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PREFACE

Organized by the Serbian Psychiatric Association, the XVI Congress of Psychiatrists of Serbia (www.upspspa.org) was held entitled „PSYCHIATRY DURING THE COVID-19 PANDEMIC: CHALLENGES AND PERSPECTIVES“. There were several sessions on the program of the Congress in which experts from the Institute of Mental Health spoke.

At the IMH Symposium entitled „Pharmacological and non-pharmacological interventions in psychiatry - the Institute is present“, experts from the IMH presented the preliminary results of their research conducted at the Institute. The pharmacology-related data were presented by assoc. prof. Nađa Marić, who focused on the maintenance therapy in people with psychotic disorders and presented data for the sample of over 250 patients of the IMH; assist. prof. Bojana Pejušković evaluated inflammatory factors and the association with pharmacotherapy in persons hospitalized in the Department of Affective Disorders during the pandemic and assist. prof. Čedo Miljević presented the initial results of the PsyCise project regarding personalized dosing of escitalopram. In the second part of the symposium, attention was paid to non-pharmacological modalities of depression treatment and to the principles of the „watchful waiting“ approach, addressed by clin. assist. Milutin Kostić. It was followed by clin. assist. Danilo Pešić's description of the therapy in small and medium groups and his personal practice with an adolescent population at the Institute. The discussion resumed that therapeutic guidelines (depressive disorders, psychotic disorders) in psychiatry have been passing through significant changes and that daily practice can be improved if the approach is careful, if the daily routine is systematically monitored, and if patients are given sufficient care in all phases of psychiatric treatment - from the acute care, throughout the maintenance phase to the remission. This remission should be considered not only as a symptomatic remission but as personal remission which leads toward premorbid quality of life, regardless of the diagnosis.

The second IMH symposium which organized by the director, assoc. prof. Dr. Milica Pejović-Milovančević, was entitled „Children and youth - what has the pandemic taught us?“. Clin. assist. Marija Mitković-Vončina spoke about emotional (dis)regulation in adolescence, with special reference to five items important for clinical practice, while the experiences of the Clinic for Children and Adolescents during the pandemic were presented by asist. prof. Nataša Ljubomirović.

Two more symposia were held at the Congress where the results of the projects of researchers from the IMH were presented. The first of them focused on the relationship between patients, doctors and medication. Dr Kostić will talk more about the participants of this symposium and about the project itself in current issue of the Bulletin. The second symposium included the results of the CoV2Soul project, which was previously presented in the Bulletin (No. 2).

At the end of the Congress, a symposium called „Youth Speaks“ was held, which was designed as an opportunity for young researchers from all over Serbia to show their achievements. Two residents in psychiatry from IMH presented their work: dr. Sanja Leštarević spoke about the reaction of parents and peers to the self-harm of adolescents and dr. Teodora Jovanović spoke about therapeutic photography. Photos from the Congress are presented.

On behalf of the Editorial Board,
Nađa P. Marić, MD, PhD, FRP

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OUR RESEARCH

Glutathione S-transferase polymorphisms and clinical characteristics in autism spectrum disorders

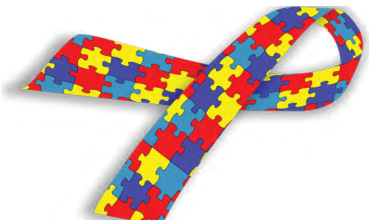
In the June 2021 issue of the journal "Frontiers in Psychiatry" a multidisciplinary research team led by psychiatrists from the Institute of Mental Health – clin. assist. Vanja Mandić-Maravić, clin.assist. assistant Marija Mitković-Vončina and assoc. prof. Milica Pejović-Milovančević (group lead) published the results of the paper entitled *"Glutathione S-transferase polymorphisms and clinical characteristics in autism spectrum disorders"* (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8267579/).

Autism spectrum disorders are a heterogeneous group of developmental disorders with different clinical expressions and levels of functioning. Recent literature in this area indicates the role of redox imbalance and oxidative stress in the etiopathogenesis of autism spectrum disorders, as well as the possible association of genetic variability in Glutathione S-transferase (GST) – an enzyme with a significant role in antioxidant protection, with the increased risk of their development. However, there have been no studies so far that have specifically explored the effect of GST polymorphisms on the severity of symptoms of autism spectrum disorders.

The aim of the research conducted by Mandić-Maravić et al. was to examine the association between different GST gene polymorphisms with the severity of symptoms and other clinical features of autism spectrum disorders such as the presence of seizures, the need for medication or inpatient diagnostics and treatment, intellectual and adaptive functioning of individuals with autism spectrum disorders. In this cross-sectional study, the sample consisted of 113 children (92 boys and 21 girls, mean age 9.4±5.9 years) diagnosed with any of the autism spectrum disorders, whereby all participants were genotyped for the GST polymorphisms - GSTA1, GSTM1, GSTT1 and GSTP1. The participants' clinical characteristics were assessed with Autism Diagnostic Interview-Revised (ADI-R), while the Vineland Adaptive Behavior Scale II (VABS-II) or the Wechsler Abbreviated Scale of Intelligence (WASI) were used to explore their adaptive functioning – depending on the development of speech and language functions of the respondents.

The results have shown that the GSTA1*CC genotype was a significant predictor of better nonverbal communication as well as of a lower lifetime chance of developing seizures. Furthermore, the presence of GSTM1 polymorphism in homozygous or heterozygous form predicted a higher adaptive functioning (a higher VABS-II total score, as well as communication score), but this genotype was also predictive of more hospitalizations. The authors explained this second finding by the fact that a greater number of hospitalizations is mostly indicated when there is a difficulty in establishing a diagnosis – which would be the case in children with better adaptive functioning when a more detailed diagnostic process is needed in order to make a distinction from typically developing children. The authors emphasized that certain risk factors during pregnancy, such as maternal smoking and medication, significantly moderated the aforementioned predictive effects of GSTA1, GSTM1 and GSTT1 genotypes. A significant effect of interaction was found between GSTA1 polymorphism, medication use during pregnancy and ADI-R diagnostic score – if the mother had used medication during pregnancy, the GSTA1*CC genotype was significantly predictive of a lower ADI-R score. Also, if the mother smoked during pregnancy, the GSTA1*CC genotype significantly predicted a decreased risk of the child taking any medication in comparison to children whose mothers did not smoke during pregnancy. When it comes to the GSTM1 polymorphisms, their presence was predictive of better functioning (higher VABS-II score) only if the mother had not smoked during pregnancy. Last but not least, this research has shown that the GSTP1* IleIle genotype was significantly associated with better cognitive functioning (higher IQ) in children with autism spectrum disorders.

This research highlighted the gene-environment interactions relevant to autism spectrum disorders – both in phenomenology and at the patient functional level. The presented results contribute to a better understanding of the role of antioxidant enzymes in neurodevelopment.



THE PROMISING PROJECT

Clin. assist. Milutin Kostić, MD
the project lead

Patients attitudes towards treatment, pharmacotherapy and psychiatrists, and how informed they are about each

Multicentric, international project "*Patients attitudes towards treatment, pharmacotherapy and psychiatrists, and how informed they are about each*" is a project that has once again united Serbia, Croatia, Bosnia and Herzegovina and Montenegro. A collaboration of 12 centres was achieved, six from Serbia (Institute of Mental Health and Psychiatry clinic KCS in Belgrade, General hospital Dr Radivoj Simonović Sombor, General hospital Požarevac, University clinical centre Niš and General hospital Leskovac), Special hospital for psychiatry Sokolac in BH, JZU General hospital Bijelo Polje in Montenegro, as well as four psychiatric hospitals in Croatia (Psychiatric clinic „Vrapče", Neuropsihichatric hospital Dr. Ivan Barbot Popovača, Psychiatry clinic and psychologic medicine KBC Zagreb and General hospital Koprivnica). Institute of Mental Health is the central hub for this non-profit project, which is being done without any financial incentives, and carried out only with the enthusiasm of all the participants. Preliminary results from 1400 patients were presented at the IX Forum of the IMH and on the XVI Congress of Serbian Psychiatric Association, while the final results from over 1700 patients will be finished in autumn.

We talked with a clinical assistant from the Faculty of Medicine University of Belgrade and a psychiatrist of the Institute of Mental Health in Belgrade, Milutin Kostić, who is the project lead.

Which are the primary research questions that you wanted to find the answers to?

In the last couple of decades, an even-greater focus is put on patients' rights. As part of this focus, more is being talked about the need of patients to be informed about their treatment, and the relationship between patient and physician is being moved from "paternalistic" to shared decision making. Wishing to figure out where the whole of western Balkans is at the moment regarding the level of information psychiatric patients have about the drugs they are taking and disorders from which they are suffering, we have formed a questionnaire that focuses exactly on that. Connected to this, some other questions were present. First, what is their relationship with their psychiatrist, drugs and their diagnosis. Also, we were interested in some things we see in clinical practice, like stopping drugs on their own initiative, compliance and similar aspects of care that are directly or indirectly connected to patient information about their treatment.

What are the results?

For now, we don't have final results since the database is massive with over 1700 patients with a huge number of questions, which are very detailed, so the coding process is lengthy too. So we currently have just some basic information, but that we think is already very interesting. Our patients are very psychologically connected to the pharmacotherapy they are taking, which we see through answers to questions about how much they perceive they are helping them, how afraid they are of stopping etc. Also, 80% of patients are very compliant regarding their pharmacotherapy and almost never forget to take their pills. They mostly have very high trust in their psychiatrist. One thing we can say is something that should be of concern is that there seem to be problems in regards to stopping pharmacotherapy and information about abstinence syndromes. Patients usually don't stop taking drugs, but when they do they usually do it without communicating with their psychiatrist. Here we may ask the question is the trust indeed as high as they claim, or do they lack the freedom to communicate with their psychiatrist in this one aspect? Under the shared decision-making model the patient has the right to his or her opinion and for the physician to be open to implementing this where possible. This is why it is important that the patient has the right to talk about everything, and that even if they want to stop taking drugs, they are not met with judgement or discouragement, but to be informed and even if after being informed about risks if they still want to stop, that they are helped to make it as safe as possible. Also, we have noticed that patients are not informed enough about abstinence and the risks, especially when stopping drugs suddenly. And patients' answers show us that abstinence syndromes are prevalent, that patients were not prepared for them and that they probably interpreted them as the return of symptoms of the primary disorder. The question is whether this is due to a lack of communication with psychiatrists or if psychiatrists themselves lack the knowledge about this topic (considering that this topic is getting more traction just in the last couple of years, including abstinence from stopping antidepressants, antipsychotics and stabilizers, while most physicians knew only about benzodiazepine abstinence). So even with just preliminary results we already have important things to think about, and we expect this to be even more when all results are processed.

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GUEST OF THE BULLETIN

Jeanne Lenzer, MD, United Kingdom

What I've learned from 20 years of medical investigative reporting?

Guest of the third Bilten is Jeanne Lenzer, physician and medical investigative reporter, who published articles in many leading world journals like T*he BMJ, Journal of Family Practice, New York Times, Washington Post, Smithsonian Magazine, the Atlantic.* She published her first book Danger Within Us in 2016. (https://jeannelenzer.com/the-danger-within) and will be a guest at the Book Club of the Institute of Mental 06.07.2022. where her book will be the topic. Our guest is known around the world for showing that many claims that come out of medical research are later shown to be false or overoptimistic. This problem could become permanent, and Jeanne Lenzer think that the following six factors play the biggest role:

Jeanne Lenzer: Medical research claims too often are subsequently proved to be unsupported, misleading, or false. The following six problems play an outsized role in perpetuating the problem.

1. Reliance on surrogate endpoints (*Surrogate endpoints are unclear endopoints, in which it is not clear whether there is benefit for the patient. For instance death is a very clear endpoint, and increase or decrease of it is a clear measure of the effect of a certain intervention. Quality of life could be clear as well. On the other hand, surrogate endopoints are measures that can be measurable for a physician or researcher, but could be unimportant for the patient, his or her quality of life or survival. If for instance we have a drug that lowers cholesterol in the blood, but quality of life and survival are unchanged , the importance of such an intervention is actually probably negligible, but is often marketed as important. editors note*): Drugs and devices are increasingly approved by the US Food & Drug Administration based on changes in a surrogate endpoint. Even so-called "validated" surrogate endpoints, like blood sugar for diabetes or progression-free survival for cancer, often fail to translate into clinical benefit.

2. Unpublished data: When researchers combine unpublished data with published data, claimed benefits tend to substantially decline or evaporate. This was the case for a review of antidepressant data published in the New England Journal of Medicine.2 (*almost half of studies researching antidepressant efficacy that were in the FDA database were never published in scientific journals, and those were almost exclusively negative studies, unlike the positive ones that were almost all published. editors note*) In addition, the deaths of some test subjects in clinical trials are legally held secret by the company and the FDA and never released to researchers who are led to believe they have been given all unpublished data.3 4

3. Irreproducibility: Most research has not been or cannot be reproduced. A poll of 1576 researchers revealed that "more than 70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have failed to reproduce their own experiments."5 6

4. Analytic overreach: Thirty-two percent of the most highly cited research claims in leading medical journals were found, in subsequent research, to be false or misleading.7 This contributes to the problems cited in the most downloaded article in the history of PLoS Medicine, "Why most published research findings are false."8

5. Lack of independent research: Most research supporting drugs and devices are conducted by profit-driven enterprises whose findings tend to minimize (if not conceal) harms and exaggerate benefit. Financial conflicts are a far more important biasing factor than so-called "intellectual" biases and have a far greater impact on the body of science.9

6. Cure as cause: Too often problems created by treatments are misinterpreted as due to underlying disease. This is a little-understood but very widespread problem.10

At the start of July, at the Book club that will be held over Zoom we will have a chance to discuss about this and many other problems that exist in modern medicine, and and that are thoroughly dissected in her book. We will also discuss how can we help in this fight to protect the integrity of medicine and science.

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GUEST OF THE BULLETIN

Stefan Jerotić, MD
PhD candidate at the Faculty of Medicine, University of Belgrade

Stefan Jerotić works as a psychiatrist at the Clinic for Psychiatry UCCS and a clin.asist. at the Faculty of Medicine University of Belgrade. At the XVI National congress of the Serbian Psychiatric Association (2022) he received the "Vladimir F. Vujić" award for the best published paper of a young psychiatrist in the past year (https://pubmed.ncbi.nlm.nih.gov/33567332/). The paper is part of Dr. Jerotić's doctoral thesis entitled "Retinal structure analysis in psychosis spectrum disorders", whose mentor is Nađa Marić, MD, PhD, FRP. On July 14, 2022 Dr. Jerotić will defend his thesis.

How did you decide to examine the retinal parameters in schizophrenia?

The relationship between the eye and psychosis is intriguing for several reasons. Retina is an integral part of the central nervous system that has the same embryological origin as the structures of neocortex and diencephalon. On the other hand, there is a fascinating fact that in the history of mankind a case of schizophrenia has never been described in a person who were born blind. This is not the case with other sensory deficits, for example individuals who were born deaf have the rates of psychosis spectrum disorders similar to the general population. Furthermore, regarding the biological basis and neurotransmitters, it is important to emphasize that the D2 family of receptors, as well as both metabotropic and jonotropic glutamatergic receptors are present in retina, and we know that glutamine and dopamine are the neurotransmitters of the greatest importance for the etiopathogenesis of schizophrenia.

Modern technology has made it possible for even very small structural changes in the retina to be noticeable (optical coherence tomography - OCT). This can be useful in practice because the retina is the only part of the CNS that is not concealed by the cranium, and retinal axons are non-myelinized which enables precise tissue quantification using the modern imaging devices – "optical biopsy"

What is the main research question in your dissertation?

We aimed to explore whether the retinal structure differs between patients with a psychosis spectrum diagnosis and healthy individuals. The current conceptualization of schizophrenia is neurodevelopmental, but there are also certain neurodegenerative aspects in the etiopathogenesis of the disorder. For example, it has been unequivocally established that changes in brain structure occur during the illness, such as cortical thinning in the frontal and temporal lobes, as well as alterations in thalamic structures. Having said that, it can be assumed that certain changes in retinal structure can be observed in patients with schizophrenia.

How did you obtain the sample and what was the study design?

The research was designed as a non-interventional cross-sectional study. The patients were recruited from the Clinic for Psychiatry UCCS, while the control group consisted of healthy subjects of a similar age and gender. Retinal structure parameters were examined using a spectral-domain OCT device – to determine the individual retinal layers' thickness (in micrometres). Afterwards, we compared the retinal structure parameters between patients and the control group and correlated retinal thinning with different clinical parameters (such as illness duration).

What are your main results?

In patients, we found a reduction in macular thickness, as well as a reduction in ganglionic cell layer and inner plexiform layer. Also, daily antipsychotic dose correlated with cup-to-disc ratio, as well as optical cup volume, which can be interpreted as a certain loss of nerve tissue. In addition, the reduction of macular thickness was more pronounced in female patients in comparison to their male counterparts.

What message would you like to convey to young researchers?

I believe it is necessary for anyone who wants to engage in scientific research to study the widest possible range of topics within their area of interest. By that, I think it is worth thoroughly studying the entire range from basic research – such as cell culture analyses and animal models, to qualitative phenomenological research dealing with the alterations in core structures of subjective experience. In my opinion that might be the right way to enrich the knowledge about a certain disorder and create ideas about how a new and original scientific-research contribution can be made.

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NEWS FROM THE WORLD

REVIEW CO-WRITTEN BY EXPERTS BY EXPERIENCE AND ACADEMICS

In the latest issue of World Psychiatry Fusar-Poli (photo) et al. published an exceptional study entitled "The lived experience of psychosis: a bottom-up review co-written by experts by experience and academics" with findings important for clinical practice, research and education (https://onlinelibrary.wiley.com/doi/10.1002/wps.20959). The authors collaborated intensively with patients whose experiences they studied to continue the rich phenomenological tradition which stemmed from K. Jaspers, K. Schneider, K. Conrad and some contemporary experts cited in the paper.

However, Fusar-Poli et al provided the first co-written bottom-up review of the lived experience of psychosis, whereby experts by experience primarily selected the subjective themes that were subsequently enriched by phenomenologically-informed perspectives. First-person accounts within and outside the medical field were screened and discussed by numerous patients, family members and careers.

The material was complemented by semantic analyses which showed differences in the illness course. Typical for the prodromal stages were existential themes - loss of common sense, perplexity and lack of immersion in the world with compromised vital contact with reality, heightened salience and a feeling that something important is about to happen and need to hide the tumultuous inner experiences. The first episode stage was denoted by some transitory relief - the onset of delusions, intense self-referentiality and permeated self-world boundaries, tumultuous internal noise, and dissolution of the sense of self with social withdrawal. The later stages (i.e., relapsing and chronic) involved grieving personal losses, feeling split, and struggling to accept the constant inner chaos, the new self, the diagnosis and an uncertain future. The experience of receiving psychiatric treatments, such as inpatient and outpatient care, social interventions, psychological treatments and medications, included both positive and negative aspects and was determined by the hope of achieving recovery, understood as an enduring journey of reconstructing the sense of personhood and re-establishing the lost bonds with others towards meaningful goals.

Although it is not easy to listen to and understand the human and experiential reality of patients who are about to relive or re-express their stories, it is not possible to "do" psychiatry and to provide treatments without starting from these inner realities – from these lacerated subjectivities that yearn to be heard and understood. The information in the presented paper proves once again that the complexity of psychosis must be studied by a combination of approaches, ie. not only by the methodology of the natural but also by the social sciences.

CANNABIS AND PSYCHOSIS

D'Souza et al. recently published a consensus article in *The World Journal of Biological Psychiatry* (WJBP - https://pubmed.ncbi.nlm.nih.gov/35315315/) on the topic of the relationship between cannabis and psychosis. A group of researchers with expert knowledge on this topic were invited into a task force of the World Federation of Societies of Biological Psychiatry (WFSBP) to synthesize the most recent evidence from literature.

The authors underlined that the potency of cannabis that is currently available in the Western countries is significantly higher, with concentrations of tetrahydrocannabinol (THC) growing from 4% during the nineties to nearly 15% during the past decade. Furthermore, more people are using cannabis in the form of edibles that are orally ingested and may have additional negative effects in vulnerable persons. Changes in legislature regarding cannabis use, medical use of cannabis, legalization and price drops may be circumstances that could increase the negative effects of cannabis use and these consequences may be even greater than what the previous studies have shown.

In the WJBP consensus, it was emphasized that use of cannabis causes clinically significant, transient psychosis-like symptoms during intoxication which manifest as increase of around 3 points on the Positive symptoms subscale of PANSS. On the contrary, use of cannabidiol (CBD) did not cause these effects. These changes were more pronounced in persons with high schizotypy scores, as well as persons with family history of schizophrenia.

Use of cannabis can cause Cannabis Induced Psychosis (CIP) which is defined as a psychotic disorder that emerges in the context of cannabis use and resolves with the termination of its use. Over 1% of everyday users are diagnosed with CIP over a ten-year period, which is an increase compared to older data and is in relationship with the increase of the THC/CBD ratios in currently available cannabis. Even though the diagnostic criteria note that CIP ends with cannabis use termination, nearly 50% of CIP may later develop schizophrenia or bipolar disorder.

Several meta-analyses have underlined the connection between cannabis use and risk of schizophrenia. There is a linear dose-response association – the highest risk is associated with more frequent and higher potency cannabis use. Even when considering confounders such as alcohol and other

drug use, as well as family history of mental disorders, there is at least a fivefold risk increase for transition to schizophrenia in persons with Cannabis Use Disorder (CUD). This risk increase is maintained even 15-20 years after CUD is diagnosed. Moreover, cannabis use increases the risk of schizophrenia in ultra-high risk patients (OR 1.75) and predicts a worse course of illness with more relapses (OR 2.73).

Cannabis can cause psychosis-like symptoms (perceptual distortions, paranoia, slowing of time, etc.) and these symptoms occur more often in persons with higher schizotypy scores, as well as in persons with an ultra-high risk (UHR) for psychosis. Cannabis use has been hypothesized to alleviate the core symptoms of schizophrenia by some investigators. This 'self-medication hypothesis' is not supported by evidence and psychotic symptomatology did not predict later cannabis use. It is likely that persons with schizophrenia use cannabis for its immediate anxiolytic effects, after which core schizophrenia symptoms become worse.

Effects of long-term cannabis use on brain structure were found in the hippocampal area and orbitofrontal cortex, as well as in amygdala, striatum, and cerebellum. Longitudinal studies also found changes in cerebellum and medial temporal lobe thickness in adolescents with minimal exposure to cannabis, which could be an indicator of disruptions in brain development and pruning processes. Changes were also found in the white matter. Interestingly, CBD use may reduce this neurotoxicity caused by THC, especially in regard to hippocampus size reduction. There is opposing evidence regarding the reversibility of these changes after long-term abstinence of cannabis.

Evidence shows that phyto- and synthetic cannabinoids can cause a range of psychosis outcomes from transient psychotic states to chronic recurrent psychoses. While cannabinoids may increase the risk for psychosis, their exposure is neither necessary nor sufficient to cause psychosis. The authors underline that there are multiple causal components that can be modified, which is important to consider when discussing possible legalization or decriminalization of cannabis so that the wider public can be adequately informed, and risk of psychosis can be decreased. This topic is meaningful at the time when legalization of cannabis is more common, and more effort should be made so that the population can be educated about the risks and harms of cannabis use. The authors also remind us about the consequences of tobacco commercialization without proper disclosure of its negative effects and call for caution when changing legislature regarding cannabis.

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