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SECOND ANNOUNCEMENT

PREFACE

The Scientific Bulletin of the Institute of Mental Health is entering its second year of publication. One of the regular sections of the Bulletin is „News from the world“. For the first issue of the Bulletin in the New 2023, we will look at the most cited publications of the leading psychiatric journals at the moment. This is, of course, only one of many possible criteria for gaining an insight into the most current topics in psychiatry today.

At the beginning of 2023, the most influential psychiatric journal World Psychiatry (WP) announced that “Understanding the burnout experience: recent research and its implications for psychiatry” (2016) was the most cited WP paper <https://pubmed.ncbi.nlm.nih.gov/27265691/>. This review paper by Canadian authors Maslach and Leiter pointed out that the topic of burnout syndrome is of particular importance for psychiatry, especially the differentiation between burnout and depression. The concept of workplace depression as a reason for absenteeism has raised many important questions for clinicians as it has major implications for employees, employers, and insurance companies. Therefore, noting that the burnout syndrome as a basis for being spared from work must have a precise and objective assessment, the authors advocate a multidisciplinary approach to this phenomenon.

When it comes to WP research papers, the most cited was work done by Correll et al (2017) “Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls” <https://pubmed.ncbi.nlm.nih.gov/28498599/>. It is an extremely large meta-analysis that provides a wealth of data on the prevalence of cardiovascular disease (CVD) in people with SMI (severe mental illness - schizophrenias, unipolar and bipolar affective disorders). The results show that about 10% of people with SMI (average age 50 years) have at least one comorbid CVD. An eight-years longitudinal analysis indicated that the incidence of CVD is about 4% in the general population, but that patients with SMI have a 78% higher risk of developing CVD and an 85% higher risk of dying from CVD compared to the general population. The conclusion was that there is an urgent need to limit the



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prescription of antipsychotics - only when they are really necessary, and to give preference to drugs with the lowest CV risk in the selection of medication. Correll et al. also emphasized that the topic requires an urgent response throughout the world because the problem is global.

The next two high impact journals are LANCET Psychiatry and JAMA Psychiatry. In the former one, the year 2022 was marked by an epidemiological study by Taquet et al. “Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients” (2022) <https://pubmed.ncbi.nlm.nih.gov/35987197/>. This analysis of two-year retrospective cohort studies of people with COVID-19 (USA, Australia, UK, Spain, Bulgaria, India, Malaysia, Taiwan) showed no difference between Delta and Omicron in neuropsychiatric aspects. In relation to COVID-19, mood disorders and anxiety disorders were characterized as transient, i.e. no difference was found in their frequency compared to other respiratory infections. In contrast, COVID-19 infection has been shown to increase the risk of psychotic disorders, cognitive deficits, dementia, or epileptic seizures. Compared to adults and the elderly, the psychiatric risk profile in children was more benign, but children were found to have an increased risk of epi-seizures, encephalitis and other primarily neurological disorders, which the authors characterized as a worrying finding. The pathogenesis of these neuropsychiatric sequelae is being investigated.

The topic of the pandemic was in the focus of the JAMA Psychiatry readers, too. In 2022, the most cited manuscript was the viewpoint of Re-ger et al. published at the very beginning of the pandemic “Suicide Mortality and Coronavirus Disease 2019—A Perfect Storm?” <https://pubmed.ncbi.nlm.nih.gov/32275300/>. The authors commented on the situation in the USA, where suicide rates have been increasing in the last two decades and become the highest since 1941. In the context of the COVID-19 pandemic, the authors suggested various ways to prevent the risk and their viewpoint had an optimistic tone, which was not frequent at that time (2020). Namely, they recalled the well-known fact that suicide rates decrease in the period after national disasters (e.g. the terrorist attacks of 11 September 2001) and explained this by the so-called pulling-together effect, whereby individuals undergoing a shared experience might support one another, thus strengthening social connectedness. Besides, they emphasized that epidemics and pandemics can change one’s views on health and death, making life more precious, death more terrifying, and suicide less likely. This article has been cited over 450 times in the past two years. Interestingly, according to the first major international survey by Pirkis et al. <https://pubmed.ncbi.nlm.nih.gov/33862016/> published in 2021, it was proven that at the beginning of the pandemic the number of suicides remained mostly unchanged or declined compared to the pre-pandemic period in high- and middle-income countries. In Serbia, according to preliminary indicators for 2020, the suicide rate also decreased compared to the period before the pandemic.

The conclusion of this editorial is self-evident - whether it’s about the pandemic or other aspects of mental health and illness, this is a time where we have a frighteningly large amount of data at our disposal. Enormously large epidemiological studies are facing the challenge of objective and thorough interpretation of results, while readers may face the burnout.. There are and will be many debates about whether quantity (the „publish or perish“ principle) has destroyed the quality. The reproducibility topic is an important scientific theme (<https://www.nature.com/articles/533452a>) that remains relevant forever.

Prof. Nađa P. Marić

OUR RESEARCH

Maintenance Therapy of Psychosis Spectrum Disorders in a Real-World Setting: Antipsychotics Prescription Patterns and Long-Term Benzodiazepine Use

In the April 2022 issue of the Journal “Frontiers in Psychiatry” a multicentre research team led by Nadja P. Marić and Sanja Andrić Petrović published the results of investigation focused on long-term prescription patterns among outpatients with psychosis spectrum disorders in the Balkans (<https://www.frontiersin.org/articles/10.3389/fpsyt.2022.796719/full>). The present study was part of the project IMPULSE (PI Nikolina Jovanović, Grant Agreement No. 779334; <http://impulse.qmul.ac.uk/>).

According to the guidelines for psychosis spectrum disorders (PSD), antipsychotic (AP) maintenance treatment is continuous treatment with the lowest effective dose of an oral or long-acting AP medication to prevent relapse. Guidelines usually recommend AP monotherapy (APM) and very limited use of antipsychotic polypharmacy (APP). However, real-world prescribing patterns often differ from guidelines’ suggestions.

Mental health-care practice in Central and Eastern European countries is sometimes described as ‘a blind spot on the global mental health map’. The



present study was designed to overcome the aforementioned gap. Its main goal was to focus on stable PSD outpatients from the Western Balkan and to elucidate trends in long-term APP, psychotropic polypharmacy, and long-term benzodiazepine (BZD) use during the 6-month period. The secondary goal was to explore potential sex-differences in psychotropic medication prescribing practices. We collected information from $n = 134$ outpatients (ICD-10: F20-29) from Serbia, Northern Macedonia and Bosnia and Herzegovina recruited through the IMPULSE study (age 41.7 ± 11.0 ; male 62.7%; mean number of lifetime hospitalizations 2.6 ± 0.7).

The daily prescription included on average 3 different psychotropic medications, of which 42.7% were APP (which can be considered a very high rate APP). Global and regional trends showed a median APP rate of 19.6% (interquartile range 13–35%). The research showed that APP rates differ between regions – higher rates were found in Asia and Europe in comparison to North America, Australia and Oceania. Interestingly, during the last few decades, in some of these regions the rate of APP increased (North America), while in Asia it decreased. No similar changes have been found in Europe, with APP rate of approx. 23%.

As opposed to the finding of a higher APP rate, the use of LAI/depot AP formulation in approximately 25% participants seems somewhat lower than reported in other regions. A possible explanation for this could be that the present study involved more compliant patients (willing to adhere to the IMPULSE protocol), or fewer schizophrenia patients (F 20: 58.2%; F21-29: 41.8%) in compari-

son to other studies of LAI formulations.

The utilization of clozapine in the present sample was higher in comparison to the USA or the UK, suggesting a low level of “clozaphobia” in our region. Our finding that clozapine was associated with more previous psychiatric hospitalizations indirectly confirmed an appropriate choice of the third-line medication, however the fact that this pharmacologically “rich” molecule was prescribed with many other psychotropic medications i.e. in APP rather than APM (the difference with high effect size) needs further consideration.

We also found a lower rate of APP in females. However, both sexes had almost the same average AP daily dose (approximately 14 mg of OLA equivalents). According to experts in the field, women’s psychotic symptoms respond to lower doses of AP than men’s, thus many women in our sample might possibly be overdosed (and experiencing unnecessary adverse effects). However, lower rates of APP in females might counteract possible higher AP DD effects.

Finally, we found an alarming number of patients with long-term BZD use, which could be associated with serious health risks. The finding of 42.7% patients continually co-prescribed with long-term BZD in the Western Balkans requires strategies to improve the knowledge about rational BZD use in the region.

To the best of our knowledge, this is the first study in the Western Balkans to show long-term psychotropic medication prescribing patterns in clinically stable real-world patients with PSD. These find-

ings may not be generalizable to the region as a whole and we analyzed prescribing patterns only, which is not always the same as the medication used by patients. Despite given limitations, the present study overcame the limitations of similar studies of AP that have focused on short-term polypharmacy which could reflect cross-titration and varying clinical conditions. Thus, the presented information could be used for future analyses of the real-world practices and for the targeted interventions. Appropriately designed interventions aiming to safely switch the inappropriate therapeutic regimens, i.e. very high prevalence of long-term AP polypharmacy and non-rational BZD co-prescription, are strongly needed in the Western Balkans.



● THE PROMISING PROJECT

Assoc. Prof. Iris Žeželj,
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IRRATIONAL MINDSET AS A CONCEPTUAL BRIDGE FROM PSYCHOLOGICAL DISPOSITIONS TO QUESTIONABLE HEALTH PRACTICES



REASON4HEALTH

The REASON 4HEALTH project examines the psychological foundations of two groups of questionable health practices: non-adherence to official medical recommendations and the use of complementary and alternative medical treatments. We talked to the principal investigator of this project, assoc. Prof. Iris Žeželj.

What was the key motive which prompted you to explore psychological dispositions, irrational beliefs, and healthy behaviors?

In an attempt to preserve their health, some people resort to questionable medical practices that can lack evidence, be already debunked or even downright dangerous. Our team gathered to solve the puzzle: Why do people take risks in order to protect themselves from risks? Why do some people follow the official medical recommendations, while others blindly follow the traditional, complementary and alternative medicine (TCAM) recommendations (folk remedies, homeopathy and crystal therapy)? How is it possible that some people buy into the promise of panacea put forward by TCAM practitioners? In this project we aim to test whether peo-

ple resort to questionable health practices partly because they have a certain set of psychological traits, because they view the world in a specific way. By exploring the digital media landscape when it comes to TCAM we are also exploring what these people are exposed to.

Were there any similar studies in our country or globally?

At present, there is no data on media reporting of TCAM practices in Serbia, and no data on prevalence of TCAM in the general population, while the data on non-adherence is scattered and restricted to several specific behaviors. Internationally, there is lack of data on the relationship between the two groups of behavior: non-adhering to official recommendations and resorting to TCAM practices.

Project REASON4HEALTH is put together very ambitiously as it integrates theoretical frameworks from cognitive psychology, social psychology, personality psychology and clinical psychology. We will employ different research methods: content analysis of digital media, daily experience sampling via a mobile application programmed specifically for this purpose, survey on a representative sample and laboratory exper-

iments. This multidisciplinary and multi method approach will allow us to triangulate the data and build a comprehensive picture on prevalence of questionable health practices, the nature of these behaviors, psychological profile of users and reporting practices in the public sphere, as well as guidelines for better practices.

Who is involved in the current project and what are the main research questions that you are addressing?

The team is composed of 14 researchers and all of them have excellent publication history (including Science, Nature Human Behavior, etc.). All members of the team are devoted to open science principles and pursue them actively, both in the activities of Laboratory for Research of Individual Differences and in all phases of REASON4HEALTH project.

Did you encounter any obstacles, what was particularly challenging in your work so far?

Although we were a bit concerned about whether we will be able to engage the stakeholders and partners to the project (representatives of institutions, media, patients' organizations, official medical practitioners and TCAM practitioners), our exper-

periences have been encouraging so far. They have been mostly responsive to our calls and gave us useful feedback. As the biggest future challenge I see projects sustainability after the financial support runs out, as well as the readiness of stakeholders to actually apply the results in practice, e.g., in public communication concerned with health or communication within a health provider-patient relationship.

When do you expect the first and final results and what would be their practical application?

Financial support of the Science Fund of the Republic of Serbia enabled us to envision very ambitious research, which will result in a rich database after three years of intense research. In my view, it is also very important that we account for close collaboration with local policy makers and initiate the public dialogue on questionable health practices and their consequences. COVID-19 pandemic has, sadly, made this topic painfully current and demonstrated how psychological and social sciences in general can centrally contribute to this societal task.

After the first year of the project, we can share three preprints which are under revision at the moment:

- What Serbian online media reports on TCAM <https://psyarxiv.com/rz2hg/>
- Psychological roots of different forms of non-adherence to official medical recommendations <https://psyarxiv.com/3yutm/>
- Typology of TCAM use and their relations to irrational beliefs
- We have prepared the results as digest tailored for general population as well:
- Media reporting https://reasonforhealth.f.bg.ac.rs/wp-content/uploads/2022/08/Alternativna_medicina_u_medijima_Reason4Health.pdf

We will continue to work hard in the next two years, follow us for more.

GUEST OF THE BULLETIN

Clin. assistant Stojan Perić, MD, PhD,
recipient of the Annual award of the Faculty of Medicine
University of Belgrade for scientific work of young
researchers in 2022

Dr Stojan Perić is a specialist in neurology and clinical assistant at the Faculty of Medicine University of Belgrade, and author of more than 100 articles in neurology. He received the Award for young researchers of the American Academy of Neurology (2011), Bruce Schoenberg award for research into acute polyradiculoneuritis (2015) and the City of Belgrade Award (2019) for the book “Polyneuropathies

- contemporary approach in diagnostics and treatment”. He defended his PhD thesis “Evaluation of functional and morphological disorders of the central nervous system in patients with myotonic dystrophy type 1” <https://nardus.mfn.gov.rs/handle/123456789/2456?-show=full> under supervision of Professor Vidosava Rakočević Stojanović in 2016.

How did you choose the topic of evaluation of neuropsychological and behavioral profile in patients with myotonic dystrophy?

Since my student days, I have been fascinated by neurology because of its picturesqueness and precision. Myotonic dystrophy type 1 is an illness where a neurologist can make a clinical diagnosis even from the facial features and extremities of the patient. Overtime, I have also become interested in the hidden

features of different disorders. One such thing is central nervous system affliction in myotonic dystrophy. The earlier literature was mainly concerned with mental retardation in patients with severe, congenital forms of myotonic dystrophy, while the neuropsychological and cognitive profiles of patients with other forms of this disorder were under researched. Furthermore, we were in a position to implement novel methods other than the typical neuropsychological tests, such as the computerized battery of tests. We could also apply modern methods, including transcranial ultrasonography, voxel-based morphometry, and diffuse tensor imaging.

What was the main research question in your PhD thesis?

The main aim was to understand cognitive and behavioral difficulties of patients with type 1 myotonic dystrophy and to correlate these findings with changes in brain structure by using ultrasonography and magnetic resonance imaging. We also sought to find biomarkers of brain damage in this disorder.

How did you collect the sample, and what was the study design?

The Serbian registry for myotonic dystrophy was formed in 2008. The number of patients in the registry is comparable to the largest registries worldwide. This allowed us to simplify patient recruitment for various research projects, including my PhD thesis. We were in the position to choose patients with juvenile and adult illness onset for the study group. The research was conducted in 2011. The study was cross-sectional, and we opted out of the longitudinal prospective design because of the slow development of myotonic dystrophy where

the clinical changes can sometimes only be seen five to ten years after the first testing.

What were the main results of the research?

We found significant cognitive and behavioral changes, including a visuospatial dysfunction in 80% and executive dysfunction in 67% of patients with myotonic dystrophy. About 15% of patients were significantly depressed and 60% had a personality disorder. Drowsiness during the day and tiredness were present in about half of the patients. These symptoms had a high impact on quality of life. Using modern neuroimaging methods, we found diffuse damage of gray and white matter, including damage to the cortex, supracortical structures, brainstem and cerebellum. Microstructure of the left hemisphere white matter changes were linked with lower scores in attention and orientation tests. Depressiveness and fatigue were significantly correlated with lower echogenicity of raphe nuclei. There was a positive correlation between tau proteins and beta-amyloid in CSF which is specific for myotonic dystrophy and is a potential biomarker for this disorder. The discovery of adequate central biomarkers is of great significance for clinical trials of gene therapy, some of which are already underway.

What message would you give to young researchers who would like to do similar research?

I would encourage young researchers not to repeat studies that have already been done in other parts of the world. We do not have to take giant steps, but it is of great importance to take new, creative steps. In modern science, great discoveries are rarely made by a single ingenious researcher. These discoveries mostly come from a string of smaller steps. Young researchers should understand that great results are only made through teamwork. Finally, it is important to “copy” ideas. We should study the methods and approaches used by other colleagues from different departments, faculties, and universities, and apply modified versions of these approaches on our own cohorts of patients. This is why it is important to primarily form good pools of patients with clearly defined clinical characteristics.



GUEST OF THE BULLETIN

Marina Mihaljević, MD, PhD,

Johns Hopkins University School of Medicine -
Department of Neuroscience (Baltimore, USA)

Dr Marina Mihaljević is a psychiatrist employed at the Clinic for Psychiatry University Clinical Centre of Serbia in Belgrade, and is currently working at the Johns Hopkins University School of Medicine - Department of Neuroscience (Baltimore, USA). After defending her PhD thesis entitled “[The effect of the FKBP5 polymorphisms, childhood trauma and neuroticism on psychotic disorders](#)” at the Faculty of Medicine, University of Belgrade (2017), she received the prestigious Fulbright scholarship which is granted by the US government to the most successful young experts from different scientific fields. Since 2019 she has been living in the USA as a postdoctoral student, and since last year she has become a member of the teaching staff of the Johns Hopkins University School of Medicine. Since 2022, she has also been teaching at the [Cold Spring Harbor Laboratory Workshop on Schizophrenia and Related Disorders](#), school with a long lasting tradition of gathering leaders in the field of neurobiological research in schizophrenia. She was interviewed by Dr. Sanja Andrić Petrović for our bulletin.

Could you tell us more about the Cold Spring Harbor Laboratory and its activities?

The Cold Spring Harbor Laboratory (CSHL) is one of the most

prestigious research facilities in the USA, especially in the fields of biology, genetics, oncology and neuroscience. I like to call it a divine “scientific resort” on Long Island. This facility is the place where eight Nobel Prize winners in physiology and medicine have conducted their research, including James Watson and Francis Crick who discovered the DNA double helix. In addition, CSHL organizes seminars and schools throughout the year covering a wide array of topics in specific fields. It is also interesting to share that it was James Watson himself during his long career as head of CSHL who initiated the development of Neuroscience Research Center as part of CSHL, including the schizophrenia school. The school’s “*Workshop on Schizophrenia and Related Disorders*” impacted my career greatly as well.

How did you decide to apply and how has this affected your professional career?

Over the course of my residency in psychiatry, I also began my doctoral studies because I have always been fascinated by the molecular basis of schizophrenia, and especially the genetics of this illness. However, I quickly realized that psychiatric genetics were rapidly evolving throughout the world, and that I needed to go some-

where else to learn more. My mentor, Professor Nađa Marić Bojović played a great role in helping my career advancement abroad and inspired me to apply to the best schools of psychiatry, including the CSHL. When I received an invitation to the CSHL schizophrenia school, my first thought was “I have to be there”. Some of the most eminent professors in the field of schizophrenia held lectures, such as Robin Murray and Daniel Weinberger who spoke on the neurodevelopmental theory of schizophrenia and presented the most recent research in the field, as well as Michael Owen who spoke on the genetics of schizophrenia and who received the honorary “Sir” title for his research achievements in Great Britain. This is how I participated in the CSHL Schizophrenia School in the now distant 2014, with the help and recommendations from my mentor.

The CSHL school lasts for a week and one of the main ideas, besides the lectures, is an informal interaction with colleagues and professors, so that ideas and opinions about lectures can be exchanged through common activities. This way of getting to meet professors and share opinions led to me getting the chance to work at the Johns Hopkins School of Medicine, as well as to study at Cardiff University, where I did a part

of my doctoral thesis research. We were already collaborating with colleagues from Cardiff on an [EUGEI project](#), and my stay helped deepen this collaboration.

[After some time you became a teacher at the same program. How was this experience for you?](#)

Yes, last year I returned to CSHL as an assistant to professors and as a lecturer. I gave a lecture on the topic “*Biological mechanisms of relapse in psychosis*”, a part of my original research at Johns Hopkins on the neurobiology of relapse in psychosis, including neuroimaging results and molecular markers in regards to epigenetics and gene expression. This experience was quite special because I had a different perspective on

the school and its participants. I can say that now I am not only convinced of the quality of the school and what it has to offer, but I also managed to see how hard the professors try to teach others and to maintain interactions in a natural and direct manner.

[Have you got any advice for young researchers in the field of neuroscience who would like to apply to participate in this programme?](#)

My advice would be simple - do not miss the chance to apply for the CSHL Workshop on Schizophrenia and Related Disorders. The experience and networking that you will receive will be vast and give you confidence for any future career challenges.



● JOURNAL CLUB OF IMH



In October 2022 the Critical Review of Literature (CRL) was held as part of the educational activities at the Institute of Mental Health. Dušan Janković, MD and resident in psychiatry analyzed and presented the methodological values and shortcomings of *Sniffing submissiveness? Oxytocin administration in severe psychopathy* <https://pubmed.ncbi.nlm.nih.gov/34182248/>, a scientific paper by Rijnders and associates. One of the aims of the study was a comparison of social dominance between individuals with psychopathic personality traits and the general population. Perhaps an even more interesting goal was the analysis of the influence of oxytocin on the manifestation of social dominance in psychopathy, the premise being that this neuropeptide would enhance therapeutic cooperation among psychiatric patients with psychopathic personality traits.

The research involved a detailed and complex methodological procedure that demonstrated the possibility of an innovative pharmacological approach to psychopathy with intranasal oxytocin. However, the effect shown in the results was present only in arbitrarily defined subgroups of psychopathic subjects, while it did not occur in the entire psychopathic sample. Furthermore, the strength of the observed correlation was weak. Having all this in mind, the reliability of the conclusion (nevertheless indiscriminately generalized) and the content of the discussion did not correspond to the data presented in the results. One had the impression of a certain „cherry-picking“ phenomenon and exaggeration of the effect in the effort to highlight the positive results of the study.

Within the limitations, the authors correctly pointed out the bias in the control group selection, but there is no reference to the fact that the psychopathic population sample was not representative either. An additional drawback is the quantification of psychopathic personality traits among psychopathic and control populations by different measurement instruments. Also, the sample size was small, which could significantly affect the results.

Nonetheless, in addition to the analysis of the paper itself, the previous CRL encouraged the young physicians at the Institute to discuss important elements of scientific-research work in general, such as the issue of effect quantification, standardization, dichotomization of numerical variables, as well as the importance of phenomenology and correct terminology in scientific papers.

The idea of a critical review of the literature stimulates the development of critical thinking, both in the scientific framework and in the clinical work of young clinicians, setting the stage for better work in psychiatric practice as a whole.

Following the same idea of progress promotion, the next CRL will be held in the Red Hall of the Institute of Mental Health, on February 1, 2023, when Tea Trajkovski MD and resident in psychiatry, will present the paper entitled *Coached Mobile App Platform for the Treatment of Depression and Anxiety Among Primary Care Patients* <https://pubmed.ncbi.nlm.nih.gov/32432695/>. As before, the door will be open to all interested employees of the Institute of Mental Health and our colleagues beyond.

NEWS FROM THE WORLD



A NEW DRUG FOR ALZHEIMER'S DISEASE - LECANEMAB - HAS BEEN APPROVED

On January 6, 2023, the U.S. Food and Drug Administration (FDA) approved lecanemab (*Leqembi*) through the accelerated approval pathway – a new drug for patients with mild Alzheimer's dementia (AD) stage or mild cognitive impairment, developed by the Japanese pharmaceutical company *Eisai* and the American *Biogen*. The aforementioned FDA procedure can be applied to serious medical conditions where there is an unmet medical need and where a drug is shown to have an effect that is reasonably likely to result in a clinical benefit to patients. Namely, lecanemab is a humanized IgG1 monoclonal antibody that binds with high affinity to amyloid-beta ($A\beta$) soluble oligomers whose abnormal accumulation in various brain regions is considered one of the crucial factors in the etiopathogenesis of AD according to the leading amyloid cascade hypothesis. Lecanemab is the second drug approved for AD, besides aducanumab (*Aduhelm*), which aims not only to control the symptoms of the disease (which was the current treatment practice), but also to modify its course by targeting the fundamental pathophysiological processes. By removing the toxic $A\beta$ accumulations from the brain the neurodegeneration process progression is slowed down, which could represent an important advancement in the ongoing fight for effective AB treatment.

The decision to approve lecanemab was made based on the findings of a double-blind, randomized controlled trial involving a total of 1795 participants with early AD with evidence of $A\beta$

accumulation (on PET or by cerebrospinal fluid testing), half of whom received intravenous lecanemab (10mg per kilogram of body weight every two weeks) and half placebo over a period of 18 months. The results were published in late 2022 in the world's leading medical journal *New England Journal of Medicine* showing that lecanemab moderately reduced $A\beta$ accumulation (difference -59.1 centiloids, 95% CI -62.6/-55.6) and slowed patients' cognitive and functional decline (as measured by the *Clinical Dementia Rating-Sum of Boxes (CDR-SB)* reduction of deterioration by 27% in the experimental group compared with the placebo group, an absolute difference of 0.45 points, change from baseline 1.21 for lecanemab vs. 1.66 for placebo, $p < 0.001$). The use of lecanemab was also associated with certain side effects that were mostly mild and did not require treatment discontinuation. Infusion-related reactions were observed in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6% (most cases were asymptomatic and detected incidentally) <https://www.nejm.org/doi/full/10.1056/NEJMoa2212948>.

The *Eisai* announced marketing authorization applications for lecanemab in Japan and the European Union by the end of March this year, and in parallel with that the continuation of testing its effectiveness and safety is underway in order to obtain more reliable data over a longer observation period.

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