data published in the specialized literature confirms the predisposition of females to hip fractures. In 2008 Van de Kerkhove et al (29) published a retrospective study covering a 20-year period and including 155 nonagenarian patients (83% women, 17% men). These authors concluded that extracapsular fractures are much more frequent in women (62%) and that this is associated with a high mortality rate. In our sample, 71.8% of women and 51% of men had an intertrochanteric fracture ($p=0.026$).

We were able to establish a correlation between type of fixation and days of hospitalization. Patients with internal fixation were hospitalized between 2 and 56 days, on average 15 days, and patients who received prosthetics stayed in the hospital between 5 and 27 days, an average of 14 days, especially women ($p=0.001$).

As for type of fracture, it was indicated that extracapsular fracture of the proximal femur generates higher mortality compared to intracapsular fracture. In our study, survival at 30, 90, and 180 days and 1 year post-fracture was better in extracapsular fracture patients: 25%, 12.5%, 10.4%, and 12.5%, as opposed to 15.1%, 19.8%, 3.5%, and 7.0% in patients with intracapsular fractures.

Associated pathology influences the evolution of patients with hip fracture. An ASA score of 1-2 increases the risk of death in the first year after surgery from 0.36 to 1.33, and for patients with an ASA score of 3-4, the risk of death goes up to 2.33. Our data were not conclusive on this matter, probably because the number of comorbidities often influences the type of treatment selected (conservative or surgical).

Our data, like that of other studies, suggest that surgical treatment remains the best option, even for nonagenarian patients. Even though mortality is high, the hospitalization period long and the functional prognosis is limited, the rate of surgical complications is acceptable.

The probability of survival in nonagenarian male patients with femoral neck fracture drops to about 60% in the first year, and 30% of men and 65% women can survive this type of fracture.

Patients receiving functional treatment had the lowest probability of survival, with about 60% of cases surviving the first year; the probability of survival at 2 years is approximately 30%.

Patients with internal fixation have a slightly higher probability of survival, although this number drops below 40% 3 years after surgery. Patients with internal fixation using 3 screws survived almost 3 years. In patients receiving arthroplasty, the probability of survival decreases to about 50% in the first 2 years after surgery (30).

As the global population ages, an increase in the frequency of hip fractures is inevitable. The medical system will face increasingly older patients with significant associated pathologies and a predisposition to postoperative complications. Although nonagenarian patients have numerous comorbidities, surgery utilizing internal fixation seems to be superior to a conservative approach.

2.5. CONCLUSIONS

A multidisciplinary approach of senior patients leads to a better outcome for most treatable conditions, an improved quality of life, and higher survival rates.

Of particular interest, falls can have severe consequences in elderly patients, which is why we established a continuous collaboration with the Orthopaedic Team in order to achieve a comprehensive therapeutic approach.

Our cohort study had some interesting findings regarding the outcome of senior patients with hip fracture. We found that mortality after hip fracture was high, especially in nonagenarians, especially in men. ASA score has a high influence in determining the type of treatment and patient survival. Although we found a low statistical significance, survival was better in patients who were surgically treated with internal fixation.

Prospective studies are required in order to gather more solid, cohesive data, with the final goal of writing National Guidelines for senior patients with lower hip fractures and impaired mobility.

3. FRAILITY – A NOVEL GERIATRIC SYNDROME

3.1. WHAT IS FRAILITY?

Just a word in the dictionary thirty years ago, frailty has become one of the most researched fields in the medical world. Over the years, it has had many definitions and different screening methods; nonetheless, all authors considered that frailty should have a multi-dimensional approach, involving a variety of psychological, social, emotional and spiritual elements, in addition to the physical ones (31, 32).

Frailty is a clinical state of high vulnerability and reduced ability to maintain homeostasis, which is correlated with age and characterized by a decline of functional reserves which involve multiple organs and systems (33). This vulnerability is not only age-related, but also related to disability and comorbidities. If disability is the result of the dysfunction of one or more systems, frailty is always an accumulation of multi-systemic dysfunctions. Disability is not always associated with instability, whereas frailty is always accompanied by this (34). All these three notions, though, often intertwine. Each of them has different prognosis on long term and needs a different therapeutic approach, this emphasizing the importance of their discovery and individual approach.

The frailty syndrome was initially considered the prerogative of older people, being associated and sometimes overlapping disability, the presence of concomitant chronic diseases and the high degree of dependence. However, there are authors that consider that there are no correlation between age and the increase of the frailty degree, thus making a clear distinction between physiological aging and the frailty syndrome (35).

Most authors (36, 37) consider that there are three stages of fragility. The first stage, preclinical, corresponds to a condition in which the body has sufficient physiological reserves to respond to external or internal aggression factors, such as the aggravation of a disease, the occurrence of a trauma or stress. Preclinical fragility is completely reversible, is the stage during which full recovery is possible, especially if they are identified the elements that need intervention.

The second stage is the stage of clinically manifested fragility, corresponding to a state in which the available functional reserves are insufficient. During this stage, recovery is incomplete, but a well thought out therapeutic plan, adapted to the patient's profile can favour the transition towards the pre-frail stage, with the obvious improvement of the health condition and quality of life (38).

The final stage is that of the complications related to fragility, and results from severe physiological vulnerability and reduction of functional reserves. The organism is no longer able to cope with aggressions, leading to an increased risk of falls, disability, polypharmacy, prolonged hospitalizations, severe infections, institutionalization and death.

The initial observations of Fried et al (39), and which were supporting an increase in the prevalence of the frailty syndrome once every five years, were confirmed by subsequent studies, one of the most important being conducted by Gill et al. in 2006 (40), within a longitudinal study which observed and confirmed the transition between the three phases of fragility during the 4.5 years of follow-up. This transition is directly dependent on the patient's initial condition of fragility, which strongly supports the necessity of screening and early diagnosis of frailty (41).

Progression towards a higher degree of fragility is more common than the evolution towards a lower one, one of the causes being also the defensive medical response, addressing in particular the fragility's complications: treatment of falls, of cognitive decline or immobilization (42). The association of sensory and cognitive deficits along with

polypharmacy and the tendency towards therapeutic and diet non-compliance participate in the aggravation of chronic diseases, with repeated decompensations, frequent hospitalizations and the progression of frailty.

The cornerstone of frailty is sarcopenia, the loss of muscle mass and strength in aging population. Physiologic age-dependent changes explain the impaired protein synthesis, the decline of muscle mass, strength, and bone density. Harmful consequences of sarcopenia in old age are loss of muscle strength, inducing itself loss of mobility, neuromuscular impairment, and homeostatic balance failure syndrome with gait and balance disorders (43).

Sarcopenia increases the risk of falls and fractures – immobilization and its dreaded consequences, interferes with the nutrition skills (empty refrigerator) and malnutrition and favours the decline of the protein reserve of the body with diminished capacity to meet the extra demand of protein synthesis associated with disease and injury. Frailty is a part of all these different "vicious loops" including sarcopenia, neuromuscular impairment, falls and fractures, immobilization, malnutrition, impaired protein synthesis, and decreased protein reserve of the body (44).

In addition to being highly prevalent in elderly population, frailty also exert a substantial impact on quality of life. It is a multifactorial condition in which many risk factors interact and affect different organ systems, influencing clinical presentation, course of disease and outcome of elderly patient. As it is extremely challenging by defying conventional medical wisdom and crossing traditional clinical boundaries, frailty fully qualifies as a new geriatric syndrome.

The clinical diagnosis of frailty is based on a multitude of signs and symptoms, such as weakness, fatigue, weight loss, decreased capacity to maintain balance, low level of physical activity, loss of motor performance, social withdrawal, mild cognitive disorder and growth of vulnerability to stress (37).

There were several approaches to identify frailty. One was developed by Rockwood K, et al. (36) and consists of measuring deficits across many different types of health conditions: functional, clinical, and physiological. A second approach considers that frailty has a distinct pathophysiology and its own clinical presentation (45). Fried LP, et al. (39) defined a phenotype of frailty with the following features:

- unintended loss of weight (4-5 kg in a year)
- self-reported exhaustion
- decrease of muscle strength (reduced grip strength, less than 20% in dominant hand)
- slowing down of walking speed (less than 20% for the walking time of 4,5 m)
- reduction of physical activity (less than 20% of caloric expenditure)

Meeting three out of five criteria define the frail elderly. There also has been identified a sub-clinical form, pre-frail, characterized by meeting one or two out of five criteria, this state having a high risk to progress to manifested frailty.

This phenotype, being the basis of screening methods and diagnosis in clinical practice, includes only the physical components of the syndrome, neglecting other domains such as psychological and social components. Thus, numerous new diagnosis scales of frailty have been developed in order to address all the aspects of patient's life, such as the Canadian Study of Health and Aging (CSHA) Frailty Index, Edmonton Frail Scale, Groningen Frailty Indicator (46).

A new system of biomarkers has been identified which could provide the early diagnosis of frailty: IL-6, TNF α , PCR, Ciliary Neurotrophic Factor (CNTF), etc. However, recent studies agree that the best evaluation and classification of frailty is made by the comprehensive geriatric assessment (CGA) (47).

To exemplify frailty as a geriatric syndrome, I present 3 representative clinical cases "built" on my own experience.

Patient 1 is an 81 years old female who has been recently diagnosed by the general practitioner with pneumonia and treated at home with antibiotics. The evolution was not favourable and she was admitted in our clinic. She had dyspnea, cough with muco-purulent sputum, sweating, nausea, weight loss (approximately 5 kg in the last year), and fatigue. She had a history of hypertension, angina with left bundle branch block, and stroke with secondary right hemiparesis. She lives in the countryside with her family and she benefits from family support. The MRC (Medical Research Council) Scale for Muscle Strength for lower limbs and right upper limb = 4/5. The Groningen Frailty Indicator (GFI) = 8/15 points. Comprehensive geriatric assessment showed a high risk of malnutrition (MNA = 16/30 points) and an almost complete need for care for daily activities (ADL) and for instrumental daily activities (IADL). Need for assistance has increased from the moment of aggravation of respiratory disease and the 3-days bed rest. The patient has geriatric frailty syndrome neglected in the last year and aggravated progressively in the last 3-4 days.

Due to the multidisciplinary approach (correct and complete medical treatment, correct diet, physical therapy and adequate family support) she did very well during hospitalization: she acquired autonomy for ADL and decreases the level of assistance for IADL, she started to eat on her own and had a weight gain of 2 kg. She started to walk, first with the support of the family members and with a walker when discharged home. Later re-evaluations showed that she maintained a good functional and nutritional baseline.

Patient 2 is a 77 years old female from an urban area. She was referred to our clinic by ambulance for fatigue, excessive sleepiness, temporal-spatial disorientation, intense pallor, and weight loss of approximately 10 kg in the last year. She has been living alone in a flat since her husband died 4 years earlier but she has a caregiver who comes every day. The family noticed depression and loss of appetite, refusing food for the last couple of weeks. She had a history of diabetes, hypertension and anemia but without any medical records. The very first investigations showed severe macrocytic anemia which requested several blood transfusions.

Comprehensive geriatric assessment was performed after the management of the acute episode. She had a mild cognitive impairment (MMSE = 23/30 points), malnutrition (MNA = 17/30 points) and clinical frailty (GFI = 9/15) but no depression. She did well during hospitalization with the help of the multidisciplinary team: she resumed feeding, initially with the help of the family and caregivers, later on her own. She started to walk under the supervision of the kinetotherapeut, initially for short distances with bilateral support, then longer distances with the help of a cane. She gained weight, approximately 3 kg. In 6 months time she surpassed her previous functional and psychological baseline, mostly due to correct multidisciplinary approach and increased family support that motivated her to fight frailty and win the battle.

Patient 3 is an 85 years old female from the rural area. She was admitted for intense fatigue, weight loss of approximately 10-12 kg in the last year and edema. She had a history of atrial fibrillation and osteoarthritis. She had no family and lived alone. GFI = 6/15 points. Comprehensive geriatric assessment showed: the MRC for lower limbs is 3/5 (can walk but prefer to stay in bed), malnourishment (MNA = 15/30 points), needs assistance for IADL, mild cognitive impairment (MMSE = 24/30 points). We started a complex therapy, including nutritional assistance, physical therapy, adequate medication and psychological support but she deteriorated progressively, developed multiple organ insufficiency probably secondary to urinary sepsis and she died after 11 days of hospitalization.

I consider that these 3 cases are illustrative for the frailty syndrome. Even if the three patients had different pathologies, they still had several common features: weight loss, no physical activity, fatigue, different degrees of depression and mild cognitive impairment. All these represent the frailty phenotype observed as being more or less pregnant with the three patients described earlier.

Our first patient is a clinically frail lady with important cardiovascular pathology hospitalized for an acute infectious episode (pneumonia). She recovers well due to simultaneous treatment of both acute episode and frailty. The constant and active family support during recovery was definitely a very important factor in regaining patient's autonomy. The evolution of the acute pulmonary infection has been influenced more by the degree of frailty than by the pre-existent cardiovascular condition.

The second patient had a more severe class of frailty so her recovery was not as good as in the previous case. It is to be noticed that frailty is a negative predictor in the evolution of geriatric patient and leads to comorbidities aggravation.

The third case represents an obvious frail elderly lady with a series of adverse events (lives alone, has no family) but no major comorbidities. Still, she didn't cope with this new stressor (urinary infection) despite the correct, multidisciplinary treatment applied.

Frailty is a continuum, ranging from latent physiological alterations to clinically manifest syndrome. This phenotype plays an important role in the outcome of elderly patients. Applying frailty scores systematically to elderly population could lead to early discovery and identifying the stage of frailty and early interventions to this syndrome, which can make a difference between autonomy and dependence, between being active and confined in bed and, finally, between an optimal quality of life and 'the burden of old age' (46).

The assessment of the degree of fragility remains an intensely discussed subject, numerous studies conducted over the past 20 years proposing various scales and tests. Different measurement tools led to different results, hard to compare in identifying frailty, which led to the conclusion that the use of at least two tools for measuring frailty are necessary (46, 47).

3.2. DETERMINING AN EFFECTIVE METHOD FOR ASSESSING FRAILTY

3.2.1. Introduction

Over the past seven years, my team and I have dedicated a significant amount of time and energy for researching frailty in the elderly. As such, we started by determining the best method for assessing frailty. We assessed several tools, but the most important one is the Groningen Fragility Index (GFI).

The GFI questionnaire screens for self-reported limitations and is widely used in The Netherlands. Higher scores indicate higher frailty levels and an increased need for integrated care (48).

Several studies have proposed different tools for measuring fragility, and it is difficult to show which is the best screening instrument; through our research, we attempted to establish a quality of life and fragility detection protocol containing the evaluation of all of the systems involved, to be easy to implement, reproduce, and whose validity should not be challenged. Such an instrument does not currently exist, the numerous questionnaires and even paraclinical evaluations on the level of the musculoskeletal system, the neuro-endocrine, immune, inflammatory systems, did not prove to meet all these criteria; the detection of fragility remains best achieved through a comprehensive geriatric assessment.

A good quality of life (QoL) is intimately linked to successful aging, which aims to preserve, for as long as possible, an acceptable health condition for the elderly (49). To achieve this goal, each elderly person should be assessed by a geriatric multidisciplinary team that would develop an individual plan of measures to ensure a smooth transition and, if possible, without the interference of diseases, through the various stages of the physiological aging process. These therapeutic-tailored plans have as final goal the maintenance of the QoL and the physical, mental, spiritual, financial and social independence for as long as possible, trying to shorten to the maximum the final period, burdened by suffering, sickness, disability and dependence.

The prevalence and definitions of successful aging vary among studies; however, there is a consensus regarding its multidimensional nature, and one of the most important components is the quality of life (50).

QoL has an individual, multifactorial and dynamic character. It is constantly related to past experiences and influenced by future expectations, which means that for an older person the QoL changes its significance while aging (51).

Successful aging must also take into account the degree of fragility of the elderly, an inherent phenomenon of progressive deterioration of the functions of all body organs and systems, which will lead to an increasing degree of vulnerability to various stress factors. Thus, fragility becomes a key element in ensuring successful aging. Initial studies focused on physical fragility because this was the most visible aspect in the physiological decline process, also having severe consequences on physical independence, on the accentuation of sedentary lifestyle and of metabolic and cardiovascular diseases, increasing the degree of disability and the need for high-cost medical care (52).

The impact of the frailty syndrome on the QoL of the elder has become a subject of interest. Recent studies focus on determining the degree of negative impact of the frailty syndrome on the QoL of the elder, but also on determining the manifestation with the highest influence on the decrease of the life quality level (53). Subsequently, attention is drawn more to the phenomenon of mental and social fragility, which, in their turn can induce physical frailty. Evaluation of all aspects of fragility is recommended in all recent studies (54).

Systematically applying fragility scores to the elderly population would lead to the identification and classification of fragility in terms of stages; early intervention to combat this syndrome can make the difference between autonomy and dependence, between active and bedridden and, finally, between an optimal quality of life and the “burden of old age”. The authors of recent studies still consider the best assessment and classification of fragility as being the result of a comprehensive geriatric assessment (37) associated with the measurement of several biomarkers, one of them being advanced glycated end products.

Advanced glycated end products (AGEs) are a heterogeneous group of macromolecules which are formed through non-enzymatic glycation of proteins, lipids and nucleic acids. AGEs from endogenous and exogenous sources accumulate in the organism. The effects of their accumulation are found in every tissue and organs. They are cited to be involved in ageing and in the pathogenesis of sarcopenia, arterial stiffness, heart failure, atrial fibrillation, chronic kidney disease, Alzheimer disease, progression of diabetes. Some studies correlated AGEs levels with cardiovascular mortality or with any cause mortality (55, 56).

The AGEs role in the pathogenesis and prognostic of heart failure was intensely studied in the past few years. Plasmatic levels of AGEs correlated with the severity and prognostic of heart failure in a study with 102 patients (57). Another two interventional studies, DIAMOND and PEDESTAL confirmed the effect of increased levels of AGEs on the prognosis of heart failure. In these studies patients with heart failure received a treatment with AGEs antagonist. The result was an improvement of diastolic function and a reduction of left ventricle mass (58). The mechanism cited to be involved in the pathogenesis of heart failure are complex and numerous. AGEs depositions determine excessive cross-linkage which leads to an increased vascular stiffness and secondary diastolic dysfunction. The linkage AGE to RAGE (receptor of AGE) leads to myocardial fibrosis and a decreased calcium uptake determining an increased repolarization in the muscular fiber contraction expressed in a diastolic dysfunction (59).

My personal researches in assessing frailty led to several papers:

Pîslaru AI, Ilie AC, Pancu AG, Sandu IA, **Alexa ID**. Detection and prevention of frailty in independently living pre-elderly and elderly in North-Eastern Romania. *Rev Med Chir Soc Med Nat Iași* 2016; 120(4): 909-914.

Ilie AC, **Alexa ID**, Moroșanu AI, Covic A, Cepoi V. Effects of oxidative stress and pharmacological treatment on geriatric syndromes in the hospitalized elderly patients. *Farmacia* 2016;64(4): 588-593.

Ștefăniu R, Abdulan I, Alexa T, Maștaleru A, **Alexa ID**, Astărăstoae V. Successful aging is influenced by frailty and health-related quality of life in community-dwelling seniors. *Rev Med Chir Soc Med Nat* 2017;121(1): 104-111.

3.2.2. Material and method

3.2.2.1. GFI as a tool for frailty assessment

The Groningen Frailty Indicator (GFI) is a widely used screening instrument for identifying frail older adults. It consists of 15 self-report items and is a feasible way to assess frailty in both community-dwelling and institutionalized older people (Table II). Psychometric studies examining the overall internal consistency of the indicator show a range of Cronbach's α values, from $\alpha = 0.68$ to $\alpha = 0.73$, indicating moderate internal consistency.

The detection of fragility using the GFI was applied for the first time in Romania in 2013 in a pilot project conducted in a community of independent seniors (60). The results of the study showed that the GFI, translated into Romanian, could be the validated instrument for Romania. We extended the use of GFI in the community of independent seniors from the North-Eastern region of Romania.

Our study for the validation of the GFI was conducted in March-April 2014 on a group of 60 persons aged 65 to 90, randomly selected from the general practitioners' offices, from Iasi city and Iasi county. All the participants signed the informed consent in the waiting room from the medical office or at home. At the same time, the doctor noted down his own opinion on the patient (fragile or robust) without having access to the data from the survey. The data obtained have been statistically analyzed with the help of the SPSS 13 program.


The descriptive data off the age of the patients does not highlight significant differences between genders ($p=0,774$). In women, the age varied between 65 and 95 years old, with a group average of $74.29 \pm 7,74$ years.

3.2.2.2. AGE as a risk factor for frailty

For assessing AGEs, we investigated the relationship between oxidative stress - expressed by AGEs - and the morbidity and mortality in a population of hospitalized senior patients. We also looked for the relationship between AGEs and geriatric syndromes, including frailty, evaluated with the CGA.

We performed a prospective cohort study and included 139 senior patients. The study subjects were selected from the patients admitted in the Geriatric Clinic - Hospital "Dr. C.I. Parhon" Iasi from July 2013 to June 2014. The protocol has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Before initiating any of study procedures, all subjects gave the volunteered and signed informed consent to participate in the study. The exclusion criteria were: lacks of informed consent, terminal stage neoplasia, alterations of the skin - such as scars, tattoos, depigmentation present on the arm were the AGE measurements were performed -, acute systemic infections, and medication with florescent properties because they interfere with the AGE levels.

Table II. The Groningen Fragility Index translated in Romanian



Stimate domn/doamna,

Va rugam sa raspundeti la intrebarile de mai jos; inercuiti ceea ce se potriveste:

Puteti efectua aceste activitati de unul singur si fara nici un ajutor (Se considera ca va descurcati singur chiar daca folositi un baston, cadru de mers sau un scaun cu rotile).		
1	Sa faceti cumparaturi	DA NU
2	Sa va plimbati pe afara (in jurul casei sau sa vizitati pe la vecini)	DA NU
3	Sa va imbracati si sa va dezbracati	DA NU
4	Sa mergeti la toaleta	DA NU
5		
Ce cifra ati folosi pentru a va aprecia activitatea dumneavoastra fizica (pe o scara de la 1 la 10) ?		
1 2 3 4 5 6 7 8 9 10		
6		
6	Aveti probleme in viata de zi cu zi din cauza slabirii vederii ?	DA NU
7	Aveti probleme in viata de zi cu zi din cauza slabirii auzului ?	DA NU
8		
8	In ultimele 6 luni ati slabit fara nici un motiv (3 kg intr-o luna sau 6 kg intr-o luna) ?	DA NU

9	Luati 4 sau mai multe medicamente diferite ?	DA	NU	
10	Aveti orice fel de probleme cu memoria ?	NU	Uneori DA	
11	Daca va aflati la locul de munca, sunteti cu familia sau la biserica simtiti ca aveti o viata sociala activa ?	Niciodata	Uneori Des Tot timpul	
12	Credeti ca cei din jur va acorda atentie ?	Niciodata	Uneori Des Tot timpul	
13	Credeti ca cei din jur v-ar ajuta la nevoie ?	Niciodata	Uneori Des Tot timpul	
14	In ultimele 4 saptamani, v-ati simtit trist sau descurajat ?	Niciodata	Rareori Uneori Des Foarte des Tot timpul	
15	In ultimele 4 saptamani, v-ati simtit calm si relaxat ?	Niciodata	Rareori Uneori Des Foarte des Tot timpul	
16	Ce varsta aveti ? ani		
17	Ce sex aveti ?	Femeie Barbat		
18	Starea civila ?	casatorit(a)	divortat(a) vaduv(a)	nu am fost niciodata casatorit(a)

Va multumim si va rugam sa returnati acest formular doamnei asistente.

All patients underwent a comprehensive geriatric evaluation in order to identify the presence of geriatric syndromes such as: Mini Mental State Evaluation (MMSE) used for detection of cognitive impairments, 16 items Geriatric Depression Scale (GDS-16) used for detection of the risk for depression, Mini Nutritional Assessment® (MNA®) used for detection of malnutrition, Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) used for the identification of the degree of dependence. Demographic data and data regarding the comorbidities and the concomitant treatment were collected.

Levels of tissue AGEs were measured as marker of the oxidative stress. Skin auto-fluorescence, a measure of skin AGE deposition was assessed using an AGE Reader™ device. Three measurements were made on the left arm in clean areas of skin (no scars, tattoos, depigmentation, and vessels near the surface of the skin). Values are expressed in arbitrary units (AU).

SPSS statistical software was used to analyze data. All variables were expressed as frequencies and percentages for categorical data, as means \pm SD for normally distributed data and as medians and inter-quartile ranges for skewed data. Comparisons between groups were made by Student *t* test, Mann-Whitney *U* test or the χ^2 test as appropriate. A 2-tailed *P* value $<$ 0.05 was considered statistically significant.

3.2.2.3. QoL as a major factor in frailty

We assessed several quality of life questionnaires and their potential correlation with frailty. In this regard, we conducted the assessments on a group of 36 elderly persons aged over 65 years, who were registered with family doctors and who have volunteered for a geriatric assessment on the occasion of the Day of the Elderly, on the 1st of October 2016. All the participants have signed an informed consent and were able to withdraw from the observational study at any time. This group included all senior persons with no acute affections at the time of the presentation and / or who were not hospitalized for acute events over the past 3 months.

The geriatric assessment tried to capture various aspects of each participant in order to achieve an appreciation that should be as close to reality as possible and to be able to generate an individualized therapeutic plan. In this regard, the participants have filled in the following questionnaires: assessing life quality (SF-36 questionnaire), assessing the presence of possible risk factors for abuse (EASY scale), assessment of fragility through the GFI, assessment of the cognitive status (MMSE scale), assessment of the nutritional status (MNA questionnaire), the emotional status (GDS depression scale), the assessment of the ability to participate in daily activities (ADL and IADL scales).

Besides these questionnaires, the participants were invited to provide information on the previous personal medical history and the medication they take at home (including OTC - over the counter drugs), and they had assessed the defining parameters for sarcopenia including the anthropometric measurements. These data allowed us to calculate the Fried fragility score (Table III).

Table III. The Fried fragility phenotype

Weakness	Grip strength $<$ 20% in the dominant hand
Slowness	$<$ 20% for time to walk 4,5m
Low level of physical activity	$<$ 20% for calorie expenditure
Exhaustion, poor endurance	Self reported
Weight loss	Unintentional loss 4-5kg in 1 year

The Short Form-36 (SF-36) is a multidimensional scale and a well-established instrument that measures health concepts and self-reported QoL (61). Using SF-36 to define successful aging is an acceptable tool because it represents the overall health status in two directions: the physical component summary and the mental component summary, which are generally used to define health status (61).

The data was loaded and processed with the help of statistical functions in SPSS 18.0.: ANOVA test - descriptive indicators on the monitored parameters (minimum, maximum, average, standard deviation, standard error, variance, confidence interval 95%), FANOVA - quantitative test applied to study the significant difference between mean values in two or more groups, the chi square test - qualitative test that compares two or more frequency distributions from the same population.

3.2.3. Results

3.2.3.1. GFI as a tool for frailty assessment

The distribution of the patients from this group, depending on the marital status, highlights a slightly higher percentage of married persons (65%).

The questionnaire applied has 15 questions, which can determine different functions such as the physical ones (questions 1-4), sensorial (questions 6-9), cognitive (questions 5, 10), social (11-13) and psycho-affective (questions 14, 15). They can be grouped in three subscales that define daily physical activities (questions 1-4), health-related problems (questions 5-10) and psychosocial activities (questions 11-15). In accordance with the literature, the two subscales that define the daily physical activity and psychosocial have good internal consistency, meeting the criteria for validation (Cronbach's alpha value = 0.778, respectively 0.630). These subscales identify more easily the needs of the seniors (social, medical, emotional), concluding a better classification in fragile or robust.

Starting from a descriptive analysis of daily activities, in our study a rate of 50% of elderly age 75 years could place themselves shopping, with no differences by gender or marital status, and could maintain their autonomy to an optimum percentage.

A percentage of 63,3% of the subjects have answered affirmatively question number 1, without significant differences in percentage between genders or based on the marital status, but in ages over 75 or more, only 50% of the subjects were able to do the shopping on their own ($p=0,046$). The percentage of the subjects which could walk alone is 83,3% and there were no significant percentage differences between sexes, age groups or marital status (Table IV).

Table IV. Affirmative answers and questions that concern statistical significance corresponding to physical functions, gender and marital status

Physical functions	Yes (%)	Demographic structure					
		Sex	p	Age	p	Marital status	p
Question 1	38 (63,3)	F 65,7%	0,856	<75 75,0%	0,046	C 61,5%	0,911
		M 60,0%		≥75 50,0%		NC 66,7%	
Question 2	53 (88,3)	F 91,4%	0,634	<75 93,8%	0,162	C 89,7%	0,966
		M 84,0%		≥75 82,1%		NC 85,7%	
Question 3	56 (93,3)	F 94,3%	0,861	<75 96,9%	0,511	C 94,9%	0,914
		M 92,0%		≥75 89,3%		NC 90,5%	
Question 4	56 (93,3)	F 94,3%	0,861	<75 96,9%	0,511	C 94,9%	0,914
		M 92,0%		≥75 89,3%		NC 90,5%	

In terms of sensorial functions, 48,3% of the subjects have daily problems due to the weakening of the hearing, and significantly more men and patients over 75 years old ($p=0,004$; $p=0,010$). Only 15% of the respondents have lost weight in the last 6 months without any reason, especially those over 75 years old, and the unmarried ones ($p=0,049$; $p=0,040$), most likely installed in the context of depressive status due to lack of a partner.

When asked about medication 61,7% of the subjects were taking 4 or more drugs, but statistically there were no significant differences between genders, age groups or marital status (Table V).

Table V. Questions that determine the statistical significance of sensory function by age, sex and marital status

	Yes (%)	Demographic structure					
		Sex		Age		Status marital	
Question 6	44 (73,3)	F 74,3% M 72,0%	0,921	<75 68,8% ≥75 78,5%	0,572	C 74,4% NC 71,4%	0,951
Question 7	29 (48,3)	F 31,4% M 72%	0,004	<75 31,3% ≥75 67,9%	0,010	C 46,2% NC 52,4%	0,850
Question 8	9 (15,0)	F 11,4% M 20,0%	0,582	<75 9,4% ≥75 21,4%	0,049	C 7,7% NC 28,6%	0,040
Question 9	37 (61,7)	F 62,9% M 60,0%	0,861	<75 62,5% ≥75 60,7%	0,901	C 56,4% NC 71,4%	0,388

The auto appreciation of physical activity went on a scale from 2 to 9, the average values recorded showed a modest appreciation of physical activity, without significant differences between genders, age groups and marital status.

Cognitive disturbances were registered in 23,3% of the subjects, without any statistical differences between genders, age groups and marital status.

The seniors with age under 75 years, regardless of gender and/or marital status had an active social life ($p=0,050$). The respondents consider that the people around them will help them in times of need. With regard to the psycho-affective component, the subjects who were divorced or widowers felt more frequently sad or discouraged (in the last 4 weeks (Table VI).

Table VI. Statistical significance related to the affective responses

Question 14	Female		Male		<75 years		≥75 years		Married		Divorced/ widower	
	n	%	n	%	n	%	n	%	n	%	n	%
Never	4	1.4%	3	2.0%	5	5.6%	2	.1%	7	7.9%	-	-
Rarely	4	1.4%	3	2.0%	6	8.8%	1	.6%	5	2.8%	2	9.5%
Sometimes	15	2.9%	8	2.0%	9	8.1%	4	0.0%	2	30.8%	1	52.4%
Often	7	0.0%	9	6.0%	8	5.0%	8	8.6%	3	33.3%	3	14.3%
Very often	3	.6%	-	-	1	.1%	2	.1%	-	-	3	14.3%
Always	2	.7%	2	8.0%	3	.4%	1	.6%	2	5.1%	2	9.5%
p	0,533				0,218				0,020			

According to the general practitioners (GP), the patients were fragile in a proportion of 65%, without significant percentage differences between genders or marital status, but with significant differences for those aged > 75 years old. The results obtained by processing the questionnaire shows that 80% of the subjects were fragile, higher in females (82,9% vs 76%), but the percentage distribution is not statistically significant ($p=0,294$). At ages over 75 there is a slightly raised fragility frequency (92,9% vs 68,8%) ($p=0,045$), with a significantly higher percentage in divorced persons or widowers (95,2% vs 71,8%) ($p=0,028$) (Table VII).

Table VII. The statistical significance of the results of the questionnaire applied and GP review

Demographic structure	GP Review			Questionnaire results DOM			GP view versus DOM
	fragile	robust	p	fragile	robust	p	
Female	65,7%	34,3%	0,891	82,9%	17,1%	0,294	0,172
Male	64,0%	36,0%		76,0%	24,0%		0,537
<75 years	50,0%	50,0%	0,020	68,8%	31,3%	0,045	0,203

≥75 years	82,1%	17,9%		92,9%	7,1%		0,419
Married	59,0%	41,0%	0,294	71,8%	28,2%	0,028	0,341
Single	76,2%	23,8%		95,2%	4,8%		0,186

3.2.3.2. AGE as a risk factor for frailty

We found that the mean age in the study cohort was 75.35 ± 6.46 with slightly more female than male patients (53.1% vs 43.9%) (Figure 7). The mean level of AGEs was 2.87 (3.27-2.56) AU (Figure 8). The general characteristics of study subjects are shown in Table VIII.

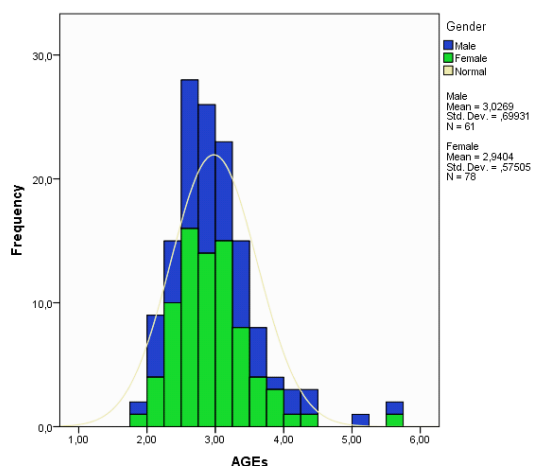


Figure 7. Histogram representing patients' distribution based on age and gender

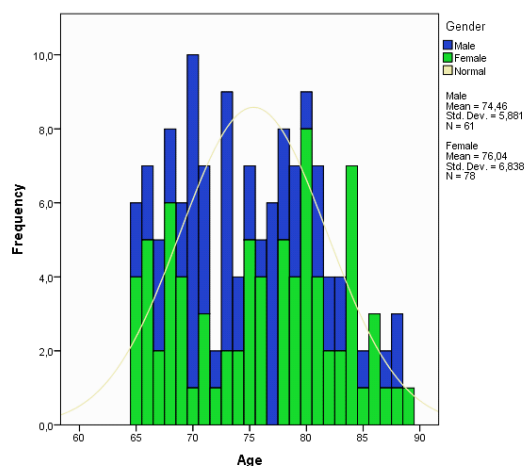


Figure 8. Histogram representing patients' distribution based on AGEs levels and gender

Table VIII: The geriatric evaluation scores of geriatric syndromes, clinical and treatment data of clinical subjects

Geriatric evaluation scales	MMSE	24 (27-20)
	MNA	21.5 (24-19)
	ADL	6 (6-5)
	IADL	7 (8-6)
	GDS	6 (9-4)
Co-morbidities	Heart Failure	108 (77.39%)
	Hypertension	84 (60.4%)
	Ischemic heart diseases	103 (74.1%)
	Atrial fibrillation/flutter	91 (65.5%)
	Stroke	30 (21.6%)
	Peripheral arterial disease	10 (7.2%)
	Diabetes	27 (19.4%)
Concomitant treatment	Beta-blockers	48 (34.5%)
	Ca blockers	37 (26.6%)
	ACE inhibitors	23 (16.5%)
	AT2R I	9 (6.5%)
	Diuretics	73 (52.5%)
	Nitrates	85 (61.2%)
	Antiplatelet	54 (38.8%)
	Anticoagulant	57 (41%)
	Amiodarone	15 (10.81%)

The levels of AGEs were significantly correlated with the presence of heart failure ($p=0.014$, $r=0.280$) (Figure 9) and MMSE score ($p<0.05$, $r=0.206$); there were no others significant correlations between AGEs and any other comorbidities. There were no statistically significant correlations between levels of AGEs deposition and any treatment associated.

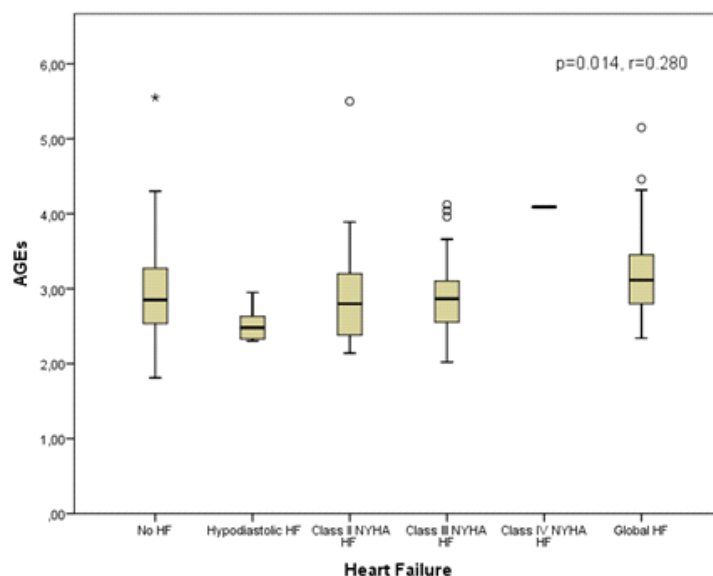


Figure 9. Correlations of AGEs with the presence and severity of heart failure

3.2.3.3. QoL as a major factor in frailty

The analysis of the demographic data indicates that the patients' age ranged between 65 and 89, the group average being of 75.5, with a significantly higher predominance of the female gender (72.22%), both in the initial group and in the 3 subgroups: 66.66 % in subgroup 1, 100% in subgroup 2 and 60% in the subgroup with frailty. These results support data from the literature showing a significantly increased prevalence of feminine frailty (53). However, there are studies showing no significant differences in the prevalence of frailty in both genders, but emphasize a higher risk of mortality in men with manifesting frailty.

The calculation of the Fried fragility score led to the division of the group into 3 subgroups:

- Subgroup 1 - robust senior persons (20 people) - no Fried criterion
- Subgroup 2 - pre-frail senior persons (6 people) - 1 - 2 Fried criteria
- Subgroup 3 - frail senior persons (10 people) - 3 or more Fried criteria

The conducted study showed a low prevalence of frailty in non-hospitalized elderly people (27.77%), but the small size of the study group does not allow us to determine statistically significant data.

The application of the GFI recorded high scores both in the subgroup of robust senior people (50%) and in the subgroup of frail senior people (80%). The two screening methods used in the study were not significantly statistically correlated ($p = 0.285$). By using two screening tools for fragility, there were identified different degrees of impairment in the study group. Thus, we observe a slight overvaluation of fragility in applying the GFI. This tool is based on the patient's self-evaluation and is thus influenced by his perception of his health. The Fried score, though more succinct, it includes quantifiable objective elements (muscle strength, walking speed decrease). Also, the ability to identify pre-frail subjects using Fried score provides extra utility in the clinical practice; the measures of inducing fragility reversibility are believed to have the best result in the stage of pre-frailty.

The evaluation of the questionnaires shows that the elderly enrolled in the study showed no cognitive deficit and have a high degree of independence in carrying out daily activities. The GDS depression score was not significantly correlated with frailty ($p = 0.184$), but there was noted the prevalence of the depressed people in the subgroup of fragile patients (40%), which confirms the role of the emotional status in the emergence and aggravation of the frailty syndrome, element often omitted by the screening tools currently available, but easily identifiable within a comprehensive geriatric assessment. The depressive syndrome in the elderly has important implications for the quality of life, nutrition, hygiene and therapeutic compliance, but once identified it benefits from specialized treatment and counselling.

The analysis of the SF-36 questionnaires showed that the life quality score, the physical component, ranged between 25.2 and 93 with an average of 65.022. There was no significant correlation with the Fried score, but there can be noted a higher level of life quality in the subgroup without fragility, and a significant decrease in those with fragility (Figures 10, 11). The score for the mental component ranged between 20.70 and 98.00, with an average of 69.58. There was no significant correlation with frailty, but there can be noted a low level of life quality in the subgroup of pre-fragile and fragile (Figures 12, 13).

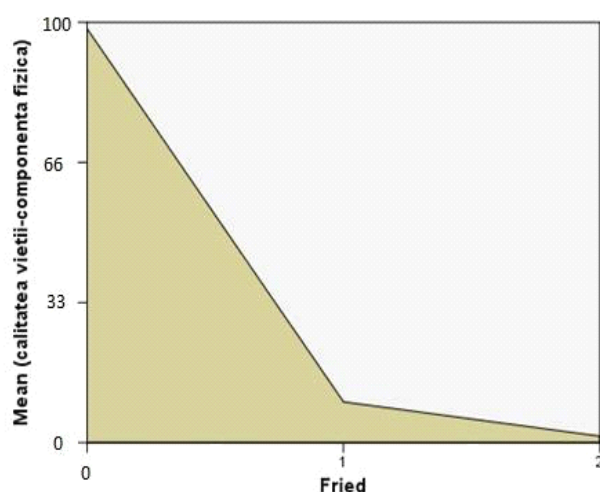


Figure 10. Quality of life – physical component and Fried

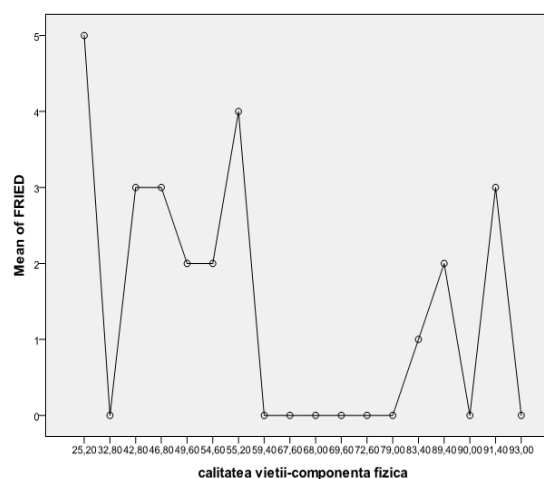


Figure 11. Quality of life – physical component and Fried

3.2.4. Discussions

Compared to the view of the general practitioners, the GFI revealed more raised frequencies of fragility in the studied population, but the ratio of the quota between genders, age groups and marital status was maintained. We believe that these results do not reflect reality, because the methodology for filling in the questionnaire does not comply with the rules necessary for a filling in close to the truth (questionnaires filled in with the help of qualified personnel, which does not manipulate the response, under stress conditions, in limited time).

The research done with the help of the questionnaire can never be completely objective. Both the researchers and the respondents are all human beings, with different psychological, emotional and social needs. Thus, the participants must have the feeling that they are collaborators to the study, without being subjected to psychological abuse (62).

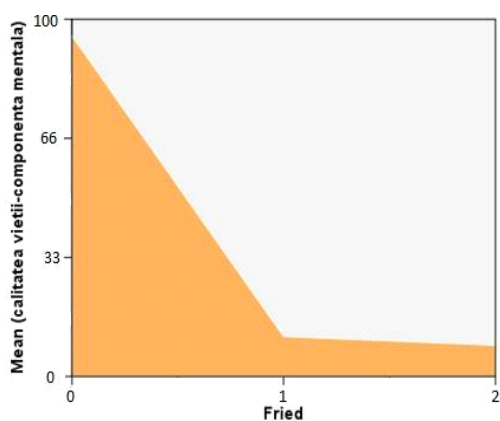


Figure 12. Quality of life – psychological component and Fried

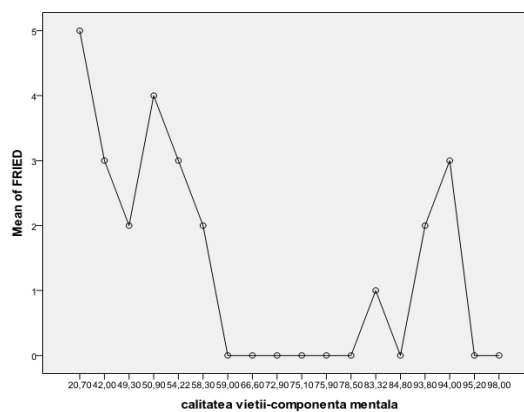


Figure 13. Quality of life – psychological component and Fried

Regarding the associations between AGEs and the presence of studied geriatric syndromes, there was a positive statistically significant association between levels of AGEs deposition and MMSE score ($p < 0.05$, $r = 0.206$). This result is in contrast with the literature data that show that there are higher concentrations of AGEs in patients with Alzheimer disease, in diabetic patients with Alzheimer disease and in elderly patient with cardiovascular disease and cognitive impairment. One mechanism involved is increased oxidative stress due to higher concentration and deposition of AGEs and the consecutive effect of the lipid profile. The different results are probably secondary to one limitation in our study where we perform the MMSE only once. In the hospitalized geriatric patient may appear variations in the MMSE due to hospitalization stress and in these cases the test must be repeated also in the ambulatory conditions (63, 64).

The ACE-I treatment was positively associated with a low depression score ($p < 0.05$, $r = 0.235$), the beta-blocker treatment was associated with an impairment in activities of daily living ($p < 0.05$, $r = 0.233$) and the anticoagulant therapy was associated with both cognitive impairment ($p < 0.05$, $r = -0.214$) and malnutrition ($p < 0.05$, $r = 0.185$) (Table IX).

Table IX. The geriatric syndromes depending on medication

	β-blocker treatment			ACE-I treatment			Anticoagulant treatment		
	Yes (n=48)	No (n=9)	P	Yes (n=2)	No (n=116)	P	Yes (n=5)	No (n=8)	P
GDS (media)	6	6	NS	4	6	$p < 0.05$	6	7	$p < 0.05$
ADL (median)	5	6	$p < 0.05$	6	6	NS	6	6	NS
IADL (median)	6	7	NS	7	7	NS	7	7	NS
MNA (median)	22	21.5	NS	22	21.5	NS	22	21.5	NS
MMSE (median)	24	24	NS	24	24	NS	26	23	$p < 0.05$

The patients with ACE-I treatment had a statistically significantly lower GDS score than the patients without ACE-I treatment ($p < 0.05$). These finding may suggest a protective role of ACE-I treatment for depression in elderly patients. A few case series and an open label study

found that certain ACE-I are effective in the treatment of depression, but in an adult population (65).

Beta-blocker treatment was associated with an impairment in activities of daily living ($p < 0.05$, $r = 0.233$), a finding also confirmed from the data presented in Table IX. In the patient group with beta-blocker therapy we found a lower score of ADL, statistically significant, and IADL, not statistically significant compared with patients with no beta-blocker therapy. The correlation between beta-blocker therapy and impaired autonomy in the elderly patient may be due to the lower tolerability of beta-blocker therapy in the elderly and due to the higher rate of side effects.

Anticoagulant treatment was negatively associated with cognitive impairment, patients with anticoagulant treatment had a higher score in MMSE than patients without anticoagulant treatment (26 vs 23, $p < 0.05$). Is there a protective role of anticoagulant therapy for cognitive deterioration? Stott et al found that older patient with increased markers of thrombin generation are at increased risk for cognitive decline and disability probably secondary to greater risk of cerebral ischemic damage due to pro-thrombotic state. Also there are a few reported cases of improvement of cognitive impairment after anticoagulant therapy in the elderly patient (66, 67).

Our third study used the GFI and the Fried scale; the results showed that the Groningen test could not determine the pre-frail stage in the study group, along with an over-diagnosis of frailty in the group of robust older persons. QoL was lower in the subgroup of fragile as compared to the robust persons. The physical component has recorded lower scores than the mental component, which leads to the need to determine the other influence factors, as well as the impact of frailty on each element related to life quality. The multiple special aspects of the senior's life quality require a more specific assessment, including the particularities of the individual in terms of expectations, social or family environment.

Disabilities, dependence and repeated hospitalizations to which they are exposed by fragility, adversely affects the quality of life. The state of physical health has a more important role in the quality of life of this age segment, thus the implementation of the measures of fragility reversibility can maintain the state of wellbeing and ensure successful aging.

3.2.5. Conclusions

A high percentage of subjects were identified as fragile with the help of the GFI. Following the results obtained, it could be determined that this instrument of research is a valid one, and that it could be applied on larger groups of population on a national level. It is important to develop the correct techniques for the application of the questionnaire, in order to prevent potential false positive or false negative results. Using the GFI among senior population in Romania should be a big step forward in assessing fragility so that prophylactic or therapeutic measures could be taken in order to prevent the evolution of fragility to more severe degrees and complications. But beside easy, accessible methods to determine fragility we studied other methods, more accurate but not so easy to access, such as the effects of oxidative stress on the ageing process (36).

Oxidative stress has an important role both in ageing process and in the pathogenesis and progression of heart failure. In senior patients anticoagulant treatment may have a protective role for the cognitive impairment, one of the most frequent geriatric syndromes. This may be in contrast with the fact that the anticoagulant treatment is underused and under-prescribed in the elderly mostly due to their side effects or the non-compliance to treatment. ACE-Is have, beside their cardio and nephro-protective effect, a protective role in the risk for depression in senior patients. However, their role in the ageing process of muscle and bone systems is yet to be studied (56).

The CGA remains the Golden Standard method for the diagnosis of frailty, provided that it is conducted by a team with experience in drafting the questionnaires and interacting with

senior persons. These findings are consistent with the numerous studies carried out throughout the world in recent years. These results underline the need to adopt a tool for diagnosing the stages of frailty that is easy to apply within primary health care or to facilitate the access of the elderly to geriatric centres with experience in the field. We presented the preliminary results of a prospective study that showed that frailty has a significant influence on the quality of life of the elderly, but medical, psychological and social particularities in this age group requires the finding of a specific life quality assessment tool (68, 69).

3.3. SARCOPENIA AND FRAILITY

The cornerstone of fragility is sarcopenia, which is a reliable marker of global presence of fragility syndrome. However, sarcopenia can lead to frailty, but not all sarcopenic patients are frail.

The term sarcopenia was first proposed in 1989 by Irwin Rosenberg (from Greek "sarx" = meat, "penia" = loss) to describe the decrease in the muscle mass characteristic to the aging process (70). Sarcopenia is defined as the loss in muscle mass and strength that occurs with age, generating a decrease in physical activity. It causes a progressive decrease in muscle mass of about 8% per decade by age 40-70 years, and of 15% after the age of 80. This condition affects 30% of patients over 60 years of age and about 50% of those over 80 years old (71).

It is unanimously accepted that sarcopenia represents the decrease in the striated muscle mass associated with either the decrease in muscle strength (grip strength) or with reduced physical activity ("gait speed"); when all these three criteria are met, we talk of severe sarcopenia (71).

There are multiple factors that contribute to the development of sarcopenia: physical inactivity, vitamin D deficiency, chronic inflammatory status, hormonal changes (low testosterone levels) and neuromuscular changes (decrease in the number of muscle fibres and motor neurons). The consequences will be severe, as the decreased muscle mass and strength will lead to a decline in physical activity, increased body instability and risk for falls and ultimately depression, poor quality of life and disability (72).

The decline in physical activity due to sarcopenia leads to a decrease in physical strength and force and will eventually lead to sedentary life and dependency with direct implications on quality of life and an increased risk of disability.

Sarcopenia decisively influences the risk of falls and fractures in older people: nearly half of accidental deaths in people over 65 are related to falls and their consequences (prolonged immobilization, respiratory tract infection etc) (73).

Unlike cachexia - that occurs secondary to a chronic disease, usually neoplasia - sarcopenia refers to a decrease in muscle mass, not necessarily associated with weight loss, but with an increase in visceral fat, and this is why overweight and obesity are particularly common in senior population. The association of these two entities has led to the emergence of a new concept termed sarcopenic obesity (73).

Sarcopenic obesity (SO) was first defined by Baumgartner (74) in 2010 as the association between sarcopenia and obesity (as measured by dual x-ray absorptiometry - DXA). SO is considered a particular category of obesity that occurs predominantly in elderly patients who experience an increase in adipose tissue associated with muscle mass loss. Studies show that SO is associated with higher mortality risk than sarcopenia and obesity alone. In fact, there is no unanimously accepted definition of SO because there are no unanimously accepted definitions for obesity and sarcopenia (75).

Obesity is a major public health problem and a major risk factor for morbi-mortality through cardiovascular and metabolic diseases. The prevalence of obesity in the adult and elderly population has doubled since 1980 and is steadily increasing (76). The World Health

Organization defines obesity - regardless of age - as associated with body mass index (BMI) values $> 30 \text{ kg/m}^2$ and waist circumference (WC) $> 102 \text{ cm}$ for men and $> 88 \text{ cm}$ for women (central obesity). Studies conducted over the past 10 years showed that this definition should be supplemented with other parameters provided by body composition measurement techniques, most commonly used being DXA and BIA (bio impedance analysis). These parameters newly included in the definition of obesity are the percentage of fat mass, muscle mass /lean body tissue and bone mass, or the ratio of visceral fat to thigh muscle area (determined by CT - computer tomography) (77).

This reassessment of the definition of obesity was necessary due to the conflicting data known as the obesity paradox. These data show that in the elderly population overweight and obesity (measured by body mass index - BMI) is associated with a decrease in all-cause mortality, particularly in cardiovascular mortality. This contradicts the unanimously accepted data that obesity is a major cardiovascular risk factor with a devastating impact on mortality in the adult population. The explanation for this paradox seems to be that aging is associated, among others, with an increase in visceral fat but also with a progressive loss of muscle mass (sarcopenia) (52).

Sarcopenia is significantly associated with the pre-existing cardiovascular risk factors; in addition, it is associated with important metabolic disorders, physical disability and increased mortality. The coexistence of sarcopenia with obesity in the seniors determines, on one hand, the prolongation of life through the beneficial effects of obesity and, on the other hand, severe impairment of the quality of life through the negative effects of sarcopenia (78).

Obesity paradox is actually explained by the presence of SO, and in order to demonstrate this phenomenon it became necessary to quantify both sarcopenia and obesity; in this context, the simple definition of obesity by BMI is unsatisfactory.

The diagnosis of sarcopenia is based on measuring muscle mass; however, the discrepancy between muscle mass and strength makes the assessment of muscle mass alone insufficient. Longitudinal studies have shown that the decline in muscle strength far exceeds changes in muscle mass, particularly in patients with constant body weight. In addition, preservation of muscle mass does not prevent the sensation of muscle weakness in the elderly (79).

The prevalence of sarcopenia is still uncertain because of the lack of homogeneity of the studied populations, but also because of the variety of techniques used to assess muscle mass. Full body scan by DXA is currently considered the golden standard for assessing muscle mass (80). Other methods are BIA, CT, magnetic resonance imaging (MRI), each of them providing objective and reliable information on muscle mass and fat. Unfortunately, such imaging equipment is not always available. In addition, MRI and CT examinations are quite expensive. Also, each of these techniques provides different estimates of body composition profile in terms of anatomical regions, making it difficult to compare the results. These and other drawbacks limit their use in routine practice (80).

Muscle mass is only one dimension of sarcopenia. The functional decline arising from muscle coordination and balance disorders are clear signs of aging, which significantly affect the quality of life (81).

Muscle strength can be easily measured through performance tests: Short Physical Performance Battery (SPPB), 4-meter walk test, handgrip strength test. These tests can be significantly influenced by comorbidities that are often present in older people, mainly through inflammatory or degenerative osteoarticular diseases. While assessing the combined muscle mass and strength is a prerequisite for identifying sarcopenia, one of the biggest current problems is to define thresholds to differentiate between "physiological" and "pathological" aging. This limits the applicability of imaging tests and biomarkers in clinical practice and research (82).

The development of biological markers that can be measured in body fluids, used in a cost-effective manner to guide diagnosis and facilitate monitoring patients with sarcopenia, would mark an important step in managing the care of geriatric patients.

Recent studies show that the combination of biochemical assays with imaging methods increase the accuracy of sarcopenia detection. However, the list of biomarkers proposed is very long and includes markers of inflammation (CRP, IL-6 and tumour necrosis factor TNF-alpha), urinary creatinine, hormone levels (testosterone, insulin-like growth factor 1, and vitamin D), and markers of oxidative stress. It was recently proposed a new set of serum markers directly associated with changes in skeletal muscle mass and function (83).

N-terminal peptide of type III procollagen (P3NP) seems to be correlated with muscle remodelling after lifestyle change, exercise done consistently or after hormone therapy with testosterone or growth factor (84, 85). Framingham Offspring study conducted on 687 people showed that P3NP levels were related to total muscle mass in postmenopausal women but not in elderly men, therefore this biomarker is highlighted as a gender restrictive one (86).

C-terminal Agrin Fragment (CAF) (87) seems to be a reliable marker in skeletal muscle mass assessment. Excessive cleavage of the native motor neuron-derived agrin by neurotrypsin into a C-terminal Agrin Fragment (CAF) leads to functional disintegration at the neuromuscular junction and may consecutively cause sarcopenia. Elevated plasma levels of CAF were correlated with impaired neuromuscular junction, which in turn is involved in fibre denervation, muscle atrophy and dysfunction (88).

Similar to CAF, plasma concentrations of extracellular heat shock protein 72 (eHsp72) were inversely related to muscle mass and function. Production of eHsp72 has been correlated with inflammation and the phenomenon of apoptosis. However, its implication in the development of sarcopenia is currently unclear (89).

Listed parameters and their partial association with pathophysiological processes involved in the development of sarcopenia underline the idea that we cannot consider the existence of a single biomarker. Comorbidities (cardiovascular disease, chronic renal disease, diabetes, lung disease, cancers) can also influence the biomarkers.

In conclusion, a complex approach can provide useful information about the pathophysiological mechanisms that lead to frailty and sarcopenia, with further implications in prevention or therapeutic strategies.

Screening elderly people in order to detect those at risk of malnutrition is the key point and involving geriatricians, nutritionists and physiotherapists is essential. In 2008 the Society for Sarcopenia, Cachexia and Wasting convened an expert panel to develop a guide of nutritional recommendations for prevention and management of sarcopenia. It concluded that protein and calorie intake is key measures associated with appropriate resistance training and aerobic exercises. However, nutritional management for sarcopenia remains unknown, recommendation ranging from one study to another (90).

In 2015, Rizzoli et al reported their recommendations for optimal protein intake from 1.0 to 1.2 g / kg, with an equal distribution for each meal. They also proposed a diet plan that includes 25 to 30 grams of high-quality protein per meal. In addition, adding to the diet 15-20 grams of whey proteins has increased the effects of exercise on muscle (91).

The intake of proteins and amino acids remains the most important anabolic stimulus of lean muscle tissue. Previous studies demonstrated anabolic effect of essential amino acids, particularly the branched chain (leucine). The β -Hydroxy β -Methylbutyrate (HMB) is a metabolite of the amino acid Leucine that, along with KIC (α keto-isocaproate) and isovaleryl-CoA, mediates the effects of leucine. Approximately 5% of dietary leucine is oxidized into HMB, and HMB appears to be the main metabolite of leucine that more effectively prevents the breakdown of muscle protein. HMB is proposed as a potential food supplement for patients confined to bed for a long period of time, but further studies is needed (79).

In addition, diets supplemented with amino acids and carbohydrates consumed one hour after physical exercise increase muscle protein synthesis (92).

Exercise is another important aspect in the prevention and management of sarcopenia. There are four types of recommended exercise, depending on the particularities of each elderly. Endurance exercises have a positive effect on the cardiovascular system. Strength training increases muscle mass and combined with nutritional supplements, improve muscle strength. Complex or simple balance exercises standing on one leg with eyes closed and hand support may decrease the risk of falls. Flexibility exercises, such as yoga or stretching can help prevent or recover from falls. Regardless of the type of exercise, it is recommended practicing them at least three times a week (93).

Nutritional intake combined with exercise has a synergistic effect that helps combat malnutrition and improves the quality of life. Physical activity should be recommended but in different intensity and complexity depending on age and possibilities of travel. Patients should be evaluated by a physiotherapist in order to assess range of motion, strength and endurance and to determine the need of using assistive devices such as canes, grab bars, shower seats.

Vitamin D deficiency is also frequent in older people, regardless of race or ethnicity. The level of 25-hydroxy vitamin D decreases with age and is associated with muscle weakness. Dosing of vitamin D should be made to all people with sarcopenia, followed by adequate treatment (doses sufficient to increase the level of over 100 nmol/L) (94). The effects were observed in postmenopausal women. Doses up to 50,000 IU of vitamin D2 or D3 per week are allowed. But recent studies show that increased doses do not provide additional benefits compared to usual doses.

The analysis of recent literature makes us conclude that sarcopenia is a fundamental element in the diagnosis of frailty syndrome. According to our results, the geriatric evaluation must include the evaluation of sarcopenia, in order to assess the response to treatment and the evolution of frailty. From our experience several nutritional supplements, such as whey protein, amino acids (leucine, glutamine), and vitamin D appear to be beneficial in promoting healthy muscle mass.

Malnutrition affects a great number of elderly persons with significant implications in health costs. In hospitalized patients, malnutrition has been shown to increase complication rates, hospital readmissions, and longer hospitalization due to low response to medication. Unfortunately, malnutrition is often under-diagnosed among senior persons, more so for residents of nursing homes or hospitalized, and is associated with increased morbidity and mortality (95).

Even when older adults are living independently, the normal changes in appetite and mobility due to ageing itself, combined with social isolation and economic problems, and with the presence of chronic concomitant diseases and the use of multiple medications can affect nutritional status. The need to identify the patients at risk of malnutrition is critical in providing optimal care and promoting good nutritional status in community.

Malnutrition may be secondary to certain conditions (disease-related malnutrition), such as cancer, diabetes, and chronic cardiac failure or chronic pulmonary diseases. It is also an independent condition. Risk factors for malnutrition (96) are:

- Clinical factors: poor appetite and dentition, loss of taste and smell, disability and limited mobility
- lifestyle and social factors: inability to shop or prepare food, isolation and loneliness, poverty
- psychological factors: depression, anxiety, dementia
- iatrogenic factors (polypharmacy)

There are several studies that confirm that malnutrition in elders is strongly favoured by depression and dementia (97) as their incidence increase with age; there are also several external

factors that contribute to mood disorders and cognition impairment and influence correct nutrition, such as social isolation, financial difficulties, loss of family members. Polypharmacy, with severe dietary restrictions, will contribute to malnutrition and depression.

Prevention becomes an important aim and screening for malnutrition must be a part of the geriatric evaluation in senior population in order to ensure a correct nutritional status that will ensure a correct response to treatment, preserve the quality of life and prevent the evolution of depression and dementia in this highly exposed age-group. We studied these effects and presented the results on several occasions.

The paper:

Crăcană I, Pişlaru A, Ştefăniu R, Ilie AC, Alexa ID. The importance of evaluating the nutritional status of the elderly patient with or without diabetes mellitus. 2nd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications. INTERDIAB 2016, p. 205-211.

presents the importance of early diagnosing sarcopenia in senior population. The rate of metabolism slows down with age due to a decrease in lean body mass and sedentary lifestyle, resulting in a reduced daily energy requirement. Protein related malnutrition is an important cause of weight loss and may result from a variety of causes including protein–energy deficiency, sarcopenia, cognitive impairment, and depression. Diabetes, of course, may cause an increase in cognitive decline in time because of vascular risk factors.

Elderly patients with diabetes are more likely to have coexistent chronic conditions like hypertension, dyslipidemia, and chronic heart failure that may change their nutritional requirements. Changing the diet is a critical task for healthy aging in this subgroup. Diabetes in the elderly increases the risk of suboptimal nutrition, hospitalizations and physical disability. The prevalence increases with frailty, physical infirmity and institutionalization (98).

A complete assessment of nutritional status includes multiple items. Anthropometric measurements and Body Index Mass (BMI) are frequently used but can't identify specific nutritional changes or the differences between acute or chronic changes. In our study patients with diabetes had a higher BMI, highlighting the presence of sarcopenic obesity (central interest points in our future studies).

Clinical assessment is a simple, practical method but incapable of detecting early cases of malnutrition. Diet history should be performed of an experienced person (dietician) or else inexperienced interviewers could suggest the answers.

Laboratory test (blood test, urine samples), part of the whole assessment, can be important indicators of nutritional status but are often influenced by other conditions in elderly (medication, hydration status). Hemoglobin examination, blood sugar levels and protein are crucial. In our study we didn't obtain any significant results in these tests probably because we didn't focus on albumin levels. Uric acid and triglycerides were significantly higher in patient with diabetes showing inadequate diet. Chronic inflammation is also present (high levels of white blood cells and elevated erythrocyte sedimentation rate). Specific lab test that are accurate and reproducible, such as serum retinol, serum iron, vitamin D, urinary iodine could detect early changes in metabolism, before clinical signs appear (99).

In Romania, the only validated test for those at risk of malnutrition is MNA. Our results show that there is a wide margin of false positive/negative test due to subjectivity. This is one of the reasons we believe that tests based on objective elements should be included in the geriatric assessment.

The dietician, working with the health care team also plays a very important role in developing a care plan. Nutrition education should be individualized and should include

attention to all details (patience, kindness, humour), so that the patient's trust and compliance would not be a problem.

3.4. CONCLUSIONS

The elderly population represents a vulnerable group at risk of nutritional deficiencies, because aging is associated with physical and physiological impairment and psychosocial as well as economical difficulty, all of which can all play a role in nutritional inadequacy. Therefore, hospitals should screen each patient's nutritional status to identify malnutrition upon admission to the hospital, and try to manage nutritional problems. Objective tests would evaluate with more accuracy their status, especially those with special needs (diabetes, hypertension, heart failure) (100).

The senior population is a highly vulnerable group not only at muscular and nutritional deficiencies, but also at fulfilling a good quality of life. Like most European countries, Romania deals with complex economic and social consequences of a population at a continuous demographic aging. In the last century, due to urbanization and modernization, the scale of values changed. From the extended family, that provided stability and security to its members we passed to the family nucleus. Today its members are independent. The most affected are the elderly. Before these changes, their place was in a home, today they are increasingly experiencing isolation, abandonment, institutionalization. Slowly, without drawing attention, the population of the European countries are currently suffering a second major evolution: the emergence of a new group "age Fourth" (those over 80 years old) with high percent, in continuing growth (101).

This situation has numerous consequences, on many different levels: economic, social, medical, spiritual, implicitly requiring the generation of new projects and policies to address the health of the elderly.

4. THE IMPACT OF SIDE EFFECTS IN MEDICAL CARE

4.1. IATROGENY AND GERIATRY

The etymology of iatrogeny is from Greek: *iatros* = physician; *gennon* = induce. The definition is very well expressed by Soubrié et Lebrun-Vigne (102): iatrogeny refers to any unwanted event induced by an intervention belonging to health system either ambulatory or during hospitalization ..., by any person involved in medical gestures: physicians, nurses, medical personnel performing kinesitherapy or physiotherapy, psychotherapists and the patient himself (lack of proper surveillance). Modern approach of iatrogeny tends to enlarge this definition: iatrogeny should include any unwanted effect induced by any diagnostic, therapeutic or prophylactic gesture performed in the health system (103).

The real dimension of iatrogenic pathology is practically unknown even in the countries with highly developed health systems and is unanimously recognized that it is underestimated, understated and sub evaluated. Present data come from sporadic studies which are unreliable and refer mainly to drug-induced iatrogeny. The exception is represented by a 10-year study performed in USA by the Institute of Medicine for Committee on Quality of Health Care in America, which reported shocking information that iatrogeny is the fourth cause of mortality (7.841.360 deaths in 10 years), more than all American army losses from the Independence Day till present times; the main causes were drug side effects, nosocomial infections and medical errors (104).

Same results have been reported by Starfield Report which communicates 225.000 deaths/year, 106.000 being due to drug side effects, 80.000 due to nosocomial infections, 12.000 due to unnecessary surgery. In USA, 7.5 million unnecessary medical and surgical procedures are performed every year and 8.9 million unnecessary hospitalizations. It is believed that 15-30% of surgical procedures could be avoidable (especially cesarean sections, hysterectomies, mastectomies, apendicectomies) (105).

But even when the best treatment is recommended (according to the guidelines) unpredictable and severe side effects can happen due to personal genetic particularities, which can greatly affect drug's metabolism and alter its efficacy and tolerability. The progresses made in the domain of human genome will stimulate pharmaco-genetics and will allow a better selection of the most appropriate molecule for each person and the most accurate dose according to genetic personal particularities (106).

The trend in iatrogenic pathology is ascendant due to:

- increase in drug consumption
- promotion of numerous and diverse type of drugs, which increases the risk of interference
- increase of the number of invasive and aggressive medical procedures due to development of interventional medicine (107).

These elements are associated with un-systematized reports of iatrogenic accidents, this being the reason why the analysis of causes and the prevention of iatrogeny remain extremely poor. This phenomenon is enhanced by the explosive increment of senior population, highly exposed to iatrogeny due to increased need of medical services.

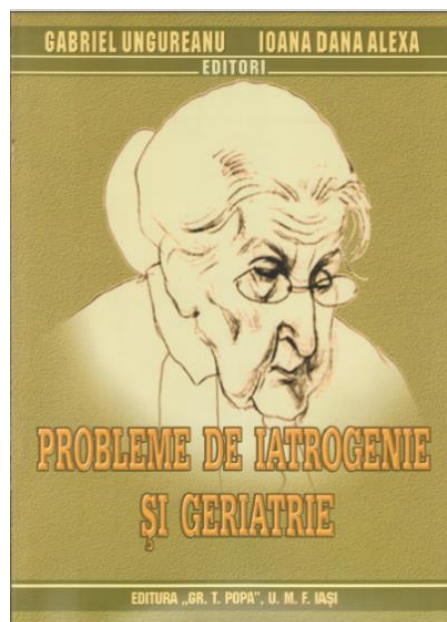
The most frequent causes that lead to error in drug therapy are:

- not choosing the best drug needed
- recommending inadequate drugs (regarding age, gender, weight, physiological status, duration of time)
- not taking care of general or special precautions considering a specific drug
- not following medical compliance of the patient or the efficacy and tolerability of the drug (107).

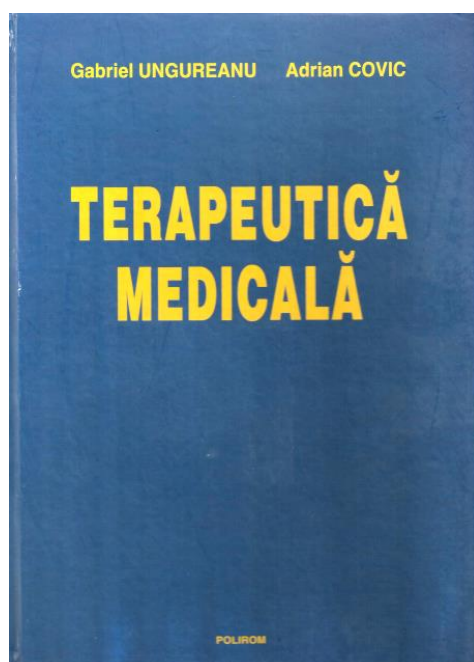
I have been interested in underlining the importance of side effects in medicine for many years, as it is an important research field that is severely under-represented, especially in Romania. Raising awareness of the serious consequences that iatrogeny can have on our patient's life has been possible by means of a multidisciplinary team that has helped me publish books and book chapters on the subject. Listed below are some of the most important ones:

Alexa ID, Ungureanu G (eds). Probleme de iatrogenie și geriatrie. Ed. „Gr.T. Popa”, U.M.F. Iași, 2010, ISBN 978-606-544-029-6.

This book was written together with Professor Gabriel Ungureanu who was one of the promoters of this subject in Romania. It aims to present a comprehensive view of the consequences that follow ignoring side-effects of drugs. Although mainly focused on senior patients, who are most susceptible to iatrogeny due to physiological and pathological cognitive changes, financial issues and difficult access to medical care, this publication offers a complex view of iatrogeny and presents the most frequent clinical scenarios physicians might encounter in their daily practice. Additionally, the book contains chapters written by several of the University's teachers and has an important didactic quality useful for students and medical residents.

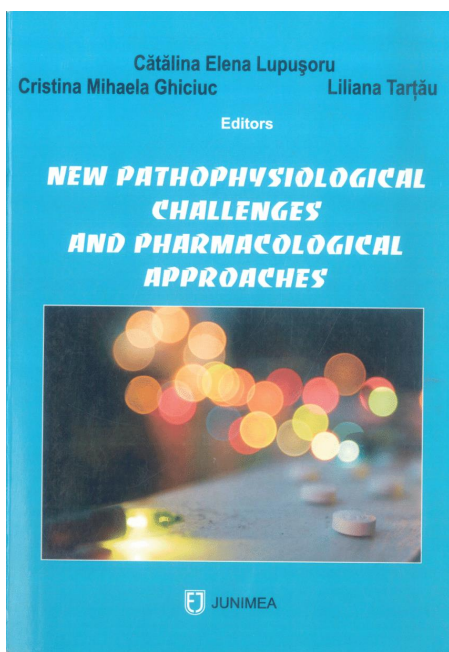


Gabriel Ungureanu, Adrian Covic (eds). Terapeutică Medicală. Cap. Patologie Iatrogenă, pg 845-857, I.D. Alexa, Ed. Polirom, 2014, ISBN: 978-973-46-4804-7.



I have had the pleasure to contribute to two editions of the treatise on "Medical Therapeutics", which became a reference book for all the specialists of the academic medical centre of Iași City. Among the chapters I have written, I believe the one dedicated to iatrogenic pathology is amongst the most important. It presents the most common scenarios that can lead to side effects, focusing on cardio-vascular drugs and on vulnerable populations. The book offers a comprehensive view of the most frequent conditions encountered in internal medicine – mostly from the fields of cardio-vascular, pulmonary, oncology and gastroenterology. Professor Gabriel Ungureanu and Professor Adrian Covic have reunited several prominent representatives from our university – each an expert in his/her corresponding field, which is why the book has ever since been recommended as reference in most regional specialist exams.

C. Lupușoru, C. Ghiciuc, L. Tarțău(eds). New Pathophysiological Challenges and Pharmacological Approaches. Cap. Updating Potentially Inappropriate Medication Use in Older Adults. I. Alexa, A. Ilie, pg. 95-112, Ed. Junimea, 2009, ISBN 978-973-37-1351-7.



This book was intended as an up-to-date in pharmacology for all medical specialists. As such, I had the opportunity of presenting the consequences of inappropriately using of some of the new drugs that have entered the market, a topic particularly important since some of the new drugs do not yet have long-term data for rare side effects. This book represents just an example of my long-term collaboration with our university's team of pharmacologists and it highlights the importance of approaching iatrogeny from both a fundamental and clinical point of view, since practical examples are explained by means of pharmacodynamics, pharmacokinetics and molecular drug interactions.

My interest for this field of research has luckily been shared by my younger collaborators, with whom I have perfected a course of continuous medical education dealing with different specialties and interdisciplinary themes with the title "Iatrogeny and Particularities of Treatment in Elderly Patients". It took place in Iasi, in 2007 and was attended by a large number of residents and young specialists. Additionally, I have organized for nine consecutive years symposia called "Geriatrics and Iatrogeny". Each year, the program consisted in different presentations that covered complex perspectives of the issue – from surgeons to radiologists, oncologists, endocrinologists, rheumatologists or neurologists. The manifestation was organized under the patronage of both the University and the Romanian Society of Geriatrics and Gerontology and had several national guests invited yearly to present the experience of other academic centres.



I have constantly had great support from my residents and students in organizing these symposia. As a result of this connection, I have always been involved in student manifestations, both as a moderator and as coordinator for those interested in my field of research. For example, I was involved in organizing scientific sessions at Congressis (a scientific congress addressed to medical students) and other medical manifestations for young doctors, such as the 7th International Congress for Medical Students and Young Doctors, CONGRESSIS breaking boundaries in medicine, Iași, 2010 – invited speaker for the workshop with the title: „What Do We Know about Iatrogenesis?” or The 6th International Congress for Medical Students and Young Doctors, Iași, 2009 – invited speaker for the workshop with the title: „Presenting a Clinical Case: Errors in Diagnosis”.

Based on our experience, we were able to conclude that geriatric population has become the favourite target of iatrogeny due to several particularities:

- A. physiologic changes due to normal ageing
- B. association of several chronic diseases that require multiple medical services from different physicians that will expose the patient to polypharmacy
- C. non-adherence/compliance to medical treatment
- D. potential inappropriate prescribing

A. There are *several physiological changes due to normal ageing* that make elderly persons more vulnerable to medical procedures:

- a progressive decline in functions of all organs and systems, which will favour drugs' side effects (due to a relative over dosage) and iatrogenic complications of interventional medicine; moreover, multiple hospitalizations favour nosocomial infections with multiple resistant germs.
- modifications of pharmacokinetics and pharmacodynamics due to normal ageing:
 - decrease of absorption due to decrease in gastric acid secretion, motility and vascularisation of digestive system
 - modifications of distribution due to reduced hydric sector and lean mass associated with major variations of fat body mass due to sarcopenia, malnutrition and/or sarcopenic obesity
 - depression of synthesis hepatic functions, which will induce decrease of albumin and transport proteins
 - decrease of hepatic functions (secondary to the decline of heart output) and liver mass induce decrease of metabolism of drugs, which would require correct adaptation of doses of drugs;
 - modifications of renal function secondary to progressive decline of number of nephrons associated with an important decline in renal vascularisation - impose reducing drugs' doses, especially in those with renal elimination; moreover, the kidneys are the main target in degenerative diseases (atherosclerosis, ischemic nephropathy) and diabetes and are the innocent targets in all contrast investigations or arterial catheterization (embolus with cholesterol crystals).

B. Senior patients have *numerous comorbidities* that need numerous medical services, which expose them to the risk of aggressive investigations (contrast investigations, endoscopy, catheterism) and to polymedication, usually prescribed by different specialists who don't realize the possible medical interferences.

C. The medical *non-compliance* is much more severe in seniors usually due to polimedication associated with difficult medical schemes recommended in patients with cognitive disorders, sensory and motor deficiencies and lack of a familial or social support for the possible handicap.

D. Drug posology usually inappropriate, sometimes due to extrapolation of trials' results (seniors being usually excluded from trials due to numerous risks of abandoning the study due to non-compliance).

These age-related alterations will make geriatric population more susceptible to iatrogeny and the treatment plans will be frequently compromised by several factors: the characteristics of the disease (cognitive impairment), the potentially inappropriate medication (PIM), social system, health care system, economic factors and patient-related factors.

A potentially inappropriate medication (PIM) exists when the risk of adverse events due to medical treatment outweighs the clinical benefits. PIMs are associated with adverse health and economic outcomes, making detection and prevention a primary goal for all health suppliers. As the geriatric population is more exposed to PIM, it was a general interest in the last 30 years to devise screening tools to assess the extent of PIMs and guide clinical practice in older adults (108).

Potential inappropriate prescribing represents situations when the medical services provider recommends a drug with an increased risk of producing undesirable effects, although the patient could have been recommended another drug, as efficient as that one but with a decreased risk of side effects occurrence (109). This represents a large field that comprises several entities, of which we mention only a few of them, more frequently encountered:

I. Overprescribing defined situations when the physician prescribes, for the same disease, many drugs, usually with similar effects or bigger doses than necessary, without obtaining a bigger benefit. It is often mistaken for polypharmacy, which refers to prescribing a great number of drugs for multiple conditions, thus exposing the patient to the risk of polypragmasia.

Overprescribing is the consequence of an excess of multiple medical examinations, often for minor conditions, out of the fear of assuming decisional responsibilities or the excess of useless investigations and examinations, irrelevant to the therapeutic decision due to onerous requirements for mutual restoration of doctor's practices (110).

Typical examples for this category are:

- medication abuse with lipid lowering drugs, without considering the indications, age, potential side effects, risk of polypharmacy
- antibiotic abuse which led to the creation of multi-resistant microbial strains, whose rhythm of occurrence exceeds the capacity to find solutions in the research laboratories in the field; antibiotic use, especially of those with the wide latest spectrum is considered to be excessive and abusive (for example, in case of superior respiratory tract infections, which are viral in 90% of the cases or in case of post-surgical prophylactic administration)
- recommendation of long-term oral corticotherapy in the treatment of chronic obstructive pulmonary disease (COPD) or in rheumatology
- recommendation of antidepressants (Prozac type = fluoxetine) more and more frequently used (especially by children and teenagers) and in association with cerebral stimulants (Ritalin = Methylphenidate type)
- abuse of proton-pump inhibitors drugs (i.v. administration), mostly unjustified

II. Underprescribing defines situations when drugs necessary in obtaining the best therapeutic results and in maintaining a good quality of life are omitted in the therapeutic scheme.

There are various comparative studies which show that in Europe approximately a third of the senior patients consulted in the ambulatory system are undertreated compared to the 50-66% registered in the USA. There is a direct relationship between the risk of underprescribing and advanced age of patients.

Undertreatment occurs frequently in patients with acute heart attack, chronic cardiac failure, atrial fibrillation, dyslipidemia syndrome. The comprehensive geriatric assessment carried out on these patients has had significantly ameliorated undertreatment by medical and psycho-social re-evaluation of the patients (including life quality and their life expectations) and drawing up a therapeutic scheme that could adapt better the needs of each of them (111).

Some classic examples of undertreatment are:

- avoiding the association of substitutive therapies for osteoporosis, of proton-pump inhibitors or high blood pressure prevention in patients treated with steroidal anti-inflammatory drugs for a long time
- avoiding the association of preventive anticoagulant therapy in patients with moderate to severe cognitive disorders, which associate cardiovascular conditions with the risk of embolism and/or bed immobilization; this situation is typical to the physician who had a negative experience with anticoagulants and avoids further recommendations of acenocoumarol to all of his patients, regardless of the risk/benefit report
- avoiding nerve medication in patients suffering from heart conditions and who suffered a transitory ischemic accident.

In most of the cases, the geriatric consult was usually followed by the occurrence of polypharmacy, not only by correcting the undertreatment, but also by identifying new conditions, which required a therapeutic approach. Drawing up an appropriate therapeutic scheme, which shall avoid over/undertreatment and which shall respond to the expectations of the patient, represents a real challenge for the practitioner.

III. Polypharmacy and polypragmasia are most common in seniors with several simultaneous diseases and a therapeutic scheme that represents the sum of all the prescriptions resulting from the multiple clinical examinations instead of reflecting an individualized approach, adapted to the functional and financial means and firstly assigned to obtain an improvement of life quality. Most of the studies consider that the risk of undesirable effects increases with the increase of recommended drugs: 13% (2 drugs), 38% (4 drugs), 82% (over 7 drugs). The emergence of side effects would be treated with other drugs, thus closing the vicious circle.

Applying the prescriptions without the final examination of a specialist with a holist and integrative vision leads, most of the times, to the administration of drugs from the same class, whose beneficial effects do not add up, but whose undesirable effects mutually enhance them. It is absolutely necessary to carry out a final examination, preferably by the geriatrician, of all the recommendations generated by the multiple medical examinations and the elaboration of a final scheme, which takes into consideration the individual profile of the patient, the risk/benefit report and the financial means, so that it ensures the best chance to obtain therapeutic adherence and maintain an acceptable quality of life (112).

IV. Incomplete knowledge or limited experience with the prescribed treatment

Recommendation of new molecules to senior people is always done carefully, due to the limited experience that the producers and physicians have with elderly population. Generally, the pharmaceutical trials have a limited participation of this age category due to a potentially reduced adherence and especially to comorbidities. Dose recommendation shall be done only after carefully assessing of the renal and hepatic functions, in order to avoid over or under dosing the medication. Most importantly, all the recommendations, the prescriptions received

by the elder at the end of the long road of inter-clinical examinations, must be centralized, analyzed and carefully evaluated in order to obtain the final prescription, perfectly adapted to the physical, functional, psychical, material and social means of the concerned person (113).

V. Potential Inappropriate Prescribing, non-compliance with the general and specific contraindications of the drug should be evaluated after considering the personal history, age, comorbidities of the patient. Evaluating the correctitude of a therapeutic scheme can be carried out by explicit methods (based on pre-established criteria) or by implicit methods (based on reasoning and medical experience). There are several explicit methods: Beers criteria, IPET (Improved Prescribing in the Elderly Tool) and STOPP (Screening Tool of Older Persons) and an implicit method, MAI (Medication Appropriateness Index) (114, 115, 116, 117).

Beers criteria represent a guide which includes potentially inappropriate medication (PIM) for seniors. It was created in 1991 by Mark H. Beers and his team - made up of other 11 specialists (geriatricians, pharmacists, psychogeriatricians); they have come up with a formula of criteria based on which they identified 30 potentially inappropriate medications for senior patients. This guide was re-evaluated in 1997, 2003 and 2012. Dr. Beers' team establishes 2 fundamental notions:

- drugs or classes of drugs which should generally be avoided in elderly patients (the actual list contains 48 such drugs)
- drugs that must be avoided in elderly patients with certain diagnoses (for example: NSAIDs in those suffering from ulcer/gastritis) (the actual list contains 20 conditions where certain pharmacological agents must be avoided) (115).

Each of the drugs on the list was assigned a degree of severity (high or low). Each revision of the list brings modifications in the sense of additions, amendments or removal of some drugs. Unfortunately, there are a great number of physicians and pharmacists who do not know these criteria and the revised options either, while 23% of the patients use at least 1 drug on that list (116).

The Canadian criteria or IPET (Improved Prescribing in the Elderly Tool) is a list of the most common 14 errors of medical prescription chosen by the Canadian Consensus Panel in 1997 (for example: using beta-blockers in patients with COPD, extended use of NSAIDs in patients with high blood pressure etc) (118).

The Screening Tool of Older Persons' Prescriptions (STOPP) Criteria is an alternative device developed in 2008 by a European Consensus Group. The STOPP Criteria includes drugs to avoid, drug-drug and drug-disease interactions, and also alternative ways to define PIMs. It was designed to be more effective in Europe as many of the medications considered inappropriate by the Beers Criteria are available only in the USA. As a result, the STOPP Criteria has modest overlap with the 2012 Beers Criteria – 55% of the 65 criteria are not found in the 2012 Beers Criteria (119).

The STOPP criteria were developed by a panel of 18 experts in geriatric pharmacotherapy including physicians, pharmacologists, pharmacists and a psychiatrist.

Unlike the Beers criteria, STOPP criteria have been significantly associated with avoidable adverse drug events in senior people. START (Screening Tool to Alert doctors to the Right Treatment) is evidence-based screening tool that can detect potential omissions in therapy of elderly patients. It includes 22 scenarios divided by physiological system (cardiovascular, respiratory, CNS, GI, locomotor and endocrine) where specific medications are recommended (117).

VI. Potentially inappropriate posology refers to potential medical errors that might occur especially due to dose inadequacy to the physiological particularities of the elderly: serum concentrations of drugs are increased compared to the adult for the same dose, due to an increase

of drug metabolism, decrease in the transporting proteins and increase in the disposal. This associated with a decrease in the circulatory volume and receptor modifications emphasize the need to initiate treatments in elders with small doses and careful monitoring of the titration development, hence the tagline: START LOW, GO SLOW. For this reason, prescribing a receipt to an elder patient involves considering the following aspects:

- drugs known for low toxicity and increased efficiency shall be recommended
- the doses shall be reduced according to the renal condition and age of the patient
- the patient shall be recommended as little drugs as possible, yet ones that can cover his therapeutic needs; the prescriptions containing many drugs risk to remain unused by the patient
- single administration drugs are preferred
- the recommended drugs must not exceed the financial means of the patients (120).

Lack of adherence, efficiency and tolerance tracking

Therapeutic adherence represents the way in which the patient complies with the medical indications of lifestyle modification recommended by the physician. Lack of adherence is the number 1 cause for therapeutic failure. Unidentified, the lack of adherence generates hospitalization, useless diagnosis procedures and treatment modifications, which finally leads to incredible increase of costs.

The causes of non-adherence are many (121):

1. Physical causes:

- tremor, balance disorders, the arthrosic lesions in the upper limbs can make it difficult for the patient to administrate the drug (for example: nebulizer use, vials opening, measuring the doses or counting the drops)
- memory impairment, very frequent, can be the cause of inaccurate administration of drugs (forgets to administrate a dose or a category of drugs, especially in treatments with several drugs)
- sight disturbances
- micturition disturbances (for example: administration of diuretics in a patient with prostate adenoma)

2. Functional causes:

- the recommended prescription exceeds the financial means
- the patient cannot procure all the drugs from one pharmacy in the proximity of his dwelling; thus, he will interrupt the treatment or administrate only those drugs that he can get easily
- the patient has a rather unsatisfactory relationship with the physician and does not comply with the therapeutic indications
- the patient did not understand the importance of complying with the therapeutic indications

One of the most used tools for measuring the adherence is Morisky Medication Adherence Scale (MMAS-8), consisting of a questionnaire made up of 8 questions. There are various studies that use this scale in order to determine the adherence of different cardiovascular diseases, especially when it comes to arterial hypertension and heart failure, due to the frequency and complexity of the recommended therapeutic schemes (122).

One of the best-known studies in the field (123) remains the CoSMO (Cohort Study of Medication Adherence among Older Adults) study, conducted on a number of 2180 of participants with arterial hypertension, where therapeutic adherence was studied. The results

of the studies showed that the adherence to the therapeutic scheme depended mostly on the number of recommended drugs and the cost of the receipt. Simultaneously, the study draws attention to the increased incidence of using simultaneous natural remedies, unknown by the practitioner and which influenced the results of the prescribed therapeutic scheme.

Hospitalization of senior patients

Hospitalization is usually associated to solving health issues of all the people, but for the seniors this can cause functional alterations that occur despite the correct treatment and favourable development of acute conditions which determined the hospitalization in the first place. These modifications might irreversibly alter the life quality of the patient even when the underlying condition (for example: pneumonia, hip fracture) was solved. A study published in 2007 shows that 30% - 60% of the patients admitted for hip fracture and who were impeccably solved in terms of surgery, is sent to a care home, since they cannot look after themselves anymore; of these, 20% - 30% cannot go back home after 1 year. Other studies report that senior patients have a fourth times greater risk to get hospitalized due to the undesirable effects of the incorrectly applied therapy (16.6% vs 4.1%) compared to those who are under 65 years old (124).

A few days of hospitalization with bed rest for seniors with limited muscle supplies but who can still take care of themselves, shall lead to muscle mass loss and decreased ventilator capacity associated with the loss of movement independence and dependence on a care taker. Regaining the lost abilities requires a long period of muscle and joint rehabilitation - reconditioning time is longer than de-conditioning time. At the same time, muscle force loss might be one of the causes of traumas by fall that are common during hospitalization (for example: fall off the bed). Moreover, bed rest accelerates the involution of bone matrix by 50 times in healthy seniors; bed immobilization for 10 days requires 4 months of treatment and 4 months of substitutive treatment for osteoporosis (125).

Hospitalization can induce urinary incontinence due to the association of many factors: unfamiliar surroundings, long and inappropriately lightened road as far as the restroom, frequently high bed, potentially foreseen with lateral bars, difficult to descend during the night; the patient can have venous catheters or oxygen masks, which hinder the frequent walks to the bathroom, while the sedative medication, usually administrated as part of the routine, decreases the perception for micturition. Thus, 40% - 50% of the senior patients become incontinent after the first 24 hours from the admission (functional urinary incontinence) (126).

Cutaneous lesions emerge in the first hours from bed immobilization, and are aggravated by inaccurately care for urinary incontinence.

Hospitalized seniors (especially at their first admission) are predisposed to confusion syndromes, especially those with sensory deficiency: sight disturbances (presbyopia, cataract), auditory deficiency, and loss of balance. The confusion syndrome might evolve towards delirium, favoured by the unfamiliar environment, diffuse light, absence of wall clocks/calendars, lack of auxiliary elements for communication and orientation: glasses, hearing aid etc (125).

Hospitalization of senior patients can lead to malnutrition and dehydration, because the food from the hospital is non-appetizing, especially if the patient is subjected to a diet imposed by the underlying diseases. In addition, the meals are served in bed, where it is difficult to handle the cutlery due to the position in bed (especially for people with motor impairments), correct hydration during the meal, the necessity of a support person that does not arrive on time – the food gets cold and unpleasant, all of these add to the altering of the nutritional status (127).

These undesirable effects can be much diminished if, immediately after the admission, the CGA is carried out in order to identify for every patient the risk factors induced by the hospitalization, to thwart them and thus avoid that the hospitalization propel them beyond the

frailty threshold in the area of dependence by another person. The physician who decides the admission must be convinced that this is strictly necessary and that the discharge will be as fast as possible. The clinics of geriatrics have friendly parlours with low beds, carpet, adequate lighting. The tables are moved to the living room, in the common space. The patients benefit from sources of information (newspapers, magazines, TV network) and are encouraged to bring glasses, hearing aids, teeth prosthesis from home, favouring the communication and contact preservation with the others.

Prevention of iatrogenic pathology is centred on a few fundamental directions (128):

A. Pharmacovigilance or adaptation of the medical prescription to the functional, cognitive, social and financial reality in which the patient lives, along with comorbidities and polymedication.

B. Systems of error and therapeutic non-adherence identification:

- educating the medical team in the sense of a relationship based on mutual trust and respect with the elder; lack of communication leads to the decrease of adherence and increases the risk of undesirable effects, caused by incorrect administration
- systems of monitoring drug administration at home (POEM – Polymedication Electronic Monitoring System)

C. Use of computerized system with the help of which different receipts are verified in terms of undesirable side effects occurrence

D. Regular re-evaluation of the therapeutic scheme, preferably by a geriatrician or the multidisciplinary geriatric team, along with medication adjustment according to the evolution of comorbidities and patients' expectations, assessment of therapeutic adherence and compliance with their lifestyle. The aim of the treatment in patients with multiple comorbidities and increased risk of handicap shall improve the symptoms (thus, the quality of life) and less to influence the development of various conditions. The wellness of the elder depends on the psychological, social and environmental context in which he lives – the therapeutic scheme must ensure the preservation if not, the increase of life quality, compared to the situation prior to the moment of addressing the physician.

E. Compulsory integration of the iatrogenic issue in any etiological medical reasoning.

Decalogue of drug prescription for the seniors (103):

1. Make sure that the diagnosis is correct and complete, evaluate the comorbidities and functional condition. In case of uncertainty, it is preferred not to prescribe at all.

2. Carry out a careful anamnesis of drug consumption, take inventory on all the drugs recommended by all the physicians for all the comorbidities. Do not forget about the self-medication!

3. Do your research on pharmacokinetics and the side effects of the concerned drugs.

4. Make sure that the treatment is correct and appropriate, with a favourable efficiency/risk report and associate non-pharmacodynamical measures.

5. Draw up the simplest therapeutic scheme and the most accurate prescription.

6. Start with the minimum dose and slowly titrate until you reach the optimum minimum dose.

7. Dynamically adjust the scheme by regulated consultations; according to efficiency and tolerance, insist that the patient bring all the drugs that he consumes to every consultation.

8. Consider the impairment in people who take care of themselves.

9. Carefully instruct the patient and/or his entourage in what the medication is concerned (for what, how, possible side effects, possible overlap with the symptoms of the disease).

10. Expect non-adherence; tell the patient what to do in case he misses one dose; ensure therapeutic adherence and check the adherence before stating the therapeutic inefficiency/resistance.

To summarize, senior patients need a careful monitorization and a refined therapeutical individualization. These patients are difficult to include in the standardized medical procedures due to comorbidities, functional deficits and very often the need of a poli-pharmaceutical approach with possible medical interferences.

Points to be taken care of for appropriate prescription in elderly or DONTs in elderly psychopharmacology are summarized as follows:

- Avoid polypharmacy
- Avoid prescribing to treat side effect of another drug
- Avoid expensive medications while cheapest alternative is available – it will increase therapeutical adherence
- Avoid the concept of "a pill for every ill"
- Avoid therapeutic duplication
- Avoid starting two agents at the same time
- Avoid drugs that are likely to cause ADRs in elderly

Therapeutical individualization must take care of the patient's and his family's needs, respecting the rules of informed consent; these patients should have a multidisciplinary approach without excessive hospitalization due to the complex psycho-social context of the patients himself.

The demographic trend of the aging of population with an increment of the old and very old persons suggests the imperious need of a geriatric education for all doctors, no matter the specialty, which should be acquired during student hood and afterwards. Geriatrics, until recently still in the process of defining itself, begins to surface in the first line of medical assistance (in hospitals and out-patient system) as every specialist would have to treat elderly persons; who is not a pediatrician will be a geriatrician (129).

The future will bring us new specialties such as geriatric cardiology. Cardiology is partly responsible for the increment in life expectancy and suffers the impact of a growing mass of senior patients who suffers mainly from a cardiological problem and implies important costs.

Iatrogenic pathology, extremely frequent in elderly, should be introduced in every specialty's curricula because avoiding drugs' side effects is as important as insuring therapeutical efficacy; iatrogeny can spoil the results of any good treatment and can increase patients' suffering and medical costs (130).

One of the main goals in fighting iatrogeny is insurance of a good compliance to therapeutic recommendations.

4.2. THERAPEUTIC ADHERENCE

The adherence/compliance to treatment is defined as the extent to which a person will correspond with the recommendations of the health-care provider. It is a complex behavioural process strongly influenced by the environments in which patients live and healthcare providers practice. Furthermore, non-adherence or "non-compliance" represents the extent to which the patient's behaviour does not follow medical recommendations. „Non-adherence is not a new phenomenon. The first recorded case took place in the Garden of Eden with dire consequences" (131).

Scientific interest into non-adherence started in 1943, but it was only 30 years ago when the seriousness of the problem was fully recognized and research began in earnest. It was noted that the senior population is particularly vulnerable to non-adherence due to several reasons: physical barriers (sarcopenia, arthritis, tremors), functional barriers (memory loss, confusion),

polimedication, polipharmacy and iatrogeny, insufficient income, familial and social circumstances, and last but not least the nature of the patient–doctor relationship (132).

We are unable to predict patients' non-adherence at rates better than chance. When any member of the medical team asks about adherence, patients tend to exaggerate ("white coat" effects); therefore, patients' self-reports usually overestimate compliance by a significant amount. Recent studies (132, 133) report that up to 60% of all medication prescribed is taken incorrectly, or not at all. 90% of elderly patients make some medication errors, and 35% make potentially serious errors. 40% of all admissions are due to medication-related problems.

Non-adherence can lead to treatment failure, unexpected side effects, further physical or mental health problems, service costs and career burden (131, 133). Non-adherence as a phenomenon spans medical disciplines but research by its nature tends to be discipline-specific in outlook, often limited to a specific diagnosis or medication. Recent reviews (129, 134) consider that effective interventions on non-adherence should be complex, combining approaches such as counselling, information, reminders and family therapy; however, statistically significant positive findings did not always lead to worthwhile improvements in clinical outcome. Most meta-analyses include only papers that are methodologically robust; however, as most research in this area is small scale, adherence is often a secondary outcome measure nested within a larger study, and the quality of papers tends to be poor (135).

Poor adherence to drug therapies still represents an unsolved problem and is much more severe in senior patients. This contingent of population often has numerous comorbidities that need numerous medical services, aggressive investigations and polimedication, usually prescribed by different specialists. Polimedication means difficult therapeutical schemes, usually with inappropriate drug posology, recommended to patients with cognitive disorders, sensory and motor deficiencies and lack of familial or social support for the possible handicap (135, 136).

The number of seniors increases as an absolute value and as a percentage of the whole population; in USA, elderly population increased from 3 million in 1900 to 35 million in 2000 and the expectancy for 2030 is 40 million. Several studies (130, 137) reported that more than 40% of elderly patients take 5 or more different types of drugs/day and 10% takes 10 or more different drugs/day. It is widely agreed that the use of ≥ 5 different drugs/day is highly associated with therapeutical non-adherence, iatrogeny, and risk for inducing geriatric syndromes such as: falls (orthostatic hypotension) and fractures, urinary incontinence (abuse of diuretics), cognitive impairment (abuse of sedatives, anti-depressants).

Therapeutical non-adherence may take many forms, e.g., not following dietary or exercise recommendations, not taking the prescribed number of pills or taking them at irregular or otherwise nontherapeutic intervals, not refilling prescriptions, and not showing up at follow-up clinic visits. As such, unexpected side-effects might appear, especially due to overdose. Especially in the elderly, mistaking one pill for the other is quite often and can also lead to unexpected results, which is why therapeutic adherence should be encouraged as much as possible by prescribing the smallest number of pills and choosing fixed drug combinations (one pill instead of two) whenever possible (138).

There are numerous studies (139, 140, 141, 142) that have proposed several methods to fight non-adherence. We consider that there are two different, yet complementary approaches to this problem: the first direction should be the medical approach and the second should be the telemonitoring and e-health services.

The first line is the multidisciplinary medical approach, due to the complex psycho-social context of the senior patients themselves. The medical team (geriatrician and general practitioner, psychologist, dietetician, kynetotherapist, nurses, social services, caregivers) should encourage treatment adherence by clearly communicate with their patients about therapeutic goals and methods to achieve them and by giving legible written instructions after

considering the complexity of dosing schedules, expense, and potential adverse effects. Moreover, the patient should be continuously supervised, controlled and encouraged in respecting medical recommendations, and also should be permanently checked for side effects and/or adverse events that can occur from the medication itself.

Our long-term experience in fighting non-adherence materialized in several papers, several books and chapters in books, symposia and workshops in many congresses and conferences in the past 15 years. I present the most significant papers and projects in this domain as follows:

Alexa ID, Stoica S, Burca P, Obreja L, Rusu RI, Ungureanu G, Covic A. Non-compliance in a large population of elderly patients with cardiovascular disease. *Maedica. A Journal of Clinical Medicine* 2006;1(3):14-18.

Ungureanu G, Stoica O, Vulpoi C, **Alexa ID**, Ardeleanu S. Iatrogenic pathology – problems of the management. *Rev Rom Bioetica* 2007; 5(1):68-74.

Ungureanu G, **Alexa ID**, Stoica O. Iatrogeny and the elderly, *Rev Med Chir* 2007; 3(4):803-810.

Alexa ID, Prada GI, Donca VI, Mos LM, Alexa O. Improving quality of life of elderly people aged 85 and older by improving treatment adherence. *Proceedings of the 4th International Conference on E-Health and Bioengineering (EHB 2013) Iasi, 2013.*

Alexa ID, Ilie AC, Morosanu AI, Cracana I, Onutu R, Prada ID. The Role of Non-Adherence as Main Cause for Hospitalization in Elderly Patients, *The 8th Congress of the International Association of Gerontology and Geriatrics European Region, Dublin, 2015.*

The project “A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multicenter, Non-Inferiority Study Comparing the Efficacy and Safety of Once-Daily Oral Rivaroxaban (Bay 59-7939) with Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects with Non-Valvular Atrial Fibrillation”.

4.2.1. Non-compliance in elderly population

We conducted a prospective study of 922 patients aged ≥ 65 years admitted during the period Jan 2004 – Jan 2006 in the Geriatric Department of “Dr. C.I. Parhon Hospital” for cardiovascular diseases. The results were published in the paper “Non-compliance in a large population of elderly patients with cardiovascular disease”. Data was collected for each person by way of an interview with the patient and compared with information from past medical records or family members. We assessed the main causes of their admittance in the hospital, carefully looking for possible or probable cases of non-compliance. We also assessed the main causes of non-compliance and based on these results we tried to find a better way to solve them. The mean age of the study group was 74.5 years, ranging from 65 to 91 years. There was a slight preponderance of women (58, 03 %). About 9% were living alone and about 59% completed high school. The average number of different drugs prescribed was more than 4 and the average number of pills taken daily was 5.8.

The analysis of interviews revealed that 90 patients (9.76%) were hospitalized for aggravation of their cardiovascular disease due only to non-compliance and 148 (16.05%) had other factors that led to non-compliance (e.g. nausea and vomiting, dizziness, negative stress). The non-compliant population lived equally in town and village area. Most of them were 70 to 80 years old (48.89%), did not complete high school (72.22%) and had an income below 350 RON. These patients had 166 admittances during study period, which means 1.84 hospitalization/patient. Most of these patients had ischemic heart disease as main cardiovascular disease (46.67%) followed by hypertension (18.89%), arrhythmias (17.77%) and dilative cardiomyopathy (16.67%) (Table X).

The most common cause of non-compliance was inadequate income, followed by low level of instruction (they did not know how to take their medication), too many drugs, physical barriers (visual disturbances or arthritis), and unpleasant side-effects from the medication. A small number of patients were living alone and experienced minor cognitive dysfunction and depression, or perceived treatment as not necessary or under-dosed medication deliberately.

The results of this study tried to identify certain characteristics that could be used to build a pattern for senior patients with cardiovascular diseases at risk of non-compliance.

Table X. Characteristics of the three groups; the results are expressed as mean values \pm SD.

* = $p < 0,01$ group 1 vs group 2 and 3; ** = $p < 0.01$ group 1 vs group 3.

	Group I (N = 90)	Group II (N = 148)	Group III (N = 684)
Mean age, years	73,5 [65-91]	74,5 [65-91]	75,5 [65-91]
Gender (% M)	51 (56,7%)	79 (53,4%)	400 (58,5%)
Living alone, %	14,4%*	6%	7,2%
Living area (% rural)	50 (55,5%)	80 (54,1%)	367 (53,6%)
Completed high school	25 (27,78%)*	62 (41,89%)	357 (52,19%)
Monthly income			
• < 100 Euro	65 (72,22%)*	85 (57,43%)	367 (53,65%)
• > 100 Euro	25 (27,78%)*	63 (42,56%)	317(46,35%)
Average number of different drugs prescribed	4.7 \pm 0,11	3.9 \pm 0,20	4 \pm 0,13
Average number of pills taken per day	6.2 \pm 0,09	5.7 \pm 0,10	5,5 \pm 0,11
Mean hospitalization, days	8.5 \pm 0,23	6.5 \pm 0,14	6 \pm 0,18
Mean cost hospitalization/day (Euro)	323 \pm 2,46	303 \pm 3,04	304 \pm 2,78
Total cost hospitalization (Euro)	2745,5 \pm 34,88*	1969,5 \pm 26,70	1824 \pm 32,45
Main cardiovascular disease			
• ischemic heart disease	42 (46,67%)	62 (41,89%)	303 (44,30%)
• hypertension	17 (18,89%)	38 (25,68%)	178 (26,02%)
• arrhythmias	16 (17,77%)	36 (24,32%)	185 (27,05%)
• dilatative cardiomyopathy	15 (16,67%)**	12 (8,11%)	18 (2,63%)
Cardiovascular risk factors			
• smoking	35 (38,88%)*	30 (20,27%)	122 (17,84%)
• alcohol	30 (33,33%)*	25 (16,89%)	116 (16,96%)
• obesity	14 (15,55%)*	43 (29,05%)	197 (28,80%)
• high level of cholesterol	45 (50%)*	38 (25,68%)	164 (23,98%)
• diabetes	16 (17,77%)**	41 (27,70%)	205 (29,97%)

Some of these characteristics included: patients with low income and expensive medical prescriptions, patients with low educational level and sophisticated medical regimens, who received too many drugs, who had only partial recall of their medical regimens.

Our data suggested, even at that moment that better education about the role of dietary recommendations and about the necessity of respecting medical regimen should help in decreasing non-compliance all along with decreasing hospitalization and medical costs.

4.2.2. Management of iatrogenic pathology

The problem of iatrogeny was a main preoccupation of our team, lead at the time by Professor Gabriel Ungureanu. The problem of identification and management of iatrogenic pathology in general population, and in seniors in particular were largely discuss in two papers that were published in 2007: “Iathrogenic pathology – problems of the management”, which was the first paper in Romania to present to causes and the implications of iatrogeny amongst doctors and their patients, and “Iatrogeny and the elderly”, which represents the review of our seven-year experience in the domain of pluripathology of elderly patients which was usually associated with iatrogenic manifestations.

Our experience showed that the practical approach of the extremely complex and delicate problematic of the prevention of the iatrogenic pathology is entailed by numerous difficulties such as: defining the domain, the epidemiological dimension (actually unknown even in the countries with the most advanced health systems), the enormous economical burden, the awful ethical dilemmas - the doctor who made a medical mistake has to face it -, the lack of a systematic education organized in the field of iatrogeny, the lack of an adequate systematic instruction for the doctors in the field of the therapeutic education of the patients, the possible confusion between the avoidable, correctable and preventable causes of the iatrogeny and the unavoidable and non-imputable causes (143).

The therapeutic education of the patient and of the entourage represents the key of the medical compliance, the guarantee of the efficiency of the therapeutic strategy and of the avoidance of the iatrogeny. The deficiencies of therapeutic efficiency and the phenomena of intolerance to drug regimens represent the main causes of a poor compliance; together with the handicaps imposed by the malady and the restrictive constraints of the medical recommendations, the inefficiency and the intolerance of the therapy wear away the capacity of the patient’s adapting to the servitudes imposed by the disease and the doctor’s recommendations and push him to abandon (144).

A first step, extremely difficult, but unavoidable in unlocking the approach of the iatrogenic pathology, should be represented by the changing of the perception upon the causes and responsibilities in launching this pathology, change which is necessary to be done both among the doctors and the great public. An efficient approach imposes first of all that the doctor should become sensitive, responsible and not to be considered guilty.

The risk is inherently part of the modern medicine: the more efficient the conduct is, the bigger the potential of iatrogeny. We have to live with this risk, to know it, to weigh it (as reported to the benefit), we have to inform the patient (the informed consent, compulsory in the modern medicine where the patient is the doctor’s partner), to take all the measures to avoid it, reduce it and finally assume it. Otherwise, the doctor has the right to err, and the error is possible and probable at every level of competence (145).

The responsibility of the health system can be invoked in the absence of the insurance of the doctors’ formation in the field of iatrogenic pathology and the therapeutic education of the patients (the education of the educators), of the organization and financing of this education by building up a pluri-disciplinary team in charge of therapeutic education (family doctor, specialist, nutritionist, nurse, kinesytherapist, psychologist etc) with provision and discount of the time allocated to the therapeutic education and the control if its efficiency; in the case of the patients that are unable to take care of themselves due to the physical and mental disabilities, the health system has the responsibility of taking them in charge, in a well structured frame, either through home assistance or in specially organized institutions (146).

This paper -“Iathrogenic pathology – problems of the management”, which was written by Ungureanu G, Stoica O, Vulpoi C, Alexa ID, and Ardeleanu S., and published in Rev Rom Bioetica is one of the very first to make a statement in the field of iatrogeny: that we must accept

iatrogeny, we must know it, we must face it and, above all, we must fight it. We should no longer ignore it but we must make sure that all doctors are well informed about the complex mechanisms of iatrogenic pathology. This statement was a major goal of Professor Gabriel Ungureanu and myself and was the foundation of other papers that illustrated the necessity of assuming and treating negative side-effects of our best treatments. It was also the foundation for an optional course for students that had an enormous success and, we hope, had an important impact for their future medical careers.

4.2.3. Treatment adherence and QoL in senior population

A rather new line of research is the study of iatrogenic pathology in senior population. It is the result of the conjugation of two major demographic phenomena: an absolute and percentage increase of senior population parallel with an increase of prevalence of iatrogenic pathology with age. That's why iatrogeny in seniors becomes a major health problem, unfortunately often ignored, neglected and even obscured despite of well-recognized impact over duration and quality of patient's life as well as over the cost of medical assistance.

We conducted a retrospective study that included 126 elderly patients aged 85 and older admitted to the Geriatrics Department of "Dr. C. I. Parhon" Hospital between January 2012 and July 2013. The results were published in the paper: "Improving quality of life of elderly people aged 85 and older by improving treatment adherence".

Patients' data were recorded in a secured database that contained demographic information (age, gender, address, income, whether the patient has any family or is living alone), clinical data such as fatigue, elements of frailty and/or sarcopenia, and compliance to treatment) and also data about patient's current medication. Information about therapeutical adherence was collected for each person by way of an interview with the patient. The questionnaire consisted in verifying their knowledge about their diet and medication and comparing it with information from past medical records or from family members.

The data were analyzed by means of version 20 SPSS software; patients were divided into two groups according to their therapeutical adherence as rated by the physician (compliant = group A vs non-compliant = group B); a correlation test was performed in order to identify factors that influence adherence to treatment. Those factors were then assessed by means of both parametric and non-parametric tests, according to data type. When possible, Fischer Exact test was employed, for detecting correlations between non-parametric dichotomous data. The statistical significance was defined as $p < 0.05$. Continuous data was expressed as mean \pm SD.

There were no statistically significant differences between groups A and B regarding gender (42,3% males and 57,7% females in the compliant group versus 35,4% males and 64,6% females in the non-compliant group) and age (mean age in group A = $83,9 \pm 2,9$ years, whereas in group B it was $83,5 \pm 2,8$ years). There was an important difference between the groups regarding income, but it did not reach statistical significance ($1058,1 \pm 902,1$ RON in group A vs $680,4 \pm 318,3$ RON in group B), with $p = 0,1$.

Clinical data was similar in the two groups, with fatigue present in 46 patients (59%) in group A and in 24 patients (52,1%) in group B ($p=0,4$); a decrease in mobility was noted in 49 patients (62,8%) in group A and 32 patients (66,7%) in group B ($p=0,7$) and a decrease in muscular force was present in 9 patients (11,5%) in group A and 3 patients (6,2%) in group B ($p=0,5$).

Among the tested parameters, one of the most important factor that influence adherence to treatment was the area where the patient had residence - living in a rural area seems to increase the probability that the patient will be non-compliant, with $p = 0,04$ as assessed by Fischer exact test. Of the patients that lived in a rural area, 53,6% were compliant and 46,4% were not as compared to patients from urban area, where 71,9% were compliant and 28,1% was not.

A second factor that influenced adherence to treatment was the number of pills that the patient was taking prior to admission, with an average of 4,79 pills/day in group A and 3,54 pills/day in group B ($p=0,02$).

Living with family had a statistically significant influence on adherence. In group A, 33 patients (42,3%) lived alone, as compared to 31 patients (64,5%) in group B ($p = 0,01$).

We were surprised to find a statistically significant correlation between a larger number of pills and therapeutical adherence (4,79 pills/day in group A and 3,54 pills/day in group B, $p=0,02$) and not other way around. It is probably due to the fact that patients that were considered compliant had a better recollection of the drugs they were currently taking, whereas non-compliant patients did not remember what medication they were under, no matter the number of pills/day.

This was a limitation of our study as we were not able to find out if all the patients in Group A really followed medical prescriptions, even if they remembered the drugs they were on. Patients with a partial recall of the posology of their medication regimen are usually at higher risk for adverse effects than those with no recall at all, possibly because patients with no recall seek assistance more readily due to rapid worsening of symptoms; patients with partial recall are more prone to experience negative side effects due to overdosing the drugs they could remember, such as digoxin toxicity, oral anticoagulants or beta-blockers overdose.

An important factor for non-adherence was living alone status ($p = 0,01$), which was consistent to other studies (147, 148). We believe that loneliness in senior people is associated with poor health outcome because lonely people do not or cannot perform healthy behaviours, such as medical adherence, physical exercise, good diet and adequate sleep. It appears that people who are lonely have a tendency to see their life circumstances as more stressful, unpredictable, and overwhelming when compared to those who are less lonely (149).

The results of our study confirm several factors involved in therapeutical non-adherence. These included patients from rural areas, with low income and expensive medical prescriptions, patients with low educational level and sophisticated medical regimens, patients who receive too many drugs, patients with cognitive dysfunction and who live alone, patients who have only partial recall of their medical regimens, smokers and/or alcohol abusers. Fighting non-adherence should rely upon two complementary directions: the multidisciplinary medical approach and the telemonitoring and e-health systems, in order to assist very old patients in taking their prescribed medical schedule throughout the rest of their life.

This paper was one of the first to present the research domain on very old patients that I wanted to focus on. As the very old population is by far the largest and the most rapidly growing proportion of the whole population and the largest group as drug consumers, I consider that there is much to be discussed about the best therapeutical approach to this particular group, highly exposed to polipharmacy and polipragmasy and at the crossword between medical treatment and palliative care.

Historically, much of the focus on this subject has been driven by the sheer scale of use and also by concerns over the propensity for older consumers to experience adverse reactions. More recently, the abandonment of inappropriate upper age limits in many major clinical trials has uncovered the failure of chronological age to diminish in any way the capacity to benefit from evidence-based drug therapy. Under-prescribing, therefore, can no longer be considered acceptable, any more than can the excessive or inaccurate use of drugs (111).

Safe and effective pharmacotherapy remains one of the greatest challenges in geriatric medicine. The diminished physiological reserve associated with ageing can be further depleted by effects of drugs and acute or chronic diseases. Age alters pharmacokinetics and pharmacodynamics of many drugs.

In most developed countries, about two thirds of the senior population take prescription and nonprescription over the counter drugs. At any given time, an average elderly person uses

four to five prescription drugs and fills 12-17 prescriptions a year. The frail elderly patients use the most drugs and persons 85 years + are the best examples of this kind. Drug use is greater in hospitals and nursing homes than in the community – typically, a nursing home resident receives at least seven to eight drugs (150).

Many drugs benefit elderly patients but, while prescribing antibiotics and thrombolytic therapy, oral hypoglycemic agents and antihypertensive drugs, analgesics and antidepressants, the important thing are to succeed in finding the best associations that is whether the potential benefits out-weight the potential risks.

4.2.4. The relationship between non-adherence and hospitalization in senior patients

This theme was the main feature in a multicenter study, that involved, beside our team, the team of Prof. dr. Gabriel Ioan Prada from the University of Medicine and Pharmacy “Carol Davila” from Bucuresti, and also involved the co-operation of the team of psychologists of Assoc Prof. Ovidiu Gavrilovici from the University “Al. I. Cuza” Iasi. Together we hoped to find several characteristics that could be used to identify aged patients at risk of non-adherence in order to prevent this phenomenon and thus decreasing hospitalization and medical costs.

We based our teaming only on patients’ admittance to compliance or non-compliance to medical advice. However, we believe that the real number of cases of non-compliance might be higher as patients were not entirely truthful in interviews, mostly because they became ashamed of not having followed medical recommendations. An important factor for non-adherence was living in a rural area. This observation is in agreement with other studies and has several explanations: longer distances from any medical institution and/or pharmacy, lower degree of education and lower understanding of the importance of following medical recommendations, lower income and impossibility to fulfil elaborate prescriptions, unsatisfactory relationship with the local general practitioner and distrust versus his/her medical advice (151).

Given the importance of the growing need to improve medication adherence, choosing the best intervention represents a challenge for healthcare providers, and we consider that telemonitoring and e-health systems are the most interesting approaches to the elderly patient of XXIst century. There are many programs that encompass this domain but one of the most interesting for our study is the polymedication electronic monitoring system (POEMS), developed by the Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland, 2013. This system allows reliable and precise measurement of patient adherence to medications by incorporating a micro circuitry into dose-dispensing drug packages of various designs, such that the manoeuvres needed to remove a dose of drug are detected, time-stamped, and stored. The personalized dose-dispensing aid organizes individual oral doses according to their prescribed intake schedule throughout the day and the week (141).

The electronic monitoring of the entire therapy would reveal an intake pattern that would have remained undiscovered with any other device and would allow a personalized intervention to correct an inadequate medication intake behaviour. POEMS may guide health professionals when they need to optimize a pharmacotherapy because of suspected insufficient adherence. Furthermore, knowing the intake pattern of the entire pharmacotherapy can elucidate unreached clinical outcome, drug-drug interactions, and drug resistance. In the near future, one could imagine that medication adherence data over the entire therapy plan would be available as soon as the electronic wires are activated, so that a failure to take medication could be detected immediately and intervention could be taken if appropriate (141).

4.2.5. Identifying efficacy, safety and side-effects of novel drugs

I had the opportunity to work in several studies focused on identifying efficacy and, more importantly, safety and side-effects of novel drugs. Amongst these, the clinical trial I think was the most important is ROCKET, the results of which contributed to establishing Rivaroxaban as a novel and useful drug in the prevention of stroke and non-central nervous system systemic embolism. The official title was “A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multicenter, Non-Inferiority Study Comparing the Efficacy and Safety of Once-Daily Oral Rivaroxaban (Bay 59-7939) with Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects with Non-Valvular Atrial Fibrillation”.

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a fivefold increase in the risk of stroke. AF affects approximately 1% of the general population and 9% over the age of 80 years. Vitamin K antagonists (VKAs) reduce the risk of stroke by two-thirds in patients with AF but have multiple drug and dietary interactions, a narrow therapeutic window and inconvenient monitoring requirements. The limitations of VKAs contribute to their under-utilization in patients with AF who are at moderate or high risk of stroke, and the effectiveness and safety of VKA treatment is reduced by the difficulty in maintaining the international normalized ratio (INR) in the target range of 2–3. Recently, several new oral anticoagulants have been evaluated as alternatives to warfarin for stroke prevention in patients with AF, such as the direct Factor Xa (FXa) inhibitor rivaroxaban (152).

The ROCKET AF study was a blinded, double-dummy, randomized-controlled trial in which 14,262 patients with nonvalvular atrial fibrillation at increased risk for stroke were assigned to rivaroxaban 20mg daily (or 15 mg daily in those with creatinine clearance [CrCl] 30–49 ml/min) or dose-adjusted warfarin (target INR: 2–3). The study started in November 2006 and I was study coordinator for the " Dr. C.I. Parhon" Hospital site. The main objective of the ROCKET AF trial was to demonstrate non-inferiority of rivaroxaban compared with warfarin for the prevention of stroke or systemic embolism in patients with AF (153).

The ROCKET AF trial recruited patients from 1178 centres in 45 countries. Patients were eligible for inclusion if they had electrocardiographic evidence of AF within 30 days prior to randomization and either a history of stroke/transient ischemic attack (TIA) or systemic embolism or at least two of the following additional risk factors for stroke: heart failure or a left ventricular ejection fraction of 35% or less, hypertension, age ≥ 75 years or the presence of diabetes mellitus. By excluding AF patients without a previous stroke/TIA or systemic embolism who did not have at least two other risk factors for stroke, and by limiting inclusion of patients with two other stroke risk factors to 10% of the cohort at each site (other patients without a history of stroke/TIA or systemic embolism had to have at least three risk factors), the ROCKET AF trial included a patient population at higher risk of stroke than those included in other new oral anticoagulant trials in AF. A higher risk population increases study power but is less representative of the broader AF population that is expected to benefit from anticoagulant treatment (154).

The primary efficacy outcome was the composite of stroke and systemic embolism. Stroke was defined as an acute, focal neurologic deficit of presumed cerebro-vascular etiology that persisted beyond 24 hours. If the deficit lasted for less than 24 h, it was defined as a transient ischemic attack (TIA). Brain imaging was encouraged for all suspected strokes and was performed in 82.1% of patients reported to have had a stroke. Systemic embolism was defined as acute vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion (not associated with another likely cause). The primary safety outcome was the composite of major and clinically relevant non-major bleeding. Major bleeding was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a

critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal or intramuscular with compartment syndrome), fall in hemoglobin concentration ≥ 2 g/dl, transfusion of ≥ 2 units of whole blood or packed red cells, or permanent disability. Critically relevant non-major bleeding was defined as bleeding that did not meet the criteria for major bleeding, but necessitated medical treatment, unplanned medical attention or temporary interruption of the study drug. The protocol specified the need for follow-up visits at 1, 2 and 4 weeks then monthly thereafter for INR measurement and surveillance of primary safety and efficacy outcomes (155).

We found that baseline characteristics and rates of prior VKA use were similar in both groups. The patients had a mean CHADS₂ score (a clinical stroke risk stratification tool for patients with nonvalvular AF that takes into account a past history of congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus and stroke/TIA) of 3.5 and a median score of 3.0 and scores were similar in each treatment group. INR values were in the therapeutic range (2.0–3.0) a median of 58% of the time for patients in the warfarin group, which is similar to that reported in community cohorts, but lower than the median time in therapeutic range (TTR) reported in the RE-LY (67%) and ARISTOTLE (66%) trials. The median treatment exposure was 590 days and the median follow-up was 707 days; the difference of more than 100 days between exposure and follow-up may, in part, explain the differences between the results of the 'per-protocol' and 'intention to treat' analyses. Only 32 patients were lost to follow-up. A total of 93 patients (50 in the rivaroxaban group and 43 in the warfarin group) were excluded from all efficacy analysis because of violations in Good Clinical Practice Guidelines (156, 157, 158, 159, 160).

5. ETHICAL AND SOCIAL PRACTICES IN ELDERLY CARE

5.1. ETHICAL DILEMMAS IN TREATING SENIOR PATIENTS

It is extremely challenging to establish a good medical approach in senior patients, which means taking into consideration the physiological changes induced by aging itself, the feature of getting the informed consent and preserving the confidentiality of medical actions, the determination of the capacity of decision, establishing a plan of treatment without depriving them of therapeutic options and at the same time keeping them away from polypragmasy, of the transfer of decisional capacity, of the recommendations of home care or institutionalization, of the need of palliative care (161).

Clinical ethics consists in the identification, analysis and settlement of moral problems arising from caring. The main universal ethical principles used as guidelines in caring and treating the elderly persons are the following: autonomy, beneficence, non-maleficence, justice and equity. The principle of autonomy refers to the right of any individual to control their life. The principle of beneficence refers to the duty of doing what is the best for each patient, while the principle of non-maleficence refers to the duty of the physician to do no harm. The principle of justice and equity refers to the duty of treating each individual equitably, depending on the needs. To these basic principles one may also add the principle of confidentiality of the medical actions, the informed consent and the informed refusal, veracity and privacy. In caring an elderly person, the clinician frequently confronts ethical dilemmas resulted from the apparent antithesis of two or more of these principles (162).

The ethical principle of autonomy underlies the initiation of the informed consent. In order for the elderly patient to be autonomous in decision-making, they must be very well informed in respect of the disease and the treatment options.

The assessment of the cognitive capacity and of the presence of serious depression in order to determine the capacity of judgment on the manner they control their life, observing the right to autonomy. More than a half of the patients with mild-moderate dementia may have their decisional capacity impaired, patients with serious dementia have a universal decisional incompetence, and 20-25% of the patients with serious depression have their decisional capacity gravely affected (163).

There is no well-established algorithm to determine the decisional capacity but a thorough CGA should determine the degree of cognitive impairment and the presence of depression and if any psychological and/or psychiatric help is needed. Those with serious dementia shall be considered with no decisional capacity, which shall be exercised by the family or by the legal representative. Subsequently, in the case of all elderly people, including those with mild and moderate cognitive impairment and those with depression, the four main aspects concerning determination of the decisional capacity should be assessed: the capacity of the patient to express a preference of treatment/diagnosis without changing it at every assessment, understands the relevant information, understands the medical situation/impairment and its consequences or treatment's consequences, and understands the treatment/diagnosis options and offers reasonable explanations for their choice. The level of the decision-making capacity must be according with the importance of the risks and benefits of the decision. The elderly patient with dementia may express their will in respect of, for example, the performance of a minimum invasive diagnostic procedure, but in the event of a diagnostic or therapeutic procedure with high risk of complications or even death, the burden of the decision should not be let solely on the patient (164).

Building a physician – patient relationship based on mutual trust and respect so that the patient is convinced that in his doctor's care, the principles of beneficence and non-maleficence,

as well as justice and equity are observed. Such a relationship is built with patience and in a significantly larger lapse of time than in the other categories of age, due to the physiological and psychological limitations of the elderly people: decrease of the auditory and visual capacity, reticence in making changes in the daily routine, the lack of trust in the “wonders” of medicine, the lack of trust in the equity of the sanitary and social systems, the fear of the unknown, of the physician, of the hospital, the decrease of the capacity of adaptation, the decrease of access to information systems (165).

Therefore, CGA will be able to determine the capacity of the senior person in exercising the right to autonomy; for those who have different degrees of cognitive impairment, dilemma occurs – is our patient able to make the correct decision related to their lifestyle? Under these conditions, does the informed consent truly respect the patient’s will? Elderly persons with cognitive impairment must have the support of the family and/or of the closest person the patient trusts to exercise and take over their rights to autonomy. This person should be named when no cognitive problem could be suspected, so that there is no further suspicion related to decision-making.

On the other hand, the principle of autonomy also underlies this principle of ensuring the confidentiality of the medical action. Being autonomous means control personal data. And ensuring confidentiality is the basis of the physician – patient relationship, which should be built on mutual trust and collaboration. However, this principle may be breached when the patient, through their decisions and actions, are hurting themselves, neglect themselves, or their behaviour exposes the others at risk (166).

Observing all ethical principles, the elderly should not be treated differently than adult patients. Therefore, observing the fact that any patient, including the elderly, must be treated equitably depending on necessities, age should not be a criterion in choosing an option of diagnosis, treatment or care. Still, there are several features to take into account:

1) The access to clinical trials is dramatically limited for very old persons so that most of the studies do not include patients over 75 or 80 years old, although this age category becomes more and more numerous. Also, the access is limited for the elderly with comorbidities – that is the majority of the patients in this contingent – due to the suspicion that the normal results would not be reliable due to the increased risk of complications, side effects, repeated hospital admissions, which may result in the end of the trial and even death. Very strict regulations applied to pharmaceutical trials limit the participation of the elderly because of the assumed risk of polipragmasy and iatrogeny (167).

2) The access to medical services is limited for the elderly patients, as they confront with difficulties in using the means of communication with the physician (telephone, email), transportation, current financial problems. Also, the medical system and the nursing network do not come to support the elderly by visits at home, ensuring prescriptions, and psychological support (168).

Establishing a good therapeutical management for our senior patient is a big challenge as it must take into consideration some particular issues characteristic to old age:

1) The physiological decline inevitable to ageing: the free water decreases, the ratio of the adipose tissue increases, changes of the hepatic and kidney metabolism occur, and changes in drug elimination. All these changes influence pharmacokinetics and pharmacodynamics of drugs, resulting in the increase of incidence of side effects, of their toxicity, even at reduced doses. There could be mild cognitive impairment, so complicated schemes and polypharmacy should be avoided.

2) The presence of several comorbidities, with numerous and various interclinical examinations with the elaboration of numerous and various therapeutic schemes (polypharmacy) is at risk, most of the times, to increase the risk and number of negative side effects (137).

The trend in establishing medical treatment is to observe the recommendations from the guidelines, but there are few guidelines specially adapted to the needs of the elderly, and in most of the cases we have just several recommendations, letting the decisional process at the choice of the prescribing physician. The ethical dilemma is: do we treat according to the recommendations of the guidelines or do we adapt medication according to the particular needs and possibilities of our patient? It is important to remember that the elderly have frequently not one, but several comorbidities, therefore the average treatment scheme of a living at home patient contains 4-5 different type of drugs, and up to 8-10 in the case of an institutionalized patient. Increasing number of studies report that 13% of the elderly taking 5 or more different drugs/day present side effects requiring medical intervention; also, they have an increased risk of non-compliance, side effects, falls, hospitalization, institutionalization and even death. According to the results of several large studies (ADVANCE, ACCORD) therapy in elderly patients does not have to be aggressive, but adapted depending on age, comorbidities, expected life quality and psychological profile (169).

3) The medical adherence is an important aspect in establishing the therapy of the elderly. It is crucial to correctly assess the availability of the patient in following the medical indications and avoid severe diets or prescribing drugs that might worsen depression or the quality of life. Ethical problems derive from the fact that the elderly are insufficiently involved in decision-making in respect of determining the therapeutic scheme, thus becoming part of the multidisciplinary team, managed by a geriatrician or/and by the family physician. They must actively participate, together with the patient, in the determination of a realistic therapeutic scheme, based in particular on the patient's desires, continuously assessing the ratio risk/benefit of medical recommendations. Another ethical dilemma in determining the treatment of an elderly person occurs when in order to simplify the treatment scheme, we need to choose – from the total of drugs correctly prescribed, according to the guidelines – only the most important ones, with low risk of side effects. How do we choose? Do we have the right to choose? There are several tools created on this purpose: Beers criteria, START/STOP criteria, The GerontoNet ADR Risk Score, Inappropriate Prescribing in the Elderly Tool (IPET) (117).

4) Ensuring the optimal surgical treatment in the elderly involves the crossing of multiple dilemmas and ethical principles. British surgeons asked if they would do a surgical intervention to a patient with dementia and intestinal volvulus, answered no in 65% of cases crossing the ethical dilemma between the observances of two principles: beneficence and non-maleficence. In elective surgery, we also meet ethical dilemmas such as the one of autonomy, beneficence, non-maleficence and informed consent. An example is the significant cognitive impairment occurring in the elderly after having a hip arthroplasty. Therefore, we observe the beneficence principle, recommending them the hip arthroplasty when necessary, which shall increase their life quality, even the degree of independence, but on the other hand, except for the secondary risks of the surgical intervention, the patient also presents the risk of cognitive impairment, which is irreversible. Do we observe the non-maleficence principle? In such situations, a main role has the principle of autonomy and of the informed consent. Therefore, most of ethical dilemmas concerning the ethics of treatment and care in the elderly find their solution in the discussion between physician and patient (170).

5.2. THE SOCIAL DIMENSION OF ELDERLY CARE

Research on quality of life and life satisfaction focuses mainly on individual determinants such as age, income, marital status, health status, physical limitations, social contacts, and social participation of citizens, whose determinants mostly show a statistically significant relationship with life satisfaction (171, 172).

Besides individual characteristics, the context in which people live should be taken into account, because life satisfaction is strongly context-related and also depends on social comparison (173). Therefore, some researchers argue to use vignettes to assess life satisfaction to correct for the so-called differential item functioning, a bias in self-reports caused by differences in personal and sociocultural context (174). Although a useful method, it does not take into account societal changes over time, including cohort effects, affecting life satisfaction. Societal changes may have a wide effect, that is, influencing the life of many people in various countries (e.g., World War II, mass migration, or an economic crisis), while others have an effect on people living in specific regions or countries (e.g., an earthquake or national legislation). Comparative studies between countries have shown the influence of specific factors, such as national income, age composition, life expectancy, and welfare provisions, on life satisfaction at societal, national level (175). Such studies may show “how data on well-being can help policy-makers identify the groups and countries that are bearing the brunt of the economic crisis, as well as those that are holding out better than expected, and provides a new layer of evidence to aid policy decisions.” (176).

Analyses on life satisfaction at national/country level use standardised national data (e.g., Gross Domestic Product (GDP), age dependency ratio, or life expectancy) and aggregate individual data (e.g., percentage of persons with long-standing illnesses or % of unmet health care needs). A comparative study of 27 European countries, describing changes in “a full range of subjective well-being” between 2007 and 2011 in all adult citizens, shows that GDP and percentage of people with disabilities are related to well-being. However, subjective well-being over time increased marginally and did not apply to all countries, indicating that national policy or culture may make a difference (176). Although it was expected that the economic crisis of 2008 would show some effect on life satisfaction, one may argue that the time frame was too short to see such effects. A recently published study analyses changes in life satisfaction in 24 European countries between 2002 and 2012, also taking into account recent, mainly income related societal changes, including the economic crisis of 2008. Income related indicators do affect life satisfaction mostly, but their effects are not uniform over European countries. However, it was stated that “economic crises tend to be followed by crises in happiness” (177).

In Romania, current medical care has several limitations which sometimes force patients to pay for investigations or treatment. Accessibility to medical care is also an issue outside of cities, since most villages only have a dispensary with limited personnel and resources. As such, the elders are amongst those who suffer most from the shortcomings of our medical system because they often face financial limitations and travel with difficulty. In this setting, family support is paramount and can successfully help a geriatric patient in receiving optimal care.

The abuse is a very sensitive and painful experience, which undermines the right of elders to a dignified life. Specialty literature suggests the presence of six types of abuse: physical, emotional, financial, sexual, neglect and abandonment. Nevertheless, things are not so simple and typologically framed. Recent studies show the existence of various types of abuse: personality abuse, system abuse, medical abuse, “invisible” abuse etc (178). Currently, the stress falls on the ways of protection against aggressiveness, violence and exploitation rather than on defining the types of abuse against old aged people.

Most of the times, abuse occurs in the household and it is carried out by the members of the family. Abusers manifest their power and control in a relationship where the old aged person depends on them, knows them and trusts them. The consequences of abuse against old aged people is associated with an increased risk of mortality and morbidity, an increased rate of medical services use, emotional distress, lack of self-confidence, depression, dementia, suicide attempts, social isolation, somatization, anxiety, deterioration of the health status, malnutrition (179).

When it comes to the behaviour of a malicious care taker, who doesn't fulfil his obligations, the linear explanation of abuse occurrence is reductionist, because it does not take into consideration the various systemic factors that contribute to its trigger: social context and discourse, personal issues of the care takers, burden of care, difficult financial situation, the behaviour of the old aged person, weak awareness among people concerning this topic, the absence of social services both for the old aged people and care takers etc.

Considered separately, family or social protection services cannot cope with the complexity of the problem. Therefore, some more proactive models are required, which would combine the informal support sources (family, friends, colleagues) with the formal services (health services, social assistance services etc.). Thus, they would contribute to empowering the old aged people from the community (180).

In Romania, the abuse against old aged people remains a taboo subject, an issue that is dealt with inside the family, without the involvement of the public opinion and social services. Only in 2015, the topic entered the attention of the authorities and in July, the National Strategy implemented a project (2015 - 2020) for promoting active old aging and protection of elders.

The abuse against old people is a complex phenomenon and there is no universally accepted definition for this term. The World Health Organization (2002) defines abuse as "any action carried out by someone who is in a relationship of trust and which leads to the injury or distress of an old aged person." Abuse against old aged people diminishes the sense of identity, dignity and personal value, jeopardizing their physical and emotional health status and even their lives (181).

The classic typology is completed by other types of abuse (182):

- ignoring the civil rights – refusal to privacy, interdiction to receive visitors, control over the telephone, deprivation of liberty, limited access to certain areas in their own house, social marginalization etc.
- system abuse – governmental politics and regulations, which facilitate situations of abuse, such as: insufficient pensions, difficulty in obtaining social allowances etc.
- personality abuse – the attitude of society towards old aged people; it treats them non-persons and perpetuates the belief that old aged people cannot contribute to the community or society anymore.

In Romania, the environment where the current generation of old aged people developed was one marked by stability during the last part of the communist period. The change of regime was equivalent to the disappearance of a more predictable and pre-established life. At the moment, the extremely low pension ensures living at the edge of subsistence, making it hard to cope with daily expenses for most of the people. The society does not have the necessary resources in order to help them, but, at the same time, silently accepts the abuse against people that live their last days in poverty.

The change that occurred in the family structure and economical needs made that young couples live separately from parents, migrate in the urban environment or work abroad. Thus, old aged people got to be deprived by the physical presence, fast control, protection and emotional support of children, the very opposite to their expectations and their own behaviour when their parents were of the same age. The tradition according to which the youngest child inherits the house and takes care of the house disappears and leaves room for solitude, neglect, abandonment or children that visit them or not, yet they claim their rights over the holdings (183).

The position of the old aged person within the family system seems to have regressed from the traditionalist "wise elder" to the current "addictive elder who needs caring and who does not understand the rules of the present life". The modifications of family dynamics to the disadvantage of old aged people are harshly judged by the society, yet the latter does not possess

the solutions and resources that would help families and caretakers to reduce the risk of abuse occurrence and ill treatments against old aged people (184).

Aging, as a form of age-based discrimination form, is widely spread and manifests itself through a series of derogatory, dehumanizing behaviours and attitudes, such as “death is looking for him in the tram” or other discriminatory messages conveyed by mass-media. The idea of differentiation between the taxpayers and pensioners is a topic of interest at the moment in Romania, with the risk of transforming the old people into resource consumers, who do not offer anything to the society, but rather represent a burden.

The tendency to “send old aged people to retirement in order to give jobs to the youth” brings about the sensation of minimalizing the professional experience and contribution they can still have and of ignoring the relevant expertise, obtained over the years. Competitiveness, emphasis on efficiency, all these taken separately and together make the society perpetuates aging, by ignoring its actual outcomes (178).

Privacy is a principle that governs every stage of implementation of the complementary multidisciplinary elder abuse service. Maintaining the privacy of personal data is ensured by assigning a code number to each of the cases. The full name and other personal data can be found on the entry sheet, which appears under a strictly confidential regime, while the rest of the documents operate with the code number. Also, the access to the personal files of the beneficiaries is limited and is reduced to the directly involved experts who manage the case and to the assistant manager.

Work meetings with old aged people are carried out in a separate space, which facilitates the conduct of face to face meetings. Usually, elders do not have the tendency to require a guarantee of privacy, yet an insurance concerning the privacy of the provided data adds to the trust in the psychologist, social worker or another member of the team. The old aged person interacts directly with the specialists from the healthcare services, according to the hospital procedures in force. From that moment on, the procedure agreed on is applied in collaboration with the medical and complementary multidisciplinary teams, with the consent of the institution management board and partners involved. In some situations, elders are unable to walk and then they particularly require carrying out the meetings in the hospital room or parlour. From what we have experienced until now, the elders sometimes mention that their life is so miserable, that it does not matter whether the other roommates hear their story or not, since they often are the first ones who listen to it (184).

It is important to always carefully consider the freedom of not answering to certain questions that we might feel are rather intimate, private or intrusive. In all the cases, elders are consulted in terms of what type of information can be disclosed to the other specialists involved in the complementary service, to the family members, social workers from the community, or even to official references.

5.3. PERSONAL CONTRIBUTIONS IN THE FIELD OF ETHICS AND SOCIAL CARE

Our work in exploring the psychologic approach of senior patients hospitalized in a Clinic of Geriatry in Romania was part of a vast ethical and social work. Our experience in this complex domain was structured in three lines of research, and our results were shared in numerous papers, brochures, books and courses, as follows.

5.3.1. Identifying abuse in senior population

Abuse is a very painful experience, especially for senior persons, as it is associated with an increased risk of mortality and morbidity, an increased rate for medical services and self-neglect. We worked in this area of research with a multidisciplinary team: psychological team,

led by Professor Ovidiu Gavrilovici from the University "Al. I. Cuza" Iasi, medical team, led by myself and social services, provided by Psiterra Association. The experience gathered was shared in several brochures and papers, as follows:

The project: "Refuz sa mai support abuzul in tacere" financed by SEE Grants 2009-2014 (RO2014_C4_62)

The project: "O viata demna pentru fiecare", 2016-2017

Gavrilovici O, **Alexa ID**, Dronic A, Sandu IA, Pancu A, Pîslaru AI. Complementary multidisciplinary elder abuse service in a geriatric clinic. Rev Med Chir Soc Med Nat Iași 2016; 120(4): 807-811.

The brochure: Sărbătorim viața! Gavrilovici O, **Alexa ID** (coord). Broșură de promovare a unei imagini pozitive și demne a persoanelor vârstnice. Iași, 2016. ISBN 978-973-0-23080-2.

Ilie AC, Pîslaru AI, Pancu A, Gavrilovici O, Dronic A, **Alexa ID**. The psychological abuse of the elderly – a silent factor of cardiac decompensation. Maedica – A journal of Clinical Medicine, 2017, 12(2): 781-788.

Alexa ID, Ilie AC, Alexandroaie B, Costin G, Emmanouil-Stamos P, Răihă I: Self-neglect in the case of the elderly. Where are we now? Rev Med Chir Soc Med Nat Iasi. 2011 Apr-Jun;115(2):337-40. 2017.

Alexa ID, Ilie AC, Morosanu A, Papaioannou Emmanouil – Stamos, Ismo Răihă: Self - neglect in elders: a worldwide issue ignored in Romania, Rev Rom Bioetica, 2012; 10(1): 34-38.

One of our first studies in abuse domain was favoured by the project: "Refuz sa mai support abuzul in tacere", financed by SEE Grants. This project was addressed to senior patients who were exposed to psychological abuse and were willing to investigate the possibilities at hand in order to fight abuse or just find solace. The results were so encouraging that we continued our collaboration on a next project: "O viata demna pentru fiecare", which aimed at facilitating the access to social and basic services for elders from Iasi county, subjected to psychological abuse.

The brochure wrote after the finalization of this project is a practical guide that presents the methodology for the implementation of a pilot complementary multidisciplinary elder abuse service in a clinical hospital from Iasi.

The brochure presents the combined perspectives of geriatric clinicians and psychologists from the Psiterra Association, which led to a complex material, addressed mostly to senior patients, but also useful for caregivers, social workers and physicians involved in the multidisciplinary care of the elderly.

This guide presents physiological changes associated with the aging process, characteristics of the Romanian elderly population, traits of successful aging and recent research performed in Iași in the field.

Several of the chapters are dedicated to discussing popular myths about ageing and the elderly and analyzing them from a scientific perspective, a trait that significantly increases the brochure's practical value.

These projects allowed us to conduct a pilot, innovative intervention project combining the adoption and adaptation for hospital use of a screening instrument designed for use in primary health care settings in Canada and a dialogical narrative therapeutic approach. The data were published in the paper: "Complementary multidisciplinary elder abuse service in a geriatric clinic".

Between June 2015 – March 2016 senior patients hospitalized in Iasi town, Geriatric Clinic and suspected of being abused had the benefit of a complementary multidisciplinary elder abuse service (CMEAS) after being screened for abuse, neglect or abandonment experiences.

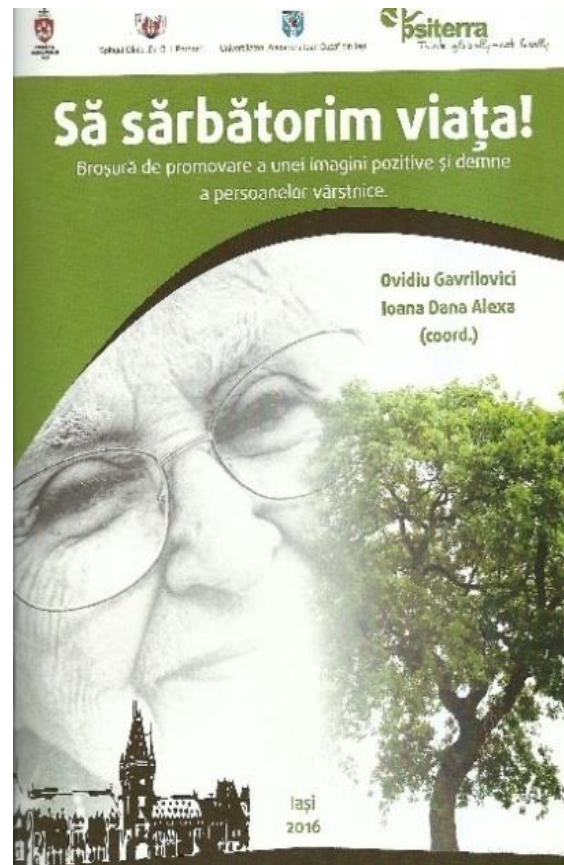
A total of 450 patients admitted to the Geriatric Clinic were invited for the study and 152 raised suspicion of abuse experiences and were screened with EASI. Of these patients, 132 were found positive and were invited to participate in CMEAS.

Implementing the complementary multidisciplinary elder abuse service involves carrying out some successive activities that allow the identification, evaluation, intervention and monitoring of elders subjected to abuse. Given the delicacy of the issue, abuse is identified after an overlapping of objective and subjective evaluations, involving the experience of the experts from various fields of healthcare, while an essential role lies with the geriatric assessment. The CMEAS requires the collaboration between the geriatric team (medical service), psychologist, social worker, legal advisor, and psychiatrist, referral of cases to relevant public and private community services and their monitoring after hospital discharge throughout project duration.

We performed CGA in all subjects. If the geriatric assessment revealed any sign or suspicion pointing to a potential abuse that the senior person could be subjected to, an informed consent concerning the possibility to benefit from the complementary multidisciplinary elder abuse service was carried out. The process of obtaining the informed consent was carried out in a way that corresponded to the needs of the elder.

In our project the informed consent was signed in front of a representative of the medical staff, with whom the patient had already established a relationship of trust. While the elder reads the document, the representative explains verbally the things that are harder to understand and the steps that follow. Given the conditions of the admission, the representatives of the medical staff represent authority, a source of security and the guarantee that they shall receive help.

The form of the informed consent contains data concerning the aim of the complementary service, the means of participating and the procedure to be followed in order to participate, and provides contact details belonging to specialists in case the intervention causes emotional



disturbances. After the elder signed the informed consent, he/she fulfilled the Elder Abuse Suspicion Index (EASI).

EASI was developed by Mark J. Yaffe, Maxine Lithwick and Christina Wolfson (2008) and piloted in Montreal, Canada (185). It is a fast screening tool for the identification of abuse in elders receiving medical care. Among the objectives of the scale, there are:

- increasing the awareness of the medical staff in what concerns the abuse against elders until it becomes reasonable to come up with a proposal for an additional evaluation by the social services, services for adult protection or other similar services.
- medical staff becomes acquainted with the abuse against elders by appealing to a simple set of support questions.

EASI scale is simple to fill in, covers the main types of abuse and is culturally transferable. It has been translated in 7 languages (Spanish, French, Japanese, German, Hebrew, Arabic, Romanian). The team that implemented the project carried out the translation into Romanian, which was agreed upon by the authors after many debates. The general conditions of application recommended by the authors entail the following:

- the elder shows no signs of cognitive deterioration
- the elder is alone (not accompanied)
- there is a relationship of trust between the elder and the physician/nurse.

Applying the scale in the Geriatric Clinic led to the identification of a series of specific conditions, added to the general ones:

- the conversation should be performed on simple terms
- the conversation should develop in a friendly and reliable environment
- the conversation requires patience and a relaxed attitude from the medical staff
- the senior person should be convinced that he/she can trust the medical staff
- it is preferable that the medical coat should be absent
- simple gestures, such as holding hands and other gestures of empathy
- the conversation should take place after at least a day or two from the admission.

If the results of the EASI scale were positive, the elder was referred to the psychologist by a representative of the medical staff. He provided information connected to the emotional and physical status of the elder, types of abuse identified during the geriatric assessment and any other useful details for understanding and managing the case. The elder was previously informed about the meetings that he will take part in, of which the first one will be with a psychologist (who becomes case manager). The psychologist goes to the hospital in order to carry out the initial psychological evaluation (186).

The assessment meeting took place in a private space, secured by the management of the clinic, where the elder was accompanied by a representative of the medical staff. The psychologist introduced himself and reminds the elder the reason of their meeting. The initial assessment carried out by the psychologist should aim at:

- creating a relationship with the elder
- evaluating the emotional impact of the abuse
- identifying the type of abuse
- identifying the special needs of the elder
- identifying the social and family support network
- collecting information about the abuser
- providing information concerning the rights of the elder
- collecting contact details

- empowering the elder by ensuring him that the responsibility of the abuse does not belong to him, that it is acceptable and that he deserves to live a dignified life (186).

The assessment meeting should take place in a warm and safe atmosphere and should start as a usual conversation. Active listening, empathy, patience, accepting long brakes and a slower verbal rhythm, avoiding confrontation and accusatory comments, ensuring privacy, treating the others with dignity and respect, are some of the necessary conditions in order to carry out the evaluation. At the same time, the psychologist pays attention to the moments when the elder speaks about the experience of abuse, about the abuser or the emotional impact of the abuse, strategies to cope with his needs.

The psychologist explains in detail and clearly what each of the options represent. The desire of the elder to accept help, to make choices and manage the change, are complied with, no matter his situation. In case there are suspicions of abuse but the elder does not admit that there would be a problem or has reservations when it comes to describe in detail this topic, the psychologist provides his contact details and stresses out the fact that he can be contacted when the person is ready or becomes preoccupied by the way in which he/she is treated. At the same time, he presents the ways in which the person could be offered help (187).

In case the elder acknowledges the existence of abuse, yet chooses not to accept the help, the reasons behind it ought to be explored. Usually, it is either about the fear of the person who abuses or the shame of being a victim or the lack of information and understanding of the possibilities of receiving support be it psychological or social. If the person is competent and informed in what concerns the options that he/she has, yet continues to refuse the services offered, then this thing is accepted. Also, the psychologist offers his contact details and points out to the fact that he/she can be contacted when the elder shall need his/her help and decides to require it (188).

In case the elder admits being subjected to abuse and chooses to benefit from the multidisciplinary and social services, then the next step is the assessment carried out by the social worker.

The psychologist accompanies the elder whose case is allotted to him/her during the support process and introduces to the social worker. The assessment takes place in a private space and aims at accurately identifying the needs and issues of the elder and establishing together some realistic objectives during the support process. The initial assessment sheet of the social situations is the work tool used to collect information concerning the house, environment, and relationships with family, network of friends and neighbours, economical situations and medical diagnosis of the elder. Also, in order to draw a general frame, it is necessary to evaluate the rate of dependence/autonomy, to correlate the identified necessities with the specialized socio-medical services, which are able to answer the specificities of each case, with regards to the desires of the evaluated person, as well as of the dependents (187, 188).

The social worker aims at promoting a series of principles during the process, such as: respecting the human dignity, privacy, freedom of expression etc. The step of support is usually followed by a meeting of the multidisciplinary team, whose members are agreed upon together with the assisted elder (189).

When drawing up the individualized intervention plan, the available services and institutions that could help are taken into consideration. Most of the time, the issues associated with abuse against the elders are complex and chronic, which means that without immediate available solutions, managing the case could take a rather long time. The individualized intervention plan involves providing the following services:

- psychological counselling
- social assistance

- legal advice
- psychiatric advice
- pastoral counselling.

At the end of the meeting, the elder is invited to consider three options:

- a) to benefit from the multidisciplinary services (social survey, psychological counselling, psychiatric counselling, legal advice, pastoral counselling)
- b) to benefit from the multidisciplinary services and be referred to the social service from the community (public and private organizations, NGOs) and to religious institutions (parishes from the home town, archpriestships)
- c) not to benefit from the multidisciplinary services and reference (190).

From this moment on, the individualized intervention plan was agreed upon together with the elder.

The step of psychological counselling was adapted to the needs and specific of each of the elders. The manner of working was centred on using principles and methodology specific to a narrative approach.

The services of social assistance provided to the abused elder were centred on (191):

- consulting in what regards the desire to resort to the social service from the available secular or religious communities
- presenting the options of social services from the community, and offering the elder support in choosing an appropriate strategy to require them
- facilitating the relationship with different public or private institutions, NGOs in the view of identifying the best suites services
- informing about the rights that he has
- offering a list with phone numbers or the available support and consultancy services, according to the home town
- identifying, in collaboration with the other members from the multidisciplinary team, the networks of support close to the elder.

The procedure on discharge, monitoring the beneficiaries and closing the case –when discharged, elders keep benefiting freely from services of psychological counselling, either face-to-face, by phone or Skype, and services of social assistance through procedures of official reference to the social services from the community and to the religious institutions and by informing the elder with regards to the results of this process.

On discharge, a questionnaire measuring the satisfaction of the beneficiaries, promptitude and specificity of the caring is applied by the psychologist or social worker. Next, elders are tracked by means of the monitoring process.

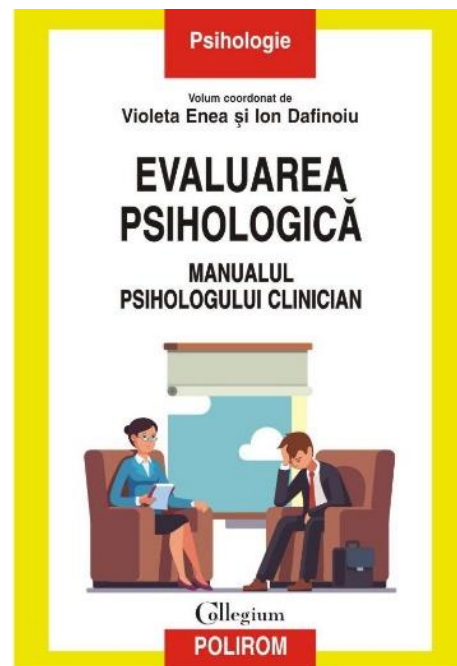
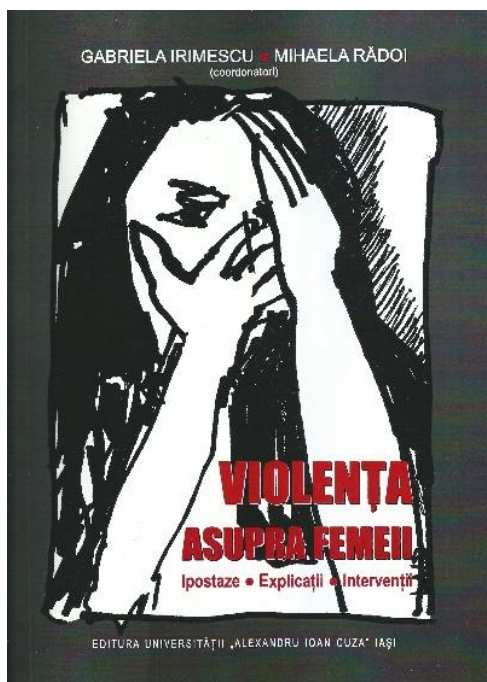
The final step involves closing the case, which occurs in the following situations:

- at the request of the elder
- in case the elder dies
- in case the elder disappears
- when finalizing the implementation of the complementary multidisciplinary elder abuse service (192).

Although mostly focused on the elderly, my collaboration with members of the Ethics Department and with psychologists specialized in social care has led to the publication of books and brochures aimed at improving self-esteem of the geriatric individual and preventing physical abuse in vulnerable populations:

Dronic A, Gavrilovici O, Alexa ID, Pîslaru AI. De la suspiciune de abuz la împărtășire: consilierea prin mijloace narative a femeilor în clinica de geriatrie. În: *Violența împotriva femeii*. Ed: G. Irimescu, M. Rădoi, Editura Universității Alexandru Ioan Cuza, Iași, 2017.

O. Gavrilovici, A. Dronic, I.D. Alexa. Evaluarea psihologică a persoanelor vârstnice. În: *Evaluarea psihologică – Manualul psihologului clinician*. V. Enea și I. Dafinoiu coord., Ed. Polirom, 2017.



We continued to share our experience on psychological abuse in senior population by publishing real cases that we analysed and solved. One of these cases was presented in the paper: "The psychological abuse of the elderly - a silent factor of cardiac decompensation", together with our firm believes that abuse will be associated with high costs of medical services, and patient's lack of self-confidence which, in time, may lead to social isolation, somatization, anxiety, depression, and suicide attempts. In this context, the identification and correction of psychological abuse becomes a desideratum of utmost importance for ensuring an optimal therapeutic response.

We illustrate this idea by presenting the case of an 80-year old patient from a rural area, who has been hospitalized several times, admitted for numerous episodes of global cardiac decompensation (about four over the last year). The causes of cardiac decompensation were, systematically, non-compliance with treatment, regardless of all attempts to readjust and simplify the therapeutic schemes. The dynamic geriatric assessment showed a deterioration of the patient's mental and nutritional status and an accentuation of depression. The EASI questionnaire used during the last admission corroborated with the psychological consultation and detected several types of abuse: abandonment, negligence and financial abuse. Given that the complexity of care, the frequency of hospitalizations and the length of stay were reduced,

therapeutic compliance increased and the mental and nutritional status improved after correcting the abuse.

A particular form of abuse is self-neglect; it is behaviour of an elderly person that threatens his/her own health and safety. It is present in a person who refuses to adequately feed, water, shelter or clothe himself, refusing medications or medical care and personal safety measures. Various studies from United States, Canada and Western Europe countries (193, 194) draw attention to the fact that in senior people self-neglect is the most frequent form of abuse. In a population-based study of Texas Adult Protective Services (195), 62, 5% of the clients were referred for self-neglect, with 90% of the self-neglect cases occurring in persons aged 65 years and older.

The self-neglected elders frequently live alone, are socially isolated, have physical or psychiatric illness (e.g. Alzheimer's disease), severe depression. This form of abuse is found more frequently in those with advanced age, in women, those with a low educational level and low income.

First described in 1960 in the United States and Great Britain, self-neglect was called the "Social Breakdown Syndrome" or "Senile Breakdown". Some are using the term "Diogenes Syndrome" for those who live in squalor, a specific feature being the fact that they gather useless things and deposit them in their home; but this illness is also identified in youngsters with psychiatric problems and personality disorders (194).

Given the importance of the problem, its ongoing growth (is mentioned an increase of 34% from 2000 to 2005), Older Americans Act Amendments of 1987 from American legislation defined three types of elder abuse: domestic abuse, institutional abuse and self-neglect – the abuse made to himself. This subject has an increased importance because self-neglect is marker for increased mortality independent of cognitive function or physical shape (196, 197).

We conducted a multicentric study of self-neglect in three geriatric units from Finland, Greece and Romania. The medical, social, psychological and behavioural profile analysis was based on a questionnaire; this questionnaire relied on existing studies and social, economic and medical facts in the three countries. The cognitive function, nutritional status, and the presence or absence of depression has also been assessed.

The data obtained until now support the importance of self-neglect among the elderly. The social-medical network should not only identify, diagnose, prevent, and treat the elderly affected by the phenomenon of self-neglect, but also educate the society to help them and, moreover, to prevent their marginalization. We published our preliminary results in two papers: "Self-neglect in elders: a worldwide issue ignored in Romania", followed by "Self-neglect in the case of the elderly. Where are we now?"

In these papers we have intended to trace the causes that lead to self-neglect and the medical, social, psychological and behavioural state of self-neglected elderly. Patients are assessed using medical files and questionnaires that included comprehensive geriatric assessment tools, economic and social details, psychological and behavioural elements. The Romanian study was conducted in the Geriatric Department of "Dr. C.I. Parhon" Hospital, Iasi.

The first results we had after 9 months of study involved 24 patients who were hospitalized for severe medical conditions either due to self-neglect or inability to comply with medical recommendations. These patients were selected based on one of the following criteria:

- persistent neglect to personal hygiene and/or compliance to medical recommendations
- repeated refusal of receiving medical/social services which can be expected to improve quality of life
- self-endangerment through the manifestation of unsafe behaviours (e.g. persistent refusal to care for a wound, creating life-hazards at home, alcohol abuse).

As part of the CGA we collected demographic data (including age, gender, urban or rural area), medical data (chronic concomitant diseases, chronic medication, and alcohol consumption), social data (non-self sufficient or complete dependent person, family support, existence of care givers), and economic data (monthly income, personal hygiene, living condition and household). All patients had a CGA including cognitive status (Mini Mental State Examination), nutritional status (Mini Nutritional Assessment) and mood disorders (Geriatric Depression Scale - 4). Data were collected by personnel involved in the study and statistically analyzed.

Our patients were aged between 65 and 88 years old with an average of 77,12; 50% were aged between 75 and 85 years, 33,33% were part of the “young-old” group (65 to 75 years) and 16,67% part of the “oldest-old” group (over 85 years). The higher number of women (58, 33%) corresponds to existing data in the medical literature. There is a definite predominance of rural-belonging patients (79.17%) versus urban, a fact that reflects the social, economic and medical realities of our region. The patients came to our hospital mostly by ambulance (58%) or by family/caregivers (37%) or even came by themselves (5%). Even though almost half of them were brought by their family, only 26,27% benefited from a good family support. None of the selected patients had a university degree, most of them graduated a primary school or gymnasium (41, 67% and 33, 33% respectively) and only 8,33% graduated from high school.

The most frequent cause for hospitalizations was acute decompensation of various cardiovascular disorders: heart failure (50% cases), arrhythmias (50% cases), hypertension (37,5%), ischemic heart disease (20,83%). All these patients had several concomitant diseases, including mental disorders with depression and dementia in equal percentages (45,83%) and metabolic disorders (diabetes mellitus in only 16,67% of all patients and malnutrition in 41 and 67% of cases); 16.67% of patients were chronic alcohol consumers, being equally distributed in the age groups.

Data about chronic medical treatment were available only in 45,83% patients who were following at least partially the prescriptions. The drugs frequently taken were cardiovascular agents (36%), pulmonary medication (18,18%), diabetes recommendations (9%) and neuro-psychiatric agents (9%).

All self-neglected elderly patients were evaluated in terms of personal appearance and environment status taking into account that self-neglect is associated with defective personal hygiene and deficient living condition and household. General appearance was various at first evaluation: 58,33% were confused, 45,83% agitated, 25% with dementia, 16,67% depressed, 12,5% aggressive and normal or with no response 4,17% each. At admission personal hygiene was poor and very poor in the majority of participants (37,5% and 33,33% of patients respectively) and in 12,5% of the enrolled elderly patients lack in personal hygiene even endangered their life.

Detailing this issue, we assessed skin, nails and hair condition, oral cavity aspect including teeth and even clothes appearance. We have found following aspects: the skin was dirty and dry in almost 80% of cases, was wounded in 25%, inflamed and with bruises in 37,5% of elderly and 12,5% of patients had pressure sores. Nails (from hands and feet) were long, untrimmed and very dirty in over half of the assessed elderly. Oral hygiene was deficient in all subjects, reflecting also social and economical status, and even medical education. Hair was dirty and very dirty in most patients and in 4,17% pediculosis was detected; clothing aspect revealed: soiled in half of patients, very soiled with door (e.g. incontinence) in 37,5% and the rest had torn and soiled clothes.

Environment status of subjects could not be evaluated in all participants; data was collected from either family members or caregivers or ambulance crew. The general condition was poor and very poor in almost 50% of cases. We also found important deficiency in house hygiene.

Economic data collected included monthly income. In our selected group we could collect data about income in 83,33% of patients; the rest of the patients were either with no income or with income-but we could not appreciate the amount. The monthly income in more than a half of elderly was less than 500 RON; the rest had an income between 500 and 1000 RON, and none of the enrolled patients had an income greater than 1000 RON. These economical facts are related with the phenomenon of self-neglect as well as the social status and the social and familial support.

A battery of assessment tools used all over the world was performed as part of CGA. All patients underwent cognitive evaluation using MMSE, nutritional evaluation using MNA® and evaluation of the existence of depression using Geriatric Depression Scale-4 (GDS-4). The assessment tools were carried out in collaboration with both the patient and family or caregivers (whenever possible).

Our results showed that the majority of our patients scored for moderate and severe dementia. Evaluation of nutritional status revealed nutritional disorders in the majority of the patients, with malnutrition or at risk of malnutrition. Approximately half of patients who underwent the GDS-4 had scores significant for depression and they were subsequently psychiatrically evaluated. Analyzing all collected data we found that in 58, 33% of cases the patient understood and recognized his status and even wanted qualified help.

The partial data obtained from the Romanian part of the multinational study confirm the importance of self-neglect among the elderly, especially as it is accompanied by low capacity to perform activities of daily living, this leading to a poor personal hygiene, an insufficient care of the home environment, a neglect of medical conditions and the lack of treatment for themselves. The great risk and severity of self-neglect was associated with multiple factors: decline in cognitive function, decline in executive function, and decline in economical and social status. Each and everyone has an important role in the severity and prevalence of self-neglect in elders therefore the team who participated in the study was complex and gathered geriatrics, emergency doctors, nurses, psychologists, social workers, emergency crews. These all contributed not only to identify but to diagnose, help with the treatment and social assistance after hospitalization (196, 197).

It is not known yet how to manage self-neglect without interfering with individual's ethical principles, civil and privacy rights. The intervention must be complex (there are involved: family, community, social and medical services) and multifactorial in order to influence the causes that lead to self-neglect (197).

5.3.2. Exploring ethical dilemmas while treating senior patients

One of the most important elements in performing CGA is assessing cognitive function, and thus the ability of the senior patient to fully understand the therapeutical options he/she has. Evaluation of the capacity of the manner seniors can control their life, observing their right to autonomy and independence was an important line of research. The experience we gathered was published in several papers, the most important being presented as follows:

Alexa O, Veliceasa B, Malancea R, **Alexa ID**. Postoperative cognitive disorder has to be included within informed consent of elderly patients undergoing total hip replacement, *Rev Rom Bioetica*, 2013; 11(4): 38-47.

Cepoi V, **Alexa ID**, Ilie AC, Alexa O. Ethical Dilemmas in Treating Elderly Patients at Risk of Polypragmasy and Polypharmacy, *Rev Rom Bioetica* 2014; 12(3): 12-18.

Prada GI, **Alexa ID**. Specific patterns of psychosomatic disorders in older people, *Proceedings of the 2nd Annual Conference of the European Association of the Psychosomatic Medicine*, Sibiu, 2014, IFMBE Proceedings Volume, 248-252, ISBN 978-88-7587-701-9.

Alexa-Stratulat T, Neagu M, Neagu AI, **Alexa ID**, Ioan BG. Consent for participating in clinical trials –Is it really informed? *Developing World Bioeth.* 2018;1–8. DOI: 10.1111/dewb.12199.

One of my most favourite domains is evaluating cognitive impairment that follows major surgeries in the elderly patients. The cause of postoperative cognitive problems has not been clearly elucidated because it is a heterogeneous and multifactorial disorder involving a complex interrelationship between a vulnerable patient with preoperative risk factors and numerous precipitating factors in the perioperative period. There is increasing evidence that impaired preoperative brain status (cognitive reserve) predicts patients at high risk for these problems (198).

I consider that this domain is a fascinating one and, since we already have a close relationship with the Orthopaedic Department, I am confident that we can continue to study postoperative cognitive changes, especially since have been reported in senior patients for over a century, and anesthesia has often been mentioned as a possible cause of this problem. In 1955, Bedford (198) published a retrospective review of 1193 elderly patients who had surgery under general anesthesia during a 5-year period. He found that cognitive problems occurred in approximately 10% of senior patients after surgery. Most of these patients experienced mild problems after surgery (inability to write a decent letter, concentrate, go shopping alone or read a book, increased forgetfulness after surgery, unable to attend to business), but were still able to function independently. Bedford also described 18 cases (1.5%) in which patients developed extreme dementia and remained confused until their death. He concluded that the cognitive problems were related to anesthetic agents and hypotension and that ‘operations on senior people should be confined to unequivocally necessary cases.

In the paper "Postoperative cognitive disorder has to be included within informed consent of elderly patients undergoing total hip replacement" we present the more common cognitive problems that can arise after orthopedic surgery. We conclude that postoperative confusion and cognitive problems are more common in elderly (≥ 65 years) than younger patients and they can be categorized as postoperative delirium, postoperative cognitive dysfunction (POCD), and dementia (199).

Postoperative delirium is characterized by a reduced clarity of awareness of the environment, a fluctuating course (waxing and waning of orientation throughout the day), and an inability to focus, sustain, or shift attention. Although delirium is usually a temporary condition, it is independently associated with increased mortality, length of hospital stay, functional disability, placement in long-term care institutions, and hospitalization costs (200).

Delirium research has predominantly focused on the identification and treatment of risk factors prior to surgery. Factors that have been associated with an increased risk of postoperative delirium include advancing age, sensory deprivation (visual or hearing impairment), sleep deprivation, social isolation, physical restraint, use of bladder catheter,

iatrogenic adverse events, polypharmacy, use of psychoactive drugs, comorbidities, severe illness (especially infection, fracture, or stroke), cognitive impairment, temperature abnormality (fever or hypothermia), dehydration, malnutrition, and low serum albumin (201).

Numerous studies have demonstrated that perioperative geriatric consultation, early surgery, effective pain management, and staff education can successfully decrease the incidence and severity of postoperative delirium in hip-fracture patients (202). In the majority of these studies, many of the patients had preoperative cognitive impairment. A recent study by Bjorkelund et al. evaluated a multifactorial intervention for postoperative delirium in cognitively intact elderly patients admitted for hip-fracture surgery. The preoperative intervention consisted of the use of supplemental oxygen, systolic blood pressure maintenance more than 90 mmHg, red blood cell transfusion for hemoglobin less than 10 g/dl, adequate pain relief, intravenous fluid supplementation, normothermia, and the avoidance of polypharmacy. Perioperative interventions included spinal anesthesia with propofol sedation and postoperative analgesia with paracetamol and opioid as needed. This multifactorial intervention resulted in a 35% reduction in the incidence of postoperative delirium in patients who were lucid at hospital admission (203).

Antipsychotics are widely used in the management of established delirium, but there are few studies that assess the efficacy of antipsychotics for the prevention of postoperative delirium. Another study randomizing 430 patients undergoing hip surgery to receive either haloperidol, 0.5 mg three times daily, or placebo did not find a reduction in the incidence of postoperative delirium with perioperative low-dose haloperidol; however, the treatment did decrease the duration and severity of postoperative delirium as well as the duration of hospital stay. All patients in this study received a geriatric consultation (204).

Postoperative cognitive dysfunction (POCD) is a subtle impairment of memory, concentration, and information processing that is distinct from delirium and dementia. Despite the fact that POCD is not a formal psychiatric diagnosis, the term is commonly used in the literature and is considered to be a mild neurocognitive disorder that can only be diagnosed if the cognitive disturbance does not meet the criteria for three other conditions (delirium, dementia, or amnesic disorder). The symptoms vary from mild memory loss to an inability to concentrate or process information and it has also been associated with increased mortality for as long as 8 years after surgery.

The mechanisms responsible for postoperative cognitive decline after noncardiac surgery are unknown, but potential risk factors can be classified into patient, surgical, and anesthetic categories. It is likely that the cause of POCD in the elderly patient is multifactorial and may include the preoperative health status of the patient, the patient's preoperative level of cognition, perioperative events related to the surgery itself, and, possibly, neurotoxic effects of anesthetic agents (205).

Numerous studies have shown that preoperative cerebral infarct or cognitive impairment is a risk factor for postoperative cognitive problems. The concept of cerebral cognitive reserve is often cited to explain why individuals with a similar degree of cerebral insult often have significant differences in the degree of cognitive symptoms. Research formally investigating the role of reserve in the development of POCD suggests that patients with preoperative vascular risk factors may be at greater risk for POCD (206).

Cognitive disturbances can be associated not only to surgery, but also to polypharmacy. In the paper: " Ethical Dilemmas in Treating Elderly Patients at Risk of Polypragmasy and Polypharmacy" we discuss ethical dilemmas while devising therapeutical approach to very old people. In this study we focused on the ethical dilemmas that confront physicians while approaching therapeutical management of senior patients, especially those exposed to polypragmasy and iatrogeny. We explore the main universal ethical principles such as autonomy, beneficence, non-maleficence, justice and equity and the challenges the medical

team faces while trying to reconcile them with several particular aspects characteristic to senior patients such as: fragility, disability, comorbidity, cognitive and functional impairment, and a greater risk of polypharmacy, polypragmasy, and iatrogeny. Building a strong physician - patient relationship based on mutual trust and respect is the key to understanding the needs and desires of the elderly, which may be completely different from other age groups, and their possibilities to adhere to medical recommendations. Multidisciplinary teams, representing professionals from diverse disciplines coordinated by the general practitioner and/or the geriatrician should help solving difficult ethical dilemmas.

A most interesting line of research is referring to the ever-changing role of the psychiatrist in the geriatric team; it is also the goal of a multicenter study that is in progress, in collaboration with "Ana Aslan" Institute from Bucuresti and Professor Gabriel Ioan Prada and his team from the Department of Geriatry and Gerontology, University of Medicine and Pharmacy "Carol Davila" Bucuresti. Our partial data were published in the paper: " Specific patterns of psychosomatic disorders in older people"

The high prevalence of mental health complaints in medical and primary care settings is now recognized: 20% of older adults have a mental health need, but only 3% of them will seek care from a mental health specialist. The majority of older adults will receive treatment for a mental health problem in a medical setting. Untreated mental illness is associated with treatment non-adherence, worse somatic morbidity, increased utilization costs, such as hospital readmissions, and increased mortality from illnesses (eg, heart disease) (207).

The need to integrate psychiatric treatment with somatic care puts psychosomatic medicine in a unique position to focus on older patients who would not otherwise seek specialized treatment. In 2004, the United Jewish Appeal Federation of New York funded an innovative program between Montefiore Home Care and the Department of Psychiatry at MontefioreMedicalCenter to treat homebound senior persons who have depression, by embedding a geriatric psychiatrist in the home care team. Nursing staff were taught to complete the Patient Health Questionnaire-9 (PHQ-9) during their initial assessment of a homebound senior person. If the score was 3 or higher or if they noted another mental health issue, the patient was referred to the social work department. Social workers were also trained to complete the PHQ-9. Over time, the program expanded from depression screening to various mental health concerns. The social workers now complete a more thorough assessment and screen for depression, anxiety, psychosis, and substance abuse. A team consisting of a geriatric psychiatrist, social workers, and nurses meet weekly to discuss patients. Those who require further psychiatric evaluation are identified and the geriatric psychiatrist completes an in-home evaluation that is shared with the clinical team and PCP. Over the years, this program has been well received by patients and PCPs and has been sustained beyond the life of the original grant funding (208).

In July 2013, this collocation model evolved to incorporate a hospital-based component by embedding a geriatric psychiatrist in a medical hospitalist unit. The geriatric psychiatrist attends interdisciplinary rounds with the medical hospitalist team 3 days per week. All admitted patients are discussed, and patients with mental health needs are proactively identified and evaluated. Discharge planning is conducted in a collaborative setting with the psychiatrist, medical team, and inpatient social worker incorporating patient/family preferences via family meetings (209).

We consider that this program is extremely important to implement in our geriatric network and we shall try all the possible channels in order to obtain financing to achieve it.

Related to the cognitive assessment is the matter of informed consent. We looked into the challenges of ensuring voluntary and informed consent which is obtained from potential research subjects in the north-eastern part of Romania. This study is one of the first empirical

papers of this nature in Romania and the data were published in the paper: "Consent for participating in clinical trials –Is it really informed?"

The study used a quantitative survey design using the adapted Quality of Informed Consent (QuIC) questionnaire. The target population consisted of 100 adult persons who voluntarily enrolled in clinical trials. As we know, the informed consent form (ICF) must contain details regarding the potential risks and benefits, the aim of the clinical trial, study design, confidentiality, insurance and contact details in case of additional questions. Our study confirmed that although all required information was included in the ICF, few clinical trial participants truly understood it. We also found that the most important predictive factor for a good subjective and objective understanding of the clinical trial was the level of education. Our study suggests that researchers should consider putting more effort in order to help clinical trial participants achieve a better understanding of the informed consent. In this way they will ensure that participants' decision-making is meaningful and that their interests are protected.

5.3.3. Promoting social care in senior population

The idea of differentiation between the taxpayers and the pensioners is a topic of great interest, due to the risk of transforming senior people into an unnecessary burden that consume medical and social services. The data obtained from our studies were published in several papers that are presented below:

The project: "Social and Sanitary Services: a Voluntary Quality System", 2010-2011, PROGRESS program financed by European Committee, contract VS/2010/0106.

Olăroiu M, Ghinescu M, Olarioiu M, Aurelian S, Halfens RJG, Dumitrescu L, Schols MGA, RahneaG, Curaj A, **Alexa ID**, van den Heuvel WJA. Assessment of care problems in Romania: feasibility and exploration. *JAMDA*, 2015;16(1):86. e9–86.e12.

Olăroiu M, **Alexa ID**, van den Heuvel WJA. Do Changes in the Welfare and Health Policy Affect Life Satisfaction of Older Citizens in Europe? *CurrGerontolGeriatr Res*. 2017: 7574040.

Ștefăniu R, Abdulan I, Alexa T, Mastaleru A, **Alexa ID**, Astărăstoiaie V. Successful aging is influenced by frailty and health-related quality of life in community-dwelling seniors. *Rev Med Chir Soc Med Nat Iași* 2017; 121(1): 104-111.

My preoccupation in this field started with my participation in the PROGRESS program with the project: " Social and Sanitary Services: a Voluntary Quality System", together with Dr. Vasile Cepoi. The partners in this project were: ARS Toscana, Italy, Porrúa Association, Spain, University "Alexandru Ioan Cuza" Iasi, Romania, and Public Health Department, Iasi, Romania. The project focused on the assistance to people in dependency situation and the promotion of their self autonomy. The challenge was to devise systems to attend to needs of people in especially vulnerable situations and that required support, to be able to carry out essential activities of daily life, to reach self autonomy and to be able to practice fully their citizen rights.

Thus, to be able to apply the social services system, different groups were created taking into account different dependency degrees:

- degree I - moderated dependency: when the person needs help to do varied activities of daily life at least once a day or has needs of intermittent or limited support for his self autonomy

- degree II - severe dependency: when the person needs help to do varied activities of daily life two or three times a day but doesn't want permanent support of a carer or has extended support needs for his self autonomy
- degree III - big dependence: when the person needs help to do varied activities of daily life several times a day and, because of his total physic, sensorial or intellectual autonomy lost, he needs indispensable and continuous support of another person or has general support needs for his self autonomy.

The standard service should guarantee:

- manner of communication and information widespread over the territory served
- prompt reading of needs
- assessment of the need conditions
- integrated customized manner of defining the assistance project
- determination of the skills required from the operators
- allocation of the resources necessary to sustain the actions envisaged in the assistance itinerary.

This project was an innovative one because it proposed to add a governing instrument of the demand of assistance to the person to the system. It would operate according to the principles of appropriateness and timeliness.

In Italy, Spain and Romania, a long-term home service was experimented concerning two groups with different levels of self-sufficiency. The social experimentation would provide all the data necessary for comparing the strategic results between the different groups of old people, one resident in urban areas and the other in rural ones. In Spain the experimentation concerned rural areas, in Romania it was activated in an urban context and in Italy in both. For each country, 20 subjects were involved, 10 for each type of disability. In all cases there was a home service where the user stayed in his/her own home.

Through this action the citizens would obtain information, by way of information points, which were clear on the replies offered to the needs of the not self-sufficient person and his/her family.

The communication promoted the advantages coming from keeping the senior person in their family context, informed of the procedures which regulated access to the service, allowed identification of the points in which access to the service occurs.

Continuing this line of research, one of our studies presents the feasibility of a recently developed instrument, LPZ-International, which assesses care problems in health care. We used this instrument to describe the prevalence of care problems in Romanian health care institutions. Large differences exist in care services in Europe. Data on quality of care are absent or incomplete in Central-Eastern European countries. These countries, including Romania, have faced dramatic socio-economic changes, which led to negative changes in quality of care.

The design of the study was cross-sectional and it took place in hospital wards, mental care institutions, and nursing homes. The National Prevalence Measurement of Quality of Care (LPZ) International was introduced in 9 health care institutions in Romania. Assessed care problems included pressure ulcers, urinary and fecal incontinence, malnutrition, falls, and physical restraints. Two health care professionals completed the questionnaire by hand at the patient's site. The data were collected between November 2013 and March 2014 and were presented in the paper: "Assessment of care problems in Romania: feasibility and exploration".

The study recruited almost 400 participants. The data showed a high consistency and only a few were missing. The most frequent care problem was urinary and fecal incontinence, especially in the nursing home. Pressure ulcers and malnutrition were less frequent care problems in Romanian patients. Physical restraints were frequently applied in the nursing home and geriatrics and oncology wards.

In conclusion, LPZ-International is a feasible instrument to assess care problems. The differences between wards and countries in the prevalence of care problems indicate differences in quality of care and the need for high-quality, comparative research.

On a more general scale, we studied the modifications of life satisfaction of older citizens not only in Romania, but in Europe, due to recent implementation of new health policies. The data were published in the paper: "Do Changes in the Welfare and Health Policy Affect Life Satisfaction of Older Citizens in Europe?".

For some decades, ageing in Europe causes serious political concerns on well-being and social participation of old citizens as well as on care for the frail old and personnel to take care for them. These concerns increased due to the economic crisis of 2008 and are related: health and need for long-term care affect well-being and social participation and vice versa (210). Therefore, in most European countries policy measures were proposed and taken to influence consequences of the economic crisis and ageing (211). Measures included new pension regulations, changing arrangements for long-term care and for access to social services, but the effects of such measures on society and life of citizens are unknown. This study explores which societal measures related to the economic crisis and ageing, may have affected the life satisfaction of older citizens. Understanding the effect of such measures on life satisfaction of older citizens could inform policy-makers about future measures to get a better life for old citizens (212).

Comparative research on life satisfaction worldwide shows a U-shape between life satisfaction and age, supposing a major influence of ageing itself. Young age (16–40) groups show relatively high life satisfaction, which decreases in middle age (40–65) groups but increases again in older age (65 and over) groups (213). Such U-shape is found to be rather consistent, but it does not apply to all countries (214), indicating that specific events or societal changes may affect it in different ways. This may also apply to the economic crisis, starting in 2008.

Therefore, our premise is that this economic crisis has affected the U-shape relationship between age and life satisfaction in European countries. The first research question is, has this U-shape changed and, if so, in which direction and in which European countries?

The second research question is which societal conditions, changed by measures due to the economic crisis of 2008, are related to life satisfaction of older citizens in Europe. We focus on older citizens because these citizens may be more vulnerable to such societal changes and therefore are an important "target group" for policy measures (210).

To answer the second question, one has to look at differences in changes between countries (215).

In order to answer these research questions, life satisfaction was assessed through international surveys in 2007 and 2013 and changes in societal conditions, using eight indicators on demography, welfare, and health, were assessed in 31 European countries in 2006 and in 2014. Data are standardised and based on official, national surveys and statistics.

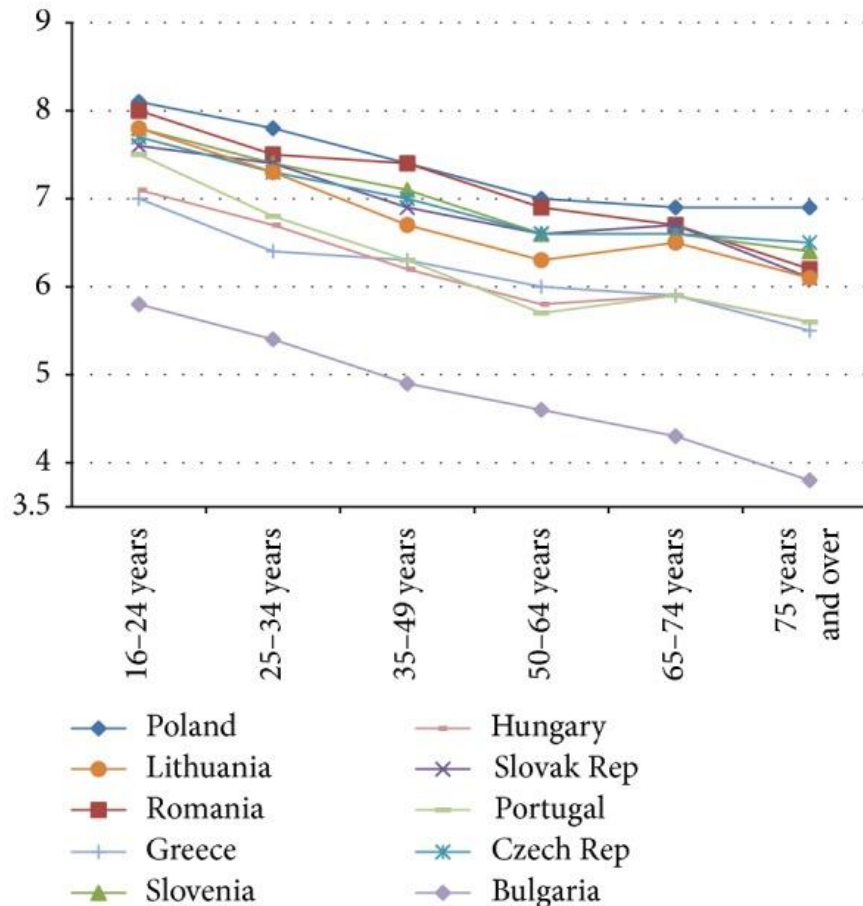


Figure 14. Relatively large decline in life satisfaction by age 2013 (126)

We found that the mean life satisfaction scores for all citizens (over 16–18 years) in 2007 and 2013 in the 31 countries are about the same 7,0 and 7,1, respectively. Overall, the tendency is that life satisfaction decreased in Western European countries and increased in central-eastern European countries. However, some considerable differences exist between countries. Mean life satisfaction decreased with at least 0,5 points in Cyprus, Denmark, Estonia, and Malta but increased with at least 0,5 points in Austria, Hungary, Latvia, and Romania.

The relationship between age categories and mean life satisfaction per country shows that a “U-shape” does not dominate in 2013. The majority of countries (19 out of 31) show a declining line in life satisfaction from young citizens (16–24 years) to old citizens (75 years and over) (Figure 14).

The mean life satisfaction for citizens till 65 years is 7,2 in 2013 and for citizens of 65 years and over 6,9. Analysis of variance of mean life satisfaction scores between adult citizens of 16 to 65 years and those 65 years and over in 2013 shows a statistically significant difference ($p = .003$); that is, for old citizens the mean life satisfaction is significantly lower in 2013.

In 2013 mean differences in life satisfaction are strongly decreased in older citizens in Romania, Bulgaria, Croatia, Greece, Lithuania, Portugal, Slovenia, and Slovakia as compared to not old citizens. Increase of mean life satisfaction in older citizens as compared to young ones is rare but occurs in Denmark and Ireland.

The difference in mean life satisfaction between 2007 and 2013 is due to lower life satisfaction in older citizens in 2013.

Before answering the second research question we present the mean or proportional scores for each indicator of societal change (demographic, welfare, and health) per country.

The demographic indicators show an increase in the old age dependency ratio in all countries (except Luxembourg) as well as in life expectancy at birth between 2006 and 2014. The welfare indicator “% of GDP on social protection” increased in all but two (i.e., Hungary and Poland) countries. This increase was relatively strong in Cyprus, Denmark, Finland, Greece, Ireland, Netherlands, and Spain. The welfare indicator “% GDP on long-term care expenditure” stayed on average the same in 2006 compared to 2014. The only decrease was in Romania; a strong increase occurred in Finland and Norway. The “aggregate replacement ratio” increased slightly between 2006 and 2014 in most European countries, but not in Austria, Estonia, Germany, Italy, and Sweden.

A quarter of citizens in the 31 European countries reported very good health in 2006 and in 2014. On average there is a slight decrease between 2006 and 2014. The score of this health indicator varies strongly between countries with low scores (<10%) in Estonia, Latvia, Lithuania, and Portugal and high scores (>40%) in Cyprus, Greece, Iceland, and Ireland. A strong decrease in subjective health is reported in Denmark and Finland. The average proportion of long-standing illness/health problems stayed about the same between 2006 and 2014 in the 31 countries as did the proportion of self-reported unmet needs for they were too expensive. Long-standing illness/health problems were more frequently reported between 2006 and 2014 in Austria, Cyprus, Greece, Malta, and Portugal and less reported in Bulgaria and Luxembourg. Self-reported unmet needs in 2006–2014 increased strongly in Greece, Ireland, Iceland, and Italy and decreased strongly in Bulgaria, Germany, Lithuania, Poland, and Romania.

The relationship between the mean scores of the eight societal indicators in 2014 and difference in life satisfaction between both age groups (16–64 versus 65 and over) in 2013 is explored by Pearson's correlations.

Older citizens (65+) with higher life satisfaction as compared to younger ones (16–64) live in countries, which have a high life expectancy at birth, which spend a high percentage of their GDP on social protection and long-term care in 2014, and have a high percentage of citizens in very good health.

Next, it is analysed which societal indicators changed significantly between 2006 and 2014. The following indicators show significant mean changes between 2006 and 2013: old dependency ratio (mean 3,26; $p = .00$), life expectancy at birth (mean 2,23; $p = .00$), % GDP social protection (mean 3,03; $p = .00$), and % long-standing illnesses (mean 1,97; $p = .05$). In 31 European countries the old dependency ratio increases on average with 3 points between 2006 and 2014 (with highest increase in Czech Republic, Finland, Malta, Denmark, Sweden, and Netherlands) the life expectancy over 2 years on average (with highest increase in Estonia, Latvia, Lithuania, and Slovak Republic), the percentage of GDP spent on social protection with 3% (with highest increase in Greece, Spain, Finland, Ireland, Cyprus, Denmark, and Netherlands), and the percentage of long-standing illnesses increased with almost 2% (with highest increase in Austria, Estonia, and Portugal). No significant mean differences between 2006 and 2014 are found for % of GDP spent in long-term care, aggregate replacement ratio, the % of very good subjective health, and % of unmet needs in health care.

Regression analysis, with life satisfaction of older citizens in 2013 as dependent variable and mean differences in the eight indicators (2006–2014) as independent variables, shows that four indicators statistically significantly contribute to explaining the level of life satisfaction in older citizens, explaining 38% of the variance.

Low life satisfaction of older citizens (65 years and over) in 2013 occurs in countries, where life expectancy decreased as well as financial means for social protection and long-term care. In countries, where the percentage of unmet needs in health care between 2006 and 2014 increased, older citizens show low life satisfaction in 2013.

Based on this study we conclude that life satisfaction of old citizens deteriorated related to policy measures, taken because of the economic crisis of 2008 and ageing of the population in Europe. These measures have changed various societal conditions negatively.

Nevertheless, some societal indicators show that social conditions clearly improved in some countries but others got worse. For example, the percentage of reported unmet needs decreased significantly in Bulgaria, Lithuania, Romania, Poland, and Estonia between 2006 and 2014 but it is not said that old citizens profited most. In Ireland, Greece, Italy, Iceland, and Belgium unmet needs in health care were more often reported. Based on our analysis, we believe that the rudimentary structure of health and welfare provisions in various central-eastern European countries still were too vulnerable to cope with the imposed policy measures and not because of attitudes or belief systems (216). At the same time, it should be stated that knowledge and understanding on how societal processes and policy measures affect quality of life of citizens are limited. Theoretical development is still poor, especially when it comes to the interaction between policy measures, societal changes (including ageing of societies), and individual preferences and behaviour. International, comparative research, based on sound theoretical concepts, is strongly needed.

Another major factor that impact social aspects of seniors' lives is frailty. This new concept in geriatric medicine was found to be the main cause of disability and death; therefore it has an important influence on quality of life in senior patients. We studied the prevalence of frailty in home-dwelling elderly and its influence on quality of life and the results were published in the paper: " Successful aging is influenced by frailty and health-related quality of life in community-dwelling seniors".

This study was one of the first to discuss about frailty in Romania. The study was conducted on a group of non-hospitalized seniors (>65 years) without any prior hospitalization in the past 3 months who volunteered to take part in a geriatric assessment occasioned by the Day of Older Persons on October 1, 2016. Frailty was assessed using Fried phenotype, Groningen Frailty Indicator (GFI) and CGA. SF-36 was used to assess the QoL, and the participants were also asked to provide information on their medical history and medical treatments.

The study showed a low prevalence of frailty in non-hospitalized elderly people (27.77%), with higher scores recorded on GFI, but given the small sample size the correlations were not statistically significant. QoL was significantly decreased in the frail subjects both in terms of physical and mental function, with lower scores on the physical component. These findings suggest that early detection and intervention are essential for improving quality of life of frail elderly, one of the main elements of successful aging.

6. TECHNOLOGY FOR BETTER MEDICAL CARE IN THE ELDERLY

6.1. INTRODUCTION

In the last years, efforts have been made in order to increase the level of care for people with various disabilities, and, in the same time, to increase their quality of life. To achieve these requirements, efforts were directed towards the use of various equipment and techniques using components of informatics and telecommunications that are more and more sophisticated (217).

Assistive technology is a generic term that includes assistive, adaptive and rehabilitation devices for people with various types of disabilities. Assistive technology ensures greater independence for people with disabilities, allowing them to perform tasks otherwise impossible or very difficult to accomplish by improving or changing the interaction with objects and equipment necessary for performing that task (217, 218).

In recent years, physical disabilities have been greatly aided by technology. Starting from the post-stroke rehabilitation program to creating a safer and easier-to-use environment at home, there are currently several devices available for individuals suffering from physical and cognitive complications of neurological disorders. As a geriatric specialist, I have worked with psychologists, neurologists, psychiatrists and bioengineers to help improve research and general knowledge in the field.

As technology has progressed, we have seen how some of the new devices are being employed for elder's use. Starting from smart homes that use computers to respond to the owner's vocal commands (including calling for help in case of a fall) to voice-activated wheel chairs and e-medicine, we have seen the development of a new industry – elder-centred technology. While the initiative is extremely useful, an important percentage of the devices and systems require clinical testing, which is where geriatricians come in (218).

Key information technology application domains in health care include telemedicine and home telecare. Telemedicine is defined as the direct provision of clinical care, including diagnosing, treating, or consultation, via telecommunications for a patient at a distance. Its primary function is to provide specialist consultation to distant communities, rather than to provide a tool for self-management of chronic disease. On the other hand, home telecare is a rapidly evolving domain focused on providing care in a home setting with the primary intent of supporting the patient rather than the health professionals. Home telemonitoring is used in a more restrictive sense and encompasses the use of audio, video, and other telecommunication technologies to monitor patient status at a distance (219).

Telemonitoring is an innovative strategy for improving seniors' quality of life by making it possible to monitor patients remotely so that clinicians can intervene early if there is evidence of clinical deterioration. A recent Cochrane review concluded that telemonitoring of patients with heart failure reduced the rate of death from any cause by 44% and the rate of heart-failure-related hospitalizations by 21% (220). Telemonitoring allows for more frequent assessment of clinical status with the opportunity to modify medical management remotely (221). Thus, telemonitoring could potentially improve patients' health status, decrease admission rates and even increase survival.

The equipment required for most telemonitoring programs is often quite simple, as devices connect to existing audio or video-technology. However, after a promising start some twenty years ago, some studies have concluded that telemonitoring brings no added benefit (222, 223), which is why this practice is not yet fully accepted by all medical societies. Together with my colleague from the Bioengineering University, we have tried to assess whether telemonitoring can be applied in the elderly patients of Romania in two major projects:

TELEMON- A complex system for telemonitoring of medical vital signs, 2007-2011. Contract 11-067/18.09.2007. Program four of PN II - Partnership in priority domains, research axis D1 (IT&C). Funded by the National Authority for Research - 947.000 RON

Programul Joint Applied Research Projects, funded by the Romanian National Authority for Scientific Research (MEN - UEFISCDI), contract PN-II-PT-PCCA-2013-4-0761, no 21/2014 (SIACT).

6.2. MATERIAL AND METHODS

The main objective of locally assessing the validity of using technology for better senior care is the achievement of an integrated system. Telemonitoring is essential for both active and disabled elderly patients and the golden standard is to integrate it with as few added devices as possible.

The telemonitoring device is usually composed of the following: a personal network of wireless medical sensors on the ill person, a personal server on the same patient (a smartphone), and a personal computer (PC). After local biosignal processing, according to the specific monitored feature, the salient data are transmitted via one of internet, GSM/GPRS or a telephonic line to the database server of the Regional Telemonitoring Centre. The personal network of sensors includes at least one medical device for vital signs acquisition, or a fall detection module, all these components having radio micro-transmitters, which allows an autonomic movement of the subject. In the case of mobile patients, data processing is done by a Personal Digital Assistant or a smartphone with GPS localization, and data transmission is done by the GSM module of the PDA (224).

6.2.1. The TELEMON project

It had the purpose to study the ability of the TELEMON system to assess health status. Its applications correlate on two levels: a local data processing, near the patient, and another device processing on database central server. As such, the general software architecture is a client-server one, and the project develops a so-called SOA –Service Oriented Architecture– which is a standards-based approach to manage services made available by different software packages for reuse and reconfiguration. The results of data processing are, in principal, and if necessary, in different locally generated alarms, transmitted to the central server, to the family or specialist doctor, to the ambulance or to a hospital. Other results of locally or on server data processing is different medical statistics, necessary for the evaluation of health status of the subject, for the therapeutic plan and for the healthcare entities.

The TELEMON system is built around a database server that receives data from local subsystems, also from mobile subsystems, and stores them. Also, the database server can be connected to another database server, for example a hospital server. The subsystems are connected to the database server through Internet (if it is available) or a GSM connection.

In some cases, the telemonitoring system can be adjusted for disabled elderly, which requires certain modifications from the above-mentioned device. The most important feature of telemonitoring severely disabled individuals is ensuring simultaneous, bidirectional communication. In this case, the two functional components (communication and telemonitoring) will have practically common hardware (except for the sensors for capturing the physiologic parameters) and most of the software will also be common.

6.2.2. The SIACT project

It continues the idea to use technology for a better care of the seniors by studying assistive technology. It ensures greater independence for people with disabilities, allowing them to perform tasks otherwise impossible or very difficult to accomplish, by improving or changing the interaction with objects and equipment necessary for performing that task. Concerning the current state of caring methods for handicapped people (including severely neuromotor disabled people) the requirements for round the clock surveillance are universally accepted; usually there are several trained persons that are taking care of the physiological needs and care of the disabled patient, that are responsible for the medical compliance and surveillance but can do very little for their psychological needs (224).

Nowadays, telemonitoring is considered an excellent method for diagnosis and surveillance, as proven by numerous studies and projects, finalized and/or still in progress. The advanced technologies applied by many researchers from different technical fields meet the needs for patients suffering from autism, effective ways of supporting people with dementia, human robot interaction system being able to recognize gestures usually employed in human non-verbal communication, aiding visually impaired people to perform ordinary activities or non-visual communication, assisting rehabilitation and augmentation of children who are suffering from motor and social function impairments or assisting people in rehabilitation after a stroke. Lately, particular attention has been focused on the implementation of assistive systems for neuromotor rehabilitation, for the recovery and reintegration into society of these types of patients (225).

The system implemented at the prototype level in this project, is the result of the interdisciplinary collaboration of specialists from the fields of electronics, telecommunication, computer science and geriatric medicine. The proposed system helps towards a drastic decrease of care costs, due to the use of keywords technology for two-way communication with neuromotor disabled patients and the Internet of Thing (IoT) concept for implementing the wireless and wearable sensor network used for telemonitoring the physiological parameters of the patients. Both functions of the system (communication and telemonitoring) share the same hardware platform (except for the sensors for capturing the physiologic parameters) and most of the software components.

From the communication perspective, the target consists of patients that are able to hear and/or see and understand, but are unable to communicate using conventional methods such as speech, writing or hand gestures. Usually these types of patients are able only to make limited movements such as muscle contractions (rising of a forearm, finger movement, foot movement) or, as is the case in most situations, eye movements and blinking. Whatever the situation, the problems always remain the same: Patient ↔ Caretaker communication and medical investigation and observation.

The telemonitoring of physiological parameters has the purpose of efficient assessment of the patient's current condition, allowing rapid intervention in case of necessity. The system will have the ability of continuous observation of previously programmed physiological parameters and of sending alarms to the caretaker when the values of the monitored parameters are beyond normal limits. All monitored parameters, alarms and caretaker interventions will be recorded in the Server memory for later analysis.

The end product is intended for use in hospitals (for acute cases), rehabilitation centres (for subacute and chronic cases), nursing homes (for senior patients with severe handicap and multiple concomitant diseases) and also in the patient's home (for chronic patients), making easy for them to prolong the period when they are independent and do not require a nursing house.

The first component of the proposed system will be used for ensuring the bidirectional communication with patients using the technology of keywords/characters: the patient is presented successively the keywords or alpha-numeric characters and he selects the desired one by using a mechanic switch or their glance; for this, a calculation unit is used. The selected word/character is sent to a server unit and from here to the mobile calculation unit of the caretaker. Depending on the situation, the caretaker gives the appropriate answer and this answer is sent back to the patient.

The telemonitoring component includes a network of sensors for the physiologic parameters selected for monitoring, whose central node is radio-coupled with the patient's calculation unit and via this - to the server. If the exceeding of certain limits considered dangerous is detected, the server, by automatic data analysis, alarms the caretaker.

The proposed system contains three subsystems (Figure 15):

- 1) **The patient subsystem (unit)** includes a hardware and a software component; it consists in a laptop (tablet PC, or other devices) for communication and data collection, different type of switching sensors for patient needs detection, connected by USB port with the patient subsystem and a network of wireless sensors for capturing the biologic parameters; the communication with severely neuromotor disabled patients is realized by detecting the patient gaze direction, using a special device based on eye tracking interface;
- 2) **The server subsystem (unit)**, is a desktop PC operating as a dispatcher, which establish and controls the communication protocol between the patient and caretaker subsystems;
- 3) **The caretaker (surveillance, supervisor) subsystem (unit)** consisting in a Smartphone (or tablet PC) for communication with the patient by server and real-time monitoring the physiological parameters of the patients.

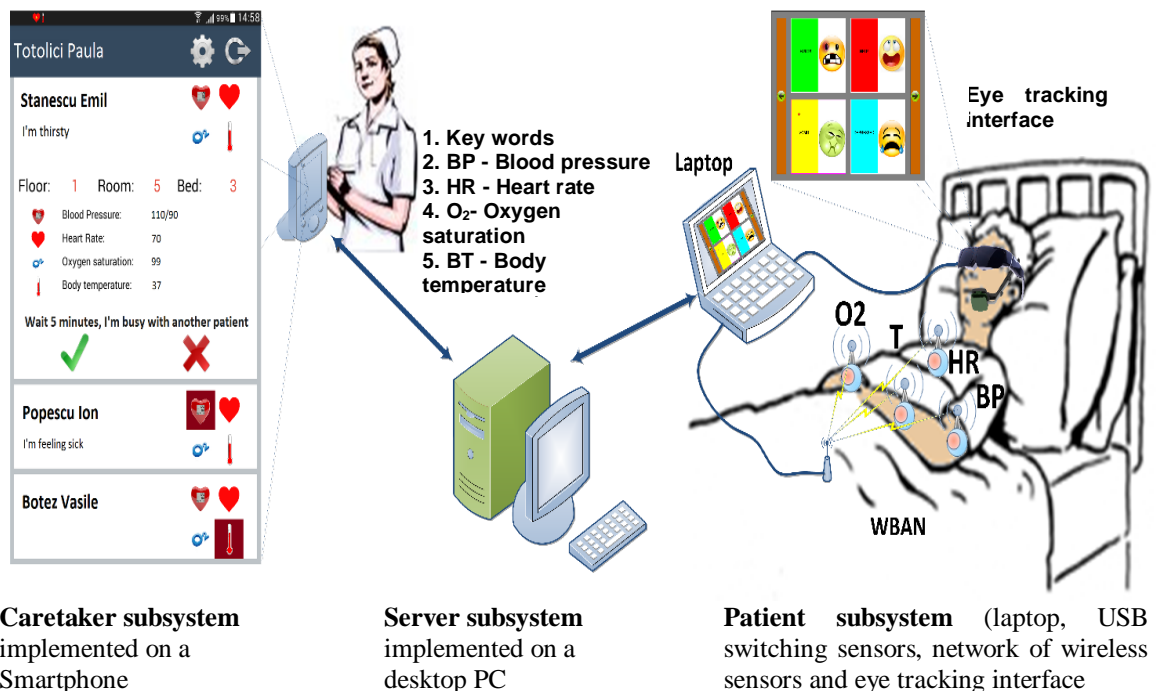


Figure 15. The structure of the proposed integrated system for assistance in communicating with and telemonitoring severely neuromotor disabled people

Both functional components of the proposed assistive system – for communication and for telemonitoring– will use the three subsystems illustrated in Figure 15.

The communication function is based on a technology which we named “keyword technology”, which can be described as follows: the patient is presented successively with precise words (for ex. “thirst”, ‘hurts”, “nurse’), which are accompanied by suggestive images or alpha-numeric characters from a virtual keyboard, as shown in Figure 16; this presentation may also be accompanied by recordings. The detection of the patient’s will or need is done by selecting a keyword by a technique imposed by the disability: (1) using a switching sensor attached (bound) to finger, arm, or sole or (2) by detecting the patient’s gaze direction, using the eye tracking interface based on an infrared videocamera.

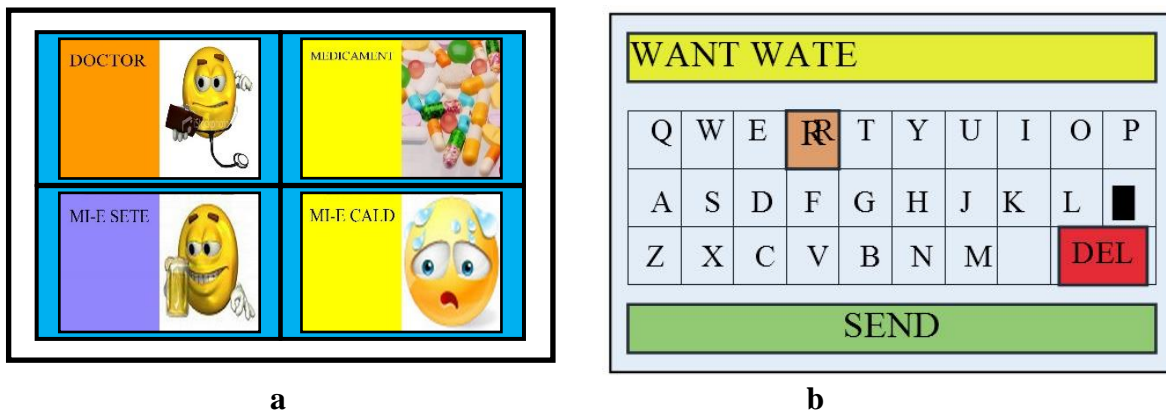


Figure 16. a) Ideogram/keywords displayed on the patient display;
b) Virtual keyboard used to build sentences

Using the keyword technology, we can select only one image for each phase, and thus, the use of the alphanumeric characters to make words and phrases is too slow. This technique is perfectly adapted to the communication technology by keywords and can be used for severely ill patients, including patients with comprehension difficulties.

The technique of patient gaze detection, by video oculography (pupil eye image analysis); can also be used for word and word group building, by selecting alphanumeric characters. This technique involves the on-screen simultaneous display of several characters and the gradual construction of words or phrases that are being displayed.

Whatever the used technique, the system ensures the reception, by the patients, of an answer matching their request – an image or/and a sound recording. Consequently, a dialogue may take place between the patient and the caretaker (doctor, nurse, ...). This is essential for the diagnosis of the patients unable to communicate normally; using our proposed system they can answer questions (e.g.: “Does it hurt?”, “Yes”; “The leg?”, “No”; “The arm?”, “No”; “The throat?”, “Yes”).

The technique of patient gaze detection also gives the possibility to identify and communicate ideas, complex moods; it may be also used in other purposes, such as commanding the computer for the use of the Internet, and even the e-mail. Furthermore, it can be used for reading books, listening to the music, watching TV and movies. Of course, all these are available to the patients intellectually able, but there are so many patients who cannot communicate normally for a limited period of time, after surgery, for example.

The telemonitoring function is based on wireless network sensors used for capturing the physiological parameters of the patients, according to their needs. The number and type of the

monitored parameters can be adapted to the medical needs of patients. The monitored data values are transmitted to the system Server device for processing and from here are wireless transmitted to the caretaker device, where are real-time displayed. The system has the possibility to alarm the supervisor when the normal value of the telemonitoring parameters is exceeded.

The history of communications between patients and caretakers and monitored data values are recorded on the Server for further investigations. The monitored data values can be processed at any time in order to see the time evolution of the physiological parameters of the patients, which is very useful for establishing the optimal treatment.

The system's final goal is to be included into a unique platform which integrates services given by multiple health care actors: doctors, pharmacists, medical laboratories. In this way, when a patient meets a doctor for a diagnostic, all data needed by the doctor to analyze the patient medical history could be found on this platform. This meaningful information gives the possibility to the doctor to find a better diagnostic independent of the patient's subjectivity.

6.3. RESULTS

The data obtained from these projects were published in several papers presented below:

Costin C, Cehan V, Felea V, Ungureanu F, Rotariu C, **Alexa ID**, et al: TELEMON – Integrated System for Real Time Telemonitoring of Patients and Elderly People. *Ukrainean Journal of Telemedicine*, 2008, Tom 6, No 1, pp. 71-75.

Costin H, Rotariu C, **Alexa ID**, et al: TELEMON – A Complex System for Real Time Medical Telemonitoring, *Proc. Of the World Congress on Medical Physics and Biomedical Engineering*, Munich, Germany, WC2009, Vol. 25, PT 5, pp. 92-95, ISSN:1680-0737, ISBN: 978-3-642-03903-4, IDS No: BPZ27.

Costin H, Rotariu C, **Alexa ID**, et al: Real Time Telemonitoring of Medical Vital Signs. Published in: *Recent Advances in Biomedical Electronics and Biomedical Informatics*, Proceedings of the Second WSEAS International Conference on Biomedical Electronics and Biomedical Informatics, Long C, Anninos P, Pham T (eds), Moscow, 2009.

Rotariu C, Costin H, **Alexa ID**, et al: E-Health System for Medical Telesurveillance of Chronic Patients. *Int. J of Computers, Communications and Control*, ISSN 1841-9836, E-ISSN 1841-9844, Vol. V (2010), No 5, pp. 892-901.

The TELEMON system was built to include the following monitoring devices (Figure 17):

a) A 3-leads ECG module to record and transmit data through a radio transceiver interface. This subsystem allows detection of various abnormalities of electric heart activity, focusing only on those which can be life threatening and thus a medical emergency, such as: (i) rhythm modifications: severe bradycardia (<45/min) or tachycardia (> 140/min or even asystole– the heart rate equals 0 for at least 3 sec); (ii) recently installed AV blocks; (iii) signs of myocardial ischemia: new, significant pathological Q wave, elevation of the ST segment >200 μ V or depression of the ST segment < 150 μ V, negative T wave; (iv) enlargement of the QRS complex > 0,12 sec; (v) prolonged QT interval > 0,45 sec. We have adapted algorithms for the extraction of the ECG features based on digital filters, especially algorithms for the QRS complex and ST segment detection. The module is useful for patients with heart complications

or at risk for myocardial/vascular problems, who represent more than 80% of the elderly population.

b) The arterial pressure module, with serial interface. This module identifies significant variation of blood pressure such as hypotension or hypertension, and is very important for senior persons, who are prone to this kind of oscillations. Postural hypotension is one of the most frequent situations a senior person must deal with; its complications are severe, impairing the quality of life and becoming life threatening (e.g.: falls, syncope, and stroke). As practical solution, a commercially available A&D UA-767PC BPM was used. The blood pressure monitor (BPM) takes simultaneous blood pressure and pulse rate measurements. It includes a bi-directional serial port connection communication at 9600 kbps. An eZ430-RF2500 module communicates with the BPM on this serial link to start threading process and receives the patient's blood pressure and heart rate readings. Once the readings are received, the eZ430-RF2500 communicates with the network and transmits them to the Personal Server (PDA). PDA computes blood pressure and defines the status of the patient by using the following blood pressure values (by default), that can be adjusted and personalized by specialized physicians (cardiologists):

- Hypotension: systolic < 90 mmHg or diastolic < 60 mmHg;
- Normal: systolic 90–119 mmHg and diastolic 60–79 mmHg;
- Pre-hypertension: systolic 120–139 mmHg or 80-89 mmHg;



Figure 17a.
eZ430-RF2500 wireless development kit



Figure 17b. *Device for telemonitoring the heart rate and blood-oxygen saturation (microcontroller and wireless transceiver)*



Figure 17c. Device for telemonitoring the respiratory system

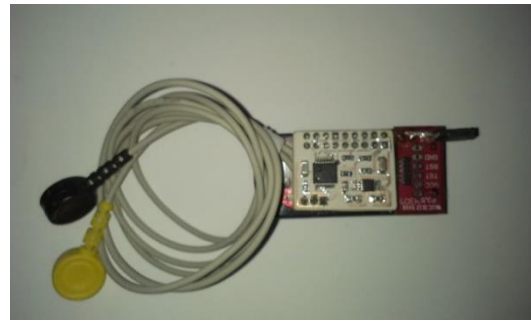


Figure 17d. Device for telemonitoring the body rhythm temperature

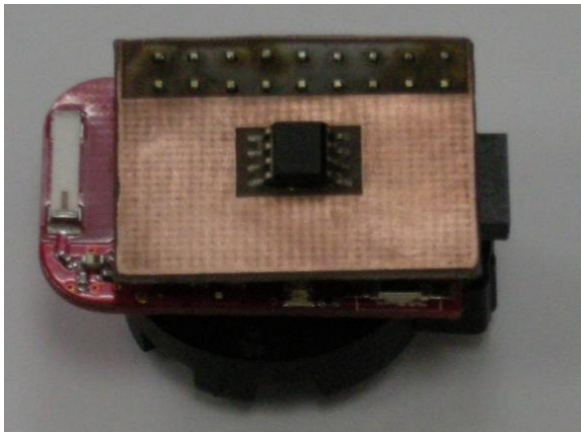


Figure 17e. Device for telemonitoring the galvanic skin response

- Stage 1 Hypertension: systolic 140–159 mmHg or diastolic 90–99 mmHg;
- Stage 2 Hypertension: systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg.

c) The oxygen saturation module (SpO₂). A large number of elderly patients have respiratory insufficiency due to chronic pulmonary diseases. The evolution of their respiratory capacity is strongly influenced by weather, exposure to allergens, humidity and compliance to treatment, therefore detection of oxygen saturation is a very useful thing. A decrease of arterial blood oxygen $< 90\%$ triggers the alarm system. The same sensor can be used for heart rate and SpO₂ detection. The probe is placed on a peripheral point of the body such as a fingertip, ear lobe or the nose. The pulse oximeter communicates with the eZ430-RF2500 through asynchronous serial channel at CMOS low level voltages. Data provided includes % SpO₂, pulse rate, signal strength, and plethysmogram.

d) The use of wireless breathing module is suitable for continuous long-time monitoring of human respiration for a number of medical conditions requiring analysis of respiratory rhythm, sleep-related breathing disorders and ischemic heart disease or can be useful during recovery from an acute event or surgical procedure. The module uses one of the most usual methods to sense breathing, i.e. using a nasal thermistor. The sensor is designed using MSP430F2274 microcontroller with an on-chip 10 bit A/D converter for data acquisition (10 Hz sampling frequency) and CC2500 2.4 GHz wireless transceiver. The thermistor detects changes of breath temperature between ambient temperature (inhalation) and lung temperature (exhalation). The used thermistor is a 0603 SMD type and has as main characteristics: $R_{nom} = 10 \text{ k}\Omega$ at 25°C , $B = 3380$, 1% tolerance.

The personal server on patient computes the following parameters:

- Breathing amplitude—calculated for every breathing cycle as a difference between minimum (Inhalation) and maximum thermistor voltage (Exhalation);
- Breathing interval—measured between two signal minima;
- Breathing frequency, calculated as a number of breaths per minute.

Normal breathing frequency is 12-20 cycles/minute. We consider two types of respiration: normal respiration, when every breath lasts more than 0.5 seconds; apnea, when the breathing is missing for more than 10 seconds.

e) The body temperature module gives important information about occurrence of fever, especially for persons with mild cognitive impairment who cannot sense temperature modifications ($> 38^\circ\text{C}$ or $< 35^\circ\text{C}$). We used the TMP275 temperature sensor (Texas Instruments). The TMP275 is directly connected to the eZ430-RF2500 module. The accuracy for the $35\text{--}45^\circ\text{C}$ interval is below 0.2°C . The Personal server samples the signal from the temperature sensor once per second and computes the status of the patient for the following temperature values: low temperature = $<35^\circ\text{C}$; high temperature = $>38^\circ\text{C}$; normal temperature—between the above values.

f) The fall detection module should be recommended to all senior persons who live alone. Elderly people are exposed to falls due to several causes: (i) postural hypotension (induced by inadequate hydration, cervical spondilosis with vertebro-basilar circulatory problems or even inappropriate medication for hypertension); (ii) inappropriate house conditions such as poor lighting conditions, narrow halls or staircases, slippery surfaces which predispose losing balance and fall; (iii) sensory disturbances (visual, postural) that induce imbalance and fall; (iv) inappropriate shoeing and/or clothing. Early detection of an elderly who had a fall is of extreme importance for recovering personal health and mental state after such a traumatizing event. Our fall detection module is based on accelerometer technique that can recognize four kinds of static postures: standing, bending, sitting, and laying. Motions between these static postures are considered as dynamic transitions. If the transition before a lying posture is not intentional, a fall event is detected. Our method uses the ADXL330 3-axes accelerometer and eZ430-RF2500 Wireless Modules. The ADXL330 is a small, thin, low power, complete, three axial accelerometer with signal conditioned voltage outputs, all on a single monolithic IC.

For advanced telemonitoring functions dedicated for neurologically impaired elderly, we had to create a complex patient subsystem in order to allow for bidirectional communication.

The hardware structure of the patient subsystem includes the devices used for communication (different types of USB switches and eye tracking interfaces), the wireless network sensors used to acquire the physiological parameters of the patients and a laptop, which

run the patient WEB application used for communication based on keyword technology and display the telemonitored data values.

The communication function of the proposed assistive system is based on patient needs detection, which is implemented in our system depending on his/her physical condition, by using:

- Switch-based sensors – which are used by the patients which can perform a controlled muscular contraction; these sensors are USB connected to the laptop and are adapted to the physical condition of the patient. Some examples of switched-based sensors with USB interface are illustrated in Figure18.
- Eye tracking interface - which is used by the fully immobilized patients who cannot perform any controlled movement, except eye balls movement.

Eye tracking is the process of measuring either the point of gaze or the motion of an eye relative to the head. An eye tracker is a device for measuring eye positions and eye movement.

There are different methods for detecting eye movement. The general classification of the eye tracking methods is as follows:

1. Scleral search coil method - consists in contact lens with an inductive sensor; in this case, alternating magnetic fields are generated by magnets positioned around the eye;
2. Infrared oculography (IROG) based on corneal reflection; gaze direction is calculated by measuring the changing relationship between the moving pupil centre of the eye and the corneal reflection;
3. Electro-oculography (EOG) – is a method for sensing eye movement and is based on recording the standing corneal retinal potential arising from hyperpolarizations and depolarizations existing between the cornea and the retina; this is commonly known as an electro-oculogram (EOG), which is captured by five electrodes placed around the eye;
4. Video Oculography (VOG) – this method is based on the video analysis of the eyeballs movement by using a video camera in visible or infrared spectrum.

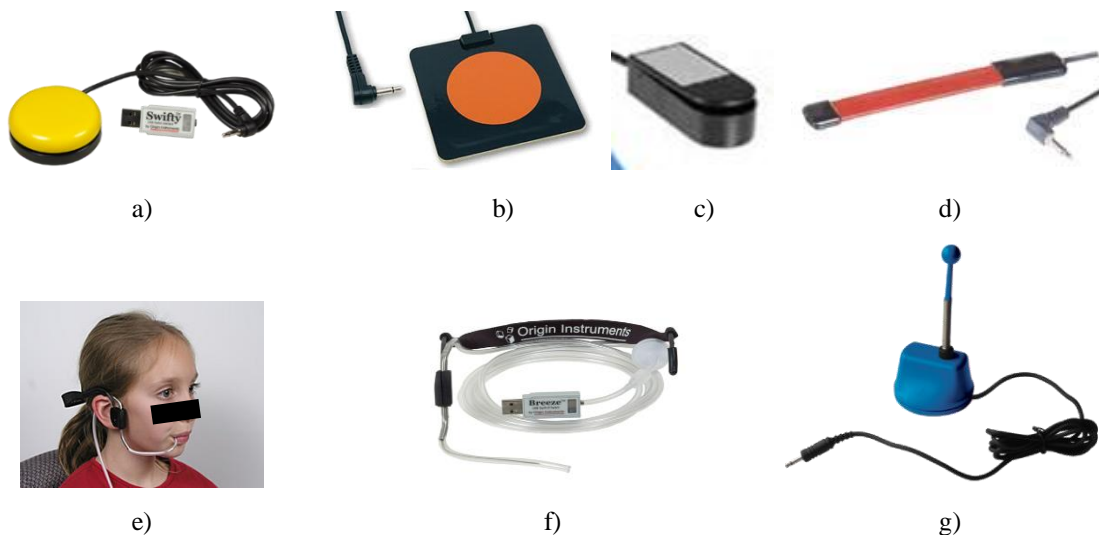


Figure18. Different types of USB switching sensors used for key words detection: a) hand switch-click (mouse button switch) with swiftly USB switch interface; b) pal pad flat switch; c) foot switch; d) ribbon switch; e) – f) sip/puff breeze switch with headset; g) wobble switch

Lately, gaze direction detection techniques have been developed in two basic directions, electro-oculography (EOG) – used by our team in ASISTSYS project, and digital image processing by using video oculography (VOG).

The digital image processing techniques use video cameras in visible and infrared (IR) spectrum to take video eye images, which subsequently are processed frame by frame by using a special software installed on a computer. Currently, increasing computing power of computers has led to diversification of pupil detection algorithms. The advantages of the methods based on the analysis of the eye images provided by the video cameras lie in their versatility, being practically independent from the individual characteristics of the eye.

The most widely used variant employs video images captured with a video camera - in the visible spectrum (day light) or in infrared light - from which the eye position coordinates are extracted.

Our system uses two types of a real-time eye tracking interfaces to communicate with neuromotor disabled patients by using key-words technology:

- “*head-mounted device*” (Figure19.a), which measures the angular position of the eye from the head; the video camera is mounted on glasses, right underneath the eyes;

- “*remote device*” (Figure19.b), which measures the position of the eye to the surrounding environment; the video camera is placed at the base of the screen.

The head-mounted eye tracking interface, illustrated in Figure19.a) consists of an infrared video camera mounted on a frame glasses right underneath the eye, connected to a patient subsystem (laptop), for eye pupil image acquisition and processing. The subjects who tested the system were asked to place their head in a chin rest and look at the user screen placed approximately 60cm away (Figure 20). This communication subsystem is used by patients with severe neuromotor disabilities who cannot communicate with the outside world through classical methods: speaking, writing, hand gestures (signs).



a



b

Figure 19. a) Head-mounted eye tracking interface consisting of an infrared video camera mounted on a frame glasses; b) Remote eye tracking interface – consisting of a commercially available infrared sensor mounted on the patient’s laptop

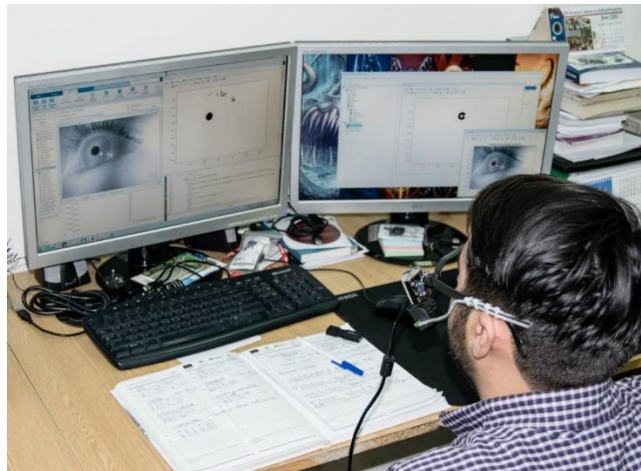


Figure 20. System operation by using a head-mounted eye tracking interface

The eye image processing algorithm takes the pictures delivered from the video camera and detects the eye pupil centre position in order to calculate the user's gaze direction. Thus, the pupil detection algorithm delivers two real-time signals corresponding to the detected pupil centre on both directions of the coordinate system Ox and Oy .

In order to improve eye pupil detection, the dark-pupil technique has been implemented. The result of the infrared illumination is that the pupil is clearly demarcated as the darkest region in the image. On the other hand, by using this illumination type, a consistent and uniform illumination of the eye can be obtained, without any user discomfort.

The type of communication depends on patient illness and his/her physical condition. Due to numerous types of available sensors, our system can be easily adapted to different types of diseases and patients.

The software structure of the patient subsystem has been developed for both communication and telemonitoring functions of our system. The software component of the communication function includes the patient WEB application (which assures both switch-based and eye tracking-based operation modes) and the software developed for eye tracking interface used for patient's needs detection.

The software component of the telemonitoring function includes a graphical interface running on the patient device used for real-time numeric and graphical display of monitored physiological parameters, alerts resulting from their processing, and the status of each node in the network (the voltage at the terminals of the battery being powered). The communication protocols used for monitored data transmission to the Server are also included.

The software component of the communication function is based on the WEB application running on the patient's computer via the Server. This WEB application implements keyword technology to communicate with neuromotor disabled patients for two types of patient need detection: switch-based communication and eye tracking-based communication.

In the case of the switch-based communication, the application performs the run of the ideograms on the user screen by their cyclical highlighting (Figure 21). The patient can select an ideogram acting on the switch sensor only during the time interval when it is highlighted. This time interval is set according to the patient experience in using the system. The data base with ideograms/keywords is organized hierarchically. Each level from the database contains a set of ideograms/keywords belonging to a class of objects defined at the previously (ascending) hierarchically level. When the patient selects an ideogram by using the switch (which can be of any type, as illustrated in Figure 18), his request is forwarded to the caretaker device through the Server.

The application running on the patient's laptop (Figure 21) displays on the right hand the messages received by the patient during the dialogue with the caretaker. The history of these conversations is stored on the Server, and can be verified as needed.

It is worth noting that the proposed assistive system has the ability to customize databases with ideograms and keywords organized in the form of trees for each individual patient. Thus, each patient has his/her own account within the system, which contains the personalized set of ideograms/keywords needed for it. Depending on the patient's evolution during treatment, this database may be easily updated as needed.

In the case of the eye tracking-based communication, the user controls the WEB application by using one of the two types of eye tracking interfaces (illustrated in Figure 19). The patient screen is the same as in previous case (Figure 22), but the ideograms are not cyclical highlighting, the user being able to fully control the application by using his gaze direction. In order to do this, the user must be able to perform two actions:

- cursor movement on the user screen according to his gaze direction only for visual inspection of the WEB application objects
- ideogram/keyword selection simulating a mouse click, by focusing the user gaze direction for a certain time on the selection area of the wanted ideogram/keyword.

In order to find the best solution for our system, different ideogram selection methods have been investigated. The first method is based on identifying voluntary eye blinking of the user in order to implement an ideogram selection. This method relies on the capability to identify voluntary blinking that can be done, using the total number of consecutive frames during the blinking or using a dynamic threshold for selection.

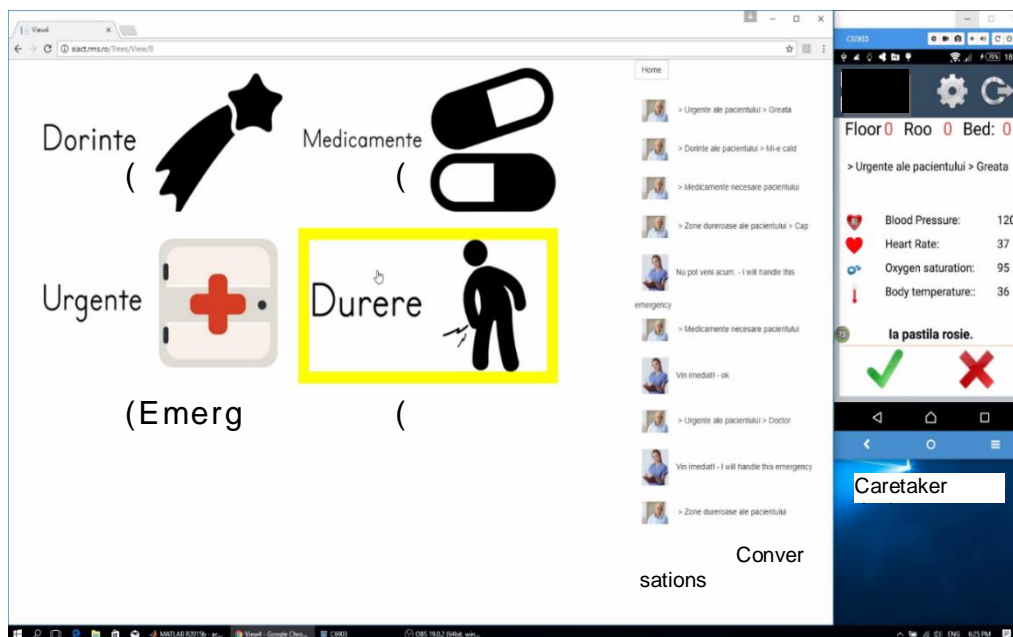


Figure 21. WEB application using switch-based communication (patient device screen – Laptop and caretaker device screen – Smartphone)

The application requires attention and concentration from the user, which can get tired after a long time of system using. This may cause errors in the detection of a voluntary blinking from an involuntary one. This method requires synchronization between the spatial localization of an ideogram (for visual inspection) and the selection of it.

Thus, for the safe selection of the wanted ideogram, two conditions must be met simultaneously:

1. the spatial localization condition of the respective ideogram, which implies the positioning of the cursor in the selection area of it;
2. the temporal condition, which requires performing a fixed duration blinking, while condition (1) is fulfilled.

The simultaneous failure to meet the above conditions may cause some uncertainty about the spatial positioning of the selected ideogram, with the risk of selecting another ideogram than the desired one. To avoid these errors in system operation, other methods for implementing a selection, represented by a “mouse click”, were also analyzed.

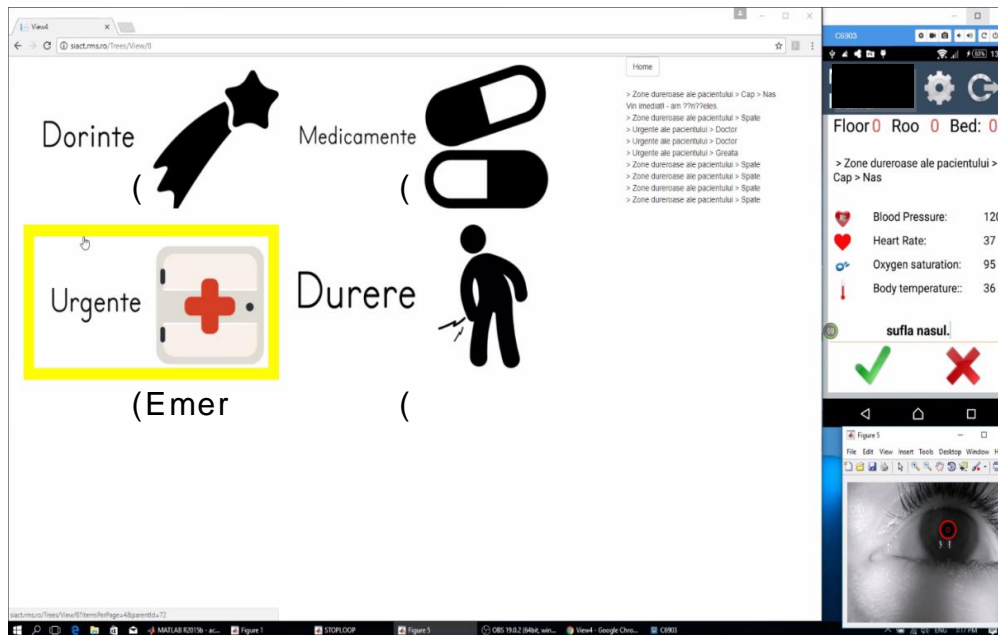


Figure 22. WEB application using eye tracking- based communication (patient device screen – Laptop, caretaker device screen – Smartphone and the eye image provided by the infrared video camera)

The second method consists in maintaining the cursor position in the specific selection area of an ideogram for a dwell time interval. This technique can determine false selection of ideograms due to Midas touch problem, which consists in random selection of the unwanted ideograms followed by the users' gaze direction.

For accurate operation, the system must be able to differentiate viewing and gaze-control. This can be achieved by setting the duration of the dwell time according to the user's ability to use the system.

One of the main problems of this technique consists in the difficulty to maintain the fixed cursor position in a selection area of the display for a certain dwell time in order to perform a selection by implementing a mouse click.

Depending on the applications, in order to increase the cursor stability on the user screen, different techniques based on real-time filtering, high frequency spikes cancelling from the signals provided by the PDA and the snap-to-point technique have been used.

In order to improve the user experience in system operation, the application provides a feedback for the user, highlighting the selection area of the ideogram, after its successful selection on the user screen.

The operation of the eye tracking interface is based on real-time detection of the pupil centre coordinates in the eye image provided by the infrared video camera. After detection, these coordinates are mapped to the cursor coordinates on the user screen. Thus, the cursor movement on the user screen is controlled by the user gaze direction. In fact, these tasks represent the operation principle of an eye tracking interface. The software components used to implement the eye tracking interface from the patient subsystem are based on different pupil detection algorithms which will be presented in the following paragraph.

The eye tracking communication subsystem used in the proposed assistive system is used in order to communicate in a bidirectional way with neuromotor disabled people by detecting their gaze direction, but can easily be adapted for other applications, like PC control (e-mail, Internet) by eye tracking. The eye tracking systems have a great potential in order to improve the quality of human-computer interfaces.

The main problem of integrating these techniques into human-computer interfaces is represented by the fact that they are invasive and too expensive for normal users. In the last years, due to progress in the field of electronics, the head-mounted video-based eye-trackers have become more and less invasive and their dimensions have been significantly reduced. On the other hand, the remote-control video-based eye tracking systems, although they minimize the intrusiveness, have got the disadvantage of a reduced accuracy and increased cost with respect to head-mounted devices.

The pupil detection techniques used in our assistive system are based on the algorithms developed for the case of infrared eye image capturing (Figure 23).

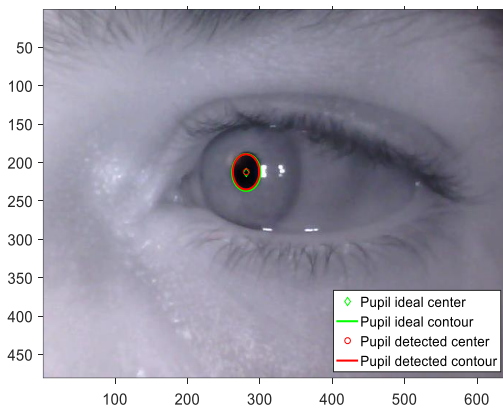


Figure 23. Eye image captured with an infrared video camera

For both techniques, the corneal reflection is always present in the eye image. In order to appreciate the user's gaze direction, the vector distance between pupil centre and corneal reflection can also be used instead of the usual detection of pupil centre position. This is possible because the vector difference is sensibleness to the user's head movements where the videocam is placed on the frame glasses.

The pupil detection algorithms (PDA) used in our assistive system use the dark-pupil technique, but can be easily adapted for the case of bright-pupil techniques, too.

Regarding the server subsystem, it includes the data base of the patients, communication protocols between patient device (Laptop) and caretaker device (Smartphone) via Server and the communication WEB application for two types of patient needs detection: switch-based communication and eye tracking-based communication. This application implements the dialog between the patient and caretaker, building the patient message and the conversation page. The

communication WEB application can be accessed, personalized and run by each patient, according to their needs.

The system uses the new SignalR technology which makes the dialog between browser and server to be very easy to implement.

Due to Internet connection between the proposed assistive system components, the Server device can be placed at the system administrator location, which simplify the system operation (for administration, installation and configuration). Since the system must be often adapted and configured to the patient's needs, the easily remote administration represents an important advantage.

The server has many functions:

- it manages the patient (communication) WEB application by using the keyword data base, which can be personalized to patients (depending on the disability degree of the patient, switch-based communication or eye tracking-based communication can be used)
- it receives, organize and process the data of telemonitoring physiological parameters of the patients and send these information to the caretaker unit (Smartphone)
- it records and organizes the evidence and the history of the patient's conversations with the caretakers, and detects alarming situations and alarms who may be concerned, etc.

The patient WEB application can be accessed at <http://siact.rms.ro>. By accessing this link, the main menu of the application is accessed and some information describing the application is presented. In the following, the main functions and operation of this application are presented in detail.

a) Institutions

The "Institutions" page is used in order to create, delete or edit an institution; thus, a first task of the application is to define the organizational framework in which the assistive system will be used.

b) Users

The system administrator can add new users to the database by accessing the "Create new user" button (Figure 24).

For each patient, the personal data are loaded, the method of communication with the supervisor is specified (by means of a switch or by using eye tracking interface), as well as the structure and content of the keyword/ideogram database used for communication. Also, depending on the patient's condition, the physiological parameters that will be monitored by the system are introduced and the normal values of these parameters are specified. When the normal values of these parameters are exceeded, the application will alarm the supervisor by means of a message accompanied by a beep that is received on the supervisor's device, represented by a "Smartphone".

From the "Configuration/Users" menu, the administrator can view the list of all users and edit each user individually. By editing a selected user, the administrator assigns one of the following roles: admin, doctor, patient, nurse. Depending on the assigned role, each user has specific access rights. In this page, the operation method (based on switch or eye tracking interface) is also set.

c) Sensors

The system is designed to be flexible and easily adaptable to the specificities of each type of patient. Thus, the list of sensors that are attached to the patient and monitors his condition is editable at any time, being possible to add new types of sensors for a particular patient. All sensors are defined in "Configuration/Sensor types" page.

The application publicly exposes a series of web services where the patient WEB application can connect and transmit to the server the values recorded by the sensors attached to the patient. These values are loaded into the system asynchronously, so services must be

active 24 hours a day. All the data values received by the server are viewed in the “*Configuration/Sensor records*” page.

Despre SIACT

- SIACT este un sistem de monitorizare a pacienților care suferă de afecțiuni neurolocomotorii, permitând acestora dialogul cu persoanele supraveghetore.
- **Obiectivul principal** al proiectului constă în realizarea cercetărilor privind proiectarea și implementarea practică la nivel de **prototip funcțional și testabil** a unui sistem de asistare pentru persoane cu afecțiuni neuromotorii severe, asigurând **comunicarea bidirecțională** cu aceste persoane, realizând în același timp telemonitorizarea parametrilor fiziologici vitali ai pacienților.

[Citește mai mult »](#)

Monitorizarea pacientului

- Sistemul include o serie de **senzori** ce înregistrează parametrii vitali ai pacientului.
- **Valorile măsurate** sunt stocate într-o bază de date de unde pot fi analizate de medicul curant pentru a îmbunătăți tratamentul pacientului. În caz ca un anumit senzor înregistrează valori critice pentru pacient, sistemul trimite o alarmă către asistentele conectate.
- Fiecarui pacient îi este asignată o anumită **configurație** aleasă de doctor.
- Fiecare utilizator își poate alege tipul afisării (**Switch sau Eye Tracker**).
- **Conversațiile** dintre pacienți și asistenta sunt salvate în baza de date, odată cu înregistrările senzorilor configurați.

Privire de ansamblu

- Pentru a crea, șterge sau edita o instituție, se folosește pagina **instituțiilor**.
- Modificarea sau adăugarea datelor personale, poate fi făcută la **pagina de profil**.
- Pentru a edita datele utilizatorilor înregistrați (doar în cazul **doctorului/administratorului**), se poate accesa pagina **utilizatorilor**.
- Adăugarea diferitelor fișiere sau ideograme se poate face la pagina **fișierelor**.
- Pentru a crea, șterge, edita sau derula un anumit arbore se poate accesa pagina **arborilor**.
- Se poate construi un **dialog bidirecțional** între **pacient și asistenta** folosind ideogramele și respectiv aplicația Android.

Figure24. Home page of the communication WEB application

d) Ideograms

Ideograms are intuitive images that characterize a particular state of the patient. By putting these ideograms in a logical sequence, the patient can build simple sentences to express a certain need or his state.

Since the diseases of the patients are different, the ideograms used by the system must be personalized for each patient. Thus, the application has a page (“Files”) where the user can define and introduce new ideograms into the system database.

The database of ideograms and/or keywords is organized hierarchically, in the form of trees, which are customized for each patient according to his needs. Ideograms are grouped on trees that implement a particular state of the patient. Thus, we have a root ideogram to which child ideograms are attached, that will continue the idea started from the root. Adding additional levels of ideograms can result in a very precise detailing of the patient's state.

d1) Sending patient messages

If the switch-based communication method is used, then the selected trees are scrolled non-stop on the patient screen. At any time, the patient can perform a mouse click, selecting a particular tree idea (ideogram) to be sent to the nurses (supervisors). For any selected ideogram, the patient can see the message he is building to be sent to the nurse (supervisor) (Figure 25). When the patient considers that the message can be sent, then he selects the “Send” ideogram and at that time the message is sent to the app on the mobile “Smartphone” of the nurse. Initially the message is sent to all nurses registered at the respective hospital, but after a nurse has

responded to the message, then the dialogue will only continue between that nurse and the patient.

If the eye tracking-based communication method is used, it is not necessary to scroll trees on the patient screen and the wanted ideograms are selected by using patient gaze direction. In this way the patient can full control the application by his gaze direction detection.

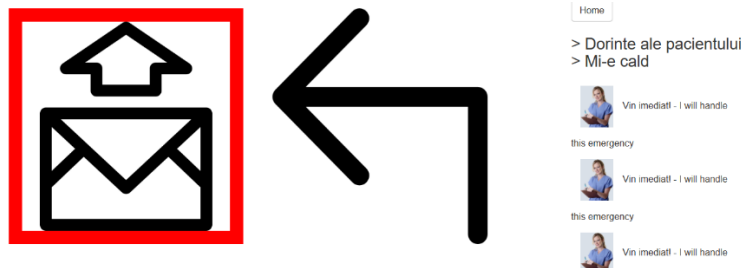


Figure 25. Sending the message to the nurse (supervisor)

d2) Viewing messages

The system administrator can view all dialogues between the patient and the nurses (by using “Conversations” page), thus following the patient's evolution and how it is treated in the hospital. Messages cannot be erased by nurses (supervisors), only the administrator has deleting rights from the database.

The hardware component of the caretaker subsystem consists in a Smartphone (or tablet PC) for communication with the patient in order to establish a bidirectional communication between patients and caretakers, medical staff, patient family and in the same time telemonitoring different physiologic parameters: heart rate, body temperature, oxygen saturation, etc. By using this device one nurse can care for more patients in the same time and permanent monitoring their physiological parameters.

The caretaker subsystem receives the patient's needs, transmitted to the caretaker via the Server in the form of written messages. The patient messages are sent to the caretaker via the WI-FI network, which in turn can send back a personalized response to the patient, thereby establishing a bidirectional communication between the two. This type of communication can be used also in the proposed system for the medical investigation of patients with severe neuromotor disorders who are unable to communicate with other people by the usual means: speech, writing or signs.

The telemonitoring parameters are tailored for each patient, depending on their physical condition and needs. The proposed system is flexible in this respect, taking into account the state and needs of patients. The monitored physiological parameters are real-time displayed on the caretaker device for each patient from the system data base. Thus, the medical staff can have easy access to the evolution of the monitored physiological parameters values over the course of treatment. In the same time, the caretaker subsystem sends an alarm notification when the normal values of the vital physiological parameters are exceeded.

The Software component of the Caretaker subsystem is represented by a Smartphone or a tablet PC wirelessly connected to database server. It is used for the following activities:

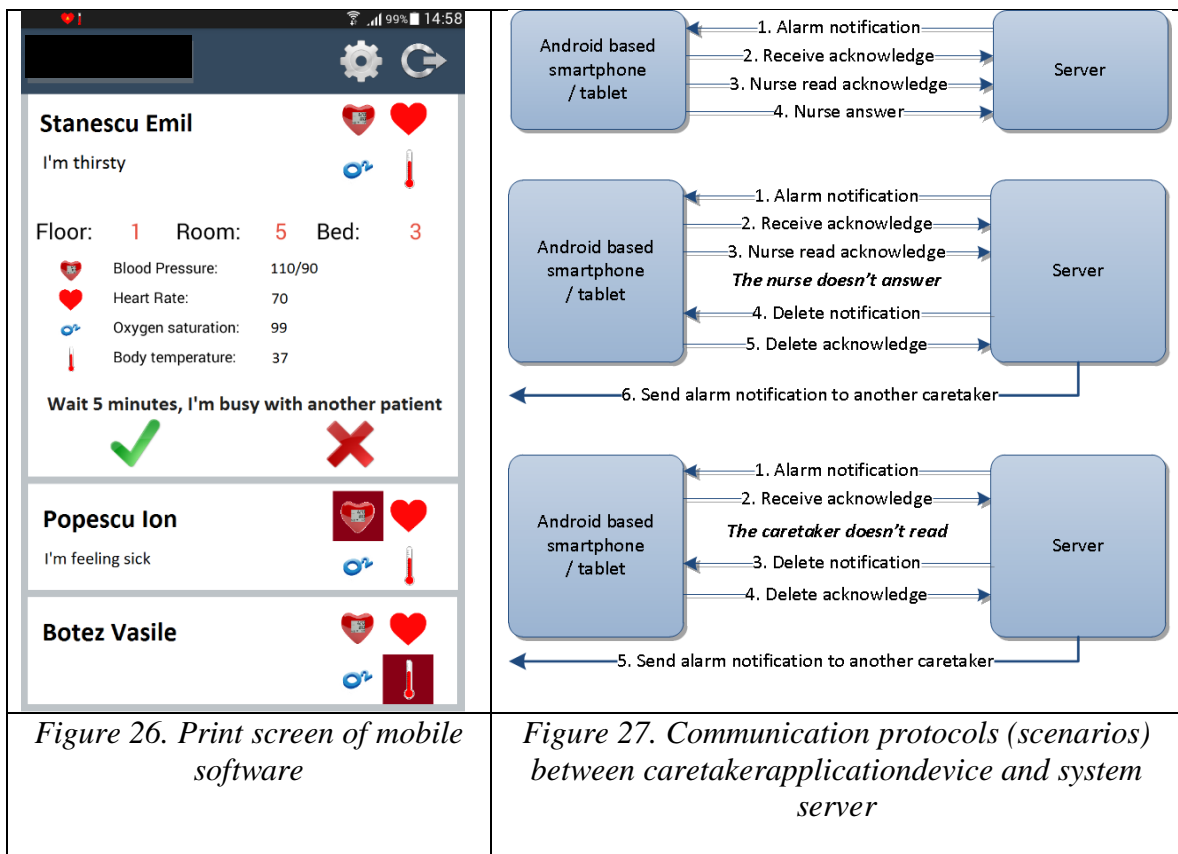
- displaying the words selected by the patient, in written or audio forms
- sending back to the patient the answer of the caretaker
- displaying the values of the monitored physiological parameters (Figure 26)
- sending an alarm notification when the normal values of the vital physiological parameters are exceeded

- displaying the evolution of the monitored physiological parameters values over the course of treatment

The caretaker application is written in Java for Android enabled mobile devices, being always connected to system server and it sends and receives data using JSON protocol. Every alarm notification consists in: message id, message priority, patient information, patient vital parameters, patient message and caretaker/nurse bed confirmation.

The initiator of a communication is always the Server unit which sends a notification when a patient has a need or a request. Also, the server sends notification alarms in case of emergency, when the values of vital physiologic parameters are outside the normal limits. In Figure 27 three communication protocols (scenarios) are presented:

- The first one is for a normal operation when the caretaker reads and answers to a notification alarm.
- The second scenario is for situation when the caretaker doesn't answer after reading the message.
- The third scenario is for situations when the caretaker doesn't read the notification alarm.



In the last two cases, when the caretaker doesn't read or answer, the server will send the message to another caretaker, deleting the one already sent to the first caretaker. All the communication is logged for further analysis.

One of the main advantages of this application is the fact that only one caretaker can assist more patients by communicating with them and telemonitoring their physiological parameters.

Since new technology requires an adequately trained staff capable of maintaining it and operating it, we applied for educational funding for physicians in Moldova country, and won the POSTDRU Grant “Brain Aging Project”. My participation in this grant was to train young physicians and nurses in recognizing the early signs of cognitive impairment and how to manage elderly individuals that suffer from various neurologic conditions.

The project:

“Brain Aging Project” –Training in new medical technologies and upgrading medical levels for physicians and nurses from ambulatories and hospitals, 2007-2013. POSDRU/81/3.2/S/46975. Funding from Programul operațional sectorial pentru dezvoltarea resurselor umane 2007-2013. Project ID:46975.

continued my work about implementing in every day practice new medical technologies. There were several topics I had to start with, in order to facilitate the information about natural and unnatural decline of the brain’s functions, emphasizing the role of medical factors on aggravating brain aging and the possibilities we have at hand to influence them, such as: the cardiovascular risk factors, the role of diabetes and the influence of life style over the brain aging.

We know that various mental skills decline at different rates as people age, and that trajectories of decline differ among people. Neuroimaging enables researchers to match changes in the brain's physical structure to changes in mental performance over time. Memory and other cognitive skills decline from the 20s onward, according to a range of research, but the pace of decline varies. Some skills, such as vocabulary and general knowledge, often improve over time and do not decline until people are quite old. In general, people reach a cognitive peak in young adulthood, level off in their 50s and 60s, then decline slowly into the 80s, with a sharp drop in the years before they die. People who have had less education or jobs that require little mental effort have lower cognitive skills at young ages and lose those skills at a sharper rate than people with more education or mentally demanding occupations. One theory is that the density of neural synapses grows with education level, protecting against cognitive impairment. Lack of physical activity and poor nutrition also appear to play a role in hastening cognitive decline.

6.4. DISCUSSIONS

The purpose of the TELEMOMON grant was to bring into attention the usefulness of communication technology. The potential market of the ageing of the population is very high for information and communications technology (ICT) systems that address the issues posed by demographic ageing and decrease the costs of healthcare. Telemonitoring senior people who want to preserve as long as possible their independence but are of medical risk (cardiovascular, respiratory, proneness to falls) represents one of the most important solutions to an aging Europe (226).

Gerontechnology is a relatively new science which has emerged because of the combination of demographic increase of ageing people and the rapid evolution of technological products, services and environments. Older people have to learn new skills and have to be convinced of extra benefits, successful aging being one of them.

Successful aging means maintain physical, cognitive, and social activities, live an independent life of one’s own choice and maintain an appropriate quality of life. Senior citizens wish to remain living at home for as long as possible, despite the appearance of motor and/or cognitive impairment. Some of these individuals require moral and/or physical support 24 hours

a day, a situation difficult to deal with without sustained family support or institutionalization (227).

Solutions supporting independent living at home and outdoors are one of the main alternatives to institutionalization, implying a significant reduction in healthcare costs. Telemonitoring is one of the alternatives that provide users and their families with confidence and satisfaction, since it allows elderly patients with chronic diseases or very frail to live independently in their own home with direct contact to the professionals, relatives and friends (228).

Autonomy and quality of life of old and disabled people living in smart private or public homes designed under the Ambient Intelligence paradigm can experience significant enhancements due to the increased support received from the environment. This support includes facilities for environmental control, information access, communication, monitoring, etc., built over diverse technologies and using different operation ways. Nevertheless, users can find accessibility barriers frequently related to the diverse user interfaces with heterogeneous devices and procedures. These problems include both physical difficulties to handle the devices, and cognitive barriers to understand how to use procedures and navigation. Consequently, accessible unified interfaces to control all the appliances and services are needed. This is only possible if the network technology used for smart homes is able to support interoperability and systems integration (229).

At the same time, the development of assistive technology for the disabled and the elderly, after a period of a slow but steady scientific progress, seems to be mature for new research and application break-through by combining human-centred design methodologies with integrated micro-mechatronic and robotic systems. New important research projects in this field have been recently launched both at academic and industrial level worldwide, e.g. in US, Europe, Japan and Korea (230).

6.5. CONCLUSION

The TELEMOM project aimed to develop a secure multimedia system designed for medical consultation tele-services. The main goal was to build a complete pilot system that will connect several local tele-centers into a regional telemedicine network. This network further enabled the implementation of complex medical tele-services (teleconsultation, telemonitoring, homecare, urgency medicine, etc.) for a broader range of patients and medical professionals, mainly for family doctors and those people living in rural or isolated regions.

A second step for using technology for better medical care was extending telemedicine and assistive devices for severely disabled elderly that have long-term neurological complications after stroke and/or neuro-degenerative disorders. As such, the SIACT project conducted by Professor Radu Gabriel Bozomitu emerged and preliminary data suggest it has a good feasibility and can be implemented with reasonable cost.

The POSDRU teaching grant came as a fortunate addition, because it allowed us to disseminate the acquired knowledge and to train nurses and young physicians for better elderly care.

The recent advances of medical rehabilitation procedures, methodologies and tools tend to include more and more the cognitive aspects of motor control, also exploiting the new technologies for brain imaging, which allows to "close the loop" from brain to action. This gives an important role to robotics, which can be fruitfully employed in the rehabilitation of neuro-motor functions and motor capabilities, by providing tools that are in their nature flexible and programmable and that allow to set and assess procedures quantitatively. Robotic tools are being effectively applied not only to motor rehabilitation but also to promote recovery of cognitive deficits and the psychological enrichment of the elderly.

SECTION II - FUTURE PROJECTS IN THE ACADEMIC, PROFESSIONAL AND RESEARCH FIELD

1. IMPROVEMENTS IN THE ACADEMIC FIELD

Over the course of my academic career, I have always strived to continuously improve my teaching skills. Having the opportunity to teach both fourth-year and sixth-year students give me the unique possibility to receive a truthful and consistent feedback from young doctors because I can directly assess their level of knowledge at these two time points. Together with my team, I am always preoccupied with updating Geriatrics and Internal Medicine textbooks and on-line resources available on the University's website. Although currently teaching relies heavily on power-point presentations, educational videos and other types of media, I believe some of the old methods, such as explaining a concept with the aid of the blackboard, deserve to be preserved as well. As such, I will keep constantly updating my courses and using slides for students to receive the material at home, but I will emphasize the key information by drawing and writing on a board and I will involve students in this activity by asking them to join in.

One essential aspect of my academic career consists in my relationship with young trainees in Internal Medicine or Geriatrics. As coordinator, I am in the unique position of supervising their progress throughout their residency and preparing them for the specialist examination and for future tenure. I intend to continue updating the courses designed for them and ensuring that they are assessed periodically by means of tests and different other evaluations. I will periodically organize sessions of case presentations and examination simulations, allowing the interns to develop the ability to speak in public and to present in a cohesive and a coherent manner a clinical case. Moreover, I plan to encourage as much as possible exchange visits or training fellowships abroad, and to help my young collaborators present their work at international congresses and conferences.

Regarding my relationship with the younger members of my teaching staff, I will encourage and stimulate their professional development. I consider this objective extremely important since this staff will be, at a given time, responsible for the training of young generations. As such, I plan on ensuring they each receive abroad training sessions through EU or University programs such as "Mobility for young researchers" or ERASMUS. Additionally, I will progressively increase the amount of responsibilities for each of my collaborators in order to better prepare them for future teaching positions such as Associate Professor.

Last but not least, I will continue to improve my own skills as a teacher and as a researcher, applying for funding and writing articles for peer-reviewed journals. By constantly collaborating with my younger peers, I will both train them and motivate myself to improve and keep on learning.

2. ADDITIONAL PROFESSIONAL DEVELOPMENT

Although the academic field has always played a crucial role in my future development plans, I believe no professor involved in clinical teaching should fail to also focus on improving his/her skills as a physician. I plan on emphasizing the importance of receiving feedback from patients in my department and, together with my team, I will constantly strive to attend national and international conferences and to keep informed of the latest discoveries in the field. Additionally, I wish to use these scientific meetings with peers in order to promote our university and my department as attractive research partners and strategic collaborators in Romania.

Networking with internationally-renowned physicians will also give me the opportunity to establish working relationships with their departments, which will in turn help me offer my collaborators a place for them to visit another hospital and learn new approaches for treating patients and innovative methods for prevention, diagnosis and management. I strongly believe that each physician should have at least one opportunity to do a fellowship/enroll in an exchange program in order to gain new skills and a different perspective on the medical system. Because I strive to keep in touch with my former trainees, many of which are now tenured physicians at major European hospitals, I believe this goal can be quite easily attained.

Another professional goal I wish to accomplish in the following years is to improve our interdisciplinary collaborations. The golden standards of medical care can no longer be obtained through the expertise of one individual, but require the input of an entire team. In terms of senior patients, this team is composed of physicians and nurses specialized in geriatric medicine, cardiology, pneumology, gastro-enterology, surgery oncology and psychiatry, which are aided by dieticians, rehabilitation medicine specialists and psychologists. By constantly cooperating and working on joint projects and research grants, we have created a vast network of like-minded professionals that are eager to lend their expertise so that each patient receives a personalized treatment. I will strive to continue and further improve this collaboration and perhaps create a more formal context – a weekly meeting in which difficult cases will be presented.

Last, but not least, I wish to continue organizing and participating in the regional chapter dedicated to the International Day of the Elderly. By involving most of my young collaborators while simultaneously offering an opportunity for interested students to join, this event has provided elderly with free and accessible medical assessments for the past eight years. I wish to increase the number of individuals that can be screened during the event and to expand the array of medical services we can provide, a target that can be achieved by involving local government and NGOs.

3. PERSPECTIVES FOR FUTURE RESEARCH

3.1. GERIATRIC ONCOLOGY

It is now well recognized that cancer is a major problem for elderly individuals. It is the second leading cause of death after heart disease in the United States, and age is the single most important risk factor for developing cancer. Approximately 60% of newly diagnosed malignant tumors and 70% of all cancer's deaths occur in persons 65 years or older. The total cancer incidence rises progressively through the middle years and then falls off in the later years. However, the age-specific cancer incidence rises progressively throughout the age range. Thus, while the rate of increase diminishes somewhat in the oldest age groups, and the rate actually falls slightly in the very oldest (perhaps a survivor effect), the overall risk for developing cancer is certainly greatest in the later years (232).

The number of individuals aged over 65 is rising rapidly and the oldest of the old, that is, those older than age 85, are increasing at the greatest rate. As such, geriatricians, generalists, and internists will be encountering increasing numbers of elderly individuals with cancer in their practice. The median age range for diagnosis for most major tumors, common to both men and women, is 68 to 74 years; the median age range at death is 70 to 79 years.

The overall pattern for the incidence of age-specific cancer shows a rise with age; overall, 60% of cancers occur in those age 65 years or older. This is not uniform for individual cancers and in some malignancies, there is an apparent decrease in incidence in people older than 80 years. This may be a result of a number of factors, including underreporting or natural selection, which would allow the less-cancer-prone populations to survive. However, cohort effects may have the most significant impact. For example, age-specific annual cancer incidence rates from the SEER Program indicate a fall in incidence in the oldest age groups for both prostate and lung cancer. This changes when the data are corrected for certain known risk factors (232, 233).

Elderly patients continue to be under screened and thus under diagnosed with cancer. The goal for initial cancer detection is to make the diagnosis as early as possible, with the hope that treatment at the earliest stages of disease would have the best survival rates. There are several geriatric assessment tools that can be used in order to identify elderly patients at risk for cancer.

Another issue regarding cancer in the elderly is treatment. Due to its high toxicity, oncologists often choose to undertreat elderly or opt for a less aggressive (and implicitly less effective) treatment in this age group. The CGA should be able to recognize those who may and may not tolerate standard treatment, identify and address remediable issues, and design special help for those who need it. Nevertheless, CGA has been hard to realize in actual practice due to the burden on patients and providers.

Rodin and Mohile (233) did one of the first reviews of CGA in Oncology in 2007 and recommended that all patients 70 years + should undergo some form of geriatric assessment including the 'Get up and go' (GUG) test or a similar test, the Vulnerable Elder's Survey-13, and a baseline cognitive screen. Those who score normally in these screening tests do not need referral to a CGA team, but those who score abnormally should be referred.

More recent attempts to detect vulnerability in elderly cancer patients have shown more promise. The group in Leuven screened 1967 patients ≥ 70 at 10 hospitals with the G8 tool (234), and if there was an abnormal score (≤ 14 out of 17) the group did a CGA. Nearly 71% had an abnormal screen, and this assessment found previously undetected geriatric problems in 51% of patients; the treatment decision was influenced in 25% of patients. A smaller pilot trial showed that if the original treatment decision was already decided before referral for CGA, then the treatment decision was only changed in 1 of 24 patients, but if the treatment had not been decided, 5 of 6 patients who underwent CGA had their treatment changed.

Attempts to discern which parts of the CGA tool are necessary and sufficient have been unsuccessful. Sutton et al. (235) reviewed all the available tools used to predict 'frailty' so that treatment could be modified for those unfit to standard treatment. The G8 and TRIST had the highest sensitivity for frailty but poor specificity and negative predictive value. Even the tools with the highest sensitivity had negative prediction value of only about 60%, meaning 40% of patients could be triaged wrongly. A systematic review concluded that CGA had value but more research was needed to enhance usefulness in the clinic.

The available data suggest that when symptoms are discovered or expected, elderly cancer patients can benefit from the same interventions used in younger patients. In a prospective study of 408 cancer patients undergoing treatment, the older patients who exercised had better self-reported health, and less shortness of breath (236). All the available data suggest that exercise improves tolerance of chemotherapy in all patients, with less fatigue and weight gain among those randomized to structured exercise such as walking.

Managing advanced cancer in the elderly is an increasing problem. The problem is compounded by older patients being a heterogeneous population. They often have comorbidities and are taking multiple drugs. Moreover, the decision as to whether or not to use cytotoxic anticancer chemotherapy is made more difficult because the elderly are under-represented in clinical trials.

For each patient the decision whether or not to have cytotoxic chemotherapy for advanced cancer is a balance between the potential benefits and adverse effects. Both of these involve value judgments by individual patients. The perspective of older patients may differ from that of younger patients. Short-term quality of life and the ability to continue managing their activities of daily living may be more important than a modest survival advantage when deciding whether to accept chemotherapy. Conversely, some fit older patients may seek aggressive chemotherapy if they can expect a similar outcome to younger patients (237).

Ethically, clinicians making decisions about chemotherapy for elderly patients are likely to be guided by a principle of non-maleficence: do no harm. This is usually interpreted as ensuring that the risk: benefit ratio is favourable. The patient will expect to be allowed to make an autonomous decision about chemotherapy, but will be reliant on accurate information about the potential risks and benefits.

In most cancers the elderly will respond as well as their younger counterparts provided the chemotherapy can be given safely. This may depend on physiological changes in organ function, particularly renal and hepatic function. Deteriorating organ function will make adverse effects and therefore an adverse impact on quality of life more likely.

Elderly patients should be given the option of chemotherapy for responsive advanced cancers. As with younger patients they make their decision balancing any predicted positive outcome against the treatment's adverse effects that, even if temporary, will impact upon their quality of life (238).

One of the research topics I plan on developing in the immediate future is factors complicating chemotherapy in the elderly. To assist decision making about the treatment of advanced cancer in the elderly we need to examine the likelihood of response to chemotherapy and survival benefit. Factors that may complicate chemotherapy in the elderly include the physiological changes accompanying ageing and the impact of concomitant diseases. Loss of organ function will affect cytotoxic drug metabolism. Changes in kidney or liver function or bone marrow reserve are particularly problematic when giving chemotherapy. It can be difficult to evaluate the physiological status of an elderly patient with the exception of renal function and the use of simple scales to assess their ability to perform the activities of daily living.

In fit senior patients with normal organ function the adverse effects will be comparable to those seen in younger patients and are managed in a similar way. Within hours many

cytotoxic drugs will cause nausea and vomiting. Patients may become neutropenic approximately 10 days after treatment. An infection at this time is potentially life threatening and should be urgently treated with intravenous broad-spectrum antibiotics. Subsequent courses of chemotherapy may require dose reductions or support with haematopoietic growth factors. Thrombocytopenia with bleeding can be managed with platelet transfusions. Mucositis occurs in the same time frame and requires symptomatic treatment with local anaesthetic mouth washes plus treatment of any secondary infections due to candida or herpes.

A further group of toxicities which require monitoring involve cumulative damage to organs over several months. This can be a particular problem in the elderly whose organ function may have deteriorated before chemotherapy. Liver and renal function should be measured with each course, and for specific drugs cardiac and pulmonary function should be monitored. Deterioration in organ function may require cessation of chemotherapy.

With worsening organ function the adverse effects of chemotherapy increase and the balance between efficacy and toxicity is no longer in the patients' favor. Adverse effects can impact on quality of life and the patients' ability to cope with daily activities.

Cardiac toxicity is one of most feared side-effects of anticancer agents so that the gain in life expectancy due to anticancer therapy might be countered by increased mortality due to cardiac problems, above all heart failure (HF), but also myocardial ischaemia, arrhythmias, hypertension, thromboembolism.

Detection of cardiac injury is crucial since it may facilitate early therapeutic measures. The incidence of cardiotoxicity depends on different factors related to oncological therapies (type of drug, dose administered during each cycle, cumulative dose, schedule of administration, route of administration, combination of other cardiotoxic drugs or association with radiotherapy) and to patient [age, presence of cardiovascular (CV) risk factors, previous cardiovascular disease (CVD), prior mediastinal radiation therapy]. This is why all patients undergoing chemotherapy should have prior careful clinic evaluation and assessment of CV risk factors or comorbidities.

Frequent vital signs monitoring is recommended during chemotherapeutic agent infusion, particularly with fluorouracil (5-FU) or paclitaxel. ECG and clinic cardiovascular evaluation are useful to screen signs of cardiomyopathy, conduction disturbances, QT interval, before beginning anticancer therapy with anthracycline or paclitaxel or small molecule TKIs.

We plan on designing a protocol for assessing elderly cancer patients in terms of pre-treatment status (CGA and other biological assessments as required) and monitoring them by means of the same tests throughout their anti-cancer therapy and during the follow-up period.

We fully understand that CGA has positive effects on a number of important health outcomes in frail older patients. Although a number of observational studies, editorials, special articles and clinical reports, suggest that CGA should be used to guide the assessment and clinical decision-making in older cancer patients, there is limited support to this view in the literature. Older patients that are diagnosed with cancer are usually healthier and less problematic than persons of the same age who are randomly sampled from the general population. In these persons, the cancer dominates the clinical picture and, therefore, instruments especially tuned for the frail elderly may provide little information.

The concept of the frailty syndrome, characterized by high susceptibility, low functional reserve and unstable homeostasis, has recently received a lot of attention by the geriatric community. A CGA approach, which also evaluates elements of the frailty syndrome, may be of great interest for those oncologists who want to identify older patients likely to develop severe toxicity and severe side effects in response to aggressive treatment. Improvements in the definition of the frailty syndrome may profit from the clinical experience of oncologists.

My interest evolved from early detection of elderly patients at risk for cancer to the side-effects of chemotherapy, especially cardiac toxicity. It is one of most feared side-effects of

anticancer agents so that the gain in life expectancy due to anticancer therapy might be countered by increased mortality due to cardiac problems, above all heart failure (HF), but also myocardial ischemia, arrhythmias, hypertension, thromboembolism.

I also plan to start two clinical trials and medical projects together with the Department of Oncology from the Romanian Institute of Oncology Iasi, Professor Lucian Miron that will perform careful clinic evaluation and assessment of CV risk factors or comorbidities in elderly patients undergoing chemotherapy. In addition, we shall study the alteration of myocardial performance after chemotherapy using several clinical and imagistic methods, including baseline Doppler echocardiogram (DEcho).

We shall use a Holter ECG as well as the most commonly described cardiotoxic effect of fluorouracil (5-FU) is angina-like chest pain, with incidence ranging from 1% to 68% in the literature; cardiac events occur generally within 5 days after first administration, and ischaemic changes on ECG have been reported in 68% of patients; risk factors are high dose (>800 mg/m²), continuous infusion of medicament, history of CVD, prior mediastinal radiation, concurrent use of chemotherapy; possible mechanisms of cardiotoxicity are coronary artery thrombosis, interaction with coagulation system, vasospasm, direct toxicity on myocardium.

3.2. THE IMPACT OF COPD ON CARDIO-VASCULAR COMORBIDITIES

Patients with COPD frequently suffer from significant, preexistent or developed comorbidities as a consequence of the underlying disease. These have a major impact on the patients' evolution, influencing their chance of survival, number of exacerbations and life quality (239). The chronic inflammatory status directly affects the development of one of the comorbidities, while some systemic signs and symptoms can, in fact, be a direct manifestation of the COPD. Wasting, osteoporosis, anemia, depression and heart diseases are examples of these (240).

The relationship between COPD and other heart diseases is a complex one, since it is determined by common etiological factors and the interdependency of the two systems, relevant in case of decompensation of one of these diseases. Heart failure is more common in patients with COPD compared to the general population, regardless of the smoking incidence in these two groups (241). The prevalence of heart failure in patients with COPD varies between 5.3% and 24.4% (240), mainly due to diagnosis difficulties. Pulmonary hyperinflation may significantly obstruct the echocardiographic visualization of the heart, may conceal its real dimension or affect the radiography accuracy when identifying the interstitial edema (242). Among the mechanisms responsible of the frequent association between heart failure and COPD, we mention: 1. Ripe old age at the moment of diagnosis; 2. Smoking; 3. Increased prevalence of hypertension. Secondary to systemic inflammation, a series of processes in the vascular endothelium are speeded up, thus increasing the severity of atherosclerosis in patients with COPD and, implicitly, the probability of the occurrence of a myocardial infarction or a stroke (243). Heart failure significantly decreases life quality and increases mortality (independent prognostic factor) in patients with COPD.

Ischemic heart disease is also more frequent in patients with COPD (244), with an incidence of 16.1%-53%, according to literature data (245). This can manifest itself as a coronary, angina disease or even myocardial infarction, and the symptomatology usually occurs in the exacerbation periods (246). The relationship between COPD and ischemic heart disease is due to some common determining factors, such as sharp systemic inflammation during the exacerbations and chronic endothelial dysfunction (247). In addition, arterial rigidity, an independent parameter linked to the incidence of heart diseases and mortality caused by these, is increased in patients with COPD and directly related to the size of the emphysema and obstruction severity. Practically, a study carried out by Patel and collaborators (248) concluded

that patients with COPD and ischemic type electrocardiographic modifications achieve a decreased score when subjected to a 6-minute walk test and do not display increased scores when measuring dyspnoea, an increased Charlson comorbidity index and a depreciated health status, modifications unrelated to COPD severity. Together, all these modifications bring about a significant increase of mortality in this population.

The presence of COPD can significantly modify the treatment of heart related comorbidities, thus determining the physicians to opt for other classes of drugs than the ones recommended in the guidebook. Such an example is represented by beta-blockers (249), often avoided due to their potential side effects on the respiratory system. In the lungs, there is a multitude of beta receptors, most frequently the beta-2 type, due to which it was long believed that therapy with beta-blockers would worsen the respiratory function on patients with COPD. Yet, recent studies (249, 250) showed that the use of these substances when carrying out therapy in such patients has brought substantial benefits, reducing mortality and morbidity. Currently, cardio-selective beta-blockers are recommended for patients with COPD and heart failure, only if a careful monitoring of the potential side effects is possible and the treatment can be continued, including when an exacerbation occurs, unless the patient is in-home oxygen-dependent.

I have been interested in the complex interrelation between COPD and cardio-vascular comorbidities in patients for a long time, as shown by different presentations and articles I wrote on this subject. More recently, together with colleagues from the Pneumology department, I have published an article regarding the effect of Roflumilast, a novel COPD drug on exacerbations. I plan on continuing this collaboration and I will focus on the effect of new drugs in elderly patients with respiratory conditions because they are often under-represented in clinical trials and available clinical data is scarce.

3.3. PALLIATIVE CARE FOR ELDERLY PATIENTS

When dealing with an irreversible, severe evolution of co-morbidities, one has to take into consideration the type of care which meets the needs and expectations of the patient, and to avoid measures which, trying to treat only extend the pain, without improving life quality. In these situations, one has to continuously take into account the desire of the elderly patient (the right to autonomy) to receive palliative care, in order to ensure a better life quality till the final end (251).

The treatment and care of the elderly shall be customized according to their needs and desires, observing the ethical principles. Therefore, the elders have the right to participate in making all decisions related to the medical action, a permanent assessment of the decisional capacity by the attending physician being required, and when necessary, the psychiatrist or even the local authorities should be called. The goal is to focus on life quality according to their expectations, and a multidisciplinary team (consisting of kinesitherapist, dietician, psychologist, pharmacist, social assistant, volunteers, nurse and geriatrician who shall coordinate the entire team) is required to achieve this purpose and to apply the therapeutic plan. The team has multiple roles, namely: to put into practice and help the accomplishment of objectives, to check and coordinate the support of the family and/or volunteers, to notice non-adherence and to identify reasons, actively participating in updating the therapeutic scheme to maintain life quality. Therefore, the care shall be ensured both by medical and social services, a customized person-centred care being necessary and ensured after a complex planning by a multidisciplinary team (252).

Senior patients have the right to a correct, customized therapeutic (pharmacological and non-pharmacological) scheme, centred on their needs, life quality and hope, avoiding poly medication and polypragmasy and fighting non-compliance by their continuous

involvement in the decisional process. They have to express the psychological and financial adherence to the treatment, as it will last a long period, being necessary a permanent collaboration with the multidisciplinary team to increase and preserve their adherence to treatment.

They have the right to be protected by the society against exploitations, self-neglect or self-injury, at the same time observing the right to autonomy. In the end, when the other measures of treatment are no longer efficient, they have the right to a respectable death, according to their expressed desires (253).

As mentioned in a previous section, in September 2018 I have started the Palliative Care Masterclass in order to obtain the Ministry-issues Certificate for physicians. It is a two-year program at the end of which participants must take a formal examination assessing their knowledge in the field. So far, this course has proven to be an excellent opportunity for me to upgrade my pain-management skills and also to network with like-minded physicians interested in palliative care and end-of-life assistance.

In my department, we started to work on a large scale project that would follow all the ups and downs of the actual therapeutical approach for the elderly patients, compare the results with the benefits and the rate of non-adherence and find the pathways to follow in order to reduce iatrogeny, improve medical adherence and patient's quality of life, find the balance between excessive and aggressive medical treatment and introducing palliative care. The solution in these situations is the proper education of physicians to devise individual therapeutic plans for complex elderly patients with multiple chronic diseases. Individualized regimens, flexibility and understanding of the wishes of the elderly, providing a psychological and emotional comfort to motivate him to maintain constant health, are just a few elements that should be considered when starting treating such patients. In this context, palliative care becomes an essential link in structuring multidisciplinary geriatric treatment (254).

In Romania, geriatric palliative care addresses especially the patients hospitalized for acute exacerbations of chronic progressive diseases such as chronic obstructive pulmonary disease, heart failure, chronic kidney disease, diabetes mellitus and its complications, worsening of dementia syndrome. Management of symptoms in elderly patients with comorbidities is based on the concept of "start low and go slow - but get there". The purpose of geriatric management team (including palliative care) becomes optimizing the physical, mental, spiritual and social condition of the patient (255).

Most old persons with terminal chronic illnesses spend months or years in need of palliative care based on optimizing the physical, mental, spiritual and social condition. Without this kind of help, more and more of them cross the threshold to death on a hospital bed, alone, depressed and humiliated by their diseases rather than wait for this transition in peace, in familiar environment, surrounded by loved ones and serene in the face of destiny. Although there are numerous studies that emphasize the importance of this aspect, we still don't apply often enough palliation in the non-oncological elderly patients.

4. FINAL REMARKS

Having the opportunity to train PhD candidates is an excellent motivation to continue my development as an academic professor and as a physician.

By working with young enthusiastic doctors, I will be constantly updated on medical and research trends and I will be able to mentor them in the spirit of curiosity, interest, thoroughness and moral medical practice.

I plan on increasing international visibility for both my department and the university and to promote scientific exchanges between Romania and other countries.

Last, but not least, I intend to get involved in the consolidation of the current prestige of the Iasi school of geriatrics and gerontology and to provide its continuity in the future by continuing and improving my training of young physicians.

SECTION III. REFERENCES

1. WHO [July 24, 2015];Global health estimates: life expectancy trends by country.2013 http://www.who.int/healthinfo/global_burden_disease/en.
2. Carney MT, Emmert B, Keefer B. The bedside capacity assessment tool: further development of a clinical tool to assist with a growing aging population with increased healthcare complexities. *J Clin Ethics*. 2018;29(1):43-51.
3. Jugdutt B.I. – Changing Demographics of the Aging Population with Heart Failure and Implications for Therapy – in Jugdutt B.I. (ed.): *Aging and Heart Failure - Mechanisms and Management*. Springer, 2014; pp. 1–14.
4. Voineagu V. (ed.) – Romanian National Institute of Statistics – Romania in cifre 2011, INS, 2011; p.13.
5. Yanamadala M, Kaprielian VS, O'Connor, et al. A problem-based learning curriculum in geriatrics for medical students. *Gerontol Geriatr Educ*. 2018;39(2):122-131.
6. English SK, van Schagen JE. Creating a geriatric medicine fellowship program in 10 “easy” steps. *J Am Geriatr Soc*. 2011;59(10):1934-40.
7. Cayea D, Eckstrom E, Christmas C. Update in geriatric medicine. *J Gen Intern Med*. 2012;27(3):371-5.
8. Martin P, Kelly N, Kahana E, et al. Defining successful aging: a tangible or elusive concept? *Gerontologist*. 2015;55(1):14-25.20(1):51-9.
9. O'Rourke HM, Ceci C. Reexamining the boundaries of the “normal” in aging. *Nurs Onq*. 2013; 56(4):223-230.
10. Rubenstein LZ, Stuck AE – Multidimensional Geriatric Assessment – in: Sinclair, A.J., John E. Morley, J.E., Vellas, B. (eds.). *Principles and Practice of Geriatric Medicine*, Fifth Edition. John Wiley & Sons, Ltd. 2012; pp.1377 – 1386.
11. Barbieri M, Ouellette N. The Demography of Canada and the United States from the 1980s to the 2000s A Summary of Changes and a Statistical Assessment. *Population (Engl Ed)*. 2012; 67(2): 177–280.
12. Perry TE, Hassevoort L, Ruggiano N, Shtompel N. Applying Erikson's Wisdom to Self-Management Practices of Older Adults: Findings from Two Field Studies. *Res Aging*. 2015; 37(3): 253–274.
13. Labella AM, Merel SE, Phelan EA. Ten ways to improve the care of elderly patients in the hospital. *J Hosp Med*. 2011;6(6):351-7.
14. Matter R, Harniss M, Oderud T, et al. Assistive technology in resource-limited environments: a scoping review. *Disabil Rehabil Assist Technol*. 2017;12(2):105-114
15. Bjerrum L, Sjøgaard J, Hallas J, Kragstrup J. Polypharmacy in general practice. *Br J Gen Pract*. 1999; 49(440): 195–198.
16. Smith G, Bernacki R, Block SD. The role of palliative care in population management and accountable care organizations. *J Palliat Med*. 2015; 18(6): 486–494.
17. Parker SG, McLeod A, McCue P, et al. New horizons in comprehensive geriatric assessment. *Age Ageing* 2017; 46(5):713-721.
18. Singhal N. Rao AV. Tools for assessing elderly cancer patients. *Cancer Forum* 2008, vol 32(1).
19. MacSorley R, White J, Conerly VH, et al. Pain assessment and management strategies for elderly Patients. *Home Healthc Nurse*. 2014;32(5):272-85.
20. Fayaz A, Croft P, Langford RM et al. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open*. 2016; 6(6): e010364.
21. Morrison A, Fan T, Sen SS, Weisenfluh L. Epidemiology of falls and osteoporotic fractures: a systematic review. *Clinicoecon Outcomes Res*. 2013;5:9-18.

22. Reuben DB, Gazarian P, Alexander N, et al. The strategies to reduce injuries and develop confidence in elders intervention: falls risk factor assessment and management, patient engagement, and nurse co-management. *J Am Geriatr Soc.* 2017;65(12):2733-2739.
23. Skelton DA, Todd CJ; ProFaNE Group. Prevention of Falls Network Europe: a thematic network aimed at introducing good practice in effective falls prevention across Europe. Four years on. *J Musculoskelet Neuronal Interact.* 2007;7(3):273-8.
24. Castellini G, Demarchi A, Lanzoni M, Castaldi S. Fall prevention: is the STRATIFY tool the right instrument in Italian Hospital Inpatient? A retrospective observational study. *BMC Health Serv Res.* 2017;17(1):656.
25. Li F, Harmer P, Fitzgerald K. Implementing an evidence-based fall prevention intervention in community senior centers. *Am J Public Health.* 2016;106(11):2026-203.
26. Lin JC, Liang WM: Mortality, readmission, and reoperation after hip fracture in nonagenarians. *BMC Musculoskelet Disord.* 2017;18(1):144.
27. OoiLH, Wong TH, Toh CL, Wong HP. Hip fractures in nonagerians - a study on operative and non-operative management. *Injury.* 2005 Jan;36(1):142-7.
28. Dyer SM, Crotty M, Fairhall N, et al. Fragility FractureNetwork (FFN) Rehabilitation Research Special Interest Group. A critical review of the long-term disability outcomes following hip fracture. *BMC Geriatr.* 2016;16:158.
29. van de Kerkhove MP, Antheunis PS, Luitse JS, Goslings JC. Hip fractures in nonagerians: perioperative mortality and survival. *Injury.* 2008;39(2):244-8.
30. Fansa A, Huff S, Ebraheim N. Prediction of mortality in nonagerians following the surgical repair of hip fractures. *Clin Orthop Surg.* 2016;8(2):140-5.
31. Sternberg SA, Wershof Schwartz A, Karunanathan S, et al. The identification of frailty: a systematic literature review. *J Am Geriatr Soc.* 2011; 59(11): 2129-2138.
32. Ferrazzoli D, Sancesario G. Development and significance of the frailty concept in the elderly: a possible modern view. *CNS Neurol Disord Drug Targets.* 2013;12(4): 529-531.
33. Bandinelli S, Lauretani F, Boscherini V, et al. A randomized, controlled trial of disability prevention in frail older patients screened in primary care: the FRASI study. Design and baseline evaluation. *Aging Clin Exp Res.* 2006;18(5): 359-366.
34. Gillear C, Higgs P. Frailty, disability and old age: a re-appraisal. *Health.* 2011;15(5): 475-490.
35. Santos-Eggimann B, Cuenoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *J Gerontol A BiolSci Med Sci* 2009; 64: 675–681.
36. Rockwood K, Fox RA, Stolee P, et al. Frailty in elderly people, an evolving concept. *Can Med Assoc J.* 1994; 150: 489-495.
37. Abellan van Kan G, Rolland Y, Houles M. The assessment of frailty in older adults. *Clin Geriatr Med.* 2010; 26(2): 275-286.
38. Hadenfeldt CJ, Darabaris M, Aufdenkamp M. Frailty assessment in patients utilizing a free clinic. *J Health Care Poor Underserved.* 2017;28(4):1423-1435.
39. Fried LP, Tangen C, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol* 2001;56A:M1-M11.
40. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. *Arch Intern Med.* 2006;166(4):418-23.
41. Long SJ, Brown KF, Ames D, Vincent C. What is known about adverse events in older medical hospital inpatients? A systematic review of the literature. *Int J Qual Health Care* 2013; 25: 542–554.

42. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process. *Gerontology*. 2009; 55(5): 539-549.
43. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, Collamati A, D'Angelo E, Pahor M, Bernabei R, Landi F; SPRINTT Consortium. Sarcopenia: an overview. *Aging Clin Exp Res*. 2017;29(1):11-17.
44. Beaudart C, Dawson A, Shaw SC, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. IOF-ESCEO Sarcopenia Working Group. *Osteoporos Int*. 2017;28(6):1817-1833.
45. Chin MJ, Dekker JM, Feskens EJ, et al. How to select a frail elderly population? A comparison of three working definitions. *J Clin Epidemiol* 1999; 52(11): 1015-1021.
46. Perna S, Francis MD, Bologna C et al. Performance of Edmonton Frail Scale on frailty assessment: its association with multi-dimensional geriatric conditions assessed with specific screening tools. *BMC Geriatr*. 2017;17(1):2.
47. Parker SG, McCue P, Phelps K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. *Age Ageing*. 2018;47(1):149-155.
48. Drubbel I, Bleijenberg N, Kranenburg G, et al. Identifying frailty: do the Frailty Index and Groningen Frailty Indicator cover different clinical perspectives? a cross sectional study. *BMC Fam Pract*. 2013;14:64.
49. Chia-Ing Li, Chih-Hsueh Lin, Wen-Zuan Lin, et al. Successful aging defined by health-related quality of life and its determinants in community-dwelling elders. *BMC Pub Health*. 2014;14: 1013-1017.
50. Depp CA, Jeste DV. Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. *Am J Geriatr Psychiatry*. 2006;14(1):6–20.
51. Beaumont JG, Kenealy PM. Quality of life perceptions and social comparisons in healthy old age. *Ageing Soc*. 2004;24:755–769.
52. Crăcană IM, Ștefăniu R, Mocanu V, et al. New developments in the approach and diagnosis of sarcopenia. *Rev Med Chir Soc Med Nat Iași* 2016;120(3): 491-496.
53. Buckinx F., Roland Y. Reginster J.Y., Ricour C., Petermans J., Bruyere O. Burden of frailty in the elderly population: perspectives for a public health challenge. *Archives of Public Health* 2015;73(1):19-26.
54. Gómez C, Vega-Quiroga S, Bermejo-Pareja F, Medrano MJ, Louis ED, Benito-León J. Polypharmacy in the Elderly: A Marker of Increased Risk of Mortality in a Population-Based Prospective Study (NEDICES). *Gerontology* 2015;61(4):301-9.
55. Luevano-Contreras C, Chapman-Novakofski K. Dietary advanced glycation end products and aging. *Nutrients*. 2010;2(12):1247-65.
56. Semba RD, Ferrucci L, Sun K, et al. Advanced glycation end products and their circulating receptors predict cardiovascular disease mortality in older community-dwelling women. *Aging Clin Exp Res*. 2009;21:182–190.
57. Hartog JW, Voors AA, Schalkwijk CG, Scheijen J, Smilde TD, Damman K, Bakker SJ, Smit AJ, van Veldhuisen DJ. Clinical and prognostic value of advanced glycation end-products in chronic heart failure. *Eur Heart J*. 2007; 28:2879–2885.
58. Little WC, Zile MR, Kitzman DW, et al. – The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure. *J Card Fail*. 2005;11:191-195.
59. Willemsen S, Hartog JW, Heiner-Fokkema MR, van Veldhuisen DJ, Voors AA. Advanced glycation end-products, a pathophysiological pathway in the cardiorenal syndrome. *Heart Fail Rev*. 2012;17(2):221-8.
60. Olariou M, Ghinescu M, Naumov V, Brinza I, Heuvel Wv. The psychometric qualities of the Groningen Frailty Indicator in Romanian community-dwelling old citizens. *Fam Pract*. 2014; (4):490-5.

61. Ware JE, Jr, Gandek B. Overview of the SF-36 health survey and the international quality of life assessment (IQOLA) Project. *J Clin Epidemiol*. 1998;51(11):903–912.
62. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. *Eur J Intern Med*. 2016;31:3-10.
63. Pesce M, Tatangelo R, La Fratta I, et al. Aging -related oxidative stress: positive effect of memory training. *Neuroscience*. 2018;370:246-255.
64. Valente T, Gella A, Fernández-Busquets X, Unzeta M, Durany N. Immunohistochemical analysis of human brain suggests a pathological synergism of Alzheimer’s disease and diabetes mellitus. *Neurobiol Dis*. 2010;37:67–76.
65. Rogers D, Pies R. General medical with depression drugs associated. *Psychiatry (Edgmont)*. 2008;5(12):28-41.
66. Feldinger LE. Recurrent and consistent improvement of cognitive impairment and depression after short time of treatment with enoxaparin. *J Am Geriatr Soc*. 2013;61(7):1240-1.
67. Stott DJ, Robertson M, Rumley A, et al. Activation of hemostasis and decline in cognitive function in older people. *Arterioscler Thromb Vasc Biol*. 2010;30(3):605-11.
68. Welsh TJ, Gordon AL, Gladman JR. Comprehensive geriatric assessment—a guide for the non specialist. *Int J Clin Pract* 2013; 68: 290–293.
69. Roppolo M, Mulasso A, Gobbens RJ, Mosso CO, Rabaglietti E. A comparison between uni- and multidimensional frailty measures: prevalence, functional status, and relationships with disability. *Clin Interv Aging*. 2015;22(10):1669-1678.
70. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boyrie Y, Cederholm T, Landi F et al. Sarcopenia: European consensus on definition and diagnosis; Report of the European Working Group on Sarcopenia in older people. *Age Ageing* 2010; 39 (4): 1-12.
71. Rosenberg I. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. *Am J Clin Nutr*. 1989;50:1231–3.
72. Marty E, Liu Y, Samuel A, Or O, Lane J. A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease. *Bone*. 2017;105:276-286.
73. Abdulan IM, Ilie AC, Ștefăniu R, Sandu IA, Pîslaru AI. Effects of sarcopenia and sarcopenic obesity on the health status of elderly population. *Rev Med Chir Soc Med Nat Iasi* 2018; 122(2): 240-246.
74. Baumgartner RN. Body composition in healthy aging. *Ann N Y Acad Sci*. 2000;904:437–448
75. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. *Proc Nutr Soc*. 2015;74:405–412.
76. Kyung Mook Choi Sarcopenia and sarcopenic obesity. *Korean J Intern Med*. 2016 31(6):1054-1060.
77. Goisser S, Kemmler W, Porzel S, et al. Sarcopenic obesity and complex interventions with nutrition and exercise in community-dwelling older persons – a narrative review. *Clin Interv Aging* 2015; 10:1267-1282.
78. Alagiakrishnan K, Banach M, Ahmed A, Aronov WS. Complex relationship of obesity and obesity paradox in heart failure – higher risk of developing heart failure and better outcomes in established heart failure. *Ann Med* 2016;48(8):603-613.
79. Martone AM, Marzetti E, Calvani R, et al. Exercise and protein intake: a synergistic approach against sarcopenia. *Biomed Res Int*. 2017;2017:2672435.
80. Blake GM, Fogelman I. An update on dual-energy x-ray absorptiometry. *Semin Nucl Med*. 2010;40:62–673.
81. Cummings SR, Studenski S, Ferrucci L. A diagnosis of disability—giving mobility clinical visibility: a Mobility Working Group recommendation. *JAMA* 2014;311: 2061–2062.

82. Scharf G, Heineke J. Finding good biomarkers for sarcopenia. *J Cachexia Sarcopenia Muscle* 2012;3:145–148.
83. Cesari M, Fielding RA, Pahor M, et al. Biomarkers of sarcopenia in clinical trials recommendations from the International Working Group on Sarcopenia. *J Cachexia Sarcopenia Muscle* 2012;3:181–190.
84. Fragala MS, Jajtner AR, Beyer KS, Townsend JR, Emerson NS, Scanlon TC, et al. Biomarkers of muscle quality: N-terminal propeptide of type III procollagen and C-terminal agrin fragment responses to resistance exercise training in older adults. *J Cachexia Sarcopenia Muscle* 2014;5:139–148.
85. Chen F, Lam R, Shaywitz D, Hendrickson RC, Opitck GJ, Wishengrad D, et al. Evaluation of early biomarkers of muscle anabolic response to testosterone. *J Cachexia Sarcopenia Muscle* 2011;2:45–56.
86. Berry SD, Ramachandran VS, Cawthon PM, Gona P, McLean RR, Cupples LA, et al. Procollagen type III N-terminal peptide (P3NP) and lean mass: a cross-sectional study. *J Frailty Aging* 2013;2:129–134.
87. Drey M, Sieber CC, Bauer JM, Uter W, Dahinden P, Fariello RG, et al. C-terminal agrin fragment as a potential marker for sarcopenia caused by degeneration of the neuromuscular junction. *ExpGerontol* 2012. Doi:10.1016/j.exger.2012.05.021.
88. Butikofer L, Zurlinden A, Bolliger MF, Kunz B, Sonderegger P. Destabilization of the neuromuscular junction by proteolytic cleavage of agrin results in precocious sarcopenia. *FASEB J* 2011;25:4378–4393.
89. Ogawa K, Kim HK, Shimizu T, Abe S, Shiga Y, Calderwood SK. Plasma heat shock protein 72 as a biomarker of sarcopenia in elderly people. *Cell Stress Chaperones* 2012;17:349–359.
90. Gonzalez MC, Heymsfield SB. Bioelectrical impedance analysis for diagnosing sarcopenia and cachexia: what are we really estimating? *J Cachexia Sarcopenia Muscle*. 2017;8(2):187-189.
91. Rizzoli R. Nutrition and Sarcopenia. *J Clin Densitom* 2015 doi: 10.1016/j.jocd.2015.04.014.
92. Ilie AC, Pîslaru AI, Macsim IC, Mataşaleru A, Ştefăniu R, Moş L, Alexa ID. Sarcopenia and the Importance of Biochemical Determinations in the Hospitalized Older Adults. The 6th IEEE International Conference on E-Health and Bioengineering - EHB 2017 Sinaia, Romania, June 22-24, 2017. (IEEE Explore).
93. Naseeb MA, Volpe SL. Protein and exercise in the prevention of sarcopenia and aging. *Nutr Res*. 2017;40:1-20.
94. Cangussu LM, Nahas-Neto J, Orsatti CL, Bueloni-Dias FN, Nahas EA. Effect of vitamin D supplementation alone on muscle function in postmenopausal women: a randomized, double-blind, placebo-controlled clinical trial. *Osteoporos Int*. 2015;26(10):2413–2421.
95. Frank M, Sivagnanaratnam A, Bernstein J. Nutritional assessment in elderly care: a MUST! *BMJ Qual Improv Rep* 2015;4(1): 245-251.
96. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. *Nutrients* 2017;9(8): 829-835.
97. Liu W, Jao Y-L, Williams K. The association of eating performance and environmental stimulation among older adults with dementia in nursing homes: a secondary analysis. *Int J Nurs Stud*. 2017; 71: 70–79.
98. Batool R, Butt MS, Sultan MT, Saeed F, Naz R. Protein-energy malnutrition: a risk factor for various ailments. *Crit Rev Food SciNutr*. 2015;55(2):242-53.

99. Scaldaferrri F, Pizzoferrato M, Lopetuso LR, et al. Nutrition and IBD: Malnutrition and/or Sarcopenia? *Gastroenterol Res Pract.* 2017;2017:8646495.
100. Reijnierse EM, Trappenburg MC, Leter MJ, et al. The association between parameters of malnutrition and diagnostic measures of sarcopenia in geriatric outpatients. *PLoS One.* 2015;10(8):e0135933.
101. Barkoukis H. Nutrition recommendations in elderly and aging. *Med Clin North Am.* 2016;100(6):1237-1250.
102. Soubrié C, Lebrun-Vignes B. Iatrogénie – Diagnostique et traitement. *Rev Prat* 2005;55: 209-216.
103. Ungureanu G, Alexa ID, Stoica O. Iatrogeny and the elderly. *Rev Med Chir Soc Med Nat* 2007;111(4):803-10.
104. U.S. State Department & National Institute on Aging Summit on Global Aging, 2007: Why Population Aging Matters: A Global Perspective: Senior Citizens News & Features Daily on Web,16-03-2007: <http://seniorjournal.com>.
105. Starfield B, Gérvas J, Mangin D. Clinical care and health disparities. *Annu Rev Public Health.* 2012;33:89-106.
106. Bank PC, Swen JJ, Guchelaar HJ. A nationwide survey of pharmacists' perception of pharmacogenetics in the context of a clinical decision support system containing pharmacogenetics dosing recommendations. *Pharmacogenomics.* 2017;18(3): 215-225.
107. Ungureanu G, Alexa ID, Stoica O. Iatrogeny and the elderly. *Rev Med Chir Soc Med Nat Iasi.* 2007;111(4):803-10
108. Morin L, Laroche ML, Texier G, Johnell K. Prevalence of potentially inappropriate medication use in older adults living in nursing homes: a systematic review. *J Am Med Dir Assoc.* 2016;17(9):862.e1-9.
109. Page RL, Linnebur SA, Bryant LL et al. Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. *Clin Interv in Ageing* 2010;5:75-87.
110. Reeve J, Bancroft R. Generalist solutions to overprescribing: a joint challenge for clinical and academic primary care. *BMC Family Practice* 2013;14:1.
111. Tulner LR, van Campen JP, Frankfort SV et al. Changes in under-treatment after comprehensive geriatric assessment: an observational study. *Drugs Aging* 2010; 27:831-843.
112. Sirois C, Laroche ML, Guénette L, et al. Polypharmacy in multimorbid older adults: protocol for a systematic review. *Syst Rev.* 2017;6(1):104.
113. Cadogan CA, Ryan C, Hughes CM. Appropriate polypharmacy and medicine safety: when many is not too many. *Drug Saf.* 2016;39(2):109-16.
114. Zhang X, Zhou S, Pan K, et al. Potentially inappropriate medications in hospitalized older patients: a cross-sectional study using the Beers 2015 criteria versus the 2012 criteria. *Clin Interv Aging.* 2017;12:1697-1703.
115. American Geriatrics Society 2015 Beers Criteria Update Expert Panel: American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-46.
116. Salbu RL, Feuer J: A closer look at the 2015 Beers Criteria. *J Pharm Pract.* 2017;30(4):419-424.
117. Brown JD, Hutchison LC, Chenghui L, et al. Predictive validity of the Beers and STOPP Criteria to detect adverse drug events, hospitalizations, and emergency department visits in the United States. *J Am Geriatr Soc.* 2016;64(1):22-30.

118. Barry PJ, O'Keefe N, O'Connor KA, O'Mahony D. Inappropriate prescribing in the elderly: a comparison of the Beers criteria and the improved prescribing in the elderly tool (IPET). *J Clin Pharm Ther.* 2006;31(6):617-26.
119. O'Mahony D, O'Sullivan D, Byrne S. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing.* 2015;44(2):213-8
120. Lavan AH, Gallagher PF, O'Mahony D. Methods to reduce prescribing errors in elderly patients with multimorbidity. *Clin Interv Aging.* 2016;11:857-66.
121. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev.* 2014;(11):CD000011.
122. Rajpura J, Nayak R. Medication adherence in a sample of elderly suffering from hypertension. Evaluating the illness perception, treatment beliefs, and illness burden. *J Manag Care Pharm.* 2014; 19(1):58-65.
123. Krousel-Wood MA, Muntner P, Joyce CJ, et al. Adverse effects of complementary and alternative medicine on antihypertensive medication adherence: Findings from the cohort study of medication adherence among older adults. *J Am Geriatr Soc* 2010;58:54-61.
124. Luzardo AR, Paula Júnior NF, Medeiros M, et al. Repercussions of hospitalization due to fall of the elderly: health care and prevention. *Rev Bras Enferm.* 2018;71 Suppl 2:763-769.
125. Calero-García MJ, Ortega AR, Navarro E, Calero MD. Relationship between hospitalization and functional and cognitive impairment in hospitalized older adults patients. *Aging Ment Health.* 2017;21(11):1164-1170.
126. Mallinson T, Fitzgerald CM, Neville CE, et al. Impact of urinary incontinence on medical rehabilitation inpatients. *Neurourol Urodyn.* 2017;36(1):176-183.
127. LeivaBadosa E, BadiaTahull M, Virgili Casas N, et al. Hospital malnutrition screening at admission: malnutrition increases mortality and length of stay. *Nutr Hosp.* 2017;34(4):907-913.
128. Segura A. Prevention, iatrogeny, and public health. *Gac Sanit.* 2014;28(3):181-2.
129. Cahir C, Bennett K, Teljeur T, Fahey T. Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients. *Br J Clin Pharmacol,* 2013;73: 124-133.
130. Sabzwari SR, Qidwai W, Bhanji S. Polypharmacy in elderly: a cautious trail to tread. *J Pak Med Assoc,* 2013; 63(5): 624-627.
131. Ryan AA. Medication compliance and older people: A review of the literature. *Int J of Nur Stud,* 1998;36:153-162.
132. van der Wal MH, Jaarsma T, Moser DK, et al. Compliance in heart failure patients: the importance of knowledge and beliefs. *Eur Heart J,* 2006;27(4):434-40.
133. Campbell NL, Boustani MA, Skopelja EN, et al. Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. *Am J Geriatr Pharmacother* 2012;10(3):165-177.
134. Allemann SS, Nieuwlaat R, Navarro T, Haynes B, Hersberger KE, Arnet I. Congruence between patient characteristics and interventions may partly explain medication adherence intervention effectiveness: an analysis of 190 randomized controlled trials from a Cochrane systematic review. *J Clin Epidemiol.* 2017; 91:70-79.
135. Salzman C. Medication compliance in the elderly. *J Clin Psych,* 1995;56 (Suppl. 1):18-22.
136. Lauffenbuger JC, Shrank WH, Bitton A, et al. Association between patient-centered medical homes and adherence to chronic disease medications: a cohort study. *Ann Intern Med.* 2017;166(2):81-88.

137. Kim J, Parish AL. Polypharmacy and medication management in older adults. *Nurs Clin North Am.* 2017;52(3):457-468.
138. Pasina L, Brucato AL, Falcone C, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. *Drugs Aging.* 2014; 31(4):283-9.
139. Brondi R, Bannò F, Bendinelli S, et al. Drugs Don't Work in Patients Who Don't Take Them: Dr. Drin, The New ICT Paradigm for Chronic Therapies. *Stud Health Technol Inform,* 2013;191:100-104.
140. Kooy MJ, van Wijk BL, Heerdink EL, et al. Does the use of an electronic reminder device with or without counseling improve adherence to lipid-lowering treatment - the results of a randomized controlled trial. *Front Pharmacol,* 2013;29:4-69.
141. Arnet I, Walter PN, Hersberger KE. Polymedication Electronic Monitoring System (POEMS)-a new technology for measuring adherence. *Front Pharmacol* 2013;13:4-26.
142. Geissler J, Sharf G, Bombaci F, et al. Factors influencing adherence in CML and ways to improvement: Results of a patient-driven survey of 2546 patients in 63 countries. *J Cancer Res Clin Oncol.* 2017;143(7):1167-1176.
143. Calleja-Sordo EC, de Hoyos A, Méndez-Jiménez J, et al. Novel ethical dilemmas arising in geriatric clinical practice. *Med Health Care Philos.* 2015;18(2):229-36.
144. Roncero C, Gómez-Baeza S, Vázquez JM, et al. Perception of Spanish professionals on therapeutic adherence of dual diagnosis patients. *Actas Esp Psiquiatr.* 2013;41(6):319-29.
145. Graber ML, Franklin N, Gordon R. Diagnostic error in internal medicine. *Arch Intern Med.* 2005;165(13):1493-9.
146. Smith AL, Ruiz I, Jirón M. Monitoring medication errors in an internal medicine service. *Rev Med Chil.* 2014;142(1):40-7.
147. Segrin C, Passalacqua SA. Functions of Loneliness, Social Support, Health Behaviors, and Stress in Association with Poor Health,” *Health Communication,* 2010;25:312–322.
148. Dekker WPH, Vergouwen ACM, Buster MCA, Honig A. Acceptance of guidance to care at the emergency department following attempted suicide. *BMC Psychiatry.* 2017;17(1):332.
149. Hawkey LC, Cacioppo JC. Aging and loneliness: downhill quickly? *Current Directions in Psychological Science,* 2007;16:187–191.
150. Jakson S, Jansen P, Mangoni A (eds): *Prescribing for Elderly Patients,* Wiley-Blackwell Publication, 2009.
151. Hugtenburg JG, Timmers L, Elders P, et al. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored medication. *Patient Pref Adh.* 2013; 7: 675–682.
152. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al. ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J.* 2015; 36(5):288-296.
153. Halperin JL, Hankey GJ, Wojdyla DM, et al. ROCKET AF Steering Committee and Investigators. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF). *Circulation.* 2014;130(2):138-146.
154. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al. ROCKET AF Steering Committee and Investigators. Use and outcomes of antiarrhythmic therapy in patients with atrial

- fibrillation receiving oral anticoagulant: results from the ROCKET AF trial. *Heart Rhythm*. 2014;11(6):925-932.
155. Hankey GJ, Stevens SR, Piccini JP, et al. ROCKET AF Steering Committee and Investigators. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. *Stroke*. 2014;45(5):1304-1312.
 156. Piccini JP, Stevens SR, Chang Y, et al. ROCKET AF Steering Committee and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R (2) CHADS (2) index in the ROCKET AF (Rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) and ATRIA (ANTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation*. 2013;127(2):224-232.
 157. Goodman SG, Wojdyla DM, Piccini JP, et al. ROCKET AF Investigators. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol*. 2014;63(9):891-900.
 158. Mahaffey KW, Stevens SR, White HD, et al. ROCKET AF Investigators. Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial. *Eur Heart J*. 2014; 35(4): 233-41.
 159. Singer DE, Hellkamp AS, Piccini JP, et al. ROCKET AF Investigators. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. *J Am Heart Assoc*. 2013;2(1): e000067.
 160. Hankey GJ, Patel MR, Stevens SR, et al. ROCKET AF Steering Committee Investigators. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol*. 2012;11(4):315-22.
 161. Mamhidir AG, Kihlgren M, Sorlie V. Ethical challenges related to elder care. High level decision-makers' experiences. *BMC Med Ethics*. 2007;10:83.
 162. Chan CP, Wong YL, Sha KY. Medical ethics and the elderly. *Asian J Gerontol Geriatr* 2009;4:83-4.
 163. Gauthier S, Leuzy A, Racine E, Rosa-Neto P. Diagnosis and management of Alzheimer's disease: past, present and future ethical issues. *Prog Neurobiol*. 2013;110:102-113.
 164. Mueller PS, Hook CC, Fleming KC. Ethical issues in geriatrics: a guide for clinicians. *Mayo Clin Proc*. 2004;79(4):554-62.
 165. Rondi C, Berney A. Patient-caregiver relationship: when illness blogs step in. *Rev Med Suisse*. 2014;10(417):380, 382-4.
 166. Reach G. Patient autonomy in chronic care: solving a paradox. *Patient Prefer Adherence*. 2013;8:15-24.
 167. Vitale C, Rosano G, Fini M. Are elderly and women under-represented in cardiovascular clinical trials? Implication for treatment. *Wien Klin Wochenschr*. 2016;128(Suppl 7):433-438.
 168. Carron PN, Hugli OW, Schreyer N, Yersin B. Access of elderly patients in the emergency department: demographic evolution and ethical perspectives. *Rev Med Suisse*. 2006;2(75):1840-3.

169. Hamet P. What matters in ADVANCE and ADVANCE-ON. *Diabetes Obes Metab.* 2012;14 Suppl 1:20-9.
170. Corvol A, Moutel G, Gagnon D, et al. Ethical issues in the introduction of case management for elderly people. *Nurs Ethics.* 2013;20(1):83-95
171. Olaroiu M, Ghinescu M, Naumov V, Brinza I, van den Heuvel W. Does frailty predict health care utilization in community-living older Romanians? *Curr Gerontol Geriatr Res.* 2016;2016:6851768.
172. Frisoli A., McNeillIngham S. J., Paes Â. T., et al. Frailty predictors and outcomes among older patients with cardiovascular disease: data from Fragicor. *Archives of Gerontology and Geriatrics.* 2015;61(1):1-7.
173. Harttgen K., Kowal P., Strulik H., Chatterji S., Vollmer S. Patterns of Frailty in older adults: comparing results from higher and lower income countries using the survey of health, ageing and retirement in Europe (SHARE) and the study on global ageing and adult health (SAGE) *PLoS ONE.* 2013;8(10):e75847.
174. Theou O., Brothers T. D., Rockwood M. R., Haardt D., Mitnitski A. Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. *Age and Ageing.* 2013;42(5):614-619.
175. Morley J. E., Vellas B., Abellan van Kan G., et al. Frailty consensus: a call to action. *Journal of the American Medical Directors Association.* 2013;14(6):392-397.
176. Peters L. L., Boter H., Buskens E., Slaets J. P. J. Measurement properties of the groningen frailty indicator in home-dwelling and institutionalized elderly people. *Journal of the American Medical Directors Association.* 2012;13(6):546-551.
177. Olaroiu M, Alexa ID, van den Heuvel WJA. Do changes in welfare and health policy affect life satisfaction of older citizens in Europe? *Curr Gerontol Geriatr Res.* 2017;2017:7574040
178. Yon Y, Mikton CR, Gassoumis ZD, Wilber KH. Elder abuse prevalence in community settings: a systematic review and meta-analysis. *Lancet Glob Health.* 2017;5(2):e147-e156.
179. Dong X, Chen R, Chang ES, Simon M. Elder abuse and psychological well-being: a systematic review and implications for research and policy - a mini review. *Gerontology.* 2013;59(2):132-42.
180. Kimsey LR, Tarbox AR, Bragg DF. Abuse of the elderly - the hidden agenda. The caretakers and the categories of abuse. *J Am Geriatr Soc.* 1981;29(10):465-72.
181. Du Mont J, Macdonald S, Kosa D, et al. Development of a comprehensive hospital-based elder abuse intervention: an initial systematic scoping review. *Plos One* 2015.
182. Mysyuk Y, Westendorp RG, Lindenberg J. Added value of elder abuse definitions: a review. *Ageing Res Rev.* 2013 Jan;12(1):50-7.
183. Steuer J, Austin E. Family abuse of the elderly. *J Am Geriatr Soc.* 1980;28(8):372-6.
184. White SW. Elder abuse: critical care nurse role in detection. *Crit Care Nurs Q.* 2000;23(2):20-5.
185. Yaffe MJ, Weiss D, Lithwick M. Seniors' self-administration of the Elder Abuse Suspicion Index (EASI): a feasibility study. *J Elder Abuse Negl.* 2012;24(4):277-92.
186. Falk NL, Baigis J, Kopac C. Elder mistreatment and the Elder Justice Act. *Online J Issues Nurs.* 2012;17(3):7.
187. Navarro AE, Wilber KH, Yonashiro J, Homeier DC. Do we really need another meeting? Lessons from the Los Angeles County Elder Abuse Forensic Center. *Gerontologist.* 2010;50(5):702-11.
188. Decker E, Philippot P, Bourgey-Trouillet M, Blain H, Trouillet R. Interventions based on mindfulness for the elderly chronic pain: review of the literature. *Geriatr Psychol Neuropsychiatr Vieil.* 2015;13(2):147-56.

189. Bollig G, Rosland JH, Gjengedal E, et al. A European multicenter study on systematic ethics work in nursing homes. *Scand J Caring Sci.* 2017;31(3):587-601.
190. Bravo G, Sene M, Arcand M. Reliability of health-related quality-of-life assessments made by older adults and significant others for health states of increasing cognitive impairment. *Health Qual Life Outcomes.* 2017;15(1):4.
191. Teaster PB, Wangmo T, Anetzberger GJ. A glass half full: the dubious history of elder abuse policy. *J Elder Abuse Negl.* 2010;22(1-2):6-15.
192. Muneeb A, Jawaid H, Khalid N, Mian A. The art of healing through Narrative Medicine in Clinical Practice: a reflection. *Perm J.* 2017;21:17-013.
193. Dong X. Elder self-neglect: research and practice. *ClinInterv Aging.* 2017 Jun 8;12:949-954.
194. Lien C, Rosen T, Bloemen EM, Abrams RC, Pavlou M, Lachs MS. Narratives of self-neglect: patterns of traumatic personal experiences and maladaptive behaviors in cognitive intact older adults. *J Am Geriatr Soc.* 2016 Nov;64(11):e195-e200.
195. Franzini L, Dyer CB. Healthcare costs and utilization of vulnerable elderly people reported to Adult Protective Services for self-neglect. *J Am Geriatr Soc.* 2008;56(4):667-76.
196. Choi NG, Kim J, Asseff J. Self-neglect and neglect of vulnerable older adults: reexamination of etiology. *J Gerontol Soc Work* 2009 Feb-Mar;52(2):171-87.
197. Smith AK, Lo B, Aronson L. Elder self-neglect - how can a physician help? *N Engl J Med.* 2013 Dec 26;369(26):2476-9.
198. Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet*, 1955;269: 259-263.
199. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*, 2008;108:18-30.
200. Smith TO, Cooper A, Peryer G, Griffiths R, Fox C, Cross J. Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis. *Int J Geriatr Psychiatry.* 2017;32(4):386-396.
201. Schenning KJ, Deiner SG. Postoperative delirium in the geriatric patient. *AnesthesiolClin.* 2015;33(3):505-16.
202. Choi YH, Kim DH, Kim TY, et al. Early postoperative delirium after hemiarthroplasty in elderly patients aged over 70 years with displaced femoral neck fracture. *ClinInterv Aging.* 2017;12:1835-1842.
203. Bjorkelund KB, Hommel A, Thorngren KG, et al. Reducing delirium in elderly patients with hip fracture: a multifactorial intervention study. *Acta Anaesthesiol Scand*, 2010;54: 678-688.
204. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc*, 2005;53:1658-1666.
205. Mosk CA, Mus M, Vroemen JP, et al. Dementia and delirium, the outcomes in elderly hip fracture patients. *Clin Interv Aging.* 2017 Mar 10;12:421-430.
206. Jankowski CJ, Trenerry MR, Cook DJ, et al. Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty. *Anesth Analg*, 2011;112:1186-1193.
207. Thomas KM, Redd LA, Wright JD, Hartos JL. Sleep and mental health in the general population of elderly women. *J Prim Prev.* 2017;38(5):495-503.
208. Mukuria C, Brazier J. Valuing the EQ-5D and the SF-6D health states using subjective well-being: a secondary analysis of patient data. *Soc Sci Med.* 2013;77:97-105.
209. Juul D, Colenda CC, Lyness JM, et al. Subspecialty training and certification in Geriatric Psychiatry: a 25-year overview. *Am J Geriatr Psychiatry.* 2017;25(5):445-453.

210. Steptoe A., Deaton A., Stone A. A. Subjective wellbeing, health, and ageing. *The Lancet*. 2015;385:640–648.
211. Ervik R, Skogedal Lindén T. Theory and practice in Europe. Cheltenham, UK: Edward Elgar Publishing Ltd; 2013. The making of ageing policy.
212. Durand M. Foreword in: OECD Guidelines for Measuring Subjective Well-Being. Paris, France: OECD; 2013.
213. Schwandt H. Unmet Aspirations as an Explanation for the Age U-shape in Wellbeing. Princeton, NJ, USA: Center for Health and Wellbeing, Princeton University; 2014.
214. Graham C, Ruiz Pozuelo J. Happiness, stress, and age: how the U-curve varies across people and places. *Journal of Population Economics*. 2016;(30th).
215. Eurofound. State of health in the EU Cycle. Paris: OECD; 2016. Third quality of life survey in Europe: subjective well-being.
216. Djankov S, Nikolova E, Zilinsky J. The happiness gap in eastern Europe. The European Bank for Reconstruction and Development. Working paper no 184 London, 2016.
217. Demers L, Mortenson WB, Fuhrer MJ, et al. Effect of a tailored assistive technology intervention on older adults and their family caregiver: a pragmatic study protocol. *BMC Geriatr*. 2016;16:103.
218. Cook AM, Polgar JM. Assistive technologies: principles and practice. 4. St. Louis: Mosby; 2014.
219. Paré G, Jaana M, Sicotte C. Systematic review of home telemonitoring for chronic diseases: the evidence base. *J Am Med Inform Assoc*. 2007;14(3):269-77.
220. Inglis SC, Clark RA, McAlister FA, Ball J, Lewinter C, Cullington D, Stewart S, Cleland JG. Structured telephone support or telemonitoring programmes for patients with chronic heart failure. *Cochrane Database Syst Rev*. 2010 Aug 4;(8):CD007228.
221. Pigni L, Bovi G, Panzarino C, et al. Pilot Test of a New Personal Health System Integrating Environmental and Wearable Sensors for Telemonitoring and Care of Elderly People at Home (SMARTA Project). *Gerontology*. 2017;63(3):281-286.
222. Anker SD, Koehler F, Abraham WT. Telemedicine and remote management of patients with heart failure. *Lancet*. 2011 20;378(9792):731-9.
223. Koehler F, Winkler S, Schieber M, et al. Telemedicine in heart failure: pre-specified and exploratory subgroup analyses from the TIM-HF trial. *Int J Cardiol*. 2012 Nov 29;161(3):143-50.
224. Shorey R. Mobile, Wireless and Sensor Network: Technology, Applications and Future Directions, Wiley, USA, 2006.
225. Jayaram NM, Khariton Y, Krumholz HM, et al. Impact of telemonitoring on health status. *Circ Cardiovasc Qual Outcomes*. 2017;10(12). pii: e004148.
226. Gingele AJ, Brunner-la Rocca H, Ramaekers B, et al. Telemonitoring in patients with heart failure: is there a long-term effect? *J Telemed Telecare*. 2017;1357633X17747641.
227. Franssen M, Farmer A, Grant S, et al. Telemonitoring and/or self-monitoring of blood pressure in hypertension (TASMINH4): protocol for a randomised controlled trial. *BMC Cardiovasc Disord*. 2017;17(1):58.
228. Buekers J, De Boever P, Vaes AW, et al. Oxygen saturation measurements in telemonitoring of patients with COPD: a systematic review. *Expert Rev Respir Med*. 2018;12(2):113-123.
229. Oliver M, Teruel MA, Molina JP, Romero-Ayuso D, González P. Ambient Intelligence environment for home cognitive telerehabilitation. *Sensors (Basel)*. 2018;18(11). pii: E3671.
230. Al-Shaqi R, Mourshed M, Rezgui Y. Progress in ambient assisted systems for independent living by the elderly. *Springerplus*. 2016;5:624.

231. Metzler TA, Lewis LM, Pope LC. Could robots become authentic companions in nursing care? *Nurs Philos*. 2016;17(1):36-48.
232. Finch CE, Schneider EL. The future of old age. In: Brocklehurst's Textbook of Geriatric Medicine and Gerontology, Eighth Edition, 2017, Elsevier, ch. 3, 10-15.
233. Rodin MB, Mohile SG. A practical approach to geriatric assessment in oncology. *J Clin Oncol*. 2007;25(14):1936-44.
234. Bellera CA, Rainfray M, Mathoulin-Pélissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol*. 2012;23(8):2166-72.
235. Sutton JL, Gould RL, Daley S, et al. Psychometric properties of multicomponent tools designed to assess frailty in older adults: a systematic review. *MC Geriatr* 2016;16:55.
236. Sprod LK. Considerations for training cancer survivors. *Strength Cond J*. 2009;31(1):39-47.
237. Peoples H, Brandt Å, Wæhrens EE, la Cour K. Managing occupations in everyday life for people with advanced cancer living at home. *Scand J Occup Ther*. 2017;24(1):57-64.
238. Johnson TM. Long-term care: safe drug handling of oral chemotherapy. *Consult Pharm*. 2017;32(2):74-83.
239. Putcha N, Puhan MA, Hansel NN, Drummond MB, Boyd CM. Impact of co-morbidities on self-rated health in self-reported COPD: an analysis of NHANES 2001–2008. *COPD*. 2013;10(3):324–332.
240. Smith MC, Wrobel JP. Epidemiology and clinical impact of major comorbidities in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2014 Aug 27;9:871-88. doi: 10.2147/COPD.S49621. eCollection 2014.
241. de Lucas-Ramos P, Izquierdo-Alonso JL, Rodriguez-Gonzalez Moro JM, et al. Chronic obstructive pulmonary disease as a cardiovascular risk factor. Results of a case-control study (CONSISTE study) *Int J Chron Obstruct Pulmon Dis*. 2012;7:679–686.
242. Mascarenhas J, Azevedo A, Bettencourt P. Coexisting chronic obstructive pulmonary disease and heart failure: implications for treatment, course and mortality. *Curr Opin Pulm Med*. 2010;16(2):106–111.
243. de Miguel Diez J, Chancafe Morgan J, Jimenez Garcia R. The association between COPD and heart failure risk: a review. *Int J Chron Obstruct Pulmon Dis*. 2013;8:305–312
244. Finkelstein J, Cha E, Scharf SM. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. *Int J Chron Obstruct Pulmon Dis*. 2009;4:337–349.
245. Divo M, Cote C, de Torres J, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186(2):155–161
246. McAllister DA, Maclay JD, Mills NL, et al. Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. *Eur Respir J*. 2012;39(5):1097–1103
247. Eickhoff P, Valipour A, Kiss D, et al. Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008;178(12):1211–1218.
248. Patel AR, Donaldson GC, Mackay AJ, Wedzicha JA, Hurst JR. The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest*. 2012;141(4):851–857.
249. Tsiligianni IG, Kosmas E, Van der Molen T, Tzanakis N. Managing comorbidity in COPD: a difficult task. *Curr Drug Targets*. 2013;14(2):158–176.
250. Stefan MS, Rothberg MB, Priya A, Pekow PS, Au DH, Lindenauer PK. Association between beta-blocker therapy and outcomes in patients hospitalised with acute

- exacerbations of chronic obstructive lung disease with underlying ischaemic heart disease, heart failure or hypertension. *Thorax*. 2012;
251. Ghosh A, Dzeng E, Cheng MJ. Interaction of palliative care and primary care. *Clin Geriatr Med*. 2015;31(2):207-18.
 252. Alexander K, Goldberg J, Korc-Grodzicki B. Palliative care and symptom management in older patients with cancer. *Clin Geriatr Med*. 2016;32(1):45-62.
 253. Reid MC, Ghesquiere A, Kenien C, Capezuti E, Gardner D. Expanding palliative care's reach in the community via the elder service agency network. *Ann Palliat Med*. 2017;6(Suppl 1):S104-S107.
 254. Harstäde CW, Blomberg K, Benzein E, Östlund U. Dignity-conserving care actions in palliative care: an integrative review of Swedish research. *Scand J Caring Sci*. 2018;32(1):8-23.
 255. Finucane TE, Nirmalasari O, Graham A. Palliative care in the ambulatory geriatric practice. *Clin Geriatr Med*. 2015;31(2):193-206.