

**“VICTOR BABES” UNIVERSITY OF MEDICINE
AND PHARMACY TIMISOARA
DOCTORAL SCHOOL
MEDICINE**



HABILITATION THESIS

**A DECADE OF PSYCHIATRY RESEARCH –
BIOMARKERS DISCOVERY, MODERN
THERAPEUTIC METHODS, PSYCHOPATHOLOGY
AND PSYCHOSOMATIC APPROACHES**

A B S T R A C T

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1. THESIS SUMMARY

The current habilitation thesis, entitled "A decade of psychiatry research – biomarkers discovery, modern therapeutic methods, psychopathology and psychosomatic approaches" is mainly focused on the information regarding my scientific, professional, and academic activity, covering the period 2008 – 2020, after I obtained a Ph.D. in medicine, specialty: psychiatry. My Ph.D. thesis focused on "The course of major depressive disorder (MDD) and its comorbidity with physical illnesses". My research conducted as part of my Ph.D. has produced some valuable results regarding clinical aspects of MDD with and without somatic comorbidities. One of the important contributions of this research led to advance knowledge regarding the amplitude of somatic comorbidities in unipolar depressive patients. Moreover, I described a specific profile of chronic medical comorbidities in patients with MDD. Another interesting observation during this project was that MDD patients presented significantly more occurrences of comorbidity consisting of malignant tumors and type 2 diabetes comparing to those existing in general population of Timis county. Furthermore, it was observed that major depression patients were at increased risk of developing several other pathologic conditions such as osteoarthritis, digestive, gynecological, cardiovascular, and metabolic pathologies.

The **first part** of the thesis, contained in Chapter 2, presents my scientific achievements in four major areas of psychiatry research: biomarkers in major depressive disorder, modern therapeutic approaches in psychiatry, the role of perinatal characteristics and personality factors in psychopathology associated with perinatal period, and the interaction between psychiatric disorders, sociodemographic and psychological factors and physical health.

In the field of *major depressive disorder (MDD)*, our research established that in our country the direct costs in psychiatric hospital are more than ten times higher than ambulatory direct costs for the same episode, so it is imperative necessary to reduce, as much as possible, the rate of psychiatric re-admissions. Moreover, although the unipolar depression was more than twice as prevalent among women, men had more severe clinical-evolutionary forms, at least in terms of the suicidal risk

associated with the depressive episode. In addition, we had emphasized once again that unipolar depression is and will continue to be one of the great challenges of the 21st century in the field of mental and general health worldwide, due to its high prevalence rate, its increased recurrence and its potential significant chronicity with extremely negative consequences due to the professional disability of the suffering people. Therefore, given the need of accurate biomarkers as objective measures in this pathology, we investigated the role of proinflammatory biomarkers and conclude that the detection of inflammatory markers should become a routine and feasible clinical approach, and treatment with celecoxib supplementation would have been justified in cases of MDD with coexisting chronic inflammatory processes. Also, the observation of the innovative pathogenic mechanisms underlying MDD is the only one possibility to find new pathways for an improved class of psychotropic medication or for the development of more clinical efficient therapeutic algorithms. Furthermore, other biomarkers, such as epigenetic (DNA methylation and micro-RNA) markers, were also investigated by us, suggesting a possible role of these markers as diagnostic and prognostic markers in MDD, also opening new possibilities for therapeutic discoveries with a more specific action compared to existing treatments.

In the field of *modern therapeutic approaches in psychiatry*, our research contributed through the first Romanian study that compared the efficacy and tolerability of atypical long-acting injectable (LAI) antipsychotics with that of oral antipsychotics in schizophrenia patients. The results of our study demonstrate the efficacy of LAI antipsychotics in a Romanian population; it was noticed these antipsychotics are superior to oral antipsychotics mainly by improving the therapy non-adherence and by reducing the level of cumulative side effects and of possible drug interactions. We have also investigated the efficacy of clonidine and other psychotropics in the treatment of alcohol withdrawal syndrome (AWS), showing that clonidine is a valuable therapeutic resource for the remission of autonomous nervous system related symptoms of AWS and it should be included in the therapeutic protocols of AWS in eligible patients.

The *role of perinatal characteristics and personality factors in psychopathology associated with perinatal period* was investigated by us through several research studies, revealing that both anxiety and depressive symptoms were overrepresented in our study population in the postpartum period. Also, the

frequency of the postpartum depression in the investigated region was quite representative: the presence of postpartum depression was detected by using a consecrated self-assessment scale (EPDS), which could have contributed to the increased percentage of cases of depression revealed by our research. In conclusion, depressive and anxious symptoms were very common in the clinical population studied due to the methodology used and there is a strong correlation between symptoms of depression, anxiety and levels of concern of the mother. A new comparative analysis of socio-demographic characteristics and the presence of perinatal suicide risk belonging to two strata of researched mothers revealed that, in the establishing of the suicide risk groups, the socio-demographic parameters of pregnant women must be considered, as well as the evaluation of the level of anxiety that has been shown to correlate. Moreover, our studies show that dimension of personality belonging to anxiety and those correlated with psychasthenia, suspicion and aggression were significantly correlated with the presence of depressive symptoms in the researched mothers, and the trait anxiety has been proved as the most stable predictor of suicide risk during the entire period of peripartum. In terms of the role of obstetrical and neonatal parameters affecting perinatal mental health, we have found that primiparity, the presence of complications during pregnancy and preterm delivery could have a predictive value for a subsequent postpartum depression.

Regarding *the interaction between psychiatric disorders, sociodemographic and psychological factors and physical health*, we have investigated medical comorbidities in major depressive disorder, showing that more constantly significant are the differences existing for high blood pressure, coronary artery disease and cerebrovascular diseases, and in the case of diabetes mellitus and malignant tumors, there were annual variation in respect with level of differences significance between patients with and without MDD, also suggesting that there is a bidirectional interrelationship between major depression and some of the chronic medical diseases. Moreover, our data indicates that an antipsychotic treatment alone is not a sufficient argumentation for somatic comorbidity appearance in MDD patients. The number of total acquired somatic comorbidity was higher in the group without antipsychotic drugs indicating that this type of comorbidity is related to depressive phenomenon rather than is caused by side effects of antipsychotic medications. Finally, the various personality types evaluated both dimensionally and categorically

could shape the profile of medical comorbidities in patients with major depression. Unequivocally, the coping profiles used may favor the occurrence of certain chronic medical diseases in patients with major depression.

We have also investigated the sociodemographic, psychopathological dimensions and personality factors influencing physical health status in coronary artery disease (CAD) patients, showing that that only negative affectivity component of type D personality has been significantly correlated with disability in the studied domains of the individual existence. In addition, the presence of type D personality has been shown to have a slightly greater effect on the severity of coronary heart disease than smoking, and clinically, type D personality D has been associated with the more frequent presence of myocardial infarction, a higher number of occluded coronary vessels in comparison with the control group. Also, the presence of type D personality in CAD patients has been significantly correlated with echocardiographic parameters, suggestive for both systolic and diastolic dysfunction. Moreover, smoking, dyslipidemia, preexisting diabetes mellitus and the level of negative affectivity and social inhibition have been predictive for the higher severity of CAD disease reflected by Syntax score.

Regarding the role of personality and the quality of life associated with type 2 diabetes and the coping styles in chronic obstructive pulmonary disease patients, showed that, somewhat unexpectedly, the presence of D type personality did not make a difference in the complications of type 2 diabetes, but it is noteworthy that it significantly contributed to reducing the quality of life in several areas of existence of this category of patients. With respect to the coping styles in chronic obstructive pulmonary disease patients, we found that coping styles have been significantly differently correlated with the spirometral parameters.

The **second part** of the thesis, Chapters 3 and 4, is dedicated to presenting my evolution and achievements in professional, scientific and academic development, followed by the plans for further development in these areas.

I graduated from the 'Victor Babes' University of Medicine and Pharmacy Timisoara (UMFVBT) in 1999, I obtained the degree as a specialist in psychiatry in 2006 and as a senior psychiatrist in 2010. Since 2001, I have been working at 'Eduard Pamfil' Clinic of Psychiatry Timisoara (consisting of two Clinical Psychiatric Wards belonging to Emergency Clinical County "Pius Brînzeu" Hospital Timisoara).

Between 2001 – 2006, I worked as a Psychiatry resident doctor and then continued as a psychiatrist from 2006 to 2011. In 2011, I became a senior psychiatrist at the same institution after I passed the exam. As a recognition of my professionalism and organizational ability, I was promoted as a Chief of 1st Psychiatry Clinic Timisoara after I have passed a contest. I was also appointed as a coordinator of Psychiatry Residency Training. At the recommendation of our university, I was also appointed as a representative of the Timis County Government in the management board of two psychiatry hospitals in our county.

In 2003, I promoted to junior teaching assistant based on a contest at the Discipline of Psychiatry of the “Victor Babes” University of Medicine and Pharmacy Timisoara. My academic career development was done by following the steps promoted competition: teaching assistant in 2006, lecturer in 2013, and associate professor in 2017. Since 2012, I was continuously elected to be a member of the Council of the Neuroscience Department no. VIII of UMFVBT.

In 2007, I graduated master’s degree in Medical Psychotherapy, and in 2017 I completed Master Psychopharmacology Program by the Neuroscience Education Institute, Carlsbad, California, U.S.A - 2015-2017 Edition. In 2015 I graduated from the Health Services Management program delivered by the Romanian Ministry of Health - National School of Public Health, Management, and Improvement in the Sanitary Issues Bucharest, 2014 – 2015 Edition. In 2016, I completed the Postgraduate Course “Teacher Training Department” by the Timisoara Vest University – 2013 – 2014 Edition.

I was a member of the research team of the type A CNCSIS Research Grant code number 755, between 2006 – 2008, and a member of an educational project team of the NEC-LINK granted by the New Europe Foundation, March-July 2007 series, Rector Professor Andrei Plesu, Bucharest. I was a manager of a research grant “Study on the role of inflammatory markers IL-6 and C Reactive Protein in the clinical management of patients with the major depressive disorder”, funded by the SC BIOCLINICA SA, no. 8/07.03.2016, contract number UMFVBT 2668 / 07.03.2016, between 2016 – 2020. I am a member of the research team of the UMFVBT grant “Exosomal miRNAs as biomarkers for major depressive disorders”, Project code 4EXP / 2020, contract no.1232 / 30.01.2020. I have opened novel and innovative directions for research using own funding, such as the role of personality factors and associated dimensions of psychopathology in coronary artery disease

patients, the role of personality characteristics, obstetrical and neonatal parameters in the development of perinatal anxiety and depression including suicide ideation, the chronic medical comorbidities in major psychiatric disorders such as major depression and bipolar affective disorder, the predicting value of sociodemographic data in establishing diagnosis of schizophrenia by comparison with other non-affective psychosis, a mirror-image study concerning the efficacy and tolerability of long-acting injectable atypical antipsychotics in comparison with oral antipsychotics in schizophrenic patients. Most of the research builds upon collaborations with psychiatrists, psychologists, resident doctors, medical students, but also with obstetricians, neonatologists, cardiologists from our university, and other national and international universities. As future directions, I want to extend the research area such as the epigenetic markers in schizophrenia, the role of neuromodulation in the treatment of major depressed patients, proinflammatory biomarkers in the clinical profile and treatment response of bipolar and schizophrenia patients, the role of biofeedback techniques in anxiety and somatoform disorders.

After I became a Ph.D., the visibility of my research activity was provided of 71 oral and poster presentations at different national and international congresses, but also 42 meeting abstracts published in ISI Web of Science indexed journals with a **Total Impact Factor = 134.354** and 15 meeting abstracts published in BDI (International Database Indexed) journals.

I have published 5 proceedings papers in ISI Web of Science indexed volumes as a principal author and 15 articles in extenso in BDI journals.

As a principal author I have published 13 original articles in extenso with a **Total Impact Factor = 25.920**, of which 2 are not yet posted in Web of Science and one is accepted for publication in the next issue of the journal, and as a coauthor 6 original articles with a **Total Impact Factor = 9.842** in ISI Web of Science indexed international journals such as Journal of Psychosomatic Obstetrics and Gynecology, Psychiatry Investigation, Journal of Mental Health, Farmacia, Applied Sciences, Antioxidants and other. Publications from various ISI international journals have been of scientific impact and recognized, accumulating a total of 119 citations in the ISI Web of Science system and a Hirsch index, **h-index = 6**.

I am a member of editorial board at two BDI indexed journals, Medical Connection and Psihiatru.ro

Since I became a Ph.D., I have published 6 monographies and 1 treatise, in CNCSIS recognized Publishing Houses. I have published 9 chapters as a first author and other 6 chapters as coauthors, some of them under prestigious Publishing House such as **Cambridge Scholars Publishing**, Newcastle upon Tyne, UK.

I organized, chaired and I was an invited speaker at 17 symposiums, workshops and postgraduate courses both independently and in international congresses, of which I would like to mention: The Ninth Workshop on Costs and Assessment in Psychiatry “Quality and outcomes in mental health policy and economics”, Venice, Scuola Grande di San Giovanni Evangelista, March 27-29, Italy, 2009; two international workshops for medical students organized by “Victor Babes” the University of Medicine and Pharmacy Timisoara; 1st International Perinatal TOTAL Health Congress, “Perinatal TOTAL Health: The First Thousand Days of Life Innovations and Transdisciplinary Collaborations” 27 - 30 June 2018 Sinaia, Romania; and 23rd World Congress of Social Psychiatry – The Social Determinants of Health / Mental Health and Access to Care, 25 – 28 October 2019, Bucharest, Romania, and other.

I was part of the steering committee at 13 regional and national conferences with international participation. Also, I was part of the scientific committee at 5 National and International Congresses. I coordinated a national course entitled “Educational Course of Schizophrenia” supported by Eli Lilly Romania that consisted of five distinct modules. The resulted material was transferred to the Romanian Association of Psychiatry and Psychotherapy as brochures. As an appreciation for this educational activity, I was awarded Eli Lilly Romania with a “Certificate of Excellence”.

I coordinated 35 Graduation Thesis, of these 34 in General Medicine specialization and 1 in Medical Assistant specialization.

As a recognition of my scientific contribution to international research, since 2014, I was elected as a counselor in the Board of European Psychiatric Association Section CL Psychiatry and Psychosomatics. Also, in 2004 I became an active member of the **New York Academy of Science**.