GRIGORE T. POPA UNIVERSITY OF
MEDICINE AND PHARMACY IASI

HABILITATION THESIS

INTEGRATED APPROACH IN THE PSYCHIATRIC PATIENT ASSISTANCE

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Contents

LIST OF ABREVIATIONS 1
LISTĂ DE ABREVIERI 3
ABSTRACT 5
REZUMAT 7
OVERVIEW OF PROFESSIONAL, ACADEMIC AND SCIENTIFIC ACHIEVEMENTS 9
  Professional activity 10
  Academic activity 10
  Scientific activity 11
SECTION I: SCIENTIFIC, PROFESSIONAL AND ACADEMIC ACHIEVEMENTS 13
CHAPTER 1. 13
PSYCHIATRIC INTEGRATED CARE 13
  1.1 Introduction 13
  1.2 Researches regarding pathways to psychiatric care 13
    A. Background 13
    B. Published paper in this field 14
  1.3 Researches regarding ways to access psychiatric services in Romania 24
    A. Background 24
    B. Published paper in this field 25
  1.4 Researches regarding prescribing practices in psychiatric hospitals 29
    A. Background 29
    B. Published paper in this field 30
CHAPTER 2. 37
CLINICAL AND THERAPEUTIC APPROACH AT PATIENTS WITH SCHIZOPHRENIA . 37
  2.1 Introduction 37
  2.2 Researches regarding the ethics of treatment in early psychosis and the importance of therapeutic adherence 38
    A.Background 38
    B. Published papers in this field 39
  2.3 Researches regarding therapeutic measures in involuntary admitted patients 44
    A. Background 44
    B. Published paper in this field 45
  2.4 Researches regarding institutionalization in schizophrenia 49
    A. Background 49

B. Published paper in this field 50
CHAPTER 3. 55
INSTITUTIONALIZATION, ETHICAL AND LEGAL IMPLICATIONS IN THE ASSISTANCE OF PATIENTS WITH DEMENTIA 55
3.1 Introduction 55
3.2 Researches regarding quality of life, ethical and legal implications in the assistance of patients with dementia 56
A. Background 56
B. Published paper in this field 57
3.3 Researches regarding institutionalization in dementia 62
A. Background 62
B. Published paper in this field 63
CHAPTER 4. 68
SUICIDE – A MEDICAL AND PSYCHIATRIC EMERGENCY 68
4.1 Introduction 68
4.2 Researches regarding alcohol abuse and its relation to suicide behaviour 69
A. Background 69
B. Published paper in this field 69
4.3 Researches regarding affective disorders and suicide 72
A. Background 72
B. Published paper in this field 73
CHAPTER 5. 79
INTERDISCIPLINARY APPROACH OF THE PATIENTS WITH PSYCHIATRIC DISTURBANCES AND SOMATIC COMORBIDITIES 79
5.1 Introduction 79
5.2 Psychiatric disturbances, stress and cardio-vascular disorders 80
5.2.1 The influence of social factors, professional conditions and psychological state on the systemic hypertension. 80
A. Background 80
B. Published paper in this field 82
5.2.2 Stress - from the concept to the neuroendocrine activation 88
A. Background 88
B. Published paper in this field 88
5.3 Interrelations between psychiatric disturbances and rheumatologic patients concerning quality of life 91
A. Background 91

B. Published paper in this field 92
5.4 Interrelations between psychiatric disturbances and obstructive sleep apnea 97
A. Background 97
B. Published paper in this field 97
SECTION II: FUTURE PROJECTS IN THE PROFESSIONAL, ACADEMIC AND SCIENTIFIC LEVEL 105
1. Perspectives in the professional activity 105
2. Perspectives in the academic activity 106
3. Perspectives in the scientific activity 106
SECTION III: REFERENCES 109

LIST OF ABREVIATIONS

5-HIAA - 5-hydroxyindolacetic Acid
AC – Abdominal Circumference
AD – Alzheimer’s disease
ADL – Activities of Daily Living
AHI – Apnea-Hypopnea Index
AP – Antipsychotic
APA – American Psychiatric Association
AUC – Area Under the Curve
BAC – Blood Alcohol Concentration
BAD – Bipolar Affective Disorder
BMI – Body Mass Index
BP – Blood Pressure
BPRS – Brief Psychiatric Rating Scale
BPSD - Behavioural And Psychological Symptoms In Dementia
CAPE-P15 - The Community Assessment of Psychic Experiences-Positive Scale, 15-item revised edition
CAR – Cortisol Awakening Response
CES-D - Centre for Epidemiological Studies Depression Scale
CGI - Clinical Global Impression
CI – Confidence Interval
CIDI-SF – Composite International Diagnostic Interview - Short Form
CLZ – Clozapine
CPAP – Continuous Positive Airway Pressure
CPS – Continuous Palliative Sedation
CSF – Cerebrospinal Fluid
CT – Computerized Tomography
DBI – Beck’s Depression Inventory
DBP – Diastolic Blood Pressure
DIS – Diagnostic Interview Schedule
DNR – Do Not Resuscitate
DR – Do Resuscitate
DSM 5 – Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG – Electrocardiogram
ECNP – European College of Neuropsychopharmacology
EEA – European Economic Area
E-ESPI – The Eastern European Scientific Initiative
ESMS – European Service Mapping Schedule
ESS – Epworth Sleepiness Scale
EU – European Union
FEV – Forced Expiratory Volume
GP – General Practitioner
GWB – General Wellbeing Schedule
HAM-A – Hamilton Anxiety Scale
HAM-D – Hamilton Depression Scale
HARS – Hamilton Anxiety Rating Scale
HBP – High Blood Pressure
HDL – High Density Lipoprotein
HDRS – Hamilton Depression Rating Scale
HIV – Human Immunodeficiency Virus
HPA - Hypothalamic-Pituitary-Adrenocortical axis
HR – Hazard Ratio

HR – Heart Rate
ICD10 – International Classification of Diseases, 10th Revision
INS – Institutionalization
LAI – Long Acting Injectable
LDL – Low Density Lipoprotein
LES – Life Experience Survey
MADRS – Montgomery – Asberg Depression Rating Scale
MCP-1 – plasma Monocyte Attractant Protein-1
MESA – Multi-Ethnic Study of Atherosclerosis
MMSE – Mini Mental State Evaluation
MOAS - Modified Overt Aggressiveness Scale
MRI- Magnetic Resonance Imaging
MS – Ministerul Sănătății
NMDA - N-methyl-D-aspartate
NS – Not Significant
ODI – Oxygen Desaturation Index
OR – Odds Ratio
OSA – Obstructive Sleep Apnea
PANSS - Positive and Negative Symptoms Scale
PSG – Polysomnography
QoL – Quality of Life
RA – Rheumatoid Arthritis
REM – Rapid Eye Movement
SBP – Systolic Blood Pressure
SD – Standard Deviation
SF-36 – Short Form Health Survey
SGA – Second Generation Antipsychotics
SPSS – Statistical Package for Social Sciences
SRRS - Social Readjustment Rating Scale
SSRI – Selective Serotonin Reuptake Inhibitors
TSST – Trier Social Stress Test
UHR – Ultra High Risk
UK – United Kingdom
UNICEF – United Nation’s Children Fund
US – United States of America
VaD – Vascular Dementia
VC – Vital Capacity
WHO – World Health Organization

LISTĂ DE ABREVIERI

5-HIAA – Acidul 5-hidroxiindolacetic
AC – Circumferința Abdominală
AD – Boala Alzheimer
ADL – Activitățile curente de zi
AHI – Indexul de Apnee-Hipopnee
AP – Antipsihotic
APA – Asociația Americană de Psihiatrie
AUC – Aria de Sub Curbă
BAC – Concentrația de Alcool în Sânge
BAD – Tulburarea Afectivă Bipolară
BMI – Indexul de Masă Corporală
BP – Presiune Arterială
BPRS – Brief Psychiatric Rating Scale
BPSD - Behavioural And Psychological Symptoms In Dementia
CAPE-P15 - The Community Assessment of Psychic Experiences-Positive Scale, 15-item revised edition
CAR – Răspunsul de Trezire al Cortizolului
CES-D - Centre for Epidemiological Studies Depression Scale
CGI - Clinical Global Impression
CI – Interval de Confidență
CIDI-SF – Composite International Diagnostic Interview - Short Form
CLZ – Clozapină
CPAP – Ventilație Mecanică cu Gradient de Presiune Pozitivă Continuă
CPS – Sedare Continuă în Paliație
CSF – Lichid Cerebro-Spinal
CT – Tomografie Computerizată
DBI – Beck's Depression Inventory
DBP – Presiune Sangvină Diastolică
DIS – Diagnostic Interview Schedule
DNR – Neresuscitarea pacientului terminal
DR – Resuscitarea pacientului terminal
DSM 5 – Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG – Electrocardiogramă
ECNP – Colegiul European de Neuropsihofarmacologie
EEA – Aria Economică Europeană
E-ESPI – The Eastern European Scientific Initiative
ESMS – European Service Mapping Schedule
ESS – Epworth Sleepiness Scale
EU – Uniunea Europeană
FEV – Volum Expirator Forțat
GP – Medic de Medicină Generală
GWB – General Wellbeing Schedule
HAM-A – Scala de Anxietate Hamilton
HAM-D – Scala de Depresie Hamilton
HARS – Scala de Anxietate Hamilton
HBP – Tensiune Arterială Crescută
HDL – Lipoproteine cu Densitate Înaltă
HDRS – Scala de Depresie Hamilton
HIV – Virusul Imunodeficienței Uman
HPA – Axa Hipotalamică-Pituitară-Adrenocorticală
HR – Hazard Ratio

HR – Frecvență Cardiacă
ICD10 – International Classification of Diseases, 10th Revision
INS – Instituționalizare
LAI – Antipsihotic Injectabil cu Eliberare Prelungită
LDL –Lipoproteine cu Densitata Joasă
LES – Life Experience Survey
MADRS – Scala de Evaluare a Depresiei Montgomery – Asberg
MCP-1 – Plasma Monocyte Attractant Protein-1
MESA – Multi-Ethnic Study of Atherosclerosis
MMSE – Mini Mental State Evaluation
MOAS - Modified Overt Aggressiveness Scale
MRI- Imagistică prin Rezonanță Magnetică
MS – Ministerul Sănătății
NMDA - N-metil-D-aspartat
NS – Nesemnificativ (statistic)
ODI – Indexul de Desaturare a Oxigenului
OR – Odds Ratio
OSA – Apnee Obstructivă de Somn
PANSS – Scala Simptomelor Pozitive și Negative (în Schizofrenie)
PSG – Polisomnografie
QoL – Indexul de Calitate a Vieții
RA – Artrită Reumatoidă
REM – Mișcări Oculare Rapide
SBP – Tensiune Arterială Sistolică
SD – Deviație Standard
SF-36 – Short Form Health Survey
SGA – Antipsihotice de Generația a II-a
SPSS – Statistical Package for Social Sciences
SRRS - Social Readjustment Rating Scale
SSRI – Inhibitori Selectivi ai Recaptării Serotoninei
TSST – Trier Social Stress Test
UHR – Risc Foarte Înalt
UK – Regatul Unit al Marii Britanii și Irlanda de Nord
UNICEF – United Nation's Children Fund
US – Statele Unite ale Americii
VaD – Demență Vasculară
VC – Capacitate Pulmonară Vitală
WHO – Organizația Mondială a Sănătății

ABSTRACT

The habilitation thesis entitled “Integrated approach in the patient psychiatric assistance” presents my clinical research in the field of psychiatry, a synthesis of my post-doctoral achievements.

The thesis was written according to the recommendations of the National Council for Attestation of University Titles, Diplomas and Certificates (CNATDCU) and was structured into three main sections: Section I – Scientific, professional and academic achievements; Section II – Future projects in the professional, academic and scientific level; Section III – References. The three sections are prefaced by an overview of my entire career with professional, academic and scientific achievements in the field of psychiatry at the “Grigore T. Popa” University of Medicine and Pharmacy, Iași, Romania.

The first section of the habilitation thesis entitled “Scientific, professional and academic achievements” has five chapters. In this section, I have included the main ideas and results of the most important articles from my scientific activity. These articles are rated by Thomson ISI Web of Science Core Collection.

Chapter 1 – *Psychiatric integrated care* – starts with a short introduction regarding the models of care in psychiatry and the accessibility of psychiatric care services including development of community psychiatric services. Subsection 1.2 *Researches regarding pathways to psychiatric care* contains data from an article rated by Thomson ISI Web of Science Core Collection which purpose was to identify personal and environmental factors when addressing a psychiatrist, and to identify models that can represent pathways to psychiatric care in Eastern Europe. In the next subsection, *Researches regarding ways to access psychiatric services in Romania,* the same methodology was applied to collect data and evaluate the models of access for patients to psychiatric services in our country. Last subsection of the first chapter analyses prescribing practices in psychiatric hospitals focusing on Eastern Europe, presenting the results of a study conducted in eight clinical centres, investigating the patterns of prescribing psychotropic drugs in five countries.

Chapter 2 – *Clinical and therapeutic approach for patients with schizophrenia* begins with an introduction for the clinical syndrome that is schizophrenia and continues with subsection entitled *Researches regarding the ethics of treatment in early psychosis and the importance of therapeutic adherence* which summarizes ethical issues related to psychiatric treatment and also continues with the results of an retrospective study where we emphasize the importance of the initiation of antipsychotic treatment and also the importance of therapeutic adherence. Subsection 2.3 *Researches regarding measures in involuntary admitted patients* presents the results of a study that assessed the properties of clozapine use for the management of aggressive behaviour in involuntary admitted patients with schizophrenia. Last subsection in this chapter treated the difficult problem of institutionalization in schizophrenia and presents the results of a study on 322 patients with schizophrenia, hospitalized between 1995 and 2015 and the factors that lead to institutionalization.

Chapter 3 – *Institutionalization, ethical and legal implications in the assistance of patients with dementia* begins with a short introduction into the global problem of dementia and

continues with three subsections bringing together the results of three articles, 2 rated by Thomson ISI Web of Science Core Collection. The studies we conducted highlighted the vulnerability of patients with dementia and the legal aspects involved in their assistance, the effect of anti-dementia medication on cognitive and behavioural symptoms and the factors involved in the institutionalization of patients with dementia.

Chapter 4 – *Suicide – a medical and psychiatric emergency* – begins also with a short introduction and then focuses on the impact of alcohol usage in suicide in a 10 years retrospective study and on the polymorphism of the suicidal motivational profile with a focus on affective disorders.

The last chapter of this section – *The interdisciplinary approach of patients with psychiatric disturbances and somatic comorbidities* – after a short presentation of *the state of the art,* this chapter offers information about the relationship between social and professional factors, psychological state and systemic hypertension, the relationship between stress and the cardiovascular status of patients and also the influence of psychological factors on the quality of life of patients with rheumatoid arthritis and the interaction between obstructive sleep apnea and psychiatric symptoms.

Section II include my future projects in the professional, academic and scientific field. Regarding the future of my professional activity, the main purpose is improving the quality of care of psychiatric inpatients. SecondarlyI have identified several other achievable goals in terms of professional activity which will be further listed in this section.

Section III include a number of 447 bibliographic references used for this thesis and for the articles included. A considerable number of these references are recently published articles, which settle the theme and subject of my thesis in actuality, for them are still problems for which definite sollutions have not been found yet.

REZUMAT

Teza de abilitare “Abordarea integrată în asistența pacientului psihiatric” prezintă activitatea mea clinică și științifică în domeniul psihiatriei, o sinteză a preocupărilor de cercetare post-doctorale.

Teza a fost redactată în conformitate cu recomandările Consiliului Național de Atestare a Titlurilor, Diplomelor și Certificatelor Universitare (CNATDCU) și a fost structurată în trei secțiuni principale: Secțiunea I – Realizări științifice, profesionale și academice din perioada post-doctorală; Secțiunea II – Proiecte viitoare în activitatea profesională, academică și științifică; Secțiunea III – Referințe. Cele trei secțiuni sunt prefațate de o trecere în revistă a activităților mele, cu realizările profesionale, academice și științifice din domeniul psihiatriei în cadrul Universității de Medicină și Farmacie „Grigore T. Popa”, Iași.

Prima secțiune a tezei de abilitare, intitulată „Realizări științifice, profesionale și academice” are 5 capitole. În această secțiune am inclus principalele idei și rezultate ale celor mai importante articole din activitatea mea științifică. Aceste articole sunt indexate de Thomson ISI Web of Science Core Collection și unele în baze de date internaționale.

Capitolul 1 – *Îngrijirea psihiatrică integrată* – începe cu o scurtă introducere despre modelele de îngrijire în psihiatrie și accesibilitatea serviciilor de asistență psihiatrică, incluzând aici și serviciile de asistență psihiatrică comunitară. Subsecțiunea 1.*2 Cercetări privind căile de acces la asistența psihiatrică* prezintă rezultatele unui articol indexat în Thomson ISI Web of Science Core Collection, a cărui scop a fost identificarea factorilor personali și de mediu care influențează adresabilitatea pacientului la psihiatru și identificarea de modele de căi de acces la îngrijirea psihiatrică în Europa de Est. În următorul subcapitol*, Cercetări privind căile de acces la asistența psihiatrică în România*, aceeași metodologie a fost implementată pentru colectarea datelor și evaluarea modelelor de îngrijire a pacientului psihic în țara noastră. Ultima subsecțiune a primului capitol analizează modalități de prescriere a medicației în spitalele psihiatrice din Europa de Est prezentând rezultatele unui studiu efectuat în opt centre din această regiune, urmărind pattern-uri de prescripție a medicației psihotrope în cinci țări din Europa de Est.

Capitolul 2 – *Abordarea clinică și terapeutică a pacienților cu schizofrenie* începe cu o introducere în sindromul clinic al schizofreniei și continuă cu subcapitolul *Cercetări privind etica tratamentului în tulburările psihotice și importanța aderenței terapeutice* care sintetizează aspectele etice corelate cu tratamentul psihiatric și continuă cu un studiu retrospectiv care accentuează importanța inițierii precoce a tratamentului antipsihotic ca și importanța aderenței terapeutice. Subcapitolul 2 – *Cercetări privind măsurile terapeutice la pacienții internați non-voluntar* – prezintă rezultatele unui studiu care a evaluat proprietățile antiagresive ale utilizării clozapinei la pacienții diagnosticați cu schizofrenie. Ultimul subcapitol abordează problema dificilă a instituționalizării în schizofrenie și prezintă rezultatele unui studiu efectuat pe 322 pacienți cu schizofrenie spitalizați în perioada 1995 – 2015 cu accent pe factorii care au determinat instituționalizarea.

Capitolul 3 – *Instituționalizarea, implicații etice și legale în asistența pacienților cu demență* începe cu o scurtă introducere în problema globală a demenței și continuă cu trei subcapitole ce prezintă rezultatele a 2 articole indexate în Thomson ISI Web of Science Core Collection şi 1 articol indexat în baze de date internaționale. Studiile accentuează vulnerabilitatea persoanelor cu demență și aspectele legale implicate în asistența lor, efectul tratamentului antidemențial asupra simptomelor cognitive și comportamentale și factorii implicați în instituționalizarea pacienților cu demență.

Capitolul 4 – *Suicidul – o urgență medicală și psihiatrică* începe cu o scurtă introducere apoi se concentrează pe problematica utilizării alcoolului în suicid și prezintă rezultatele unui studiu retrospectiv și polimorfismul profilului motivațional în suicid cu accent asupra tulburărilor afective.

Ultimul capitol al acestei secțiuni – *Abordarea interdisciplinară a pacienților cu tulburări psihiatrice și comorbidități somatice*, după o scurtă prezentare a datelor din literatură asupra acestor teme oferă informații despre legătura dintre factorii sociali, condițiile profesionale, statusul psihologic al pacienților și hipertensiunea sistemică, relația dintre stres și statusul cardiovascular și de asemenea influența factorilor psihologici asupra calității vieții pacienților cu artrită reumatoidă.

Secțiunea II include proiectele mele viitoare în domeniul profesional, academic și științific. În ceea ce privește activitatea profesională, scopul meu principal este îmbunătățirea calității îngrijirilor medicale oferite în spital, de asemenea am identificat mai multe obiective realizabile în ceea ce privește activitatea profesională care vor fi listate în această secțiune.

Secțiunea III include un număr de 447 referințe bibliografice utilizate pentru această teză și pentru articolele incluse. Un număr considerabil de referințe sunt noi, ceea ce înseamnă că subiectul și temele din teză sunt actuale și încă nu au găsit soluții.

OVERVIEW OF PROFESSIONAL, ACADEMIC AND SCIENTIFIC ACHIEVEMENTS

The habilitation thesis entitled "Integrated approach in the psychiatric patient assistance" presents my clinical research after achieving my PhD title with the thesis entitled "Diagnosis, statistical and therapeutical correlations in the management of Alzheimer's disease" which was confirmed by the Ministry of Education (Order no. 3824 / 2006).

In my doctoral thesis I approached the issue of the diagnosis, evolution and the treatment of Alzheimer's disease, based on the historic landmarks of the concept since the beginning of the last century, passing through the etiopatogenical factors, management of the affective and behavioral disturbances and finally bringing the arguments for implementing a program to support clinical and ambulatory patients with the disease and also a program to combat the stigma associated to the psychiatric patients. Developed between the years 1999 – 2005, under the coordination of Professor Vasile Chiriță, the thesis has a number of 484 pages, 20 chapters and 488 references.

The main research topics of the thesis were structured in three directions:

- Assessment of the prevalence of dementia in a population of patients with psychiatric disorders;
- Evaluating the effectiveness of the administration of therapy with acetilcolinesterase inhibitors in patients with mild cognitive deterioration;
- Assessment of the importance of non-cognitive symptoms in the evolution of Alzheimer's disease and identifying adverse prognostic factors.

One of the conclusions of the thesis was the necessity of implementing a programme for early identification of Alzheimer's dementia and other type of dementias, as well as the need for a therapeutic plan and clinical assistance for these patients, with an emphasis on establishing and maintaining a therapeutic collaboration between all factors involved in the therapeutic process, including theeducation and support given to patients' families.

Presently, I hold the title of Associate Professor at the Discipline of Psychiatry, Faculty of Medicine "Grigore T. Popa" University of Medicine and Pharmacy Iași, Romania.

At the same time, I am working as a senior psychiatrist at the Institute of Psychiatry "Socola" Iași, the only of its kind in the country and the largest hospital of psychiatry in the Moldavian region. Beginning with 2009 I am the head of the VIth acute psychiatric clinic at "Socola" Institute of Psychiatry.

Throughout my career, I have been permanently interested to integrate the research activities with teaching, academic, professional development and also sanitary management. Between the years 2011 – 2014 I held the Medical Director position at "Socola" Psychiatric Hospital Iași, as it was then named, a management activity that involved monitoring the quality of the medical services at the hospital level, coordinating the health programs, elaborating the annual development plan of the hospital and managing income and expenses.

My professional activity, my academic activity and my scientific and research activity are in a closed correlation and I try to avoid neglecting any of them, by working all the time on subjects that covers my entire activities. My activity on all levels, professional, clinical, academic, scientific and research, are in close correlation one to another, as I constantly try to give them equal importance, dedication in the effort to not be neglecting any of them. One of the ways by which I strive to do so is engaging in subjects that cover my entire activities.

Professional activity

I have graduated "Grigore T.Popa" University of Medicine and Pharmacy Iasi in 1996 and the next year I was admitted by national competition to enter the training program required to qualify as a psychiatrist. I got my professional experience working in the field of psychiatry at "Socola" Clinical Hospital of Psychiatry Iași where I achieved my specialist title in 2001 (Ord. MSF nr. 866 / 03 XII 2001),and later in 2008 the title of senior psychiatrist (Ord. MS nr. 1971 / 03 XII 2008).During my clinical activity I was interested in continuing medical education by enrolling and completing several postgraduate courses such as: "Seminar Programme Evidence-Based medicine in Dementia and Old-Age Depression" – Lundbeck Institute, Denmark, June 6-10, 2011; "Dementia Center of Excellence Tour" – Bayerische Landesarztekammer, Munchen, Germany, 2012, 26 – 27 October; "Berlin Summer School Course on Psychiatry – a Science" on 26 aug – 1 sept 2000 and 13 – 17 November 2002 organized in Berlin by Berlin Brandenburg Academy of Sciences and Humanities; Maudsley Forum, London, September 6 -10, 2004 and the 2nd Advanced Maudsley Forum, a course for European Psychiatrists, organized in September 13 – 15, 2006.

In 2009, as a recognition for professionalism and organizational capacities I was named Chief of VIth Acute psychiatric clinic at "Socola" Institute of Psychiatry.

Between the years 2009 and 2011 I was President of the Discipline Committee of the Clinical Hospital of Psychiatry "Socola" and between the years 2011 and 2014 I held the Medical Director title at the same institution.

Academic activity

In 1999 I decided to start a teaching career and I obtained by contest a tutor position in the Discipline of Psychiatry – Psychology at the University of Medicine and Pharmacy "Grigore T. Popa" Iași. In 2002 I have advanced to Assistant Professor, in 2009 I became Lecturer and later in 2018 Associate Professor.

From the beginning, in collaboration with my other colleagues from the discipline, we implemented new methods of approaching the didactic plan, with changes in the analytical program for students in dental medicine, in accordance with the modern classification systems in psychiatry.

At the same time, I actively participated in rethinking the methodology for examining the knowledge accumulated by students in practical and theoretical terms, by developing multiple choice question tests that would include a coverage of information,as wide as necessary forour graduates.

I guided the the graduation theses of students that were very well appreciated in the bachelor's exam. The graduation theses were focused on the research topic of clinicalpsychiatry – current problems of nosology, etiopatogeny, psychopathology and clinical assistance of psychiatric disorders, problems of psychopharmacology and psychotherapy.

During this period of time, I participated in a series of courses, both national and international, being trained in communication techniques, presentation of medical materials both from a scientific, research and teaching point of view. These aspects of vocational training have given me the possibility of a modern approach of the teaching plan, adapted for the medical students who have undergone psychiatry internship.

I have been constantly involved in coordinating the teaching and scientific activities of the resident doctors in psychiatry. I have developed teaching materials for the preparation of theresidency program, especially in the field of my doctoral thess, involving Alzheimer's disease management.

I have guided the clinical case presentations and reports developed by the psychiatry residents working in our clinic leading them on a very special career path, getting to work as specialists in different clinics in the country or abroad.

I am the main author of a textbook entitled “Notes and seminars of medical psychology” published in 2007, co-author of a textbook for medical students entitled “Basic psychiatry for medical students” in 2007 writen in English and developed for the students studying in our University in the english program, . I am also the the author of a monograph entitled “Alzheimer disease. Clinical-therapeutic management”, of the “Training curriculum in the psychoeducation domain for caregivers of patients diagnosed with mental disorders”, of another monograph entitled “Current events in Alzheimer disease” published in 2014 and of a guide adressed to Family Medicine doctors who treat patients with dementia entitled “Practical aspects of the management of behavioral disorders in Alzheimer’s dementia” in 2016. I am also a co-author of a manual entitled “Psychiatry – the essential in clinical presentations” published in 2018.

Scientific activity

The results of my scientific and research activity have been published in articles indexed by the Web of Science Core Collection and in other international databases. I have also disseminated the results as a speaker in local, national and international congresses, conferences, seminars and workshops. I have also published books and book chapters, as principal author or co-author.

In my PhD thesis, I approached the issue of diagnosis, evolution and treatment of Alzheimer’s disease, the etiopatogenical factors, management of the affective and behavioral disturbances and finally bringing the arguments for implementing a program to support clinical and ambulatory patients suffering from the disease and also a program aimed at combating the stigma associated with psychiatric patients.

I participated in the elaboration of 7 books and a book chapter, 73 articles published in extenso, of which 16 articles ISI quoted, 9 of which as principal author, 17 articles indexed BDI of which 14 main author, 27 articles published in extenso in the volumes of scientific events and 13 articles published in non- BDI indexed journals.

I participated in the elaboration of 45 articles published in summary in ISI-listed journals – 11 articles, and the volumes of scientific events with ISBN / ISSN – 34 articles. I have 44 poster communications and presentations at national or international scientific events (other than those published in volumes with ISBN / ISSN). As a result of national and international visibility, these articles were citeda total number of 161 citations in the Clarivate Analytics Web of Science Core Collection and a Hirsh-Index of 8, 159 articles listed in the Scopus collection (7 Hirsh-Index), and a total of 231 citations (h-index 6) in the Google Scholar database.

In 2005 as part of the EEPSI group I received the “OKASHA Award for Developing Countries” for the paper “Pathways to psychiatric care in Eastern Europe” at the XIIIth WPA World Congress of Psychiatry – “5000 years of Science and Care: Building the Future of Psychiatry”, Cairo, Egypt.

The areas of scientific interest have focused largely on the topic of the doctoral thesis but also on the quality of life of the mentally ill patient, the issue of suicide and ethical implications in psychiatric care, clinical-therapeutic approach of patients with schizophrenia, ethics of treatment and institutionalization.

I collaborated with the University community, with colleagues from other medical specialties, especially those working in clinical fields. This collaboration is not limited only to clinical consultations and collaboration, but has also materialized in the elaboration of studies and scientific paperspublished in periodicalsand disseminated through oral communications,both national and internationals, including in ISI quoted articles in the field of interdisciplinarity.

I had participated in competition funded research projects such as “Evaluation of the usefulness of salivary alpha-amylase determination as a possible novel noninvasive biomarker for autonomic nervous system dysfunction in heart and metabolic diseases (contract no.29234 / 20. 12.2013), project director Dima-Cozma Corina; in the Project ID POSDRU / 81 / 1.2 / S/ 62597 – MEDICALIS Educational Management and Quality Education in Information Society, 2010 – 2013, as an expert in the Project “Professional counselling for medical students and integrated practice program in the field of general and dental medicine” – POSDRU 139991, project manager prof. dr. Norina Consuela Forna, 01.04.2014 – 30.11.2015, and as a Project manager (COR 2421010) within the “Social inclusion through the provision of integrated services at the community level – Parenting education component”, project funded by the Norwegian and EEA grants and UNICEF funds – 04.09.2015 – 29.02.2016.

SECTION I: SCIENTIFIC, PROFESSIONAL AND ACADEMIC ACHIEVEMENTS

CHAPTER 1.

PSYCHIATRIC INTEGRATED CARE

1.1 Introduction

The current, segregated model of care in psychiatry has led to the development of competing medical and psychiatric patient approaches that have resulted in a lack of dialog among health providers and thus in less than optimal patient outcomes.

We have to change the system and the result has to be a patient-centred model where the therapeutic experience for the patient, the medical care itself and the cost outcomes improve as the system changes from fee-for-service to population based health.

The World Health Organization (WHO) recommended in 2001, in the World Health Report, the partial transfer of psychiatric services to the mental health services provided in the community. The aim was to increase the quality of life of the psychiatric patient by changing the pattern of care in a framework that respects their rights and also has economic benefits in the long-term by reducing care costs and social pressure. The effect will be that a large proportion of these patients will be rehabilitated so that they can provide a useful input in society, even in a protected system and that subsequently, this will increase their self-esteem and well-being (1).

A multidisciplinary team specialized in providing medical and social community based services, in according with European standards can be created at the level of local communities, developing a formal and informal network of people trained in community assistance. Patient centred medicine, accessibility of psychiatric care services, patient's access routes to these services, treatment protocols, the development of community psychiatric services are also important elements in addressing the patient.

1.2 Researches regarding pathways to psychiatric care

A. Background

The purpose of the pathway to care research is to provide early addressability to psychiatric services, to minimize the effective cost of treatment and to improve prognosis.

When talking about the access to mental health services, patients firstly identify personal and environmental factors which can be a problem when addressing a psychiatrist. These factors include the inability to recognize and accept mental health problems, reluctance to discuss psychological distress, negative perception of and social stigma against mental health and/or financial factors. Significant emphasis can be made on cultural identity and the stigma associated with mental health as barriers to access psychiatric services. Also, people with mental illnesses are less likely to have health insurance than those without mental health problems (2, 3). In a survey published in 2011, Garfield et al found that 37 percent of working-age adults with severe mental illnesses were uninsured for at least part of the year, compared to about 28 percent of people without severe mental illnesses (3).

The stigmatization of the mentally ill is still an important issue in our society, because the fear induced into the general population by the mentally ill, a general population which in it's majority is ignorant about this problem. Stigma attached to mental illness can be found in every country, society or culture, but alsostigmatization varies depending on the type of the disorder. A patient with schizophrenia will suffer far more from stigmatization than for example a person with depression (4).

The process of deinstitutionalization enhanced public awareness about the associated risk and pushed forward discussions about community psychiatry. We should not forget about self-stigma which is a process in which an individual with mental illness internalizes the stigma and then experiences diminished self-esteem and self-efficacy, and limited prospects for recovery (5). In principle, there are three general approaches that we can use to reduce stigma and discrimination: information / education campaigns about mental illness; protest against unfair descriptions of mental illness; and direct contact with the mentally ill. To mediate this strategies we can use: mass media, leaders of opinion and persons of trust (5).

Factors causing delay in the initiation of appropriate treatment vary from country to country and region to region, depending upon education, socio-cultural background, the attitude taken by society and /or by family members towards mental illness, upon the stigma attached to psychiatric disorders, accessibility to psychiatric services and previous experience (6). The first care provider is the most important for the referral to psychiatric care (7). No significant relationship was found between symptoms' intensity measures and the level of disability and help-seeking. Willingness to discuss mental health issues with a general practitioner was predicted by the perceived helpfulness of the general practitioner and by no other variables (8).

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which intended to evaluate the role of primary care in mental healthcare in both detection and management of mental disorders and the other pathways to psychiatric care.

Gater R, Jordanova V, Maric N, Alikaj V, Bajs M, Cavic T, Dimitrov H, Iosub D, Mihai A, **Szalontay AS**, Helmchen H, Sartorius N. Pathways to psychiatric care in Eastern Europe. *British Journal of Psychiatry* 2005; 186: 529 – 535**. IF 2005 = 4.956**

- **Introduction**

A study group named The Eastern European Scientific Initiative (E-EPSI group) had decided to obtain information about mental health services in Central and Eastern Europe and to make suggestions concerning their improvement. For this article the E-EPSI group was awarded World Psychiatric Association Okasha Award for Developing countries, for research in psychiatry, of high impact strengthening international collaboration in the field of psychiatry and training and education in psychiatry in developing countries.

Pathways studies have been used to investigate the roles of previous carers and time on the pathway (9 – 15) and to monitor the effects of service developments over time (16, 17).

An understanding of the way people seek care for mental disorders is increasingly recognized as important for planning mental health services, provision of appropriate training and referral from other sectors of health and social care.

The aim of the study was to improve understanding of prior care-seeking and treatment of new patients seen in mental health services.

- **Material and Method**

It was a collaborative study that was carried out in eight centres: Belgrade in Serbia-Montenegro, Bucharest, Iasi and Tg. Mures in Romania, Sofia in Bulgaria, Strumica in Macedonia, Tirana in Albania and Zagreb in Croatia, using the methodology of the World Health Organization Study of Pathways to Care (3). Taking into accountof the feasibility issues in the participating centres and previous experience using the pathways method, a sample size of 50 was estimated to be sufficient for a meaningful analysis. All those that were newly referred to the psychiatric services and agreed to participate were interviewed until the target of 50 participants were recruited in each centre. Newly referred patients were defined as those who had not sought care from the mental health services during the previous year. There were no exclusion criteria. The fieldwork was carried out between February and May 2003. Those eligible were interviewed using an encounter form, which was previously used in a study coordinated by the World Health Organization (9). The form gathers information on socio-demographic characteristics of participants and sources of care before reaching the mental health service. The encounter form was translated into Albanian, Bulgarian, Croatian, Macedonian, Romanian and Serbian. The psychiatrist in charge completed the questionnaire, which took 5-10 minutes. An instruction and coding manual was supplied to each psychiatrist who took part in the fieldwork.

The routes taken by participants from each center were combined in a "pathways diagram". The proportion taking each route was marked on the pathways diagram. The time intervals between the onset of problem, first seeking care and arrival at the mental health services were compared between centers and diagnostic groups. Comparisons according to individual diagnostic groups were made by groups of centers with sufficiently large numbers of cases. Diagnostic groups were based on ICD-10 categories (World Health Organization, 1992) (18): mental and behavioral syndromes associated with psychoactive substance misuse (F10-19), schizophrenia, schizotypal and delusional (F20-29), mood disorders (F30 – 39), and neurotic, stress-related and somatoform disorders (F40 – 49). Schizophrenia, schizotypal and delusional disorders were further divided into schizophrenia or schizoaffective disorder (F20 and F25) and other psychotic disorders. Other diagnoses did not occur in sufficient instances for meaningful analysis. Categorical data was analyzed using the X^2 test. Continuous variables (such as duration of problem) were highly skewed; therefore average values are presented as medians; analysis employed Kruskal – Wallis analysis of variance.

The participating centers share a number of important characteristics. All were in transition from predominantly institutional to community-based care, but at that time, the mental health services were almost entirely hospital based. Although in most centers primary care is widely distributed and accessible, general practice has yet to establish its place in mental healthcare. Communications between general practitioners and psychiatrists are rare at an individual, institutional and guild (professional society) level. In most countries involved, regulations require that a psychiatrist recommends an antidepressant before the general practitioner can prescribe; there are limited numbers of psychotropic medications on the "positive" list (available without charge), whereas others on the "negative" list have to be paid for. In Belgrade there are about ten psychiatrist per 100000 population, participants were recruited at a large general psychiatric hospital. This is a state institution and all costs of treatment are covered by regular insurance. In Bucharest individuals were seen in the emergency and outpatient wards of the largest general psychiatric hospital in Romania. There are about 8.3 psychiatrists per 100000 population and all public psychiatric services are covered by the regular medical insurance. Those in Iasi were seen in the University Hospital of Psychiatry, which is a state institution where costs are covered by insurance. There are 8.5 psychiatrists per 100000 population. The service in Sofia is a private medical center, replacing a former polyclinic (community primary and secondary care clinic), which receives donations from the municipality and state. There are four psychiatrists per 100000 population. Since this psychiatric service was only recently established, a substantial number of those with severe mental illness continue to receive psychiatric services elsewhere. In Strumica, an out-patient clinic and ward provide the only mental health service in the region, with 3.3 psychiatrists per 100000 population. These are state institutions and the National Health Insurance Fund covers treatment costs. At the

University Psychiatric Clinic of Tirgu Mures costs of treatment are covered by regular insurance. There are 5.4 psychiatrists per 100000 population. In Zagreb, the study was carried out in the emergency service of a large general psychiatric hospital. This is a state institution where national insurance covers admission and treatment costs, and there are about ten psychiatrists per 100000 population. At each center, data was collected from 50 new patients seen as new out-patients, emergency assessments or new patients referred for admission. There were no refusals in any of the centers. The samples in all eight centers included approximately 60% women, but in other respects the demographic profile differed between centers. The mean age was 40 years, with an older average age in Sofia (50 years) and younger average in Belgrade, Iasi, Strumica and Tirana (33 -36 years). In Sofia and Tirana, two-thirds of the participants were married and living together or cohabiting, whereas those in Belgrade, Bucharest, Iasi and Strumica were usually single. In Bucharest, Strumica and Zagreb the majority of participants were rated of below average social class, whereas only a minority were so rated in Belgrade.

- **Results**

The most frequent diagnoses in all centers combined were mood and neurotic disorders (23% each), followed by schizophrenia (16%), other psychotic disorders (15%) and mental disorders due to substance misuse (11%). However, this distribution does not reflect the situation in any of the individual centers, which varied significantly (P<0.001) (Table 1.1). These differences are most likely to reflect differences in the mental health services and should not be interpreted as differences in the prevalence of mental illness. Between 28 and 38% of new patients from most centers had a previous psychiatric history but higher rates were found in Iasi (64%) and Tirgu Mures (46%) (P<0.01).

Table 1.1. Previous history, current diagnosis and patients who suggested seeking care at each centre

Centre	**ICD-10 diagnostic group[9]**						**Previous psychiatric history n (%)**	**Patient suggested seeking care n (%)**
	Schizophrenia[1] n (%)	**Other psychotic disorders[2] n (%)**	**Mood disorder n (%)**	**Neurotic disorder[3] n (%)**	**Substance misuse[4] n (%)**	**Other mental disorder n (%)**		
Belgrade	0 (0[5])	14 (28)	9 (18)	23 (45)	1 (2)	3 (6)	14 (28)	25 (50)
Bucharest	13 (26)	6 (12)	7 (14)	2 (4)	12 (24)	10 (20[6])	16 (38)	16 (32)
Iasi	15 (30)	11 (22)	12 (24)	0 (0)	8 (16)	4 (8)	32 (64)	8 (16)
Sofia	1 (2)	2 (4)	19 (38)	21 (42)	1 (2)	6 (12[6])	18 (36)	21 (42)
Strumica	15 (30)	12 (24)	10 (20)	5 (10)	1 (2)	7 (14[7])	19 (38)	16 (32)
Targu Mures	2 (4)	5 (10)	13 (26)	12 (24)	11 (22)	7 (14[8])	23 (46)	26 (52)
Tirana	5 (10)	2 (4)	17 (34)	22 (44)	0 (0)	4 (8)	14 (28)	6 (12)
Zagreb	15 (30)	8 (16)	7 (14)	8 (16)	8 (16)	4 (8)	15 (30)	21 (42)
Combined	66 (16)	60 (15)	94 (23)	93 (23)	42 (11)	45 (12)	151 (38)	139 (35)

1. *Schizophrenia and schizoaffective disorders.*
2. *All other diagnoses in the schizophrenia, schizotypal and delusional disorders group, excluding schizophrenia and schizoaffective disorders.*
3. *Neurotic, stress-related and somatoform disorders.*
4. *Mental and behavioural disorders due to psychoactive substance misuse.*
5. *Participating psychiatrists in Belgrade usually do not diagnose schizophrenia in new patients until a short period of observation has been completed.*
6. *In Bucharest and Sofia, 12% had an organic mental disorder.*
7. *In Strumica, 8% had behavioural syndromes associated with physiological disturbances and physical factors.*
8. *In Tirgu Mures, 8% had learning disabilities*
9. *World Health Organization, 1992.*

The suggestion to first seek care most often came from family or friends for those initially presenting with psychotic symptoms (70%), violent, aggressive or other disturbed behavior (100%) and attempted suicide (90%). Family members first suggested psychiatric care more frequently than either previous careers or individuals themselves for all diagnostic groups.

In all centers combined, 87% first sought care from a doctor, usually a general practitioner (40%) or by directly accessing the psychiatric services (33%), and less frequently from a hospital doctor (14%). However, the initial and subsequent sources of care were very different from center to center. General practitioners were the predominant careers in Sofia and Tirgu Mures (Fig. 1.1.) where 60 – 70% of participants first sought care from a general practitioner; the others were divided equally between hospital doctor (12 – 14%) and direct access to psychiatric services (14 – 16%). These were also the only two centers with a substantial flow between general practitioners and hospital doctors.

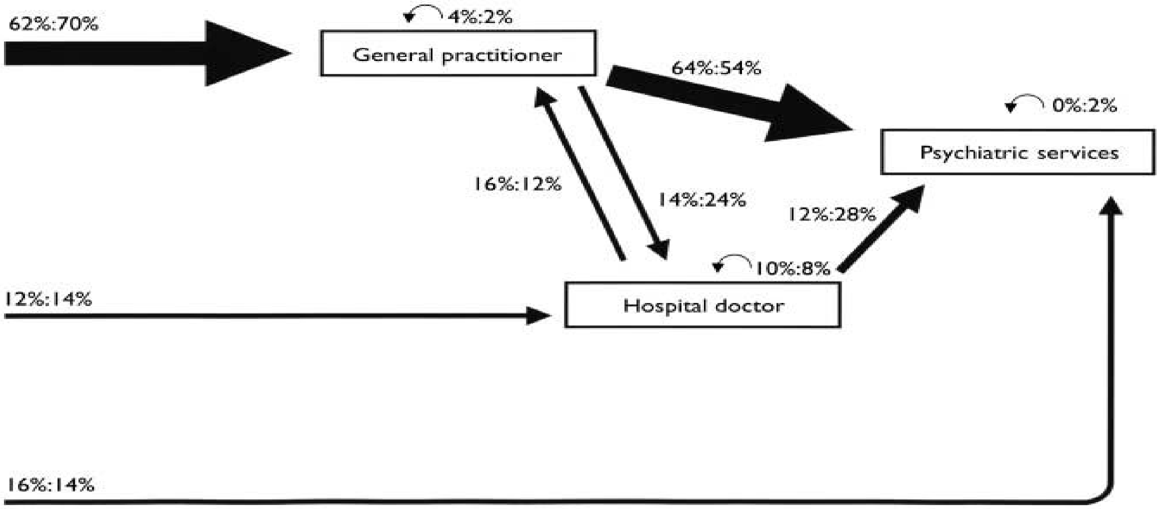


Figure 1.1. Pathways to psychiatric care in Sofia and Tirgu Mures. Percentage of those taking each step in Sofia and Tirgu Mures respectively for carers involved in more than 5% of pathways. (Curved arrows above carer boxes indicate recursive pathways, where patients have gone from one to another of the same type of carer.)

General practitioners played a substantial but less prominent role in Belgrade, Bucharest, Iasi, Strumica and Zagreb (Fig. 1.2.). In contrast to Sofia and Tirgu Mures, individuals in these five centers made more frequent use of direct access to psychiatric services (32 – 46%). Within this group there are some notable variations, such as the low use of hospital doctors in Bucharest and Strumica, the involvement of the police in 12 % of cases in Bucharest and Iasi, native or religious healers in 10% in Strumica and priests in 6% in Iasi; 10% of patients in Belgrade and 30% of those in Bucharest had seen another psychiatrist before they arrived at the study psychiatric service.

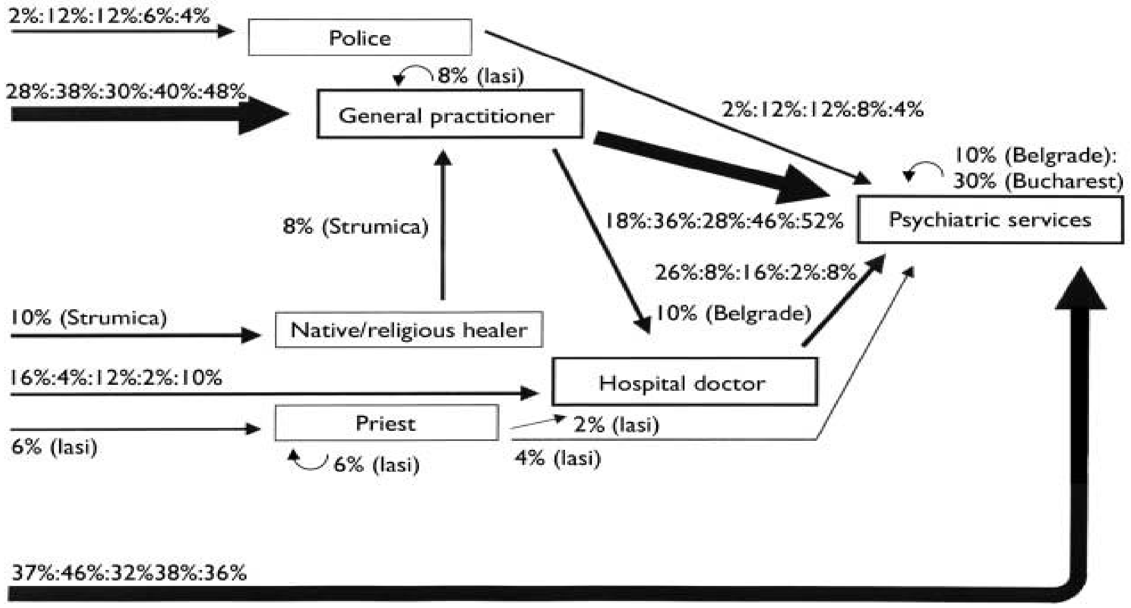


Figure 1.2. Pathways to psychiatric care in Belgrade, Bucharest, Iasi, Strumica and Zagreb. Percentage of those taking each step for each centre respectively, for carers involved in more than 5% of pathways. Steps occurring in only one or two centres are indicated as a single figure followed by the centre name in brackets. (Curved arrows above carer boxes indicate recursive pathways, where patients have gone from one to another of the same type of carer.)

Entry to psychiatric services in Tirana is almost exclusively through hospital doctors and direct access, with a few patients arriving via community / specialist nurses and native or religious healers (Fig. 1.3.). General practitioners are not shown in Fig. 1.3. because they were involved with only 2% of participants.

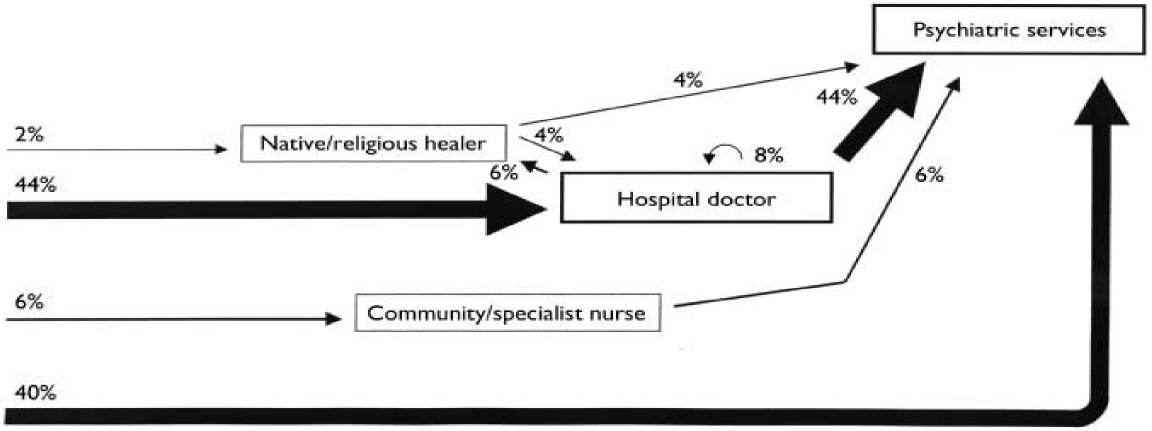


Figure 1.3. Pathways to psychiatric care in Tirana. Percentage of those taking each step for carers involved in more than 5% of pathways. (Curved arrows above carer boxes indicate recursive pathways, where patients have gone from one to another of the same type of carer.)

Subsequent results are based on the ICD-10 diagnostic groups, with data presented for those centers with the largest number in the relevant groups. In all centers combined, more than half of those with schizophrenia made direct contact with psychiatric services and less than a quarter first sought care from a general practitioner (Table 1.2.). Direct access was less frequent among those with other disorders. More participants with schizophrenia had a previous psychiatric history than those with other diagnoses, but previous history was not significantly associated with the choice of the first career and did not account for the greater use of direct access among those with schizophrenia.

Table 1.2. Number of first carers according to diagnosis and centre (for centres with largest numbers in the diagnostic group)

	New patients with the diagnosis n	New patients who first sought care from each type of carer			
		General practitioner n (%)	Hospital doctor n (%)	Police n (%)	Psychiatric services n (%)
Schizophrenia					
Bucharest	13	3 (23)	0 (0)	1 (8)	9 (69)
Iasi	13	1 (8)	1 (8)	2 (15)	7 (54)
Strumica	15	2 (13)	0 (0)	2 (13)	10 (67)
Zagreb	15	7 (47)	0 (0)	0 (0)	7 (47)
All centers combined	64	14 (22)	3 (5)	5 (8)	36 (56)
Other psychotic disorders					
Belgrad	14	3 (21)	0 (0)	1 (7)	6 (43)
Iasi	11	5 (46)	1 (9)	1 (9)	2 (18)
Strumica	12	6 (50)	0 (0)	0 (0)	4 (33)
All centers combined	60	26 (43)	3 (5)	5 (8)	18 (30)
Mood disorder					
Sofia	19	13 (68)	1 (5)	0 (0)	4 (21)
Tirana	17	1 (6)	6 (35)	1 (6)	6 (35)
All centers combined	93	40 (43)	15 (16)	2 (2)	28 (30)
Neurotic disorder					
Belgrad	23	11 (48)	4 (17)	0 (0)	6 (26)
Sofia	21	11 (52)	4 (19)	0 (0)	3 (14)
Tirana	22	0 (0)	10 (46)	0 (0)	10 (46)
All centers combined	93	39 (42)	23 (25)	0 (0)	24 (26)
Substance misuse					
Bucharest	12	4 (33)	1 (8)	1 (8)	6 (50)
Targu Mures	11	6 (55)	1 (9)	0 (0)	3 (27)
All centers combined	42	16 (38)	3 (7)	4 (10)	18 (43)

First carers varied between centers for schizophrenia (P=0.001), mood disorder (P<0.01), and neurotic disorder (P<0.01). More than two-thirds of those with schizophrenia in Bucharest and Strumica went directly to the psychiatric services compared with about half of those in Iasi and Zagreb. In Zagreb half of those with schizophrenia first went to a general practitioner compared with only 10% in Iasi and Strumica. Police were the first source of care for 15% of those with schizophrenia in Iasi and 13% in Strumica.

Those with mood or neurotic disorders often visited general practitioners first in Belgrade and Sofia, whereas in Tirana the most frequent first carers were hospital doctors or the psychiatric services. Police were rarely involved with those with mood or neurotic disorders.

In all centers combined, the median total duration of time from the onset of main problem to arrival at the psychiatric service were shorter for those with schizophrenia and other psychotic disorders compared with neurotic disorders and substance misuse (P<0.001) (Table 1.3.). For individual diagnostic groups, the total duration of problems did not differ significantly between centers. There were significant differences between centers for the duration before seeking care for those with other psychotic disorders (P<0.05; shortest durations in Zagreb and Bucharest) and for mood disorders (P<0.05; shortest durations in Iasi and Strumica).

Table 1.3. Durations (weeks) on the pathway to care according to centres and diagnostic groups.

	Duration of main problem *Median (interquartile range)*	**Time from onset of problem to first of problem to first seeking care** *Median (interquartile range)*	**Time from first seeking care to arrival care to arrival at psychiatric services** *Median (interquartile range)*	**Time from first seeking care from GP to arrival at psychiatric services**[1] *Median (interquartile range)*	**Time from first seeking care from hospital doctor to arrival at psychiatric to arrival at psychiatric services**[1] *Median (interquartile range)*
Schizophrenia					
Bucharest	3 (1-11)	3 (1-11)	0 (0-1)	-	-
Iasi	5.5 (2-11)	2.5 (1-8)	0 (0-3)	-	-
Strumica	6 (1-10)	4 (1-8)	0 (0-2)	-	-
Zagreb	5 (3-6)	2 (0-3)	3 (3-4)	-	-
All centers combined	5 (2-8)	2 (1-6)	0 (0-3)	2 (1-4)	2 (0-48)
Other psychotic disorders					
Belgrad	8 (4-24)	3.5 (0-18)	0.5 (0-4)	-	-
Iasi	4 (2-8)	3 (1-4)	2 (0-5)	-	-
Strumica	6.5 (4-9)	4 (2-7)	2 (0-5)	-	-
All centers combined	6 (3-11)	3 (0-5)	2 (0-4)	2 (1-6)	3 (0-4)
Mood disorder					
Sofia	12 (8-34)	10 (4-12)	2 (0-3)	2 (0-3)	-
Tirana	8 (2-16)	4 (1-12)	0 (0-1)	-	-
All centers combined	7.5 (3-15)	4 (2-12)	1 (0-3)	2 (1-6)	2 (0-5)
Neurotic disorder					
Belgrad	24 (8-28)	18 (3-24)	2 (0-6)	6 (4-24)	-
Sofia	20 (4-44)	4 (2-26)	3 (0-14)	3 (0-4)	-
Tirana	8 (3-26)	4 (1-19)	0 (0-1)	-	-
All centers combined	14 (4-27)	4 (1-19)	1 (0-6)	4 (1-11)	3 (1-12)
Substance misuse					
Bucharest	80 (0-202)	80 (0-201)	0 (0-0)	-	-
Targu Mures	4 (0-52)	4 (0-52)	0 (0-1)	-	-
All centers combined	9 (1-56)	7 (1-55)	0 (0-1)	1 (0-2)	0 (0-0)

[1] *No data presented for centres with counts of 12 or less*

The median time between first care seeking and arrival at the psychiatric services was 3 weeks or less for all diagnoses. Those who had seen a general practitioner or hospital doctor were typically referred to psychiatric services within a median of 2 or 3 weeks. In Belgrade there was a tendency towards a longer median duration after seeing a general practitioner (6 weeks) but this was not statistically significant.

The most common initial presention factors to the first career were psychotic (24%), depressive (19%), somatic (17%), and anxiety (12%) symptoms. This pattern had changed by the time individuals presented to the mental health services, with a greater proportion of psychotic

(31%) and fewer somatic (10%) symptoms. Interpersonal problems and suicide attempts were infrequent at all centers (6% or less).

In all centers combined, approximately half of of the new patients have been offered a treatment by their general practitioner, most often a sedative or hypnotic. Those with schizophrenia or other psychotic disorders were more likely to have been offered a treatment by their general practitioner than those with other diagnoses. This treatment was most often antipsychotic medication (24%) or a sedative (20%). Nevertheless, 40% have not often been offered any treatment by the general practitioner.

Mood, neurotic and substance misuse-related disorders had similar previous treatment profiles in all centers combined: over half had received no treatment from the general practitioner and 20 – 33% had been prescribed sedatives or hypnotics. Antidepressants were seldom prescribed to those with mood disorders (5%) and neurotic disorders (8%); they were prescribed almost equally to those with schizophrenia and other psychotic disorders (4%).

- **Discussions**

This study was the first project of the E-EPSI group, initiated during the attendance of the authors at the Berlin Summer School 2002 and supported by a grant from VolkswagenStiftung Hannover. It is the first serious scientific collaborative effort in these countries since the wars of the 1990s. The study was carried out with minimal resources, relying on the voluntary contributions of all concerned. The pathways study is not a comprehensive epidemiological investigation but can rapidly provide meaningful insights into the functioning of mental health services. This study has also consolidated the E-EPSI group and inspired future efforts to build an evidence base for the development of mental healthcare in Eastern Europe.

This study has some clinical implications:

- Completion of this research marks a successful starting point for evidence – based mental healthcare in the region
- In six centers, more than half of new patients made a direct approach to psychiatric services and general practitioners had a limited role as ‘gatekeepers’ indicating the need to review and change the system of care for the mentally ill.
- General practitioners had often provided no treatment for new patients arriving at psychiatric services; the most common treatments were sedatives or hypnotics; antidepressants were rarely prescribed, indicating the need for additional training of general practitioners.

Also, there are some limitations of the study, such as:

- The sample size is modest and limits the power of comparisons for diagnostic groups.
- Organizational differences between centers limits the direct comparison of all new patients between centers.
- Self-reporting without confirmation from contemporary records may be subject to recall bias.

Pathways

The study has demonstrated that three models, determined by the extent to which general practitioners, hospital doctors and direct access are used, can represent pathways to psychiatric care in Eastern Europe. Direct access was the route for more than one-third of new patients in six centers. Irrespective of diagnosis, general practitioners played a limited role in the pathways to psychiatric care. A small proportion of patients consulted general practitioners; the only treatment provided by general practitioners was sedatives and hypnotics. Many factors contributed to this and included: lack of training and experience in psychiatry in primary care, absence of incentives, poor communications between the general practitioners, availability of medication and regulations limiting the autonomy of general practitioners in managing mental disorders. If mental health is to be integrated into primary care, then an educational approach is more likely to succeed if a broader complex of factors is also addressed through the formal inclusion of mental health as a component of primary care and the further development and implementation of evidence-based national programs for mental health. Factors limiting the integration of mental health-care into general healthcare and interventions to overcome them have been described by Sartorius in 1999 (19).

Family involvement

Families and friends most often suggested seeking care, particularly if there were psychotic problems or behavioral disturbance with a risk to self or others. Families appear to be willing to help those with an illness but seek help when socially disturbing symptoms become prominent. If community mental healthcare is planned, then it will be important to realize the potential positive role of families through public education and partnership between mental health professionals and the families of people with mental illness.

Variations between centers

Organizational differences account for much of the variation in proportions of mental disorders between centers. The out-patient-based service in Sofia was established recently and most individuals with severe mental illness continue to attend the City State Psychiatric Dispensary; hence the low rates of schizophrenia and other psychotic disorders. In contrast, other centers such as Bucharest, Iasi and Zagreb recruited new admissions to acute psychiatric wards with relatively high rates of schizophrenia and low rates of neurotic disorders. In Strumica, general practitioners are ‘gatekeepers’ for patients with neurotic disorders, and relatively few are referred to the psychiatrist; in Belgrade there are psychotherapeutic treatments available which attract such referrals. In the three Romanian centers there are no special units for alcohol dependence, which is treated in psychiatric hospitals. Primary care is not involved in care-seeking pathways in Tirana, and therefore the mental health service itself manages a relatively high proportion of patients with mood and neurotic disorders (78%). The pathways in some centers included routes that reflect their individual circumstances. Native healers are popular in Strumica, particularly among the rural population. Bucharest retains six mental health laboratories from the communist period, and psychiatrists from these public institutions may refer to the study psychiatrists (hence the 30% recursive pathways due to mental health laboratory psychiatrists as the previous careers). In the east of Romania, people are more religious and more often seek care from a priest, whereas in the west there is a mixture of cultures, including Romanian, Hungarian, German and Romas.

Durations and previous treatment

The time between first seeking care and arrival at mental health services for mood and neurotic disorders was generally short, so there was insufficient time for first-line treatments to be tried. Similar results are noted by a recent study, finding that the median time to presetantion in Eastern Europe is around 3 months (20). General practitioners were more likely to prescribe sedatives or hypnotics than other treatments. Antidepressants were prescribed to very few participants and were almost as likely to be given to those with schizophrenia as those with depression. This pattern may arise in part from the constraints imposed by prescribing regulations and by the limitations imposed by the ’positive’ list; there may also be reservations of both patients and doctors to the use of ‘strong’ medicines (such as antidepressants or antipsychotics), with connotations of severe mental illness, in favor of ‘mild’ medicines (such as sedatives or hypnotics), which are less taboo. These patterns of prescribing are not unique; they do not differ greatly from those reported from several centers in the original World Health Organization pathways study (9), nor in a Eastern Europe based study in which less than one third of general practitioners considered their job to treat depression (21).

In Bucharest the longer duration before first seeking care for substance misuse may be related to the increasing numbers of drug users, especially of a younger age. There is also a negative attitude towards illegal drug use, which the authorities consider to be a criminal issue, and this renders treatment services less likely to be available or used. This is controversial as one review study finds that over 21 studies indicate that the police have arrested about one quarter of patients with mental disorders. The review also notes, that similar to our results, for one in ten patients the police is involved in their first presentation to a mental health professional. The same study also notes that the results from 13 studies indicate that one percent of police dispatches involve mentally ill patients (22).

A recent systematic review citing this paper, found similar results, on the base of other 25 articles incuded in the review process. Their results show that there are limitations in general practitioners’ capacity to identify and treat mental health issues. An important factor for the initial rrecognition of mental health problems is the patient’s social nethwork. (23) A similar study in the Southest of Europe found that the limitations that general practitioners had in identifying and treating depression are to do with the patient’s unwillingness to discuss their symptoms and their reluctance to be reffered to a psychiatrist. Other reasons refered to the limited time allowed for a consultation and the barriers in prescribing psychiatric medicine. Most of the general practitioners who participated in this study acknowledged that it is their responsibility to recognize depression but only a minority considered that it is their mandate to treat it. (21) One Canadian study found that general practitioners’ involvement was greater in areas in which patients had a larger number of health care services (24).

Considering patients’ reluctance to seek specialist care, a study that took place in Eastern Europe found that the stigma associated to mental illness was the number one impending factor in all of the countries participating in the study. The second and third places were occupied by feelings and lack of knowledge, with interchangeable positions dependind on the country. Another concerning issue that this study found is the fact that in Romania, 90% of patients lacked a caregiver and the social support necessary for seeking medical attention. (25). The same research team found in 2018 that the average profile of a new psychiatric patient was female, married, older that 40 years with no mental health history and of average economic status. The same study also found that the currently avaible treatment options can also influence the patient’s willingness to seek help (20).

Surmounting research is recently emerging from developing countries on the pathways issue. While our findings show that, a minority of patients are refered to psychiatrists by other alternative caregivers such as religious figures, studies from Africa report a different statistics. In Ghana, although the majority of the population seeks out formal medical care, faith based and traditional healers were highly represented. Interestingly in this study is the fact that care seeking is inversely proportional with education level (26). Further implications of this can be found in the work of Ikwuka et al. Their study based in Nigeria found similar results regarding the high prevalence of spiritual and traditional pathways and further more, the last two being preferred by patients with low educational level (27). Similar results are found in Saharan Africa, in Egypt (28, 29) and in Tunisia (30). High representation of non-formal sources are reported in Singapore as well (31). These results are relevant in the socio-economical context of Romania, considering that a large rural part of the country has educational and economical levels similar to a developing country. Community psychiatry can focus its efforts in those areas by working together with the local figures of non-formal care in order to bring medical attention to those in need.

A key strength of this study was that it used the same methodology and standard encounter form in all centers. Trained and experienced psychiatrists completed the encounter forms and made diagnoses using the ICD-10 classification. However, diagnoses were not based on a standardized diagnostic interview and algorithm. The sample size of 50 participants per center is modest, but sufficient to give a representation of pathways to care and some inter-centers differences. The response rate was high in all centers, so minimizing selection bias. Recall bias might have occurred as all information was based on self-report, and defining the onset of the main problem could be influenced by cultural factors, including the strong stigma associated with mental illness.

Although the sample and its size restrict the extent to which firm conclusions can be drawn from this study, there are clear indications for areas of further research. These include questions about the most effective and efficient target disorders for the specialist mental health services and the balance between hospital and community care. More apparent are questions about the role of primary care in mental healthcare in both the detection and management of mental disorders, and the barriers and solutions to incorporating mental health into primary care. The police and traditional healers could be trained to recognize mental illness in some centers.

The study has highlighted the important role of family and friends and suggests a significant impact of the stigma associated with mental disorders. These factors suggests the development of a public mental health approach and exploration of the best ways to collaborate with families. The pathways study has posed many questions, but if further progress is to be made there needs to be a shift to a more evidence-based culture and a reduction of the stigma associated with mental illness.

1.3 Researches regarding ways to access psychiatric services in Romania

A. Background

The number of psychiatric hospitals has dropped from 38 in 2006 to 36 in 2019 (Romanian Ministry of Health, 2019) (32). There are also 4 high security psychiatric hospitals and 91 psychiatric departments in the general hospitals. The total number of beds for patients with both acute and chronic mental disorders is 16.073 (32). Nonetheless, the number of psychiatrists is below the EU requirements. In 2019, the Romanian Ministry of Health analyzed all the psychiatric hospitals and departements across the country and concluded that the centres with chronic mental illness patients were overcrowded, whereas those dealing with acute cases of mental illness, were occupied at a 60% rate, a fact that raises questions about the necessity of a better management of the mental health system in Romania (32). Even though there are ways to access psychiatric services in Romania, people are often reluctant in doing so for reasons regarding their cultural beliefs, fear of stigma being one of the most important factor keeping them away from seeking professional help.

B. Published paper in this field

Part of the extensive European multicentre study and using the recommended methodology of WHO in "WHO Study of Pathways to Care" (9), in 2005 authors published a study which purpose was to highlight ways to access psychiatric services of patient new cases and the role of general practitioners in the management of mental disorders in Romania.

Mihai A, Iosub D, **Szalontay A**. Cai de acces la serviciile psihiatrice din Romania. *Revista Romana de Psihiatrie* 2005; VII (1-2): 31 – 36.

- **Introduction**

The functionality of the public health system also depends on the pathways to care to available psychiatric services. Conducting studies that highlight ways of access to care is useful both for planning psychiatric services and for improving training methods for medical staff.Knowledge of referral mechanisms in and from other health services or social care sectors is proving useful in public health management. The purpose of this study was to collect data on the ways of access to psychiatric services in Romania, data that the competent forums use in organizing mental health services and to formulate recommendations for postgraduate training of doctors of different specialities, especially family doctors.

- **Material and Method**

Three university centres from Romania participated in this study, Bucharest, Iasi and Tg Mures, enrolling 150 patients. The study was conducted simultaneously in the three centres during February – May 2003. All new patients sent to these psychiatric services, if they accepted entering the study were included until the target number of 50 patients per centre had been reached. "New sent" patient was considered the patient who did not refer to mental health services the year before the study. The patients included in the study were interviewed on the basis of WHO-recommended "inclusion form" translated into Romanian. The psychiatrist who evaluated the patient completed the questionnaire, which lasts for 5 – 10 minutes. The questionnaire provides information about the patient's socio-demographic characteristics as well as about other therapeutic trials used before being consulted in the mental health service concerned. The profession of each person involved in the therapeutic route, the duration of the period from the occurrence of the symptoms to each consultation, the most important symptom of the clinical picture presented, the treatment provided and the time required for access to the services were recorded and compared to other similar international studies (9-15).

The psychiatric diagnosis according to ICD-10 was made by a psychiatrist upon inclusion into the study (WHO, 1992) (18). The "access ways" followed by patients in each evaluated university centre were combined and a chart was made representing the routes followed by patients to solve their mental health problem. The percentage of patients who followed each route as well as the duration of the time from the onset of the psychiatric condition to access to psychiatric service was evaluated. The delay in diagnosis and the establishment of specialized treatment was analysed comparatively with the diagnosis and symptoms presented. Statistical analysis was performed using SPSS 2003.

- **Results**

The demographic characteristics of the study group consist of 55.33% women, and an average age of 41, with the predominant young age in Iasi (35 years old). The most common marital status was "unmarried" in Iasi and Bucharest (42%, respectively 46%). In Bucharest most of the patients were below the social average (70%) (Table 1.4.).

Table 1.4. Demographic data on patients in each centre

			Marital status			
	Women (%)	**Average age**	**Unmarried**	**Married or partnership**	**Separated, divorced, widow**	**Below the average social position**
Bucharest	54	41	42	34	24	70
Iasi	54	35	46	34	20	22
Tg. Mures	58	46	24	48	28	36
Statistical significance	NS	<0.001	<0.001	<0.001	NS	<0.001
Mean	55	41	37	39	24	43

The most common diagnoses in all three combined centres were affective disorders and those caused by the substances misuse each with 21%, followed by schizophrenia by 20% and other psychotic disorders 15%. The final distribution does not reflect the situation in any of these centres, this varying significantly between them (Table 1.5).

Table 1.5. Psychiatric antecedents, current diagnosis, and percentage of patients who have requested care in each centre

	Percentage in each ICD-10 diagnostic group					**Personal psychiatric antecedents**	**Patient seeking care**
	Schizophrenia[1]	**Other psychotic disorders**[2]	**Affective disorders**	**Neurotic disorders**[3]	**Substance abuse**[4]		
Bucharest	26	12	14	4	24	38	32
Iasi	30	22	24	0	16	64	15
Tg.Mures	4	10	26	24	22	46	52
Mean	20	15	21	9	21	49	33

1. *Schizophrenia and schizoaffective disorders*
2. *All other diagnoses of psychotic disorders excluding schizophrenia and schizoaffective disorders*
3. *Neurotic disorders, somatoform disorders or other stress-induced mental disorders*
4. *Mental and behavioral disorders caused by the use of a psychoactive substance*
5. *In Bucharest 12% of the patients had psychiatric disorders of organic origin*

This difference between centres reflects the difference between the psychiatric services analysed – emergency departments (Iasi and Bucharest) or psychiatric wards with hospitalization through programming – Tg. Mures – and cannot be interpreted as a difference in the prevalence of mental illness.

On average, half (49%) of the "new patients" had a personal psychiatric history, the highest rate being in Iasi (64%). For all types of diagnosis, family members were the ones who first suggested psychiatric consultation, much more frequently than the patient himself did or any other group of people involved in his care. The suggestion of first consultation came from others in 70% of cases for patients who had psychiatric symptoms, in 100% of cases for those with physical or verbal aggressivity or other behavioural disturbances and in 90% of cases for those with suicidal attempts. For the other symptoms, the treatment suggestion came from others as well as from the patients themselves. About 75% of those with schizophrenia the initial treatment suggestion came from others and in 60% of cases for the other diagnostic groups.

In all centres combined, 86% first consulted physician, a general medicine specialist in 46% of cases or directly a psychiatrist in 30% and much less often (10%) other specialist doctor. These modalities of access to healthcare vary from centre to centre.

Tg. Mures is the only centre among those studied where there is a significant number of referrals from general practitioners, to doctors of other specialities or vice versa. It is noticed that only half of the patients attended by doctors of other specialities receive referrals to psychiatric services, the rest being sent to general practitioners or other specialities without their psychiatric condition or avoiding the referral to psychiatric care services.

General practitioners had a substantial but not so important role in Bucharest and Iasi (38 and 30% respectively) where an similar percentage of patients preferred direct access to psychiatric services (32 and 46% respectively). 30% of the patients from the study had previously received at least one psychiatric consultation. More than two-thirds of patients diagnosed with schizophrenia in Bucharest come directly to psychiatric services compared to half of those in Iasi. 10% of patients with schizophrenia in Iasi have been consulted by a general practitioner and 15% reach psychiatric services through the police. “New patients” with affective and neurotic disorders are often sent to psychiatric services by family doctors or other specialists, police being rarely involved.

The time elapsed between the first medical check-up and reaching the studied psychiatric service was 3 weeks or less for all types of diagnosis. The most common symptoms for which patients have been consulted were psychotic (24%), depressive (19%), somatic (17%), anxiety (12%) and suicide attempts (6%). In all the combined centres about half of the patients received treatment from family doctors, most commonly sedative or hypnotic drugs. Patients with schizophrenia were given more frequent treatment than other diagnostic groups, representing antipsychotics in 24% of cases or sedatives in 20%. 40% of patients with schizophrenia seen by the family doctors received no treatment and 20 – 30% received sedative or hypnotic drugs. Antidepressants were prescribed in 5% of these cases.

The access paths specific to only one centre were mentioned using the percentage and the name of that centre. Figure 1.4 indicates the percentage of patients using a particular access path, more than 5% were considered. The curved arrows indicate the recurrent paths where the patient goes from one doctor to another of the same speciality in search of service satisfaction.

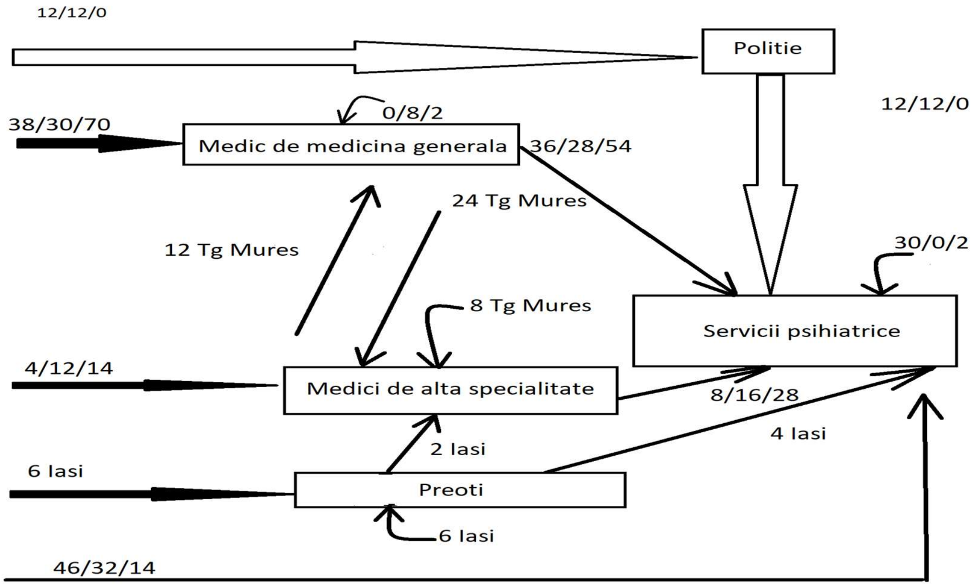


Figure 1.4. Percentage of patients using a particular access path, more than 5% were considered.

In all combined centres more than half of patients with schizophrenia have directly accessed psychiatric services and less than a quarter were first seen by the family doctor. Direct access was less common for other mental disorders. More patients with schizophrenia had a psychiatric history compared to other diagnostic categories but the presence of psychiatric antecedents was not statistically significant in choosing how to access psychiatric services.

- **Discussions**

This study does not claim to be an epidemiological study, but can quickly provide information on pathways to care to mental health services in the studied centres.

In all the combined centres, the average duration from the onset of symptoms to access to psychiatric services was relatively short compared with the literature (3 – 9) in all the diagnostic groups: 5 weeks for schizophrenia, 6 for other psychotic disorders, 7,5 for affective disorders, 12 for neurotic disorders and 9 weeks for substance misuse.

We noticed the limited implication of doctors of other specialities in Bucharest and the important involvement of the police in Bucharest and Iasi (in 12% of the psychiatric cases in each centre), similar to the results of other studies (22). The involvement of priests in Iasi in 6% of cases makes access to psychiatric services more difficult because all patients who have recourse to religious services have been recalled or turned to another priest and only then sent to psychiatric hospital or other speciality, delaying diagnosis and the establishment of treatment. This issue is furthermore investigated in recent articles (26-31). The higher percentage of cases who reach psychiatric services in Iași compared to the other centers can be as the studies show, due to the lower economic and educational levels in the region compared to the capital, Bucharest and to Tg. Mureș, an enthnically diverse and westernalized region.

Because the study evaluates only those who have reached a psychiatric service it can be assumed that a certain number of patients remain undiagnosed and untreated. According to this study, the main pathways to care in these centres are represented by referrals from family doctors, doctors of other specialities and direct access to psychiatric services. There is a limited role played by general practitioners in psychiatric treatment – most patients do not receive any treatment. Many factors could be the cause of this: limiting the autonomy of general practitioners in the management of mental illness by laws and rules, the availability of psychotropic medication, lack of training and experience in the administration of psychiatric treatment, absence of initiative, lack of communication between the general practitioner and the psychiatrist. These factors are evidentiated in the work performed by Duric et al. 2019, which additionally states that the majority of the general practitioners interviewed don't consider that it is their job to treat for psychiatric illnesses, only to recognize them (21).

Educational measures are one of the ways in which mental health could become a component of primary care as well as the implementation of national mental health programs. Factors limiting the introduction of mental health into health care in general and the necessary interventions were described by Sartorius in 1999 (19).

Families and friends are frequently involved in asking for the initiation of psychiatric treatment, especially when psychiatric disorders, especially when psychotic and behavioural disturbances pose a risk to oneself and others. The Bucharest and Iasi centres recruited patients hospitalized in emergency departments, which explains the increased rate of patients with schizophrenia and the relatively low numbers of those with neurotic disorders, similar to the results found by Assad et al. 2016 and Khiari et al. 2019, although in the last example, psychotics symptoms are reasons to seek attendance from spiritual and religious healers (29,30).

Alcohol-addicted patients are often treated in psychiatric hospitals and not in specialized centres, which explains the relatively high number of those admitted with the diagnosis of “substance abuse”. Most patients with schizophrenia and schizoaffective disorders have directly accessed psychiatric services regardless of whether the episode presented was the first, or whether they have previously had similar episodes.

The high stigmatization level is highlighted by the relatively low collaboration with the family doctor. Even in Tg Mures where 70% of patients call for first consultation the family doctor, their referral to psychiatric services were postponed in many cases, frequently asking for neurological consultation instead of psychiatric. This rationale was later confirmed by Tritinica et all, in 2016 (25).

The duration from the onset of symptoms to access to psychiatric services is still relatively short, due to the lack of effective treatment and the persistence of symptoms after these interim consultations. The treatment provided by family doctors consists often of sedative and hypnotic drugs. These models of therapeutic approaches are also imposed by the constraints of prescribing rules and prescription lists that the family doctors can prescribe, as well as the retentions that GPs have in prescribing so-called “strong” drugs such as antidepressants and antipsychotics that are commonly associated with severe psychiatric disorders and the preference for so-called “light” medications such as sedatives and hypnotics. These prescribing patterns are similar to those described by Gater et al in 1991 (9). In Bucharest the relatively high duration from first contact with medical services to access psychiatric wards for drug abusers can be correlated with the increase in the number of drug users at very young age as well as with the increasing degree of social acceptance of using “legal” drugs like alcohol, tobacco and psychotropic medication.

The study group, although modest, offers the opportunity to graphically represent the way of accessing the psychiatric services taken into study, as well as observing some differences between these centres. The selection rate was high in all centres, minimizing errors. These could have occurred due to the fact that the information was obtained by reporting by the members of the patient’s family or the patient, and the presentation of the symptomatology can be influenced by cultural factors as well as the strong stigmatization associated with mental illness. A strong point is the fact that all centres used the same methodology and the same enrolment form, its application and diagnosis being performed by well-trained psychiatrists. The size of the study group, however, restricts the possibility of obtaining firm conclusions but raises questions about the place of primary care for mental health, the role in the detection and management of psychiatric disorders. The study also highlights the role of friends and family in stigmatizing mental illness.

1.4 Researches regarding prescribing practices in psychiatric hospitals

A. Background

Principles of prescribing practices are available all over the world but in our clinical practice we know we prescribe for individual patients and also we take into account all pertinent factors. Treatment needs to be evidence-based and prescribed so that it takes into account all of the side effects and their impact on the quality of life of patients. Physicians can support their decisions with the Clinical Practice Guidelines and also take into account the patients’individual characteristics and expectations regarding the outcome of their disease. Nonetheless, when it comes to prescribing psychotropic medication, Nguyen et al (2019) found that clinical practice doesn’t always align with the guidelines, one of the reasons being that psychiatry doesn’t rely on blood markers like other clinical specialities, to make decisions (33). Furthermore, not all the drugs are available worldwide, which makes it impossible to transform research into clinical practice (33). There are always subtle ethical, spiritual, bio-psycho-socio-cultural systems of influence and each of these components, in turn, have an impact on each other (34). Prescription is not first pharmacological. Multiple factors can have an impact on pharmacological choices, responsiveness to medication and safety issues.

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which intended to evaluate the use of polypharmacy and difference of prescribing among five countries in the Eastern Europe.

Jordanova V, Maric NP, Alikaj V, Bajs M, Cavic T, Iosub D, Mihai A, **Szalontay A,** Sartorius N, Prescribing practices in psychiatric hospitals in Eastern Europe. *European Psychiatry* 2011; 26 (7): 414 - 418. **IF 2011 = 2.766**

- **Introduction**

There are great variations in the way psychotropic drugs are prescribed across the world. Despite the emerging evidence of the advantages of psychopharmacological monotherapy, multiple drug prescribing is still common in clinical practice of many countries (35). A multicentre survey of the prescription of antipsychotic drugs for hospitalized patients in the UK (36) found that nearly 50% were receiving more than one antipsychotic drug. Holloway found that overprescribing of sedatives and anticholinergic drugs was common practice in the UK (37). A recent survey in Ireland also revealed high prevalence of prescribing of benzodiazepines and hypnotics (38). An Austrian survey found that a quarter of psychiatric patients received three or more psychotropic agents (39). A US survey found that antipsychotic polypharmacy was low in the year after the initiation of therapy and that polypharmacy was more common in patients with indicators of more severe mental illness (40).

There is very limited evidence about the prescribing practices in psychiatric care in Eastern Europe. Cross – sectional survey of prescribing habits provides a quick, global estimation of treatment practices. This study was conducted by the eastern European Psychiatric Scientific Initiative (the EEPSI), a research network of psychiatrists in Eastern Europe that aims to develop evidence-based research in the region (41). The main objective of the study was to investigate the patterns of prescribing of psychotropic drugs in psychiatric hospitals in five countries in Eastern Europe.

- **Material and method**

We conducted a one day census in psychiatric hospitals in eight centres: Belgrade in Serbia, Bucharest, Iasi and Targu Mures in Romania, Strumica in Macedonia, Tirana in Albania and Zagreb in Croatia. The census included all patients (aged 18 – 65 years) that were hospitalized in participating centres at the time of the survey. The study obtained ethical approval before the fieldwork was conducted. A total sample of 1304 patients was examined. The naturalistic design of this study has limitations but is more reflective of the real-world practice.

The data was extracted from clinical records and medication charts for each patient across the centres. We recorded data about socio-demographic characteristics, duration of current hospitalisation and clinical diagnosis using the tenth edition of the International Classification of

Diseases (ICD-10) (18). The data about prescribed psychotropic drugs included the generic and trade names of each drug prescribed in the 24 hour period of the survey. General data about numbers of available beds, staffing levels, clinical and technical facilities of each centre was collected using the European Service Mapping Schedule (ESMS) version 3 (42).

All psychotropic drugs were included in the survey:

- Antipsychotics;
- Antidepressive drugs;
- Benzodiazepines;
- Anxiolytics;
- Mood stabilizers;
- Anticholinergic drugs.

Diagnostic groups used for comparison were based on ICD-10 categories:

- Mental and behavioural disorders due to psychoactive substance use;
- Psychosis;
- Depression;
- Bipolar affective disorder (BAD);
- Anxiety;
- Personality and eating disorders.

Data was analysed with SPSS version 16 and SATS (SPSS Inc, Chicago, IL, USA).

The participating psychiatric services share a number of important characteristics. All are representative state institutions and the costs of treatment are covered by national health insurances. The patients in Belgrade were recruited from two different psychiatric hospitals, a large psychiatric hospital that serves Belgrade and its surroundings and (Belgrade – 1) and a university hospital (Belgrade – 2). The patients were recruited from inpatient wards and daycentre services. In Bucharest, patients were recruited from five adult inpatient units of the largest psychiatric hospital in Romania. In Iasi, the study was carried out at the university psychiatric hospital; patients were recruited from inpatient wards. In Strumica the patients were recruited from a psychiatric inpatient unit and an outpatient clinic that provides the only psychiatric service in the region. In Targu Mures, the study was conducted at a university psychiatric hospital; subjects were recruited from the inpatient service. In Tirana, patients were recruited from the inpatient wards at the university psychiatric hospital. In Zagreb, the study was conducted at the University Clinic of Psychiatry; subjects were recruited from the inpatient psychiatric service.

- **Results**

The demographic profile differed between centres (Table 1.6). The mean age was 45.8 years, with a younger average age in Tirana (37.1 years) and an older average age in Iasi (49.2 years). The duration of hospitalisation varied between centres, with patients in Belgrade – 1 having average duration of hospitalisation of 421.3 days. The most frequent diagnosis in all centres combined was psychosis (44.3%), followed by “other” mental disorders (22.4%) and depression (22.1%) (Table 1.7). The “other” mental disorders category included the ICD-10 diagnoses with low prevalence in our sample (personality disorders, substance misuse and eating disorders). The highest proportion of patients with psychosis was seen in Strumica, Belgrade-1 and Tirana (63.5, 59.2 and 57%, respectively). In Iasi, Targu Mures and Zagreb, the most frequent diagnosis was depression. Anxiety disorders were not commonly seen across the centres, apart from Targu Mures and Zagreb (22.9 and 16%, respectively).

Table 1.6. Demographic characteristics and duration of hospitalisation at each centre

Centre	Gender (male)	Age	DoH[a]
	N (%)	**Mean (95% CI)**	**Mean (95% CI)**
Belgrade – 1	260 (51.7)	46.5 (45.3 – 47.8)	421.3 (288.6 – 1131.2)
Belgrade – 2	43 (51.2)	45.3 (42.9 – 47.6)	37.3 (32.0 – 42.6)
Bucharest	112 (33.8)	46.6 (45.1 – 48.1)	26.1 (22.3 – 29.8)
Iasi	67 (60.9)	49.2 (46.9 – 51.4)	9.1 (8.2 – 10.0)
Strumica	33 (63.5)	38.4 (35.5 – 41.2)	193.5 (153.0 – 234.0)
Tg Mures	34 (48.6)	48.7 (45.4 – 52.0)	17.0 (15.5 – 18.5)
Tirana	51 (64.6)	37.1 (34.8 – 39.3)	18.4 (15.0 – 21.7)
Zagreb	33 (44)	45.1 (42.1 – 48.2)	15.1 (12.7 – 17.6)

[a] *Duration of hospital admission in days*

Table 1.7. ICD-10 diagnosis across centre

Centre	Depression	Anxiety	Psychosis	BAD[a]	Other
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Belgrade – 1	49 (9.7)	3 (0.6)	298 (59.2)	16 (3.2)	137 (27.2)
Belgrade – 2	21 (25.0)	2 (3.3)	32 (38.1)	6 (7.1)	22 (26.2)
Bucharest	109 (32.9)	25 (7.6)	116 (35.0)	25 (7.6)	56 (16.9)
Iasi	31 (28.2)	/	23 (20.9)	12 (10.9)	44 (40.0)
Strumica	3 (5.8)	2 (3.3)	33 (63.5)	5 (9.6)	9 (17.3)
Tg Mures	28 (40.0)	16 (22.9)	10 (14.3)	3 (4.3)	13 (18.6)
Tirana	15 (19.0)	1 (1.3)	45 (57.0)	16 (20.3)	2 (2.5)
Zagreb	32 (42.7)	12 (16.0)	21 (28.0)	1 (1.3)	9 (12.0)
Combined	288 (22.1)	61 (4.7)	578 (44.3)	84 (6.4)	292 (22.4)

[a] *Bipolar Affective Disorder*

The mean number of prescribed drugs was similar across centres (table 1.8). The mean number of drugs used in all centres combined was 2.8 (SD 0.9). Only 6.8% of patients received monotherapy. Forty-two decimal one percent of patients in all centres combined received three psychotropic drugs, while 23.2 received four or more drugs. None of the patients in Strumica was on monotherapy. Across other centres, monotherapy was used between 4.4 and 8.9%, apart from Iasi were 20.0% of patients received only one drug. Polypharmacy was also present in Iasi, where 25.5% of patients received three psychiatric drugs. None of the patients in Belgrade – 2, Strumica, Targu Mures and Tirana was medication-free. The use of polypharmacy was frequent across all diagnostic groups (Table 1.9). Monotherapy was rarely used for patients whose first diagnosis was depression or anxiety (6.6 and 5.0%, respectively). None of the patients with anxiety was medication-free, while 39.3% received three different psychotropic drugs.

Table 1.8. Use of polypharmacy across centres

Number of drugs	0	1	2	3	4 or more	Mean
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**(s.d.)**
Belgrade - 1	2 (0.4)	22 (4.4)	90 (17.9)	243 (48.3)	146 (29.0)	3.0 (0.8)
Belgrade – 2	/	7 (8.3)	25 (29.8)	33 (39.3)	19 (22.6)	2.8 (0.9)
Bucharest	4 (1.2)	19 (5.7)	98 (29.6)	117 (35.4)	76 (28.1)	2.9 (1.1)
Iasi	14 (12.7)	22 (20.0)	43 (39.1)	28 (25.5)	3 (2.7)	1.9 (1.0)
Strumica	/	/	9 (17.3)	31 (59.6)	12 (23.1)	3.1 (0.6)
Tg Mures	/	6 (8.6)	21 (30.0)	33 (47.1)	10 (14.3)	2.7 (0.8)
Tirana	/	7 (8.9)	39 (49.4)	31 (39.2)	2 (2.5)	2.4 (0.7)
Zagreb	1 (1.3)	5 (6.7)	20 (26.7)	33 (44.0)	16 (21.3)	2.8 (0.9)
Combined	21 (1.6)	88 (6.8)	345 (26.5)	549 (42.1)	301 (23.1)	2.8 (0.9)

Table 1.9. Use of polypharmacy across diagnostic groups

Number of drugs	0	1	2	3	4	>4
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Depression	3 (1.0)	19 (6.6)	91 (31.5)	124 (42.9)	46 (15.9)	6 (2.1)
Anxiety	0 (0.0)	3 (5.0)	23 (37.7)	24 (39.3)	10 (16.4)	1 (1.6)
BAD$_a$	1 (1.2)	3 (3.6)	20 (23.8)	36 (42.9)	21 (25)	3 (3.6)
Psychosis	12 (2.1)	16 (2.8)	113 (19.6)	261 (45.2)	165 (28.6)	11 (1.9)
Other	5 (1.7)	47 (16.1)	98 (33.6)	104 (35.6)	36 (12.3)	2 (0.7)

$_a$ Bipolar affective disorder

93.1% of patients with psychosis received antipsychotic treatment. 69.2%of patients with psychosis were prescribed one antipsychotic, 22.2% received two and 1.7% received three different antipsychotics concomitantly. In Strumica, 66.7% of patients with psychosis received three psychotropic drugs, while 27.3% were given four different drugs. In Belgrade – 1, 50% of psychotic patients received three and 33.6% received four different psychotropic drugs. In Belgrade – 2, 31.3 % of patients with psychosis received three and 34.4% were given four psychotropic drugs. In Tirana, 55.6% of psychotic patients received two, 26.7% three and 4.4% four different drugs. In Bucharest, 44% of psychotic patients received three and 26.7% were given four psychotropic drugs. Typical antipsychotics were given in 63.3% of psychotic patients. Atypical antipsychotics were prescribed to 40% of those with psychotics. Depot antipsychotics were given to 15.4% of psychotic patients. Antipsychotic polypharmacy continues at a high rate to affect patients with a diagnosis of schizophrenia in state psychiatric inpatients hospitals.

- **Discussions**

In a study published in 2016, Ortiz et al stated that the prevalence of antipsychotic polypharmacy was 18% (43). Study was to explore antipsychotic medication prescribing practices in a sample of 86034 patients discharged from state inpatients hospitals and to find the prevalence of patients discharged with no antipsychotic medication or antipsychotic monotherapy and on antipsychotic polypharmacy. Patients were prescribed antipsychotic polypharmacy primarily to reduce the symptomatology (43).

Patient factors may also contribute to prescription patterns. Some patients may not adhere to their medications as prescribed and as a consequence to experience significant psychotic symptoms. The outpatient psychiatrists may resort to antipsychotic polypharmacy (43, 44).

Even if a number of treatment guidelines recommend against the use of antipsychotic polypharmacy and there is a clear evidence that antipsychotic polypharmacy presents complications for the patient, risk of adverse effects, increased risk for metabolic disorders and complex medication regimens, however clinical factors, societal and patient factors can perpetuate the practice of antipsychotic polypharmacy (44-46).

Among those diagnosed with depression, 83.4% received an antidepressant. The SSRIs were given to 29.4% and other newer antidepressants to 46% of depressed patients. Older generations of antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) were prescribed to 29.1% of patients. Nineteen percent of patients with depression received two antidepressants concomitantly. In Strumica, Tirana and Targu Mures, depressed patients frequently received three different psychotropic drugs (66.7, 60.0 and 53.6%, respectively). In Bucharest, 19.3% of patients with depression received four different psychotropic drugs.

There is still little research to examine antidepressant prescribing practices. Studies were general in nature, focusing on prescribing trends over time and / or between physician disciplines. In a study published by Petersen et al in 2002 we found that 93% of clinicians indicated SSRIs as their first line preference. Mirtazapine (56%) was endorsed as most likely to be associated with weight gain, fluoxetine (57%) with sexual dysfunction, paroxetine (48%) with discontinuation syndrome (47). For the treatment of anxious, atypical and melancholic depression, SSRIs were the first choice of treatment (58%, 57% and 57%), and for depression with prominent insomnia, mirtazapine and nefazodone (31% and 27%) were the first choice of treatment (47). Among patients with anxiety disorders, 67.2% received an anxiolytic drug.

Benzodiazepines were given to 75.1% and antipsychotic drugs to 37.7% of those with anxiety. Antidepressants were prescribed to 82%, but SSRI were given to 36.1% of patients with anxiety disorders. In Targu Mures, one half of patients with anxiety received three psychotropic drugs. In Zagreb, 41.7% of patients with anxiety received three psychotropic drugs and 25% four different drugs. In Bucharest, 32% of patients with anxiety received three psychiatric drugs, while 24% were given four different drugs. Mood stabilizers were given to 77.4% of patients with BAD. Antipsychotic drugs were prescribed to 75% and atypical antipsychotics to 34.5% of those with BAD. One third of patients received anticholinergic treatment on a regular basis. Among patients with psychosis, 48.3% received an anticholinergic drug concomitantly with their antipsychotic treatment. Benzodiazepines were prescribed to 68.5% of all patients. Seventy-five percent of patients with psychosis and those with BAD received benzodiazepines.

Our study found high prevalence of polypharmacy across participating centres for all clinical diagnoses. Monotherapy in the treatment of psychiatric disorders is recommended by a number of guidelines, yet, only small minority of our patients received only one drug. Psychotropic prescribing deviated considerably from the recommendation by these guidelines. We found high prevalence of concomitant use of two or more antipsychotic drugs in patients with psychosis. This pattern was evident across all study centres. Our findings are in line with the prescribing surveys in Western European countries (48, 49). Taylor et al. found that conventional and atypical antipsychotics are commonly co-prescribed and the combination of a conventional antipsychotic and clozapine is a common practice (50). There have been reports that conventional antipsychotics are used in around a third of those receiving clozapine in some European countries (51). Similarly, Divac et al. (52) found that 68% of psychiatric patients in Serbia received two or more antipsychotic drugs concomitantly.

The evidence base shows that the routine use of combined antipsychotics are not more effective than a single antipsychotic and such use may increase the likelihood of additive side-effects. Centorrino et al. showed that patients receiving combined antipsychotics have longer hospital stay and more frequent side-effects (53).

Our study revealed that typical antipsychotics and older generation antidepressants are more commonly prescribed than newer drugs. This is contrary to the trend in developed countries where “second-generation” agents have come to dominate the clinical practice. The recent evidence points that atypical antipsychotics are not more effective than typical drugs (54, 55). However, a recent meta-analysis showed that newer drugs have advantages over the older drugs due to their different profile of side-effects (56).

All hospitals involved in our study are state institutions that have restricted resources. This directly influences the treatment choices in the clinical practice. The availability of medication and prescribing regulations limit the autonomy of the clinicians. However, the appearance of generic new drugs in these countries made the price difference less likely to be the main reason for the use of the older drugs.

We found considerably lower rate of use of depot antipsychotics compared to the evidence from the UK. The national household survey in the UK found that approximately 30% of non-hospitalized individuals with psychotic disorders were receiving depot treatment (57). This pattern in our centres may arise from the absence of community psychiatric services and the consequent prolonged use of inpatients facilities for those with enduring mental illness where treatment compliance is closely monitored and therefore oral medication commonly used.

Monotherapy was rarely used for those whose first diagnosis was a neurotic disorder. Patients with anxiety disorders were all treated with polypharmacy. None of the patients with anxiety was medication-free. The extensive use of polypharmacy in the management of anxiety may reflect the limited access to psychological interventions in the participating services.

Benzodiazepines are widely prescribed in general practice. They are effective as antianxiety, sedative, anticonvulsant and muscle-relaxant, but there is a huge difference between best-practice guidance which recommend short-term use and the reality of general practice (58).

There was very high prevalence of use of benzodiazepines. Previous studies conducted in the general population of Serbia found that the utilization of benzodiazepines has increased over the last decade, indicating a trend to self-medication, particularly in the period of recent war crisis (59). Our findings are in line with those from the Western European Countries. Previous surveys in the UK and Ireland found high prevalence of benzodiazepine use in psychiatric hospitals (60, 61), despite the recommendations by a number of guidelines that their use should be restricted to less than four weeks.

In a meta-analysis of 8 studies published between 1993 and 2010, Sirdfield et al (2013) found that GPs were ambivalent towards prescribing benzodiazepines and inconsistently applied strategies for managing their use. This was due to the changing context of prescribing, differing perceptions of the role and responsibility of the GP, variation in GP’s attitudes to benzodiazepines, lack of alternative treatment options, GP’s perceptions of patient’s expectations and the doctor-patient relationship (62).

Anticholinergic drugs were commonly prescribed as a regular medication across all centres. This pattern arises due to common treatments with typical antipsychotics with higher propensity to extrapyramidal side-effects compared to atypical antipsychotics. The sample size for single centres was relatively small to draw definite conclusions, but sufficient to give a representation of prescribing practices. The response rate was almost 100% in all centres, so minimising selection bias.

One of the surprizing features of our study is the similarity in the patterns of prescribing among five countries in East Europe. In a series of similar studies (63 - 65), which surveyed the prescription patterns of antipsychotics and antidepressants among six countries of East Asia (China, Hong Kong, Japan, Korea, Singapore and Taiwan) the pattern of prescription differed greatly country by country. The differences in government policies and service organization were considered to play a major contribution to the variations in clinical practices in East Asia. Although patterns of prescription might vary country by country, as also shown by another multicentric study (Spain, Estonia and Sweden) (66), polypharmacy with antipsychotic drugs is considered as an international phenomenon. The striking similarity in the patterns of prescribing in our participating centres could be explained by the similar economic and educational opportunities, collaboration and bidirectional influences during the past decades, mostly based on government policy. All countries involved in our study share similar organisational characteristics. They are going through a period of transition of psychiatric services and gradual deinstitutionalization, but none of them have yet developed community based services and day centres. Another shared characteristic of these countries is the lack of national guidelines for psychotropic prescribing at the time of the survey.

Common prescribing patterns in psychiatric services included in our survey should be improved and action in relation of polypharmacy prescribing is required. This could be achieved with an introduction of clear national guidelines and routine audit of prescribing practices in psychiatric care. There needs to be a shift to a more evidence-based culture. We recommend that consideration be given to the inclusion of a research and quality improvement agenda in the national programmes of mental health.

CHAPTER 2.
CLINICAL AND THERAPEUTIC APPROACH AT PATIENTS WITH SCHIZOPHRENIA

2.1 Introduction

Schizophrenia is a collection of mental and behavioural phenomena, a clinical syndrome (67). Its features may include: abnormal perceptions in the form of hallucinations, aberrant inferential judgements that result in extraordinary beliefs and delusions; distorted though construction manifest as a disorder of language; unusual, often restricted emotion, hedonia and volition, widespread cognitive problems particularly affecting memory and cognitive functions, seemingly strange behaviour explicable only in the context of these unusual experiences and deviant control systems.

According to DeLisi, the younger the age at onset of psychosis, the worse the prognosis of the disease. Moreover, it seems that younger onset is also linked to a more severe pathological process and thus, leading to a more rapid cognitive decline (68). On the other hand, current research focuses on the importance of the timing of exposure to developmental psychological trauma or stress during late pregnancy, and potential alterations of the dopamine system, making an individual vulnerable to mental illness, including schizophrenia (69).We can treat schizophrenia symptoms and we know a lot about genetic and environmental causes (70) but we cannot cure it yet. The complex mechanisms that lead to an individual developing schizophrenia are far from being completely understood, but major progress has been made over the past years. Neuroinflammation is one exciting topic not only in the neurology field, but also concerning pshychiatric disorders. There is increasing evidence suggesting blood brain barrier disruption in mental illnesses, including schizophrenia.

No two cases are exactly the same. After a first episode, all outcomes are possible (71). Some patients recover completely, many have a relapsing and remitting course for a decade or more, others experience a severe progressive disabling disorder. For many patients, the first psychotic episode implies involuntary commitment and treatment which raises a lot of ethical debate and legal issues. However, such measures are necessary because patients don’t have a true insight of their actions in the acute phase. After treating the first pshychotic episode, relapse should be prevented with maintenance therapy.

The first generation of antipsychotics had extrapyramidal side effects and could lead to severe cases of neuroleptic malignant syndrome and tardive dyskinesia (69). Nowadays, there are many options for controlling the symptoms of schizophrenia, the first line of treatment approved by the American Psychiatric Association, being the second generation antipsychotics (SGA), among whitch clozapine is not a good first option because of its serious adverse events – agranulocytosis and seizures and should be kept only as a backup for schizophrenia patients resistant to treatment (10 to 30% of cases) (72). The other SGAs have metabolic side effects like weight gain, diabetes and sexual dysfunction, cardiovascular and also cognitive side effects.

The disease is highly variable with episodes of exacerbations and remissions. Almost 90% of patients have at least one relapse, which can be triggered by drug withdrawal, stressful situations, substance misuse, but most of the episodes are due to non-adherence, schizophrenia being an illness prone to chronicity, high hospitalization rates and worse treatment response, functional and social decline with every relapse (72). Reasons for non-adherence are medication side-effects, use of illicit drugs or alcohol, lower level of education and socio-economic status.

Cannabis use is an important relapse predictor, affecting the dopamine release, but also some studies suggest it may be a predisposing factor to schizophrenia, which lead to the endocannabinoid hypothesis and ongoing research to whether or not, new pharmacological treatment targeting the endocannabinoid system, could help in the management of pshychosis. Furthermore, chronic cannabis use in patients with schizophrenia and schizoaffective disorders has been linked to smaller volumes of frontotemporal white matter and neurocognitive defficits (73).

We now have the option of introducing a long-acting injectable (LAI) antipsychotic, thus increasing the patient's compliance to medication alongside psychosocial interventions (74). Risperidone is the first atypical antipsychotic in the form of a LAI, followed by paliperidone palmitate, the first once monthly LAI atypical antipsychotic approved for the acute and maintenance treatment of schizophrenia in adults. Despite their major advantage of preventing a relapse by increasing compliance, their use is limited to less than 30% of patients across countries (75).

Other treatments like electroconvulsive therapy or repetitive transcranial magnetic stimulation should be used only for schizophrenia resistant treatment, which was defined as no symptom improvement after at least two adequate antipsychotic trials (64). Clinical practice shows antipsychotic drugs work predominantly on positive symptoms. The most rephractory positive symptoms are the auditory verbal hallucinations. Around 20% of people have negative symptoms that do not respond to current available medication, giving a poor prognosis to the disease. These symptoms are grouped in the following categories: blunted affect, avolition, anhedonia, alogia, asociality. Psychosocial interventions like cognitive behavioural therapy, are aimed for this type of symptoms and seem to bring an improvement in the functional outcome (77).

For a sufferer and their friends and family schizophrenia can be a devastating and bewildering condition; for the clinician it's a continuous and complex challenge, as well as being fascinating and puzzling from the social, biological and philosophical angles. These patients have to deal with discrimination being stigmatized and many times leading to isolation and preventing them from having a social life. Also, the disease has a considerable impact on family and increases the economic burden. This is why, considerable efforts are being put into psychosocial interventions, the results allegedely being an increase in patient treatment adherence, with reduced number of relapses and reduce hospital stay (78).

About 20% of patients can be recovered and socially reintegrated (79). Nonetheless, severe cases of patients with schizophrenia end up being institutionalized, among the factors leading to this can be mentioned: young age at onset, hebephrenic schizophrenia and substance misuse (80).

2.2 Researches regarding the ethics of treatment in early psychosis and the importance of therapeutic adherence

A.Background

Schizophrenia can have a variety of presentations and it can run a variable course. These facts limit the usefulness of schizophrenia as a diagnosis and underpin the current practice of referring to the umbrella term of psychosis. Psychosis is a less pejorative term and people may experience less stigma and be more accepting of the diagnosis themselves. When we use the term psychosis we need to be more specific about what we mean, in terms of positive symptoms, negative features, social functioning, etc.

Features of the prodromal period include withdrawal from previous social roles, impairment in general functioning, behaviours others see as odd, altered emotions (blunted affect or inappropriateness) deterioration in personal hygiene, difficulties communicating with others, unusual perceptual experiences, restricted drive, initiative, interests or energy. Others often sum up these features as the person "not being themself" patients in the prodromal phase will sometimes say that "something is not quite right". The duration of the prodrome is variable and its onset may be difficult to date. Sometimes the onset is insidious and in such cases the loss of function and the more general concept of "social capital" can be important. In addition to the length variability of the prodrome, the length of the active psychosis can vary, commonly being measured in months or even years before people get help.

The length of the duration of untreated psychosis does appear to be related to the outcome. The longer the duration of untreated psychosis, the worse the prognosis. Clearly, it's important to identify people with psychosis as soon as possible after the onset of positive psychotic symptoms. The cognitive decline associated with schizophrenia occurs quite early in the evolution of the disorder, possibly within the first year or two. Consequently, the opportunity to intervene and minimize this decline may be missed if psychosis persists for more than 1 year before the patient is treated.

Clinicians who treat patients with schizophrenia may encounter a variety of ethical issues related to both psychiatric and medical treatment of patients. Informed consent is a crucial aspect of the care of all patients, but it may present special challenges for patients with schizophrenia (81, 82). Early treatment may improve course and prognosis, and this has initiated shift in thinking about the risks and benefits of early intervention (83).

B. Published papers in this field

Our interest in this domain has been materialized in the publication of a review article, which highlighted the importance, and ethics of treatment in schizophrenia and an oral presentation emphasizing the importance of rapid initiation of atipsychotic treatment in the first psychotic episode.

Ifteni PI, Burtea V, **Szalontay AS**, Moga MA. Ethics of treatment in early psychosis. *Revista Romana de Bioetica*; 2015; 13(3). **IF 2014 = 0.462**

Introduction

Clinicians who treat patients with schizophrenia often encountered ethical issues related to psychiatric treatment. Schizophrenia is a severe mental disorder frequently accompanied by cognitive impairment. These impairments with psychotic symptoms and lack of insight, can affect the patients' abilities to make fully informed decisions about their own mental care. In these cases, ensuring that consent for treatment is informed, voluntary and competent can become a difficult achievement. Informed consent, as a core of these ethical principles, represents the expression of the individual's rights in both clinical and research contexts.

Ethics is a field implicated in understanding the moral aspects of human nature and action (84). One of the major ethical issue concerning schizophrenia includes a relatively low prevalence of the disorder but with a potentially devastating effect on the person life and, a critical effect on their families. After the onset, untreated schizophrenia may be followed by loss of productivity and high costs for the community, lasting throughout the patient's lifetime. There is undeniable evidence that demonstrates that many patients have difficulty receiving psychiatric treatment after the onset of symptoms of schizophrenia. Delay of treatment can profoundly affect the future development of the patients, representing a major burden to themselves and their families.

The therapeutic research was mainly as expected, focused on the neurobiological aspects as the fundamental basis in the developmentof various types of therapeutic interventions. As known, the characteristic change process starts with probability in the womb, as the result of the interaction between multiple factors, such as genetic defects, trauma factors, infections, immunological factors and stress.

Mental health management in particular for psychotic disorders, is often long and sinuous. Recent studies on the first episode of schizophrenia have shown that the average duration between the onset of symptoms and initiation of treatment is over two years, three years not being exceptional (85). Moreover, early but nonspecific signs such as mood disorders, suicidal ideation and impaired concentration may occur even ten years before the onset of psychotic symptoms (86). Neurodegenerative theory involves behavioural and cognitive deterioration of the disease. Cognitive deficits are a highly significant psychopathological feature when they are used and included in the long-term prognosis of the disorder. Therefore, these deficits are a target of the current pharmacological therapies, and they can have a major impact on therapy compliance. Likewise all benchmarking showed a strong correlation between the negative symptoms, cognitive impairment, and the poor results on neuropsychological tests in patients with focal brain lesions. Ethnic groups, social and economic status, the predominance of negative symptoms, personality disorders may be factors affecting prognosis and disease progression.

Diagnostic process

Accurate and comprehensive assessment of the onset of symptoms made by an experienced psychiatrist and early initiation of treatment, constitute decisive factors in the evolution and prognosis of patients with schizophrenia. The role of pharmacological interventions in schizophrenia is to cure specific symptoms and prevent psychotic relapses. These two objectives are plausible if therapy is initiated early on the onset of the disease. Moreover, it is known that schizophrenia is an enduring psychopathological process within which the early stages are the most active, aggressive and significant for the further development of the patient. Another dimension of the pharmacological treatment is conservation cognitive and affective fund. The biggest challenge is early recognition of symptoms of disease while minimizing the risk of false diagnosis.

It is possible to consider that treatment in the early stages of schizophrenia may be intrusive and sometimes invasive due to the patient's lack of insight and furthermore, the differential diagnostic process is difficult.

The average duration of prodromal symptoms before the onset of psychotic symptoms may be 2 years (women have a shorter prodromal period). Time to initiation of antipsychotic treatment is about three years, depending on the tolerance level of the community to substantial levels of psychopathology (87). During the prodromal phase, 80% of patients have depression and social decline and stagnation in personality development begins even before the first hospitalization (88). The onset of schizophrenia often occurs in teenagers. This is a critical period with an increased risk of developing psychotic disorders, especially in vulnerable people. Neuroimaging techniques have made it possible to reveal the changes in brain structure puberty.

Unfortunately for the long-term prognosis of the disease, many of the symptoms of the prodromal phase of schizophrenia with onset in adolescence are misinterpreted by parents, teachers, and relatives as "a passing phase of adolescence". However, diagnising schizophrenia is not easy given the non-specificity of symptoms in the prodromal phase. This is why the assessment of potential indicators for schizophrenia are taken into account both the objective neuropsychological deficits and the subjective self-perception.

Abnormalities in information processing could play an important role in identifying prodromal states of psychosis and predict the probability of transition, and are thus neuropsychological markers. Disruption of attention has been described as one of the strongest markers of susceptibility for schizophrenia represents a high-risk for individuals developing schizophrenia (89). Verbal fluency tests have been proven neuropsychological indicators for deficits associated with more sensitive performance (90).

Informed consent

In the clinical setting it is a legal and ethical obligation for clinicians to inform patients about the their illness, alternatives for care and assist them in making decisions about treatment. In the research setting the investigators must inform participants about the research protocol and help them understand the purposes, risks and benefits. In schizophrenia, disability justifies involuntary admission and involuntary treatment as a significant reduction in ethical freedom. The absence of insight about the disease is a cognitive disability justifying the intervention in those circumstances in which it interferes with making informed decisions. There is a broad societal, ethical and medical consensus that the use of coercive measures including involuntary treatment should be highly restricted (91) and it is important to find risk factors.

In a retrospective analysis published in 2019 by Schmitz – Buhl and colleagues on 3991 mental health records of inpatients, results showed that on the level of patient-related factors, several clinical, socio-demographic and socioeconomic characteristics might contribute to an increased risk for involuntary psychiatric treatment (92). Among socio-demographic factors, male gender and a migratory background were associated with involuntary psychiatric treatment in many European countries (United Kingdom, the Netherlands, Ireland, Norway, France, Belgium, Luxembourg, Denmark) the United States and New Zealand (93).

Respect for the autonomy of the individuals, in the process of obtaining informed consent, means recognition and appreciation of their specific capacities. This means that individuals should not be interfered with when making medical decisions, thus enabling them to act as they choose. Respect for autonomy involves the acknowledgement of another's right to their own decisions, whereas disrespect for autonomy "involves attitudes and actions that ignore, insult, or demean others". This implies, from an ethical point of view, that we should respect not only actions we consider to be correct, but also one with which we may not agree to.

On the basis of this argument, it cannot be claimed that all individuals suffering with schizophrenia are incapable of giving informed consent. This capacity varies with individuals and over time. Some patients will retain the capacity to make informed decisions while others will not. It is vital when treating schizophrenia to recognise that patients are heterogeneous and vary so greatly in personality, values and ideals. Mental illness carries a very important stigma, there is often "a presumption of an association between mental illness and impairment of autonomy", and in many ways, these two reasons are related.

Expectations

The average time to remission under treatment is about 3 months. When time required to obtain remission is greater then, the degree of remission is lower. Cognitive performance is considered to be the most important factor contributing to the recovery in functionality (93). Examination of longitudinal short-term patients in the first episode of schizophrenia, demonstrate a pattern of neuropsychological deficits remarkably constant over time (94). Recent studies highlight the correlation between the duration of untreated psychosis and cognitive deficits in patients with a first episode of schizophrenia. The duration of untreated psychosis is greater, the greater the extent of cognitive deficits. It appears that the function of the prefrontal cortex begins to deteriorate from the beginning of psychosis and it is more pronounced for those with a longer duration of untreated psychosis (95). Moreover, some studies have found an association between the tracking duration of untreated psychosis and poor prognosis as evidenced by the rate of relapse and the remission achieved (96).

Stigma

The stigma attributed to this worldwide disorder, can also be so powerful for families and for the suffering individuals that it may determine the delay of treatment. Despite recent programs for public education campaigns, there is a view that schizophrenia has poor prognosis and this may have induced a negative or denialing view. This could result in demoralisation or even depression in the patient's family. Some authors have also suggested that the stigma that lies on mental illness in many societies may cause denial of their symptoms in order to keep the social status and social relationships. Such an individual may reject a medical explanation, not because of the lack of consciousness, but because he gives priority to maintaining relations and social position which otherwise would be lost.

The length of time between the onset of the psychotic symptoms and initiation of therapy (also known as the duration of untreated psychosis) is found to be variable depending on: ethnic and cultural heritage, the degree of community tolerance, the level of stigma, and the levels of psychopathology. The length of untreated psychosis was found to be particularly traumatic for patients and their families with high rates of self-harm, suicide or suicidal intentions, family distress, interference of the police, forensic acts, drug use, and threatening perturbing behaviour (97).

Compulsory admissions have a strong effect on psychiatric patients. A review published in 2016, which included 13 randomized clinical trials totalizing 2970 psychiatric patients showed that compliance enhancement, and integrated treatment had no significant reduction in compulsory admissions (98). In a study that examines demographic and diagnostic factors associated with involuntary admission in a general adult psychiatric service, after controlling for age, occupation, marital status and diagnosis, the only independent predictors of admission status were place of origin and male gender (99). Another study that explored risk factors for involuntary treatment revealed that the risk of coercion was the highest in the first admission and decreased with the number of admissions and that the following socioeconomic variables were associated with an increased risk of coercion: male sex, unemployment, lower social class and immigrants from low and middle-income countries. The risk was reduced when patient was married and having children, and had good social relations (100).

Confidentiality

Confidentiality is an important tool for protecting the population from discrimination and other forms of stigmatization. The challenge of obtaining consent is closely related to problems of patient's privacy and confidentiality. Some ethicists explain that our notions of confidentiality have traditionally been built on the 'personal account' model, in which health information belongs to that patient alone. The setting for treatment determines confidentiality. If it is attempted through general hospitals, it is difficult to be kept confidential because the patient may be evaluated by many physicians in order to eliminate other possible diagnostics. Full confidentiality is more easily preserved if the treatment process is performed in specialized or through other medical services (private practice). The concept of confidentiality therefore may extend beyond secure medical records. It may include not only what is told and to whom, but in the same time, what type of language is used and what kind of messages are implied.

Conclusions and discussions

The decision *"to treat"* must have an ethical significance to justify the intervention. The current laws, justify involuntary admission and treatment through the Law on Mental Health and Protection of Persons with psychiatric disorders. Involuntary treatment is justified on the basis of lack of insight and must be judged very carefully. The risk of disability justifies involuntary treatment even if it represents a significant reduction of freedom as it is written in ethical concepts. The absence of insight towards the disease is a cognitive disability justifying the intervention in those circumstances in which it interferes with making best and appropriate decisions for mental health. All this leads to the conclusion that delaying the treatment causes a further development conditions. Minimizing the time elapsed from the onset of symptoms and therapy initiation remains a major goal in schizophrenia. Ethical guidelines for the research and implementation of treatment are necessary and should be followed by psychiatrists, general practitioners and families in order to ensure the right and optimal access in the early stages of schizophrenia.

The last decades have seen two important advances in the treatment of psychotic disorders. One is the renewed interest of providing optimal care at the earliest possible point in the course of illness (101). This interest has arisen from evidence suggesting that the earlier effective treatment is initiated, the better the clinical outcomes (102). The first two or three years of a psychotic disorder have been termed the "critical period" during which the future course of the illness may be determined (103). The opportunity exists, therefore, for secondary prevention; that is, to minimise the disability so commonly associated with psychotic disorders. But to do so requires optimal care, including support for the patient and their family, to facilitate adherence to a treatment plan which may include log-term, continuous pharmacotherapy. Achieving this goal has been greatly enhanced by the lasts generation of antipsychotic medications which have proven to be significantly more tolerable for patients. Non-compliance, or the failure to adhere to an agreed treatment regimen, is common; estimates vary as to prevalence, but it appears to be a universal phenomenon, affecting all areas of medicine. In the treatment of schizophrenia, noncompliance with long-term antipsychotic treatment has been estimated by Corrigan et al at up to 48% within the first year and up to 74% within the first two years (104). It is tempting to attribute noncompliance in schizophrenia to lack of insight, cognitive impairment or other factors but explanations such as these are almost certainly an oversimplification. As a problem, noncompliance appears to be multi-factorial in origin, although patients' beliefs about their experience of side-effects, notably extrapyramidal symptoms, are particularly influential (105). Poor compliance is, without doubt, one of the major determinants of outcome in schizophrenia. Therefore, there is ample evidence that indicates that we should take seriously our patients' perception of their condition, treatment, progress and side-effects.

More optimist scholars endorse the concept of primary prevention in schizophrenia. This concept arose after the development (106) and latter validation (107) of the ultra high risk (UHR) criteria for schizophrenia. The UHR criteria as they evolved through time, take into account different variables in order to predict the risk of developing a psychotic disorder. Initially the transition rates were around the 30 to 40% mark (107), making them usefull prognostic tools. The UHR critleria naturally pushed for the development of early interventions aimed at the high risk population in order to reduce the transition rates, with initial favourable results. These interventions ranged from cognitive therapy (CT) to dietary supplements and administration of antipsychotic (AP) medication. (108-111). Follow up research though established that the interventions have no long term benefit in preventing psychosis (112-114). This raises the ethical question of whether to intervene in the prodromal phase of the disease. Appelbaum signs a paper published in 2015 discussiong the ethical question that have to be taken seriously in regards to primary prevention. (115). While the administration of CT or omega 3 polyunsaturated fatty acids, arguably have no serious side effects, antipsychotic medication comes with it's established side effects, even at low dosages. We argue that until the UHR criteria have good predictive outcomes, our efforts should remain focused on secondary prevention, early identification and reducing the time of untreated psychosis. Finally, early treatment with second generation antipsychotics might reduce specific schizophrenia behaviour (106).

As a recent personal contribution, our interest in this domain has materialized through a presentation of a study entitled "The importance of early initiation of antipsychotic treatment and maintenance of good therapeutic adherence in schizophrenia" at ECNP Barcelona and published as a summary in European Neuropsychopharmacology, vol 29, supplement 1, 2019, page 298, with the authors: Szalontay AS, Radu D, Bolos A, Untu I.

Aims of the study were to emphasize the importance of the initiation of the antipsychotic treatment since the first episode in patients with schizophrenia and implicitly the need for early diagnosis by observing the diagnostic criteria (ICD 10 and DSM 5) and to emphasize the importance of therapeutic adherence to maintain good overall functionality in schizophrenia.

100 patients hospitalized between January 2015 and January 2016 at "Socola" Institute of Psychiatry Iasi, Romania, were recruited into the study. There were only male patients aged between 18 and 25 years, residing in Iasi, in the first psychotic episode with symptoms of schizophrenia. We analysed the presence of a premorbid personality, the manifestation of symptoms, with the dominance of the positive / negative / cognitive symptoms and the antipsychotic used in initiating the psychopharmacological treatment. These patients were searched in the hospital database by December 2017, following the number of emergency relatives that coincided with new recurrence of symptomatology. In the case of relapsed patients, the new observation sheets were analysed in order to underline the therapeutic adherence of each individual.

Results showed that 82% of patients with first psychotic episodes with symptoms of schizophrenia were treated with atypical antipsychotics:

- 58% with *done's*
- 32% with *pine's*
- 10% Aripiprazole

As the current literature shows, most patients in the first psychotic episode have a favourable evolution under antipsychotic treatment. Thus, the remarkable issue that remains to be debated is that of therapeutic adherence. Antipsychotic treatment as a sine qua non pharmacological therapy has proven to be remarkable by improving or removing positive symptoms, by improving long-term prognosis and by decreasing the number of emergency hospitalizations in psychiatric services. The issue of adherence and the promise that long acting injectables offer will be discussed later in this thesis, under chapter 2.3.

2.3 Researches regarding therapeutic measures in involuntary admitted patients

A. Background

In settings for acute psychiatric patients dealing with "challenging behaviour" is one of the most common and difficult situation. Violence by schizophrenic patients can be prevented if the patient is monitored before, during and after hospitalization. In patients with acute psychosis, the use of typical antipsychotics, especially haloperidol can be necessary. Atypical antipsychotics may decrease hostility over the long term. Clozapine, olanzapine, risperidone, aripiprazole, ziprasidone are the atypical antipsychotics most often used in the long-term treatment for hostility, impulsivity and aggression in patients with schizophrenia (117).

Clozapine decreases hostile, aggressive and violent behaviour when used for treating persistent aggression in patients with schizophrenia and it represents the best long-term medication choice (118).

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which aim was to emphasize the growing interest for the prevention of using coercive measures in patients with schizophrenia.

Ifteni P, **Szalontay AS**, Teodorescu A. Reducing restraint with clozapine in involuntarily admitted patients with schizophrenia. *American Journal of Therapeutics* 2017; 24: 222 –226. **IF 2017 = 1.000**

Introduction: In the entire world, restraint and seclusion are common interventions in psychiatric inpatients settings because of aggressive behaviour (119). Since the 1990s, there is a growing interest in the incidence of coercive measures in most European countries (120). During the last years, there have been a few European studies in which psychiatric hospitals were compared regarding the frequency and duration of coercive measures. These studies are from the UK (119,121), Switzerland (122), Finland (123), and Germany (124). To date, there is no available data for Romania regarding this topic. Because of possible physical and psychological damage of patients affected by coercive measures (125), the use of coercive measures can be seen as an indicator of the quality of psychiatric inpatient treatment.

In this study, we assessed antipsychotic (AP) use in involuntarily admitted patients with schizophrenia to (1) test the antiaggressive properties of clozapine by recording time until first use of restraint past admission and (2) to identify risk profiles for early restraint use in this population.

Material and method: Data was collected from medical records, covering the period 2011 – 2014 during routine clinical care in the Psychiatry and Neurology Hospital Brasov, Romania. This hospital is a public care facility, which covers a population of 400,000 people. The admission ward is a 120-bed facility with 24-hour service of board certified psychiatrists. Data from all subjects with schizophrenia (clinical DSM IV diagnosis), who were admitted involuntaroy with the diagnosis of schizophrenia were extracted. Because of our earlier report on fast titration of clozapine (126), our hospital policy permitted the early use of clozapine as an equal alternative to other first-generation and second-generation antipsychotics (SGA). AP choice during the early admission was however the sole responsibility of the respective psychiatrist on duty in the emergency department / the admission wards. Restraint order was written whenever subjects appeared to be a threat for staff or fellow patients. Because of clinical departmental policy, Positive and Negative Symptoms Scale (127) and Clinical Global Impression (128) were recorded during admission in all subjects. This study was approved by the local ethics committee and with the Helsinki Declaration of 1975 / 2000.

We divided the patients in 2 groups. The clozapine group (CLZ-group) included all cases treated with clozapine during admission. In the nonclozapine group (non-CLZ), we entered all patients treated with other AP (haloperidol, olanzapine, quetiapine, risperidone, amisulpride, and aripiprazole). The primary aim of the study was to identify the index incident of restraint and the duration until restraint past admission. Demographic data included sex, age, duration of illness, and age of onset. We also collected data regarding reason for admission, number of restraints, and length of stay, previous involuntary admissions, and history of violence.

Group comparisons were performed using Fisher exact test or Wilcoxon rank-sum test as per data type and distribution, as well as nominal logistic fits, and a Kaplan-Meier survival analysis. Two-sided tests with alpha=0.05 were used without correction for multiple comparisons because of the purely descriptive nature of the study. Statistical calculations used JMP 5.0.1, 1989 – 2003, SAS Institute Inc, Cary, NC.

We collected data from 115 consecutive patients with schizophrenia who were admitted involuntary to Psychiatry and Neurology Hospital Brasov, Romania during January 01, 2011 and December 31, 2014. The demographic characteristics of the study groups were: 51.3% male, 39.6±11.05 years; mean / SD. Base on clinical decisions of their treating psychiatrists, subjects were started on the following AP: haloperidol (n=81; 70.4%) clozapine (n=13; 11.3%), olanzapine (n=12; 10.4%), or other SGAs (7.9%; including amisulpride: n=3, quetiapine: n=3, aripiprazole: n=2, risperidone: n=1). Clinical and demographic characteristics of the full cohort and the clozapine subgroups are provided in Table 2.1.

To test the immediate effect of early clozapine use, restraint characteristics were contrasted for subjects receiving clozapine as the first AP during this hospitalization. Moreover, these analyses were repeated for the CLZ-group and for the non-CLZ group. Accordingly, clinical and demographic characteristics were analysed and compared for these respective subgroups (Table 2.1). In addition to the 13 subjects who received clozapine as the first AP immediately after hospitalization (and receipt of white blood count), 11 subjects received clozapine as the second intention. The median duration until clozapine was started as a second opinion was 11.1±4.1 days. The median duration of clozapine treatment was 19.5 (11.2; 23) days; clozapine was up-titrated during 5 ± 2.2 days, to a mean maximal dose of 437.5 ± 132.1 mg. We performed a secondary survival analysis for the first week of hospitalization for all subjects, who had not needed restraint within the first hour past administration. This analysis involved 69 (60%) of the initial 115 subject and included the CLZ-first subgroup in total (18.8% of this 1-hour restraint-free group) as well as the 56 (81.1%) non-CLZ subjects, who were restraint-free past 1 hour.

Results: Because of the naturalistic nature of the study, demographic, clinical, and treatment characteristics of subgroups differed slightly (Table 2.1). In particular, the subgroup of subjects, in whom clozapine was used as first AP (CLZ-first) included a significant higher proportion of subjects who were admitted involuntary because of self-destructive behaviour (53.8%) compared with the remaining cohort (21.5%; P = 0.002), whereas the externally targeted violence was the main reason for involuntary admission in the remaining cohort (Table 2.1). Moreover, the CLZ-group included more subjects with a longer hospitalization-free period prior the current admission (median period past prior hospitalization 220 days vs. 90 days: P = 0.005; Table 2.1). Nevertheless, all other clinical and demographic parameters, in particular those characterizing disease severity and aggressive potential, did not differ between AP treatment groups (Table 2.1).

Table 2.1. Demographic, illness and treatment characteristics in involuntary admitted subjects with schizophrenia

	Total (n=115)	**Clozapine (n = 24, 19.30%)**	**Subgroup: CLZ-first AP (n = 13, 11.3%)**	**Non-CLZ (n = 91)**	**P, CLZ versus non-CLZ**	**P, CLZ-first versus others**
Age, yrs, mean ± SD	39.67±11.05	36.92±8.42	37.15±8.59	40.40±11.57	0.17	0.37
Sex, male, n (%)	59 (51.30)	15 (62.5)	10 (76.92)	44 (48.3)	0.25	0.08
Age at onset, yrs, median (25th; 75th percentile)	25.0 (22.0; 30.0)	18.25 (22.5; 24.75)	23 (21; 24.5)	26 (22; 33)	0.002	0.07
Illness duration, yrs, median (25th; 75th percentile)	12 (3; 20)	11 (6; 22)	11 (9; 16)	9 (3; 20)	0.22	0.30
Reason for involuntary admission, n (%)					0.06	0.02
Threat for / violence against others / objects	86 (74.78)	14 (58.33)	6 (46.15)	72 (79.12)		
Threat for / violence against self	29 (25.22)	10 (41.67)	7 (53.85)	19 (20.88)		
MOAS total, mean ± SD	11.25 ±1.67	11.23±1.56	11.61±1.66	11.23±1.70	0.92	0.46
MOAS verbal aggression, mean ± SD	3.19±0.67	3.41±0.65	3.38±0.65	3.13±0.70	0.06	0.27
MOAS aggression against property, mean ± SD	2.53±0.98	2.60±0.97	2.69±0.27	2.51±1.00	0.50	0.54
MOAS physical aggression, mean ± SD	3.04±0.67	2.80±1.02	2.92±0.28	3.07±1.01	0.18	0.76
MOAS auto-aggression, mean ± SD	2.49±0.87	2.50±0.93	2.61±0.77	2.8±0.65	0.90	0.53
PANSS at admission, median (25th; 75th percentile)	100 (98; 104)	102.7 (99; 106.5)	101 (98.5; 106)	100 (98; 104)	0.43	0.58
PANSS hostility, median (25th; 75th percentile)	5 (5;6)	6 (5;6)	6 (5;6.5)	5 (5;6)	0.14	0.28
CGI at admission, median (25th; 75th percentile)	6 (6; 6; 5-7)	6 (6;6;5-7)	6 (6;6;6-7)	6 (6;6;5-7)	0.47	0.40
History of violence, n (%) *	66 (57.90)	21 (91.30)	10 (83.33)	45 (49.45)	0.0003	0.07
History of involuntary admission, n (%)	21 (18.26)	11 (45.83)	7 (53.85)	10 (10.99)	0.0003	0.002
No. previous hospitalizations within prior 12 months, median (25th; 75th percentile; range)	1 (0;1;0.5)	1 (0;1;0-3)	0 (0;1;1-3)	1 (0;2;0-5)	0.94	0.31
Days since prior hospitalization, median (25th; 75th percentile) **	120 (60; 240)	210 (121; 300)	220 (104.75; 300)	90 (45; 217)	0.005	0.14
Length of stay, mean ± SD	27.33±9.14	26.3±9.77	24.23±9.61	27.5±9.02	0.46	0.06

**Based on n = 114; missing information for 1 subjects*

***For subjects with at least 1 hospitalization within last year*

CGI, Clinical Global Impression; MOAS, Modified Overt Aggressiveness Scale; PANSS, Positive and Negative Symptoms Scale

Restraint was used in the vast majority (n = 103, 89.5%) of the cohort anytime during the hospitalization. Mostly, restraint was used very early during the admission (median time until restraint: 3 hours; 25th; 75th percentile: 0.25; 48 hours). These parameters were strikingly lowered in the CLZ-first group, in which only 3 subjects (23%) experienced restraint ($P > 0.0001$ relative to the remaining cohort), with a median time until restraint of 408 hours (25th; 75th percentile: 48; 540; $P > 0.0001$; Table 2.2). In the non-CLZ-group, the proportion of restraint was significantly higher (n = 87, 95.6%). Similarly, restraint reduction and delay of restraint was observed for the CLZ-group (Table 2.2). Moreover, the rate of restraint was 23% for clozapine compared with 95% for haloperidol and 100% for another SGAs (risperidone, olanzapine, amisulpride, aripiprazole and quetiapine).

Table 2.2. Use of restraint in involuntary admitted subjects with schizophrenia

	Total (n = 115)	**Clozapine (n = 24)**	**Subgroup: CLZ-first AP (n = 13)**	**Non – CLZ (n = 91)**	**P, CLZ versus non - CLZ**	**P, CLZ-first versus others**
Restraint anytime during hospitalization, n (%)	103 (89.5)	16 (66.6)	3 (23.0)	87 (95.6)	0.0003	<0.0001
Hours until restraint, * median (25th; 75th percentile; range)	3 (0.25; 48)	118 (24; 426)	408 (48; 540)	1.1 (0.2; 24)	<0.0001	<0.0001
Restraint during first 24h, n (%)	71 (61.7)	5 (20.8)	1 (7.6)	66 (72.5)	<0.0001	<0.0001

**For subjects without any restraint, the length of stay is substituted as restraint-free period.*

A significant group separation was noticeable during the first 24 hours and persisted throughout the observation period (Log-rank $x^2 = 9.96$; $P = 0.0018$).

To exclude the possibility that the delay of restraint was primarily mediated by clinical factors but treatment characteristics, we used stepwise forward regression including subgroup CLZ-first, age, sex, and reason for admission as potentially predictive factors. Of these, only CLZ-first and the reason for admission entered the final significant model, and CLZ-first was the sole significant factor within the model.

Within the limiting framework of a retrospective observation of naturalistic treatment, this study suggests the possibility that the antiaggressive properties of clozapine can be clinically efficient when used in a highly problematic cohort of involuntary admitted subjects with schizophrenia.

Discussions: Therapeutic strategies to reduce violence in patients with schizophrenia suffer from a lack of guiding information from randomized studies and prospective studies are methodologically highly limited because of an inherent selection bias related to informed consent in a predominantly uncooperative study group (123). Thus, our naturalistic small cohort is thought to contribute to existing clinical expertise despite the limitation of a nonrandomized retrospective study design.

Coercive treatment includes both, physical restraints and involuntary medication; however, rarely can involuntary medication be replaced by physical restraint, whereas the reverse is realistically achievable. Both of these measures are unfortunately frequent during involuntary admissions (128). Because of the high medical risks including death associated with restraint (129) and because of the traumatic experience associated with restraint (130), these numbers sorely need to decrease. Based on our earlier observation of fast clozapine titration

(131), the hospital policies permitted the use of clozapine as an emergency medication without written consent from the patient; we were thus in the exceptional position to make use of the well- established antiaggressive properties of clozapine (132) during early hospitalization. Our data showed a striking reduction of restraint rates with clozapine use, relative to the predominantly haloperidol treated remaining subjects. Importantly, despite the naturalistic study design, clinical and demographic factors did not significantly influence the restraint-free period; the use of clozapine as the first AP was the sole characteristic significantly associated with delayed restraint. These results are in line with earlier studies on the effect of clozapine on restraint frequencies chronic schizophrenia (133, 134) but our results are novel in that clozapine was used as first-line medication.

Clozapine is one of the most frequently used second generation AP for treating schizophrenia in emergency psychiatrical setting over a 16 year observation period (135), although newer agents such as Olanzapine is gaining ground. A systematic review published in 2019 regarding violence treatment in schizophrenia found that clozapine is not effective in treating predatory driven aggression, but very efficient in the cases of impulsive and psychosis-driven aggression (136). A multicentric prospective study established that psychotic disorders are the group of psychiatric disorders most associated with involuntary admission and to a more than 7 days isolation in hospital (137). Another systematic reviewd published in 2019 looked at the efficiency of clozapine compared to other antipsychotics reducing restraint times in a forensic psychiatry setting. They found that the literature is varying in this subject, finding that clozapine is better for the aforedmentioned purpose than typical antipsychotics but Risperidone and Olanzapine might be better, although not in a forensic psychiatry context (138). This is crucial as new antipsychotics become avaible and should be tested in regards to their ability to reduce restraint time especially when recently, a case report was published describing the fatal case of a female patient who died from presumed cardiac arrest induced by clozapine and physical restraint (139). Other research suggests that clozapine can be efficiently used without life threatning complications in vulnerable patients with dementia and associated refractory aggression (140).

First limitation of the study is the relative small number of patients treated with clozapine. The second limitation is the retrospective chart review character of the study. Despite those, the clinical meaning of the findings is very important for psychiatrists. Further studies are necessary to validate our results. These retrospective data suggest an early antiaggressive effect of clozapine during the immediate use of clozapine in highly problematic patients. Further randomized and controlled studies are necessary to validate our results. Reducing stress and stigma of patients with schizophrenia must be the core objective of professionals in this field alongside with achieving remission.

2.4 Researches regarding institutionalization in schizophrenia

A. Background

Diagnosis is a strong predictor for the length of hospitalization (141). Patients with schizophrenia requiring long-term institutionalization represent those with the worst outcome, leading to higher costs for patients and their relatives and constituting a large economic burden for society (142). Factors predicting institutionalization for patients with schizophrenia are: lower education level, single parent, multiple antipsychotic treatments and suboptimal response under first generation long acting antipsychotics (143). There is a tendency to institutionalize patients with schizophrenia at younger age compared with past decades, which is why the need for early intervention in psychosis emerged by making use of second generation antipsychotics in order to avoid a too early institutionalization of these patients (143).

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which shared the potential factors predicting institutionalization and emphasizes the need for early intervention in psychosis.

Szalontay AS, Pascu AM, Teodorescu A, Minea D, Ifteni P. Actual tendency in institutionalization of patients with schizophrenia. *Revista de Cercetare si Interventie Sociala* 2015; 51: 64 – 72. **IF 2015 = 0.424**

Introduction: At the beginning of the 20th century long stay institutional treatment was the norm for people with schizophrenia in absence of antipsychotic drugs. Hospitals with many beds were established in isolated forests or in rural areas where patients remained for extended periods of time. This situation had led to the amplification of the stigma associated to mental illness, particularly for schizophrenia. There were a lot of pictures in magazines and journals with dishevelled and strange looking people, often assuming unusual poses or grimacing and gesturing in incomprehensible ways. There were a lot of scary stories about these patients and about the treatments used by physicians trying to cure them. As a result, society tried to isolate those patients and only in a few cases they manage to be accepted in local community.

When chlorpromazine was introduced for the treatment of people with schizophrenia in the 50's, reduction of psychotic and disorganized symptoms had an enormous and significant impact on lengthy hospital stays for schizophrenic patients. As a consequence the number of beds for chronic patients was reduced in the majority of western countries by the late 1970s. Long-stay care was maintained only for those who were non-responsive to antipsychotic treatment. The treatment model for schizophrenia has changed during past decades, in terms of antipsychotics types and admission periods that averaged 6 – 12 weeks for acute patients 25 years ago, to up to 21 days in Romania or even 5 – 7 days stays in some countries like United States. In Brasov County, despite the development of private psychiatric sector there is a tendency to institutionalize patients with schizophrenia at a young age. The factors involved in this situation could be economic status, short time allocated by parents, lack of support from institutions and local authorities, low level of education, and treatment resistance. In contrast to non-institutionalized patients, they had substantial positive and negative symptoms (144), had cognitive impairment (145), significant functional impairment (146) and substantial levels of aggressive and unpredictable behaviours (147).

Within this context, the aim of the study was to identify factors that lead to early institutionalization of schizophrenia patients and to find if the age of patients admitted for long stay in a chronic setting is lower now, compared to 15-20 years ago.

Material and method: The study was conducted in Psychiatry and Neurology Brasov Romania in 2015. The patients described in this report were admitted to a 120-bed, free-standing psychiatric teaching hospital located in Brasov, Romania. Patients referred for hospitalization are admitted, on alternate days, to one of the two units. The clinical care is coordinated by board-certified psychiatrists affiliated with the local medical school. Data was collected of 322 patients with schizophrenia according to the DSM-IV-TR (APA, 2004) who were institutionalized after discharge in Hospital for Chronic patients Vulcan, Brasov. The time period was between 1995 and 2015. The data included demographics, age of onset, duration of illness, treatment, education, marital status and economic status and the age of institutionalization. From patient's files we obtained information regarding relapses in previous 2 years before institutionalization, time from discharge to the next admission, the length of stay and the reason for family request for this hospitalization.

We divided patients in two groups: A, admitted between 1995 and 2004 and B admitted between 2005 and 2014. The aims were to verify if the age of the patients admitted for long stay in a chronic setting is higher in group A compared with group B. The hypothesis was the age of patients admitted in present days is lower than 15 – 20 years ago.

Statistical analyses were performed using SPSS version SPSS 15.0. The differences between the two groups were compared using Student's t test. The chi squared and Fisher's exact tests were used to assess categorical variables. Age adjusted odd ratio (OR) and 95% confidence interval (CI) were calculated by multivariate analysis using multiple, unconditional, logistic regression. P values less than 0.05 were considered to be statistically significant.

Results: Of the 322 patients 189 were female (58.7%) with the mean age of 54.31 years (SD = 9.32) and 133 male (41.30%) with mean age 52.60 years (SD = 11.22). In group A of patients admitted between 1995 and 2004 were 150 cases, with mean age 57.08 years (SD = 5.67), age of onset 21.73 years (SD = 3.34), and age of institutionalization 49.34 years (SD = 8.86). In group B of patients admitted between 2005 and 2014 were 172 cases, mean age 51.15 (SD = 9.15), age of onset 23.56 years (SD = 4.11), and mean age of institutionalization 42.22 years (SD = 7.76). The number of patients with age below 40 years was 12 (8%) in group A and 28 in group B (16.2%). In the table 2.3 are presented the demographic data of institutionalized patients.

Table 2.3. Demographics

Variables	**All patients N= 322**	**Institutionalized patients**				**p value**
		Group A 1995 – 2004 (N = 150)		**Group B 2005 – 2014 (N = 177)**		
		N	**%**	**N**	**%**	
Age (mean, SD)	53.45 (8.23)	57.08 (5.67)	-	51.15 (9.15)	-	p<0.05
Age of onset	20.95 (2.47)	21.73 (3.34)	-	23.56 (4.11)	-	NS
Age at institutionalization	45.78 (8.22)	49.34 (8.86)	-	42.22 (7.76)	-	p<0.05
Duration of illness	21.67 (9.33)	25. 16 (7.56)	-	18.18 (8.54)	-	p<0.05
Patients with age below 40	40	12	8.00	28	16.2	p<0.05
Number of admission in 2 years period before institutionalization (mean)	-	6	-	7	-	NS
Type of schizophrenia						
Paranoid	217	105	70.0	112	65.11	NS
Disorganized	71	30	20.0	41	23.83	NS
Undifferentiated	27	14	9.33	13	7.55	NS
Other	7	1	0.66	6	3.48	NS
Place before institutionalization						
Home	253	120	80	133	77.32	NS
Hospital	50	20	13.3	30	17.44	NS
Other	19	10	6.66	9	5.24	NS
Patient living						
Alone	37	14	9.33	23	13.37	NS
With husband / wife	25	13	8.66	6.97	1.16	NS

Variables	All patients N= 322	Institutionalized patients				p value
		Group A 1995 – 2004 (N = 150)		Group B 2005 – 2014 (N = 177)		
		N	%	N	%	
With one parent	78	33	22	45	26.16	NS
With both parents	23	11	7.33	12	6.97	NS
With son / daughter	35	17	11.3	18	10.46	NS
With brother / sister	80	33	22	47	27.32	p<0.05
Other	44	22	14.6	22	12.79	NS
Education						
1 – 4 years	45	23	15.3	22	12.79	NS
5 – 8 years	175	87	58	88	51.16	NS
9 – 12 years	80	33	22	47	27.32	NS
More than 12 years	22	9	6	13	7.55	NS

The Cox analysis for the middle aged sample showed that persons with schizophrenia aged 40 – 55 in 2005 – 2014 have 3.40 times increased risk for institutionalization compared with individuals of similar age in 1995 – 2004 period (table 2.4). Other risk factors for institutionalization among the middle-aged cohort are age (HR = 1.23), being female (HR = 1.45), and having only one parent (HR = 1.72). The patients living with brothers are at higher risk for institutionalization.

Table 2.4. Cox Proportional Hazards Models of Institutionalization

Variable	Group A, 1995 – 2004 (N = 150)		Group B, 2005 – 2014 (N = 172)		p value
	HR	95% CI	HR	95% CI	NS
Disorganised type	3.40	2.77 – 4.98	1.43	1.15 – 2.44	p<0.05
Age (years)	1.11	1.08 – 1.12	1.23	1.11 – 1.15	NS
Charlson score >0	1.21	0.88 – 1.66	1.10	1.06 – 1.41	p<0.05
Female	1.36	1.05 – 1.76	1.49	1.17 – 1.46	p<0.05

All the patients were treated with antipsychotics (table 2.5). The vast majority of patients received haloperidol, even if the second generation antipsychotic were available. There were few patients treated with clozapine before 1995. The treatment was not available, underutilized due to fear of agranulocitosis, myocarditis and seizures.

Table 2.5. Treatment categories used in patients with schizophrenia

Antipsychotics	All patients	Discharged patients				p value
	322	1995 – 2004 (N= 150)	%	2005 – 2014 (N = 172)	%	
Haloperidol	137 (42.54%)	67	44.66	70	40.69	NS
Flupentixol	22 (6.83%)	12	8.00	10	5.9	NS
Zuclopentixol	27 (8.35%)	17	11.00	10	5.9	NS
Olanzapine	55 (17.08%)	23	15.33	30	17.44	NS
Quetiapine	12 (3.72%)	5	3.3	7	4.12	NS
Clozapine	33 (10.24%)	12	8.00	21	12.20	p<0.05
Risperidone	23 (7.1%)	16	10.5	7	4.12	p<0.05
Amisulprid	13 (4.1%)	6	4.00	7	4.12	NS

Discussion: Our findings show that despite the relative reduction of hospitalization in acute settings there is a tendency of families to push institutionalization of patients with schizophrenia even if those patients are still young. There are some predictive factors which include: aggressive behaviour, living with brother or sister, male gender and multiple admissions to the acute psychiatric units in short period of time. In the present days we noticed less time allocated by relatives to talk and spend time with schizophrenic patients. The main reason declared is the economic situation of those families. Having a career was associated with longer length of stay for schizophrenia and bipolar disorder patients. It is possible that if carers experience a significant carer burden from patients with high level of need, length of hospitalization may be prolonged, in the interest of protecting carer's health and wellbeing (142).

Patients with schizophrenia requiring long-term institutionalization represent those with the worst outcome, leading to personal costs for patients and relatives and constituting a large economic burden for society (143). A recent article published in July 2019 correlates the length of hospitalization for patients with schizophrenia and activity performance as it was measured using an adapted version of the Modified Barthel Index. (148)

Aggressive and disruptive behaviour remained the reasons for admission in "acute settings", in the current days. In the same time represents a major difficulty to discharge patient due to fear of violent behaviour towards relatives. When aggressive behaviour is accompanied by cognitive impairment the delay of discharge are even longer (149). In a systematic study of aggression (147) researchers found that the prevalence of aggression in long stay patients was equivalent to that seen in acutely admitted patients admitted within the last 3 days in earlier studies. Several studies show that negative symptoms are associated with aggressive behaviour (150). These negative symptom correlate results have been interpreted in terms of frontal lobe dysfunction as alterations in emotional functioning are common in individuals with frontal lobe damage. The majority of the participants showed enhancements in social functioning despite the fact that functional impairment is common in persons with schizophrenia, which indicates that even long-stay patients could achieve better functioning by deinstitutionalization. Although the stability in symptoms might be due to continuous schizophrenia course, moving to the community may also lead to improvement (151). A recent study (OPUS) indicates that hospital-based rehabilitation together with weekly supportive psychodynamic therapy was associated with a continued increased use of psychiatric bed days and days in supported housing (152). Discharged patients had more leisure activities, more often a "good friend", and more frequent social contacts. They were less often victim of a crime within the last year. In a cross-sectional comparison, they were significantly more satisfied with their life than patients who were still in hospital (153). Our study show that the number of patients who were discharged after institutionalization in 1995–2004 was significantly higher compared with period 2005–2014.

Despite the access to LAIs there are a large number of patients who was institutionalized before treatment with a depot antipsychotic or clozapine. Clozapine as well as LAIs remained highly underutilized in patients with schizophrenia even if they are non-adherent or nonresponsive to other antipsychotics (154). In the vast majority of cases they were declared "schizophrenia treatment-resistant" but the evidence is for highly non-adherent to treatment patients. Non-adherence is a major challenge in schizophrenia treatment. While long-acting (depot) antipsychotic medication are often recommended to address adherence problems, evidence on the comparative efficacy of depot versus oral antipsychotics is, as of yet, inconsistent. While no single intervention is universally effective, depot medication is considered one of the most important pharmacologic interventions available to address adherence problems in schizophrenia. However, the findings in the clinical literature regarding the comparative effectiveness of depot versus oral antipsychotics have been inconsistent. There is a hypothesis that states that the study design is an important factor possibly affecting estimates of comparative effectiveness of antipsychotic medications (155-157). Further studies are needed to demonstrate the beneficial of treatment with LAIs in prevention of institutionalization of young patients with schizophrenia.

Antipsychotic monotherapy is recognized as the treatment of choice for patients with schizophrenia. Nonetheless, the coprescription of more than one antipsychotic drug to an individual patient (polypharmacy) is suggested by some expert consensus guidelines as the last resort after exhausting monotherapy alternatives. More so, the empirical use of combinations of antipsychotic agents appears to be increasing with little research to support the relative efficacy, safety or cost-effectiveness of this practice. The pharmacological justifications for antipsychotic combinations include seeking to achieve greater therapeutic potential by optimization of dopamine D2 receptor occupancy, or activity across a wider range of receptors, on the basis that certain non-dopaminergic receptors, such as serotonergic, glutamatergic and adrenergic receptors, may be relevant to the pathogenesis of positive and negative symptoms (158,159). A comparative study between U.S. and E.U. estimates that in the U.S. 33% of patients receive two antipsychotics and almost 10% receive three, while in Europe, there are around 20% of patients with schizophrenia receiving combinations of antipsychotics. According to its data, when risperidone was added to clozapine, it showed a modest difference in the group of patients in terms of BPRS total symptoms (160). Different open-label studies documented the fact that combinations involving antipsychotics resulted in some degree of symptom improvement. The combinations most commonly referred to in this limited literature were olanzapine with amisulpride or risperidone, and quetiapine with risperidone. However, on the basis of early case reports, these authors noted that combining aripiprazole with a non-clozapine secondgeneration antipsychotic could possibly worsen the psychosis (161-166). Moreover, the prescription of combined antipsychotics includes the risk of adherence problems associated with a more complicated regimen and an increased adverse effect burden due to drug interactions (167,168). In certain clinical situations, antipsychotic co-treatment may be superior to monotherapy, however the available evidence for the overall efficacy of combining antipsychotics is sparse, thus being unable to draw firm conclusions (169).

Hospitalization for people with schizophrenia is a consequence of several different behavioural and psychosocial factors. Middle-aged persons with schizophrenia have almost four times greater likelihood of early institutionalization in nursing homes compared with their same age peers with no mental illness. The chronic, highly debilitating and refractory nature of these disorders means that stabilization of an individual’s condition regularly requires long stays in hospital and often for lifetime.

Second generation LAIs can serve to prevent cognitive and functional decline in schizophrenia. Clozapine treatment has been shown in several studies to be efficient in treatment-resistant patients. We concluded that continued efforts are needed to engage people with schizophrenia in treatment in order to prevent early institutionalization.

CHAPTER 3.
INSTITUTIONALIZATION, ETHICAL AND LEGAL IMPLICATIONS IN THE ASSISTANCE OF PATIENTS WITH DEMENTIA

3.1 Introduction

Over the last 20 – 30 years, many countries encountered increases in obesity, diabetes and hypertension, all of which have been linked to an increase risk for dementia. A study published by Norton et al in 2014 used current estimates of the proportion of Alzheimer's dementia cases that are due to various cardiovascular risk factors, including hypertension, diabetes and physical inactivity, to identify the proportion of cases that could theoretically be avoided by prevention or control of these risk factors (170). The study estimated that about 3% of worldwide cases of dementia in Alzheimer's disease (AD) are due to diabetes, 5% to hypertension, 13% to physical inactivity, and suggest that better prevention and control of these risk factors could prevent millions of cases decades ahead.

Alzheimer disease is characterised by neuropshychiatric symptoms like apathy, depression, anxiety, sleep disturbances, irritability, appetite disturbances, motor problems, delusions, disinhibition, hallucinations, and euphoria (171).

Since the neuropathological changes begin in the brain, almost 20 years before the clinical onset of symptoms, focus is now on the research concerning biomarkers to early detection of patients at risk to develop Alzheimer's disease. Most studied biomarkers are the CSF concentration of 42 amyloid β peptide, total tau and phosphorylated tau 181 (172). However, up to date, there hasn't been an established biomarker for diagnosing Alzheimer disease, nor can the above mentioned biomarkers differentiate between AD and other forms of dementia (173). In the advanced stages of the disease, neuroimaging like structural MRI can help support the diagnosis of Alzheimer disease.

Treating Alzheimer's disease remains a challenge. So far it can't be cured and the drugs available are only regarding the symptoms of the disease, with cholinergic agonists or NMDA-receptor antagonists, having little effect on the cognitive function.

The two pathological processes in research nowadays, are the extracellular amyloid plaques initially discovered by Alzheimer in 1906 and the neurofibrillary tangles composed of the tau protein. Neuronal loss progresses as these proteins build up in the brain. Efforts are being made to develop a disease modifying treatment and a lot of research has been done in therapies targeting Aβ, but so far have failed, one of the alleged reasons being that interventions were too late and the disease was too advanced (174). Another interesting topic about the management of AD is the use of ketogenic diet for its neuroprotective effects against the production of Aβ plaques, but also because there is growing evidence suggesting an impaired glucose metabolism in AD. This diet comprised of low carbohydrate, normal proteins and high fats, induces a state of ketosis in the body, switching the energy consumption from glucose to ketone bodies and fatty acids, triggering the inhibition of glutamatergic excitatory transmission with increased production of gammaaminobutyric acid from glutamate (175).

New emphasis is being put on neuroinflammation, as there is a number of growing evidence showing that Aβ activates microglia and determines a vicious circle of inflammation with cytokines increasing the number of amyloid precursor protein, which then increases the number of Aβ (176).

Dementia often associates with depression, especially in people who already have a psychiatric personal or family history, thus decreasing the quality of life, imparing the activities of daily living, but also increasing the burden on caregivers. (177). Brain pathology studies have shown that the neurodegenerative process is more advanced in people with comorbid depression and dementia. Moreover, evidence suggests inflammation plays a major role in the pathogenesis of both diseases. Understanding the underlying mechanisms of these common molecular pathways, can help to develop new drugs to treat these two disorders.

Another common feature of Alzheimer's disease, with an increasing prevalence in the course of the disease, is psychosis, characterised by hallucinations and delusions, with poor disease prognosis and very difficult to manage. There are no medications approved to treat dementia related psychosis, the management being the off-label use of antipsychotic medication, with minimal efficacy and safety concerns regarding increasing cognitive decline, infections, weight gain, metabolic syndrome, hypotension, increasing the risk for falls and stroke, but also the potential increase in mortality in these patients. Pimavanserin, a potent, selective 5-HT2A inverse agonist is a drug approved especially for psychosis-associated Parkinson's disease and is also sometimes used as an off-label medication to treat dementia related psychotic symptoms, with apparently good efficacy (178, 179).

Dementia related psychosis increases the risk of institutionalization. Also, results from the Needs in Young Onset Dementia study (NeedYD) show that people with young-onset dementia, are being cared for at home for a longer period of time (approximately 9 years), whereas people with late onset dementia are being institutionalized at 4 years after clinical onset of symptoms (180).

There is an important worldwide trend relevant to brain health over the last decades which is attributable to the large growth in educational attainment in both developed and developing countries. The proportion of population with a college education has increased in wealthy countries from 12% in 1970 to 27% in 2010 and from 3% to 11% in low and middle-income countries (181). Rising levels of education may be contributing to a decreasing risk for AD and dementia among the individuals around the world by increasing the stock of cognitive reserve among people who have been able to take advantage of educational opportunities. Worldwide dementia cases will likely grow significantly over the next 40 years because of increasing life expectancies and the aging of population worldwide (182).

The future course of global dementia epidemic through 2050 is likely to depend to some extent, upon the success of continuing efforts to improve public health (183 – 185). Efforts to prevent detect and control obesity, hypertension, diabetes and dyslipidaemia are likely to have maximum positive impact upon brain health and dementia risk in later life (184, 185). Public health strategies are likely to result in a progressive decline in age-specific incidence of dementia in high-income countries.

A growing number of studies now suggest a declining age specific risk of dementia in high-income countries over the last 25 years, which, if continued, could help moderate the future worldwide growth in dementia cases (182).

3.2 Researches regarding quality of life, ethical and legal implications in the assistance of patients with dementia

A. Background

Dementia, as a disease, raises a lot of ethical and legal questions about a patient's ability to do things like driving, voting, working in certain job fields, all of which can have a major impact on the quality of life of these patients. Furthermore, the economic burden on caregivers and society, raises questions about the insurance coverage for this illness (186). The legal aspects of dementia are also related to a person's capacity to make personal decisions and being able to do so without endangering themselves or the people surrounding them. However, at some point in the course of the disease, they all end up incapable of making decisions and they have to become the responsibility of a second person, which eventually will decide for every aspect of their lives. Patients with dementia are vulnerable and sometimes they can be the target of bad care by family members, a fact that raises another legal and ethical issues about the moral and legal obligation of the physician to intervene and report the misconduct of caregivers, in order to protect the patient.

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which highlighted the vulnerability of persons with dementia and legal aspects involved in their assistance.

Cretu OC, **Szalontay AS**, Mircea R, Chirita V, Chirita R. Ethical-normative conceptual evaluations in assisting people affected by Alzheimer's disease. *Revista Romana de Bioetica* 2010; 8(2): 134 – 140. **IF 2010 = 0.471**

Introduction: Occupying a central place in contemporary psychiatry, Alzheimer's disease is a priority of this science through the theoretical interest and the reflection of the disease in the current pathology. Described by Alois Alzheimer in 1907, Alzheimer's disease has become a "timeliness" being outlined as a "medical-social emergency". We can consider that Alzheimer's disease is aimed at "brain psychiatry" on the one hand, but on the other hand it raises great challenges in terms of its ethical and legal approach, taking into account the particularities of this disease.

Clinical and evolutive aspects of Alzheimer's disease: Alzheimer's disease can begin at preinvolutive age (before 65 years) and involutive (after 65 years) and represents more than 50% of all dementia according to literature. It is a primary degenerative dementia, morphologically manifested by generalized cortical atrophy, but with evident temporal- parietal accentuation, by the presence of amyloid plaques and neurofibrillary tangles generated by abnormal tau proteins. Dementia syndrome is characterized by the memory disorders and the aphasia-apraxia-agnostic phenomena, which are defining. Dementia syndrome may be associated with confusional state, depressed state, delusional ideas or behavioural disturbances.

The clinical picture recognizes three phases: the onset phase, the status and the terminal phase. The onset is insidious and in the early stages it may go unnoticed. Depression may be an early manifestation of Alzheimer's disease. As the disorder progresses memory and language disturbances, and the dramatic decrease in intellectual functions become more and more obvious. Cognitive skills are gradually lost, which will also be reflected in changing the patient's behaviour and in the loss of various functions. In terminal stages echolalia and verbal negativity occur and the neurological picture worsens. Identifying the cognitive functions that have been affected or even abolished in the patient may be useful to the clinician to explain specific behaviours to the family and to find the best ways to assist patients with dementia.

In any medical treatment involving human beings it is widely accepted in Western medicine that the patient should be informed by the doctor about any intervention in the field of medical assistance and that he must give his consent to the procedure on a voluntary, autonomous and unambiguous basis (187). Due to the progressive deterioration of Alzheimer's disease, the patient loses the ability to understand the information needed to make an autonomous decision as to the personal situation in order to arrive at an opinion based on independent reasoning and to express that opinion. This loss of informed consent or loss of competence will make it much more difficult to care for and treat the patient without violating his or her own views (188).

The right to know: The term knowledge refers to the process that places the subject in relation to the world and the result of its putting into action. Myths, the primordial events that have taken place since the beginning of time teach us and warn us that profound knowledge can be a danger: the danger of knowing the future. We can talk about the limits of our knowledge and why they exist, or we can only recognize the phenomena: what is shown, revealed or manifested in experiences. To know the reality, it is certain that we need to use our cognitive capacities, including reason. The right to know is a matter of respect for human dignity. Informing the patient is allowed to plan an optimal life experience in years when his capacities are still intact; to prepare a solid health care directive to be implemented in case of future incompetence. Certainly the desire for suicide will increase if we cannot give these individuals the assurance that their right and decisions will be respected.

The advance directives: In the United States, so-called advanced directives began to be used in the 1960s. These documents contain written indications in which patients decide whether or not to accept a number of medical, surgical or intensive care interventions for the time they will be incapable of making these decisions. Advanced directives were designed to solve the problem of the right to self-determination in patients who are no longer able to exercise this right for various reasons. They can provide legal support for the individual still in good health to exercise the right to self-determination in the case of medical treatment. In Western countries, all medical institutions are required to inform the patient about their right to self-determination in these respects (189).

Initially, the written forms of the advanced directives were used to specify the particular desires of an individual in special medical situations such as persistent vegetative state (190). They mentions to what point the patient accepts the artificial prolongation of life in these conditions and the medical interventions that are not accepted. Due to similarities, these documents have also been called “lifetime wills”.

Apart from this type of written instructions, there is also the possibility for a person to make decisions on behalf of the individual who has appointed it, decisions regarding personal care and medical treatment. Both ways could be combined to respect the incompetent patient’s rights (189, 191, 192). Advanced directives are increasingly accepted in Europe as well (193, 194). Many countries accept the early appointment of a person empowered to make decisions instead of the patient. However, “lifetime wills” are not a legally binding obligation. They are regarded as important indications of the patient’s will in the situation where medical treatment is needed. Some professional organizations are sceptical about the validity of these directives, scepticism based on the doubts that may arise over the authenticity and credibility of such a document. An act of an individual is authentic if written by that person and is the production of his will. In medical ethics there are different concepts in terms of authenticity and different requirements in determining whether a patient’s decisions are real. However, it is generally accepted that “authenticity” cannot be equated with “admissibility” or “rationality” and remains the question of a valid definition of “authenticity” (195).

In the legal acceptance of advanced directives a person has the right to refuse medical treatment that he does not want as many advantages as he would have. From an ethical point of view, the situation is more complicated. In determining the validity of these directives, the doctor cannot question their authenticity merely by arguing that the decision of the individual is irrational or that there is a better treatment at the moment. Many such decisions taken by different individuals by exercising the right to self-determination may seem irrational but are applicable since they do not violate the right to self-determination in a democratic society.

The equivalence of "the authentic" with "the rational" is therefore unconvincing and cannot serve as a basis for justifying the validity or invalidity of these directives. The validity of these directives cannot be invalidated by demonstrating the existence of "better treatments" than those specified in the patient's instructions simply because the very purpose of such an act is precisely the choice of the individual not to receive certain treatments at any given time disease progression or under certain medical circumstances (196).

Having as a starting point these theoretical considerations, it should be noted that there are important ethical differences between the advanced directives of a patient diagnosed with Alzheimer's dementia and those of a patient with any other illness. As a general rule, individuals suffering from Alzheimer's dementia are in the vast majority of cases elderly people who have had many experiences throughout their biography, have structured a personal attitude and can set priorities in the value system and life situations. More often than a younger individual, the elderly generally passed through the experience of the disease and convalescence, pain and its removal, the need for help and support.

Statistically speaking, elderly people use health services more frequently and have generally had contact with hospitals, doctors and other health institutions. They had the experience of death, mourning and pain of losing a family member or friend. This life experience can be considered a solid basis for expressing one's own will for personal care in the form of written guidelines from the perspective of personal experience and values.

The right to self-determination: Alzheimer's disease is a chronic, progressive disorder that causes progressive loss of cognitive skills. The fact that at an early stage of the disease the patient retains the ability to make self-determined decisions by considering incompetence in advanced stages of illness, makes Alzheimer's dementia and other chronic conditions an ideal indication for prior care guidelines. So, we can say that individuals affected by Alzheimer's disease formulate their care guidelines with the benefit of life experience and the presence of actual symptomatology.

In order for the patient with dementia to have the opportunity to exercise the right to self-determination, he should be informed about the diagnosis at an early stage of the disease as well as on the character of the disease, the evolution and the therapeutic and prognostic possibilities.

Some psychiatrists or other specialists who oppose this patient information accuse the particular diagnostic procedure in Alzheimer's dementia by a process of excluding other diagnostic possibilities, especially in the early stages of the disease, and in fact that it is possible be involved in this process a probability of error. Against these objections must be said that the probability of an error does not automatically justify hiding this diagnosis from the patient. Such a procedure will prevent the patient from shaping his own life when he is still in control of it and is capable of exercising his own will in view of a condition that will lead to the development of incompetence. Postponing the presentation of this information to the patient in order to obtain a greater certainty of the diagnosis leads to progression of the disorder, while the ability to exercise self-determination decreases accordingly (197).

The current limited therapeutic possibilities as well as the lack of curative treatment are another reason why we are ethically justified to inform the patient with dementia about his diagnosis at the early stage of illness. The patient's benefit and the principle of "primum non nocere" compels us to be cautious about how to communicate this information.

We should not overlook the fact that patients with dementia, particularly in early stages of illness, frequently suffer from a depressive syndrome, thus representing a vulnerable group (198). Events or stressful situations may precipitate symptoms of dementia or may cause catastrophic reactions. It is possible, in this case that the stress caused by diagnosis may precipitate or accentuate functional decline, depression or psychiatric symptoms such as agitation, aggression or paranoia (199).

Screening: Performing a screening by applying neuropsychological, assessment tests to population at risk would increase the prevalence of dementia cases diagnosed at an early stage. In an era of increasing disease detection and management capacities at an early stage, screening has become an accepted method for many medical conditions. Both medical professionals and the public accept screening for breast, cervical, colorectal cancer, diabetes, and hypertension, obesity with hypercholesterolemia, osteoporosis and even depression. However, screening for dementia is currently avoided. We must not forget that the prevalence of dementia in the world doubles every 20 years, rising from 24 million people with Alzheimer's dementia diagnosis in 2001 to 40 million in 2020 and probably 80 million in 2040. From the view of respecting the individual's autonomy, this test would have the advantage of communicating the diagnosis at a time when the patient could exercise his right to self-determination in a timely manner. On the other hand, should not be forgotten the potential danger of labelling the patient with this diagnosis and stigmatization by society (199).

Disscussions: The ethics of caring for patients with dementia have evolved in recent times, especially with the increase in the number of palliative care services in recent years and with medicine's increased ability to extend life. Many debate wheter or not the life extension that is provided through palliative care services, specifically through pain allivieation therapy and artificial nutrition and hydration is offering enough life quality to the patient, so that the patient considers it to be worth living. The answers to these questions vary extensively depending on the cultural background of the society that the patient is a part of (200). The Netherlands is a country which took a very progressive approach towards the ethics of dementia, compared to Roamania. At the present moment, in The Netherlands, not only euthanasia or assisted suicide is permited, but also the ending of a patient's life without his or her request. In 2005 a national guideline on palliative care was introduced in The Netherlands, describing the procedure of continuous palliative sedation until death (CPS). Following this guideline, a study published in 2012 shows that from a random sample of 1580 physicians, 38% had assisted a patients death through continuous sedation. Most of the patients assisted had a diagnosis of end stage cancer but a minority were suffering from dementia. Most of the physicians felt no pressure initiating countinuous sedation until death, and did so without the intention for death to occur (201). Considering the lack of remorse or intent for causing death that physicans had, one could argue that continuous sedation until death is different than euthanasia. The authors of an article published in 2014 argue exactly that by saying that the intention is the principal difference between the two. They also ad the fact that, unfortunately, this has led to a change of thought in hospices around the Netherlands, with diminished motivation to care for the terminaly ill. This is in part, the authors argue, due to the removal of the responsibility and the impact of CPS from the psysicians, and that this is why the boudries between CPS and euthanasia are dissipating (202). The results study from 2011 regarding advance directives for euthanasia can be an argument supporting the fact that CPS is different for euthanasia. The results show that only a small proportion of physicians adhere to advance directive of euthanasia. In this study, only 5 in over 400 elderly physicians adhered to an advanced directive for euthanasia, and furthermore, all of the cases the patients were competend of expressing their wishes at the time of the assisted suicide (203). Another ethical issue about the end of life care in patients with dementia is concerning the advance directive to not resuscitate (DNR). Arguments against DNR include the fact that it is beyond a doctors competence to determine for how much a patient could live after resuscitation and that even if that time is short, it could be important for the patients and their families, allowing them to communicate and to say their goodbyes (204). One study published in 2013, evaluated the shift in DNR and do resuscitate (DR) with time among nursing home residents. The patients that entered with DR status, had less severe diseases than those that entered with DNR status. Furthermore, patinets that entered with DNR status did not changed their status, while about 40% of the patients that enterd with DR status chaged with DNR during their stay. Authors state that periodical revision of the DR/DNR status should be periodically revisited in hospice care residencies (205).

Another issue we didn’t discuss at the time of publishing the article was the ethical matter of research involving patients with dementia. As AD is marked by progressive and irreversible cognitive impairment, the struggle to find new treatment methods and even cures is at record levels, but unfortunately and specifically because of the progressive cognitive impairment, obtaining an informed consent from the patient is difficult. Advanced dirrectives for inclusion in clinical trials are not a competent tool at our disposal as one cannot forsee and explain to the patient the various therapies that might be avaible for trials at a future moment (206, 207). One promising solution is that the patients sign an advance directive allowing their families to decide in their place whether they should partake in a clinical trial. Research shows that the probability that families would accept is low, but through democratic debates and education, their willingness will increase (208).

Conclusions: When we make the decision to inform the patient about the diagnosis of dementia, we must balance the benefits and harm to the patient by finding this diagnosis, in terms of medical ethics. For clinical practice we can say that the general rule is for patients to be informed about their condition and that exceptions are justified on a case by case basis by the principle of “non-harm”.

A diagnosis of Alzheimer’s disease is the beginning of a long and difficult “journey” that spans a period of about 10 years. Alzheimer’s disease affects not only the patient but also his/her family and relatives, travelling companions sharing the same experience with the patient. Even the patients make decisions about their final years of life, when they will be mentally and physically badly harmed, their relatives have to cope financially and make a decision for their medical care. The choices they make can only be based on assumptions and suppositions that may be false, since there is no longer the possibility of checking the veracity of these choices, the one on which they have done not being able to confirm.

No matter what decisions they make about the wishes of the sick, they will live with doubts, frustrations and feelings of guilt for the rest of their lives. It is therefore in everyone’s interest to make all the commitments in time (192).

Advanced directives as a legal act should be used especially in people with Alzheimer’s dementia diagnosis. Although there are reticence both from a medical and psychological point of view, patients should be informed about their condition and prognosis at an early stage of illness when the individual is still competent to make self-determined decisions.

Because of the rich experience of living, elderly patients are qualified to make decisions for their future based on preferences and the system of individual values.

3.3 Researches regarding institutionalization in dementia

A. Background

Psychosis and agitation associated with dementia contributes significantly to patient and caregiver suffering, accelerated functional and cognitive decline, and premature institutionalization (209, 210). Agitation is a collective term for a number of disruptive behaviours that can occur over the course of dementia (211). Agitation includes physical aggressiveness, verbal irritability, hallucinations, delusions, hyperactivity such as wandering, tearfulness and anxiety, and can be a major source of burden to caregivers of dementia patients.

Population-based samples also note high prevalence of psychotic symptoms in those with dementia. The first study of psychosis in AD reported the prevalence to be 16% with another 20% of subjects experiencing paranoid ideation (212). Visual and auditory hallucinations were present in 13% and 10% of the subjects, respectively. In addition, 30% of the subjects experienced misidentification syndromes. As many as 90% of people with dementia experience agitation at some point during the course of the illness (213).

Aggressive behaviours include hitting, kicking, spitting, tearing things, hurting self or others, grabbing, pushing and physical sexual advances. Correlates of aggressive behaviours include male gender, severe cognitive impairment, premorbid aggressive personality, psychosis, and the perception that others are intruding into one’s personal space (214, 215). Although the relationship between physical health and aggressive behaviour is unclear, those with greater neurological brain damage may demonstrate more severe disturbances (216).

Physically nonaggressive behaviours include hiding objects, hoarding objects, general restlessness, pacing, aimless wandering, eating inappropriate things, inappropriate dressing and performing repetitions mannerism. People with dementia who manifest physically nonaggressive behaviours tend to have fewer medical conditions and may have been more active throughout their lives (216). Verbal and vocal agitated behaviours tend to occur most frequently and include repetitive sentences or questions, unwarranted requests for attention, complaining, making strange noises, screaming, verbal sexual advances, cursing and verbal aggression. Correlates of verbally agitated behaviours include female gender, poor health, pain and depression (216). The risk of institutionalization is higher at a person with dementia when we encounter associated agitation, aggressive behaviours, severe cognitive impairment and reversal of the nocturnal sleep rhythm. Institutionalization from an elderly person’s point of view means the loss of their home, their familial and social environment and also the loss of memories, identity, independence, autonomy and dignity. Institutionalization also requires the adaptation of all persons involved (217). There can be positive effects of institutionalization such as improvement of physical symptoms and the functional level (217) and also negative effects such as decreased psychological and physical health and increased mortality.

In a study published in 2013 by Eska et al, results showed that institutionalization is determined multifactorial by only a few significant variables, which seemed to have diverse influences on different subgroups: the dementia patients’ and caregivers’ age, cohabitation of the patient and caregiver, caregiver burden and the use of community-based health services (218). Only the caregiver’s age seemed to determine institutionalization of the patient: the older the caregiver, the more likely because institutionalization.

The risk of institutionalization increased for dementia patients who did not live in the same house or apartment with the caregiving children. A higher educational level of the caregiver was found to indicate a significantly higher risk of institutionalization (218).

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which highlighted the factors involved in the institutionalization of patients with dementia, hospitalized for the treatment of other symptoms than cognitive decline.

Szalontay A, Burtea V, Ifteni P. Predictors of institutionalization in dementia. *Revista de Cercetare si Interventie Sociala* 2015; 49: 249 – 256. **IF 2015 = 0.424**

Introduction: Worldwide there are currently 25 to 35 million individuals with these illnesses, with 5 to 7 million new cases diagnosed each year, or one new case every 7 seconds (219). New reports estimate that more than 5 million people have Alzheimer's disease or another form of dementia in the United States. Projections indicate as many as 16 million older Americans will be affected by dementia by mid-century (220). New reports estimate that more than 5 million people are diagnosed with Alzheimer or another form of dementia in United States. The prognosis indicates that above 16 million older Americans will be affected by dementia by mid-century (220). As a consequence there will be a growing demand for assistance and educational programs for care givers. Also, it will be necessary that new shelter homes to be build. The goal of treatment for behavioural and psychological symptoms of admitted patients with dementia is the rapid remission of symptoms and then return patients to their home as soon as possible. Because of stigma (221), many patients experience difficulties being accepted by their family or communities following their discharge from a psychiatric hospital, even if they are in remission. Self-stigma (222) is another problem, even stronger if the patients are hospitalized for a long period. During hospitalization, some patients may die, others are transferred to medical hospitals due to somatic comorbidities and other are candidates for institutionalization. Family complains, residential circumstances, a patient's clinical characteristics strongly contribute to the decision of institutionalization. Findings suggested that predictors of institutionalization are mainly based on severe cognitive and functional impairment. Lack of support or assistance in daily living (223) is another contributing factor. To our knowledge, there are no studies for demented people in Romania for investigation of factors contributing to prolongation of hospitalization or institutionalization. The aim of the present study was to determine the predictive factors for institutionalization in patients hospitalized for the treatment of other symptoms than cognitive decline.

Material and method: 127 consecutive patients who meet DSM IV criteria (APA, 2004) for dementia hospitalized in the Psychiatry and Neurology Hospital Brasov between January 2010 and December 2011 were enrolled in the study. The study was approved by the institutional ethics committee board. In all eligible patients, the following items were evaluated: demographics, reason for admission, and type of dementia, cognitive status, daily living activities, BPSD, and treatment. Information was obtained for each patient regarding gender, age, education, marital status, living situation, and care caregiver.

Data were provided by patients, family members or staff employed caregivers, and psychiatric social worker. Residency prior to hospitalization was classified in: living in their own home, care facility, or medical hospital. The relationship between the patient and primary caregiver were categorized as partner, son or daughter, other family member or relative, or staff. Behavioural problems causing distress for the caregiver, which had become the primary reason for hospitalization, were recorded on the basis of interviews conducted with the caregiver. The reason for hospitalization include aggressive behaviour, over activity, psychosis and delirium. Aggressive behaviour comprised physically or verbally aggression towards patient or others. Over activity included non-aggressive behaviour that required constant monitoring, such as aimless wandering, trying to reach a different place, and restlessness. Delirium was also evaluated as an important factor for admission in acute psychiatric setting. A diagnosis of dementia was made according to DSM-IV criteria following interviews with patients and family members or staff, as well as on the basis of psychiatric, psychological and neurological findings, laboratory data, and head CT scans.

Behavioural and psychiatric symptoms were evaluated using the Behavioural Pathology in Alzheimer's disease (BEHAVE-AD) rating scale (224). The presence or absence of symptoms in each of seven clusters comprising a subscale of BEHAVE-AD was recorded, including psychosis, aggressiveness, activity disturbances, and agitation. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) by experienced psychiatrists (225). Activities of daily living were scored using ADL questionnaire (226). Treatment was recorded in terms of type and dose. Statistical analyses were performed using SPSS version SPSS 15.0. The differences between the two groups were compared using Student's t test. The chi-squared and Fisher's exact tests were used to assess categorical variables. Age adjusted odd ratio (OR) and 95% confidence interval (CI) were calculated by multivariate analysis using multiple, unconditional, logistic regression. P values less than 0.05 were considered to be statistically significant. The primary endpoint of the present study was the prevalence of institutionalization defined as patient transfer to chronic cases hospital or a private care facility. Patient's demographic and clinical characteristics at the time of hospital admission were analysed for their association with time to HD using univariate Cox's proportional hazards regression model.

Results: Demographic characteristics of the 129 patients identified as eligible for inclusion in the present study are list in table 22. Of these, 98 patients (76%) were discharged to their own home, 29 patients (24%) were institutionalized or putted on the waiting list. There were 10 cases transferred to another hospital and 4 died during hospitalization which were not included in the statistic. Analysis of the demographic characteristics revealed there were fewer men in the HD compared with INS (institutionalization) group, and that Alzheimer's disease was more frequent in the HD group. In the HD group, patients were more likely to have resided in their own homes with husband or wife as caregiver ($p<0.001$). Also, the BPSD symptoms at admission in the DH group were less likely to be aggressiveness and delirium.

MMSE and ADL scores were higher in patients in this group. In Alzheimer's case the majority of patient were discharged to home (72.8%). High education level was strongly correlate with low risk for institutionalization as well as high MMSE score ($p<0.001$), and good daily living activities ($p<0.001$). Table 3.8 shows the psychotropic medications used during hospitalization. The daily dose of antipsychotics was equal in both, as well as cholinesterase inhibitor and NMDA. Remarkable is the low number of patient treated with antidementials such as donepezil, rivastigmine, galantamine or memantine despite their availability.

The univariate analyses revealed that patients living in their own home prior to hospitalization with high MMSE scores and well capacity of day living activities are predictors of a shorter hospital stay. Male gender, living with son or daughter, aggressive behaviour as the reason for admission, was significant predictors of a longer hospital stay and institutionalization. Our results revealed that MMSE scores >16 predict the shortest hospital stay, whereas the combination of MMSE scores ≤ 12 and aggressive behaviour as the reason for hospitalization predicts the longest hospital stay and institutionalization.

Table 3.1. Demographics

Variables	**All patients N= 127**	**Discharged Patients**				**P value**
		HD (N=98)		**INS (N = 29)**		
		N	**%**	**N**	**%**	
Age (mean, SD)		70.6 (5.1%)		76.4 (5.5%)		0.005
Type of dementia						
AD	70	65	72.8	5	27.2	0.005
VaD	40	23	42.5	17	57.5	0.83
Other	17	10	58.8	7	41.2	0.19
Place before hospitalization						
Home	110	95	86.7	16	13.3	0.005
Hospital	5	2	40.0	3	60.0	0.27
Care facility	15	9	60.0	6	40.0	0.27
Other	7	3	42.8	4	57.2	0.33
Patient living						
Alone	24	17	70.0	7	30.0	0.15
With husband / wife	67	65	97.0	2	3.0	0.001
With son or daughter	26	10	38.5	16	61.5	0.17
Other	10	6	60.0	4	40.0	0.26
Caregiver						
Husband / wife	67	65	97.0	2	3.0	0.001
Son or daughter	20	8	40.0	12	60.0	0.005
Relatives	30	17	56.6	13	43.4	0.45
Employed caregiver	10	8	80.0	2	20.0	0.01
Education						
1 – 4 years	39	19	48.7	20	51.3	0.32
5 – 8 years	46	42	91.3	4	8.7	0.001
9 – 12 years	30	27	90	3	10.0	0.001
More than 12 years	12	10	83.3	2	16.7	0.18
MMSE						
21 – 25	5	5	100.0	0	0.0	0.001
12 – 19	42	30	71.4	12	28.6	0.06
<12	82	65	79.2	17	20.8	0.005
ADL						
5 – 6	10	10	100.0	0	0.0	0.001
3 – 4	40	35	87.5	5	12.5	0.005
0 - 2	79	55	69.6	24	30.4	0.36
Reason for admission						
Agitation	27	20	74.0	7	26.0	0.09
Aggression	55	35	63.6	10	26.4	0.005
Psychosis	20	15	75.0	5	25.0	0.1
Delirium	14	8	57.1	6	42.9	0.57
Alcohol	13	12	92.3	1	7.7	0.001

Table 3.2. Treatment categories used in patients with dementia

Psychotropic medication	**All patients**	**Discharged patients**				**P value**
	129	HD (N = 98)	%	INS (N = 29)	%	
Antipsychotics	46	34	34.7	12	41.3	0.34
Benzodiazepines	110	66	67.0	29	100.0	0.11
NMDA	10	7	7.0	3	10.3	0.23
Cholinesterase inhibitors	22	17	17.3	5	17.2	0.46

Discussions: To our knowledge, the present Romanian study is the first to investigate the factors involved in institutionalization of patients hospitalized for the treatment of other symptoms than cognitive decline. In addition to family and residential factors, multivariate analysis identified three clinical factors independently associated with institutionalization: MMSE score, aggressive behaviour as the reason for admission, and male gender. Cognitive function is strongly associated with performing ADL, which encompasses complex behaviours such as dealing money, cooking, cleaning, and taking medications (227 - 229). The need for continues care is greater for patients with lower MMSE scores, and may be a major obstacle to discharging patients even after remission of BPSD. Our results shown that aggressive behaviour is the primary reason for admission, and it is an independent factor for prolong hospitalization. Antipsychotics are currently widely used in treatment of aggressive behaviour in psychiatric hospital, even in demented people; however, the available data regarding the efficacy of antipsychotics are inconsistent (230, 231) and the doses that can be used are small because of the potential risk of considerable side effects (232) or death. Alternatives including sedative/hypnotics, anticonvulsants, serotonergic agents, lithium, α-blockers may be used but there is insufficient evidence (233). Patients with lower cognitive function admitted primarily because of combative behaviour had the lowest likelihood of discharging to home. In patients exhibiting aggressiveness, pharmacological or non-pharmacological treatment involving both patients and caregivers may be required from the early stages of dementia before the BPSD. In terms of relationships between caregivers and patients, it has been reported that children are less strongly committed to the caregiving relationship than spouses (234), and stronger support systems are needed for patients living alone. Other social factors that may have an impact on the time to SD could include economic status or the availability of care resources.

Our study has some limitations that are need to be acknowledged. As described above, the study included a relative small number of patients and we did not evaluate caregivers despite findings indicating the potential association with time to discharge and institutionalization. Pharmacotherapy was optimized for demented patients to achieve remission of BPSD as soon as possible, but there is no protocol for routine practice and treatment option remain mainly to the responsibility of physicians. These issues need to be taken into consideration in future studies, as well as in clinical practice. Finally, despite the heterogenic population from Brasov, characteristic for the biggest cities in Europe, the present study was conducted in a single institution in Romania. Future well-designed prospective and larger-scale studies are warranted to confirm our results.

Clinical characteristics, such as lower MMSE scores, aggressive behaviour as the primary reason for hospitalization, male gender and living with daughter or son, could be predictors of institutionalization in patients with BPSD. These findings should be taken into consideration when managing patients with BPSD to ensure administration of optimal treatment and care strategies to improve inpatient treatment outcomes. The pharmacological intervention with antipsychotics is recommended for patients who present severe agitation or violent behaviour, for a short period of time and under specialized supervision. In clinical practice, the therapeutic choice between first or second generation antipsychotic should be focused on the risk-benefit balance. In the future, more research is needed in effort to identify optimal strategies, which may combine pharmacological therapy and other interventions both for patients and caregivers in order to maintain the individuals with dementia as long as possible in their settings.

Full-text reviews of 360 papers showed that white race, greater dementia severity and older age increased the risk of long term care placement (235).

Married persons with dementia and living with their caregiver had a lower risk. Behavioural and psychological symptoms of dementia, the degree of functional impairment and caregiver burden had an important effect on the risk of institutionalization (235).

Results showed that the risk of institutionalization was higher in women than in men, in a study published by Runde in 2018 (236). The risk was also influenced in men by their relationship to their caregiver, in women by duration of care at baseline.

CHAPTER 4.
SUICIDE – A MEDICAL AND PSYCHIATRIC EMERGENCY

4.1 Introduction

Suicide is a significant public health problem worldwide, being the tenth leading cause of death (237, 238). Estimating prevalence in different countries is problematic because in many countries suicide is hidden and therefore estimate rates from national records will probably underestimate real suicide rates. Many of those who commit suicide do not seek help and do not inform others about their plans. In many cultures suicide is seen as shameful, sinful, weak or selfish. This acts to reinforce secrecy and silence. Identification of factors that may increase or decrease a patient's level of suicide risk can help clinicians to establish an estimate of the overall level of suicide risk for an individual patient and target modifiable behavioural, psychosocial, environmental and personality factors.

The so-called 'gender paradox of suicidal behaviour' states that females are more proned to suicidal ideation and attemps, whereas males actually complete suicide (239). Difficulty of coping with stressful life events like separation from the partner or financial problems seem to be the most frequent and unrelated to a specific gender. Other risk factors are immigration, gender identity, widowhood especially for men, having a somatic disease and young age in males having a mental illness – the two most common being affective disorders and substance disorders, sexual abuse in women (240). The process of suicide begins with the ideation and planning of the suicide, then increasing communication about the suicidle act which leads to several attempts, each times increasing the intent of completing the act until finally, it succeds. This process can take a long time, but it can also happen very quickly, males being more proned to commiting suicide much quicker than females.

After a first episode of self-harm or suicide attempt, clinicians can use different scales to assess the patient's potential suicide risk. One of the first scales to be used in research and clinical practice, was the Suicide Intent Scale, a list of 15 items covering the characteristics of a recent suicide attempt like the risk of being found, the plans to commit the act, the perceived lethality of the method and the wish to die from the attempt (241). Also, sometimes clinicians used the Scale for Suicide Ideation to quantify the intensity of the suicidal intent (242), a useful tool not only to descover patients at high risk of commiting suicide, but also to evaluate the efficacy of treatment.

Among people with a mental illness, those that suffer from mood disorders have the highest risk of suicide, major depressive disorder ranking second after bipolar disorders (243). Patients that have a substance abuse disorder also have an increased risk of suicidal ideation. Alcohol is a central nervous system depressor, but also, in acute intoxication, it can increase impulsive and aggressive behaviour, and eventually put in practice the suicidal thoughts.

A report from Romania – insider regarding suicide rate in Romania, published by Irina Marica at 20 March 2014 showed that the suicide rate in Romania was above the European average for some of the most predisposed categories, according to Eurostat survey quoted by Mediafax local agency (244). According to the survey, the age groups with highest suicide incidence are 15 – 19, 50 – 54 and over 85. In Romania, suicide among teenagers aged between 15 and 19 had a rate of 6.3 deaths per 100000 inhabitants, over the European average of 4.6 (245). For the 50 – 54 years age group, Romania has a rate of 22 suicides per 100000 inhabitants for both sexes, compared to the European average of 18.3. The rate of suicide among Romanian women aged 50 – 54 was below the EU average, but the rate in the case of men was very high – 40.6 compared to the EU average of 28.7 per 100000 inhabitants (245).

In World Population Review, a report regarding suicide rate by country in 2019 showed that this year, among the top five highest suicide rates there are Lithuania (31.9 suicides per 100000 inhabitants), Russia (31 suicides per 100000 inhabitants), followed by Guyana in South America (29.2 suicides per 100k) and South Korea (26.9 suicides per 100k). Moldova is occupying 24 place, with 15.9 suicide per 100k and Romania is on 63 place, with 10.4 suicides per 100k (male suicide rate 17.9 and female suicide rate 3.3, with a total number of 2029 suicides per year) (245).

4.2 Researches regarding alcohol abuse and its relation to suicide behaviour

A. Background

A 2002 WHO first time report on violence and health, found that almost 1 million people died from suicide in 2000, with percentage rates varying between countries, the highest remaining those in the developing countries and triggering national prevention strategies (246).

The factors contributing to suicide risk are divided into two major categories: individual factors and social factors (247 – 249). The first category includes mental health issues (e.g. alcohol or drug addiction, mood disorders, severe personality disorders, schizophrenia, etc.), repeated engaging in deliberate self-harming behaviours, and relapses of suicide attempts throughout one’s lifespan, hereditary vulnerability (history of suicide events within the family-of-origin), chronic medical conditions (e.g., terminal stages of cancer diagnosis), as well as other psychological vulnerabilities (e.g., predisposing personality traits, emotional instability or social isolation accompanied by a chronic feeling of loneliness). The second category includes socioeconomic factors (e.g., status on the labour market, marital status), familial factors (e.g., severe marital troubles), and stressful life events. The cumulated effects of the two categories of factors can contribute to reduced individual tolerance in relation to psychological stress and to increased risk of suicide behaviours (250).

Alcohol abuse and addiction have been linked to a number of health problems and other consequences. One of the consequence that is commonly overlooked is the increased risk of suicide**.** Reasons that lead to this terrible outcome are the impulsivity, aggressiveness and hopelessness associated with alcohol abuse, but also the co-accurence of stressful life events (251). Also, pre-existing depression contributes to increasing the risk for suicide in alcohol consummers, especially in the elderly people (252). Alcohol represents one main contributing risk factor for disability life-adjusted years as there is an established causal link between alcohol consumption and a considerable number of diseases (almost 200 illnesses ans injuries according to WHO), like hepatitis, cirrhosis, cancer, epilepsy, haemorrhagic stroke, cardiomyopathy, pancreatitis, infectious diseases such as tuberculosis and HIV etc. but also mental health diseases, especially alcohol dependence (253). After major depressive disorder, alcohol abuse was found to be the most common psychiatric disorder in people attempting suicide (254). Although some studies have found that alcohol dependency is associated with a lower lethality of suicide attempts, the risk of reattempting is higher in this group, requiring special attention and prevention strategies (255).

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which evaluated the impact of alcohol usage in suicide.

Szalontay AS, Burtea V, Ifteni P. Blood alcohol concentration in suicide: a 10 years study. *Revista de Cercetare si Interventie Sociala* 2014; 46: 144 – 152. **IF 2014 = 0.798**

Introduction: Suicidal behaviour is a major health problem worldwide. The high number of suicides drew attention to medical professionals. Last Report of WHO on the overall rate of suicide in the world dating back to 2000 and showed that the rates of suicide were 25 men for 10000 inhabitants and 6 women for 10000 inhabitants with 2000 new cases / day and a million / year (WHO, 2000). In Europe of 2002, suicide is the leading cause of death caused by intentional and unintentional injuries, in fact 21% of the total, and the same time represents more than half of all intentional injuries exceeded more than twice the rate of hetero-aggression and 10 times the rate of lesions in wars (256). In Romania, the number of suicides varies geographically and is ranked between 7 – 15 cases per thousand inhabitants, with a higher incidence in areas inhabited by ethnic Hungarians at the same rates as in other European countries (257). There are strong evidences of genetic background of this phenomenon but frequently the cultural, socio-political or economic aspects of these countries influenced the phenomenon (258, 259).

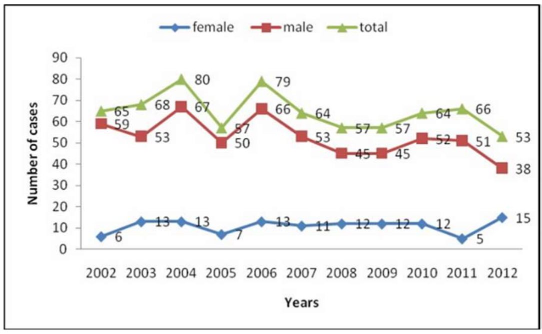
Risk factors for suicide include mental disorders such as schizophrenia, major depression, bipolar disorder and substance abuse disorders (260, 261). Economic status, marital separation or divorce, jobless, financial loss, chronic illness or cancer are other important risk factors for suicide (262). Long-time alcohol usage is linked to impulsivity, aggression, lack of inhibition and refusal to obey the social norm. Alcohol abuse as drugs usage often impairs the course of mental disorders, especially in case of major depression, schizophrenia, bipolar disorder and anxiety in term of quality of life, relapses, loss of social status, increasing suicide risk (263 – 265).

The aims of the study were to evaluate the suicide in the geographic area of Brasov between 2002 and 2012. We tried to determine if the cases of suicide remain constant in this interval. We also evaluate the impact of blood alcohol concentration in suicide.

Material and method: The retrospective study was based on existing documents in the archive of forensic services and included all cases of suicide that took place in Brasov County, Romania during 2002 – 2012. In the retrospective studyenetered a total of 719 cases. Brasov is one of the biggest Counties in Romania with about 400000 inhabitants. The population are heterogenic with Romanians, Hungarians and German ethnics. In the summer and winter it is visited by many tourists from Europe and Asia.

Data were collected on age, sex, year of death, suicide type and BAC (blood alcohol concentration). Statistical analyses were performed using SPSS version SPSS 15.0. The differences between the two groups were compared using Student’s t test. The chi-squared and Fisher’s exact tests were used to assess categorical variables. Age adjusted odd ratio (OR) and 95% confidence interval (CI) were calculated by multivariate analysis using multiple, unconditional, logistic regression. P values less than 0.05 were considered to be statistically significant.

Results: The study included 589 men (83%) and 121 women (17%), sex ratio B: F = 4.87. The mean age of the study group was 48.15 years. The annual number of suicides was relatively constant during the studied period, around 70 cases per year. There were a decreasing in cases in 2011 and 2012. Figure 4.1 shows stagnation or a slight decrease of the suicide rate in women between 2007 and 2011.



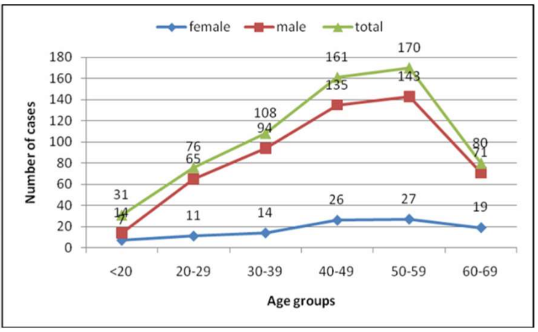


Figure 4.1. Number of suicides between 2002 and 2012 **Figure 4.2.** Suicides on various age groups

The main method of suicide was hanging with 556 cases (78.3%), followed by jumping from heights with 61 cases (8.5%) and poisoning with medicines 32 cases (4.5%). Other ways chosen to commit suicide was by poisoning with insecticide, cutting wrist, self-immolation, drowning, firearms and disposal in front of train. In the studied period there was a variable distribution of the number of suicides by age group. It is noted a steady increase in suicide with age once touching a peak in the 6th decade of life, when there were 170 suicides (Figure 4.2).

The results showed a great proportion of cases in which patients were intoxicated with alcohol before attempting suicide. In 329 cases (46.33%) alcohol was found in deceased persons, from whom 306 (93%) were males. In table 4.1 is presented the results regarding high levels of BAC. A significant number of individuals were intoxicated in the moment of suicide. In 208 cases (29.29%) values of BAC were above 1.00 g/ dL. The mean age of individuals were significantly lower (40.00 years vs 47.02 years) in cases with BAC above 2.00 g/ dL compared with BAC lower than 1.00 g / dL ($p < 0.005$).

Table 4.1. The BAC concentration and mean, mean age and number of cases

BAC (g/dL)	Number (N)	BAC Mean (g/dL)	Age mean (years)
<1.00	123	0.53	47.02
1.00 – 1.99	157	1.42	44.52
2.00 – 2.99	40	2.31	40.00
>2.00	11	3.51	42.36

Only 2 cases (14.28%) were intoxicated in individuals with jumping from heights as a suicide method which may demonstrate a strong willingness to die. Similar studies conducted in European countries revealed that alcohol usage are frequently found in individuals dead through suicide.

Discussions: The work is one of the first studies on the suicide rate among the population of Brasov which is heterogeneous as ethnicity, including Romanians, Hungarians and Germans). In the geographical area of Brasov like in most European Countries, suicide rates mainly increase with age, with exceptions in Ireland and Finland where suicide rates are maximal in middle-aged people with declines in elderly (266, 267).

The main finding is that alcohol was present in the blood of a significant proportion of cases and the average age of those who consumed alcohol were significantly lower than those without alcohol in the blood. Most of the cases were males which confirm studies of other authors (268). The main method of suicide was hanging. There are a growing number of cases who used firearms. Individuals who choose to commit suicide by jumping from heights had the lowest rate of alcohol use which demonstrates readiness to die (269). It is well known that alcohol is linked with poor response to bad social stimuli and with decrease serotonin levels (270). There were significantly differences between cases in terms of age and blood alcohol concentration. Those with the highest BAC were younger than those with low BAC.

These findings are important because others studies reported that in many cases individuals who committed suicide were previously hospitalized or treated for alcohol abuse (271). In some cases the psychological evaluation during hospitalization revealed anxiety or depression symptoms caused by emotional or financial problems but the treatment was stopped after discharge. The younger age of those who kill themselves being intoxicated demonstrated that alcohol abuse represents currently a major problem in national health and needs special programs of prevention (271). One of the study limitations was the degree of underreporting of suicide. It is known that some car crashes or falling from heights were initially reported as accidents and after criminal evaluation the conclusion was changed to suicide (272). In other studies, authors reported that hanging or firearms are more accurately reported as suicide than nonviolent methods, such as poisoning (273). The study showed that the traditional methods to commit suicide like hanging or jumping from heights are the most common methods and are quite similar worldwide (274, 275).

Firearms used in suicide were lethal at the same proportion with hanging (80 – 90%) (276). This raises once again the issue of access to weapons, either for hunting or protection. Pesticides should have a strict storage and sale only in special circumstances. Prevention of suicides by restricting access guns, medicine potentially lethal and pesticide are methods that can be easy considered by authorities and must be reconsidered (277). Mass-media can help prevent suicide by linking suicide with negative outcomes such as pain for the suicide and his survivors (278). Suicide is an important cause of mortality worldwide including Romania. We observed that hanging and jumping from heights were the leading causes of death by suicide in men and women. Those methods are extremely lethal and somewhat facile to the individuals. This study demonstrated the impact of alcohol usage in suicide. Preventive efforts to reduce the alcohol intake in group risk may decrease the annual number of suicide as well as the restrictive access to fire arms and pesticides.

4.3 Researches regarding affective disorders and suicide

A. Background

Suicide is one of the leading causes of death in the world, and depression is among the top causes of morbidity and mortality at international level. The main complication of any depression is precisely suicidal behaviour, with all its facets.

Suicide is a severe problem, with complex implications, its overall rate being 18 / 100000, with variations related to gender, age, ethnicity, etc. Suicide is, beyond the individual impact, a priority public issue. According to the WHO, suicide is the act by which an individual seeks to physically self-destruct, with more or less genuine intention of losing his life, being more or less aware of his motives. "Suicide is 3 – 12 times more common in psychiatric patients than in the general population (279). The main disorders associated with suicidal behaviour are emotional disorders (major depression and bipolar disorder), schizophrenia, alcohol abuse, personality disorders (borderline and antisocial), organic disorders (epilepsy, dementia), anxiety disorders (posttraumatic stress disorders), unipolar depression (280). Of the victims of suicide, 45 – 64% suffer from a depressive spectrum pathology and, on the other hand, 15%of patients commit suicide. Depressive states appear in many mental illnesses, and may be accompanied by autolytic behaviour, which is why depression should be approached as a genuine medical – psychiatric emergency. Identifying suicide risk is one of the most challenging diagnostic in psychiatry, often targeting patients with marked dissimulation behaviour (281).

Depression is estimated in current practice at primary care at 20% of all patients with psychiatric disorders. The clinical experience suggests that 30% of depressed patients at some point in the development of their psychiatric disorder, experience a mood swing, becoming bipolar depression (282). Ethnic variations can be significantly correlated with genetic differences in different populations, explaining different epidemiological values and indirectly confirming the neurobiological background (283). Thus, studies on the Chinese population have estimated prevalence values of 0.4% for bipolar disorder and 1.4% for major unipolar depression (284). The incidence of depression – 80 – 200 / 100000 / year in the male population and 250 and 7,800 / 100000 / year in women (285). The average age of onset – towards the end of the third decade of life, but can begin at any age, starting from childhood (286).

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which intended to highlight patterns of depression that associate suicidal behaviour and autolytic attempts.

Untu I, Bolos A, Radu DA, **Szalontay AS**, Chirita R. Particularities of suicidal behaviour in depressive spectrum. *Revista de Cercetare si Interventie Sociala* 2019; 65: 149 – 162. **IF 2018 = 1.076**

Introduction: Depression is undoubtedly one of the most common disorders in the population; the risk of developing a depressive disorder throughout life is 15% (287). According to the World Health Organization (WHO), depressive disorder is currently the fourth most disabling cause and is expected to reach the second place after the cardiovascular disease in 2020. The exact prevalence of this disorder is not yet established due to the variety of diagnostic criteria used in epidemiological studies, estimated to be 5 – 12% in males and 12 – 20% in females (288). The term “depression” is inappropriate because it refers to a single illness (289), while depression has a number of clinical manifestations, and the phrase “depressive disorders” is more appropriate (290, 291). In the American Psychiatric Association (2000) data, the incidence of major depressive disorder was 1% in males and 3% in females, the mean age is 40 years for both sexes, 50% of cases starting 40 years ago, and 10% 60 years old.

According to biological theory, autolytic conduct is indissolubly linked to the level of 5-hydroxyindolacetic (5-HIAA), a serotonin metabolite, which modulates affectivity, impulsivity, aggressiveness (292). Thus, a serotoninergic activity decreased in the prefrontal cortex will lead to a behavioural and cognitive disinhibition, resulting in aggressive and consecutive impulses of suicide (293). Suicidal behaviour has several aspects (294). One of these is the suicidal ideation, which is the existence of thoughts expressed in various forms, without having a concrete autolytic purpose (295). Another aspect is the threat of suicide that constitutes the oral or written expression of suicidal intention without the well-intentioned desire to commit this act (296). Suicide attempts (parasuicide) are self-actions performed either with the real intention of committing suicide (unsuccessful suicide) (297), or with the intention of transmitting various states, messages to the entourage (298). Complete suicide is the end point and irreversible element of self-limiting behaviour (299), producing deadly lesions with a clear previous intention of dying (300).

According to the Practical Intervention Guide of the American Psychiatric Association (APA), suicidal risk assessment is a multi-axial process that corroborates data gathered on the subject’s behaviour as well as its psychosocial factors and history (301). The purpose of the suicide risk assessment is to identify the factors that may increase or decrease the risk of suicide and allow the rapid formulation of a safety plan that addresses those favourable factors (302).

The purpose of the assessment is to quickly guide the subject to a certain degree of risk and then to allow an immediate individual intervention to secure the subject and attack the targets of the care program (303). Granello & Granello (2007) (304) identifies 12 principles underpinning the suicide risk assessment process. He starts from the idea that trying to evaluate a suicidal individual, the clinician is tempted to adopt a detailed, focused, detail-based attitude and thus presents a vision in the tunnel that ignores the wider picture of the subject's life, interests, and situation.

Essential Principles of Suicidal Risk Assessment are: (1) Every person is unique, different; (2) Evaluation is complex and challenging for both subject and clinician; (3) Evaluation is a continuous process that extends throughout the care of the subject; (4) Leads to possible errors generated by excessive caution (e.g false positives); (5) Evaluation is as activity that is based on collaboration and consultation; (6) Evaluation is based on clinical judgment; (7) Take seriously all threats, alarm signs and risk factors; (8) Ask hard questions, incommode, embarrassment; (9) Suicidal risk assessment is part of the therapeutic intervention; (10) Evaluation seeks to uncover the hidden messages of the subject; (11) The evaluation is done in a cultural context that must be taken into account; (12) All evaluation actions must be documented in the subject file.

The present paper refers to the detection of basic clinical correlations in order to highlight patterns of depression that associate suicidal behaviour, including ruminative, ideological, and autolytic attempts.

Material and method: The integral part of the research on the motivational patterning of the suicidal behaviour in the depression spectrum focuses on the detection of clinical correlations and implicitly diagnostics of various forms of depression with or without psychotic symptoms that associate rumina, or even self-help attempts. The batch targets only male patients to avoid including an additional variable and to provide better homogeneity to the group as it is a narrow study that highlights behavioural peculiarities that may undergo variations on gender. Thus, we have recruited a consignment of 170 patients admitted to the Socola Institute of Psychiatry, having main diagnosis of the depression spectrum, including: (1) Severe Depressive Episode with Ideation or Autolytic Attempt; (2) Severe Depressive Episode with Psychotic Symptoms and Autolytic Ideation or Tentative; (3) Major Recurrent Depressive Disorder, current severe episode with suicidal ideation or attempt; (4) Major Recurrent Depressive Disorder, current severe episode with psychotic symptoms and autolytic ideation or attempt; (5) Bipolar affective disorder, current depressive episode with psychotic symptoms and with suicidal ideation or attempt; (6) Bipolar affective disorder, current depressive episode with suicidal ideation or attempt.

Positive diagnostics (WHO, APA):

- Disposition: depressive, irritable or anxious
- Associated psychological manifestations: lack of self-confidence, low self-esteem, concentration deficit, loss of interest in ordinary activities, negative expectations, and death and suicide ideas.
- Somatic manifestations: psychomotor inhibition (or agitation), anorexia with weight loss (or weight gain), fatigue, insomnia (or hypersomnia), anhedonia, loss of sexual desire.
- Psychotic symptoms: delusion or devaluation and sin, reference and persecution, negative health change, poverty, depressive hallucinations.

- Exclusion criteria: absence of a somatic and/or cerebral condition, and the possibility of inducing symptomatology by a psychoactive substance.

Evaluation: For the standard depression assessment we used Hamilton Depression Scale (HAM-D). The clinical evaluation of the patients included in this section of the study necessary included the following: (1) family history and heredocolateral history; (2) psychiatric history, treatment history (compliance issues, responsiveness to treatment, duration of treatment; (3) somatic resistance factors (ferrites anaemia, hypoproteinaemia, and thyroid dysfunction), alcohol addiction and alcohol consumption, lack of socio-familial support.

The exclusion criteria, aimed precisely not to include cases of: (1) depressive disorder due to a general medical condition; (2) substance – induced depressive disorder; (3) mourning; (4) schizoaffective disorder; (5) schizophrenia; (6) personality disorder; (7) depressive mood disorder; (8) primary sleep disturbances; (9) anxiety disorders with depression. The present study is retrospective, descriptive, clinical anamnestic and paraclinical information being omitted from patient's clinical charts.

Results: The results of the study outline the predominant symptoms of depressive episodes, highlight the distribution of depressions depending on the anxious or inhibited form and mark different patterns of autolytic behaviour. This analyses the frequency of autolytic ruminations, the actual autolytic idea, and the unique and multiple attempts at patients in the study group. It also includes the category of autolitic ruminations in the context of the appearance of these as suicidal thoughts, which can gradually evolve towards ideation and suicidal attempt. In addition, the results highlight the frequency of psychotic symptoms associated with depressive episodes, as well as its relationship with the motivation of suicidal behaviours. Later, the correlation between ideation / suicidal rumination / suicidal attempts and the presence of the main motivational springs revealed by the observation sheets of the patients included in this study is analysed. Finally, Hamilton scores for depression are associated with the different types of suicidal behaviour. The frequency of main symptoms of depression in the study group is similar to international statistics; depressed mood, anhedonia and fatigability are the most consistent signs of depression. These symptoms create by themselves an unfavourable context to the patient, making room for thoughtless thoughts that gradually evolve towards the only viable solution that the patient can think of, namely self-annihilation (Figure 4.3).

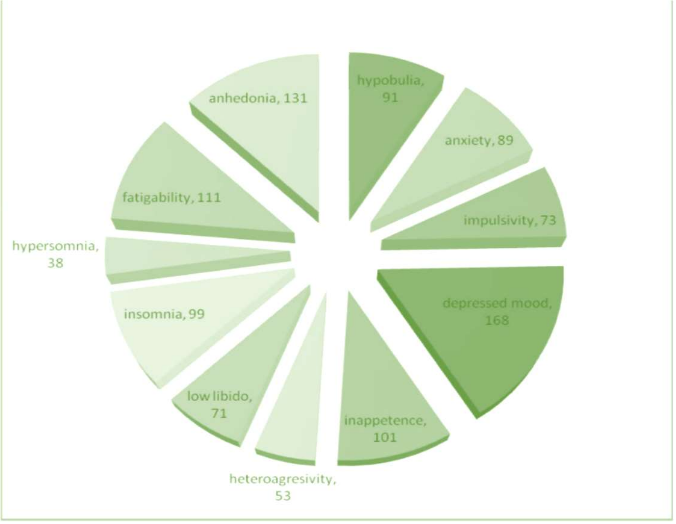


Figure 4.3. Distribution of main symptoms in depression

Inhibited depression correlates sensitively with several cases of suicide versus anxiety. However, the increased incidence of suicidal behaviour among patients with dominant anxiety elements is explained by the fact that paradoxically, anxiety is a universally acknowledged predictor / risk factor for suicide. On the other hand, inhibited depressions imply marked hypobulia, so the patient requires a strong determination to move to the act, the suicide remaining for him, the only solution to exit from a seemingly unresolved situation. In addition, it is important to note that in the study group, the most common manifestation of suicidal behaviour is a single attempt, followed by persistent suicidal ideation and recurrent attempts. Suicidal rumination have the lowest frequency precisely because they often remain unidentified / undeclared by patients.

The unique attempts detected in this study occurred in 38% of cases after ingestion of alcoholic beverages, the patients included in the batch not being alcohol dependent and having no psychiatric pathology related to the use and abuse of alcohol, due to the debilitation state it can cause ethanol on the central nervous system (Figure 4.3). In 42% of cases of a single suicide attempt and the new cases of attempted recurrent attempts are made by voluntary drug or polymedicine intake, while 12% of them have tempted suicide by ingestion of pesticide or other toxic substances. Of the 42% who ingest the medication, 85% have ingested psychotropic medication, the rest having suicidal attempts by ingestion of various drugs, from non-steroidal anti-inflammatory drugs to prescription medication for cardiac pathology. Of the patients who inhaled psychotropic medication, 62% used their own medication, prescribed for depression, and the rest had ingested medication from relatives who had a psychotropic background medication. The most commonly used psychotropic agents were benzodiazepines, and in most cases where benzodiazepines were involved in the patient's personal prescriptions, they were present in the baseline treatment regimen of at least 60 days.

With regard to cases of depressive episodes with psychotic symptoms, most patients have committed suicide attempts under the influence of psycho-productive phenomena, especially against the background of a delusional idea. A smaller proportion of patients with depressive episode with psychotic symptoms had suicidal motivations independent of associated psychotic phenomena. Thus, among those who have experienced suicidal behaviour in a psychotic context, most have presented a delusional idea of futility and self-deprivation, the rest having either other delusional forms of depressed delusional ideas or even hallucinations in the context of a true Cotard syndrome (2% of patients in the study group). Of the patients who experienced degrading or defamatory hearing hallucinations, 41% committed suicide attempts, and 36 % of those experiencing imperative hallucinations, who dictate suicidal acts, autolitized themselves. The rest presented only suicidal behaviour independent of psycho-productive phenomena (Figure 4.4, 4.5, 4.6). In this respect, the fundamental importance of the correct management of delusional-hallucinatory symptoms associated with depressive episodes, which by their content can increase the suicidal risk of the targeted patients, is underlined.

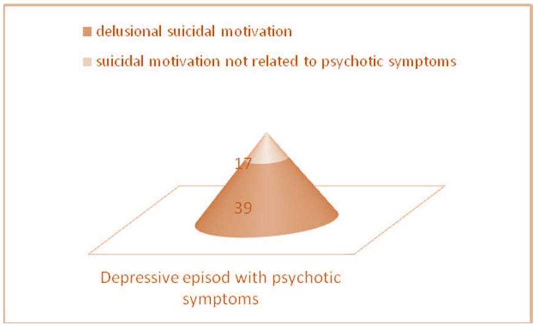


Figure 4.4. Presence/absence of psychotic motivation for suicidal behavior in depressive episod with psychotic symptoms

Figure 4.5. Correlation between type of delusional idea and type of suicidal behaviour

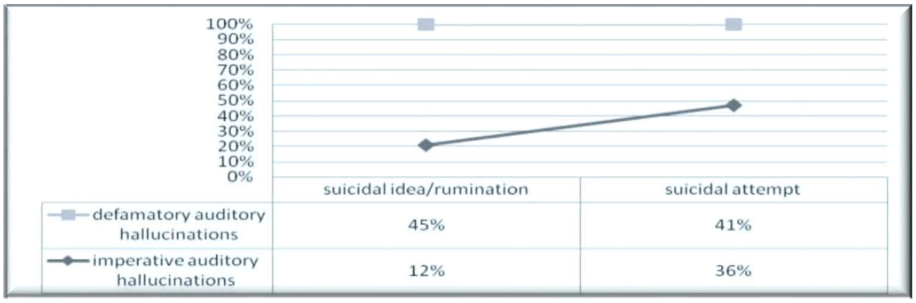
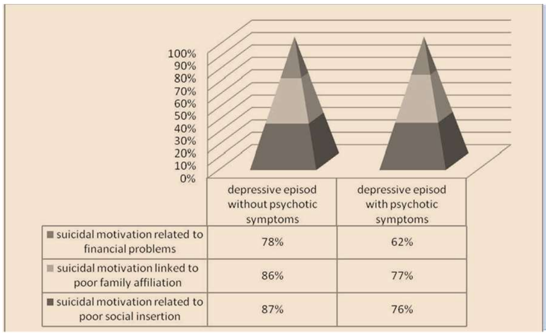


Figure 4.6. Main types of hallucinations in psychotic depression and type of suicidal behaviour

Regarding unrelated motifs of psychotic phenomena, occurring in all types of depressive episodes in the endogenous pseudo, the most common reasons were the rationale for financial difficulties, those related to poor family affiliation (including couple issues) and those related to poor social and professional insertion (Figure 4.7).



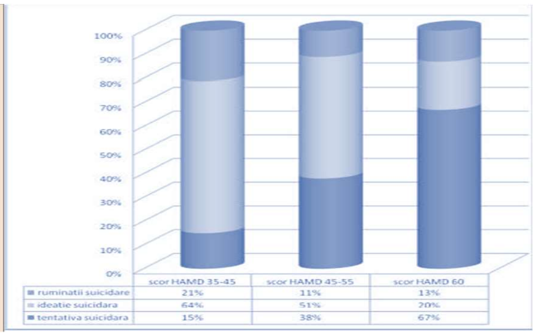


Figure 4.7. Main social reasons for suicide

Figure 4.8. Suicidal behavior correlated to HAMD

Regarding the correlation between the presence of different types of suicidal behaviour and the scores of the Hamilton scale for depression, there is a direct proportionality between the inward scores and the increase in the frequency of suicidal attempts, while for inferior scores defining all the severe depression, the suicidal ideation is more frequent (Figure 4.8).

Discussions: A recently published systematic review including data from 33370 respondents, identifies a two fold risk of increased suicidal related behaviour (suicidal ideation, suicidal plans and attepmpts) for patients suffering from a psychotic event compared to non-psychotic patients.(305). Another systematic review and meta-analysis published the same year, found the same ods ratio regarging the risk of associate suicide behaviour in patients with unipolar depression with psychotic symptoms versus patients without psychotic symptoms.(306)

Our results, regarding the correlation between the psychotic events and suicidal motivation are in accordance to these results. One study published in 2015, evaluated college students using the CAPE-P15 scale. They concluded that lifetime history of perceptual abnormalities and persecutory ideation are associated with a higher risk of lifetime suicidality, while the presence of bizzare experiences has no association with an overall icreased risk (307). Another study obtained similar results concluding that suicidal behaviour is correlated with the intensity of the presence and intensity of psychotic symptoms. (308) Here, the authors used the Beck depression inventory and Beck's scale for suicidal ideation to quantify the extent of suicidal related behaviour. In our study, we used the Hamilton scale for depression, which does not account for the extent of psychotic symptoms. Nonetheless, our results indicate in an arguably similar fashion with the aforementioned study that suicidal behaviour is correlated with the intensity of the depression, without taking into account psychotic symptoms. This, is further investigated by Sulivan et al., and although the subjects included in the study were underage adolescents, the results show that psychotic events and depression are independent predictors for suicidal behaviour. Also, the author found that, adding the measure of depressive symptoms on top of the psychotic symptoms' measure, increases the predictive value of the measurement. (309). We conclude from this results that it is important that psychotic symptoms and depressive symptoms are to be taken simultaneously into account when assessing the risk for suicide. In conclusion, the results obtained in this section of the research on motivational patterns of suicidal behaviour are related to major milestones, re-analyses and trends in international suicide research. The relationship of direct proportionality of the severity of depression with the higher ability to commit suicide is confirmed, in the context of reaching an unbearable ceiling of despair. This paper is a preamble for more specific future research that takes into account particular items on depression and suicide scales and correlations between items that directly target suicidal behaviour and different forms of suicidal behaviour. The results also reveal that the usual scales used to quantify the severity of depression can be important predictors of potential suicidal behaviour, similar to the results obtained by other published papers (307-309). In addition, the present study requires an extension to provide picture of the revealed elements related to male gender and in terms of female population, with specific gender specifics.

At the same time, we can observe the polymorphism of the suicidal motivational profile, reflecting once again the imperious need to not neglect the psychotic symptoms that can be associated with depression, which can often bring about an autolytic behaviour. In addition, there are a number of differences regarding suicidal behaviour according to the socio-familial insertion level of patients with depression. Thus, the importance of the bio psychosocial concept in the integrated and multidimensional understanding of the motivational resorts of suicidal behaviour is reconfirmed

CHAPTER 5.
INTERDISCIPLINARY APPROACH OF THE PATIENTS WITH PSYCHIATRIC DISTURBANCES AND SOMATIC COMORBIDITIES

5.1 Introduction

Comorbidity is associated with serious implications for health due to the impact on diagnosis and treatment. The term comorbidity was introduced for the first time in general medicine years ago and was defined as "that extra clinical entity which existed in or started during the clinical evolution of the assisted patient for the primary disease" (310). This definition reflected the care for the importance of the presence of secondary diseases for the prognosis, the choice of treatment and its efficiency for the main disease. Patients with mental illnesses often have somatic comorbidities, meaning that one or more somatic diseases co-occur with the mental illness. We can say that in many cases we have a mutual dependence between the psychiatric illness and somatic disease. There is a higher risk of getting a psychiatric disorder when we have a person with somatic diseases (310).

On the other hand, also the risk of having a somatic disease is approximately twice as high for persons with severe mental illnesses than for people without mental illnesses (311, 312). In spite of the fact that clinical comorbidity is more and more acknowledged as a defining reality of medical care and that the problem of comorbidity has begun getting importance for the public health, there is not a unitary approach of this complex issue yet. Prevention strategies are needed and a better screening of comorbidities in patients with mental illness in order to decrease the overall mortality and morbidity. There are still questions regarding the connections between the main disorder and the coexistent disorders as far as the impact on symptoms, prognosis and disorder evolution is concerned, including here the lack of proper taxonomy. A major concept for evaluating the health condition is the quality of life, a variable for whose assessment a range of instruments have been taken into account including various items like adequate physical condition or spiritual fulfilment (313).

The comorbid disorders can interact on multiple levels thus influencing the occurrence, manifestations, evolutions and prognosis of the pathological conditions involved. Therapeutically interventions can be proven to be ineffective or may require significant adaptation when comorbidity is present. Moreover, not taking into account the coexistent comorbid conditions, like treating that is considered to be the main cause, may postpone instilling the effective treatment of associate comorbidity and result in prolonging morbidity and suffering and causing extra cost, too. From the clinical perspective, the relationship between comorbid conditions can be described in this way: a disorder can predispose to the occurrence of a second disorder, representing a causative or participative risk factor, or a disorder may change the manifestation of the other disorder, causing difficulties in recognizing and stating the diagnosis of the other disorder and the third possibility – a disorder may change the course of treatment and the reaction to it for the other disorder, thus influencing the result and the general prognosis of the disorder.

People with mental illness have an increased cardiovascular risk because of associated risk factors like smoking, obesity, dyslipidemia, lack of exercise, hypertension, improper diet, diabetes mellitus etc. Furthermore, cardiovascular mortality rates are two times higher for people with mental illness than the general population (314). The use of antipsychotic medication, especially clozapine, a drug used for refractory schizophrenia, may have metabolic side effects like weight gain, hyperglycemia, high cholesterol levels, increasing the cardiovascular risk.

Antidepressants – tricyclic agents like amytriptiline, and mood stablizers have also been associated with increased weight gain.

In order to decrease the cardiovascular risk, a number of studies have been made on interventions to manage the modifiable risk factors associated with the lifestyle of people with mental illness: encouraging smoking cessation, decrease weight by adopting a healthier diet, exercising at least 30 minutes on most days of the week, better control of the blood glucose with treatment, diet and regular medical checkups, management of cholesterol levels with statins and appropriate diet, good control of blood pressure with antihypertensive drugs. All of these measures, even if initiated in a hospital setting, can not be continued afterwords by the patient, if the doctor doesn't show empathy and doesn't take into consideration the psychiatric symptoms interfereing with the patient's ability to follow the medical recommandations. Caregivers should provide all the support for the patients already struggling with the burden of mental illness, to be able to change their lifestyle (315).

Currently, there are a number of studies investigating a possible biological link between a mental illness and a somatic comorbity. Depression for example, is being researched as a metabolic disorder with inflammatory and endocrine mechanisms involved, which can lead to a number of somatic problems, like heart failure (316). During psychosocial stress, the hypothalamic-pituitary-adrenal axis activates, but also there is an inflammatory cascade with elevation of cortisol levels and acute-phase reactants like C-reactive protein. Research investigating the different pathophysiological mechanisms and the link between diseases like diabetes, rheumatoid arthritis etc and depression, could be the first step towards developing new anti-inflammatory drugs to treat depression (317).

In the case of modern classifications of the mental disorders there are many theories about the relationship between the comorbid conditions, among them, the so-called primary – secondary distinctions has distinguished itself. This refers to the following potential relationships between comorbid conditions (318). The first and the most intensely studied is the chronological ordering of the disorders without involving the cause – effect relationship. This refers simply to the reciprocal ordering the starting points of the disorders. The second primary – secondary distinction refers to the strict causal inference, where the disorder has occurred as a direct, significant consequence of a pre-existing one, like the organic affective disorder caused by a somatic disorder or the affective disorder induced by a substance. The third distinction refers to the prevalence of the clinical symptomatology of a disorder towards that of the other, according to the present acuity and the past persistence of the pathology. The empirical testing of these relationship is still limited.

5.2 Psychiatric disturbances, stress and cardio-vascular disorders

5.2.1 The influence of social factors, professional conditions and psychological state on the systemic hypertension.

A. Background

Studies shows that depression is highly prevalent in cardiac patients with 20 to 40% of patients meeting criteria for major depressive disorder or experiencing an elevation in depressive symptoms. These depressive symptoms are chronic and persistent, and they have been associated with the development and progression of coronary artery disease, worse health-related quality of life, poor physical functioning, recurrent cardiac events, and a 2 to 2.5-fold increased risk of mortality (319). Pharmacologic and psychotherapeutic interventions appear to be safe and effective at reducing depressive symptoms in patients with cardiovascular disease and may impact cardiac outcomes. Persons with depression are more likely to develop cardiovascular diseases and also have a higher mortality rate than the general population. There is a graded relationship: the more severe the depression, the higher the subsequent risk of mortality and other cardiovascular events (320).

Systemic hypertension is a pathological condition common in the population and is one of the most important risk factors that contribute to the occurrence of redoubtable cardiovascular complications: stroke, myocardial infarction, sudden death, heart failure, peripheral artery disease and chronic kidney disease. Considering the pathological values of over 140 / 90 mmHg (321) hypertension prevalence reaches 28% in USA, 44% in Europe so that in 2025, it is estimated to be 1.56 trillion worldwide hypertensive people (322). In our country, the overall prevalence was of 44.92%, mainly higher in males (50.17%) than females (41.11%), especially until the age of 55, due to protective hormone influences in women. Data belong to SEPHAR study have reported significant differences in prevalence between urban (41.58%) and rural (49.47%, $p<0.02$) environment indicating the possible influence of social and economic factors on the development of this pathological conditions in our country (323).

Most large epidemiological studies (Scottish Heart Health Study, WHO MONICA project) have documented not only an increased prevalence of hypertension and a lack of screening, treatment, and control that respects the rule of “halves” (half of patients with hypertension are diagnosed, among these only half are treated and of those treated only half had effective control of blood pressure). Epidemiological studies are based on standardized measurements (usually two successive measurements at a single medical visit) but these are usually insufficient. Within the MONICA program, it was estimated that the shortage of measurements could lead to an overestimation of the prevalence of hypertension, and also an underestimation of the number of treated hypertensives who have a good control of blood pressure (324). However, epidemiological surveillance MONICA or USA National Health and Nutrition Examination Survey (NHANES) programs confirmed a better detection and treatment of hypertension in recent decades due to the development of new therapeutic classes and the creation of social and medical education programs. A meta-analysis of 24 studies predicted that the ‘halves’ will no longer be valid in the future in developed countries, but only in developing countries (325).

Social factors have an impact on the prevalence and mode of treatment or the risk of hypertensive complications. The authors reported positive and negative results about the impact of social factors. Lang and colleagues (326) have published data supporting a better control of hypertension in people with higher educational and socioeconomic level, while Chen et al (327) argue that people with better educational level is often based on their own opinions, listen and make decisions without expert advice. In general, full time employed persons, with a fully daily program were insufficiently detected with hypertension due to sporadic medical controls. Among employees, medium aged females have addressed the doctor more frequently and received an earlier diagnosis (324, 327).

The impact of social factors is explained by several pathogenic components that contribute to the onset and perpetuation of hypertension and emphasize the potential role of social work in addition with other specialized care systems. In addition to low interest of healthy eating, combating sedentary lifestyle and smoking were studies that said the job strain is especially important for males. In men, socio-occupational stress was associated with excessive activation of the sympathetic nervous system. Some stressors can act in the mother during the gestational period, and will have adverse effects on the fetus. Women with pregnancy hypertension, subjected to a stress during gestation had births with a poor fetal growth pattern, which subsequently had an exaggerated postnatal increase obesity, developed early obesity and type 2 diabetes mellitus (327, 328).

According to recent studies, social factors are closely related to some psychosocial factors, especially anxiety and depression. However, the relationship between depression, anxiety, anger or panic attacks and the risk of hypertension are quite controversial. In 2010, Delaney J et al. (329) perform the MESA (Multi-Ethnic Study of Atherosclerosis) study, which has discordant results from older studies. The study population consisted of 6814 adults belonging to 4 different ethnic groups. A slight association between the presence of depressive symptoms at baseline and subsequent increases in blood pressure has been reported, without any relationship with ethnic groups or sex of patients. Influence on depression symptoms was more important to systolic than diastolic blood pressure (329). Compared with this study, other results were previously published, in which the manifestations of depression were correlated with blood pressure values. Some differences can be explained also by the type of antidepressant medications used to treat patients, knowing that, for example, tricyclic antidepressants may have side effects of increasing blood pressure. Other differences may arise from the type of questionnaire used to assess depression. In the study published by Delaney and colleagues (329), the score obtained by applying CES-D (Centre for Epidemiological Studies Depression Scale) was also used in other researches applying scales such as: General Wellbeing Schedule (GWB – D), the Diagnostic Interview Schedule (DIS), or the Composite International Diagnostic Interview Short Form (CIDI-SF). In psychiatry, depression is one of the pathological elements subjected to several studies and psychometric scales (330). In our country we used several scales, the most popular being the Hamilton-Depression Rating Scales – HDRS, introduced in 1960 by Hamilton (331), Montgomery – Asberg Depression Rating Scale – MADRS and the Beck's depression Inventory – BDI. Hamilton Rating Scale was significantly used in clinical trials because it is easily applied and developed in parallel with a Hamilton Anxiety Rating Scale _ HARS, which allowed assessment of dissociative and time tracking features of depression and anxiety of patients studied (331, 332).

Anxiety is the second psychopathological symptom which was very much related to cardiovascular diseases, particularly hypertension and ischaemic heart disease in a bisensual approach. In cardiology there are emergency situations (angina pectoris, myocardial infarction, hypertensive crisis) in which the alteration of haemodynamic parameters is so large that triggers catecholamines releasing that contribute to the occurrence of severe states of anxiety in the patients under stressful situations encountered in social and professional lives, increases the risk of hypertension or ischaemic heart disease at younger ages and with a reserved prognosis. Given the highly variable and psychosocial Features in Romania in the last decades, we have proposed a prospective analysis of social and psychological factors, in a group of newly diagnosed hypertensives, compared with the control population.

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which has evaluated the impact of social, psychological and economical factors on cardiovascular status of patients.

Dima-Cozma C, Mitu F, **Szalontay AS**, Cojocaru DC. Socio-economic status and psychological factors in patients with essential hypertension. *Revista de Cercetare si Interventie Sociala* 2014; 44: 147 – 159. **IF 2014 = 0.798**

Introduction: The literature has documented that cardiovascular disease in general and hypertension in particular, have a socioeconomic and psycho-social component. In most populations, hypertension is more common in disadvantaged stratum of society, in people with low income and low educational level, where smoking is common and concerns for diet, exercise, relaxation, are sporadic and contribute to cluster components of metabolic syndrome, focused on hypertension, obesity and insulin resistance (333, 334).

Material and method: The study included 80 patients, over 18 years, with newly diagnosed systemic hypertension (at the first visit in ambulatory, blood pressure had values above 140 / 90 mmHg on at least two measurements), in parallel with a control group consisting of 69 subjects, comparable from the age and sex point of view. The patients signed informed consent to participate in the study and information resulting from specific questionnaires, medical history and clinical examination were used respecting the principle of confidentiality. Patients previously diagnosed and treated for hypertension, or chronic patients diagnosed with previous psychiatric disorders or other chronic diseases were excluded from the study.

Medical evaluation. Initially, patients underwent a complete medical history and physical examination, highlighting the personal and family history, current symptoms; height and weight were measured and we calculated body mass index (BMI, kg/m2) and abdominal circumference (AC) to assess nutritional status. For each patient, the systolic and diastolic blood pressure were measured while seated using an aneroid sphygmomanometer (ERKA, Germany) and heart rate was determined while resting (Hellige electrocardiograph registered, Germany). The next morning, blood was collected, fasting, for determining some biological parameters: glucose, total cholesterol, LDL – cholesterol, HDL – cholesterol, triglycerides.

Evaluation of socio-economic variables. Socio-economic status could be assessed by conducting a questionnaire which sought to record more data: age, sex, marital status (married, single, divorced), education level, quantifying the number of working hours per day (an increased risk was considered in patients who work more than 10h/day), level of physical training and professional and socio-familial stress, smoking status (current, ex-smoker, never), alcohol consumption (risk level is considered to over 20h pure alcohol / day).

Psychological evaluation. Psychometric tests used Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale. In our study, we used the Hamilton Rating Scale for depression monitoring consisting of 17 items quoted at 0 – 4, with which we could evaluate different aspects such as the stated of depression and feelings of guilt, suicidal tendencies, insomnia, agitation, inhibition and somatic symptoms, hypochondriac, self-criticism, weight variations. Scores below 7 are considered normal, between 8 to 13 mild depressions, 14 – 18 moderate depression, 19 – 22 severe depression and more than 23 severe depressions.

Hamilton anxiety rating scale is similar, can be performed in about 15 – 20 minutes, includes 14 items scored from 0 – 4, studying the anxiety, fear, insomnia, cognitive and organic symptoms. Between 0 – 17 the score is normally, between 18 to 25 mild anxiety, 26 – 30 represents a moderate anxiety and between 31 – 56 severe anxiety. For each patient, were calculated the scores of depression and anxiety at entry into the study.

The data were processed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL). The descriptive statistics parameters for the two groups (cases and controls) were determined for all the variables included, using mean values ± standard deviation, frequency tables and cross-tabulation method. The significance of differences between groups was tested using t-Student test for all parametric variables, which respected the normal distribution law and Mann-Whitney U test in the case of nonparametric variables. Statistical significance was considered at $p < .05$.

In order to test the association between ordinal variables (Hamilton scales) and the items of the applied questionnaire we used Chi-square test, through a crosstab dialog box, with nominal variables encoded in a binary form.

Results: Descriptive analysis of the data indicated that patients in the two groups had comparable average ages (51.22 ± 4.083 years versus 52.60 ± 4.610 years, p = .054), but there were statistically significant differences for anthropometric parameters (height, weight, BMI and AC), which had higher mean values in patients with hypertension. It is noted that the presence of overweight and obesity is more common in hypertensive persons who have especially abdominal obesity and low height, falling more frequently *picnic* physique of fat. Also, among the biological studied parameters, fasting blood glucose and serum triglycerides were higher in hypertensive, and HDL-cholesterol, with vascular protective effect, was significantly lower. Mean values and statistical significance for anthropometric parameters, systolic and diastolic blood pressure and biological constants are shown in Table 5.1.

The data studied has shown that abdominal obesity, atherogenic dyslipidaemia and hyperglycaemia, known components of the metabolic syndrome have accompanied in different proportions, the elevated blood pressure values, increasing the total cardiovascular risk.

Table 5.1. Anthropometric parameters, biologic values, systolic and diastolic pressure

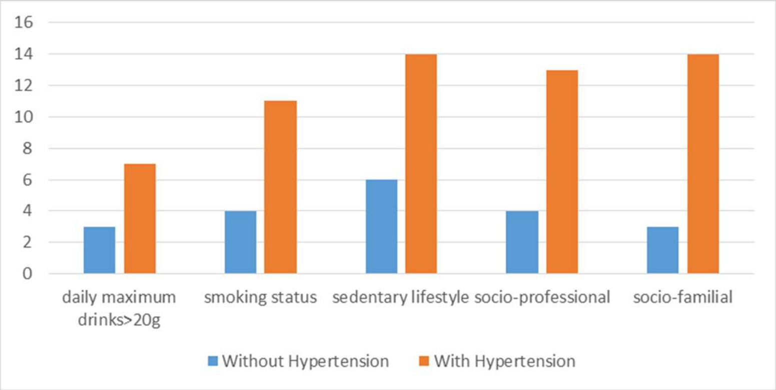
Studied variables	**Cases (n = 80)**	**Controls (n = 69)**	**P value**
	(mean ± SD)	**(mean ± SD)**	
Weight (kg)	75.91 ± 14.37	68.28 ±11.00	.000
Size (m)	1.62 ± 0.09	1.66 ± 0.08	.006
Body mass index (kg / m²)	28.53 ± 5.08	24.51 ± 2.50	.000
Abdominal circumference (cm)	94.41 ± 11.45	84.61 ± 8.65	.000
Patient age (years)	52.60 ± 4.61	51.22 ± 4.08	.054
Heart rate (b/min)	75.34 ± 13.67	73.20 ± 11.95	.311
Diastolic BP (mm Hg)	92.28 ± 8.11	73.84 ± 6.97	.000
Systolic BP (mm Hg)	176.49 ± 19.49	120.43 ± 9.14	.000
Total cholesterol (mg / dl)	202.71 ± 35.226	211.33 ± 67.59	.321
Fasting glucose (mg / dl)	92.40 ± 11.47	86.33 ± 10.42	.001
HDL – cholesterol (mg / dl)	46.30 ± 9.95	49.94 ± 11.60	.043
LDL – cholesterol (mg / dl)	128.31 ± 29.94	137.72 ± 63.37	.239
Triglycerides (mg / dl)	140.48 ± 80.80	118.35 ± 57.08	.053

Analysis has indicated significant influence of social factors on the status of hypertension. One can see significant proportion of married and divorced in the category of patients with hypertension, for both sexes, while unmarried subjects seem protected in terms of developing hypertension; their percentage is very low in both sexes. In the group of patients with hypertension, 52.3% of women and 52.8% of men were married and 40.9% of women and 38.9% of men were divorced (Table 5.2).

Table 5.2. Gender and marital status distribution of cases (HBP=High Blood Pressure)

Sex patient				**Hypertension presence**		**Total**
				0	**1**	
F	Marital status	m	Count , % within HBP	26, 72.2%	23, 52.3%	49, 61.3%
		d	Count, % within HBP	4, 11.1%	18, 40.9%	22, 27.5%
		u	Count, % within HBP	6, 16.7%	3, 6.8%	9, 11.3%
	Total		Count, % within HBP	36, 100%	44, 100%	80, 100%
M	Marital status	m	Count, % within HBP	26, 78.8%	19, 52.8%	45, 65.2%
		d	Count, % within HBP	1, 3%	14, 38.9%	15, 21.7%
		u	Count, % within HBP	6, 18.2%	3, 8.3%	9, 13%
	Total		Count ,% within HBP	33, 100%	36, 100%	69, 100%

Studying the lifestyle and mark of some social factors on the development of hypertension risk, we classified these factors in terms of protection or the potential risk. Figure 16 summarizes the effect of potentially harmful factors. It is noted that the impact of social factors is particularly important for the onset of systemic hypertension: in our study, the importance of factors such as socio-family and professional stress, prolonged work time of over 10 hours / day, sedentary lifestyle was higher than even some harmful well known factors, such as tobacco and alcohol medium consumption of 20g / day. This underlines the necessity of a comprehensive approach at global, socio-psychological and medical level of public health issues of paramount importance to modern society as hypertension.



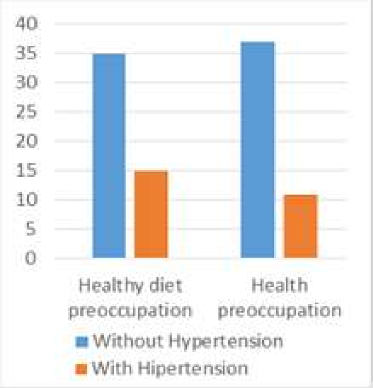


Figure 5.1. Social and lifestyle harmful factors in patients with and without hypertension

Figure 5.2: Protective factors in patients with and without hypertension

At the same time, a positive effect was the concern for healthy eating and health in general (adherence to health issues and articles devoted to health programs and regular health checks), especially among women (Figure 5.2).

There were highly statistically differences between case-control groups regarding the scores obtained on the Hamilton Rating Scale for Anxiety (Z = -10.024, p = .000) and Hamilton Rating Scale for Depression (Z= -10.004, p = .000) – Mann Whitney test. There is a slight preponderance, not statistically significant, of the mild and moderate forms of anxiety and depression in women. Tables 5.3 and 5.4 present the distribution of patients according to sex and degrees of severity obtained in HARS and HDRS scores.

	Age,Sex		**Hypertension**	
			Yes (n = 80)	**No (n = 69)**
Hamilton Anxiety Rating Scale	**0 - 17**	F	11	36
		M	5	33
	18 - 25	F	17	0
		M	14	0
	26 - 30	F	11	0
		M	10	0
	31 - 36	F	5	0
		M	7	0

	Age, Sex		**Hypertension**	
			Yes (n = 80)	**No (n = 69)**
Hamilton Depression Rating Scale	**0 - 7**	F	2	29
		M	2	24
	8 - 13	F	14	7
		M	6	9
	14 - 18	F	12	0
		M	13	0
	19 - 22	F	10	0
		M	7	0
	23 - 50	F	6	0
		M	8	0

Table 5.3. Distribution of studied patients according to gender and score on HARS

Table 5.4. Distribution of studied patients to gender and score on HDRS

Both in terms of HARS and HDRS, there is an aggregation of cases in the lower scores in patients from the control group for both sexes, which suggests an early stage of anxiety or depression in non-hypertensive persons, while the high blood pressure predisposes most patients to moderate-severe forms of the disease. It is also noteworthy that patients with very severe forms of neuropsychological impairment are relatively few, probably due to their preferential hospitalization in psychiatric clinics. We tested if there is a relationship between HAS and HDS scores and the questioned items of our questionnaire / the nominal studied variables, using the Chi-square test, which can be obtained through the crosstabs dialog boxes, the significance of these associations being summarized in Table 5.5 for all the patients included in our study.

Table 5.5. Association between studied variables and score on HARS or HDRS

Variable	**Pearson Chi-Square Value (p)**	
	Hamilton Anxiety Scale Score	**Hamilton Depression Scale Score**
Concern for health	46.031 (p = .023)	57.699 (p = .000)
Concern for diet	47.690 (p = .016)	39.860 (p = .012)
Sedentariness	46.534 (p = .021)	38.864 (p = .021)
Professional stress	53.859 (p = .003)	47.748 (p = .002)
Social and familial stress	65.099 (p = .000)	66.018 (p = .000)
While working over 10 hours/day	67.869 (p = .000)	69.211 (p = .000)
Marital status	72.415 (p = .096)	72.699 (p = .007)
Sex	40.083 (p = .083)	19.397 (p = .678)
Alcohol ingestion min. 20g /day	55.878 (p = .002)	19.304 (p = .683)
Smoking	60.827 (p = .000)	36.551 (p = .036)
The presence of hypertension	123.145 (p = .000)	117.940 = .000)

Discussions: Our study provides results justified on socio-psychological comorbidity of hypertensive patients in a representative community of our country, in line with contemporary trends. More and more epidemiological studies draw attention to the pandemic size of cardio-metabolic diseases, especially of high blood pressure. Ever-increasing prevalence was explained by an aging population, the increase of smoking and chronic alcohol consumption, the changes produced in the hormonal regulatory systems under stress and unhealthy food but social factors were not always highlighted enough. Some studies have referred, lately, to two important social aspects: education level and monthly or annual income. In general, persons with a monthly income and a lower educational level had a higher probability of cumulative risk of hypertension and diabetes (335 – 337).

After classification of the factors contributing to harmful and protective factors, we observed that a strong negative impact was the prolonged working hours of over 10h/day and perception of a high level of stress, both in the family and in the professional life. Since MONICA surveillance program, which was initiated before 1990, it was stated that, regarding working hours, full-time employees and overtime have increased risk of developing late-diagnosed hypertension (324). The prevalence of hypertension was relatively equal between the sexes, explained by the average age that exceeded 50 years, age at which most women are in menopause and their cardiovascular risk increases, equalizes and sometimes exceeds that of males. This menopause phenomenon has important medical, psychological and social connotations. A large percentage of women are subject to greater social and family pressure and hormonal changes predispose to depression, anxiety, sleep disorders. One of the studies that examined the risk of hypertension in women at menopause notes that after a multivariate analysis, the age of menopause, BMI and familial risk of hypertension were the strongest predictors of blood pressure (338).

Among the studied parameters, patients' gender was the only one uncorrelated with any of the Hamilton scales; also no significant association was revealed between alcohol consumption, HDS and marital status of subjects, nor between the marital status of the subjects and the HARS score. Otherwise, all items included in our survey were correlated with assessment scores on both Hamilton scales. Regarding assessment of anxiety, the most significant items were those related to social and family stress, working time more than 10 hours/day, smoking and the presence of hypertension and for investigating depression – concern for health, social and family stress, work time of more than 10 hours/day, and the presence of hypertension. It is worth noting that hypertension has a strong statistically significant relationship with both the Hamilton depression scale and with the anxiety scale, highlighting the role of the two major neuropsychiatry disturbances in broader clinical cardiovascular diseases. Hence, results the utility of psychological assessment and counselling of hypertensive patient, for the most efficient management of the disease beyond medical pharmacological intervention. Also, reassessment and improvement of working daily time, shortening its period and by ensuring a protective family microclimate could be additional effective measures in reducing the impact of hypertension on quality of life.

The Whitehall II Prospective Cohort Study brings important data because it provides a long follow-up of 24 years, between 1985 and 2009, of a total number of 6889 men and 3413 women who were aged between 35 and 55 years at study entry. Patients were regularly monitored for the emergence of depressive episodes using the General Health Questionnaire – Depression subscale, and blood pressure values. Longitudinal analysis adjusted for socio-demographic characteristics, indicated that patients who could be included in the group "increasing depression" had a significant higher risk of hypertension at the end of the follow-up, compared with patients in the low/transient group (339).

In summary, the present research provides a link between social factors and scores of depression and anxiety in patients with hypertension detected in our region. Patients who were classified into mild and moderate degrees of anxiety and depression had increased tension values and presented social and family risk factors. These results suggest the usefulness of comprehensive health blood pressure management programs in population, which represents a major public health problem. Depending on preliminary assessment performed by the general practitioner or specialist cardiologist, some patients should be included in regular assessment programs on anxiety and depression detection and improved of some harmful social factors, in collaboration with specialist sociologists and psychologists. The advantage of this study relate to a better track for a long time, which identifies the periods of depression and may correlate with the occurrence of hypertension. In addition, the study highlights the importance of psychosocial distress on the occurrence of prolonged cardiovascular consequences, as we highlighted in our patients study.

There is a strong relationship between chronic somatic diseases and mental disorders. Mood, anxiety and somatoform disorders were most frequent when we refer to patients with cancer, musculoskeletal, cardiovascular and respiratory tract diseases (340). Studies showed that the prevalence rate of mental disorder was significantly higher in patients with chronic somatic diseases (56.8%) compared with physically healthy subjects (48.9%). Prevalence of depressive and anxiety disorders is higher among individuals with neurological, oncological or liver disease (341). 30-50% of patients experiencing psychiatric disorders have clinically relevant comorbid physical diseases (342), including cardiovascular disease, diabetes and respiratory and lung diseases (342, 343). Main finding of another study from 2016 was that both men and women with hypertension were more likely to have a recorded diagnosis of depression and anxiety disorder, with slightly greater risk for men than for women.

5.2.2 Stress - from the concept to the neuroendocrine activation

A. Background

Stress, a booming concept in modern society, is used both in everyday vocabulary to describe certain incidents considered disruptive to the individual and his life experience ("In that moment, I was really stressed out") and in social and medical terminology, related to disease risk and protection of health (344). Since the late 1950s, stress and coping with stress have been identified as important variables affecting health. Different disciplines (sociology, psychology, medicine, and nursing) recognized the importance of stress in pathogenesis and onset of many diseases: cardiovascular pathologies (336, 345, 346, and 347), obesity, metabolic syndrome and diabetes mellitus (334, 348 – 350), cancer (351, 352) and other respiratory (353), digestive (354), endocrine (355), neurological and psychiatric (356) diseases.

The brain is the organ that closes the vicious circle between potential and actual stressors and behavioural or endocrine adaptive response. Glucocorticoids and catecholamines are the two defining stress hormone response, regulated by the central nervous system, but there are many other mediators, such as pro- and anti-inflammatory cytokines and the parasympathetic nervous system, that are also involved in the adaptation to stressors (357). The effect of the social environment load stress is acting mainly on three important body systems: endocrine, immune and autonomic nervous system, which are known as being first attacked by the chronic stress and an unhealthy lifestyle.

Hans Selye (1907 – 1983) had described in 1936 "the general adaptation syndrome" in response to stressors and had anticipated the most important paradox, revealed during the unfolding of rapid and tardive adaptation to stress. Bruce McEwen, neuroendocrinologist, another scientist dedicated to the "stress" field, has recognized and described this effect of stress, acting in 2 stages; he used the term "allostatis" describing the adaptive processes that maintain homeostasis in stress condition, by synthesis and releasing of mediators such as adrenalin and cortisol and explained that a long period stimulation of these systems will determine the phenomenon of "allostatic overload", characterized by persistent high levels of stress mediators and damaging effects on human health (358). The author explain that chronic stress ("bad stress" or "stressed out") affects negatively physical and psychosocial condition of the person expressing chronic fatigue, frustration and inability to cope.

Stress is involved in the pathophysiology of cardiovascular and metabolic disease, by activating sympathoadrenal system and the hypothalamic-pituitary-adrenocortical (HAP) axis. The degree of the activation of the sympathetic nervous system may produce only an increase in heart rate, blood pressure and free fatty acids in patients with uncomplicated forms of the disease, or can precipitate angina, myocardial infarction, ventricular arrhythmia and acute heart failure, in patients with significant coronary lesions (359). By elevating sympathetic activity, chronic stress could contribute to rapid evolution of the atherosclerosis, acting in combination with inflammatory pathway, elevated cortisol levels, unhealthy lifestyle and other components of the metabolic syndrome.

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which has evaluated the relationship between stress and cardiovascular status of patients.

Dima-Cozma C, Patacchioli FR, Ghiciuc CM, **Szalontay AS**, Mitu F, Azoicai D. Current perspectives in stress research and cardiometabolic risk. *Revista de Cercetare si Interventie Sociala* 2014; 45: 175 – 188. **IF 2014 = 0.798**

- **Introduction**

The main objectives of this research were selection, synthesis, discussion and presentation of the current relationship between stress definition or investigation methods and the coexistence of high cardiometabolic risk in population, as an important component of health status in different countries. The study was based on a literature review, including books, published articles and internet resources, as well as on the author's own experience in this field.

Evolution of the "stress" concept: Incidentally, the concept has some ancient origins, because Seneca, a Roman stoic philosopher, preceptor of the emperor Nero, noted in one of his wise quotes that "A man who suffers or stresses before it is necessary, suffers more than necessary". In biomedical regard, Charles Darwin, famous British naturalist, the originator of the biological theory of evolution, has been emphasized the relationship between neuroendocrine and cardiovascular system: "We know that the vasomotor system, which regulates the capillary circulation, is much influenced by the mind" (360). From these beginnings, it was far to the results of large-scale studies supporting evidence-based data about stress impact on cardiovascular health; citing large scale research results contained in INTERHEART Study evaluating cardiovascular risk factors in 29972 people from 52 countries predicting risk of first myocardial infarction, Richard Milani and Carl Lavie emphasized in an editorial commentary, published in 2007, that psychosocial risk factors, increased the odds of first myocardial infarction by 3-fold, a magnitude similar to standard risk factors, such as smoking, diabetes, and hypertension (360, 361).

In the scientific literature, the term began to be used frequently after 1930, but did not become popular until the late 1970s and early 1980s. Largely, the term is attributed to Hans Selye, who explained stress as a 'nonspecific response of the body to noxious stimuli" (359) and developed the first pertinent theory regarding stress from a psychological and medical point of view. He described the pattern of physiological response to stress, aimed to maintain the homeostasis of the internal medium of the body (glucose and lipids levels, temperature, blood pressure and heart rate) known as general adaptation syndrome. He accepted the possible polarization of the phenomenon including both negatively and positively facets (negative and positive stress – "eustress"). Failure of the adaptation to chronic stress was called exhaustion, raising the issue of an increased risk for particular illness (hypertension and diabetes mellitus, arthritis and cancer) (362). The most important stress theories (363) described in medical and sociological field, with characteristic terminology and concepts, are synthesized in Table 5.6.

Table 5.6. Characteristics of principal stress theories

Promoters authors, year	Terminology	Concepts	Sociological and health outcomes
Selye, 1956	Negative and positive stress (eustress), general adaptation syndrome	Response-based theory about stress	Physiological response to stress will maintain the homeostasis of the internal medium
Holmes & Rahe, 1967	Stress as stimulus	Stimulus-based theory about stress	Importance of stress quantification by utilization of specific scales
Lazarus & Folkman, 1984	Stress, coping, transaction with stress	Transaction-based theory about stress	Active and conscious response to a stressful event, using coping strategies
McEwen,	Allostasis and allostatic	Acute and	Neuroendocrine activation realize

Promoters authors, year	Terminology	Concepts	Sociological and health outcomes
1998, 2000	load, stress hormones	chronic stress concept	adaptation to stress, but chronic stress, in stage of allostatic load has negative consequences on health

Neuroendocrine activation and stress mediators: With the new methods of research, the concept of stress has evolved from the original theory proposed by Hans Selye. The activation of stress systems and releasing of stress mediators were most studied in the last years. Glucocorticoids are produced by the adrenal cortex and norepinephrine are released by the activation of the sympathetic nervous system. Both, glucocorticoids and catecholamines plays an important regulatory role in production of pro-inflammatory cytokines: usually, glucocorticoids inhibit this production whereas catecholamines can increase pro-inflammatory cytokine level. The parasympathetic nervous system is the main opponent of the neuroendocrine activation, slows the heart and has anti-inflammatory effects (357, 364).

The brain is the organ capable to coordinate the other systems, to decide what is stressful, and to promote behavioural and physiological reactions, sometimes prolonged and health-damaging. The excessive stress may cause changes in lifestyle, habits and psychological profile: anxiety, depression, and isolation, disorders of eating and sleeping, smoking and drinking alcohol. Short and long-term consequences of excessive stress ("stressed out") are more evident on metabolic, endocrine, cardiovascular and immune system. Lifestyle modification is interconnected with endocrine, metabolic, and cardiovascular disorders and determine long-term complications. Chronic stress initiates an inflammatory response in adipose tissue, resulting in perturbation of glucose metabolism and a pro-coagulant state (decline in insulin sensitivity, pro-thrombotic reactions and increased plasma monocyte chemo attractant protein – 1: MCP-1 (365).

Stress assessment and cardiometabolic complications: Complex evaluation of stress effects on human health are based on self-assessment of strained states and medical quantification of stress hormones or it's repercussions on physiological parameters.

Over the years, the work of the researchers resulted in the development of different rating scales, created for assessment of exposure and self-perception of the state of stress, from which we selected:

- Social Readjustment Rating Scale (SRRS) and Schedule of Recent Experiences were based on the model that too many life changes could increase the level of stress; the SRRS consisted of 42 life events (like marriage, loss of a loved one, pregnancy, vacation, divorce, retirement, change in residence and other) and the evaluation of stress and adaptation required by this states (366);
- Life Experiences Survey (LES), a 57-item self-report measuring life events impact on health, widely used in stress studies (367);
- Internal-External Locus of Control Scale, the Alienation Test, and the Achievement Scale of the Personality Research Form, introduced by Kobasa, who used the term of hardiness, as a moderator factor between the personality and the environment (368);
- Hassles Scale consisting of 117 items and the Uplifts Scale containing 135 items, evaluating daily experiences versus major life events (369).

Some of this scales could be combined with neuroendocrine laboratory determinations, in order to create standard reproducible tests, useful in clinical trials. Thus was standardized the "Trier Social Stress Test" (TSST), at the University of Trier, Germany, for the experimental induction of moderate psychological stress. This test was very important for the evolution of stress research because it combine the social and medical facet of stress assessment in human (370).

From the medical point of view, the most important step forward in the stress research was made by using salivary stress markers. Investigating the physiology of stress has shown that rapid effects appear in 20-30 seconds by releasing epinephrine and norepinephrine from sympathetic nervous system and prolonged or mixed effects (from minutes to weeks) depend on activation of HPA and other hormonal axis. Measuring some of this hormones (cortisol, alpha-amylase, dehydroepiandrosterone) in saliva became a reliable method of investigating stress in human because avoid venepuncture and offer the possibility of self-collection at home or at work, many times of the day, using a disposable sample device called salivette. The last component of the evaluation is the detection of the long-term negative consequences of stress on the body, in the allostatic load period, a very important link with cardiometabolic pathologies. Cardiovascular activity could be fallow by repeated measurements of systolic and diastolic blood pressure, heart rate and 24-hour continuous monitoring of these parameters and detecting heart rate variability, using holter systems. Metabolic consequences are evaluated by nutrition state, lipid profile and glucose metabolism (glycosylated haemoglobin). The parameters to be monitored are synthesized in Table 5.7, after Seeman and McEwen (371, 372).

Table 5.7. Cardiometabolic evaluation in chronic stress

Organs and Systems	**Measurement of allostatic load**
Cardiovascular system	Systolic and diastolic blood pressure, ambulatory blood pressure monitoring, heart rate variability
Endocrine system	Activation of HPA axis (salivary cortisol, over-night urinary cortisol excretion). A functional HPA axis antagonist (serum and salivary dehydroepiandrosterone). Activation of sympathetic nervous system (salivary alpha-amylase, serum norepinephrine, overnight urinary noradrenalin and adrenalin excretion)
Metabolism	Nutrition state (body mass index, abdominal circumference) Lipid profile (total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) Glucose metabolism (fasting and postprandial glycaemia, glycosylated haemoglobin)
HPA- Hypothalamic-Pituitary-Adrenocortical axis, HDL= High Density Lipotrotein, LDL= Low Density Lipoprotein	

In conclusion, as can be seen from the publications and evidences discussed in this review, stress it is an important component of psychosocial risk factors (by the side of social isolation, personality factors, anxiety and depression) and determine a neuroendocrine activation, origin of significant increase in cardiometabolic risk. The new non-invasive methods for testing cortisol and alpha-amylase in saliva will permit an active search of dangerous levels of stress in target risk population. Understanding and avoiding stress in future will represent a novel social and medical tool for cardiovascular and metabolic prevention.

5.3 Interrelations between psychiatric disturbances and rheumatologic patients concerning quality of life

A. Background

Rheumatoid arthritis (RA) is a destructive inflammatory joint disease, which is affecting synovial joints and can have serious consequences if not treated promptly, patients being constrained from functioning or working, with long-lasting effects on mental and physical well-being. Accelerated atherosclerosis and cardiovascular morbidity, infection, some cancers including lymphoma, and chronic mental ill-health are only some of the key comorbid conditions adding to the lifetime burden of RA and increasing mortality (373). The incidence of RA is 0.1 – 0.2 per 1000 of the population for males and 0.2 – 0.4 per 1000 for females. Age and gender are two of the principal factors contributing to disease occurrence. The female sex preponderance implies that hormonal and reproductive factors strongly influence risk (374).

Rheumatoid arthritis is characterized by four distinct stages of progression. The first stage (stage I) involves initial inflammation in the joint capsule and swelling of the synovial tissue and induces clear symptoms of joint pain, swelling and stiffness. The second stage (stage II) is represented by inflammation of the synovial tissue which becomes severe enough to cause cartilage lesions, the symptoms of loss of mobility and the range of movements become more common. The third stage (stage III) is represented by severe rheumatoid arthritis. Inflammation in the synovia destroys not only the cartilage of the joint but also the bone. Potential symptoms of this stage include increased pain and swelling and a further decrease in mobility and even in muscle strength. Physical deformities of the joint may begin to develop. In the final stage of rheumatoid arthritis, the inflammatory process stops and the joints stop working altogether. Pain, swelling, stiffness and loss of mobility are still the primary symptoms at this stage (375).

For many years, rheumatic arthritis was an illness viewed as chronic and not very dangerous for people. But the evolution of medicine overcome this and brought arguments that the illness shortened life by 10 years on average. Nowadays, rheumatic arthritis is considered an incurable illness that impacts the body as well as the mental and social domains.

The assessment of health – related quality of life in rheumatoid arthritis is becoming increasingly common in both research and clinical practice (376).

The principal problems leading to the negative influence on the quality of life are pain, joint stiffness and the mobility limitations connected to it (377).

The interest in incorporating the concept of quality of life (QoL) in the evaluation of clinical and medical interventions is increasing considerably. The ultimate goal of medical care is to improve patient's enjoyment of life, quality of life and to achieve a better control of the disease process and also improvement of the disease impact domains. Personality seems to play an important role in these relations (378). QoL is defined by the World Health Organization (WHO) as a broad ranging concept incorporating in a complex way the person's physical health, psychological state, and level of independence, social relationships, person's beliefs and their relationship to salient features of the environment (376, 379). The presence of anxiety and depression has an impact on the quality of life of patients with RA, but not on the presence of comorbidity or disease activity. Depressive symptoms are common in patients with RA, and should therefore be considered when evaluating this rheumatologic disease (380).

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which highlighted the influence of psychological factors on the quality of life of patients with rheumatoid arthritis.

Szalontay AS, Dima-Cozma C, Ifteni P, Paraschiv M, Duca DS, Padurariu M, Rezus E. Studying the relevance of some factors that influence the quality of life in rheumatoid arthritis patients. *Nobel Medicus* 2014; 10 (3) : 12 – 17. **IF 2014 = 0.051**

Introduction: Patients diagnosed with RA usually have complains of chronic pain, stiffness and decreased mobility with significant impact on individual independency. Given the fact that the individual is limited in overall functioning, the quality of life of these patients is faily impaired. (381). An important goal in non-pharmacologic management is represented by the improvement of quality of life (382). It is important to highlight that RA affects the life of the patients globally and profoundly. Some of the patients with RA may also show psychological reactions to the disease, such as depression or anxiety. Also, RA affects many areas of life such as mood and emotions, energy level, sleep, health, occupational performance, social life, hobbies, everyday tasks, personal and social relationship (383, 384). The factors that influence the quality of life in patients who suffer from RA are not well understood. In the present study, we analysed how different factors dependent or independent of the disease may influence the quality of life, including some demographic factors, duration of the illness and also the presence of depression and anxiety.

Material and method: The patients selected for the present study were recruited from the Department of Rheumatology Clinical Rehabilitation Hospital Iasi. 75 patients met the American College of Rheumatology revised criteria (385). All the patients gave informed consent and the study was approved by the local ethic committee. Demographic data was recorded for each patient including age, gender, provenance, marital status and number of children. Also, data regarding the duration of the illness and number of hospital admissions were recorded (Table 5.8 and 5.9). All statistically analyses were conducted with the statistical software package SPSS STATISTICS VERSION 16 (Inc., Chicago, Il USA). Descriptive statistics were used to describe demographic characteristic of participants at the baseline. The statistical tests used in this study were represented by independent samples t test (for continuous variables). ANOVA one way, Pearson correlations and regression. The statistical significance was indicated by a $p<0.05$. Categorical variables were expressed as frequencies.

For evaluation of the quality of life (QoL) we used the Short Form Health Survey (SF – 36). The SF-36 scale, a reliable scale which is used both in clinical and research purposes and is currently the most recommended instrument for measuring physical function in patients suffering from RA (386), is a short form of Medical Outcome Study (387). The form applied has 11 items and measures 8 important parameters for estimating the quality of life such as physical function, physical role, body pain, general health, vitality, social function, emotional role and mental health. The scores are varying from 0 to 100, with greater scores indicating less limitation or discomfort (387).

For the evaluation of depression in patients with RA we used the Hamilton Rating Scale for Depression – 17 (HAMD-17) scale. HAMD-17 is a 17 item questionnaire used to measure depression and is a good indicator for intensity of depression. The scale includes items for evaluation of cognitive, behavioural and somatic aspects. Usually, a score above 14 is a sign of depression and an individual could reach a maximum score of 50 (388). In order to assess the presence of anxiety symptoms and the intensity of anxiety we used Hamilton Anxiety Scale (HAMA). HAMA is a semi-structured interview that comprises items for anxiety and also for somatic and cognitive symptoms associated with anxiety. The total score varies between 0 and 56, and the anxiety is indicated by a higher score (389).

Results *Demographic data:* In the present study 75 patients with RA were included majority of whom were women (91%). Age varied from 17 to 78 years with an average of 54.5 years. Provenance was registered as a dichotomous variable. 59% of the subjects had a rural origin. Most of the patients were married (78%), majority of the patients had 2 children (45%), and regarding education status, most of the patients had secondary education (62%) and few (13%) had higher education (Tabe 5.8).

Demographic data	**N (%)**
Gender	N: 75
Men	7 (9%)
Women	68 (91%)
Age (mean)	54.5
Range	17 – 78
Provenance	
Urban	31 (41%)
Rural	44 (59%)
Marital status	
Married	58 (78%)
Widowed	12 (16%)
Divorced	3 (4%)
Unmarried	2 (2%)
Education	
Secondary school	19 (62%)
High school	46 (25%)
College	10 (13%)
Number of children	
Without children	10 (13%)
One child	17 (23%)
2 children	34 (45%)
3 children	6 (8%)
>3 children	8 (11%)

Duration of the disease	**N (%)**
0 - 12 months	18 (24%)
1 - 5 years	30 (40%)
6 – 10 years	16 (21.3%)
> 10 years	11 (14.7%)
Number of hospital admissions	**N (%)**
1	17 (22.7%)
1 – 5	27 (36%)
6 – 10	9 (12%)
> 10	22 (29.3%)

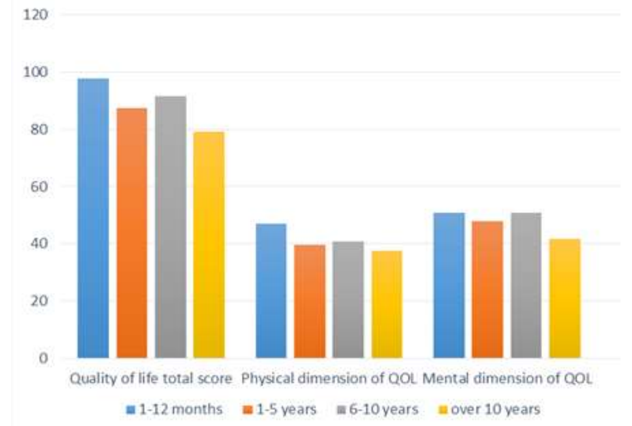


Table 5.8. Demographic data for the patients included in the study
Table 5.9. Duration of the disease and number of hospital admissions in patients included in the study
Figure 5.3. Quality of life scores in RA according to disease duration

Duration of disease and QoL: Duration of the disease was recorded as the time between the diagnosis and the inclusion in the study. The majority of the patients had duration of illness between 1 and 5 years (40%) (Table 5.9). Regarding the number of hospital admissions, most of the patients had more than one hospital admission. The duration of the disease did not influence the total QoL scores (F=0.68; p=0.56), the physic dimension (F=0.481; p=0.476) or mental dimension (F=0.628; p = 0.59) of the scale. There was a negative weak correlation between the quality of life and the duration of the disease(r=-0.13; p=0.25). Also, the results showed a tendency of reduction of QoL scores in patients who had been suffering from RA from 1 to 5 years and more than 10 years (Figure 5.3). *Depression and OoL dimensions:* We analysed the correlation between QoL scores and depression measured with HAMD scale using Pearson correlation. The results indicated a significant negative correlation between the scores of depression scale and QoL scores for all the domains measured with the QoL scale (p<0.05), including physical function, physical role, body pain, general health, vitality, social function, and emotional role and mental health (Table 5.10).

Table 5.10. Correlation between anxiety and depression and QoL domains

Quality of life dimensions	**r (Depression)**	**p (Depression)**	**r (Anxiety)**	**p (Anxiety)**
Physical function	-0.404	<0.001	-0.41	<0.001
Physical role	-0.379	P=0.001	-0.34	0.002
Body pain	-0.394	<0.001	-0.37	0.001
General health	-0.502	<0.001	-0.56	<0.001

Quality of life dimensions	**r (Depression)**	**p (Depression)**	**r (Anxiety)**	**p (Anxiety)**
Vitality	-0.592	<0.001	-0.47	<0.001
Social function	-0.404	<0.001	-0.5	<0.001
Emotional role	-0.555	<0.001	-0.52	<0.001
Mental health	-0.621	<0.001	-0.52	<0.001

The results showed that the higher the intensity of depression was, the lower was the quality of life in patients with RA. The best models of regression are indicated below:

- The predictor physical function explains a significant percent from depression variance (15%), F (1.73) = 14.211; p<0.001. F (1.73) = 14.211.
- The predictors physical function and physical role explain a significant percent of depression variance (195), F (2.72) = 10.09; p<0.001.
- The predictors physical function, physical role, somatic pain and general health explain 26% of the depression variance and the model is statistically significant F (4.70) = 7.63; p<0.001.
- The predictors physical function, physical role, somatic pain, general health and vitality explain 36% of depression variance F (5.69) = 9.36; p<0.001. The predictor vitality explains further 10% of variance depression.
- The predictors physical function, physical role, somatic pain, general health, vitality, social function, emotional role and mental health explain almost 50% of depression variance F (8.66) = 8.841; p<0.001.

This last model was the most powerful model to explain the depression variance and the mental health predictor was the strongest predictor.

Anxiety and QoL dimensions: The correlation between quality of life and anxiety measured with HAMD scale, indicated a significant negative correlation between the scores of depression scale and QoL scores for all the domains measured with the QoL scale (p<0.05) including physical function, physical role, body pain, general health, vitality, social function, emotional role and mental health (Table 5.10). The results indicated that the higher the intensity of anxiety was, the lower was the quality of life in patients with RA. The most powerful models for predicting anxiety variance were:

- The predictors physical function, physical role, somatic pain and general health explain 31% of the anxiety variance and the model has statistical significance F (4.70) = 9.36; p<0.001.
- The predictors physical function, physical role, somatic pain, general health, vitality, social function, emotional role and mental health explain 50% of anxiety variance. The predictor mental health has the greatest power of prediction regarding anxiety criteria.

Discussion: The analyses of demographic characteristics in patients with RA demonstrated an increase in the prevalence of RA in female gender group (ratio f: m= 10:1). Our results are comparable with the data found by other authors who reported that many rheumatic diseases, including rheumatoid arthritis (RA) are more frequent in females than males (387, 388). Frequently, RA starts more early in females, meaning that the females in average are exposed to the inflammation longer than males (390).

Women are 2 - 4 times more likely to develop RA, even if conditions associated with excess oestrogen and progesterone in women often appear joint protective. Studies have shown that women with RA report decreased joint symptoms during the postovulatory phase of the menstrual cycle and during pregnancy, when estradiol and progesterone levels are high. The incidence of RA is also correlated with aging. Among women, the highest RA incidence seems to be between 45 and 49 years of age, suggesting an influence of perimenopausal hormonal changes (391).

A published a study that had the main objective to examine the female versus male perspective regarding prevalence / incidence, etiological factors, disease severity / outcomes, access to therapy and therapeutic responses. The research group have found that the prevalence of RA is higher in females than males, the incidence being 4-5 times higher below the age of 50, but above 60-70 years the female / male ratio is only about 2. Smoking was a consistent predictor of RA in males, but findings have been more irregular in female. The study also has shown that female have less access to health services (392).

The analyses of demographic characteristic of the subjects with RA included in the present study, in relation with the quality of life, indicates that generally these factors did not seem to influence the level of perception of the individuals quality of life. However, a slight difference was seen in how education was associated with the quality of life in patients suffering from RA. When analysing the duration of the disease in relation to quality of life, we obtained a weak negative correlation between quality of life and duration of disease without statistical significance.

Regarding psychological status analysis, we found that both anxiety and depression symptoms were negatively correlated with the subdomain QoL scores. The results showed that the more depressed or anxious person was the lower the quality of life was. Analysing the models for predicting depression, we found that the most powerful predictor for depression was represented by mental health parameter.

Generally, studies show that the main affected areas in RA patients are pain, fatigue and depression (393). Patients with chronic diseases are at higher risk for psychological distress. Unfortunately, depression is an aggravating factor for the evolution of the illness, symptoms of chronic conditions being deteriorated in the presence of comorbid anxiety or depressive disorders. Psychological symptoms have a substantial negative impact on the quality of life, on the course and outcome of the chronic disorders and also on mortality, morbidity, and service utilization (394).

In the case of patients with RA, major depressive disorder affects between 13 to 17% of subjects. In fact, major depressive disorder is two to three times as common in patients with RA as in the general population. Actually, depression associated with RA is often considered to result from the experience of chronic pain and is a factor that worsens the prognosis and increases the risk of mortality (394, 395). Other causes of depression may be chronic inflammations, dysregulation of the hypothalamic-pituitary-adrenal axis, socioeconomic decline, functional and social impairment associated with RA (396).

In our study, anxiety level of the RA patients was measured with HAM-A scale. The Pearson correlation showed a significant negative correlation between the HAM-A scale scores and the QoL subscale scores. Regarding prediction of anxiety, as in depression, mental health was found to be the most powerful predictor ($r = -0.52$; $p<0.001$).

The challenge of identification and management of depression within the rheumatology clinic should be seriously considered. If depression is not correctly identify or treated, patients may erroneously attribute the source of their symptoms to their rheumatic disease, or there is a risk that patients will underestimate the symptoms of depression. Even in the situation when RA patients recognize the symptoms of depression, they may be circumspect to bring into discussion the topic with the rheumatologist because of time constraints, lack of provider continuity in an academic training centre, or because they feel that mental health concerns are best discussed with other providers. Additional problems may occur in the case of ethnic or underserved population, because the patients may encounter supplementary barriers, including language, or the lack of psychotherapy services available in the public clinic setting.

A challenge is given by the patient's acceptance of their mental illness. Most rheumatologists do not routinely screen their RA patients for depression, first because of time constraints and second, because of defective referral services, lack of training and confidence in dealing with mental health issues, or because they consider that other healthcare professionals will handle mental concerns of their patients (397).

In conclusion, in the present we did not find a significant influence of demographic factors on the quality of life in these patients. Also, it seemed that the duration of the disease did not have an important impact on the level of quality of life perceived, either. However, the presences of psychological disturbances, such as anxiety or depression greatly influenced the QoL scores. Moreover, the QoL dimensions predicted the depression and the anxiety criteria.

5.4 Interrelations between psychiatric disturbances and obstructive sleep apnea

A. Background

Obstructive sleep apnea (OSA), characterized by repetitive upper airway occlusion episodes leading to apnea and associated with snoring and excessive daytime sleepiness, is a chronic condition with prevalence rates ranging from 2–10% to greater than 26% of the general middle-aged population (398-400). The hypothalamuspituitary-adrenal (HPA) axis activity and impaired sleep levels exhibit a complex bidirectional relationship (401). OSA is expected to activate the HPA axis, most likely through autonomic activation (402), which is responsible for the increase in daytime blood pressure in OSA patients (403-405).

Neuropsychological symptoms associated with severe OSA, including difficulty concentrating, cognitive impairment, depression, and a general decrease in daytime quality of life (Huang et al., 2008), and OSA-related neuroendocrine and metabolic dysfunctions have been transiently reversed by nasal continuous positive airway pressure (CPAP) application, the gold standard therapy for OSA syndrome (404-407).

B. Published paper in this field

Our interest in this domain has been materialized in the publication of a study which highlighted the influence CPAP therapy on the variance of the psychometric variables in patients with obstructive sleep apnea.

Ghiciuc, C. M., Dima Cozma, L. C., Bercea, R. M., Lupusoru, C. E., Mihaescu, T., **Szalontay, A.S.**, ... & Patacchioli, F. R., Restoring the salivary cortisol awakening response through nasal continuous positive airway pressure therapy in obstructive sleep apnea. Chronobiology international, 2013, 30(8), 1024-1031. **IF 2013 = 2.878**

Introduction: Cortisol production is characterized by a circadian fluctuation, with hormone levels in the morning being significantly higher than those in the evening (408-410). The salivary cortisol awake response (CAR), which reflects changes in the cortisol concentration that occur during the first hour after awakening from night sleep (411,412) is currently used to assess HPA axis activity under different physiopathological conditions. The available studies do not provide clear evidence of a relationship between OSA syndrome and alterations in the levels of cortisol, the major end product of the HPA axis (413).

Materials and Methods: *Study Population* This prospective study was conducted (on consecutives patients) over 1.5 yrs between May 2011 and December 2012 in the Sleep Laboratory in the Clinic of Pulmonary Diseases (Iasi, Romania). The experimental protocol of the study, conforming to international ethical standards (414), was formally approved by the local ethics committee (protocol no. 14, April 29, 2011). All Caucasian subjects were recruited among patients visiting the Centre for Sleep Disturbances and provided their written informed consent before the start of the study. We estimated that at least 14 subjects (7 per group) were required to detect a mean absolute difference corresponding to a 50% variation induced by OSA on the expected peak concentration of salivary CAR in healthy male subjects (14.0 ng/mL; SD =7) with a two-tailed a of 0.05 and 80% power. Thus, 10 patients (OSA group) were selected based on the following inclusion criteria: male, 40 to 60 yrs old, nonsmoker, obese with body mass index (BMI) 430 kg/m2 , and newly diagnosed with severe OSA based on nocturnal polysomnography (PSG) evaluation (apnea-hypoapnea index, AHI 30 h1) and excessive daytime sleepiness (415). The exclusion criteria included the following: acute or chronic associated diseases, smoking, use of any chronic medication (in particular none of them would have to take any immunosuppressive/corticosteroidal drug in the previous 6 mos or consume any vasoactive drugs that could influence cortisol secretion, e.g., antihypertensives, antidepressants, thyroid agents), or unwillingness to undergo to a sleep study. In addition, participants were asked to follow their usual nutritional habits; none of them had begun physical activities in the previous 6 mos. Subjects with suspected OSA were hospitalized for four consecutive days. On the morning of admission, blood samples were collected for biochemical-hematological parameter determinations; pulmonary function assessment (spirometry) and psychometric evaluations with the Hamilton Rating Scale for Depression (331) and the Hamilton Anxiety Rating Scale (416) were performed. A baseline resting electrocardiogram (ECG), heart rate (HR) (BTL08; BTL Industries Inc., Framingham, USA), and systolic and diastolic blood pressures were recorded (M3; Omron, Matsusaka Co. LTD, Japan). Full standard polysomnography (SOMNOlab V2.01, equipped with an audiovideo recording system; Weinmann, Weinmann GmbH, Hamburg, Germany) was obtained from 22:00 h to 07:00 h (day 2). According to standard criteria (417), sleep recordings included electroencephalogram, electrooculogram, electromyogram, and electrocardiogram, respiratory flow measurement (using a nasal transducer), measurement of thoracic and abdominal movements, and oxygen saturation measurement (finger pulse oxymetry). The AHI was calculated as the mean number of apneas plus hypopneas per hour of sleep; apneas were scored when the absence of airflow was lasting at least 10 s and hypopneas when there was at least a 30% drop in the oronasal airflow, with coincident oxygen desaturation of at least 4%, lasting at least 10 s. Oxygen desaturation index (ODI) was calculated as the ratio between the total number of oxygen desaturations lasting at least 10 s and the total sleep time. Sleep efficiency was defined as Total sleep time/Time in bed x 100. All sleep events were manually scored by an experienced technician, blinded to other variables of the patient. The participants were instructed on how to collect saliva using the Salivette sampling device (Sarstedt, Verona, Italy) and asked to avoid food, coffee, and alcohol consumption, teeth brushing, and any physical exercise during the 90 min after awakening or for 30 min before each saliva collection (418,419). Thus, on the day after (day 3), saliva was collected upon awakening (between 06:30 and 07:30 h) and at 30, 60 (for measuring the CAR), and 90 min thereafter; on the same day, additional samples were collected at 12:00, 19:00, and 22:00 h for measuring the daily cortisol fluctuation. The exact time of saliva sampling was monitored by a staff member. Finally, a night of PSG evaluation was performed for the titration of CPAP (SOMNOsmart2; Weinmann). The therapy pressure was set at 5.9 ± 0.4 cm H2O (day 4). Among the patients hospitalized with suspected OSA, we selected 7 adult male subjects for the control group who had the same somatic characteristics of the OSA subjects but did not suffer from sleep apnea (AHI <$5h^{-1}$, ESS<10).

After 3 and 6 mos of CPAP therapy, the OSA patients, contacted regularly by phone, were hospitalized to evaluate all psychometric and hematological-biochemical parameters measured before CPAP treatment as well as the nocturnal PSG and salivary cortisol production profile (CAR and diurnal fluctuation). During these visits, compliance with treatment was scored with data recorded in the CPAP internal compliance meter. Compliance measures recorded were mean daily use of CPAP (h), percentage of days on which CPAP was used, and CPAP usage index (ratio between the number of days on which CPAP was used for 45 h and the total number of days on which CPAP was used).

Salivary Sampling Procedure and Cortisol Measurement Saliva was collected using the Salivette (Sarstedt, Verona, Italy) sampling device, which allows for quick and hygienic saliva recovery from a polyester swab through centrifugation at 3000 rpm for 15 min (Groschl et al., 2008). The salivary samples were immediately frozen at 20 °C until analyzed. For each sample, duplicate measurements were performed on 25 mL of saliva using commercial immunoenzymatic kits (Diametra, Milan, Italy) for the direct salivary assay of cortisol (interassay coefficient of variation was <10%, and intra-assay coefficient of variation <7%, with a minimum detectable concentration of 0.5 ng/mL).

Data analysis and Statistical Procedure All data were reported as the means ± SE. The statistical analyses and graphics were performed using SigmaPlot 11 software (SxST.it, Milan, Italy). Comparisons between the somatic characteristics of the OSA and control groups were performed using Student's t test or the Mann-Whitney test. A one-way analysis of variance (ANOVA) followed by the Fisher least significant difference (LSD) method for post hoc multiple comparisons test were computed to determine the ''group'' effects on each parameter measured in the control group and the OSA subjects before and after 3 and 6 mos of CPAP therapy. A two-way ANOVA followed by the Fisher LSD method for post hoc multiple comparisons test were computed to reveal ''group,'' ''time,'' and ''group time'' effects on salivary cortisol concentrations measured in the control group and the OSA subjects before and after 3 and 6 mos of CPAP therapy. The area under the curve (AUC) of salivary CAR was calculated from the AUC determined for each subject by the trapezoidal method using the 3 salivary cortisol values measured at awakening and 30 and 60 min thereafter for the awakening response; to compute the AUC of salivary cortisol diurnal production, the 7 samples collected from awakening to 22:00 h were used. The AUCs were expressed as ng/mL/h of salivary cortisol (420). Statistical significance was set at $p<0.05$.

Results *Characteristics of the Study Population* No significant differences were detected between the two groups with respect to the population characteristics. The subjects had a similar mean age (control: 51 ± 3 yrs; OSA: 53 ± 3 yrs; Mann-Whitney: $p>0.05$). There were no significant differences (Mann-Whitney: p40.05) in the BMI values, which indicated obesity for both groups (control: 32.1 ± 0.6 kg m2 ; OSA: 32.3 ± 0.7 kg m2). The mean waist size was above the normal range accepted for men (OSA: 109 ± 2 cm; control: 105 ± 2 cm; Student t test: $p>0.05$). Individual hematological and serum biochemical parameters for glycemia and lipids (total cholesterol and triglycerides) were within normal ranges for both groups. The results of the pulmonary function tests (spirometry), forced expiratory volume in 1 s (FEV1) and FEV1/vital capacity (VC) ratio were within the normal limits for subjects from both groups. Regarding the measures of the CPAP therapy compliance, the average daily CPAP use was 331 ± 4 min during the first 3 mos of CPAP and 332 ± 2 min during the next 3 mos of therapy. Furthermore, the percent of days of CPAP use was 92%, with a CPAP use index of 89% during the first 3 mos. In addition, a 91% of days of CPAP use, with a CPAP use index of 90%, was recorded during the next 3 mos of therapy.

Table 5.11 Polysomnography parameters and psychometric variables of the study population.

Parameter	Control (n = 7)	OSA (n = 10)	OSA, 3 mos of CPAP (n = 10)	OSA, 6 mos of CPAP (n = 10)
Polysomnography parameters				
AHI (h^{-1})	2.6 ± 0.5	63.5 ± 9.3**	1.0 ± 0.4##	0.8 ± 0.2##
Minimum SpO2, %	87.6 ± 1.5	68.5 ± 4.3**	88.0 ± 0.7##	89.9 ± 0.2##
ODI, h^{-1}	4.9 ± 0.8	58.4 ± 9.4**	21.2 ± 8.5**##	6.8 ± 0.6##
Microarousal, h^{-1}	9.9 ± 0.9	46.7 ± 6.3**	9.8 ± 0.6##	8.0 ± 0.2##
Total sleep duration, min	419 ± 9	395 ± 8**	386 ± 3**	388 ± 2**
Sleep efficiency, %	79.9 ± 0.7	78.6 ± 0.7	78.5 ± 0.3	78.2 ± 0.2
Stage 1, %	5.1 ± 0.4	4.7 ± 0.4	3.2 ± 0.2*#	2.8 ± 0.2*#
Stage 2, %	42.6 ± 1.6	54.1 ± 1.5**	34.4 ± 1.4**##	34.5 ± 0.7**##
Slow wave sleep, %	17.1 ± 0.9	5.8 ± 0.2**	18.6 ± 0.6##	18.8 ± 0.5##
Stage REM, %	19.8 ± 0.6	16.6 ± 0.4**	19.0 ± 0.3##	20.9 ± 0.2##
Systemic blood pressure and HR				
SBP (mm Hg)	117 ± 3	127 ± 2*	122 ± 2	124 ± 3
DBP (mm Hg)	69 ± 4	76 ± 2	74 ± 1	77 ± 1
Heart rate (beats/min)	67 ± 1	75 ± 2	75 ± 3	79 ± 2
Psychometric variables				
ESS	4.0 ± 0.8	12.9 ± 1.2**	7.8 ± 0.4*##	7.2 ± 0.3*##
HDS	5.0 ± 0.9	10 ± 0.5**	8.1 ± 0.3**	5.4 ± 0.4
HAS	2.0 ± 0.7	5.3 ± 1.0*	4.5 ± 0.5	3.4 ± 0.5

Data are presented as mean values ± standard error. *$p<0.05$ and **$p<0.001$, respectively, versus control; #$p<0.05$ and ##$p<0.001$, respectively, versus OSA (post hoc Fisher LSD method for multiple comparisons). AHI = apnea-hypopnea index; Minimum SpO2 = minimum oxygen saturation; ODI = oxygen desaturation index; REM = rapid eye movement; SBP = systolic blood pressure; DBP = diastolic blood pressure; ESS = Epworth Sleepiness Scale; HDS = Hamilton Depression Score; HAS = Hamilton Anxiety Score.

Table 5.11 shows the PSG parameters recorded in the control group and OSA patients before and after 3 and 6 mos of CPAP therapy. All measured parameters were within normal ranges in the control group. A one-way ANOVA followed by the post hoc Fisher LSD method revealed significant differences between the groups in AHI ($F_{3,36} = 39.388$, $p<0.001$): the OSA group had significantly higher values ($p<0.001$) than the control group. At 3 and 6 mos after CPAP therapy, the AHI in the OSA group returned to normal levels, being significantly lower than in OSA ($p<0.001$). As also reported, there was a significant decrease in the minimum SpO2 (one-way ANOVA, $F_{3,36} = 18.445$, $p<0.001$) of the OSA group ($p<0.001$), characteristic of a severe OSA condition (American Academy of Sleep Medicine Task Force, 1999), which was significantly restored 3 and 6 mos after CPAP therapy ($p<0.001$ versus OSA, not different from controls). In addition, the ODI was significantly (one-way ANOVA, $F_{3,36} = 13.221$, $p<0.001$) increased in the OSA group ($p<0.001$). The ODI was partially restored after 3 mos of CPAP therapy ($p<0.05$ versus OSA) and normalized after 6 mos of CPAP therapy ($p<0.001$ versus OSA and not different from controls). The one-way ANOVA showed significant differences between the groups in microarousal events ($F_{3,36} = 31.053$, $p<0.001$): this variable was significantly higher in the OSA group than in the control group (p50.001). CPAP therapy led to the normalization of this parameter ($p<0.001$ versus OSA patients and not different from controls). Total sleep duration was significantly lower in OSA patients ($p<0.001$) and was not modified by CPAP therapy (one-way ANOVA, $F_{3,36} = 6.601$, $p<0.001$). No significant changes were monitored in the measures of the sleep efficiency in the study population (one-way ANOVA, $F_{3,36}$ =2.118, p = 0.117). OSA subjects presented no changes of percentage of stage 1 sleep, which was reduced ($p<0.05$) during the CPAP therapy (one-way ANOVA, $F_{3,36}$ =15.626, $p<0.001$). A significantly higher percentage of stage 2 has been recorded in OSA subjects, with a significant reduction induced by 3 and 6 mos of CPAP therapy (one-way ANOVA, $F_{3,36}$ =52.766, $p<0.001$). OSA significantly affected the percentage of the slow wave sleep (one-way ANOVA, $F_{3,36}$ =159.272, $p<0.001$) as well as that of REM (one-way ANOVA, $F_{3,36}$ =25.142, $p<0.001$); CPAP therapy significantly restored these variables. Table 1 shows that the mean values for systolic blood pressure were slightly elevated ($F_{3,36}$ =3.808, $p<0.05$) in the OSA group compared with the control group, with no change in diastolic blood pressure ($F_{3,36}$ =2.244, nonsignificant [n.s.]). The patients with OSA showed a tendency toward increased HR, which was not modified by CPAP therapy ($F_{3,36}$ =3.066, $p<0.05$). Among the psychometric variables, Table 1 reports that the excessive daytime sleepiness, as evaluated with ESS, was significantly (one-way ANOVA, $F_{3,36}$ =18.332, $p<0.001$) increased in the OSA group ($p<0.001$) and partially restored after 3 and 6 mos of CPAP therapy ($p<0.001$ versus OSA and still $p<0.05$ versus control after 3 and 6 mos of CPAP therapy). The Hamilton Inventory Scores for Depression (HDS) and Anxiety (HAS) measured in the study population are also reported in Table 5.10. A one-way ANOVA followed by the post hoc Fisher LSD method revealed significant differences between the groups in HDS ($F_{3,36}$ = 19.657, $p<0.001$): OSA patients showed a significantly higher score than the controls ($p<0.001$). After 3 and 6 mos of CPAP therapy, the depressive symptom scores of the OSA patients gradually shifted to the level of the control group. Regarding the psychometric scores of anxiety, there was a significant difference between the groups ($F_{3,36}$ = 3.553, $p<0.05$): the OSA subjects presented a slight but significant increase in HAS compared with the control group (<0.05), but only before CPAP therapy.

Salivary cortisol daily trajectories Figure 5.4 shows the mean levels (±SE) of salivary cortisol measured on the sampling days in the control and OSA groups before and after 3 and 6 mos of CPAP therapy. A two-way ANOVA showed significant differences between and within groups at different times of the sampling day (for the factor group: $F_{3,258}$ = 15.295, $p<0.001$; for the factor time: $F_{6,258}$ = 82.347, $p<0.001$; for the factor group ± time interaction: $F_{18,258}$ = 4.469, $p<0.001$). The salivary cortisol concentrations measured in the control group upon awakening and at 30 and 60 min thereafter reflected a typical CAR course: the salivary cortisol concentration measured at awakening (7.2 ± 0.6 ng/mL) rose to 12.6 ± 1.7 ng/mL ($p<0.001$) and 7.4 ± 0.4 ng/mL, respectively, 30 and 60 min later and then declined significantly 90 min after awakening (3.5 ± 0.3 ng/mL; $p<0.001$). In contrast, the OSA patients showed a loss of CAR; the salivary cortisol concentration at awakening (4.6 ± 0.6 ng/mL) did not increase after 30 min (5.04 ± 0.51 ng/mL) or 60 min (4.2 ± 0.7 ng/mL) and was slightly reduced at 90 min (3.9 ± 0.4 ng/mL). CPAP therapy restored CAR after 3 mos (9.2 ± 1.4 ng/mL; $p<0.001$ versus OSA) and 6 mos (9.9 ± 0.5 ng/mL; $p<0.001$ versus OSA) of treatment. In addition, CPAP therapy significantly reversed the reduction of the salivary cortisol level detected in the OSA group at awakening (07:00 h) compared with the control group. As also shown in Figure 5.4, physiological diurnal cortisol fluctuation was significantly present in all the experimental groups: salivary cortisol levels in the evening were lower than those measured in the morning in the control group (at 19:00 h: 2.5 ± 0.2 ng/mL; at 22:00 h: 1.9 ± 0.1 ng/mL; $p<0.001$) and the OSA group (at 19:00 h: 2.1 ± 0.1 ng/mL; at 22:00 h: 2.1 ± 0.2 ng/mL; $p<0.001$) and at 3 mos (at 19:00 h: 3.1 ± 0.3 ng/mL; at 22:00 h: 1.8 ± 0.1 ng/mL; $p<0.001$) and 6 mos (at 19:00 h: 2.4 ± 0.1 ng/mL; at 22:00 h: 2.3 ± 0.2 ng/mL; $p<0.001$) after CPAP therapy.

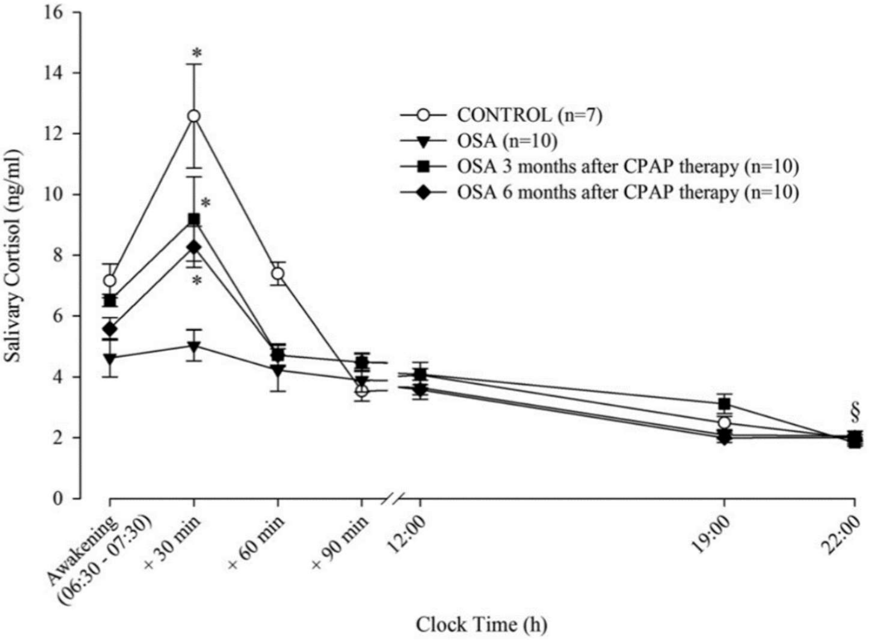


Figure 5.4 Diurnal trajectories of salivary cortisol in the study population. The data are presented as the mean values ± standard error. Statistical analysis: two-way ANOVA and a post hoc test: *$p<0.05$ versus OSA at 07:00 h; ξ$p<0.05$ indicates that each point is significantly different from the associated 07:00 h value.

Salivary Cortisol AUCs: CAR and Cortisol Diurnal Production Table 5.12 shows the salivary cortisol AUCs calculated in the study population. A one-way ANOVA of the CAR AUC showed a significant difference between the groups ($F_{3,36} = 9.547$, $p<0.001$), with a significant reduction in the OSA subjects compared with the control group ($p<0.001$). Furthermore, CPAP therapy partially restored the 50% reduction detected in the OSA group after both 3 and 6 mos of therapy, leading to a final reduction of approximately 25%. The final salivary cortisol levels in the OSA group after therapy were still significantly different from those of the control group ($p<0.05$) and significantly higher than those in the OSA group before CPAP therapy ($p<0.05$). Finally, no significant variations were found in the cortisol diurnal production AUC (one-way ANOVA: $F_{3,36} = 2.558$, n.s.).

Table 12. Salivary cortisol AUCs (ng/mL/h) in the study population.

Population	CAR AUC	Diurnal cortisol production AUC
Control (n = 7)	9.9 ± 0.9	53.0 ± 2.8
OSA (n = 10)	4.9 ± 0.6**	44.4 ± 3.6
OSA, 3 mos of CPAP (n = 10)	7.4 ± 0.8*#	55.0 ± 3.0
OSA, 6 mos of CPAP (n = 10)	7.3 ± 0.3*#	50.6 ± 1.9

Data are shown as the mean values ± SE. *$p<0.05$ and **$p<0.001$, respectively, versus control; #$p<0.05$ versus OSA (post hoc Fisher LSD method for multiple comparisons). The CAR AUC was computed from the 3 salivary cortisol values measured at awakening and 30 and 60 min thereafter. The diurnal cortisol production AUC was computed from the 7 salivary cortisol concentrations measured from awakening to 22:00 h.

Discussion: The main finding of this study is that compared with a nonapneic obese control group, male obese OSA patients showed a flattening of the CAR that was restored after 3 and 6 mos of CPAP therapy. In addition, we showed that OSA patients presented lower levels of cortisol at awakening than controls. CPAP was able to counteract the distinction in the morning cortisol level between the OSA and control groups. Additionally, OSA subjects maintained the physiological circadian activity of the HPA axis, with the highest hormone concentrations produced in the morning and the lowest in the evening. These outcomes are only in partial agreement with a previous paper in which the maintenance of a regular circadian rhythm of cortisol in OSA subjects was reported, although no difference in the morning concentration of the hormone between the OSA patients and controls was described (421). These discordant outcomes may be related to differences in some characteristics of the population sampled: here, we enrolled male subjects only aged from 40 to 60 yrs, whereas Raff et al. enrolled both males and females with a larger age range, from 18 to 90 yrs. Altered CAR has been associated with psychiatric disorders (422-424); in addition, CAR dysregulation has been reported in subjects suffering from stressrelated illness (425, 426) and fatigue-related symptoms (427). A reduced cortisol morning peak and attenuated circadian rhythm have been demonstrated in obese subjects, regardless of the presence of OSA, compared with healthy controls in a population of males aged from 18 to 70 yrs (428). We have shown that CAR, characterized by a 50–160% increase in salivary cortisol 30 min after awakening (411,429), was detectable in the nonapneic obese control group only, whereas normal hormonal diurnal fluctuation was detected in both groups. Potentially confounding effects of BMI or abdominal fat distribution on cortisol production can be excluded in our study, as both the control and OSA groups presented comparable BMIs and similar abdominal circumferences. Several authors have hypothesized that OSA might be associated with alterations in HPA activity (428, 430), but these reports have shown contradictory results. It has been shown that hypocortisolism may occur as the system loses its resiliency in response to chronic or recurring stress, reflecting a reduced ability of the system to respond to such challenges (431, 432). In fact, consistent with McEwen's (1998) allostatic load model, dysregulation of the HPA axis in response to repeated challenges might be manifested in a flatter diurnal pattern of cortisol production. Thus, the intermittent upper airway obstruction and subsequent hypoxia and autonomic arousal during sleep may represent OSA-induced chronic stressor-like perturbations of the sleep-wake homeostasis (421), which can compromise HPA axis functioning and ultimately compromise health. However, the allostatic hypothesis can be applied as well to the autonomic system dysfunction induced by the alterations of cardiovascular baroreflex sensitivity, controlling sleep-dependent changes (402, 433) which also could play a role in the lack of CAR in OSA subjects. Enhanced cortisol secretion has been reported in obese hypertensive OSA patients (404). Hypertension itself has also been shown to stimulate HPA axis activity in obese patients (434), but the potentially confounding effects of hypertension on HPA axis activity were avoided in our study. Indeed, we enrolled obese patients with the following categories of blood pressure levels: optimal (n = 2), normal (n = 1), and high normal (n = 7), with no or only slight alterations in systemic blood pressure (435). In agreement with previous studies (404, 405, 421, 430), the present work, reporting good compliance scores of CPAP therapy, confirmed the efficacy of this treatment in the amelioration of OSA-related HPA activity dysregulation. In the present study, the HDS and HAS measured in the control group indicated the absence of signs of depression and anxiety. Furthermore, we confirmed the presence of excessive daytime sleepiness in severe OSA subjects and other neuropsychological symptoms related to mild depression and overall anxiety, which were also partially or fully resolved after CPAP therapy (436-438). Finally, from a methodological viewpoint, the salivary sampling schedule was fully complied with in the present study (439-441). The advantages of using salivary cortisol measurements to reflect the free fraction of cortisol in the plasma are that they are noninvasive, stress-free, and reliable sources for monitoring changes in HPA axis activity (409, 442). In addition, the AUCs calculated with the trapezoidal formula are widely used parameters to summarize repeated measures of a response variable (443, 444). In addition, we confirmed that multiple diurnal samples, especially within 1 h after awakening, are necessary to reliably measure HPA activity and monitor changes in salivary cortisol diurnal trajectories, which are thought to have implications for health (445-447).

SECTION II: FUTURE PROJECTS IN THE PROFESSIONAL, ACADEMIC AND SCIENTIFIC LEVEL

1. Perspectives in the professional activity

As the Head of VI acute psychiatric clinic within the Institute of Psychiatry “Socola” Iasi I have tried to establish a team of highly qualified professionals in order to optimize patient care. By setting high standards, careful monitoring and establishing clear and attainable goals, I believe that I have provided means for the medical staff to improve their knowledge and skills. Nonetheless, I admit that competition in the clinical setting is vital for the improvement of health care quality.

Given the complexity of the management of psychiatric conditions, as well as that of the relationship between patients and the medical staff I believe that the issue of improving the quality of care in hospital settings requires a multifaceted response. As yet, I have identified several achievable goals in terms of professional activity.

- First and foremost, I wish to continue to update my knowledge on the management of psychiatric conditions through a constant research of the currently available literature (recent protocols, research articles, textbooks);
- Also, I intend to promote the betterment of the medical staff’s (doctors, and/or nurses) knowledge and skills by allowing and facilitating their participation in ongoing projects or workshops, while also encouraging professionals to register for courses on specific aspects of patient assessment and / or care;
- Knowing that effective doctor-patient communication is crucial especially in psychiatry for the development of personalized care, I intend to improve my team’s relationship with patients by encouraging feedback from both sides;
- In order to increase our patient’s knowledge of disease pathogenesis, risk factors, evolution / prognosis, treatment options and possible side-effects, I intend to organize doctor – patient discussion groups on specific subjects / diseases, or to encourage participation to support groups;
- I wish to encourage Romanian psychiatric patients to participate in the patient’s section of scientific congresses by providing details on the subject, in order to better understand their condition and to fight self-stigma;
- Admitting that early diagnosis and correct therapeutic approach are of paramount importance in psychiatric conditions, I intend to organize workshops with general practitioners and to propose postgraduate courses focusing on diagnosis criteria, treatment options and side-effects;
- Also, I intend to update my knowledge of current laws governing patient and physician rights;
- The management of psychiatric conditions requires often the evaluation and follow-up of a team of specialists that is why I intend to continue to enhance the collaboration between our clinic and other medical specialties for a better approach and treatment of psychiatric patient.

2. Perspectives in the academic activity

Heretofore, I have held lectures for medical students of the Faculty of Dental Medicine, the Faculty of Dental Technique, the Faculty of Pharmacy and General medicine in both Romanian and English teaching series.

I have held the optional lecture “The pathology of aging – elements of psychiatric geriatrics” to the students of 4th year of the Faculty of General Medicine.

I have guided the resident physicians in the psychiatry specialty of the “Socola” Psychiatric Institute. I am the author of 7 books and one chapter. My interest in providing quality information for medical students and psychiatry trainees is supported by a strong belief that remarkable teaching can lead to a more profound understanding of psychiatric conditions and their management.

Improving my teaching system as well as the medical students’ and trainee doctors’ learning strategy represents a priority. The main perspectives in my academic work involve the following:

- Updating the content of lectures in order to provide the newest relevant and reliable information on psychiatric disease management (evaluation, diagnosis, treatment);
- Organizing workshops, debates on specific topics and clinical case report presentations with students and trainee doctors;
- Proposing new optional courses;
- Promotion of continuous training for residents, specialists and senior specialists by a diversified offer of postgraduate courses;
- Promoting diversified and transparent methods to get student feedback on teaching performance;
- Encouraging and coordinating students and residents to embark on and persevere in scientific activity, promoting the current rigors of science paper presentations;
- Assisting 6th year medical students in writing their final thesis;

3. Perspectives in the scientific activity

In order to continue my research activity in the future, I will have to make more efficient and effective the professional interaction between the current and future collaborations, between my ability of coordinating original researches and the need to supervise young students and PhD students, respecting the current norms regarding clinical and experimental research.

The future perspectives of my scientific work include the following objectives and activities:

- Conducting further research on institutionalization, treatment, ethical and legal implications in the assistance of patients with dementia keeping in mind that there is an increasing interest in this condition due to the future course predicted for global dementia epidemics and the fact that there is still no curative treatment for it. Prevention, disease-modification or cure are future goals of anti-dementia therapies;
- Further studying the relationship between psychiatric disturbances and somatic comorbidities highlighting the influence of social factors and psychological state on the evolution of somatic disorders;
- Further studying the influence of chronic pain on the quality of life of patients and relationship with psychiatric disorders;

- Further creating interdisciplinary scientific teams in order to give response to multifaceted medical issues;
- Accessing additional funding for research activities (analysis kits, access to information, participation in congresses);
- Supervising and ensuring the compliance with the ethical and deontological aspects of clinical research;
- Preserving a transparent approach to our research in order to secure scientific integrity;
- Ensure a rigorous selection of young researchers, able to enter a doctoral or postdoctoral training program;
- Promote the dissemination and visibility of research results by publishing the results in journals and cited by international databases and communicating them at congresses.

Future doctoral projects:

Implementing cognitive rehabilitation and cognitive training by means of digital technology

Dementia is marked by a continuous, worsening evolution, with little hope of cognitive rehabilitation after the first stage of the disease. The cognitive rehabilitation programs are strenuous, time demanding and frequently require specialized assistance. Considering the projected increase of dementia cases in the near future, and its evolution, it is foreseeable that the capacities of the mental health systems will be overwhelmed, not only by means of human resources available, but also financially. Emergent new technologies such as Kinect© and Virtual reality devices such as Oculus® represent relatively cheap rehabilitation options for persons diagnosed with early stage dementia, by allowing to immerse themselves in an environment designed with rehabilitation purposes in mind. These technologies are promising especially because they offer the perspective of unassisted rehabilitation programs, in the patient's natural environment, from the comfort of their home. Although the price of such devices is still relatively high, the real financial challenge is the cost of the specially designed programs. In this sense I consider opportune to see the influence that cheap commercially available programs have on the rehabilitation process and on the patient's quality of life.

Virtual reality assisted therapy in patients with anxiety disorders

Exposure therapy is one of the choices available to patients suffering from specific phobias. One of the presumed mechanism through which it works is desensitizing the pathways coupling the trigger with the fear reaction. In this sense, it was proved effective in managing conditions like specific phobias in which the patient can be physically exposed to the trigger. In cases of agoraphobia of social phobia, especially severe cases, the patient is afraid of actually leaving their homes or interacting with other members of society. Thus, even the visit to the physician's office could induce a panic attack of intense anxiety, impeding the patient accessing medical services or interfering in the doctor-patient relationship. Virtual therapy and telemedicine can interfere in this vicious cycle by facilitating at home assisted exposure therapy and eventually enabling the patient to visit a psychiatrist face to face. With the challenges described in the previous project, we wish to test the efficiency of virtual reality assisted group therapy in patients with anxiety disorders with agoraphobia.

The role of vagus nerve electrical stimulation in patients with somatoform disorders

Vagus nerve stimulation is a neuromodulation technique developed for treatment resistant epilepsy. It works by electrically stimulating of the left vagus nerve, which produces an inhibition of neural processes. Since its development, the technique has been approved depression and pain management. Somatoform disorders are a group of psychiatric disorders, which manifest through somatic symptoms, without any underlying organic or functional cause. Most frequently, the manifestations of such disorders are pain, neurological and gastroenterological symptoms. These manifestations can appear alone, under the term of somatoform disorders or they can accompany depression and anxiety disorders and as such, their frequency is high in psychiatric populations. Vagus nerve stimulation has been proven able to reduce the sensitivity of mechanical and somatic pain and heat perception and modulate visceral pain perception. Old stimulation techniques implied surgically implanting the device subcutaneously and directly connecting the stimulating electrodes on the surface of the vagus nerve making it an invasive procedure but recently, transcutaneous vagus nerve stimulation has become a non-invasive widespread available alternative. We wish to determine the effects this new noninvasive modulation technique can improve the symptoms of patients with somatoform disorders.

Polysomnography and multidisciplinary approach in sleeping disorders

Polysomnography is a multiple parameter test used to diagnose a wide range of sleeping disorders. It monitors, among others, brain activity, cardiac activity, oxygen blood saturation and airflow. Normally, it is used in clinical settings which involves removing the patient from its natural environment. For this reason it can return false results due to the fact that the patient may be unable to accommodate to the new sleeping conditions. Recently, the devices became smaller in size, with wireless connectivity and can be used at home by the patient. The usefulness of polysomnography can stand beyond diagnosis, as it may be particularly useful in adapting the pharmacological treatment and environmental conditions to the patient's specific needs. Also, polysomnography is an useful tool for diagnosing obstructive sleep apnea, a condition frequently associated with psychiatric sleeping disorders and it's implementation in psychiatric practice can facilitate the multidisciplinary approach of sleeping disorders. Our particular interest in this field is represented by the possibility of using polysomnography as a tool to adapt the administration schedule of hypnotic drugs and the election of the drug itself by considering it's pharmacokinetic proprieties and the patient's test results.

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