



SCIENTIFIC BULLETIN

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● PREFACE

In 2023, we will mark an important milestone – 60 years of the Institute of Mental Health in Belgrade. The Institute was formed on the 14th of April 1963, as the Center of Mental Health and since 1978. has been renamed into Institute. Today, we are presenting an institution of 248 employees, working in the areas of child, adolescent, and adult psychiatry, epileptology, as well as medicinal genetics, pharmaceutical activity, and laboratory diagnostics. The Institute also cooperates with multiple Faculties of the University of Belgrade and the Singidunum University, providing practical learning opportunities for their students.

The staff, the patients we help every day, temporary collaborators, colleagues, and friends are all part of the Institute. Our devoted staff is our biggest value, making the Institute what it is. Their devotion comes from gratitude for the opportunities which the Institute provides. Our diversity and versatility help us find the best solutions to all the challenges we face. A lot of young employees who have been hired based on outstanding academic performance are our greatest pride and a valuable resource for the future of the Institute. Their motivation and desire to work in the Institute is the best proof of our status as a leading institution in the region. We want to make work in the Institute stimulating to allow everyone to realise their potential. By sharing our successes and helping each other through hardships, we strive to develop cooperation which boosts morale and allows employees to feel a strong sense of belonging.

The work of the Institute is continuously realised in the fields of clinical treatment, education, and research. Our employees have multiple roles, both within the Institute, and in the wider social context. They are members of various national and international associations of experts, leading projects which contribute to a better understanding of the causes of mental health problems, increasing our capacity to address them. Through cooperation with governmental, non-governmental organisations and international organisations, we strive to improve the position of our patients and their families, as well as increase public awareness of mental health, in general. The Institute of Mental Health significantly contributes to reforms and the improvement of status of mental health in the country and in the region.

Psychiatry is in the process of great change. Even science is unequivocally leading towards a deeper understanding of illness, diagnostic evaluation,



psychopharmacology; there is still a need to deepen the knowledge of an expert in psychotherapy. The value of the Institute precisely lies in the wide field of our engagement and our continuous striving for the new.

The future of psychiatry is in many ways already here, and we hope that the Institute will continue to follow the trends of the field. What was known as the concept of ‘chemical imbalances’ is evolving into models of progressive neuroplasticity. With developments in mapping the genes associated with psychiatric illnesses, clinical practice which uses pharmacogenetic screening is becoming a routine, allowing psychiatrists to provide individualised approaches to pharmacotherapy. Currently, our main focus is early intervention. We believe that optimal psychiatric practice is an integrated cooperation model between psychiatrists, general practitioners, and other specialised services, which grants patients access to holistic treatment (<https://pubmed.ncbi.nlm.nih.gov/28946952/>).

Even if we do not know what the following decades hold for the future of psychiatry, we strive to claim a place in it. We develop models of telepsychiatry and plan to join projects related to artificial intelligence. The possibilities for a better future are endless, however, despite all developments, we believe that the fundamental clinician–patient relationship is here to stay as a constant. which will preserve the integrity of psychiatry as a profession.

We will devote various programmes to the anniversary of the Institute of Mental with our patients and their closest ones, as well as with colleagues from Serbia and abroad. We will organise a concert, podcasts, film screenings, as well as academic events, which will be featured on our website: <http://www.imh.org.rs>.

On this occasion, we especially announce the Tenth Forum of the Institute: **“60th years of the Institute – the past and the future are here”**. The Forum will take place between 19th –21st April, 2023. We invite everyone who is interested to join us on our anniversary.

Prof. Milica Pejović-Milovančević, MD, PhD

● THE PROMISING PROJECT

Prof. Ivanka Marković, MD, PhD
vice-dean of the Faculty of Medicine,
University of Belgrade



ESTABLISHING A MASTERS PROGRAM IN RESEARCH ETHICS AT THE FACULTY OF MEDICINE UB

University of Belgrade Faculty of Medicine is the leading Serbian institution for biomedical research and collaborator of the NIH Fogarty International project entitled „Establishing a Masters Program in Research Ethics at University of Belgrade School of Medicine“. This program was designed to meet the needs of Serbian institutions for trained faculty members who could provide requisite expertise and assure compliance with international ethical standards for conducting animal and human subject research. We talked to Prof. Ivanka Marković, the project lead.

When did this project start? Who is involved?

The project started in 2018, as a result of a previous collaboration between the University of Belgrade School of Medicine (UBSM) with Icahn School of Medicine at Mount Sinai, New York, with Prof. Rosamond Rhodes and myself as co-PIs. This project is a continuation of our previous 5-year project: „Research Ethics Education in the Balkans and Black Sea Countries“, also funded by Fogarty International Center/NIH, with 33 trainees from different Balkan countries that have completed the Certificate program in Research Ethics.

The UBSM faculty members from the previous project (prof. Nebojsa Lalic, prof. Zoran Todorović, prof. Janko Janković, prof. Nataša

Maksimović, prof. Nataša Milić), as well as faculty members who obtained MBE degree from the Clarkson-ISMMS Masters program (prof. Miroslav Radenković, prof. Dragan Hrnčić, doc. Vida Jeremić Stojković and doc. Tatjana Gazibara) have been the driving force behind this project.

What are the most important goals achieved by now?

During the project, a cohort of 8 trainees from Serbia and Bulgaria completed the Certificate program, with the courses being planned and executed by the UBSM and ISMMS Faculty members together. This co-teaching experience served as a laboratory to develop the Masters curriculum in Bioethics at the UBSM (http://med.bg.ac.rs/?page_id=12212&script=lat), which received national accreditation in June 2021, and the first generation of eight Master students was enrolled in the 2021/2022 school year.

What is the best possible scenario after achieving these goals?

We hope that Master studies at the UBSM will enable future students to develop the requisite knowledge and skills to provide research review and education, and assure compliance with international standards for the ethical conduct of animal and human subject research at their home institutions. As the only program

of its kind in the region, it will continue serving the need for research ethics education in the Balkan region and be a valuable resource for clinicians, researchers and Institutional Review Board (IRB) members, enabling the scientific community to assure that the conduct of scientific research is trustworthy and ethical.

Are there any recommendations for those interested to participate in the Program?

In October 2022, we will enroll our second generation of Master students, and hopefully, our first generation in English. We would like to encourage basic and clinical researchers to enroll and expand their knowledge in Bioethics, not just as a matter of professional improvement, but also as a window into a different way of thinking and acting in resolving potential dilemmas in their practice. The program relies on our experienced teachers, vast on-line resources, use of a student-focused approach, and lively and inspiring weekly discussions about ethical dilemmas in basic and clinical medicine.

GUEST OF THE BULLETIN

Prof. Rosamund Rhodes,
Director of Bioethics Education,
Icahn School of Medicine at
Mount Sinai, USA



Prof. Rhodes is a philosopher with expertise in moral and political philosophy. She is professor of Medical Education at Mount Sinai and Director of Bioethics Education. She also serves on the Institution Animal Care and Use Committee and the Liver Transplant Review Committee, and she is Co-Chair of the Ethics Committee of The Mount Sinai Hospital. She was interviewed by Ivan Ristić, MD.

Could you briefly describe a case which illustrates the role of a bioethicist from your work experience?

The cases that get referred for Ethics Committee consultation are among the most exciting in the hospital. They typical involve situations that the treating team has not previously encountered. A common scenario involves a patient who lacks decisional capacity and for whom medical decisions must be made. These cases are challenging when no one has any information about what the patient would have wanted and when the staff has been unable to locate any family member or friend who would be willing to take on the responsibility of making decisions on behalf of the patient.

In such situations, members of the Ethics Committee meet with members of the treatment team to develop a plan. I lead the group through an analysis of the anticipated benefits and burdens associated with continued medical interventions, the complicat-

ing factors that we foresee, and we continue the conversation until we arrive at a consensus on how to proceed.

What would you describe as the main challenges in bioethics in regard to mental health?

Patients with a mental illness often have the capacity to make decisions for themselves. Challenges arise when a patient with a mental illness also has a medical illness and refuses recommended treatment that is likely to provide significant benefit. In such cases, it can be difficult to determine whether the refusal is an effect of the mental illness (e.g., paranoia) or an autonomous choice that should be respected.

Can you describe your collaboration with Faculty of Medicine University of Belgrade? How did it begin and what did you achieve over the past years?

My collaboration with the Faculty of Medicine University of Belgrade (FMUB) began more than ten years ago, when the then Dean of the Medical Faculty, Bogdan Đuričić, agreed to partner with Icahn School of Medicine at Mount Sinai in a grant application to the U.S. National Institute of Health (NIH), Fogarty International Center. The aim of our original project was to provide research ethics education for people working in areas related to biomedical research in the region.

We were awarded a five-year grant and we provided hybrid on-site/on-line Certificate level

training to 33 individuals from six countries in the region: Serbia, Bulgaria, Romania, Montenegro, Macedonia, and Albania. Later we received a new grant for developing a Master program in Bioethics at FMUB. With that funding, we provided additional Master training for faculty members from the FMUB who had previously completed the Certificate in Research Ethics. Under the leadership of Prof. Ivanka Markovic, the Master program in Bioethics received accreditation in 2021.

Can you recommend literature for readers who would like to get more acquainted with bioethics in mental health?

I recommend my own recent book, *The Trusted Doctor: Medical Ethics and Professionalism*, Oxford University Press: New York (<https://academic.oup.com/book/29475>). It explains why the ethics of medicine is distinct and different from common morality and describes the key elements of medical ethics. In sum, it provides explanations of the core ethical commitments of every medical professional, including psychiatrists. The book demonstrates how those obligations arise in clinical situations and demonstrates what is required to fulfill those duties.

● GUEST OF THE BULLETIN

Nataša Dostanić, MD, PhD,
Special Hospital for Addictions
in Belgrade



Dr. Nataša Dostanić is the head of department for alcoholism and polytoxicomania at the Special Hospital for Addictions in Belgrade. She defended her PhD thesis entitled: “Assessment of the influence of sociodemographic, health, and marital characteristics on the mental health among women whose partners have been treated for alcohol dependence” recently, mentored by Prof. Mirjana Jovanović at the Faculty of Medical Sciences, University of Kragujevac. Her research article has been published in *Journal of Family Violence*.

How did you decide to evaluate family violence, depressiveness, and anxiety among women whose partners have been treated for alcohol dependence?

Throughout my clinical practice, working with male patients treated for alcohol dependence, I noticed that the overall health of the patients' partners tends to be diminished. Alcoholism of spouses increases the risk of psychiatric disorders of their partners, particularly depression, anxiety, and alcohol dependence. Alcohol use, especially heavy intoxication is linked with family violence of men towards women. Family violence by men is a significant predictor of later psychiatric disorders of their partners. Most women with psychiatric illness were verbally and physically abused by their husbands who have alcohol dependence. Treatment of these patients is a unique opportunity to concurrently deal with their problem of violent behavior. On the other hand, wives of men with alcohol dependency also need help, support, and timely

interventions regarding their mental health to be able to diagnose and treat psychiatric disorders in a prompt manner.

What is the main research question in your PhD?

The main aim of the research was assessment of the influence of sociodemographic characteristics of the marital partners, health characteristics of women, and male partner violence on mental health of women whose partners are being treated for alcohol dependence.

How was the sample gathered and what was the study design?

The study was designed as a cross-sectional study. Research participants were partners of male patients who were being treated for alcohol dependence at the Special hospital for addiction in Belgrade. The main outcome was the women's mental health. We assessed for depressiveness (Beck's depression inventory – BDI-II), anxiety (Beck's anxiety inventory – BAI), suicidality (Mini International Neuropsychiatric Interview – MINI), and alcohol dependence (Alcohol Use Disorders Identification Test (AUDIT)). We also used a questionnaire for sociodemographic and health characteristics that was made for the purposes of the research. We assessed family violence with the Conflict Tactics Scale (CTS –2).

What were the main results?

The results of the study showed that more than 70% of women whose partners are being treated for alcohol dependence fulfill criteria for mild/moderate depression, with more than 50%

women suffering from moderate/severe anxiety. Relationship length and exposure to male violence significantly influenced mental health outcomes, with longer relationship increasing the odds of moderate/severe depression in women. Almost half the subjects (48.1%) were exposed to physical/sexual violence in the past 12 months. Exposure to violence in the past 12 months increased the odds of depression, especially for moderate/severe depression (22-timefold) and increased the odds of moderate/severe anxiety threefold.

Suicidality of subjects was increased almost tenfold if the subject was exposed to violence in the past 12 months, even more so when controlled for the woman's age. Resilience of women older than 50 was significantly reduced and future research in women of this age whose partners abuse alcohol could be significant.

Which would be the message to young researchers who would like to study similar topics?

So far in Serbia there is a lack of data that are related to the analysis of overall health of women whose partners were treated for alcohol dependence and were also subjects of marital violence, making research in this topic important. Women are often discouraged to talk about this topic. Active participation of researchers and a firm therapeutic relationship could provide us with better odds of preventing abusive relationships in wives of patients with alcohol dependence.

● OUR RESEARCH

The influence of personality, parenting styles and early exposure to alcoholism – risks for the development of alcohol use disorders and pathological gambling

In a recent issue of the *Journal of Gambling Studies*, Assist. prof. Ivana Peruničić-Mladenović and Assist. prof. Snežana Filipović published a study on how personality factors and parental styles in upbringing and early exposure to alcoholism shape vulnerability to addictive behaviours and alcohol use disorder (AUD) as well as pathological gambling (PG) (<https://pubmed.ncbi.nlm.nih.gov/35037139/>).

AUD and PG have grown to become significant problems affecting people across the globe. The main challenge facing their study is their high comorbidity. Bearing this in mind, this study examined whether the variables of basic personality dimensions, mothering and fathering styles in one's upbringing as well as early exposure to parental alcoholism affected proneness to AUD or PG.

The sample consisted of 252 participants: 150 inpatients (78 AUD, 72 PG) and 102 healthy controls. They were administered a personality test, a test measuring their mother's and father's parental styles in their upbringing, a questionnaire assessing the intensity of the participant's exposure to alcoholism as a child, as well as screening tests for alcoholism and gambling. Comorbidity was removed thereby yielding a "pure" AUD and "pure" PG. The novelty of this research is its use of machine learning statistical techniques (a random forest tree using Python 3.7.7, Scikit learning package version 0.22) in order to generate simulations of empirical data and ensure that they are robust.

From the results, it was concluded that low conscientiousness and high neuroticism were the factors leaving one most vulnerable to both AUD and PG. Fathers who were more authoritarian and mothers who were less flexible were also found to increase the risk of AUD and PG. Conversely, flexible parental styles in the same children might serve as protective factors against AUD and PG. Around 79% of participants with addiction were correctly classified according to their scores on the Parental Authority Questionnaire and Children of Alcoholics Screening Test.

The most significant finding was that proneness to AUD and PG are highly impacted by personality and early parental factors. The same tests were able to classify 88% of AUD in their own group in relation to



PG. Participants with PG were found to be less open and more extroverted than those suffering from AUD. The influence of authoritarian fathers was indicated to be more important than the mother's influence in general. On the converse, the inadequate setting of boundaries by the mother as well as the permissive style and alcoholism of the father is shown to have more of an impact on proneness to AUD. These results point to there being different risk factors for developing AUD and PG within the nuclear family.

The main strength of this study is that "pure" AUD and "pure" PG are examined with comorbidity being removed and that early parental personality factors were studied in unison. The limitations are male predominance (the PG group consisting solely of males) and retrospective self-report data on the parental styles, therefore, the authors recommend future studies utilize more direct measures.

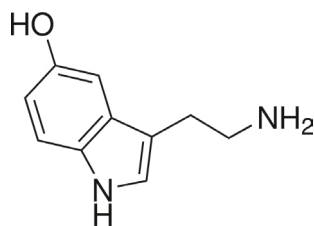
Flexible parental styles, setting adequate boundaries and expectations as well as empathetic capacities in response to children's needs were all strongly indicated to be protective factors against AUD and PG. This finding is of particular importance for psychodiagnostic and for preventive and interventional programs that target families. The parents require support to both develop and apply more functional parental behaviours in relation to their children.

NEWS FROM THE WORLD

THE SEROTONIN THEORY OF DEPRESSION – A SYSTEMATIC UMBRELLA REVIEW OF THE EVIDENCE

In late July 2022, a paper was published in the journal *Molecular psychiatry* (<https://www.nature.com/articles/s41380-022-01661-0>), which raised a lot of dust on social networks, along with a series of articles on portals and websites in which findings of this work were interpreted. It can already be said that it will be one of the most read works in psychiatry. Results of this research were reported even by the BBC, the *Economist*, the *Guardian* and *Rolling Stone*. This review paper is a systematic umbrella literature review which analyzed the results from all aspects of the serotonin hypothesis studies – serotonin levels, serotonin metabolites and 5-HIAA and their concentrations in body fluids; serotonin binding to the 5-HT_{1A} receptor; *post-mortem* analyses, measurement of serotonin transporter (SERT) levels; tryptophan depletion studies; studies of the SERT gene (either independently or in interaction with stressful events). It showed that there is no consistent evidence about the connection between serotonin and depressive disorder and no support for the hypothesis that this disorder is caused by a decrease in serotonin activity or concentration. Moreover, it is noted that there are multiple reasons to suggest that long-term use of antidepressants reduces serotonin concentration.

This review did not include any pre-clinical (animal) studies (probably because it has been shown that there is a big difference between animal models and human research and that their practical applicability in psychiatry is quite low) or studies that focused specific subtypes of depressive disorder – postpartum de-



pression, depression in children, in parkinsonism, and the like. Initially, 845 papers were identified, which were then reduced to 17 that met the inclusion and exclusion criteria. By research area, the following was found:

1. Serotonin and 5HIAA concentrations in plasma and cerebrospinal fluid (three meta-analyses) – moderate certainty evidence of no difference between persons with depression and controls.
2. Binding to 5-HT₁ receptors (two meta-analyses) – very low certainty evidence of increased serotonin activity in persons with depression is found.
3. Binding to the serotonin transporter (SERT) (three meta-analyses) – very low certainty evidence of increased serotonin activity in persons with depression.
4. Tryptophan depletion studies – effect on mood in healthy volunteers, with and without family history of depression and in patients in remission (meta-analysis and systematic review) – very low certainty evidence of reduced activity or no change in serotonin activity in susceptible populations.
5. Association of SERT gene (5-HTTLPR) and depression (five meta-analyses) – high certainty evidence of no association.
6. Gene (5-HTTLPR) – stress interaction (five meta-analyses) – high certainty evidence of no interaction.

The resulting uproar was not caused so much by the results themselves, which not much peo-

ple disputed, but because of the implications in clinical practice. The authors have been very open in advocating against the current practices of prescribing antidepressants and they believe that this class of drugs is prescribed without due consideration and for too long. Therefore, the debate arose not about the serotonin hypothesis itself, which, we can freely say, is effectively „dead“ (and consequently there is no justification for informing patients that they have a reduced level of serotonin), but about the interpretation of the impact this should have on treatment and use of antidepressants. Nevertheless, that debate is fundamentally flawed because the serotonin hypothesis is not the only thing necessary to justify the use of antidepressants. The efficacy of antidepressants is evaluated in randomized control studies by how effectively they relieve the symptoms, regardless of how they achieve that effect.

As far as the efficacy of antidepressants is concerned, there is some news on this front. *British Medical Journal* has just published the largest meta-analysis by Stone and colleagues with extremely interesting results that will be presented in the next issue of the Bulletin.

THE USE OF PSYCHOTROPIC DRUGS IS INCREASING SIGNIFICANTLY

In the December 2021 issue of the journal „*Lancet Psychiatry*“ an original research article entitled „Psychotropic medicine consumption in 65 countries and regions, 2008–19: a longitudinal study“ was published <https://pubmed.ncbi.nlm.nih.gov/34801129/>, whose primary objective was to examine global trends in psychotropic medicines consumption from 2008 to 2019 across 65 countries and regions with different country income levels. Present research is the largest and the most comprehensive assessment of twelve-year consumption trends of all

major classes of psychotropic medicines for 65 countries grouped according to county income level and geographical region. The pharmaceutical sales data from the IQVIA-Multinational Integrated Data Analysis Sistem (see here) were collected, and the authors analysed average annual sales trends of psychotropic medicines (antidepressants, antipsychotics, mood stabilizers, tranquilizers, sedatives and hypnotics), as well as relative changes in their annual consumption – expressed as defined daily dose (DDD) per 1000 inhabitants.

The increase in sale of psychotropic medicines is obvious – from 28.5 DDD (2008) to 34.8 DDD (2019), corresponding to a 4.1% relative average increase annually. The relative average annual increase in psychotropic medicine sales during the observed time period was greatest in upper-middle-income countries (7.9%), which is much more compared to the both comparators – lower-middle-income countries (2.9%) and high-income countries (1.0%).

- Globally, annual increase of 3.5% DDD was evident for antidepressants, followed by the 2.5% for antipsychotics
- Globally, the annual consumption of mood stabilizers, tranquilizers (-1.0%), sedatives and hypnotics (-0.9%) has decreased minimally
- In Serbia, the highest consumption of tranquilizers was observed (94.5 DDD) when compared to other European countries.

The consumption of psychotropic medicines increased significantly over the observed period, whereby the relative growth was highest in middle-income countries (especially upper-middle-income countries). Psychotropic medicines have become more available globally, but consumption rates vary significantly in different countries.

What were the main limitations of this study?

- 1) The pharmaceutical sales data do not reflect individual-level treatment for mental disorders, but only reflect the country level supply side of psychotropic medication, and for that reason it was not possible to analyse consumption trends by sex, age, indications or appropriateness of prescribing.
- 2) Another limitation is the use of DDD, a measure that facilitates comparisons between different population groups, but does not provide an opportunity to analyse the quality of prescribing.
- 3) Finally, this research did not consider certain societal differences and attitudes towards mental

health. Previous studies have suggested the association of higher country spending on health care and positive cultural attitudes towards mental illness with regular use of psychotropic medicines.

The comprehensive data on the epidemiology of psychotropic medicine consumption obtained in this research provide baseline consumption rates that will be used as benchmark to measure and monitor future global, regional, and national use of psychotropic medicines, as well as for the assessment of the relationship between psychotropic medicine consumption and the prevalence of mental disorders, life expectancy and health expenditure at the country level.



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