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CONTENTS

INTEGRATIVE MEDICINE: COMORBIDITY AND MULTIMORBIDITY BRING SEPARATED BRANCHES OF MEDICINE CLOSER TO EACH OTHER

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The simultaneous presence of multiple diseases and illnesses in the form of multi-comorbidity and comorbidity is more a rule than an exception, particularly in the elderly (see Jakovljevic & Ostojic 2012). According to some authors 60-80% of adults over 65 years suffer from two or more diseases. Comorbidity, multi-morbidity and multisystem diseases represent huge problems and challenges to contemporary medicine in theory and practice. Medical specialization and specialist fragmentation, disease-centered approach, clinical guidelines developed for single diseases and fragmentary approach reducing complex disease problems to their biological aspects demand holistic approaches that offer a promising framework for increasing effectiveness and efficiency in contemporary medicine. Trans-disciplinary integrative medicine addresses the challenges, problems and complications posed by multi-morbidity and comorbidity in a new way. It also offers all health scientists and practitioners a common language that may bridge epistemic gaps and facilitates the exchange of insights and paradigms across academic borders.

EPISTEMOLOGICAL CHALLENGE: UNDERSTANDING MULTISYSTEM DISEASES, COMORBIDITY AND MULTI-MORBIDITY

Few topics are as familiar yet not as well understood as integrative medicine, multisystem diseases, multi-morbidity and comorbidity – largely due to confusing and inconsistent definitions. Multisystem diseases, multi-morbidity and comorbidity are the rock on which many attractive theories are wrecked and upon which better ones can be built and these issues are of the paramount epistemological importance to contemporary medicine (see Jakovljević & Crnčević 2012). Surprisingly, comorbidity and multi-morbidity are commonly used in literature and research as interchangeable terms. The term comorbidity was introduced by Feinstein (1970) to denote presence of any additional condition co-occurring with an index or primary disease. Some authors denote comorbidity as the simultaneous presence of two or more medical conditions more frequently that it would be expected to happen by chance and which are associated with each other through pathogenetic mechanisms in contrast to multi-morbidity when medical conditions appear randomly not having any pathogenetic connection (Jakovljevic & Ostojic 2013). Multisystem diseases or systemic disorders are medical conditions affecting multiple mind-body systems and which are treated by different medical specialists. According to some authors more than 45% of all illnesses are systemic diseases or have systemic implications. As simultaneous existence or sequential appearance of two or more diseases or disorders are multi-interpretable phenomena, there are several options and perspectives how to evaluate, explain and describe them:

- etiological vs. non-etiological relationship
- primary vs. secondary disease
- concurrent or simultaneous vs. sequential or successive diseases
- causal vs. random relationship
- undirectional vs. biderctional relationship
- homotypic vs. heterotypic entities
- concordant vs. discordant entities
- syntropic or direct vs. dystrophic or inverse entities (see Jakovljevic et al. 2021).

Our journal stresses importance of conceptual clarity, whole person assessment, collaborative health-care and multimodal treatment interventions.

THE INTEGRATIVE MEDICINE FRAMEWORK

With advent of modern biomedicine or allopathic medicine, the older regional medical approaches were categorized as complementary and alternative medicine (CAM) and recently the term CAM has been replaced with “integrative medicine” (Mukhopadhyay et al.2022). In addition to the CAM, integrative medicine has been known by several other names such as holistic medicine, traditional medicine, mind-body medicine, functional medicine (see also Mukhopadhyay et al. 2022). Integrative systems network medicine is a holistic, comprehensive, complementary and individualized approach to

healthcare that combines official or conventional medicine with nonofficial or nonconventional medicine considering the whole person dimensions: somatic, psychic, social and spiritual (Jakovljevic & Bevanda 2024). The concept involves several essential elements:

- Comprehensive and complementary interdisciplinary approach enabling information and knowledge synergism in theory and practice
- Person (body/brain-mind-spirit) centered care, not only to decrease illness, but also to increase mental, social and spiritual wellness, resilience and support salutogenesis
- Emphatization-based clinical relationship and therapeutic partnership
- Promoting human rights at individual, family, community and global level
- Holistic healthcare continuity understanding
- Public and global health promotion

This concept is attractive as it offers all health scientists and practitioners a common language that may bridge epistemic gaps and facilitates the exchange of insights and paradigms across academic borders. It also offers more effective promotion of health, wellness and well-being, as well as more effective and efficient treatment of comorbidity, and multi-system diseases. Integrative medicine promotes the empathic therapeutic communications and relationship between healthcare workers and patients aiming to establish empathic partnership between them involving also families of the patients. The goal is not only to decrease and eliminate illness, but also to increase wellness and promote integrative health.

Comorbidity and multi-morbidity are indifferent to professional specialties and ever growing sub-specialization in medicine so integrative multi-system medicine bringing separated branches of medicine close to each other is more and more important. Integrative medicine as a conceptual scientific frame and practical approach attempts to bring coherence to theory and practice of health care.

THE HEALTH CARE SYSTEMS

The Corona Virus Disease 2019 (COVID-19) as a unique global disaster has stressed the extreme importance of the four issues for health care systems: multi-system diseases, comorbidity, syndemic and infodemic (see Jakovljevic et al. 2021). A syndemic (a blend of “synergy” and “epidemics”) or synergistic epidemic refers to “the aggregation of two or more concurrent or sequential epidemics or disease clusters in a population with biological interactions, which exacerbate the prognosis and burden of disease (https://en.wikipedia.org). Shifting the paradigm from vertical and mono-morbid interventions to comorbidity, multi-morbidity and multi-system disease approaches increases effectiveness and efficiency of health-care systems (Jakovljevic et al. 2021). Each patient is a unique individual in health and diseases who should get highly specific and personally tailored treatment for her or his multisystem or systematic diseases, multi-morbidity or comorbidity (see Jakovljevic et al. 2010). Integrative multi-system medicine also supports global health care systems meeting global challenges in the context of sustainable development and social responsibility of healthcare entities (Czerska &Skweres-Kuchta 2021).

CONCLUSION

Integrative medicine represents a promising framework for fixing the complex challenges posed by the raising prevalence of multisystem diseases, comorbidities and multi-morbidities. There is a need to promote collaboration between different disciplines offering health care approaches optimally person-centered and created to a given patient’s needs, health problems, number of diseases, and lifestyle.

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NARRATIVE REVIEW OF USING PSYCHOBIOTICS AND NUTRITIONALLY BALANCED DIETS TO PROMOTE MENTAL HEALTH AND WELLNESS

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SUMMARY

Introduction: *The gut microbiota is essential for digestion, nutrient absorption, and overall health, with the gut-brain axis linking it to mental and neurological function. Dysbiosis, an imbalance in gut bacteria, is associated with mental health disorders like anxiety and depression. Psychobiotics, a promising subgroup of probiotics, may help treat these conditions by reducing inflammation, stress, and improving cognitive function. Objectives were to analyse the gut-brain axis and its impact on mental health issues.*

Results: *Bidirectional communication between the brain and gastrointestinal tract regulates homeostasis and nervous, immune, and hormonal functions, with the vagus nerve linking the gut and brain. Psychobiotics, such as Bifidobacteria and Lactobacilli found in fermented foods, support cognitive and emotional health by influencing neurotransmitter synthesis and reducing inflammation. While promising, psychobiotics are most effective when used alongside conventional treatments for mental health conditions like depression and anxiety.*

Discussion and conclusion: *The brain-gut axis regulates homeostasis at neuronal, immunological, and hormonal levels, with psychobiotics like Bifidobacteria and Lactobacilli supporting both digestive and mental health. Found in fermented foods, psychobiotics show potential in improving neuropsychiatric conditions, reducing inflammation, and enhancing cognitive and emotional functions, particularly as part of synbiotics or complementary therapies.*

Key words: *probiotics; mental health; diet; supplement; mental disorders.*

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INTRODUCTION

The gastrointestinal tract (GIT) is colonised by a diverse range of micro-organisms collectively known as the gut microbiota. It is estimated by scientists that there are more bacterial cells in the body than there are genes in the entire genome. The microbiota plays a crucial role in maintaining overall health and wellbeing, facilitating the functioning of the gut and enabling the digestion and absorption of essential nutrients (Butler et al. 2019a). The gut microbiota represents a significant mechanism for the gut-brain axis (GBA), also known as the microbiota-gut-brain axis (MGB) (Butler et al. 2019b, Dziedzic et al. 2024). The GBA encompasses a range of interconnected systems, including the central nervous system, the neuroendocrine system, the neuroimmune system, the sympathetic and parasympathetic nervous systems (autonomic nervous system), the enteric nervous system and the gut microbiota (Bermúdez-Humarán et al. 2019). The concept of the bidirectional communication between the brain and the gut was first identified and acknowledged in the early 19th and 20th centuries. Research conducted during this period demonstrated that an individual's emotional state can exert an influence on the functioning of the gastrointestinal tract (Zhou & Foster 2015). The mechanism of action of bidirectional communication is complex and involves the communication of information between the gut microbiota and the brain, and vice versa (Dinan & Cryan 2017). A disruption in the gut microbiota can result in an imbalance, leading to the development of a disorder known as dysbiosis. Dysbiosis is defined as an instability of the microbial balance, characterised by alterations in functional composition and metabolic processes. Dysbiosis has been associated with a number of diseases, including anxiety, depression, autism and neurodegenerative disorders (Cocean & Vodnar 2024). Although a number of different approaches can be taken to treat mental health problems, there has recently been a significant increase in research activity in the area of psychobiotics and their impact on mental health (Adikari et al. 2019, Butler et al. 2019c).

Psychobiotics represent the latest class of agents that are believed to possess psychotropic properties. The term "psychobiotic" is used to describe living organisms that, when ingested in sufficient quantities, are believed to confer health benefits to patients with mental health disorders (Misra & Mohanty 2019, Mosquera et al.

2024b, Evrensel et al. 2019, Zawistowska-Rojek & Tyski 2022). They are classified in a subgroup of probiotics that have the potential to increase the number of beneficial bacteria in the gut, thereby reducing inflammation, lowering cortisol levels, relieving symptoms of depression and anxiety, reducing the body's stress response and improving cognitive function, including memory, learning and behaviour (Misra & Mohanty 2019, Mosquera et al. 2024b, Cheng et al. 2019, Sarkar et al. 2016, Zawistowska-Rojek & Tyski 2022). In addition to their role in maintaining overall health, they are also instrumental in regulating neurological function, as they synthesize psychoactive compounds and influence brain activity (Giri & Sharma 2022). The available evidence indicates that they play a crucial role in the synthesis of neurotransmitters, including dopamine, norepinephrine, GABA, serotonin, and acetylcholine. These neurotransmitters are vital for maintaining optimal brain and central nervous system (CNS) function (Mosquera et al. 2024a, Zawistowska-Rojek & Tyski 2022). The interaction between psychobiotics and the gut-brain axis represents a significant emerging field of research with important implications for mental health and general well-being (Sarkar et al. 2016).

The objective of this study is to conduct a comprehensive review of the existing literature on psychobiotics. This will entail defining the mechanisms of action of these bacteria, identifying the different types of psychobiotics and their sources, and examining their potential as supportive treatments for mental health problems. Our objectives were to analyse the gut-brain axis and its impact on mental health problems; to review and present the literature on psychobiotics and their role in the treatment of mental disorders.

RESULTS

The brain-gut axis, mental health and disorders

Bidirectional signalling between the brain and the gastrointestinal tract is of vital importance for the maintenance of self-regulating homeostasis, as well as for the regulation of processes at the nervous (central and enteric nervous system), immunological and hormonal levels (Margolis et al. 2021, Warren et al. 2024)

The enteric nervous system, also known as the "second brain", comprises networks of neurons that regulate gastrointestinal functions. It is comprised of the myenteric and submucosal plexuses, which are involved in information processing and function independently or in conjunction with the central nervous system. The principal component of the GBA, the nervus vagus, is also implicated at this level and directly connects the gut and the brain, thereby enabling signals to be transmitted in both directions. Sensory signals from the gut can influence brain functions via the vagus nerve and vice versa, including signals from gut bacteria (Chowdhury 2024, Cryan et al. 2019, Margolis et al. 2021, Radford-Smith & Anthony 2023, Zhu et al. 2017). Furthermore, there is an immunological connection between the gut and the brain. The microorganisms present in the gut have the potential to impact the immune system, which plays a crucial role in maintaining homeostasis and transmitting signals to the CNS. Consequently, an imbalance in the microbiota may result in inflammation that affects the brain's functionality, potentially leading to adverse outcomes (Sherman et al. 2015, Wang & Wang 2016, Warren et al. 2024). From a hormonal perspective, various hormones (cortisol, ghrelin) facilitate the transmission of signals between the gut and the brain, which in turn influence behaviour, stress responses and appetite. Additionally, neuroendocrine signals from the gastrointestinal (GI) tract exert influence over the smooth muscles, blood vessels, and glands within the digestive tract, thereby regulating digestive processes (Cussotto et al. 2018, Sun et al. 2020, Verma et al. 2024).

Psychobiotics are a subcategory of probiotics that frequently synthesize vital neurotransmitters, including gamma-aminobutyric acid (GABA) and serotonin. They also mitigate the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, they possess anti-inflammatory properties that are beneficial in the treatment of various neuropsychiatric conditions (Suravi 2016, Warren et al. 2024). Additionally, Sharma & Bajwa (2022) identify potential benefits associated with appropriate intake in individuals experiencing mental health challenges. Psychobiotics have the capacity to modulate specific neurotransmitters and proteins (glucagonate, serotonin, GABA) and exert a pivotal influence on the regulation of inhibitory and excitatory receptors, the memory process, and cognitive function.

Psychobiotics are a subcategory of probiotics and prebiotics. The most commonly cited effective psychobiotics are bifidobacteria, lactobacilli, Escherichia coli, enterococci, and streptococci (Choudhary et al. 2023, Zagórska et al. 2020). Probiotics are primarily sourced from fermented foods such as yoghurt, kefir, tempeh, kimchi, and others (Chowdhury 2024, Dimidi et al. 2019, Oroojzadeh et al. 2022). In order for a food or probiotic product to exert beneficial effects on the gut and brain, it is necessary for the product to contain a minimum of 107 colony-forming units (CFU) per gram or 107 CFU per dried viable probiotic cells (Homayouni-Rad et al. 2020, Oroojzadeh et al. 2022).

Bifidobacteria can produce and synthesize a range of vitamins, including riboflavin, thiamine, vitamin B6 and vitamin K. Additionally, they are able to synthesise other biologically active molecules, such as folic acid, niacin and pyridoxine. In comparison to lactic acid bacteria, bifidobacteria demonstrate a proclivity for the production of L(+)-lactic acid, which is more readily metabolised by humans and may prove to be a crucial factor for infants or individuals with metabolic acidosis (Sharma et al. 2021). The most prevalent Bifidobacterium species that

colonise the human gut and are employed as probiotics are B. animalis, B. adolescentis, B. bifidum, B. breve, B. infantis and B. longum. The majority of these bacteria have been demonstrated to possess both probiotic and postbiotic properties (O'Callaghan & van Sinderen 2016, Sharma et al. 2021).

Lactobacillus is a type of bacteria that is indigenous to the digestive, urinary, and genital tracts of humans without causing disease (Arshad et al. 2018). They are Gram-positive, non-spore-forming and facultatively anaerobic bacteria. Lactobacilli are classified as lactic acid bacteria on the basis of their capacity to ferment sugars into lactic acid, which creates an acidic environment and, as a consequence, inhibits the growth of other pathogenic microorganisms (Goldstein et al. 2015, Seddik et al. 2017, Zhang et al. 2018). In humans, Bacillus species are found in the digestive tract, where they facilitate digestion and maintain a healthy gut environment. They are also present in the urogenital tract, where they help maintain a proper pH and protect against various urinary tract infections. Finally, they can be found on the skin (Di Cerbo et al. 2016, Mu et al. 2018).

Lactobacillus helveticus is a bacterium that produces lactic acid (LAB) and has a variety of rods. It has been found to be able to relieve visceral pain caused by stress (Ait-Belgnaoui et al. 2018). Furthermore, the coadministration of Bifidobacterium longum has been demonstrated to alleviate feelings of anxiety and depression (Sharma & Bajwa 2022).

Lactobacillus rhamnosus is a facultatively anaerobic and gram-positive bacterium with probiotic properties (Sharma & Bajwa 2022). Rieder et al. (2017) posit that Lactobacillus rhamnosus modulates the central expression of GABA receptors, and its use is indicated in the treatment of depression and anxiety. Additionally, Slykerman et al. (2017) demonstrated in a randomised controlled trial that this strain of the bacterium significantly reduced feelings of anxiety and symptoms of depression in female children.

Bifidobacterium longum is a Gram-positive, catalase-negative, rod-shaped bacterium that inhabits the human gastrointestinal tract. Several strains within the Bifidobacterium genus have been identified as a valuable addition to a healthy lifestyle, offering benefits in the management of various health conditions. These include the regulation of neural function, the normalisation of the hypothalamic-pituitary-adrenal (HPA) axis, and the treatment of stress-induced visceral pain (Sharma et al. 2020).

Psychobiotics and treatment of mental health disorders

Sharma & Bajwa (2022) & Cocean & Vodnar (2024) define psychobiotics as all symbiotics (combinations of probiotics and prebiotics (Borrego-Ruiz & García 2024)) that contain a specific combination of bacteria that have a positive effect on neuropsychiatric diseases and mental health. It is hypothesised that psychobiotics may exert anxiolytic and antidepressant effects, in addition to improving neurological, emotional and cognitive functions (Cocean & Vodnar 2024, Radford-Smith & Anthony 2023, Sarkar et al. 2016). Sarkar et al. (2016) categorise the effects of psychobiotics into three groups: psychological effects on cognitive and emotional processes; systemic effects on the hypothalamus-pituitary-adrenal gland; and glucocorticoid stress response and inflammatory properties. The advantage of psychobiotics is that they have few side effects. However, it is challenging to achieve an immediate effect with psychobiotics. For this reason, they are recommended as a supportive therapy when the disease is under control (Zou et al. 2021). By influencing the gut microbiota and the brain-gut axis, psychobiotics provide a multifaceted approach that could be beneficial in the management of specific psychiatric disorders. Their capacity to regulate neurotransmitters such as tryptophan and serotonin, in addition to their anti-inflammatory effect, may markedly enhance psychiatric symptoms associated with brain inflammatory conditions (Mosquera et al. 2024b).

As the prevalence of depression and anxiety increases and psychological stress becomes a daily companion of human life, it is imperative that effective, easily accessible treatment options be developed to help overcome the burden of these conditions. The current treatments for mental illness are costly and have adverse side effects. In contrast, psychobiotics have been demonstrated to alleviate the symptoms of mental illness. In addition, the administration of psychobiotics has been demonstrated to result in a reduction in gastrointestinal disturbances, a decrease in inflammatory processes, and an enhancement of the immune response (Mosquera et al. 2024a, Smith et al. 2021, Warren et al. 2024). Given the association between depression and increased gut wall permeability, immunological and inflammatory activation, and gut disorders, probiotics may be employed as a supportive therapy for depressive symptoms (Dao et al. 2021, Romijn et al. 2017).

A beneficial effect on depressive symptoms was observed in a study by Schaub et al. (2022), where probiotics were administered concurrently with conventional therapy. The findings indicated that 55% of participants achieved remission, characterised by reduced depressive symptoms, when taking probiotics consistently, compared to a control group (40%). Additionally, the combination of SSRI antidepressants and probiotics demonstrated effective therapeutic action, with a notable reduction in depressive symptoms, and positive outcomes were observed in individuals with anxiety (Denysov et al. 2023a, Denysov et al. 2023b). Baião et al. 2023 additionally document an improvement in mild to moderate levels of depression with regular consumption of multiple probiotic strains. In cases of moderate to severe depression, however, a mixture of Lactobacillus

helveticus and Bifidobacterium longum did not demonstrate a statistically significant effect on depressive symptoms (Romijn et al. 2017). This finding suggests that psychobiotics may serve as a supportive therapy to conventional antidepressant treatment. Based on their impact on gut microbiota and the metabolism of neurotransmitters, including tryptophan (a vital precursor for serotonin synthesis), dopamine, noradrenaline and GABA, it can be postulated that these compounds influence the transmission of nerve signals within the enteric nervous system (Mosquera et al., 2024a, Zielińska et al. 2022).

People coping with schizophrenia are in a long process of different psychiatric problems, with around 20% of people dealing with chronic symptoms and disabilities. In addition, the illness results in a shorter life expectancy, which can be caused by suicide, co-morbid health problems and a high risk lifestyle - from unhealthy diet, addictions, lack of physical activity and the side effects of the medications used to treat schizophrenia, which can add to the incidence of metabolic syndrome. People affected by schizophrenia show changes in the composition of the gut microbiota that indicate the severity of the condition (Mosquera et al. 2024a, Warren et al. 2024). Gut microbiota has been found in several research studies to influence brain function, and has been associated with conditions such as schizophrenia through interactions with the immune system and the effects of neurotransmitters. Factors such as inflammation, stress and circadian rhythms can significantly modify the gut microbiota, reducing the number of beneficial bacteria and therefore increasing susceptibility to disease (Minichino et al. 2021, Mosquera et al. 2024b, Munawar et al. 2021, Warren et al. 2024). Substances with antipsychotic effects cause dysfunction within the gut barrier (Misera et al. 2023). Faecal microbiota transplantation (FMT) can be performed to improve the gut barrier and metabolic function. FMT is the transfer of faecal bacteria from a healthy donor to a recipient, which directly reduces metabolic function and the beneficial bacteria have a similar role to probiotics (Alagiakrishnan & Halverson 2021, Castro-Vidal et al. 2024, Mosquera et al. 2024a).

In some cases, antidepressants and antipsychotics have a positive effect on other pathologies, including irritable bowel syndrome, where the antidepressant is used in lower doses. Benefits are also claimed for premenstrual syndrome, but vulvovaginal candidiasis has been reported. From which they concluded that antidepressants have a negative impact on the growth of Candida albicans (Caldara & Marmiroli 2021). A study by Ait Chait (2021) demonstrates that psychotropic drugs have antimicrobial effects on the composition of the microbiota and, consequently, on the metabolism of the human gut, leading to the conclusion that probiotics or psychobiotics may alleviate gut dysbiosis.

DISCUSSION

In the interest of collecting relevant literature, we limited the time period to 10 years and searched in English. We reviewed articles summarizing the main findings of previous research on psychobiotics, specific brain-gut axis links and where the probiotics in interest are located.

The brain-gut axis is key to homeostasis and functions at three levels (Margolis et al. 2021, Arneth 2018, Zhou & Foster 2015). It operates at the neuronal level where the nervus vagus transmits bidirectional signals between the gut and the brain, including signals from the microbiota (Zhu et al. 2017, Mayer et al. 2015, Margolis et al. 2021). At the immunological level, where the microbiota affects the immune system and imbalances can lead to inflammation and brain dysfunction, and at the hormonal level, where hormones such as cortisol and ghrelin modulate stress, appetite, behaviour, and influence digestive processes (Cussotto et al. 2018, Wang & Wang 2016, Makris et al. 2021, Sherman et al. 2015, Hattori & Yamashiro 2021). Psychobiotics are considered a sub-type of probiotics and prebiotics and include bifidobacteria and lactobacilli. The main source is fermented food such as yoghurt, kefir, tempeh and kimchi. To have a beneficial effect on the gut and brain, a product should contain at least 10^7 CFU/g or 10^7 CFU/dried probiotic cells (Chowdhury 2024, Del Toro-Barbosa et al. 2020, Dimidi et al. 2019, Homayouni-Rad et al 2020, Oroojzadeh et al. 2022, Casertano et al. 2022). The main psychobiotics come from the strains of lactobacilli and bifidobacteria, both are beneficial bacteria that support both digestive tract health and brain health. Therefore, both types of bacteria play an extremely important role in improving and regulating mental and physical health (Sharma & Bajwa 2022, Sharma et al. 2021, Slykerman et al. 2017). Psychobiotics are classified in the group of symbiotics (combinations of both probiotics and prebiotics), which have proven benefits on mental health and neuropsychiatric diseases. They have both antianxiety and antidepressant effects and enhance neurological, emotional and cognitive functions (Abhari & Hosseini 2018, Aththanayaka 2024, Cheng et al. 2019, Cohen Kadosh et al. 2021, Smith et al. 2021, Warren et al. 2024). People with schizophrenia often experience chronic symptoms, a shorter life expectancy and alterations in the gut microbiota, which impacts the brain through the immune system and neurotransmitters (Kelly et al. 2021, Nguyen et al. 2019, Szeligowski et al. 2020). Faecal microbiota transplantation (FMT) can enhance gut balance and metabolic function by introducing beneficial bacteria (Alagiakrishnan & Halverson 2021, Castro-Vidal et al. 2024, Mosquera et al. 2024a). Medications with antidepressant and antipsychotic effects may be beneficial for irritable bowel syndrome and premenstrual syndrome, but increase the risk of Candida albicans (Caldara & Marmiroli 2021) and Clostridium difficile (Misera et al. 2023) infections, and affect microbiota and intestinal metabolism (Ait Chait,

2021). Psychobiotics are helpful in dysbiosis, and prebiotics are effective in reducing constipation due to antipsychotics such as clozapine (Munawar et al. 2021).

CONCLUSION

The bidirectional brain-gut communication axis is very important in mental health issues, where the use of antidepressant and antipsychotic drugs can lead to gut dysbiosis. The evidence suggests that psychobiotics are effective in relieving these problems where they are used as supporting therapy when taken alongside regular therapy. With psychobiotics, it should be remembered that the products must contain a sufficient amount of beneficial bacteria to have an effect on the microbiota (107 CFU/dried viable probiotic cells). We also need to be aware that psychobiotic products take longer to have a beneficial effect, so we need to be consistent in their use in the longer term. As registered nurses, we recommend and encourage all health technicians, nurses and doctors to promote the use of psychobiotics in practice, as they improve the gut microflora, reduce the side effects of medications, improve the functioning of the gastrointestinal system and have a beneficial effect on mental health with long-term use. Patients should be educated and made aware of the benefits of taking psychobiotics, both in the form of food and dietary supplements. Finally, we recommend that further studies be conducted in our region to investigate the effects of psychobiotics and that clinical trials be conducted to learn more about this important area of research.

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ROLE OF PSYCHEDELIC DRUGS IN MENTAL HEALTH CARE: A NARRATIVE REVIEW

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SUMMARY

Good mental health is foundational for individual and societal well-being, enabling resilience, personal growth, and active community engagement. Despite the availability of pharmacological and non-pharmacological treatments, many individuals experience partial or non-response, delayed therapeutic effects, and adverse side effects. Increasingly, individuals are exploring the use of psychedelics for self-guided psychotherapy beyond clinical settings, highlighting their potential for transformative mental health benefits. However, the definition and application of psychedelics vary across contexts, underscoring the need for nuanced understanding and cautious use. While earlier prohibition was driven by exaggerated perceptions of harm, modern evidence recognizes psychedelics as powerful substances capable of eliciting profound positive and negative outcomes. Safety remains a paramount concern, and current research is constrained by methodological limitations. Addressing these gaps is essential to advancing the therapeutic potential of psychedelics, ensuring their responsible integration into mental health care while mitigating risks.

***Key words**: psychedelic drugs, mental health care, psychedelic-assisted therapy.*

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INTRODUCTION

Good mental health is essential for the holistic well-being of individuals and society, as it enables effective coping with life's challenges, the development of potential and active contribution to the community. Individuals facing mental health issues encounter obstacles that impact their lives, potentially resulting in poorer educational outcomes, higher unemployment rates, and deteriorating physical health (The Organization for Economic Cooperation and Development [OECD] 2022; World Health Organization [WHO] 2022). Mental health is not merely the absence of disorders but encompasses a broad spectrum and various levels of distress (WHO 2022). Notably, mental illnesses rank among the top ten most common causes of limitations in daily life, posing significant social and economic challenges and placing a burden on societal and economic structures (Eurostat 2021).

Current treatments, including pharmacotherapies such as selective serotonin reuptake inhibitors, first- and second-generation antipsychotics, lithium, benzodiazepines ect. (Khan, 2020), as well as nonpharmacological approaches like cognitive behavioral therapy, electroacupuncture, and psychomotor therapy (Guedes de Pino et al., 2024), benefit many patients. However, high rates of partial or no response, delayed therapeutic effects, and undesirable side effects remain significant challenges (Menke, 2018). Kopra et al. (2023) says that more people are turning to psychedelics for personal psychotherapy outside formal clinical settings. How we define psyhedelics is dependent on the context.

Heal et al. (2018) examines and contrasts definitions from the Oxford English Dictionary, the Merriam-Webster Medical Dictionary, and the MediLexicon Medical Dictionary. The Oxford English Dictionary describes "psychedelic" as referring to substances, particularly lysergic acid diethylamide (LSD), that induce hallucinations and seemingly expand consciousness. The Merriam-Webster Medical Dictionary characterizes psychedelics as drugs, such as LSD, that can cause unusual psychological effects, including hallucinations and occasionally psychotic states. Meanwhile, the MediLexicon Medical Dictionary defines the term more broadly, associating it with a loosely defined category of drugs that primarily act on the central nervous system and are believed to enhance or amplify consciousness, including substances like LSD, hashish, mescaline, and psilocybin. These varying interpretations highlight the absence of a consistent definition for "psychedelic." However, a shared emphasis across the definitions is the capacity of these substances to induce profound shifts in perception, thought processes, and emotions (van Elk & Yaden 2022).

For instance, psilocybin is a psychedelic compound in certain mushrooms, which have been used in sacred ceremonies among indigenous peoples in Mexico and elsewhere for centuries. Other psychedelic compounds,

such as mescaline and DMT (*N*,*N*-dimethyltryptamine), have likewise been used for hundreds or thousands of years in ritual contexts. The psychedelic LSD (lysergic acid diethylamide), which the Swiss chemist Albert Hofmann synthesized in 1938, led to innovations in understanding serotonin pharmacology and, eventually, to the development of therapeutics that modulate serotonin function such as selective serotonin reuptake inhibitors (Yaden et al. 2021). The earliest recorded medical use of a classical psychedelic in Western medicine dates back to 1895, when Prentiss and Morgan documented the ceremonial use of peyote cactus buttons by Central American indigenous communities (Prentiss & Morgan 1895). MDMA, also recognized as ecstasy in recreational contexts, was once widely employed in psychotherapy, particularly in couples therapy, where it was termed "empathy" for its ability to enhance emotional connection (Sessa & Nutt 2015). Ketamine, a well-established dissociative anesthetic, has more recently been repurposed in lower doses for pain relief and is also used recreationally for its mind-altering, psychedelic-like properties (Lener et al. 2017).

Psychedelics have inspired new hope for treating brain disorders due to their unique ability to produce sustained therapeutic effects after a single administration, offering broad potential for conditions like depression, PTSD, anxiety, addiction, and psychological distress associated with end-of-life experiences (Menke 2018; Vargas et al. 2021). Despite their long history, they remain a contentious topic in Western culture, as their highly context-dependent effects necessitate carefully controlled studies in supportive environments supervised by trained professionals (Menke 2018). The Food and Drug Administration (FDA) ruled to reject MDMA for assisted psychotherapy for PTSD, citing insufficient evidence and the need for more research. The ruling is consistent with a letter APA sent the FDA earlier this year that stated that a review of the literature on MDMA-assisted psychotherapy by a multidisciplinary panel of experts determined that there is insufficient evidence to be able to recommend MDMA-assisted psychotherapy for patients with PTSD (Stinger 2024). For decades, psychiatric treatments have experienced limited advancements. Emerging research on psychedelics suggests they could offer promising new therapeutic options for a range of psychiatric disorders (Yaden et al. 2021).

This narrative review examines the role of psychedelic drugs in modern mental health care, focusing on their therapeutic potential, effectiveness, and challenges. The importance of this research lies in its potential to uncover innovative approaches for treating mental health conditions that often resist traditional therapies. By exploring the historical context, analyzing recent clinical studies, and understanding how psychedelics affect the brain and emotional well-being, this review provides a comprehensive synthesis of existing knowledge. Using the PIO framework, it identifies theoretical foundations, key findings, and gaps in the research. This exploration offers promising insights and could pave the way for breakthroughs in addressing complex psychological challenges through the effects, risks, and therapeutic applications of psychedelics.

MECHANISM OF ACTION OF PSYCHEDELIC DRUGS

Serotonin is widely recognized as a neurotransmitter that influences neural activity and plays a crucial role in regulating various neuropsychological functions. Medications designed to interact with serotonin receptors are commonly utilized in the fields of psychiatry and neurology (Berger et al. 2009; Lv & Liu 2017). Building on this foundation, psychedelic drugs exert their distinctive effects primarily by interacting with the brain's serotonin (5-HT) neurotransmission system. Specifically, these compounds act as partial agonists at the 5-HT2A receptors, which are critically involved in the regulation of mood, perception, and cognitive processes (Bamalan et al., 2024). These receptors are particularly abundant in brain regions such as the medial prefrontal cortex and the visual cortex, which are integral to emotional and sensory processing (van Elk & Yaden, 2022). Upon activation, 5-HT2A receptors stimulate cortical layer 5 pyramidal neurons, triggering Gq protein-coupled signaling cascades. This process leads to intracellular calcium release and the activation of various kinases, influencing neuronal dynamics in ways that produce the characteristic altered states of consciousness associated with psychedelics (Hatzipantelis & Olson, 2024). The central role of 5-HT2A receptors in psychedelic effects has been demonstrated through experiments showing that drugs like ketanserin, a receptor antagonist, block these effects, while genetic models that lack 5-HT2A receptors fail to respond to hallucinogenic compounds altogether (López-Giménez & González-Maeso, 2017; van Elk & Yaden, 2022). Notably, not every compound that targets these receptors induces hallucinations. This distinction is explained by the concept of biased agonism, wherein hallucinogenic compounds activate both the Gq/11 and Gi/o signaling pathways, whereas non-hallucinogenic agonists engage only the Gq/11 pathway. Such intricate interactions at the receptor level highlight the complex mechanisms underlying the differentiation between hallucinogenic and potentially therapeutic effects of 5-HT2A-targeting compounds (López-Giménez & González-Maeso, 2017).

Research into psychedelics was effectively halted for decades due to societal and political factors rather than a lack of scientific interest. The 1960s and 1970s saw a wave of public concern and media-driven panic regarding the widespread use of psychedelics, culminating in the enactment of restrictive laws like the 1970 Controlled Substances Act. These regulations imposed severe

limitations on clinical research, making it nearly impossible for scientists to conduct studies during this period (Nichols, 2016).

Isomeric forms of psychedelics: Differences in effects and activity

Popik et al. (2022) investigated whether fast-acting antidepressants like ketamine and psilocybin influence time perception and whether this effect relates to their therapeutic action. While (S)-ketamine at high doses led to time underestimation alongside severe cognitive impairments, (R)-ketamine improved cognition without affecting time perception. Psilocybin and psilocin caused nonspecific behavioral changes but did not alter time perception. Thus, the study concluded that changes in time perception are not essential for antidepressant efficacy, as both (R)-ketamine and psilocybin remain clinically effective without this effect. In the same way, (±)-MDMA has shown promise in treating PTSD and other psychiatric disorders, yet its widespread use is limited by adverse effects. A potential solution is using its enantiomer R(−)-MDMA, which offers comparable therapeutic benefits with lower toxicity, hyperthermia, hypertension, and abuse potential. However, placebo-controlled human studies are still needed to confirm its safety. Further research could establish R(−)-MDMA as a safer alternative for psychiatric treatment (Pitts et al. 2018). It is essential to highlight LSD, a potent centrally acting drug, with only the d-isomer being pharmacologically active. It selectively inhibits the brain's raphe system, stopping the spontaneous firing of serotonin-containing neurons in the dorsal and median raphe nuclei, making it an indirect serotonin antagonist. However, this inhibition alone does not explain LSD's hallucinogenic effects, as lisuride, a stronger raphe inhibitor, lacks psychedelic properties. This suggests that other mechanisms, such as glutamate or serotonin receptor interactions, play a role. Additionally, LSD may indirectly affect the cytoskeleton by reducing serotonin release from the raphe system (Jenkins & Gates 2020).

While isomers influence how psychedelic drugs work, some new compounds take a different approach. DLX-001, a novel orally active molecule, exhibits rapid and long-lasting antidepressant effects similar to ketamine and psilocybin. It enhances synaptic connectivity in the mPFC without inducing hallucinogenic effects, distinguishing it from psychedelics. Given its potential to provide antidepressant benefits without the drawbacks of ketamine or psilocybin, DLX-001 may represent a promising advancement in depression treatment (Rasmussen et al. 2024).

MENTAL HEALTH DISORDERS CAUSED BY PSYCHEDELIC DRUGS

Aday et al. (2020) identified 34 contemporary human-sample studies on classic psychedelics, with most focusing on psilocybin and published within the last five years, documenting lasting changes in personality, attitudes, depression, spirituality, affect, mood, anxiety, wellbeing, substance use, meditative practices, and mindfulness. Commonly proposed mechanisms for these changes included mystical experiences, a sense of connectedness, emotional breakthroughs, and increased neural entropy. However, concerns have emerged regarding potential negative psychological effects, with 37.5% of participants in one study reporting psychiatric diagnoses after psychedelic use, including worsening anxiety symptoms in 87%. In-depth interviews revealed contributing factors such as unsafe environments, unpleasant acute effects, psychological vulnerabilities, high or unknown dosages, and youth, with approximately one-third of interviewees receiving new psychiatric diagnoses after use (Bremler et al. 2023). These findings underscore the importance of cautious use, particularly given the prevalence of substance-related health issues reported at rave parties, where around one-third of attendees seeking first aid attributed their problems to substances like ecstasy or alcohol, although life-threatening incidents were rare (Krul et al. 2011). Similarly, microdosing, while generally associated with minor and short-lived negative effects such as anxiety, led some users to discontinue due to co-occurring psychological and physical impacts or a perceived lack of efficacy, often influenced by unrealistic media-driven expectations (Huten et al. 2019). Together, these studies highlight both the transformative potential and risks of psychedelic substances, emphasizing the need for careful consideration and responsible use.

Other studies challenge the notion that psychedelics pose significant risks to mental health, with evidence showing no consistent link between lifetime psychedelic use and negative outcomes such as psychological distress, mental health treatment, or disorder symptoms. Adjusted odds ratios demonstrate no elevated risk, and some findings suggest lower rates of mental health problems among users, potentially reflecting benefits or favorable baseline mental health (Nesvåg et al. 2015). While rare cases of prolonged negative psychological responses have been reported, they are often associated with specific factors like pre-existing personality disorders, emphasizing the need for individualized psychological support (Marrocu et al. 2024). Furthermore, documented cases of severe outcomes, including suicides or deaths directly linked to psychedelics, remain exceedingly rare and are often unsubstantiated (Johansen & Krebs 2015). Research has consistently demonstrated the relative safety of psychedelics, especially when administered with proper

preparation, supervision, and integration, leading to lasting psychological benefits (Aday et al. 2020). The absence of neurotoxicity or addiction potential further supports their use in controlled therapeutic settings, where emerging evidence indicates significant and lasting improvements in psychological well-being, contrasting with earlier reports highlighting concerns over adverse effects (Schlag et al. 2022).

PSYCHEDELIC DRUGS IN TREATMENT OF MENTAL HEALTH DISORDERS

Two studies (Bahji et al. 2020; Shahrour et al. 2024) have examined the impact of MDMA in psychotherapy, showing consistent benefits such as increased clinical response, higher remission rates, and reduced PTSD symptoms. This effectiveness may be attributed to MDMA's prosocial effects, including heightened feelings of empathy, connection, and sociability, which strengthen the therapeutic bond between therapists and patients and support the therapeutic process (Bahji et al. 2020). Additionally, MDMA promotes the extinction and consolidation of traumatic memories by restoring brain-derived neurotrophic factor levels in key brain regions like the amygdala, vmPFC, and hippocampus. This mechanism facilitates memory consolidation and weakens fear-associated memories, reducing emotional reactivity (Shahrour et al. 2024). Preclinical studies further support these findings, showing that acute MDMA administration before extinction training significantly enhances long-term fear extinction in mice models (Young et al. 2015). These treatments, often referred to as drug-assisted psychotherapy, are complex and require significant therapist involvement. Patients must be adequately prepared for the profound effects of psychedelic sessions, typically through a dedicated preparatory session with a trained therapist or guide. This session educates patients about the rationale, purpose, and procedures of the treatment to ensure a safe and effective therapeutic experience (Nutt 2019).

Shahrour et al. (2024) highlights that there is no significant difference in the incidence of adverse events or suicidal tendencies between participants undergoing MDMA-assisted therapy and those in control groups, suggesting that the therapy is generally safe and well-tolerated when administered in controlled clinical settings. This finding supports the view that MDMA-assisted psychotherapy does not inherently increase the risk of severe adverse effects compared to other therapeutic interventions. Similarly, Bahji et al. (2020) reviewed multiple studies and found that the majority reported no MDMA-related serious adverse events, further supporting its safety profile. However, one study included in the review (Mithoefer et al. 2018) did document four serious adverse events, which included increased depressive symptoms and suicidal ideation. It is important to note, though, that three of these events were determined to be unrelated to the study drug, indicating that while such events occurred, they may not have been directly caused by MDMA. Adverse events have also been noted in other systematic reviews of psychedelic-assisted therapies. Graziosi et al. (2024) in their review on the potential therapeutic use of psychedelics in OCD and related disorders, reported an increase in adverse events associated with LSD use. Similarly, Maia et al. (2022), in their systematic review on the therapeutic potential of psychedelic-assisted therapies for symptom control in patients with serious illnesses, observed mild to moderate intensity adverse events. In 20% of studies, no complications were reported, while 55% noted mild to moderate, self-resolving adverse effects, both physical (e.g., nausea, headaches) and psychological (e.g., anxiety, hallucinations). Some studies reported distress under LSD without psychotherapy, with 50% needing intervention and 30% unwilling to repeat the experience. In 25% of studies, adverse effect data were not reported.

Studies on ayahuasca and other psychedelics consistently highlight their significant therapeutic potential for mood disorders, showing marked reductions in depression and anxiety symptoms alongside notable improvements in mood, self-transcendence, and quality of life (Jiménez-Garrido et al. 2020; Sarris et al. 2021; Yao et al. 2024). Yao et al. (2024), through a comprehensive systematic review and meta-analysis of 126 articles, identified substantial decreases in depression, anxiety, and negative mood. Among the psychedelics studied, psilocybin emerged as the most effective, demonstrating the strongest therapeutic impact, followed by ayahuasca, MDMA and LSD. Additionally, the study found emerging evidence supporting the use of psychedelics in addressing other conditions, including substance-use disorders, obsessive-compulsive disorder, PTSD, and eating disorders, highlighting their broader mental health applications. Importantly, adverse effects were minimal, with headaches being the most frequently reported, and nearly one-third of studies reported no lasting adverse effects.

These findings are reinforced by Jiménez-Garrido et al. (2020), who conducted a longitudinal and cross-sectional study on the effects of ayahuasca on mental health and quality of life. In one part of the study, among ayahuasca-naïve users, over 45% initially met diagnostic criteria for psychiatric disorders. However, following ayahuasca use, more than 80% experienced significant and lasting clinical improvements in depression and psychopathology scores, which persisted for six months. In another part of the study, long-term ayahuasca users displayed lower levels of depression and higher scores in self-transcendence and quality of life compared to their peers who had never used ayahuasca. Sarris et al. (2021) further bolstered these insights in their cross-sectional study of 11,912 individuals who consumed ayahuasca,

including 1,571 participants with depression and 1,125 with anxiety. Among those with depression, 78% reported that their symptoms were either "very much" improved or "completely resolved". Similarly, among participants with anxiety, 70% reported significant improvements. Factors contributing to these positive outcomes included the intensity of mystical experiences, the number of ayahuasca sessions, and the depth of personal psychological insights experienced during treatment. However, 2.7% of participants with depression and 4.5% of those with anxiety reported worsening symptoms. It is important to note that this study is a cross-sectional analysis and cannot directly assess treatment efficacy. Additionally, potential selection bias may exist, as participants with favorable experiences might have been more likely to respond to the survey, skewing the results.

Psychedelic drugs, particularly psilocybin, show promising potential in the treatment of obsessive-compulsive disorder (OCD) and related disorders. Graziosi et al. (2024) reviewed 23 articles, including clinical trials, preclinical studies, and case reports, and found that psilocybin was generally well-tolerated, with no serious adverse events reported. Significant reductions in OCD symptoms were observed within 24 hours of treatment, though long-term efficacy remains uncertain due to limited follow-up data. Romeo et al. (2021) highlighted the importance of acute psychedelic experiences as predictors of response across psychiatric disorders but noted limited evidence specifically for OCD due to small study sizes.

An innovative method was chosen to present the results of the articles in the synthesis table (Table 4.1). Instead of standard numerical values, words and symbols were used. The symbol ↑ indicates an increase in a parameter (e.g., clinical response), while the symbol ↓ signifies a decrease (e.g., symptoms). If supervision showed no noticeable effect, the symbol − was used. This approach facilitates easier understanding of the key findings and the evaluation of supervision effectiveness for each article or study.

Table 1. Psychedelic-Assisted Therapies Research Overview

Research, country	Type of research	Sample	Intervention	Outcome
Bahji et al. (2020) Canada	A systematic review and meta-analysis	n = 5 randomized and quasirandomized clinical trials using MDMA-assisted psychotherapy for PTSD in comparison with other medications, placebo or no medication	Efficacy of MDMA-assisted psychotherapy for posttraumatic stress disorder	↑ clinical response ↑ remission rates ↓ PTSD symptoms ↑ adverse events
Yao et al. (2024) China	A systematic review and meta-analysis	n = 126 articles	Efficacy and safety of psychedelics for the treatment of mental disorders	↓ depression ↓ anxiety ↓negative mood
Graziosi, et al. (2024) USA	A systematic review	n = 23 articles (2 non-systematic reviews, 11 preclinical studies investigating the use of classic psychedelics or analogs in preclinical models of OCD, 8 case studies or case reports, and 2 clinical trials)	Potential therapeutic use of psychedelics in OCD and related disorders	↓ OCD symptoms ↑adverse events (LSD)
Romeo, et al. (2021) France	A systematic review	n = 20 studies investigating addictive disorder, treatment-resistant depression, obsessive-compulsive disorder and depressive and anxiety symptoms in patients with life-threatening cancer	Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders	↑ clinical response ↓ substance use behaviors ↓ depressive symptoms − no predictive effect identified in OCD
Maia et al. (2022)	A systematic review	n = 20 studies	Therapeutic Potential of Psychedelic-assisted Therapies for Symptom Control in Patients Diagnosed With Serious Illness	↑ symptom control ↑ mild/moderate intensity adverse events
Shahrour et al. (2024) Jordan	A systematic review and meta-analysis of randomized controlled trials (RCTs)	n = 9 studies with a total of 297 participants with PTSD	MDMA-assisted psychotherapy for the treatment of PTSD	↑improving PTSD symptoms ↑ clinical response ↑ remission rates − treatment-emergent adverse events, severe adverse events, and suicidal ideation
Jiménez-Garrido et al. (2020) Spain	A longitudinal and crosssectional study combination	n = 63 participans	Effects of ayahuasca on mental health and quality of life in naïve users	↓ psychopathology scores ↓ depression, ↑ self-transcendence ↑ quality of life
Sarris et al. (2021) Australia	Cross-sectional study	n =11,912 consumers of ayahuasca with depression (n = 1571) or anxiety (n = 1125)	Ayahuasca use and reported effects on depression and anxiety symptoms	↓ depression ↓ anxiety

n = nubmer of sample; ↑ increase ; ↓ decrease; − no noticeable effect

DISCUSSION

Safety is a critical consideration in the use of psychedelics for therapeutic purposes. Although the prohibition of these substances was largely based on exaggerated claims of harm, it is clear that psychedelics are potent mind-altering substances that can create both deeply positive and negative experiences (Carbonaro et al. 2016). One major clinical challenge involves patients who are on medications, such as antidepressants, that interfere with the effects of psychedelics. Medications like quetiapine and olanzapine completely block psilocybin's interaction with 5-HT2A receptors, rendering it ineffective, while SSRIs reduce the psychedelic response by desensitizing these receptors. To allow for effective treatment, patients often need to discontinue these medications gradually and carefully to avoid withdrawal symptoms or exacerbation of depression (Nutt 2019). Furthermore, psychedelics are not suitable for individuals with a predisposition to or family history of psychotic disorders or bipolar mood disorders. They are also contraindicated for people with cardiovascular issues, as these substances can elevate heart rate and blood pressure (Wsół 2023).

Psychedelic research in the US has evolved over more than 20 years, transitioning from its early resurgence to a more advanced and established stage. The field's future remains unclear, with the potential to either revert to prohibition and stagnation or advance toward broader acceptance and clinical use. Achieving the best possible outcomes will depend on upholding rigorous standards in both research and clinical applications (Yaden et al. 2021). Current research on psychedelic therapies and related interventions is limited by several factors that must be addressed in future studies. Firstly, the findings often rely on small sample sizes, which reduces statistical power and limits the generalizability of results (Bahji et al. 2020; Yao et al. 2024). Furthermore, heterogeneity in study designs, dosing regimens, and outcome measures complicates comparisons and meta-analyses (Shahrour et al. 2024; Yao et al. 2024). The exclusion of non-English publications and gray literature restricts cross-cultural insights and the inclusion of diverse perspectives (Graziosi et al. 2024). Additionally, challenges such as publication bias, functional unblinding, and placebo effects raise concerns about the reliability of current evidence (Yao et al. 2024).

Future research should prioritize large-scale, placebo-controlled randomized trials to ensure robust and replicable findings (Yao et al. 2024). Standardized protocols for assessment methods, treatment regimens, and long-term follow-up are necessary to enhance reliability and comparability across studies (Shahrour et al. 2024). Efforts to include diverse populations and address biases in participant demographics are essential to ensure broader applicability (Maia et al. 2022). Research should also expand into underexplored areas, such as the effects of psychotherapeutic methods on psychedelic efficacy and their potential applications for related disorders (Romeo et al. 2021; Graziosi et al. 2024).

Psychedelics must prove their deliverability and cost-effectiveness to gain acceptance as established treatments. Many therapies fail to meet these criteria. In practical healthcare settings, psychedelic treatments are likely to be costly compared to other interventions, reinforcing the view that their investigation should focus on addressing socioeconomically burdensome psychiatric conditions, like treatment-resistant depression, where more affordable, conventional therapies have failed (Rucker et al. 2018).

CONCLUSION

Psychedelics show significant potential in advancing mental health care, with research highlighting their effectiveness in treating conditions such as depression, anxiety, PTSD, and OCD. Therapies like MDMA- and psilocybin-assisted psychotherapy hold promise for addressing treatment-resistant psychiatric disorders but require a thoughtful approach, including trained therapists, preparatory sessions, and controlled administration. While the risk of severe side effects appears low, challenges remain in understanding long-term impacts, interactions with other medications, and the development of clear clinical guidelines.

Open questions include how to optimize dosing and therapy protocols, assess long-term efficacy, and enhance accessibility and cost-effectiveness. Future research must focus on larger, more standardized studies and prioritize diversity in study populations to ensure broader applicability of these treatments.

These findings mark a significant step forward for the field, offering new treatment avenues, reducing the burden of mental illness, and providing hope for improved outcomes in cases where traditional approaches have fallen short. For the wider public, they represent the potential for advanced and more effective treatment options, while emphasizing the need for education and regulation to ensure safe integration into clinical practice.

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Research article

THE ROLE OF SPIRITUALITY IN PROMOTING MENTAL HEALTH AND EMOTIONAL WELL-BEING AMONG HIGH SCHOOL STUDENTS

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SUMMARY

Background: *Spirituality is becoming increasingly recognized as a key factor which influences mental health, and offers coping strategies and emotional support, particularly among adolescents. The connection between spiritual practices and reduced stress levels has been widely acknowledged in prior research.*

Aim: *This study aims to explore the relationship between spirituality and mental health among high school students, focusing on the role of spiritual practices in fostering emotional stability, reducing stress, and enhancing overall well-being.*

Results: *The study revealed that 73% of participants believe in God and engage in spiritual practices. These individuals report lower levels of acute stress and greater emotional stability. Students who perceive their families as harmonious and complete (74%) also showed higher levels of emotional resilience. Key symptoms of stress, including somatization, loneliness, and interpersonal sensitivity, were less pronounced in students actively involved in spiritual activities. Spirituality was found to reduce feelings of isolation, provide social support, and contribute to better coping mechanisms for stress. All hypotheses, including the protective role of spirituality, its connection to emotional well-being, and its social benefits, were confirmed.*

Conclusion: *The findings confirm that by reducing stress and improving emotional stability and resilience, spirituality significantly enhances mental health. Spiritual practices act as effective coping strategies and provide social and emotional support, making spirituality a valuable component in mental health interventions for adolescents. Integrating spiritual dimension into educational and preventive programs is crucial for fostering students' mental well-being.*

Key words: *spirituality, mental health, adolescents, emotional stability, stress reduction, coping strategies, social support*

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INTRODUCTION

Numerous studies have demonstrated the impact of spirituality and religion (S/R) on a person's quality of life, well-being, discomfort, and life satisfaction. Rosmarin and Koenig (2020) stated that although some psychiatrists, like Freud for example, were very unenthusiastic about religion (they considered it a form of neurosis) and others, like Jung and Frankl were more favourable, spirituality still "remains at the side lines of mental health science to this day". The fact is that around 85% of world population identify themselves with religion. It is a large social phenomenon, which was almost completely ignored by academia until recent years.

Until the end of the twentieth century, official psychiatric practice, or science, refused to accept that spirituality played a (major) role in defining and maintaining mental health for a large number of people (Kao, Peteet and Cook 2020). Historically, psychiatry focused primarily on biological and medical models, often ignoring spiritual or existential dimensions of mental health. However, over the past few decades, there has been an increasing recognition that spirituality plays a vital role in psychological resilience, coping strategies, and overall well-being.

World Psychiatric Association in 2016 statement has urged the inclusion of S/R in clinical encounters and training with the goal of providing a more holistic and comprehensive form of mental health care (Luchetti, Koenig and Luchetti 2021).

On the other hand, relationship between spirituality and mental health has been recognized as an important research field. Large number of studies have found that S/R is related to lower levels of hospitalization and pain, greater survival, and better functional status and cardiovascular outcomes (Wachholtz, Pargament 2005; Wachholtz, Pearce and Koenig 2007; Baetz, Bowen 2008; Nsamenang et al. 2016; Luchetti, Koenig and Luchetti 2021). As far as mental disorders are concerned, research has demonstrated that S/R has important effects on prevalence (particularly depressive and substance use disorders), diagnosis (e.g., distinguishing spiritual experiences from mental disorders), treatment (e.g., compliance, mindfulness, and complementary therapies), outcomes (e.g., recovery and suicide), prevention, and quality of life and wellbeing (Moreira-Almeida et al. 2016). Although religiosity and spirituality have been

associated with positive mental health outcomes in adults, their influence during adolescence and the mechanisms through which they function in this developmental stage remain less well understood (Aggarwal et al. 2023).

RESEARCH METHODOLOGY

The aim of this study is to explore the relationship between spirituality and mental health of high school students, with an emphasis on identifying the impact of spiritual activities, a sense of meaning, community support, and coping strategies on mental well-being. In line with the study's aim, the following hypotheses are proposed:

- **H1**: Regular spiritual practices (meditation, prayer, contemplation) are associated with better mental health and reduced stress.
- **H2**: A deeper sense of meaning and purpose in life contribute to emotional stability and stress resilience.
- **H3**: Participation in spiritual communities reduces feelings of loneliness and improves mental health.
- **H4**: A sense of connection with transcendental contributes to emotional well-being.
- **H5**: Spirituality serves as a coping strategy for dealing with difficulties and stress.

The research was conducted through individual interactions with students in the city of Orašje, Bosnia and Herzegovina. The topic, objectives, and purpose of the study were explained to students, and anonymity and confidentiality of the data were ensured. A total of 140 final year students from Fra Martin Nedić School Center (N=58) and the Secondary Vocational School Orašje (N=82) participated in the study. Consent to participate was obtained verbally, and written consent was provided by the parents of underage participants. Completing the anonymous questionnaire took approximately 15 minutes. The results were analysed and shared with the schools included in the research.

The questionnaire consisted of two parts:

1. Fourteen questions on sociodemographic data and health-related habits (e.g., smoking, exercise, substance use)
2. The SCL-90-R scale for self-assessment of psychological symptoms (Derogatis and Savitz 2000).

Data analysis was based on descriptive statistics, ANOVA tests, and post hoc analyses. Descriptive statistics was used to calculate basic measures such as arithmetic mean and standard deviations, while ANOVA examined differences in mental health levels concerning spirituality. The Newman-Keuls test further clarified significant differences between groups.

RESULTS

The results of all analytical methods used were interpreted within the context of the research question, providing a comprehensive understanding of the relationship between mental health and spirituality among students.

- The sample consisted of 52% female and 48% male participants, with the majority being 18 years old (85%).
- Most participants had a grade point average of 4–5 (31%), while others had averages of 3–4 (28%) and above 5 (26%).
- Physical activity was practiced infrequently by 33% of respondents (1–2 times per week), while 29% engaged in exercise almost daily. Very infrequent physical activity (up to twice a month) was reported by 30%, and 8% did not engage in any physical activity.
- Alcohol consumption was reported by 51% of participants, and 9% had used psychoactive substances.
- The majority (93%) had not undergone psychological treatment.
- Subjective evaluations revealed that 74% of respondents considered their families to be harmonious and complete, while 14% described their families as incomplete.
- Belief in God was present in 73% of participants, and the same percentage practiced their faith through various activities.

These results indicate significant differences in habits and perceptions among the respondents, confirming the importance of spirituality for mental health.

Results of the SCL-90-R Scale:

- **Most prominent symptoms**: Feeling faint when among people (M=2.61, SD=0.924), fear of riding the bus (M=2.55, SD=0.892), and globus sensation (lump in throat) (M=2.55, SD=0.907).
- **Physical symptoms**: Stomach pain (M=2.52, SD=0.833) and dizziness (M=2.48, SD=0.935) emerged as key physical issues.
- **Emotional symptoms**: Frequent feelings of loneliness (M=2.31, SD=0.753), restlessness (M=2.21, SD=0.851), and feeling "trapped" (M=2.48, SD=0.824) pointed to significant emotional discomfort.
- **Behavioural issues**: Yelling and throwing objects (M=2.56, SD=0.912) indicated potential problems with impulse control.
- **Psychological symptoms**: Fear of open spaces (M=2.51, SD=0.942), suicidal thoughts (M=2.49, SD=0.768), and auditory hallucinations (M=2.54, SD=0.774) were reported.

Table 1: ANOVA results

Particle	**N=140**	**AS (SCL-90-R)**	**SD**
Feeling faint when among people	99	2.61	0.924
Fear of riding the bus	104	2.55	0.892
Globus sensation	91	2.55	0.907
Stomach pain	89	2.52	0.833
Dizziness	92	2.48	0.935
Feelings of loneliness	70	2.31	0.753
Feelings of restlessness	80	2.21	0.851
Feeling "trapped"	87	2.48	0.825
Yelling and throwing objects	94	2.56	0.912
Fear of open spaces	103	2.51	0.942
Suicidal thoughts	101	2.49	0.768
Hearing voices	103	2.54	0.774

In the context of the most significant psychological symptoms of distress among these students, the following issues stand out: Feeling faint when among people, fear of riding the bus, globus sensation, stomach pain, dizziness, feelings of loneliness, feelings of restlessness, feeling "trapped", yelling and throwing objects, fear of open spaces, suicidal thoughts, hearing voices.

These symptoms indicate a more severe acute psychological distress and encompass a range of psychological and physical discomforts. Their prolonged persistence may signal a more serious mental or physical illness, potentially leading to diagnoses beyond the acute stress-related discomfort model.

This multidimensional assessment, conducted using the SCL-90-R index, was calculated by determining the intensity of distress value for each dimension. This value was obtained by summing the response values for each dimension and dividing by the number of responses (Derogatis and Lazarus 1994). The analysis identified primary and secondary dimensions of stress experienced by high school students in Orašje. The most significant primary stress dimensions identified in the study include somatization, paranoid ideation, anxiety, and interpersonal sensitivity.

DISCUSSION

The results indicate a wide range of issues, from physical symptoms to emotional and social discomfort. Feelings of isolation and stress highlight the need for enhanced support for young people, both through individualized approaches and programs that promote mental health and stress management. Identifying the most prominent symptoms, such as faintness, fear of riding the bus, and emotional loneliness, is crucial for the further development of preventive interventions. Additionally, the data emphasizes the need for raising awareness of the importance of spiritual practices in coping with mental health challenges. Mental health, as a state of well-being, enables an individual to realize their potential, cope with the usual stresses of life, be productive, and contribute to the community. At the same time, spirituality, which involves seeking answers to questions about the meaning of life, death, and illness, and includes practices like prayer, can play a significant role in preserving and enhancing mental health.

Previous research indicates that individuals with mental health disorders often have higher morbidity and mortality rates due to physical illnesses, along with increased exposure to stigmatization and prejudice (Fiorillo et. al. 2019, Plana Ripoll et al. 2020, Luciano et al. 2022, Jurčević 2021, Dučkić Sertić 2021, Komadina 2016). Individuals with mental disorders are often blamed for their condition, making their integration into society more difficult (Sartorius 2007, Rössler 2016, Ahad, Sanchez Gonzalez and Junquera, 2023, Vukotić, Kosić 2021). While healthcare workers' attitudes toward mental health disorders are more favourable than those of the general population, negative stereotypes still persist (Lauber et al. 2006, Petak, Narić and Matković 2021).

In their study, Skoko et al. (2021) conclude that religious individuals often use their beliefs and religion as a mechanism for establishing and maintaining mental health. They emphasize that spirituality and inner peace play a crucial role in preserving mental well-being, highlighting that religious individuals tend to cope more easily and successfully with challenges that may threaten their mental health. However, they note that spirituality does not provide absolute protection against mental disorders but facilitates the process of coping with illness and recovery. The findings of the present study, in comparison with those of Skoko et al. on the impact of mental health on spirituality, further support these conclusions, emphasizing the significance of spirituality among the respondents and its connection to their mental health. The research indicates that the vast majority of respondents believe in God and practice their faith, suggesting a strong presence of spirituality that may be essential for their mental well-being. For instance, spirituality has proven to be an important factor in

reducing stress and improving emotional stability among respondents, which is in concordance with other research (Margetić et al. 2022). This connection is reflected through various mechanisms, including social support, a positive influence on emotions, and assistance in coping with crisis situations (Kerkez and Sanli 2024).

One of the key aspects of improving mental health is changing societal attitudes toward mental disorders. Although mental disorders are no longer seen as divine punishment, individuals with these disorders are often excluded from society (Schomerus 2012, Škugor and Sindik 2017). Education and attitude change are crucial to ensuring equality and rights for individuals with mental health issues (Goodfellow et al. 2023).

The connection between mental health and spirituality is evident through the support that spirituality provides. Practices such as prayer and meditation can improve mood, reduce stress, and facilitate acceptance of illness. Present research confirmed that 73% of participants stated that they believe in God and practice their faith, indicating the significance of spirituality as a protective factor for mental health (Brown et al. 2013; Bovero et al. 2019; Tolentino et al. 2022). The research results show that the level of acute stress among students is low, despite the presence of stress factors related to school and personal life. Primary dimensions of stress, including somatization, paranoid thoughts, anxiety, and sensitivity in interpersonal relationships, were identified, which aligns with findings from previous studies (Komadina 2016, Jurčević 2021, Dučkić Sertić 2021, Leung and Pong 2021). These findings suggest a potential role of spirituality in maintaining mental stability (Brown Stewart 2018).

The connection between spirituality and mental health is also recognized in the scientific community. Regular religious practice, prayer, and meditation have a positive impact on emotional states and stress reduction (Rosamarin and Koenig 2020). Spirituality also offers social support and reduces feelings of loneliness, which is particularly important during adolescence. The psychological mechanisms of spirituality help individuals cope with crisis situations and support emotional stability (Krok 2008).

Koenig (2012) stated that a substantial body of research demonstrates that individuals with higher levels of S/R tend to exhibit better mental health and adapt more effectively to health challenges compared to those with lower levels of S/R. These potential benefits to mental health and well-being have physiological implications, influencing physical health, disease risk, and treatment outcomes. This is in line with the results of this study, which confirm that spirituality plays a key role in reducing stress and improving emotional stability. Both studies emphasize the importance of spirituality as a significant factor contributing to better mental health and quality of life. Spirituality helps with coping with mental illness and the healing process, while the results of this study show that spirituality reduces stress and improves emotional stability among the participants. Both studies highlight the need for further research and interventions that support spiritual and mental development, especially among young people in educational settings (Jennings et al. 2014).

In addition to psychological effects, spirituality may have bio-physiological benefits. Regular spiritual practice can improve the functions of the cardiovascular, endocrine, and immune systems, thus further contributing to the overall well-being of the individual. In conclusion, spirituality proves to be a crucial resource for preserving mental health. Prevention and support, including the development of healthy lifestyles and the promotion of spiritual development, can enhance the well-being of individuals and communities. Based on the results and data analysis, we can assess the status of each hypothesis from the study:

H1: Individuals who regularly engage in spiritual practices (meditation, prayer, contemplation) have better mental health, lower stress, and less anxiety – **confirmed**.

- 73% of participants believe in God and practice their faith.
- A relatively low level of acute stress was observed among the participants despite the presence of stress factors, implying mental health stability for most.
- The connection between lower stress levels and religious practice was confirmed by empirical data, consistent with previous research (Komadina 2016, Jurčević 2021).

H2: Individuals who feel a deeper sense of meaning and purpose in life (often linked to spirituality) have greater emotional stability and resilience to stress – **confirmed**.

- Subjective evaluations of family harmony (74% consider their families harmonious) and the significant presence of spirituality indicate emotional stability.
- The low level of acute stress among students further supports this claim.

H3: Participation in spiritual communities (churches, spiritual centers) provides social support and reduces feelings of loneliness, positively affecting mental health – **confirmed**.

- The majority of participants practice their faith, including participation in communal religious activities.
- The connection between spirituality and lower loneliness was supported by the results of the SCL-90-R scale (e.g., M=2.31 for loneliness).

H4: Individuals who had transcendental experiences (a sense of connection to something greater than themselves) may have better emotional well-being – **confirmed**.

- Participants with high levels of religious practice exhibit signs of emotional stability and resilience, which may be related to transcendental experiences.
- The results confirm the positive impact of spiritual practices on emotional well-being.

H5: Spirituality can serve as a coping strategy for difficulties and stress, positively affecting mental health – **confirmed**.

- Participants who engage in spiritual practices show lower levels of acute stress and better emotional well-being.
- Identified dimensions of stress, such as somatization and anxiety, were less pronounced in most participants.

All hypotheses were confirmed by the empirical data from the study. The results clearly indicate the significant role of spirituality in preserving and enhancing mental health, reducing stress, and improving emotional stability.

CONCLUSION

This study highlights the significant relationship between spirituality and mental health among high school students. The findings indicate that spirituality, including practices such as prayer, meditation, and participation in spiritual communities, plays a vital role in reducing stress, fostering emotional stability, and improving overall mental well-being. Students who engage in regular spiritual activities or perceive a deeper sense of meaning and purpose in life demonstrate greater resilience to stress and exhibit enhanced emotional stability. Moreover, the data suggests that spirituality can serve as a protective factor against feelings of loneliness and social isolation, providing a critical support mechanism during adolescence.

The results confirm that spirituality acts as a coping strategy for navigating life's challenges and contributes positively to mental health. Students who actively engage in spiritual practices reported lower levels of acute stress and a better sense of emotional balance, aligning with existing literature on the benefits of spiritual engagement. Furthermore, participation in spiritual communities was associated with improved social support and reduced loneliness, underscoring the social dimension of spirituality in mental health.

In summary, the study reaffirms the importance of incorporating spiritual dimensions into mental health interventions and educational programs, particularly for adolescents. Promoting spiritual practices and fostering environments that support spiritual exploration may enhance students' mental well-being and resilience. These findings advocate for a holistic approach to mental health that integrates spirituality as a core component in preventative and supportive strategies. Future research should further explore the mechanisms underlying the relationship between spirituality and mental health, focusing on diverse populations and longitudinal impacts to develop comprehensive interventions.

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Research article

THE IMPACT OF VISUALISATION ON EMOTIONAL STATES AND OXYTOCIN SECRETION IN PATIENTS AFTER MYOCARDICAL INFARCTION

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SUMMARY

Background: *Psychological interventions are increasingly used in the rehabilitation process after myocardial infarction. Previous studies have shown that guided visualization, which was also used in our research, is one of the most effective interventions.*

Subjects and methods: *The study involved 20 participants undergoing rehabilitation after myocardial infarction at the Internal Clinic of the University Medical Centre Ljubljana. They were divided into two groups, experimental and control. Participants in the experimental group performed guided visualization daily for 28 days. At the first and last sessions, two saliva samples were collected from all participants - before and after guided visualization. Participants measured their heart rate variability (HRV) parameters using a mobile application during visualization. Statistical methods used to determine the effects of visualization included t-test for two dependent samples and Wilcoxon test. Independent samples t-test and Mann-Whitney U test were used for comparisons between groups.*

Results: *The study results show a significant impact of visualization on reducing negative affective states, while other variables showed changes in the expected direction that were not statistically significant.*

Conclusion: *Study findings can contribute to the development of a more comprehensive psychophysiological approach to patients recovering from myocardial infarction, and they can also serve as a basis for the development of non-invasive post-infarction treatment with oxytocin.*

Key words: *visualization, oxytocin secretion, myocardial infarction, emotional states, heart rate variability*

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INTRODUCTION

According to WHO data (World Health Organization 2021) cardiovascular diseases are the leading cause of death worldwide, with approximately 17.9 million individuals dying each year from their consequences. Heart attacks and strokes account for 85% of these deaths. Myocardial infarction (MI) occurs as a result of arterial blockage, most commonly caused by atherosclerosis, which is characterized by the accumulation of atherosclerotic plaques in the arterial walls (Noč & Radšel 2008). The symptoms faced by individuals after an MI are both physiological and psychological. Most common physiological symptoms include difficulties with breathing, fatigue, and sleep problems (Kwekkeboom & Bratzke 2016). Research shows that psychological factors play an important role in the occurrence, development, and rehabilitation of coronary heart disease (Richards et al. 2017). More than 55% of coronary patients are reported to experience negative psychological symptoms, such as anxiety and depression (Eriksson et al. 2013), making it important to also offer patients psychological interventions.

Guided visualization is a cognitive intervention that involves mental imaging of content, which can be conveyed through listening to audio material (Kwekkeboom et al. 1998). It is said to help reduce pain following surgical procedures (Álvarez-García & Yaban 2020), as well as alleviate depression, fatigue, and regulate cortisol levels (McKinney et al. 1997). Psychological interventions have shown to reduce anxiety and depression in cardiac patients (Zhang et al. 2021).

Positive mental health is a combination of emotional, social, and psychological well-being (Keyes 2007). In

our study, we focused on the latter, which is indirectly associated with cardiological health through behaviors that promote a healthy lifestyle, including increased physical activity and balanced nutrition (Giltay et al. 2006), or directly through changes in the neuroendocrine, cardiovascular, and inflammatory systems (Steptoe et al. 2009). Guided visualization enables individuals to relax, impacting emotional well-being, reducing stress, and lowering negative emotionality (Ofentavšek 2023, Watanabe et al. 2005).

Depression is a common response to MI and according to the results of a meta-analysis by Van Der Kooy et al. (2007), depression increases the risk of developing cardiovascular diseases by 46 %. Lang et al. (2012) investigated the impact of visualization on the severity of depression symptoms in a sample of 26 depressed individuals. After two weeks of daily visualization practice, participants from the experimental group showed improvement in depressive symptoms compared to the control group.

Guided visualization as an intervention for reducing anxiety has proven to be effective by significantly lowering anxiety levels in patients with various health issues (Serra et al. 2012).

Chronic distress is associated with negative health outcomes. These include heart disease, depression, anxiety (Iglesias et al. 2012). Elevated stress indirectly affects the occurrence of atherosclerosis and ischemic heart diseases (Grewal et al. 2011). A study by Whitehead et al. (2005) showed that upon hospital admission for acute MI, 22% of patients reported high levels of stress, while 52% reported moderate levels of stress.

Non-pharmacological interventions, such as guided visualization, are increasingly used in medicine to alleviate many somatic symptoms (McDonald et al. 2015). Research has shown that visualization has positive effects on both psychological and physiological symptoms that occur in patients after MI. The psychological effects of visualization, such as reducing stress, depression and anxiety, are linked to physiological effects, as evidenced by changes in heart rate variability (HRV) parameters, regulation of heart rate, and breathing (Machida et al. 2018, Malik et al. 1996).

The key task of the autonomic nervous system (ANS) is to regulate the functioning of organic systems, including the cardiovascular system. Indicators of ANS function are HRV parameters, which reflect an individual's cardiovascular health (Malik et al. 1996). They demonstrate how the autonomic nervous system affects the sinoatrial node, responsible for initiating the heartbeat. The length of one cardiac cycle is represented by the RR interval. Since our heart beats irregularly, RR intervals vary. HRV represents the variation of these time intervals in milliseconds (Malik et al. 1996). HRV parameters are divided into time domain and frequency domain. In the time domain, the most commonly used measure is the standard deviation of NN intervals (SDNN), which are intervals occurring during the depolarization of the sinus node. In the frequency domain, time indicators are converted into frequency components, reflecting the power spectrum. This spectrum represents the total variability, divided into four components: very low frequency (VLF), low frequency (LF), high frequency (HF), and very high frequency component of the spectrum (VHF). HF, ranging between 0.15–0.4 Hz, is considered to reflect the activity of the parasympathetic nervous system, while LF reflects the activity of the sympathetic nervous system (Kšela 2020).

Malik et al. (1996) report that patients post-MI have statistically lower frequency component indicators of HRV, indicating an increased influence of sympathetic activity on heart rhythm regulation. Limmer et al. (2022) studied the effect of using a mobile device to increase HRV in patients post-MI. Participants performed breathing exercises for five minutes three times a day for 12 weeks, concurrently using a mobile device that measured real-time HRV. They found a significant increase in HRV values.

Oxytocin is an endogenous neuropeptide hormone synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and released in the posterior part of the pituitary gland (Gimpl & Fahrenholz 2001). It plays a central role in promoting social behavior, attachment mechanisms, the formation of pair bonds and trust, and maternal behavior (Carter 2014). Through the central and peripheral nervous systems, it participates in the regulation of the cardiovascular system (Petersson & Uvnäs-Moberg 2007).

The study by Wsol et al. (2008) demonstrated that rats, in which endogenous secretion of oxytocin was stimulated, exhibited a significantly lower stress response and lower increase in heart rate compared to rats that did not receive oxytocin. Therefore, stimulation of oxytocin receptors in the brain plays a crucial role in inhibiting cardiovascular responses to stress. Kobayashi et al. (2009) in their research on post-infarction treatment in rabbits, found that oxytocin contributes to the reduction of MI size.

Vižintin (2021) studied psychophysiological responses to visualization with calming music and found a significant impact on increasing SDNN. Due to the small sample size, the results did not show significant effects on affective mood states, increased oxytocin, and parasympathetic activity, but the average values on the observed variables indicated expected effects. Machida et al. (2018) hypothesized that meditation focused on altruism, respect, and gratitude towards others could stimulate oxytocin secretion, using the Arigato-Zen method. The study involved 32 participants who had saliva samples taken before and after the meditation session. After the intervention, a sigificant increase in oxytocin levels was observed. A pilot study by Klaus et al. (2000) explored the effect of using guided visualization in patients with heart failure, and the results indicated a positive effect on reducing stress, anxiety, and depression.

AIMS AND OBJECTIVES

The objective of the study is to determine the impact of the guided visualization technique on oxytocin

secretion, HRV parameters, and affective mood states (depression, anxiety, stress, and psychological well-being) in patients recovering from MI.

We hypothesized that:

H1: After the first session of guided visualization, there will be a statistically significant increase in oxytocin levels in the experimental group (EG) compared to before the session.

H2: After the first session of guided visualization, the oxytocin levels in the EG will be statistically significantly higher compared to the control group (CG).

H3: After 4 weeks of guided visualization, there will be a statistically significant increase in oxytocin levels in the EG at the final measurement compared to before the intervention started.

H4: After 4 weeks of guided visualization, there will be a statistically significant increase in oxytocin levels in the EG at the final measurement compared to before the last visualization.

H5: After 4 weeks of guided visualization, there will be a statistically significant increase in oxytocin levels in the EG at the final measurement compared to the CG.

H6: After 4 weeks of guided visualization, there will be a statistically significant increase in positive emotionality and a decrease in negative emotionality in the EG compared to before the intervention started.

H7: After 4 weeks of guided visualization, there will be a statistically significant increase in positive mental health in the EG compared to before the intervention started.

H8: After 4 weeks of guided visualization, there will be a statistically significant reduction in depression, anxiety, and stress in the EG compared to before the intervention started.

H9: After 4 weeks of guided visualization, there will be a statistically significant increase in positive emotionality and a decrease in negative emotionality in the EG compared to the CG.

H10: After 4 weeks of guided visualization, there will be a statistically significant increase in positive mental health in the EG compared to the CG.

H11: After 4 weeks of guided visualization, there will be a statistically significant reduction in depression, anxiety, and stress in the EG compared to the CG.

H12: After 4 weeks of guided visualization, there will be a statistically significant increase in HF (parasympathetic activity) in the EG at the final measurement compared to before the intervention started.

SUBJECTS AND METHODS

Ethical considerations and informed consent

Prior to the commencement of the study, we received an ethical approval from the Republic of Slovenia National Medical Ethics Committee (number 0120-403/2022/7). The committee confirmed that the study was ethically acceptable and gave consent for its execution. Participants received both oral and written explanations of the research process and signed informed consent to participate in the study.

The study was designed to compare measurements before and after a 4-week intervention. Participants were randomly assigned to either EG or CG by drawing lots. Participants randomly drew a slip of paper numbered either 1 (EG) or 2 (CG) from an envelope. Each group consisted of 10 participants.

Participants

Participants were invited to take part both orally and in writing, during a psychophysiological examination at the Internal Clinic of the UMCL. The study included 20 male participants aged between 35 and 68 years (M = 55.85; SD = 7.68).

Inclusion Criteria

Male gender, participation in a rehabilitation program after a heart attack at the Clinical Department for Vascular Diseases at UMCL, same initial diagnosis (MI – STEMI, NSTEMI), and possession of an Android operating system phone.

Exclusion Criteria

Risk of complications during rehabilitation (e.g., individuals with diabetes), patients with 20 or more breaths per minute of average spontaneous breathing while seated, individuals with uncontrolled heart rhythm disorders, uncontrolled heart failure, age over 70 years, and individuals with severe psychiatric psychopathology.

Methods

Each participant who met the inclusion criteria was invited to the clinic for an initial meeting where they completed psychological questionnaires and provided two saliva samples for measuring the amount of oxytocin secreted. After the first saliva sample, participants in the EG downloaded the mobile application ecg4everybody on their smartphones and were taught how to use it. We then conducted the guided visualization technique titled Visualization of Positive Emotions (Enova in Jakša 2006), which lasts 18 minutes. After completing the visualization, we collected another saliva sample 10–15 minutes later. Research (Weisman et al. 2012) has shown that the peak level of oxytocin secretion occurs 10–15 minutes after intranasal administration of oxytocin. After the second saliva collection, we provided the participants with instructions for practicing the technique at home, along with written instructions and a link to the audio recording. During the first and second saliva collection, participants in the CG spent 10–15 minutes reading emotionally neutral text. We informed participants in the CG that their activities over the next four weeks would proceed as usual.

Participants in the EG practiced the guided visualization technique daily for 18 minutes over four

weeks, listening to it as an audio recording. While listening, they used the ecg4everybody app, which continuously measured their heart rate and HRV parameters. The measurement results were automatically stored in a cloud accessible only to the researchers.

After four weeks, each participant attended the final measurements where they completed psychological questionnaires, and another saliva sample was collected. We repeated the guided visualization technique with participants from the EG, followed by the last collection of a saliva sample 10–15 minutes after performing the visualization. CG read emotionally neutral text between the first and second saliva collections.

Instruments

We measured positive and negative emotionality with the Positive and Negative Affect Scale (PANAS) (Watson et al. 1988). It consists of 2 scales, each containing 10 items. An individual rates how often each emotional state is expressed in them on a Likert scale ranging from 1 (very rarely) to 5 (very often). The authors report high internal reliability coefficients for positive emotionality scale (α = .90–.96), and for the negative emotionality scale (α = .84–.87).

To assess the emotional and social aspects of well-being, we used the 9-item Positive Mental Health Scale (PMH) (Lukat et al. 2016). Participants rate how much they agree with each statement on a 4-point Likert scale ranging from 0 (disagree) to 3 (agree). The authors report high internal reliability (α = .93).

The Depression Anxiety Stress Scales (DASS-21) (Lovibond & Lovibond 1995) measure negative emotional states with 21 items. Individuals rate how much each statement applies to them on a 4-point Likert scale ranging from 0 (Does not apply to me at all/never) to 3 (Applies to me very much or most of the time). Authors report high internal consistency for depression dimension (α = .91) anxiety dimension (α = .84) and for stress dimension α = .90).

Anxiety as a state was measured using the 20-item State Trait Anxiety Inventory (STAI X-1) (Spielberger et al. 1983), which assesses the presence and intensity of current anxiety symptoms. Individuals rate how they feel at the moment on a 4-point Likert scale from 1 (not at all) to 4 (very much). The authors report high internal consistency (α = .86–.95).

Trait anxiety was measured using the Trait Anxiety Inventory (STAI X-2) (Spielberger et al. 1983). This 20-item scale assesses an individual's tendency to perceive situations as threatening and respond accordingly. Individuals rate how they generally feel on a 4-point Likert scale from 1 (almost never) to 4 (almost always). High reliability is reported by the authors (α = .90).

We measured positive and negative emotionality using the Scale of Positive and Negative Experience (SPANE) (Diener et al. 2009), which consists of 12 items. Six items assess positive emotionality, while six items assess negative emotionality. Individuals rate how often they experience certain moods on a 5-point Likert scale, ranging from 1 (never or very rarely) to 5 (very often or always). The authors report high internal reliability for the positive experience (α = .87) and for the negative experience subscale (α = .81).

In the study, participants used the mobile application ecg4everybody, which they installed on their Android smartphones. It was created by Dr. Stevan Jokić from the University of Novi Sad, Serbia, who provided us with free access to the collected data. The application enables the measurement of HRV parameters and heart rate using photoplethysmography through the smartphone camera, where participants placed their finger.

The enzyme immunoassay Elabscience Oxytocin ELISA Kit (Oxytocin ELISA Kit Catalog No. E-EL-0029, Elabscience) was used to determine the amount of oxytocin in saliva. The study used a competitive ELISA analysis. The measurement range of the analysis is from 15.63 to 1000 pg/mL. To perform the analysis, 50 μL of the saliva sample was added to the reagent. The analysis of the saliva samples takes 120 minutes and was performed according to the reagent manufacturer's instructions.

Statistical Analyses

The data was processed using statistical software RStudio and IBM SPSS Statistics 29. To analyze significant effects between the EG and CG, we calculated the differences between the first and last measurements, as well as the average differences, and used tests for equality of means to compare the obtained averages. We used the paired t-test, Wilcoxon test, independent t-test, and Mann-Whitney U test. The normality of the distribution of individual variables was checked with the Shapiro-Wilk test.

RESULTS

Oxytocin

Table 1 shows that the measured amount of oxytocin in the saliva of participants in CG is not normally distributed in any of the time conditions. The measured amount of oxytocin in the EG participants is normally distributed in all time conditions. The average amount of oxytocin in saliva increased in all time conditions and for both groups, except before and after the first visualization in the EG, where the average amount of oxytocin decreased. The large standard deviations indicate substantial variation in the measured amount of oxytocin in the saliva of both groups.

The results of the tests for equality of means of oxytocin levels, indicate that there was no significant increase in secreted oxytocin among participants in EG before and after the first visualization ($t(9) = 0.78$, $p = .46$), before and after the last visualization ($t(9) = 1.42$, $p = .19$), and there was also no significant increase in oxytocin secretion before the first

visualization and after the last visualization ($t(9) = 1.46$, $p = .18$).

Table 1. Descriptive Statistics and Normality Tests for Oxytocin Before the Start of the Intervention, After the First Visualization, and After the 4-week Intervention Before the Visualization for EG and CG, and After it

		N	*M (ng/L)*	*SD*	*Min*	*Max*	*Sk*	*Ku*	*S-W*
1. measurement									
EG	before	10	599.73	599.22	40.20	1790.50	0.79	-0.98	0.85
	after	10	477.90	396.67	85.90	1228.80	0.58	-1.24	0.89
CG	before	10	524.61	566.05	18.80	1843.20	1.13	0.17	0.84*
	after	10	546.80	525.26	40.90	1649.10	0.88	-0.74	0.83*
2. measurement									
EG	before	10	750.93	523.24	22.60	1403.00	-0.06	-1.70	0.92
	after	10	876.97	663.46	68.10	1724.80	0.02	-1.84	0.89
CG	before	10	435.71	456.16	16.40	1167.70	0.64	-1.53	0.80*
	after	10	509.08	542.08	50.30	1541.00	0.90	-0.92	0.80*

Note. *Sk* = skewness coefficient; *Ku* = kurtosis coefficient; *S-W* = Shapiro-Wilk normality test.
* $p < .05$.

Table 2. Descriptive Statistics and Normality Test for Average Differences in Oxytocin levels Before and After the First Visualization, Before and After the Last Visualization, and Before the First and After the Last Visualization for EG and CG

	N	*M (ng/L)*	*SD*	*Min*	*Max*	*Sk*	*Ku*	*S-W*
EG								
Before and after the first visualization	10	-121.83	497.11	-1023.50	637.00	-0.55	-0.78	0.90
Before and after the last visualization	10	126.04	279.99	-204.00	701.80	0.72	-0.78	0.91
Before the first visualization and after the last visualization	10	277.24	600.09	-400.70	1404.40	0.77	-1.05	0.84*
CG								
Before and after the visualization	10	22.19	207.46	-225.50	464.10	0.71	-0.49	0.93
Before and after the last visualization	10	73.37	172.24	-156.40	373.30	0.48	-1.32	0.91

Note. *Sk* = skewness coefficient; *Ku* = kurtosis coefficient; *S-W* = Shapiro-Wilk normality test.
* $p < .05$.

The results from Table 2 indicate that the average difference in the amount of oxytocin in the saliva of participants in the EG before the start of the first visualization and after the end of the last visualization is not normally distributed. The average difference in the amount of oxytocin in participants in the EG decreased by M = -121.83 ng/L after the first visualization compared to the state before the first visualization. After the last visualization, it increased by M = 126.04 ng/L compared to the state before the last visualization, and it increased by M = 277.24 ng/L compared to the state before the first visualization. The standard deviations of the average amount of secreted oxytocin indicate data dispersion and variation in oxytocin levels in the saliva of participants within each group.

Comparison of oxytocin levels between the EG and CG shows that there were no significant differences in the amount of oxytocin secretion between the groups after the first ($t(12.04) = -0.85$, $p = .41$), and after the last performance of the visualization exercise ($t(14.96) = 0.51$, $p = .62$),.

Mood Affective States

Table 3. Descriptive Statistics and Tests of Normality for Psychological Questionnaires Before and After the Intervention for the EG

		N	*M*	*SD*	*Min*	*Max*	*Sk*	*Ku*	*S-W*
PANAS									
Positive emotionality	before	10	35.70	3.65	30	43	0.52	-0.58	0.94
	after	10	35.20	3.62	31	42	0.67	-1.13	0.89
Negative emotionality	before	10	21.10	5.34	14	30	0.10	-1.40	0.94
	after	10	17.70	5.91	10	29	0.25	-0.93	0.92
SPANE									
Positive emotionality	before	10	25.20	2.10	22	28	-0.17	-1.72	0.92
	after	10	25.70	2.50	22	30	0.23	-1.40	0.93
Negative emotionality	before	10	10.10	3.03	7	17	0.99	-0.10	0.84*
	after	10	9.10	2.73	7	15	0.97	-0.51	0.81*
Emotional balance	before	10	15.10	3.73	10	20	-0.02	-1.85	0.90
	after	10	16.60	4.93	7	23	-0.50	-1.05	0.95
PMH	before	10	30.00	4.52	20	36	-0.69	-0.12	0.91
	after	10	31.30	3.50	25	36	-0.34	-1.29	0.96
DASS-21									
Depression	before	10	9.00	1.56	7	12	0.63	-1.03	0.90
	after	10	8.30	1.83	7	13	1.56	1.47	0.72*
Anxiety	before	10	8.90	1.79	7	13	0.97	0.04	0.87
	after	10	8.10	1.29	7	11	0.96	-0.16	0.82*
Stress	before	10	11.00	3.33	7	17	0.45	-1.25	0.92
	after	10	9.70	3.09	7	17	1.15	0.32	0.84*
STAI X-1	before	10	27.60	5.68	21	36	0.21	-1.86	0.88
	after	10	25.30	4.30	20	32	0.39	-1.58	0.90
STAI X-2	before	10	30.90	6.92	21	46	0.77	-0.14	0.91
	after	10	29.30	6.06	20	36	-0.24	-1.61	0.90

Note. Sk = skewness coefficient; *Ku* = kurtosis coefficient; *S-W* = Shapiro-Wilk normality test.
* $p < .05$.

From Table 3, it is evident that the average score of Positive Affect and Emotional Balance on the SPANE questionnaire, as well as the total score on the PMH questionnaire, after a 4-week intervention, is higher compared to the average score before the intervention. It is also evident that after the intervention, the average score of Negative Affect on the PANAS and SPANE questionnaires is lower compared to the average score before the intervention. Furthermore, it is evident that there is a decrease in average scores on all depression, anxiety, and stress questionnaires after the intervention, indicating an improvement in scores. The distribution of scores is normal on all questionnaires, except for the dimension of Negative Affect (SPANE), both before and after the intervention, and dimensions of depression, anxiety, and stress after the intervention.

The positive average differences in scores on the dimensions of Positive Affect, Emotional Balance (SPANE), and the PMH questionnaire in Table 5 suggest an improvement in positive affectivity and positive mental health after the intervention. The negative average differences in scores on the dimensions of Negative Affect (PANAS) and Negative Affect (SPANE) indicate a decrease in negative affectivity after the intervention. Furthermore, it is evident that participants in the EG achieved lower average scores on all dimensions and questionnaires after the intervention compared to before the intervention, indicating a reduction in symptoms of depression, anxiety, and stress.

Table 4. Tests of Equality of Means for Paired Samples for Psychological Questionnaires for the EG

	N	*t*	*df*	*p*	*d*
PANAS					
Positive emotionality	10	0.43	9	.68	0.14
Negative emotionality	10	2.80	9	.02*	0.89
SPANE					
Positive emotionality	10	-0.54	9	.60	0.17
Emotional balance	10	-0.82	9	.44	0.26
PMH	10	-1.54	9	.16	0.49
STAI X-1	10	1.51	9	.17	0.48
STAI X-2	10	0.91	9	.38	0.29
	N	*T*	*z*	*p*	*r*
SPANE					
Negative emotionality	10	17.50	-0.60	.55	.17
DASS-21					
Depression	10	10.50	-1.07	.29	.23
Anxiety	10	13.50	-1.08	.28	.23
Stress	10	5.50	-1.77	.08	.30

* $p < .05$.

From Table 4, it is evident that significant differences in average scores before and after the intervention only occur in the dimension of Negative Affect (PANAS).

Table 5. Descriptive Statistics and Tests of Normality for the Average Differences in Scores on Psychological Questionnaires Before and After the 4-week Intervention for the EG

	N	*M*	*SD*	*Min*	*Max*	*Sk*	*Ku*	*S-W*
PANAS								
Positive emotionality	10	-0.50	3.66	-5	5	0.34	-1.63	0.89
Negative emotionality	10	-3.40	3.84	-12	3	-0.66	0.34	0.90
SPANE								
Positive emotionality	10	0.50	2.92	-4	6	0.33	-0.98	0.96
Negative emotionality	10	-1.00	3.86	-9	4	-0.66	-0.62	0.94
Emotional balance	10	1.50	5.82	-6	10	0.13	-1.76	0.91
PMH	10	1.30	2.67	-4	5	-0.45	-0.87	0.96
DASS-21								
Depression	10	-0.70	1.89	-4	2	-0.30	-1.27	0.97
Anxiety	10	-0.80	2.04	-3	4	-0.46	-0.81	0.92
Stress	10	-1.30	2.11	-6	2	-0.73	0.13	0.90
STAI X-1	10	-2.30	4.81	-10	6	-0.28	-0.78	0.89
STAI X-2	10	-1.60	5.52	-10	7	0.10	-1.51	0.95

Note. *Sk* = skewness coefficient; *Ku* = kurtosis coefficient; *S-W* = Shapiro-Wilk normality test.
* $p < .05$.

Table 6. Tests of Equality of Means of Average Differences Before and After the 4-Week Intervention for Psychological Questionnaires Considering the EG and CG

	N	*U*	*z*	*p*	*r*
PANAS					
Positive emotionality	20	41	-0.68	.53	.18
Negative emotionality	20	44.5	-0.42	.68	.15
SPANE					
Emotional balance	20	36	-1.07	.29	.23
PMH	20	30	-1.51	.13	.28
STAI X-1	20	50	0.00	1.00	.00
	N	*t*	*df*	*p*	*d*
SPANE					
Positive emotionality	20	1.34	17.94	.20	0.60
Negative emotionality	20	-0.90	15.25	.38	0.40
DASS-21					
Depression	20	1.23	17.81	.23	0.55
Anxiety	20	0.88	14.80	.39	0.39
Stress	20	0.23	14.54	.82	0.10
STAI X-2	20	-0.47	12.65	.65	0.21

The results presented in Table 6 indicate that there were no significant differences in scores on the psychological questionnaires PANAS, SPANE, PMH, DASS-21, STAI X-1, and STAI X-2 between the EG and CG before and after the intervention. This means that participants in the EG did not achieve significantly better results compared to the CG on the questionnaires.

Heart Rate Variability

To assess the average change in HF before and after 4 weeks of guided visualization practice, we used the Wilcoxon signed-rank test. The change in HF before starting the intervention (M_{before} = 221.20, *SD* = 117.25) is not significantly higher than the change in HF after completing the intervention (M_{after} = 413.80, *SD* = 492.17), *T* = 36, *p* = .39, *r* = .29.

Results for the normality test of the average differences in HF change show that, on average, we measured higher values of HF in participants after the 4-week intervention compared to before the intervention (*M* = 192.60, *SD* = 529.01), indicating that the visualization intervention has influenced an increase in HF values.

DISCUSSION

The study investigated the physiological and psychological effects of guided visualization on post-MI patients, focusing on examining oxytocin hormone secretion, HRV parameters, and mood affective states (anxiety, depression, stress, psychological well-being). The EG practiced guided visualization technique daily for 4 weeks while monitoring HRV parameters through the mobile application ecg4everybody. The CG did not engage in any activities. We hypothesized that guided visualization would lead to a significant increase in oxytocin levels in saliva already after the first visualization session, and that the changes in oxytocin levels would be significantly higher compared to the CG. However, our findings did not align with the hypotheses we set.

Previous studies (Klaus et al. 2000, Machida et al. 2018, Vižintin 2021) have indeed demonstrated the influence of relaxation techniques on oxytocin secretion. The discrepancy with past findings could be attributed to the participants' inability to relax during the initial session in the EG, as they received a lot of new information and were still learning how to perform the technique and use the mobile application. There was no significant increase in oxytocin levels even at the final session, and the oxytocin levels in the saliva of participants in the EG were not significantly higher compared to the CG. The reasons for the discrepancy with the hypotheses can again be attributed to the conditions under which the participants performed the visualization. They had to be mindful of keeping their hand still to avoid tremors and inaccurate measurements in the mobile application, while there was also a lot of noise in the area around the clinic where the measurements were taken, which may have hindered participants' relaxation and focus on performing the visualization. At the final measurements, the results of the study showed that after the 4-week visualization intervention, the oxytocin levels in patients did not significantly increase compared to the pre-intervention state, although the results indicate an increase in oxytocin in the expected direction. One reason for rejecting the hypothesis could have been the choice of visualization technique, which in our case focused on promoting positive emotions. Machida et al. (2018) study found that visualization focused on gratitude stimulates oxytocin secretion in participants. It would be advisable to verify the influence of visualization on a larger, more representative sample.

With the exception of the subscale of negative affectivity on the PANAS questionnaire, where there was a significant decrease in negative affectivity in the EG after the 4-week intervention, there was no statistically significant increase or decrease in any of the other mood affective states. The study by Kaplan et al. (2014) has shown a significant influence of

guided visualization on increasing positive affectivity and decreasing negative affectivity. Therefore, we can partially confirm the hypothesis that after the 4-week intervention, positive affectivity will increase and negative affectivity will decrease, as there were statistically significant differences in the latter at the final measurement compared to the pre-intervention state.

We also rejected the hypothesis that guided visualization would significantly impact reducing depression, anxiety, and stress, as some previous studies have shown (Broadbent et.al. 2012, Lang et.al. 2012, Zhang et.al. 2021).

Additionally, we assumed that the results would significantly differ from the CG, which did not undergo the 4-week intervention. There could be several reasons for the discrepancy with previous research. Our participants did not have diagnosed depression, unlike some other studies (Lang et al. 2012). Furthermore, the choice of guided visualization technique may have influenced the results, as it did not focus on visualizing a safe place compared to previous research (Serra et al. 2012). Moreover, participants in the visualization did not perform it immediately after the occurrence of MI but rather as part of rehabilitation, so their perceived stress might have been lower than in the period immediately after MI.

Based on past research (Limmer et al. 2022) we assumed there would be a statistically significant increase in HF values reflecting parasympathetic activity in the EG after the 4-week intervention compared to before the intervention. Although the results suggest changes in the expected direction, these differences are not significantly large, so we can reject our hypothesis. Therefore, the results do not align with the findings of previous research, which could be attributed to different methods used in the studies. Limmer et al. (2022) used a breathing exercise technique in their study, and the intervention lasted for 12 weeks. In contrast, our intervention only lasted for four weeks, thus we suggest future research to explore the timeframe in which significant differences in HF value increases may appear.

The study suggests a complex interplay of psychophysiological variables, which would be worthwhile to expand in future research. The results of the study indicate changes in all average values in the expected direction. It would be essential to increase the sample size, and potentially, participants in future studies could listen to a variety of guided visualization recordings. It would also be necessary to provide more suitable conditions for conducting the first and last sessions in calm environments to give participants the opportunity for relaxation and focus on listening to the guided visualization.

CONCLUSIONS

The study did not show significant effects of guided visualization technique on increasing oxytocin or parasympathetic nervous system activity, nor did it significantly affect the majority of affective mood states. However, the results demonstrated a significant decrease in negative affectivity on the PANAS questionnaire, indicating the method's effectiveness in reducing negative emotional states. Despite the average values on all observed variables suggesting expected effects, it would be necessary to verify the effects on a larger sample of patients. The method is simple, cost-effective, and time-efficient, making it a potential for the development of non-invasive oxytocin therapy post-MI. It also allows for a comprehensive assessment of effectiveness both at the psychological and physiological levels and transfer of findings to other clinical areas. The use of an application for measuring HRV parameters enables safe and accessible monitoring of individuals' psychophysiological state post-MI and has no adverse side effects.

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Research article

THERAPEUTIC RESPONSE AND TOXICITY OF CYCLIN-DEPENDENT KINASE 4/6 INHIBITORS IN THE TREATMENT OF HORMONE RECEPTOR-POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 NEGATIVE METASTATIC BREAST CANCER– A SINGLE-CENTER EXPERIENCE

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SUMMARY

Background: *The aim of the study was to determine the therapeutic response and toxicity of CDK 4/6 inhibitor therapy in patients with hormone-positive HER2-negative metastatic breast cancer. Additional aims were to determine whether there is a difference in survival and response to therapy in relation to age, ECOG status, other visceral diseases, the length of time waiting for drug approval, side effects, and consequently, treatment interruption and dose reduction.*

Methods: *The study analyzed all available medical documentation for 65 patients who were treated with CDK 4/6 inhibitors for hormone receptor-positive HER2-negative metastatic breast cancer at the Oncology Clinic of the University Clinical Hospital Mostar during the period from January 1, 2020, to December 31, 2023. Data for analysis were obtained by processing the medical documentation. Additionally, data were obtained from the Federal Fund of the Health Insurance and Reinsurance Institute of the Federation of Bosnia and Herzegovina. A retrospective cohort study was conducted based on the obtained data.*

Principal conclusion: *There was no statistically significant difference in response to therapy regarding PFS between patients who received CDK 4/6 inhibitors in four different therapeutic lines. However, a statistically significant difference in OS was found, i.e., patients who received this therapy in the first and second lines of treatment had longer survival compared to those who received therapy in later lines, partially confirming the hypothesized hypothesis.A statistically significant majority of patients on CDK 4/6 inhibitor therapy did not experience side effects, thus confirming the hypothesis.*

Key words: *Breast Neoplasms, Neoplasm Metastasis, Cyclin-Dependent Kinase Inhibitor*

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INTRODUCTION

Breast cancer is the leading type of cancer among women worldwide, accounting for about one-quarter of all cancer cases in women (1). Its incidence is rising worldwide, with the highest rates observed in developed countries, where nearly half of all cases are found. This increase is largely attributed to factors associated with a western lifestyle, such as unhealthy diet, smoking, excessive stress, and lack of physical activity. Despite advances in diagnosis and treatment, breast cancer remains the leading cause of cancer-related mortality among women worldwide, with the highest mortality rates in developing countries, which is attributed to inadequate screening and treatment options. Breast cancer risk is influenced by gender, age, economic development, hormonal factors (estrogen exposure, reproductive history, breastfeeding), genetics, hormone replacement therapy, diet, obesity, and factors like hormonal birth control, alcohol, and ionizing radiation(2). Breast cancer develops from DNA damage and genetic mutations, often worsened by estrogen exposure. In some cases, inherited gene mutations like BRCA1 and BRCA2 increase the risk. Normally, the immune system eliminates abnormal cells, but in breast cancer, this defense is compromised, leading to uncontrolled tumor growth and metastasis (3).

Hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer is common, representing two-thirds of advanced or metastatic cases. When diagnosed early, it has a better prognosis. For metastatic HR+/HER2- breast cancer, endocrine therapy (ET) is often combined with CDK inhibitors like palbociclib, ribociclib, and abemaciclib, which have shown clinical benefits (4).Cyclin-dependent kinases (CDKs) play a crucial role in regulating the progression of the cell cycle and the final cell division. Palbociclib, ribociclib, and

abemaciclib are orally administered, highly selective, and reversible CDK4 and CDK6 inhibitors. They are used in the treatment of metastatic breast cancer with hormone receptor-positive (HR+), HER2-negative receptors, along with specific hormonal therapy (5). CDK4/6 inhibitors block the G1-S transition in the cell cycle, which is regulated by cyclins D, CDK4, and CDK6. These cyclins activate CDK4/6, leading to the phosphorylation of pRb, releasing its inhibition on E2F transcription factors and allowing cell division. In hormone receptor-positive breast cancer, cyclin D overexpression and intact pRb function make this checkpoint a key target for therapy. CDK4/6 inhibitors stop the cell cycle at this stage (6). These therapies extend progression-free survival (PFS), delay chemotherapy, and improve quality of life. However, they do not provide a cure, as cancer eventually progresses, and some cancers show resistance (4).Phase II and III clinical trials have shown that combining CDK4/6 inhibitors with hormonal therapy (HT) significantly extends progression-free survival (PFS) compared to hormonal therapy alone, with an acceptable toxicity profile. However, overall survival (OS) benefits have not been proven as a primary endpoint. In the PALOMA study, OS was numerically longer with palbociclib, but not statistically significant(7). All three CDK4/6 inhibitors have been tested with various AIs in first-line therapy and with fulvestrant in second-line therapy for HER2-negative metastatic breast cancer. Palbociclib with letrozole nearly doubled median PFS in the PALOMA-1 study, leading to FDA approval. Ribociclib with letrozole also extended PFS in the MONALEESA-2 study, and abemaciclib showed similar results in the MONARCH-3 study.

For patients resistant to endocrine therapy (ET), CDK4/6 inhibitors combined with fulvestrant significantly extended PFS. In the PALOMA-3 study, palbociclib with fulvestrant extended PFS, and abemaciclib showed similar benefits in the MONARCH-2 study.

CDK4/6 inhibitors like ribociclib have also been studied in premenopausal women, with the MONALEESA-7 study showing significant PFS extension. Additionally, abemaciclib's use in a neoadjuvant setting in the neoMONARCH study showed a significant reduction in Ki-67 expression (8).

New molecular changes induced by CDKi therapy may reduce the effectiveness of future treatments. Additionally, overactivation of the PI3K pathway, common in HR+/HER2- metastatic breast cancer, can lead to resistance to ET and CDKi. While PI3K inhibitors have been effective for tumors with PI3K mutations after CDKi therapy, it's unclear if targeting this pathway can prevent resistance. Rapid disease progression after stopping CDKi highlights the need for better understanding and more refined treatment strategies, as there are no clear clinical guidelines for post-CDKi therapies (4). The aim of the study was to determine the therapeutic response and toxicity of CDK 4/6 inhibitor therapy in patients with hormone-positive HER2-negative metastatic breast cancer.

Other objectives included assessing whether survival and therapy response vary based on age, ECOG status, other visceral conditions, the duration of waiting for drug approval, side effects, and treatment interruptions or dose reductions. Additionally, the study aimed to examine the occurrence of side effects during treatment (such as neutropenia, elevated liver transaminases, thrombocytopenia, etc.) and determine if there are differences in side effects between different CDK 4/6 inhibitors.

SUBJECTS AND METHODS

The study analyzed all available medical documentation for 65 patients who were treated with CDK 4/6 inhibitors for hormone receptor-positive HER2-negative metastatic breast cancer at the Oncology Clinic of the University Clinical Hospital Mostar during the period from January 1, 2020, to December 31, 2023.

Data Collection and Processing Methods

Data for analysis were obtained by processing the medical documentation from the Oncology Clinic of the University Clinical Hospital Mostar, primarily by reviewing medical histories and the hospital's information system. Additionally, data were obtained from the Federal Fund of the Health Insurance and Reinsurance Institute of the Federation of Bosnia and Herzegovina.

A retrospective cohort study was conducted based on the obtained data.

The following characteristics were analyzed:

Hormone receptor status (ER, PgR), HER-2 receptor expression, proliferation index Ki-67, age at diagnosis of metastatic disease, age at initiation of CDK 4/6 inhibitor therapy, year of therapy initiation, menopausal status, comorbidities, therapeutic line for metastatic disease, partner therapy with CDK 4/6 inhibitor (fulvestrant or any aromatase inhibitors), use of LHRH agonists in premenopausal women, number of metastatic sites, location of metastases (bones, liver, etc.), previous therapies, time from metastatic disease diagnosis to initiation of the indicated therapy, ECOG status before treatment initiation, PFS (Progression-Free Survival), patient status (progression),response to therapy (stable disease, partial regression, complete regression, progression), side effects during treatment, hematological toxicity, elevated liver transaminases, treatment discontinuation due to toxicity, dose reduction due to toxicity, OS (Overall Survival),patient status (death).

Statistical Data Analysis

The results of the statistical analysis of categorical data are presented in tables as absolute and relative frequencies, while numerical data are displayed as mean ± standard deviation (for parametric data) or as median and interquartile range (for non-parametric data). The significance of differences in categorical data was tested using the χ^2 test or Fisher's exact test, and for numerical data using the Student's t-test for independent samples and one-way ANOVA test (for parametric data) or the Mann-Whitney test and Kruskal-Wallis test (for non-parametric data). Statistical analysis of the collected data was conducted using IBM SPSS Statistics software (version 25.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA). Differences between groups were considered statistically significant for $p < 0.05$.

RESULTS

No statistically significant difference in therapy response was found between patients who received CDK 4/6 inhibitors in four different therapeutic lines (Table 1).

Table 1. Comparison of therapy response between patients who received CDK 4/6 inhibitors in different therapeutic lines.

Best Response	**First Line**	**Second Line**	**Third Line**	**Fourth Line**	**χ^2**	**p***
Progression of disease	3 (7.0%)	1 (7.7%)	1 (14.3%)	1 (50.0%)	7.629	0.608
Stable disease	15 (34.9%)	4 (30.8%)	3 (42.9%)	0 (0.0%)		
Partial regression	24 (55.8%)	7 (53.8%)	3 (42.9%)	1 (50.0%)		
Complete response	1 (2.3%)	1 (7.7%)	0 (0.0%)	0 (0.0%)		

Fisher's exact test

Patients who received CDK 4/6 inhibitors in the first and second lines had statistically significantly longer overall survival compared to patients who received the treatment in the third and fourth lines (Table 2).

Table 2. Comparison of overall survival between patients who received CDK 4/6 inhibitors in different therapeutic lines.

	Therapeutic line									
Overall survival	first		second		third		fourth		χ^2	p*
	n	%	n	%	n	%	n	%		
yes	36	83,7	11	84,6	3	28,6	0	0,0	13,580	**0,001**
no	7	16,3	2	15,4	5	71,4	2	100,0		

**Fisher's exact test*

No statistically significant difference in treatment response was observed between patients receiving palbociclib and those receiving ribociclib (Table 3).

Table 3. Comparison of treatment responses between patients receiving two different CDK 4/6 inhibitors.

	CDK 4/6 inhibitor					
	palbociklib		ribociklib		χ^2	p*
Best response	n	%	n	%		
Disease progression	3	9,1	3	9,4		
Stable disease	12	36,4	10	31,4	1,927	0,671
Partial regression	18	54,5	17	53,1		
Complete response	0	0,0	2	6,3		

**Fisher's exact test*

There was no statistically significant difference in overall survival between patients
treated with palbociclib and those treated with ribociclib (Table 4).

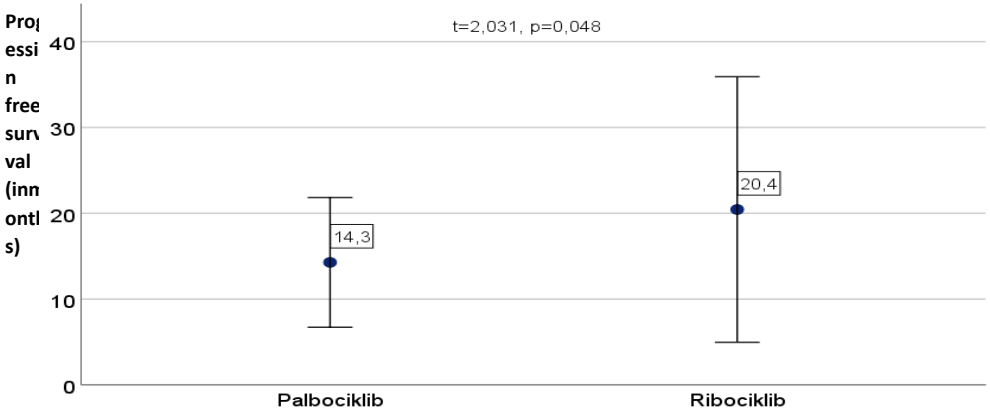
Table 4. Comparison of overall survival between patients treated with two different CDK 4/6 inhibitors.

	CDK 4/6 inhibitor					
Overall survival	palbociklib		ribociklib		χ^2	p*
	n	%	n	%		
yes	25	75,8	24	75,0	0,005	1,000
no	8	24,2	8	25,0		

** Fisher's exact test*

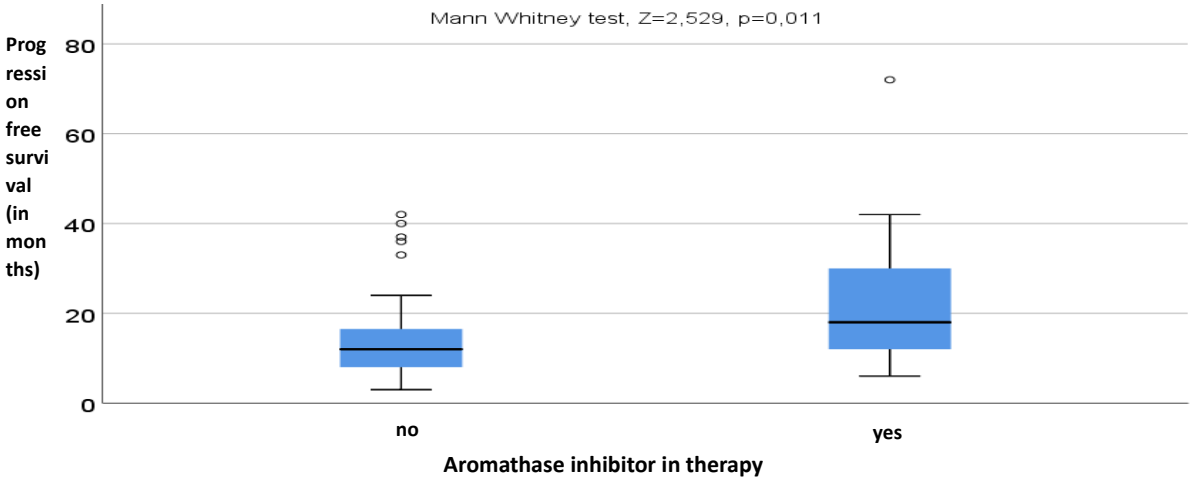
Patients receiving ribociclib had a statistically significantly higher PFS compared to patients receiving palbociclib (Figure 1). There was no statistically significant difference in OS (t-test, t=0.656, p=0.514) between patients receiving palbociclib (24.6 ± 20.8) and those receiving ribociclib (28.5 ± 26.4).

Figure 1. Comparison of progression-free survival between patients receiving two different CDK 4/6 inhibitors.



Patients who received a CDK 4/6 inhibitor along with a second aromatase inhibitor had a statistically significantly higher PFS compared to patients who did not receive a second aromatase inhibitor (Figure 2).

Figure 2. Comparison of progression-free survival between patients receiving a CDK 4/6 inhibitor along with a second aromatase inhibitor.



The statistically significant majority of patients on CDK 4/6 inhibitor therapy did not experience side effects (Figure 3).

Figure 3. Comparison of the number of patients with and without side effects caused by CDK 4/6 inhibitor therapy.

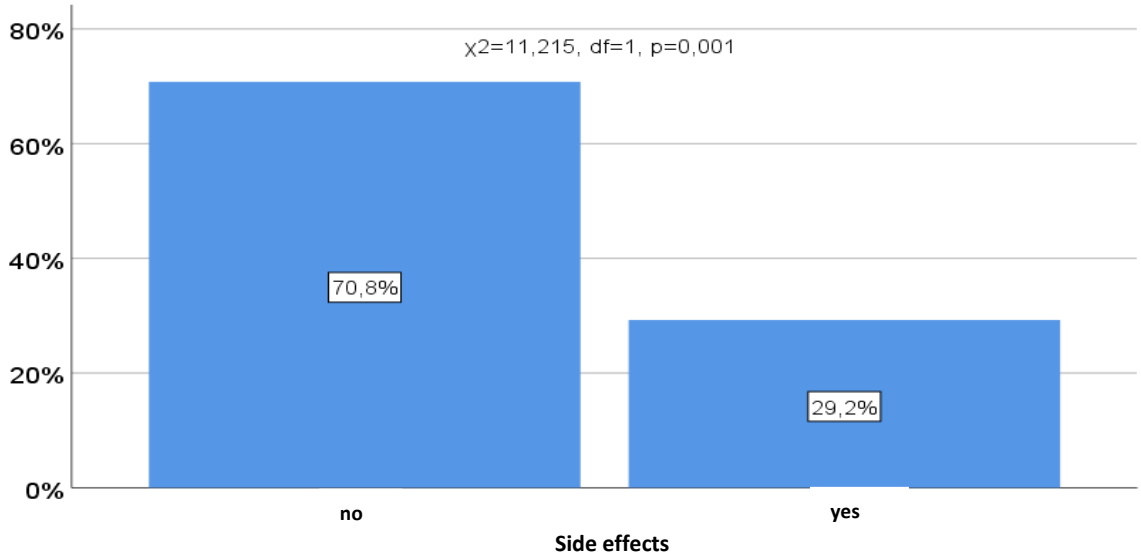


Table 5 shows the frequency of side effects experienced by patients in the study. Hematological toxicity was the most commonly recorded. We could not statistically calculate the differences between individual side effects, as the distribution of side effects among the patients was uneven, i.e., in the patients of this study, not only one type of side effectwas recorded, but multiple or none at all.

Table 5. Overview of side effects experienced by patients in the study.

Side effects	n	%
Hematological toxicity	18	27,6
Elevated liver transaminases	1	1,53
Discontinuation of therapy due to toxicity	14	21,5
Dose reduction due to toxicity	18	27,7
Neutropenia	16	24,6
Trombocytopenia	4	6,2
Other	2	3,1

We also compared the number of specific side effects during the use of different CDK 4/6 inhibitors. Since there was no statistically significant difference in the occurrence of any individual side effect between the two drugs, those results were not presented.

There was no statistically significant difference in the age at which metastatic disease was confirmed and the age at which treatment was started between surviving and deceased patients (Table 6).

Table 6. Comparison of the age at which metastatic disease was confirmed and the age at which treatment was started between surviving and deceased patients.

	Death				t	p
	yes (n=16)		no (n=49)			
	x̄	SD	x̄	SD		
The age at which metastatic disease was confirmed	57,75	10,847	61,92	10,352	1,382	0,172
The age at which treatment with CDK 4/6 inhibitors began	60,2	10,847	62,37	10,319	0,704	0,484

DISCUSSION

Statistical analysis of the data from this study revealed that there was no statistically significant difference in the response to therapy (PFS) between patients who received CDK 4/6 inhibitors in four different therapeutic lines. However, a statistically significant difference in OS was found between patients who received CDK 4/6 inhibitors in different therapeutic lines, partially confirming the hypothesis of this study. Patients treated with CDK 4/6 inhibitors in the first and second lines of treatment had statistically significantly longer survival compared to those who started treatment with this therapy in later lines. Additionally, as we anticipated, the majority of patients did not experience side effects during treatment with CDK 4/6 inhibitors.

Studies that have established CDK 4/6 inhibitors as the first therapeutic option in patients with metastatic hormone receptor-positive, HER2-negative breast cancer have shown a benefit for this therapy regarding PFS and OS (9, 10-12). As noted, our study confirmed this for OS, but not for PFS. This may be explained by the small sample size, short follow-up period, and variability in treatment response among the patients.

It is important to emphasize once again that the hypothesis was confirmed that the majority of patients would not experience side effects during treatment with CDK 4/6 inhibitors. Also, among the most frequently reported side effects, neutropenia was the most common, which aligns with results from previous studies (9, 11-12).

Regarding other results, it should be noted that PFS was statistically significantly higher in patients who received ribociclib compared to those who received palbociclib, although no such difference was observed for OS.

As for other studies on this topic, a similar study conducted in Italy investigated PFS and OS in patients treated with endocrine therapy and various CDK 4/6 inhibitors. It was found that ribociclib showed a statistically significant improvement in OS, but palbociclib did not. We can observe that the results of our study differ from those of the study conducted in Italy. The heterogeneity test suggests that the different OS results among the different CDK 4/6 inhibitors could be explained by chance (10).

The limitations of this study include a small number of participants, a short follow-up period, and the single-center nature of the study, all of which should be considered when analyzing and interpreting the data obtained.

To obtain more detailed results, future studies will require prospective research with a larger number of participants, as well as the inclusion of patients from multiple centers (i.e., multicenter studies) to reduce bias and increase the general applicability of the results.

It would also be very important to investigate how CDK 4/6 inhibitor therapy affects tumor biology to identify biomarkers of resistance and optimize therapy. Special attention should be paid to the molecular characterization of tumors before and after the use of CDK inhibitors. Understanding the molecular mechanisms of intrinsic and acquired resistance could present a new approach in the application of CDK 4/6 inhibitors.

In conclusion, we can say that this study confirmed the hypothesis that OS is significantly higher in patients who started therapy with CDK 4/6 inhibitors in the first and second lines of treatment, compared to those who started the therapy in later lines. This was not confirmed for PFS. Additionally, the majority of patients did not experience side effects during treatment, confirming that this is a well-tolerated therapeutic option.

All these results show and confirm that CDK 4/6 inhibitor therapy is a safe and optimal treatment strategy for patients with metastatic hormone receptor-positive, HER2-negative breast cancer, and that earlier inclusion of this therapy certainly contributes to improving the quality

of life, delaying the use of more toxic therapeutic options such as chemotherapy, and having an overall positive impact.

CONCLUSION

In this study, there was no statistically significant difference in response to therapy regarding PFS between patients who received CDK 4/6 inhibitors in four different therapeutic lines. However, a statistically significant difference in OS was found, i.e., patients who received this therapy in the first and second lines of treatment had longer survival compared to those who received therapy in later lines, partially confirming the hypothesized hypothesis.A statistically significant majority of patients on CDK 4/6 inhibitor therapy did not experience side effects, thus confirming the hypothesis.

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Research article

PHENOLOGICAL OBSERVATION OF ALLERGIC PLANTS AND IMPACT ON HEALTH

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SUMMARY

Background: *For the last 40 years, allergies have been presented as diseases of modern lifestyle, which affect more and more people. Furthermore, they are becoming an increasing social problem, burdening society economically, through absence from work, school, daily activities, but also through treatment costs. Allergies are becoming a reason for difficult social contact for an increasing number of people.*

Subjects and methods: *The materials used are the results of laboratory research and data collected during 2021, 2022 and 2023 from patients allergic to pollen at the Mostar Health Center. The Microsoft Excel 2013 software system was used to process the results.*

Results: *The most common disease during 2021, 2022 and 2023 in the city of Mostar was vasomotor and allergic rhinitis, followed by rhinitis, nasopharyngitis and pharyngitis. The age group from 19 to 64 years was most susceptible to these diseases, and the age group from 7 to 14 years had a high percentage of these diseases. The other age groups studied did not stand out in terms of the frequency of the disease in any of the diseases.*

Conclusion: *The research found that the most common disease during 2021, 2022 and 2023 was vasomotor and allergic rhinitis. The use of the globe protocol can help people suffering from pollen allergies. When monitoring phenological changes, no major deviations in the occurrence of leafing and flowering were found, except for the church grass, which is high in June. All other grasses had moderate concentrations during 2021, 2022 and 2023. There is a connection between the time of appearance of allergens in the air (spring) and the appearance of allergy symptoms.*

Keywords: *Rhinitis, nasopharyngitis, pharyngitis, Allergies, Allegic plant*

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INTRODUCTION

The term allergy was first mentioned in 1906 as a “specifically altered reaction of the organism” (Ring, 2014). As air pollution continuously and long-term affects the health of the population, especially the urban population, it has become an increasingly important public health problem in today's civilized environment. Urbanization and increased emissions of exhaust gases are associated with an increase in the frequency of allergic respiratory diseases caused by the most powerful natural allergenic pollen. Since these are the most widespread diseases of today, i.e. pollen allergies, and pollen is transmitted through the air and as such is the main source of respiratory diseases. The main source of allergenic pollen in our area are woody plants. Most woody plants that bloom from February to May are characterized by a short but very intense pollination period, during which high and very high pollen concentrations in the air are reached, especially in March and April when pollination is most intense. This is followed by a long flowering period of grasses, from April to September. Allergies to multiple pollen types are becoming more common, while a small percentage of people are allergic to only one type of pollen. Pollination by plants from three botanical groups: trees, grasses, and weeds is important for the development of allergic diseases (Bulat –Kardum, 2013).

Despite differences in the frequency, intensity, and structure of allergies in different countries, the incidence and prevalence of allergic diseases, including allergic

asthma, rhinitis, and conjunctivitis, have shown an increasing trend in recent decades (Subbarao et al. 2009). Over the past 40 years, allergies have emerged as diseases of modern lifestyles, affecting more and more people. There is no single explanation for the dramatic increase in these diseases that has been recorded since the second half of the 20th century. Allergies are no longer just a problem in industrialized countries; atopic eczema and severe forms of asthma are also common in developing countries. Furthermore, they are becoming an increasingly serious social problem, burdening society economically, through absenteeism from work, school, and daily activities, as well as through medical costs. Furthermore, they are becoming a reason for the difficulty of social contact for an increasing number of people.

Human health is directly affected by weather and climate. Changes in the phenological cycle of plants affect the frequency and severity of allergic diseases, as plant responses to climate change are also reflected in changes in plant growth, distribution, yield, and the length of the pollination season. Experts predict a further increase in allergic problems due to air pollution, climate change, changes in society's eating habits, exposure to cigarette smoke, and the increasing use of antibiotics. All of these environmental changes also affect the amount of pollen in the air and plant pollination, the length of flowering, and the spread of weed species, especially ragweed, which is a highly allergenic plant (Hrga et Stjepanović 2013).

According to the World Health Organization (WHO), as many as 300-400 million people suffer from symptoms of pollen allergy. Pollen allergy is linked to genetic predisposition and environmental factors, and occurs during the pollination period of the causative agent, most often from spring to autumn, and sometimes persists throughout the year. An allergen (plural allergens) is any substance that the body recognizes as foreign and potentially harmful, and against which it creates specific antibodies. There is a wide range of allergens that can be divided into groups according to their source: aeroallergens, food allergens, drugs, animal venoms or insect stings, contact allergens and occupational allergens. If one parent has some form of respiratory allergy, in 20-40% of cases the child will be faced with allergy symptoms. Twelve percent of children with no family history of allergies, 30% to 50% of children with allergies from one parent, and 60% to 80% of children with allergies from both parents can develop allergic disease (Ownby, 1990).

Pollen allergy is a hypersensitive reaction of the immune system to otherwise harmless substances (pollen) that we inhale or come into direct contact with. When the body is exposed to an allergen for the first time, immune cells called macrophages are activated, which transmit information about the first contact with the allergen to B lymphocytes. These cells mature into plasma cells and produce specific IgE that bind to mast cells (in the mucous membranes) and basophils (in the blood). Other immune cells - T lymphocytes - store information about the allergen. This phase is called sensitization and passes without visible symptoms. The period between the first contact with the allergen and the manifestation of allergy symptoms upon re-exposure can occur even after 10 years (Galli et al. 2008). The second phase of a true allergic reaction occurs upon re-exposure to the allergen (antigen). Specific IgE on cells (e.g. mast cells) are activated and bind allergens, which stimulates cell degranulation by releasing (histamine, heparin, carboxypeptidase A, tryptase, chymase, cathepsin G, etc.) and synthesizing prostaglandins, leukotrienes and cytokines that result in the appearance of various symptoms.

In the later stages of the allergic reaction (after 3-6 hours), eosinophils, basophils and Th2 lymphocytes are activated. Due to constant exposure to the allergen, activation of Th2 lymphocytes, production of eosinophils, immunoglobulin IgE and other specific factors, chronic forms of the disease may occur (eg chronic rhinitis, chronic asthma) (Galli et al. 2008). The diagnosis of pollen allergy is based on history, specific clinical picture and diagnostic tests. In assessing a person's allergic status, laboratory tests are also indispensable: skin allergy testing for inhalation allergens (in some cases also for individual types of pollen); number of eosinophils in blood, nasal swab and sputum (cough); total and specific IgE; determination of eosinophil cationic protein (ECP). For the past thirty years, skin-prick testing (SPT) has been used in skin allergy testing for inhalant allergens. It is more specific, less painful, cheaper and correlates better with bronchoprovocation tests than the previously used intradermal test. In the diagnosis of allergic asthma in adults and children (older than 5 years), in addition to the above tests, spirometry and measurement of peak flow (PEF) and measurement of nitric oxide concentration in exhaled air are used. These methods provide insight into lung capacity, airway flow and the occurrence of airway narrowing. Sometimes, radiological findings of the lungs and paranasal sinuses are also performed for more detailed diagnostics.

In order for a particular plant species to be considered an allergen, it must meet 3 essential conditions (Coca et al. 1932):

1) must be pollinated by the wind - Plants that are pollinated by the wind (anemophilous plants) are the most common cause of allergic reaction symptoms. Their pollen is carried by the wind for kilometers and lifted up to 2-3 meters in height, since it is very dry and small (30-35 μm) and therefore light. The wind carries the male gametes in pollen grains to the pistil of the female flower of the same species, where the female gamete is. Plants that are pollinated by insects (entomophilous plants) are much less likely to cause allergic reactions because their

pollen has a sticky surface and is therefore more difficult to fly through the air.

2) must produce pollen in large quantities - In order for pollination to occur in anemophilous plants, the pollen must accidentally hit the pistil of the egg cell of another plant, and therefore significantly more pollen is needed for wind pollination, which is smaller and more aerodynamic, which facilitates dispersal over greater distances. On the other hand, entomophilous plants produce much less pollen because they are pollinated by insects that transfer pollen much more precisely.

3) pollen must have allergenic properties - The structure of the pollen grain must contain allergenic compounds that will cause an allergic reaction when they come into contact with the mucous membrane.

Late winter (February) and spring (May) are the times when trees bloom and their pollen appears in the air. Late spring (May) and early summer (July) are the times when grasses bloom and their pollen is dominant in the air, while late summer (July) and early autumn (September) are when weeds bloom and their pollen concentration in the air is highest (Maleš, 2006). The morphology of plants and pollen grains is adapted to the mode of transport. Simpler-looking plant species are pollinated by amenophily (by wind) and produce large quantities of pollen grains, making them the main source of aeroallergens. In Europe, the pollination season lasts from spring to autumn. Weather conditions affect the beginning and duration of the pollination season. Dry and warm weather during flowering promotes a higher concentration of pollen grains in the air, while the concentration is lower during cold and rainy weather (Trkulja et al. 2009).

Aeroallergens are divided according to their location:

1. indoor (dust mites, cockroaches and their secretions, hair, epithelium and secretions of mammals, damp spaces - mold spores) - are related to human activity in the apartment, house or at work, are often year-round or have an extended annual duration
2. outdoor (pollen, fungal spores and mold) - are related to natural sources and partly to products of human activity, occur regionally, depending on the flora and fauna, and their period of distribution and prevalence in the air is usually seasonal (Ostojić et al. 1992).

For patients whose complaints make everyday activities difficult and reduce their quality of life, information about the movement of pollen allergens, i.e., pollen concentrations in the air and their variations, is of utmost importance. Such answers can be provided by aerobiological research conducted daily throughout the year. The analysis of these results includes meteorological parameters that have the greatest influence on pollen concentrations in the air, such as: air temperature and humidity, precipitation, and wind speeds and directions, and in addition to pollen forecasts and weather forecasts (Maleš et Topovec 2005).

By measuring the concentration and determining the type of pollen in 〖1m〗^3 of air in an area, the dynamics of pollination and the distribution of vegetation are monitored. Based on this information, a pollen calendar is created. It differs from year to year, because it depends on meteorological parameters (temperature, wind, precipitation, etc.), climate changes and environmental factors. In 1986, the European Aeroallergen Network (EAN) database was established in Vienna, which collects data on pollen concentrations from the so-called "monitoring units", located in almost all European countries. From there, data on the occurrence, types and concentration of pollen in the air are sent weekly to national centers, which forward the data to the European coordination center (Durmić, 2014). Pollen allergens are divided into 29 protein families, the most important of which are: profilins, calcium-binding proteins, beta-expansins, Bet v 1 homologs, lipid-transfer proteins, etc. There are hypothetical claims about the possibility of pollen grains bursting due to osmotic shock (during storms and thunderstorms). Submicrobial fragments and/or released starch grains can be carriers of allergens and cause asthma attacks.

SUBJECTS AND METHODS

The materials used were the results of laboratory research and data collected during 2021, 2022 and 2023 from patients allergic to pollen at the Mostar Health Center.

Over the course of three years (2021, 2022 and 2023), pollen monitoring in the air was conducted in the city of Mostar. The monitoring was conducted at the Faculty of Agronomy and Food Technology, University of Mostar. Phenological research for allergenic plants was organized according to literature data and the GLOBE server. The laboratory part of the work was carried out in the Laboratory for Biology and Applied Biology, Faculty of Agronomy and Food Technology, University of Mostar.

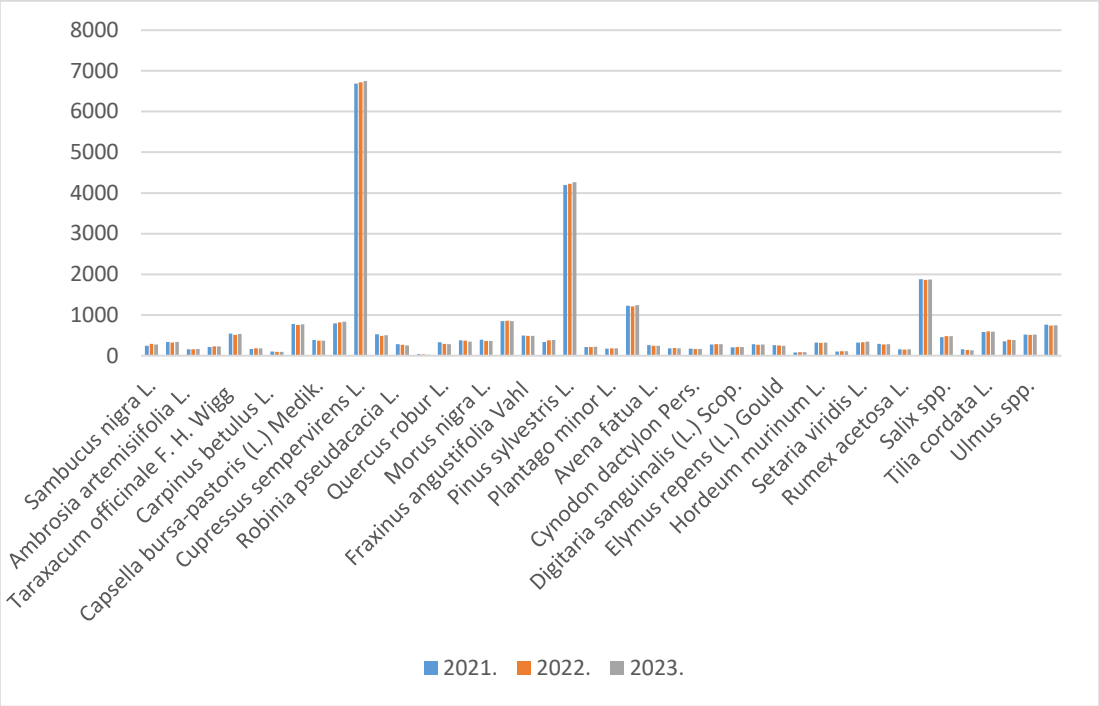
RESULTS

By collecting and analyzing data in the city of Mostar during 2021, 2022 and 2023, different types of pollen grains in the air were identified, dominated by grass, weed, cypress and pine pollen. The allergenic properties of different plant species vary from weak to strong. (Table 1).

Table 1. Pollen prevalence in the city of Mostar for 2021, 2022 and 2023

Type	Family	2021.	2022.	2023.	Allergic potential
Sambucus nigra L.	*Adoxaceae*	240	287	272	Low
Amaranthus retroflexus L.	*Amaranthaceae*	341	320	336	Mild
Ambrosia artemisiifolia L.	*Asteraceae*	160	155	163	Very high
Artemisia absinthium L.	*Asteraceae*	209	225	230	Very high
Taraxacum officinale F. H. Wigg	*Asteraceae*	540	511	538	Low
Alnus spp.	*Betulaceae*	165	177	182	Mild to high
Carpinus betulus L.	*Betulaceae*	102	98	96	High
Corylus avellana L.	*Betulaceae*	780	753	767	Mild to high
Capsella bursa-pastoris (L.) Medik.	*Brassicaceae*	386	370	367	Low
Chenopodium album L.	*Chenopodiaceae*	796	820	831	Low to mild
Cupressus sempervirens L.	*Cupressaceae*	6690	6720	6751	Low to mild
Juglans regia L.	*Juglandaceae*	524	490	502	Low to mild
Robinia pseudacacia L.	*Fabaceae*	279	266	254	Low
Castanea sativa L.	*Fagaceae*	36	28	25	Mild to high
Quercus robur L.	*Fagaceae*	328	294	285	Mild
Morus alba L.	*Moraceae*	381	367	349	Low
Morus nigra L.	*Moraceae*	392	360	358	Low
Fraxinus excelsior L.	*Oleaceae*	849	854	850	Mild to high
Fraxinus angustifolia Vahl	*Oleaceae*	496	490	485	Mild to high
Olea europaea L.	*Oleaceae*	338	374	386	Mild
Pinus sylvestris L.	*Pinaceae*	4193	4225	4267	Low
Plantago major L.	*Plantaginaceae*	216	211	220	Low to mild
Plantago minor L.	*Plantaginaceae*	170	184	182	Low to mild
Platanus spp.	*Platanaceae*	1223	1208	1240	Mild
Avena fatua L.	*Poaceae*	260	243	240	Very high
Bromus erectus Huds.	*Poaceae*	180	185	184	Very high
Cynodon dactylon Pers.	*Poaceae*	175	168	164	Very high
Dactylis glomerata L.	*Poaceae*	277	284	279	Very high
Digitaria sanguinalis (L.) Scop.	*Poaceae*	204	213	215	Very high
Echinochloa crus-galli (L.) P.Beauv.	*Poaceae*	284	265	274	Very high
Elymus repens (L.) Gould	*Poaceae*	257	249	246	Very high
Hordeum bulbosum L.	*Poaceae*	81	86	85	Very high
Hordeum murinum L.	*Poaceae*	321	315	320	Very high
Secale cerale L.	*Poaceae*	102	106	112	Very high
Setaria viridis L.	*Poaceae*	324	330	346	Very high
Reynoutria japonica Houtt.	*Polygonaceae*	289	273	281	Mild
Rumex acetosa L.	*Polygonaceae*	154	148	156	Mild
Populus spp.	*Salicaceae*	1879	1865	1872	Low
Salix spp.	*Salicaceae*	457	479	480	Low
Acer campestre L.	*Sapindaceae*	154	140	137	Low to mild
Tilia cordata L.	*Tiliaceae*	581	594	590	Low
Tilia platyphyllos L.	*Tiliaceae*	352	394	386	Low
Ulmus spp.	*Ulmaceae*	520	510	517	Mild
Urtica dioica L.	*Urticaceae*	764	740	748	Low

During 2021, 2022 and 2023, the most prevalent pollen in the city of Mostar was cypress, pine, poplar, platinum, grass and weed pollen. Pollen concentration is variable, but according to the results, it can be seen that the results did not differ much and the pollen concentration was approximately similar from year to year (Graph 1).



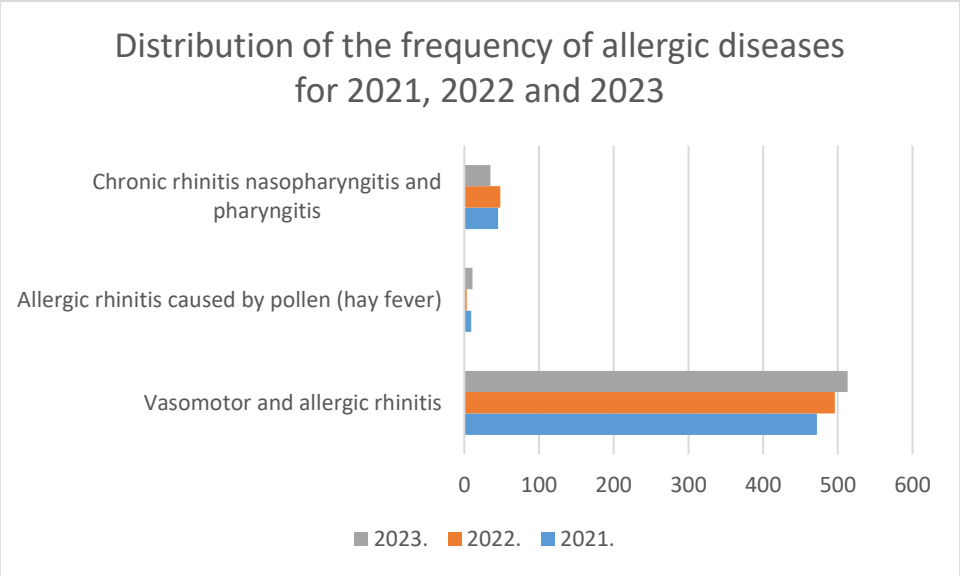
Graph 1. Prevalence of pollen grains of different plants in the city of Mostar

Based on the data obtained for the city of Mostar, a breakdown was made by types of allergic diseases (Table 2).

Table 2. Types of diseases for 2021, 2022 and 2023

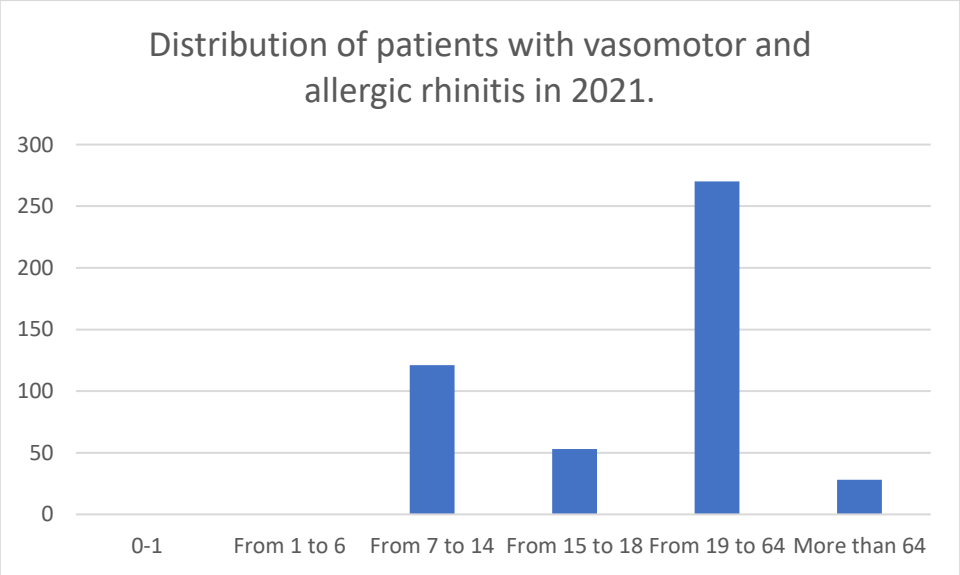
	2021	2022	2023	TOTAL
Vasomotor and allergic rhinitis	472	496	513	**1481**
Allergic rhinitis caused by pollen (hay fever)	9	3	11	**28**
Chronic rhinitis, nasopharyngitis and pharyngitis	45	48	35	**128**

The most common disease in the city of Mostar was vasomotor and allergic rhinitis, which was experienced by 513 people (35%) in 2023, 496 people (33%) had a problem with this disease in 2022, and 472 people (32%) had a problem with vasomotor and allergic rhinitis in 2021. During 2023, 35 people suffered from chronic rhinitis, nasopharyngitis and pharyngitis, which is less than in 2022 when there were 48 patients in the city of Mostar, as well as in 2021 when there were 45 patients. Allergic rhinitis caused by pollen (hay fever) was present in 11 people in 2023, while it was poorly represented in 2022, with three patients in the city of Mostar, and in 2021, the prevalence of this disease was nine people (Graph 2).



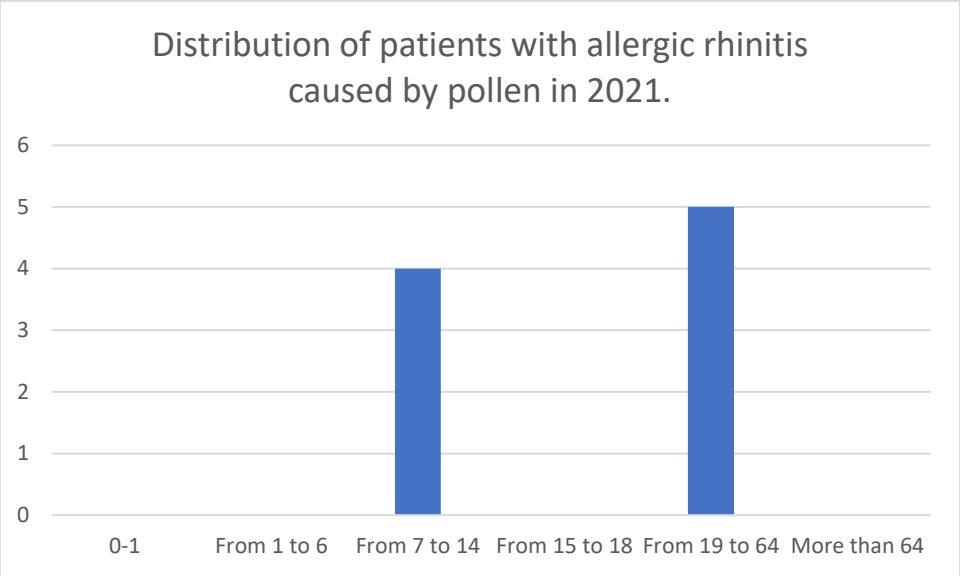
Graph 2. Distribution of the frequency of allergic diseases for 2021, 2022 and 2023.

The age group most susceptible to vasomotor and allergic rhinitis during 2021 was from 19 to 64 years old with 57% of sufferers, sufferers from 7 to 14 years old were represented by 26%, the age group from 15-18 years old had a representation of 11%, and in the group of sufferers over 64 years old the percentage was 6% (Graph 3).



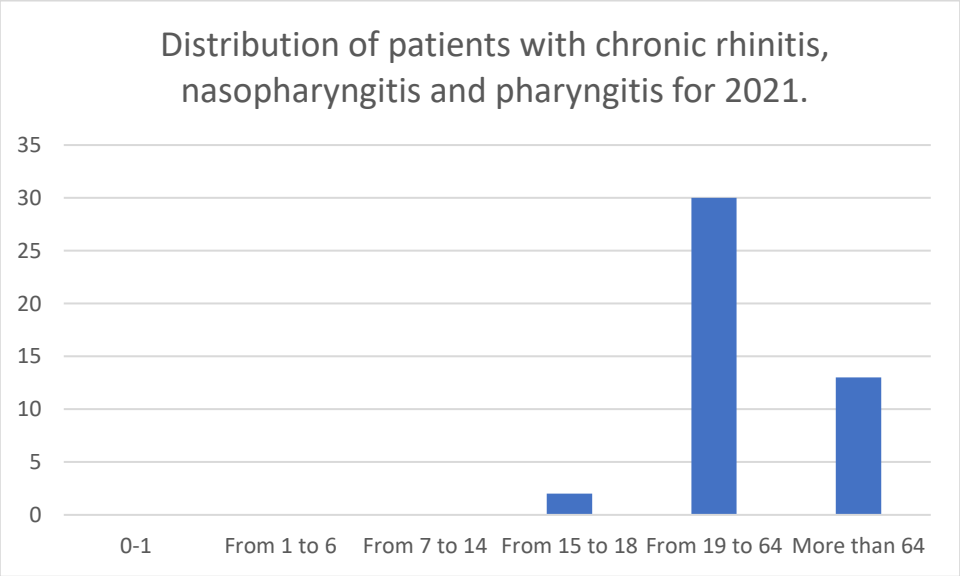
Graph 3. Age distribution of patients with vasomotor and allergic rhinitis for 2021

During 2021, the most susceptible age group of patients with allergic rhinitis caused by pollen was from 19 to 64 years old with 56% of patients, patients from 7 to 14 years old were represented by 44%, other age groups did not have this type of disease for 2021 (Graph 4).



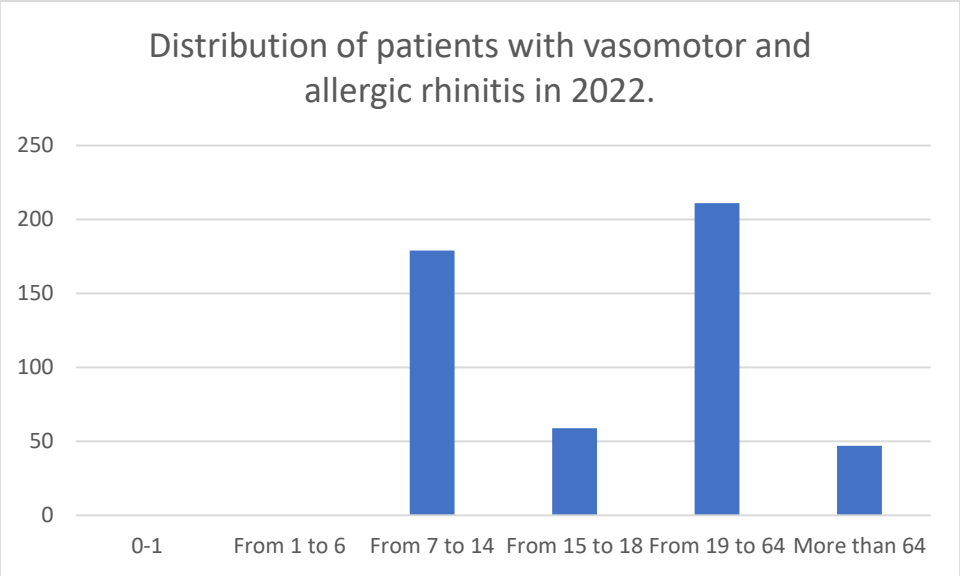
Graph 4. Age distribution of people suffering from allergic rhinitis caused by pollen in 2021

The age group from 19 to 64 years during 2021 was most susceptible to chronic rhinitis, nasopharyngitis and pharyngitis with 67% of sufferers, 29% of sufferers were older than 64 years, and the age group from 15 to 18 years had 4% of sufferers (Graph 5).



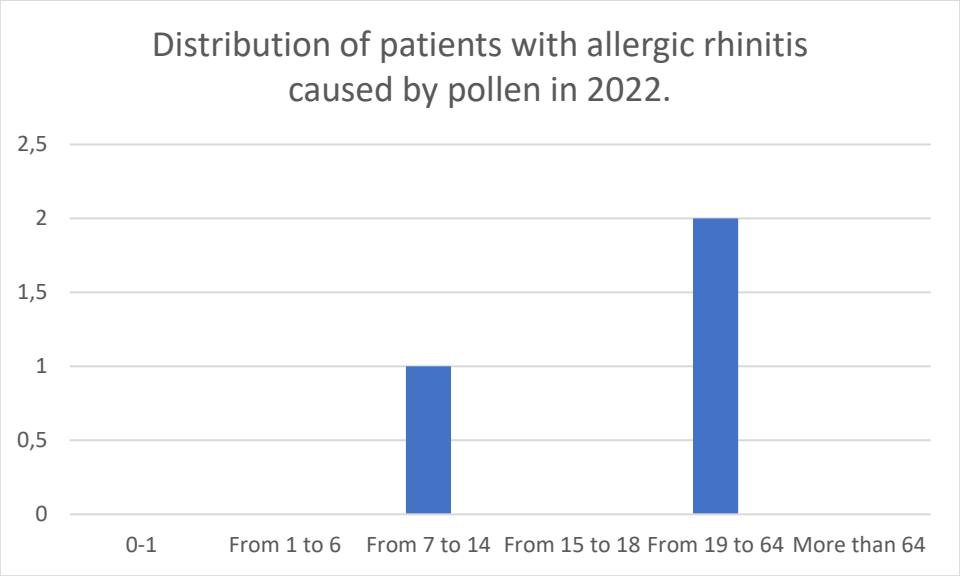
Graph 5. Age distribution of patients with chronic rhinitis, nasopharyngitis and pharyngitis for 2021

During 2022, the most susceptible age group of patients with vasomotor and allergic rhinitis was from 19 to 64 years old with 43% of patients, patients from 7 to 14 years old were represented by 36%, the age group from 15 to 18 years old had 12% of patients, while people older than 64 years were represented by 9% of patients (Graph 6).



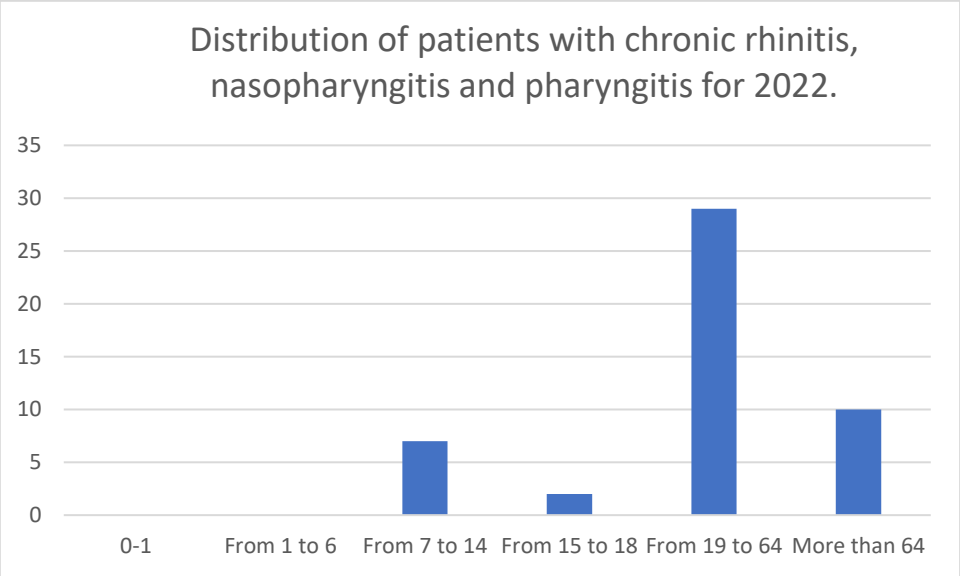
Graph 6. Age distribution of patients with vasomotor and allergic rhinitis for 2022

Patients with allergic rhinitis caused by pollen for 2022 were again in the age group of 19 to 64 years with two patients and one patient belonging to the age group of 7 to 14 years (Graph 7).



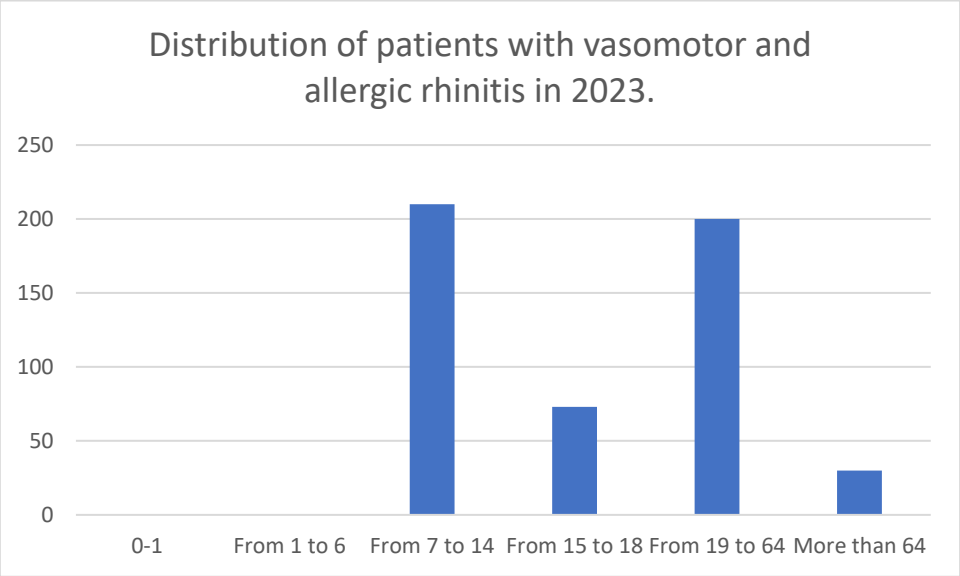
Graph 7. Age distribution of allergic rhinitis patients caused by pollen in 2022

The age group from 19 to 64 years during 2022 was the most susceptible to chronic rhinitis, nasopharyngitis and pharyngitis with 60% of patients, 21% of patients were older than 64 years, and the age group from 7 to 14 years had 15% of patients. The age group from 15 to 18 years had a low representation with 4%, while children under 7 years of age did not show symptoms of this disease (Graph 8).



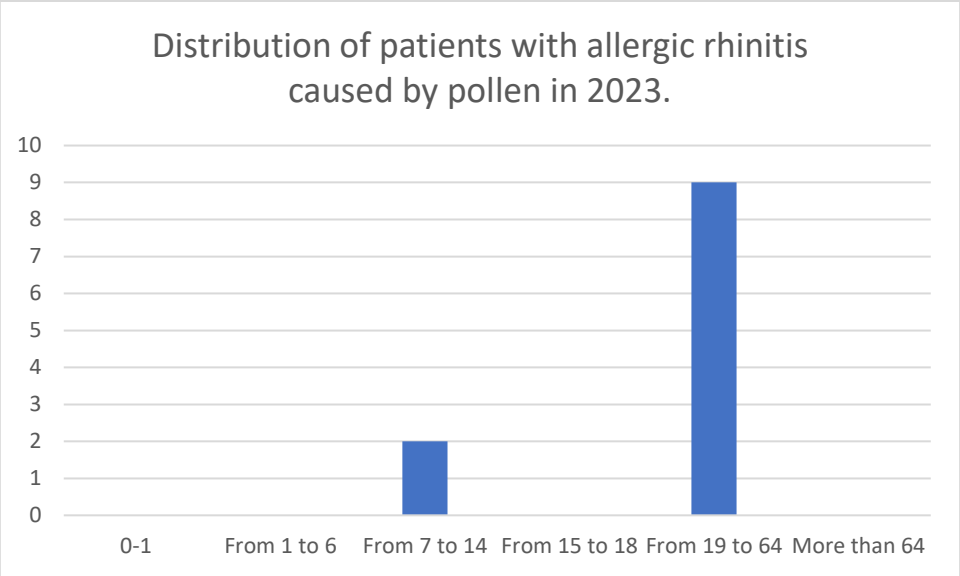
Graph 8. Age distribution of chronic rhinitis, nasopharyngitis and pharyngitis sufferers in 2022

The age group from 7 to 14 years had the most problems with vasomotor and allergic rhinitis in 2023 with 41%, followed by the age group from 19 to 64 years with 39% of sufferers. The age group from 15 to 18 years had 14% of sufferers, and sufferers older than 64 years accounted for 6% (Graph 9).



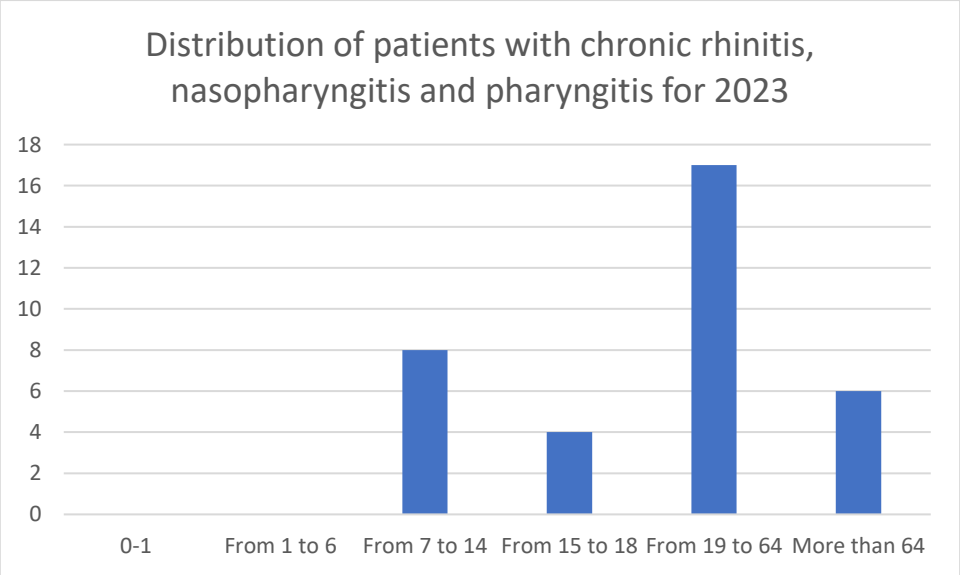
Graph 9. Age distribution of patients with vasomotor and allergic rhinitis for 2023

The largest number of patients with allergic rhinitis caused by pollen for 2023 was in the age group 19-64, 82% of them, followed by those in the age group 7 to 14 with 18% of patients (Graph 10).



Graph 10. Age distribution of patients with allergic rhinitis caused by pollen for 2023

The highest percentage of patients with chronic rhinitis, nasopharyngitis and pharyngitis was in the age group 19 to 64 years, 49%, the age group 7 to 14 years with 23% of patients. Those older than 64 years were represented with 17%, while the lowest number of patients was in the age group 15-18 years, 11% (Graph 11).



Graph 11. Age distribution of patients with chronic rhinitis, nasopharyngitis and pharyngitis for 2023

DISCUSSION

The results of the study showed that the most common disease in the city of Mostar during 2021, 2022, 2023 was vasomotor and allergic rhinitis.

The age group from 19 to 64 years was most susceptible to vasomotor and allergic rhinitis, allergic rhinitis caused by pollen, and chronic rhinitis, nasopharyngitis, and pharyngitis during the three years of follow-up. Allergic rhinitis is often accompanied by other diseases associated with hypersensitivity. This primarily refers to allergic conjunctivitis, which occurs in slightly less than half of patients with allergic rhinitis. 20-40% of patients with allergic rhinitis have asthma, and 70-90% of patients with asthma have allergic rhinitis (Bayar Muluk, 2019). Senile rhinitis or rhinitis in the elderly is a condition that affects people over 65 years of age, and is characterized by clear rhinorrhea with the presence of pathology of the nasal mucosa Papadopoulos et al. 2019). The pathophysiology of rhinitis in the elderly is not fully understood, but it is associated with cholinergic hyperreactivity (Tran et al. 2015). Due to its cholinergic basis, this disease responds well to anticholinergic therapy such as ipratropium bromide. The immune system has a perfect memory and every time it comes into contact with a substance to which it is allergic, an allergic reaction occurs. Most

often, harmless reactions occur on the nasal mucosa in the form of sneezing and watery discharge, but sometimes a potentially fatal reaction, anaphylactic shock, can occur. (Popović-Grle, 2007).

Plants that were observed during 2021, 2022, 2023 in the city of Mostar are: pines, cypresses, poplars, plane trees, elms, hazel, ash, alder, hornbeam, grasses, olives, sorrel.

In addition to these plants, ragweed also occurs, its concentration is moderate in early September but its pollen has a very high allergic potential and causes problems in humans and animals (Laaidi, 2003). Grass pollen is moderate in June and July. Grass pollen (*Poaceae*) is also the most common allergen causing allergic rhinitis and conjunctivitis. In the Netherlands and France, more than 80% of allergic individuals are sensitive to their pollen (Weeke et Spieksma 1991). Some grass species show strong cross-reactivity between allergens on pollen structures (Singh et Kumar 2003). *Cuppresus sempervirens* is highly prevalent, which is often grown as a horticultural product and planted as an ornament in urban green spaces (Agea et al. 2002). Urban cultivation contributes to the spread of large amounts of allergenic pollen, so exposure to cypress pollen has been steadily increasing in recent decades. Cypress trees produce pollen in large quantities, with measured allergenic potential, and pollen is most often present from January to the end of June. The first cases of rhinoconjunctivitis caused by cypress pollen were described in 1945 in South Africa and in 1962 in France (Odman, 1945; Panzani 1962). An ecological study was conducted in cities in central Italy that confirmed a direct link between allergenic flora and urban characteristics of cities, concluding that urban phytoallergic potential depends on the geographical location of the city, the type and duration of human influence in correlation with the ecological conditions of the individual city, and on the layout of urban areas and the ecosystem of the surrounding area (Ciferri et al. 2009). It is important to emphasize that weather conditions affect the beginning and duration of the pollination season. Dry and warm weather during flowering promotes a higher concentration of pollen grains in the air, while the concentration is lower during cold and rainy weather (Trkulja et al. 2009).

According to these data, people aged 19 to 64 should carefully monitor the pollen calendar. For patients whose symptoms make everyday activities difficult and reduce their quality of life, information about the movement of pollen allergens, i.e. pollen concentrations in the air and their variations, is of utmost importance. Aerobiological studies conducted daily throughout the year can provide such answers. The analysis of these results includes meteorological parameters that have the greatest influence on pollen concentrations in the air, such as: air temperature and humidity, precipitation, and wind speed and direction (Maleš et Topovec 2005). Meteorological conditions accompanied by variations in temperature, air humidity, wind direction and strength, insolation, and precipitation (fog, rain) significantly affect the occurrence of pollen in the air (pollination). At optimal temperatures (18-20°C) and humidity (70-75% relative humidity), a large number of pollen grains are explosively released, which is especially noticeable in grasses and species from the Betulaceae, Pinaceae, Salicaceae, Fagaceae families (Peternel, 2006). Pollen grains can remain stable in a dry atmosphere for years, so pollination by wind (anemophily) is of particular importance for the development of allergic diseases, because pollen grains can be transported up to 175 km at a wind speed of 10 m per second (Taketomi 2006).

Therapeutic guidelines for the treatment of allergic rhinitis include patient education, environmental control, pharmacotherapy, allergen-specific immunotherapy and possibly surgical treatment. Patient education includes: avoiding contact with allergens, an appropriate level of home hygiene, planning outdoor activities, and showering after outdoor activities. The use of the GLOBE protocol can help people suffering from pollen allergies. The beginning of flowering and leafing of trees whose pollen is allergenic can be monitored through the GLOBE protocol for greening (Green up), thus warning citizens in time and thus contributing to the preservation of their health.

CONCLUSION

The study found that the most common disease during 2021, 2022 and 2023 was vasomotor and allergic rhinitis. The age group from 19 to 64 years was most susceptible to vasomotor and allergic rhinitis, allergic rhinitis caused by pollen, and chronic rhinitis, nasopharyngitis and pharyngitis during the three years of follow-up. According to the duration and severity, vasomotor and allergic rhinitis can be intermittent or permanent, and mild or severe. Due to the model of minimal persistent inflammation and non-specific nasal hyperreactivity, the clinical division into seasonal and perennial forms has been abandoned today. For example, a person with allergic rhinitis and hypersensitivity to grasses and even tree pollen often has problems outside the pollen season, often in winter.

The use of the GLOBE protocol can help people suffering from pollen allergies. The beginning of flowering and leafing of trees whose pollen is allergenic can be monitored through the GLOBE protocol for greening (Green up), thus warning citizens in time and thus contributing to preserving their health.

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SCIENTIFIC COMMUNICATION IN BIOMEDICINE AND HEALTH: UNIVERSITY TEXTBOOK REVIEW

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Authors: Josip Šimić & Branko Krišto

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The University of Mostar recently published the university textbook "Znanstvena komunikacija u biomedicini i zdravstvu" ("Scientific Communication in Biomedicine and Health") by Professor Josip Šimić and Professor Branko Krišto.

The authors have been noted for many years as excellent and renowned experts in the scientific and professional fields they deal with, and this textbook is the result of the need to professionally and scientifically process and present all the most important concepts of scientific communication with a focus on the field of biomedicine and health in one place and at the University of Mostar.

The reviewers of the textbook were: Professor Miro Leventić from the University of Mostar. Professor Sonja Špiranec and Professor Slobodan Mihaljević from the University of Zagreb.

In the author's preface and introductory part, the authors discuss science and bring into context the entire system of scientific information whose development cannot be separated from the development of scientific activity and modern science in the field of biomedicine and health. The textbook consists of a total of nine chapters – “Science”, “Scientific Communication”, “Scientific Communication Systems”, “Scientific Productivity”, “Information Literacy as a Basis for the Implementation of Scientific Communication”, “Characteristics of Scientific Information in Biomedicine and Healthcare”, “Artificial Intelligence and Scientific Publishing in Medicine”, “The Role of Libraries in Strengthening Scientific Research Infrastructure” and “Education and Lifelong Learning”.

The chapter “Science” provides basic knowledge related to the beginnings of science in biomedicine and healthcare, but also examples of how science has developed more than ever in the last twenty years, as well as the role of researchers and the need for mutual interaction between science and society, which the authors believe is greater than ever. The chapter “Scientific Communication” explains in more detail the types of scientific publications and parts of a scientific book, as well as what a scientific article is, with its structure and examples from medical and healthcare practice. It also discusses the influence of modern ICT (information and communication technologies) on scientific communication and the role of scientific journals in the field of biomedicine and healthcare. The chapter "Scientific Communication Systems" is important because of its detailed presentation of scientific information retrieval systems without which today's scientific communication is unthinkable. In addition, universities and their solutions for storing (primarily scientific) data, review systems for papers and identification systems in scientific communication are also presented, along with software solutions for managing references. The chapter "Scientific Productivity" provides practical examples of the productivity of the University of Mostar in the Web of Science and Scopus databases and also provides an overview of the basic principles of bibliometrics, scientometrics and informetrics with citation analysis of authors, the basis for assessing the quality of scientific work of a scientist or group of scientists.

The chapters "Information literacy as a basis for the implementation of scientific communication", "Characteristics of scientific information in biomedicine and healthcare", "Artificial intelligence and scientific publishing in medicine", "The role of libraries in strengthening scientific and research infrastructure" and "Education and lifelong learning", although shorter in scope, provide practical examples of the areas mentioned above and it is particularly important to mention that the authors bring some new

concepts to scientific and research practice in our field, such as the application of artificial intelligence and scientific publishing in the field of medicine, modern information environments and connect the concepts of information literacy and scientific communication, which are closely related concepts within the academic field, but encompass different aspects and goals.

Engaging in science and the profession in the field of biomedicine and healthcare requires scientists, decision-makers, as well as entrants into the world of science and scientific work and students to have lifelong education and training in the field of medical information, evidence in medicine and scientific communication, and this book will be important for students of biomedical professions, students of information and communication sciences, healthcare professionals and information experts.

In creating this textbook, the authors used recent and recognized literature by foreign and domestic authors: textbooks, internationally relevant journals, their own research and research by other authors related to the topics covered in the textbook. It fully meets the requirements of scientific and educational literature, and it can be safely said that this is a publication that is of high content and quality.

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13TH GASTROENTEROLOGY INTERNATIONAL SYMPOSIUM IN MOSTAR: NEW CHALLENGES AND ACHIEVEMENTS IN GASTROENTEROLOGY

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From 22 to 24 November 2024, Mostar hosted the 13th Gastroenterology International Symposium, one of the most important events in the field of gastroenterology in the region. This prestigious gathering brought together eminent experts and scientists in the field of gastroenterology, who exchanged the latest research, clinical approaches and innovations in the diagnostics and treatment of digestive system diseases.

NEW OPPORTUNITIES FOR COOPERATION IN THE REGION

The meeting was officially opened by the President of the Government of Herzegovina-Neretva Canton, Marija Buhač, who in her address emphasized the importance of such international events in promoting cooperation and progress of medical sciences.

Buhač also emphasized that such symposia not only enable professional training, but also connect experts from different parts of the world, which contributes to progress in the fight against the most serious diseases of the digestive system.

KEY TOPICS AND LECTURES

During the symposium, participants had the opportunity to follow a series of lectures that dealt with the latest therapeutic approaches, innovative techniques in endoscopy, and the prevention and treatment of chronic diseases such as IBD (inflammatory bowel disease) and liver cirrhosis. Experts who presented the results of new research in the field of the microbiome and its connection with the development of gastrointestinal diseases stood out in particular.

One of the key moments of the meeting was a session dedicated to personalized medicine in gastroenterology, which has become increasingly important in the treatment of patients. This topic aroused great interest among those present, as it opens up new possibilities in adapting therapies to the specific needs of each individual, which can significantly improve treatment outcomes.

INTERACTIVE FORMAT AND WORKSHOPS

The symposium also included a series of workshops and interactive sessions that enabled the practical application of new techniques and methods in gastroenterology practice.

Participants had the opportunity to participate in demonstrations of advanced endoscopic procedures and discussions on challenges in everyday clinical practice, which enabled a deeper understanding of complex diagnostic and therapeutic procedures.

REGIONAL COOPERATION AND INTERNATIONAL CONTRIBUTION

In addition to experts from Bosnia and Herzegovina, lectures were given by renowned gastroenterologists and surgeons from other countries in the region, including Croatia, Serbia, Montenegro and North Macedonia, making the symposium an important place for regional and international cooperation.

Interestingly, the organizers paid special attention to engaging young experts, who had the opportunity to present personal research and exchange experiences with colleagues from different parts of the world.

THE PATH TO NEW HORIZONS IN GASTROENTEROLOGY

The 13th Gastroenterology International Symposium in Mostar ended with a series of conclusions that emphasize the importance of integrating new technologies and approaches into everyday clinical practice.

Participants agreed that innovations in therapies, such as personalized medicine and new endoscopic techniques, are crucial for improving the quality of life of patients.

This symposium was not only an opportunity for professional development, but also encouraged stronger cooperation between gastroenterologists in the region and the world.

Mostar once again demonstrated and proved that it is a place of meeting and dialogue among experts who are dedicated to progress in gastroenterology and the fight against digestive system diseases.

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